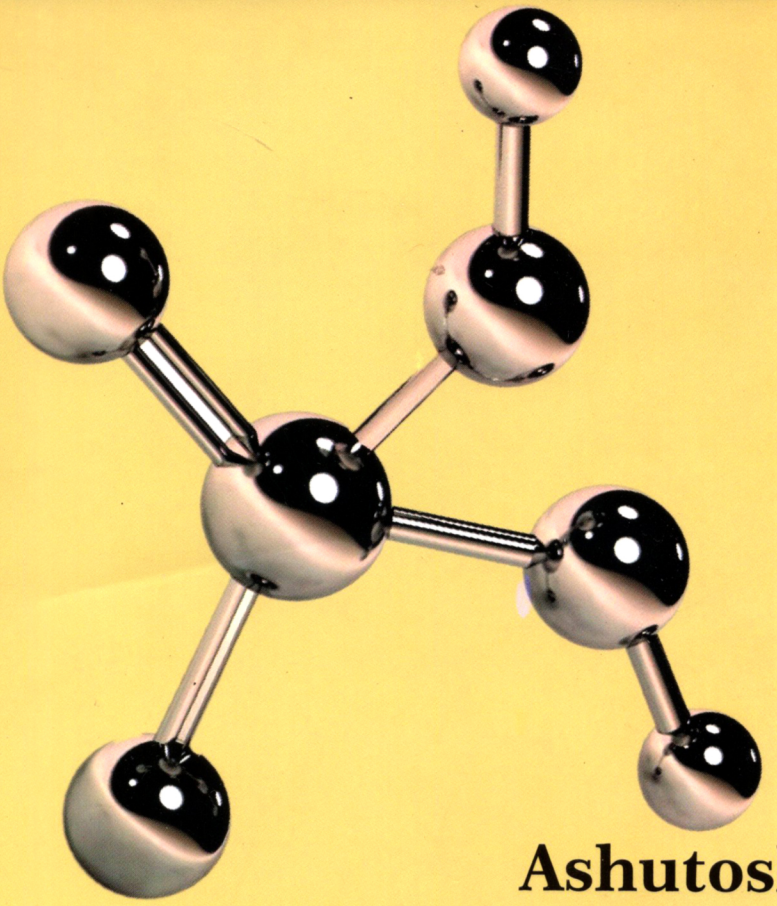
Advanced Organic Chemistry

(Structure & Mechanisms)



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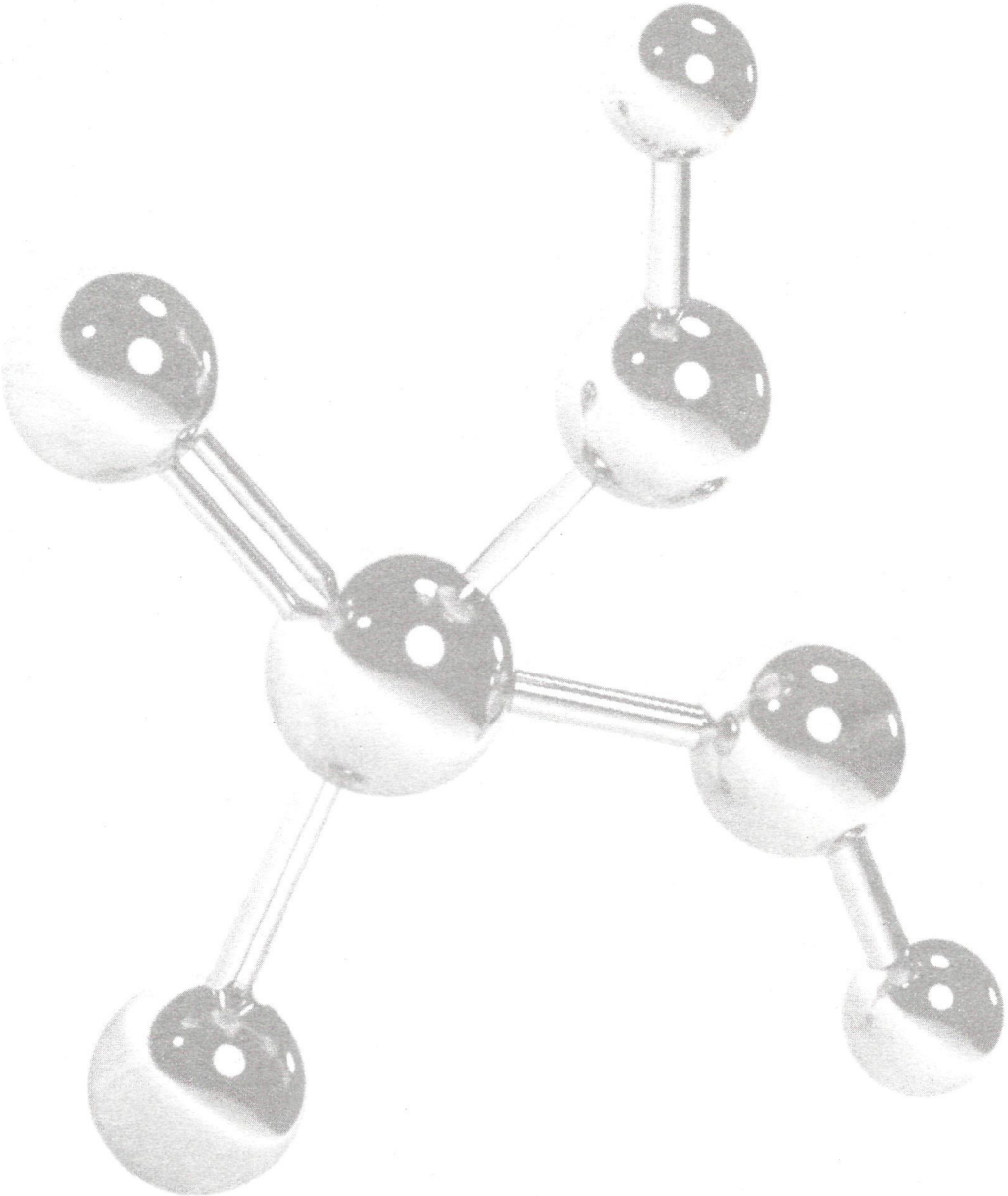

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Advanced Organic Chemistry

(Structure & Mechanisms)

[For B.Sc. (Hons.), M.Sc., and Research Scholars]

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"One Important Key to Success
Is Self-Confidence.
An Important Key to Self-Confidence
Is Preparation"

—Arthur Ashe

"The Future Belongs to Those—
Who Believe in the Beauty of Their Dreams."

—Eleanor Roosevelt

"Dreams Will Only Help You Actualize Your Goals.
I Started Dreaming When I was a Child .....
I Became a Scientist Because I Dreamt."

—APJ Abdul Kalam

Knowledge Begets Efficiency

Dedication

To My Beloved Paretns, Sisters and Brother
To Others and My Wife
Who Helped Me Build-up My Life,
To Our Sons, Daughters-in-law and Grandchildren
Who Thrilled My Life with Joy and Cheers
To My Esteemed Teachers and Taughts
(in India, Nigeria, Libya and Ethiopia)
To the August Authors-Home and Abroad,
To Whomsoever the Book Owes,
To The People Who Meticulously Toil,
To Make Fruitful the Soil,
For Ever and Now,
To Almighty God's Eternal Blessings,
I Respectfully Bow, Bow and Bow.

Preface

The fundamentals of **Organic Chemistry** may be understood in a comprehensive manner only through *three* important channels that would ultimately open up the scope of this branch of chemistry into a leading subject of choice, creativity, and versatility amongst the students, researchers and scientists alike. *First,* it would be mandatory for one to get adequately familiarized with the physical and chemical properties of the *Organic Chemical Entities* (compounds). Secondly, one would understand critically their reactivities together with their inherent options and/or intricacies of various range of reactions. Thirdly, it would be an absolute must to develop the enormous ability to *Design Synthesis* in a big way with knowledge, wisdom, skill, intellect, perseverance and above all the dogged determination.

The students of present generation opting to study chemistry do often experience a significant drawback perhaps caused by an overwhelming growth and advancements taken place in all the sciences that are accompanied specifically by the students of **Organic Chemistry** to muster, learn and adapt to a relatively huge number of reactions that was never a situation previously.

A survey of literature would certainly ascertain the underlying fact that older concepts, ideas and knowledge are being transformed rapidly by: Modern methodologies, theories, innovation of ideas/thoughts, newer scientific observations and a virtual war on revolution in the advancement in the domain of **Organic Chemistry.** It essentially comprises: Orbital Theories, Wave Mechanics, Combinatorial Chemistry, Chiral Chemistry, 3D-NMR Techniques, FTIR-Spectroscopy, X-Ray Diffraction (XRD) Analysis, Optical Rotary Dispersion (ORD) Studies, HPLC-Analysis, LC-MS/GC-MS/IR-MS Hyphenated Methods, CADD-Methods, and the like, which have rendered the **Organic Chemistry** into an obvious **'World of Science'** itself.

The textbook on **Advanced Organic Chemistry** has been written integrity, passion and a mission to make it into a student-friendly campanion for the *M.Sc., B.Sc. (Hons.), and Research Scholars pursuing for Ph.D. programmes.*

For the benefit of brilliant students in the Indian Universities and abroad as well—the entire textual matter has been arranged meticulously into **Twenty-Five Chapters** contained in **Five Sections (1, 2, 3, 4 and 5)**—as stated under:

Part A : Fundamentals of Organic Chemistry [Chapters 1 to 3];

Part B : Name Reactions Based on Product Formed [Chapter 4 to 11];

Part C : Rearrangements : Classifications and Mechanisms [Chapters 12 to 19];

Part D : Organic Reactions and Mechanisms [Chapters 20 to 24], and

Part E : Some Novel Reactions in Organosilicon Chemistry [Chapter 25].

The major strengths of the textbook have been developed carefully starting each chapter with : a brief introduction, fundamentals of organic reactions, reaction mechanisms, classical examples, nomenclature of reactants and mechanisms to enable the readers to grasp the in-depth of Organic Chemistry, followed by footnotes, references on each page (wherever required) and other relevant references under *Suggested Reading* at the end of each chapter.

The esteemed readers will be benefited grossly with vital divergent aspects of **Advanced Organic Chemistry** with particular reference to such critical areas of interest as given below:

• Atomic Bonding • Stereochemistry • Reaction Intermediates • Factors Governing Reactivity Profile • Rearrangements in Organic Chemistry Related to : Electron Deficient Heteroatoms—Acyl Carbenes—Induced by Electron-rich sites—Addition-Elimination Mechanism—Pericyclic Reactions—Aromatic Rearrangements—Scope and Mechanism of Substitution Reactions—Addition Reactions—Elimination Reactions; and Novel Reactions in Organosilicon Chemistry.

Special attention has also been paid to all the aspects of *synthetic processes* included in the text matter.

It is believed earnestly that the present compendium would certainly prove to be an asset and a reliable source of authentic information(s) not only to the students but also to the valued teachers dealing with the subject.

The author would like to place on record the excellent help and candid cooperation from Shri Rajan Jain, Director, Scientific International (Pvt) Ltd., New Delhi, in bringing out the book in a scheduled time-frame.

Gurgaon (India) **Ashutosh Kar**

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Section 1

Fundamentals of Organic Chemistry

Chapter 1. Atomic Bonding

Chapter 2. Stereochemistry

Chapter 3. Reaction Intermediates and Factors Governing Reactivity

Chapter 1

Atomic Bonding

LESSON AT A GLANCE

1.1 Introduction
- 1.1.1 Covalent Bonding
- 1.1.2 General Methods of Approximation
- 1.1.3 Variants in Molecular Orbital Procedure

1.2 The Valence-Shell Electron-Pair Repulsion [VSEPR] Theory

1.3 Metallic Crystals
- 1.3.1 Guiding Factors Governing the Formation of Metallic Bond
- 1.3.2 Nature of the Metallic Bond
- 1.3.3 Certain Physical Characteristic Features of Metals *vis-a-vis* their Explanations Based Upon Electron-Gas Theory

1.4 Metallic Crystals

1.1 INTRODUCTION

What is an 'Atom'? The **'atom'** relates to the smallest unit of an element that can exist. In fact, **'atoms'** have long been known to be made up of subatomic particulate matters invariably termed as:

- **Protons** • **Neutrons** **and** • **Electrons**

The nucleus of an **atom** contains *one or more proton,* which are positively charged; and *two or more neutrons* (except in **hydrogen**), which critically bears **no electric charge.** Besides, each **proton** and **neutron** has a ***mass number* of 1**; and they are bound together so intimately in the nucleus by means of the so-called **exceedingly strong forces.**

The **electrons** do move around the nucleus in **shells** (*groups of orbitals*) that are eventually determined by their inherent:

- **energy levels** or
- **wave functions**

Thus, an *electron* happens to be a **negatively charged unit** that more or less behaves as both

- **a particle** (*viz,* **partly wave**), and

NOTE: **Importantly, every atom has the same number of *electrons* as *protons*, and is thus '*neutral*' electrically.**

Covalent Bond

The **covalent bond** refers to **"a chemical bond resulting from the sharing of a pair of electrons by two atoms, each atom donating one electron from its outer shell (bond energy ~ 100 kcal. mole^{-1})."**

In other words, the **'covalent bond'** is duly formed by the *sharing of electrons*; and, therefore, it would be quite possible to regard the critical sharing of ***two* electrons** by the aid of ***two* atoms** for the making of a ***chemical bond.*** In addition, the atoms is capable of sharing **one, two** or **three electrons** thereby giving rise to the formation of:

- **a single (—) bond**
- **a double (═) bond and**
- **a triple (≡) bond**

Salient Features: These essentially include:

1. The **electrons** do have the same **spatial energy** as well as **distribution profile***, but they actually differ in their respective **'spin'** according to the **Pauli's exclusion principle.****

2. In a broader perspective, the *electrons in an atomic nuclei* predominantly occupy:
   - **orbitals of *fixed energy* and *spatial distribution*;** and
   - **each individual orbital contains exclusively a maximum of *two electrons* having critical anti-parallel spins.**

3. **Wave Equation:** It may be added at this point in time that the **'wave equation'** almost directly predicts the desired solutions in a specific manner, such as:
   - **expressed in one dimension**;
   - **equation determines the *energy profile*; and**
   - **defines the *spatial distribution* of each and every electron.**

4. **Respective Solutions of Wave Equations:** In actual practice, one determines the **3D-calculations** pertaining to the ***'shape'*** of *each orbital.* Nevertheless, one may explicitly depict the **first-five solutions of the *'wave equation'*** for an ***'electron'*** linked intimately with a ***'proton'*** (see Fig. 1.1).

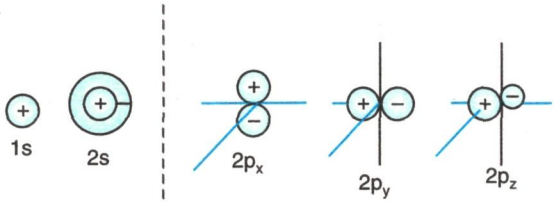

Fig. 1.1: Diagrammatic representation of first-five solutions of wave equation

* That is, they usually occupy the same orbital.

** **Pauli's Exclusion Principle:** It dictates that *no two electrons* in atom may have an **identical set of quantum numbers;** and thus, restricts those electrons occupying the same orbital to those of **opposite (antiparallel) spins.**

1.1.1 Covalent Bonding

Wave* mechanics is critically based upon the *fundamental principle* that the **electrons** invariably behave as ***waves*** (*viz.*, these could undergo *diffraction*). Besides, one may even express the so-called **'wave equation'** for them just in the same manner as:

- **Light waves** and
- **Sound waves,**

may be adequately described by the **'wave equation'.** Therefore, the **specific equation** which usually serves as a **mathematical model** for the *electrons* is normally termed as the ***Schrödinger equation*****; and the same may be written for a **one-electron system** is as given under:

$$\frac{\partial^2 \psi}{\partial x^2} + \frac{\partial^2 \psi}{\partial y^2} + \frac{\partial^2 \psi}{\partial z^2} + \frac{8\pi^2 m}{h^2}(E - V)\,\psi = 0$$

where, m = mass of electron

E = total energy

V = potential energy, and

h = Planck's constant

The physical perspective the function ψ expresses the *square root* of the probability of determining the electron at any position as duly defined by the **coordinates** x, y and z (with **'nucleus' as the origin**).

NOTE: **However, the systems comprising more than one electron the equation is very much identical but much more complicated.**

Remarks: Unfortunately, the **Schrödinger equation** may be solved exclusively for ***one-electron systems***, for instance: **The Hydrogen Atom.**

Interestingly, if it could be possible to solve exactly for such **molecules** consisting of ***two* or *more* electrons*****, it could have provided a *precise picture* of:

- ***shape* of orbitals duly available to each electron;****** and
- ***energy* of each orbital.**

Obviously, as the **exact solutions** are not readily available, we are left with no other alternative than to make the required **'drastic approximation'.**

1.1.2 General Methods of Approximation

As to date, there are ***two* general methods of approximation,** namely:

(*a*) **Molecular orbital method,** and

(*b*) **Valence-bond method.**

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* **Wave:** It refers to the **signal that propagates *via* space**

** It represents a **'differential equation'.**

*** Stewart Q : *Rev Chem Soc,* **24** : 95-118, 1970.

**** That is, especially for the important **ground state.**

1.1.2.1 Molecular Orbital Method

In this particular instance, the bonding is assumed to take place right from the ensuring **overlap of the atomic orbitals,** as illustrated in Fig. 1.2.

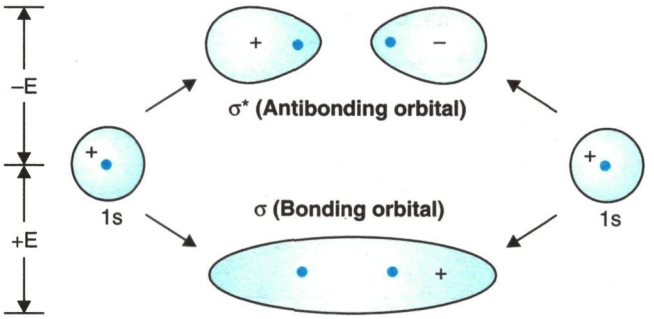


Fig. 1.2: Diagrammatic representation of the overlap of two 1s orbitals to give rise to a σ bond and a σ* orbital

Explanations: The various steps involved may be explained as under:

1. When any number of **atomic orbitals** do overlap, they usually combine to form an **equal number of newer orbitals** – known as the ***molecular orbitals.***

2. The resulting ***molecular orbitals*** invariably differ from the respective ***atomic orbitals*** in such a manner that they actually form **'clouds'**—that initially surround the nuclei of either *two* or *even more atoms*, rather than **just one atom only.**

3. Nevertheless, in *localized bonding* the precise number of the **'atomic orbitals'** which overlap is *two* (*i.e.,* **each of them comprising one electron**)—thereby causing the generation of ***two*** **molecular orbitals,** such as:

- **Bonding Orbital:** having a lower energy in comparison to the **'original atomic orbitals'** (rest a **'bond'** would never be formed); and
- **Antibonding Orbital:** having a definite much higher inherent energy level.

4. Obviously, the orbitals having **lower energy** fill first. Besides, as the ***two*** **original atomic orbitals** each essentially held **one electron only;** hence, both of these ensuing electrons may now be engaged into the creation of an altogether ***new molecular bonding orbital***, because *any orbital* may hold **two electrons** justifiably.

5. The **antibonding orbital** virtually remains empty when it is in the **ground state.**

6. Thus, larger the *extent of overlap*—the stronger would be the bond, though the **'total overlap'** encountered may be duly prevented by the prevailing repulsion between the ***two*** **nuclei.**

7. In Fig. 1.2, since the **antibodying orbital** bears a *node between the nuclei,* there is hardly any **electron density** in that area; and hence, this **'orbital'** cannot be expected to bond very well.

8. **Sigma (σ) Orbitals:** The *molecular orbitals* that are duly formed due to the overlapping of ***two*** **atomic orbitals,** *whereby the centres of electron density do essentially fall upon the axis common to the two nuclei,* are usually known as the **sigma (σ) orbitals;** whereas, the resulting bonds are termed as **sigma (σ) bonds.**

1.1.2.2 Molecular Orbital Calculations

In this procedure, a typical **'wave function'** is being formulated which designates a *linear combination of the atomic orbitals* that have virtually overlapped. Therefore, this method is quite often also named as the **linear combination of atomic orbitals (or LCAO).**

Thus, the sequential addition of the so-called *atomic orbitals* provides specifically the **bonding molecular orbital:**

$$\boxed{\psi = C_A\psi_A + C_B\psi_B} \qquad \ldots(a)$$

where, ψ_A and ψ_B = Functions for the atomic orbitals A and B respectively, and
C_A and C_B = Represent the weighing factors

Likewise, the **'subtraction'** does also designate a ***linear combination.***

$$\boxed{\psi = C_A\psi_A - C_B\psi_B} \qquad \ldots(b)$$

NOTE: **Hence, it gives rise to the corresponding *'antibonding molecular orbital'*.**

1.1.2.3 Valence Bond Method

Here, a *wave equation* is duly written for each of the different feasible **electronic structures** which a molecule may ultimately possess*; and the total ψ is accomplished by the summation of as many of these as seem to be possible, each having its *individual washing factor:*

$$\boxed{\psi = C_1\psi_1 + C_2\psi_2 + \ldots} \qquad \ldots(c)$$

Comments: Eqn. (*c*) resembles to the Eqn. (*a*), but in the former each ψ designates a wave equation for an ***imaginary*** **canonical form**; and each **'c'** is the exact quantity duly contributed to the **entire picture by that form.**

Example: A wave function may be written for each of the following **canonical forms** of the ensuing **hydrogen molecule.**

$$H{-}H \qquad {}^{\ominus}H\ \ H^{\oplus} \qquad {}^{\oplus}H\ \ H^{\ominus}$$

1.1.3 Variants in Molecular Orbital Procedure

There are *five* important variants in the domain of **molecular orbital procedure,** namely:

(*i*) Bonding Molecular Orbital (BMO);
(*ii*) Antibonding Molecular Orbital (ABMO);
(*iii*) Guidelines for Linear Combination of Atomic Orbitals;
(*iv*) Guidelines for Filling up of Molecular Orbitals; and
(*v*) Molecular Orbital (MO) Diagram.

which shall now be discussed briefly in the sections that follows:

* Each of these is termed as a **canonical form.**

1.1.3.1 Bonding Molecular Orbital (BMO)

The **Bonding Molecular Orbital (BMO)** is also known as the **additive overlapping of *two* atomic orbitals;** and consequently, the careful addition of ***two*** **orbitals** to produce the desired **BMO**, as shown in Fig. 1.3.

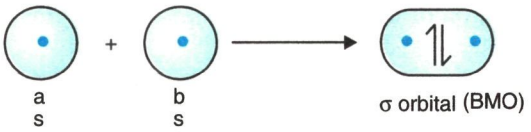


Fig. 1.3: Critical formation of BMO.

Observations: Importantly, in a **BMO** the electron density is found to be duly concentrated in the particular region located strategically between the ***two*** **nuclei**; and hence, **protects the repulsive influence of one nuclei over the other nuclei.** Thus, the overall enhancement in the **electrostatic attraction** reduces the energy of the system appreciably.

Figure 1.4 (*a*) and (*b*) depict explicitly the due formation of **BMO** by p_a and p_b orbitals respectively.

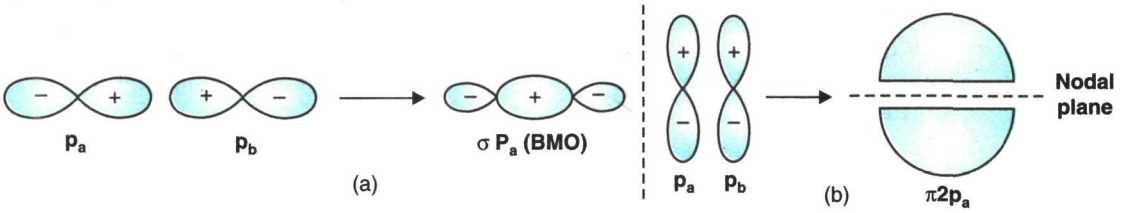


Fig. 1.4: (a) Formation of BMO by p_a orbitals; (b) by p_b orbitals

1.1.3.2 Antibonding Molecular Orbital (ABMO)

The **ABMO** is also called as **subtractive overlapping of *two* atomic orbitals.** In true sense, an **ABMO**, the *electrons* are not located densely in between the ***nuclei*** and ***electron density***—that remains **'zero'** at the respective **nodal plane***. Importantly, by virtue of the critical formation in the particular segment of *destructive interference* (caused due to the so-called *subtractive overlapping* between the ***two*** **atomic orbitals**), the overall observed **wave-functions of *two* oppositely signed atomic orbitals get cancelled on this plane.** Perhaps this is accomplished based on the fact that the ensuing **atomic orbitals** do cancel for values located equidistant from the *two* nuclei, thereby giving rise to **zero electron density.**

The following Fig. 1.5 clearly shows the formation of **antibonding molecular orbital (ABMO).**

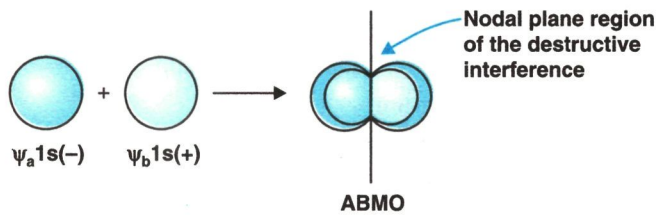


Fig. 1.5: Diagrammatic representation of formation of ABMO

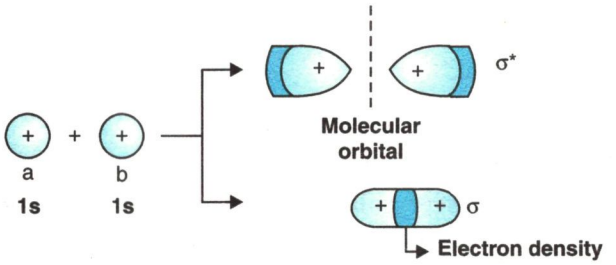
* **Nodal Plane:** It relates to a plane on which the wave-function passes through zero. Besides, the plane very much lies halfway between the nuclei and cuts through the *internuclear axis*.

Remark: Thus, one may definitely observe a distinct *reduction* in the **electrostatic attraction** and also an *enhancement* in the ensuing *repulsion existing between the nuclei.* However, in this particular instance, the ***final energy of the system*** is obviously higher *vis-á-vis* the ***separated atoms.***

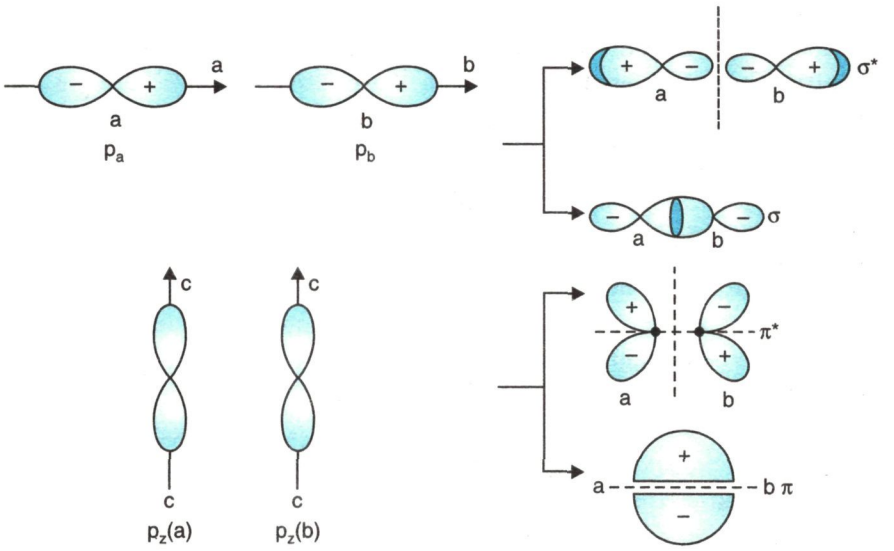
In short, it may be added vehemently that there could exist *two* clear cut situations:

- **BMO:** Wherein the *electrons* do have a tendency to hold the atoms together; and
- **ABMO:** Wherein the *electrons* do tend to force the atoms apart.

The aforesaid ***two*** **distinct situations** *i.e.,* **BMO** and **ABMO formation** may be explicitly depicted in Figs. 1.6 (*a*) and (*b*) respectively.



(a) **Bonding Molecular Orbital (BMO): Showing S—S formations**



(b) **Antibonding molecular orbital (ABMO) : Showing p—p combinations**

Fig. 1.6: (a) BMO–Showing S—S formations; (b) ABMO–Showing p—p combinations

Figure 1.7 illustrates the prevailing **energy levels** of **S—S atomic orbital (OB)** and **S—S molecular orbitals (MO),** which is solely based upon the following established relationship:

$$E_{ABMO} - E_{BMO} = \Delta E + \Delta E_2$$

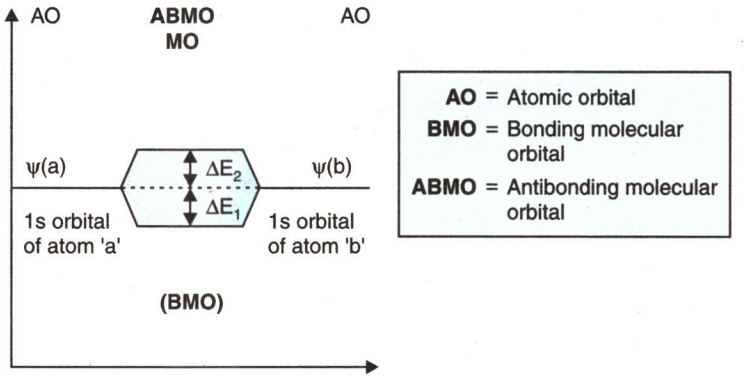


Fig. 1.7: Energy levels of S—S atomic and molecular orbitals

1.1.3.3 Guidelines for Linear Combination of Atomic Orbitals

Importantly, the following **guidelines** or **rules** are fully applicable for deciding which ***atomic orbitals*** may actually **undergo the phenomenon of overlapping** to give rise to the formation of **molecular orbital,** such as:

- **Preferentially the *'atomic orbitals'* having both *energy* as well as *symmetry profile* would undergo overlapping.**
- **Predominantly the specific effective overlapping between the *two* atoms–in producing the requisite 'bond', solely depends upon the relative distance between the two; and**
- **Eventually the *two* atomic orbitals either:**
  - **undergo absolute 'no change', or**
  - **similar change in the symmetry profile, in order to form BMO or ABMO respectively.**

1.1.3.4 Guidelines for Filling up of Molecular Orbitals

It has been duly observed that in the typical instance of **molecular orbitals,** the ensuing electrons are duly filled exactly in the same manner as those filled in the so-called **atomic orbital of atoms;** and hence, we have ***three*** **cardinal guidelines,** as stipulated under:

- **Aufbau Principle:** The **Aufbau principle** (*German* meaning: **"buildup principle"**) tells us how to determine the **electronic configurations** precisely. According to this principle–place the respective electrons one by one right into the orbitals of the lowest possible energy in a manner very much consistent with the following *two* dictums:
  - **Hund's Rules** and
  - **Paul's Exclusion Principle.**
- **Hund's Rule:** The **Hund's Rule** may be illustrated by taking into consideration the so-called *electronic configuration* of *C-atom* undoubtedly an extremely important element in the domain of **Organic Chemistry.** Obviously, a **C-atom** does possess ***six*** **electrons** having the following distribution profile.

- ***First two* electrons: (with *opposite spins*) go into the 1*s* orbital exclusively;**
- ***Second two* electrons: (also with opposite spins) go into the respective 2*s* orbital;** and
- **Remaining *two* electrons: The Hund's Rules tell us how to distribute the remaining *two* electrons very much amongst the *three* equivalent 2*p* orbitals.**

In short, the **Hund's Rules** clearly state, first, that to distribute the electrons amongst *similar orbitals with equal energy levels viz.,*

- **Single Electrons** are duly placed into altogether separate orbitals before the orbitals are actually filled; and
- **Unpaired Electrons:** the *spins* of these *unpaired electrons* usually remain the same.

However, one may appropriately represent the **'electrons'** as the ***coloured arrows;*** and thereby allowing their **relative directions** correspond to their *relative spins.* Thus, the ultimate **electronic configuration of C-atom** may be shown as given under (Fig. 1.8):

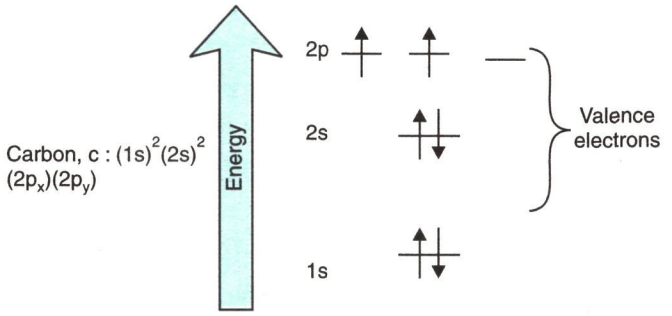


Fig. 1.8: Representation of electronic configuration of C-atom

Comments: These essentially include:

1. As per **Hund's Rules,** the electrons present in the **carbon 2*p* orbitals** are duly *unpaired with identical spin.*

2. Now, placing *2-electrons* in different **2*p* orbitals** rightly ascertains that the repulsions between the *electrons* are brought to a bare minimum level, since the electrons in different **2*p* orbitals** do critically occupy **different regions of space.**

3. As depicted in the above diagrammatic representation, one may also express the so-called *electronic configuration* of ***C*-atom** more explicitly and concisely as given below:

$$(1s)^2\ (2s)^2\ (2p_x)\ (2p_y)$$

that obviously shows the ***two* 2*p* electrons** in *different orbitals.*

Paul's Exclusion Principle

The Paul's exclusion principle states that **"no *two* electrons may possess all *four* quantum numbers the same".**

Therefore, as a result of this principle, a maximum of ***two* electrons** could be **placed** in any **one orbital**; and hence, these prevailing electrons should have altogether **different spins.**

Example: Let us take the typical example pertaining to the **electronic configuration of Helium (He) atom:** that critically contains **2-electrons.** Thus, both the electrons may be placed legitimately

into the **1*s* orbital** as long as they have *different spin.* Consequently, it is quite possible to express the **electronic configuration of He** as stated below:

Helium, He : $(1s)^2$

1.1.3.5 Molecular Orbital (MO) Diagram

The typical formation of the so-called ***homomolecular diatomic molecules*** due to the meticulous overlapping of ***two*** **identical atoms with similar nucleus,** for instance: **Hydrogen (H_2), Nitrogen (N_2), Oxygen (O_2), and Fluorine (F_2).** Thus, we usually come across *two* different situations, namely:

- **Molecular orbital treatment for homonuclear diatomic molecules;** and
- **Molecular orbital treatment for heterodiatomic molecule,** which shall now be treated separately in the sections that follows:

1.1.3.5.1 Molecular Orbital Treatment for Homonuclear Diatomic Molecules

In this specific instance, we invariably encounter ***two*** **distinct typical examples,** such as:

Hydrogen (H_2) Molecule

One *molecular orbital,* known as the **'bonding molecular orbital ($\psi_{molec.}$)'** comprises both electrons in the critical *lowest energy state* (*i.e.,* **ground state**), of a **H_2-molecule.** However, it is formed when the *atomic orbitals* do combine in the manner as illustrated in Fig. 1.9.

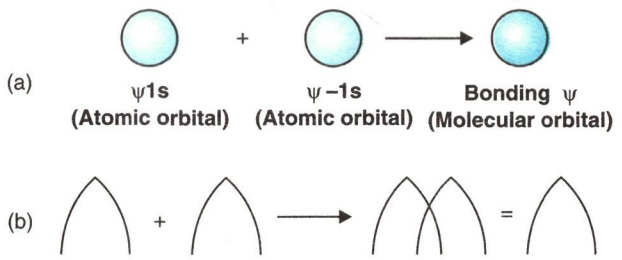


Fig. 1.9: (a) The overlapping of two hydrogen 1s atomic orbitals having the same phase sign to form a bonding molecular orbital. (b) The analogous overlapping of two waves having the same phase (Resulting in constructive interference and increased amplitude).

Explanations

1. In the above specific instance, the ensuing **atomic orbitals** do combine due to **'addition'**; and thereby it suggests strongly that the said **atomic orbitals bearing the similar phase sign overlap each other.**

2. Thus, the resulting phenomenon of overlapping ultimately leads to ***reinforcement*** of the critical **wave function** in the region located strategically between the ***two*** **nuclei.**

3. Furthermore, the reinforcement of the prevailing **wave function** indicates explicitly the value of ψ* is obviously larger between the ***two*** **nuclei** and this also suggests that ψ^2 is also larger as *per se.*

4. Importantly, because ψ^2 particularly signifies the most glaring possibility of indentifying an *electron* in this segment of space, one may now clearly understand the exact *modus operandi* whereby the **orbital** of such a nature does lead to the phenomenon of **'bonding'.** In fact, such a **'bonding'**

---

* That is, the **'bonding orbital'.**

invariably comes into play due to an ***enhanced electron probability density*** in precisely the **'right spot'** *i.e.,* the particular region of space located between the nuclei.

NOTE: **Nevertheless, in such a situation when the *'electron density'* is found to be significantly higher, one may critically take cognizance of the *two* underlying aspects:**

- **attractive force of the nuclei for the electrons more than offsets the so-called ensuing force acting between the *two nuclei*; and**
- **also between the *two electrons* as well.**

5. Interestingly, the overall **'extra-attractive force'** represents critically the ***'glue'*** which actually holds the ***two*** **atoms together firmly.**

H_2^+ Molecular Ion

The **second molecular orbital** is termed as the ***antibonding molecular orbital*** (ψ^*_{molec}), has virtually no electrons particularly in the *ground state* (low energy level) of the molecule. In general, it is being formed due to the interaction of **orbitals having opposite phase signs.** Fig. 1.10 (*a*) and (*b*) illustrates that the *wave functions* do cause interference with each other particularly in the specific region located strategically between the ***two*** **nuclei** and a **node** is generated ultimately.

Explanations

1. It may be observed critically that at the ***'node'*** $\psi = 0$; and on either side of this ***'node'*** the value of ψ remains small. Hence, it indicates explicitly the region located between the nuclei ψ^2 also remains small.

2. In this manner, one may draw the inference that if the ensuing *electrons* were intended to occupy the so-called **'antibonding orbital'**, there lies an abundant opportunity for the said electron may critically avoid the region between the **nuclei.**

Ultimately, it would show up merely a **small attractive force of the nuclei for the electrons.**

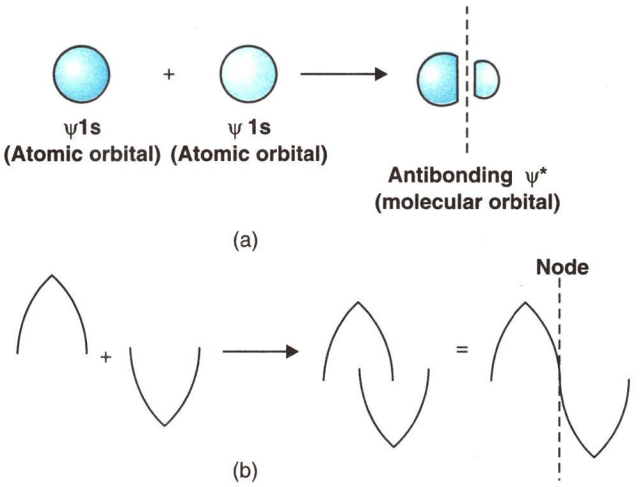


Fig. 1.10: (a) Illustration of the overlapping of two hydrogen 1s atomic orbitals (AOs) with opposite phase signs (as shown by their different shades) to form antibonding molecular orbital (ABMO). (b) Representation of the analogous overlapping of two waves with the opposite sign, resulting in destructive interference and reduced amplitude.

3. Furthermore, the prevailing emanated *'repulsive forces'** will be certainly greater than the so-called *'attractive forces'*. Obviously, had the *electrons* present strategically in the **antibonding orbital (ABO)** would not actually held the atoms together, it could have made them to fly apart definitely.

NOTE: **The appearance of a *'node'* takes place at a critical point where the so-called *total cancellation by the opposite phases* renders the value of the *combined wave function 'zero'*.**

Linear Combination of Atomic Orbital (LCAO) Method

The **LCAO method** relates to *mathematic treatment*, wherein the *wave function* of the ensuing **atomic orbitals (OBs)** are duly combined in a *linear modality* (*i.e.*, either accomplished by *addition or substraction*) so as to obtain an altogether ***new wave function*** for the ultimate **molecular orbitals (MOs).**

Molecular Orbitals (MOs)

The **MOs**, very much akin to **AOs**, do correspond to specific **'energy states'** with respect to an *electron*. However, it has been amply ascertained with the help of *'calculations'* that the so-called ensuing ***'relative energy'*** of an *electron* present duly in the respective **bonding molecular orbital (BMOs)** of the ***hydrogen molecule*** (H_2) is found to be significantly lower *vis-a-vis* its corresponding energy in a ***ψ1s atomic orbital.*** In addition, the aforesaid *calculations* vehemently demonstrate that the respective ensuing *energy of an electron* in the **antibonding molecular orbital (ABMO)** is appreciably higher in comparison to its energy in a ***ψ1s atomic orbital.***

Energy Diagram for the Molecular Orbitals of Hydrogen Molecule (H_2)

Figure 1.11 depicts the energy diagram for the **hydrogen molecule (H_2).**

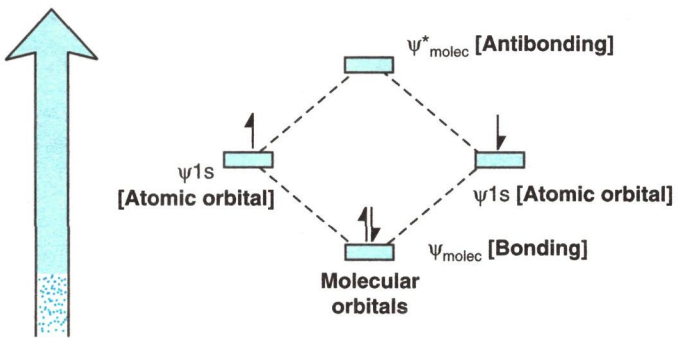


Fig. 1.11: Representation of energy diagram for hydrogen molecule (H_2). Combination of two atomic orbitals [ψ1s] results two molecular orbitals (ψ^*_{molec} and ψ_{molec}).

Explanations

1. In Fig. 1.11 one may observe critically that the ensuing energy of ψ_{molec} is obviously lower *vis-a-vis* the separate *atomic orbitals;* and is found to be in the **lowest electronic energy level** of the *molecular hydrogen* (H_2)—the **bonding MO** essentially comprises both electrons.

---

* That is, the forces between the ***two*** **nuclei** and between the ***two*** **electrons.**

2. It may also be seen that the respective electrons are meticulously placed in the correspondingly **molecular orbitals (MOs)** usually in the same fashion as if they were located in the **atomic orbitals.**

3. Interestingly, ***two*** **electrons** (having *'opposed spins'*) do occupy the respective **bonding molecular orbital (BMO),** wherein their ***complete energy level*** is found to be less *vis-a-vis* the individual **atomic orbitals.**

NOTES: 1. In true sense, this relates to the critical *'ground state'* (*i.e.,* the *lowest electronic state*) of the respective hydrogen molecule (H_2).

2. Besides, an *'electron'* may also occupy the *antibonding orbital* (ABO) which designates truely the *excited state* for the hydrogen molecule (H_2). In fact, this specific state comes into play when the molecule remains in the *'ground state'* (low-energy state) that eventually absorbs a *'photon'* of light with proper energy.

1.1.3.5.2 Molecular Orbital Treatment for Heterodiatomic Molecule

Importantly, in this particular instance the ***two*** **atomic orbitals (AOs)** pertaining to altogether *different atoms* must possess the following ***three*** **characteristic features,** namely:

- **same energy levels;**
- **identical symmetry;** and
- **maximum degree of overlapping to produce *'molecular orbitals'*.**

It may, however, be observed that the specific **heterodiatomic molecules** do comprise ***two*** **different atoms.**

Examples: Following are the *two* typical examples pertaining to the so-called **molecular orbital diagrams of the heterodiatomic molecules,** namely:

- **Carbon Monoxide (CO)** and
- **Nitric Oxide (NO)**

Carbon Monoxide (CO)

Since, the **C-atom** possesses 4 ($1s^2$, $2s^2$, $2p^2$), and **O-atom** has 6 ($1s^2$, $2s^2$, $2p^4$) electrons located strategically in their ***valence shell****, the so-called **CO molecule** critically has (4 + 6 =) **10 electrons** in its corresponding ***valence shell.***

Thus, we may have the *molecular orbital configuration* of the **CO molecule** expressed as:

$$\sigma\, 1s^2,\ \sigma^*1s^2,\ \sigma\, 2s^2,\ \sigma^*2s^2,\ \begin{Bmatrix}\pi\, 2p_y^2\\ \pi\, 2p_x^2\end{Bmatrix}\sigma\, 2p_x^2,\ \begin{Bmatrix}\pi\, 2p_y^0\\ \pi\, 2p_x^0\end{Bmatrix}\sigma^*2p_x^2$$

From the above expression, the **bond order of the molecule** = (8 – 2) ÷ 2 = 3, which indicates explicitly that in a **CO molecule**, there would exist predominantly ***three*** p_x^2 **bonds between C and O atoms.**

---

* **Valence Shell:** It usually relates to the number of electrons in the outer orbit of an atom *i.e.,* an index of the bonding capability of an atom or group of atoms with another atom or group of atoms.

Remarks: These essentially include:

1. Importantly, **one** of the ***two*** **electron pairs** specifically residing in: $\sigma\ 2s^2$ and σ^*2s^2 is located strategically on **C-atom**, while the *'other electron pair'* is duly positioned on the respective **O-atom.** Obviously, the ensuing **'electron pairs'** on these atoms are not at all engaged in any sort of **bonding phenomenon.**

2. The configuration of the ***three*** p_x^2 **bonds** in the **CO molecule** are as stated under:
   - ***one*** p_x^2 **bond** is σ which is duly formed by the electrons present in $\sigma\ 2p_x^2$; and
   - ***two*** π **bonds** $[2p_y^2$ **and** $2p_x^2]$ are located between the C and O, thereby resulting into the formation of the respective electron pairs duly present in $2p_y^2$ and $2p_x^2$.

3. Thus, one may observe vehemently, that the **CO molecule** is completely devoid of ***'unpaired electron'***; and hence, is found to be **diamagnetic*** in character.

4. Therefore, in this manner the critical formation of the so-called ***CO molecular orbitals*** right from **C and O atomic orbitals do undergo *sp*-hybridization.**

We may now have the following expressions:

- ***C-Atom*** **[Ground State]:** $2s^2,\ 2p_x^1,\ 2p_y^1,\ 2p_z^0$
  [*sp*-Hybrid State]: $(sp)^2,\ (sp)^1,\ 2p_y^0,\ 2p_z^1$
- ***O-Atom*** **[Ground State]:** $2s^2,\ 2p_x^1,\ 2p_y^2,\ 2p_z^1$
  [*sp*-Hybrid State]: $(sp)^2,\ (sp)^1,\ 2p_y^2,\ 2p_x^1$

Thus, we can write the following *three* relationships:

$(sp)^1$	+	$(sp)^2$	⟶	$\sigma^2_{sp\text{-}sp}$	+	$\sigma^*_{sp\text{-}sp}$
AO		AO				
From C-Atom		**From O-Atom**		**MO of CO**		
$2p_y^0$	+	$2p_y^2$	⟶	$\pi 2p_y^2$	+	$\pi^*2p_y^0$
AO of C = Atom		**AO of O-Atom**		**(MO)**		
$2p_x^1$	+	$2p_x^1$	⟶	$\pi 2p_z^2$	+	$\sigma^*2p_z^0$
AO of C-Atom		**AO of O-Atom**		**(MO)**		

Hence, the **molecular orbital (MO)** of **carbon monoxide (CO)** is represented duly as given under:

Figure 1.12 depicts clearly the **molecular orbital (MO) diagram of carbon monoxide (CO).** Hence, according to this **MO-diagram,** the respective ***bond order*** is found to be $(6 - 0) \div 2 = 3$. Therefore, **C and O in Carbon Monoxide (CO)** are duly linked by the **triple bonds** (*i.e.,* ***one*** σ **bond + two** π **bonds**) that are eventually made up of ***two*** **individual *electrons* as well as *protons.*** (See Fig. 1.12).

* **Diamagnetic:** It refers to the typical magnetism caused due to a change in the *orbital motion* of the electrons of the atoms of the substance consequent on the application of an **external magnetic** field.

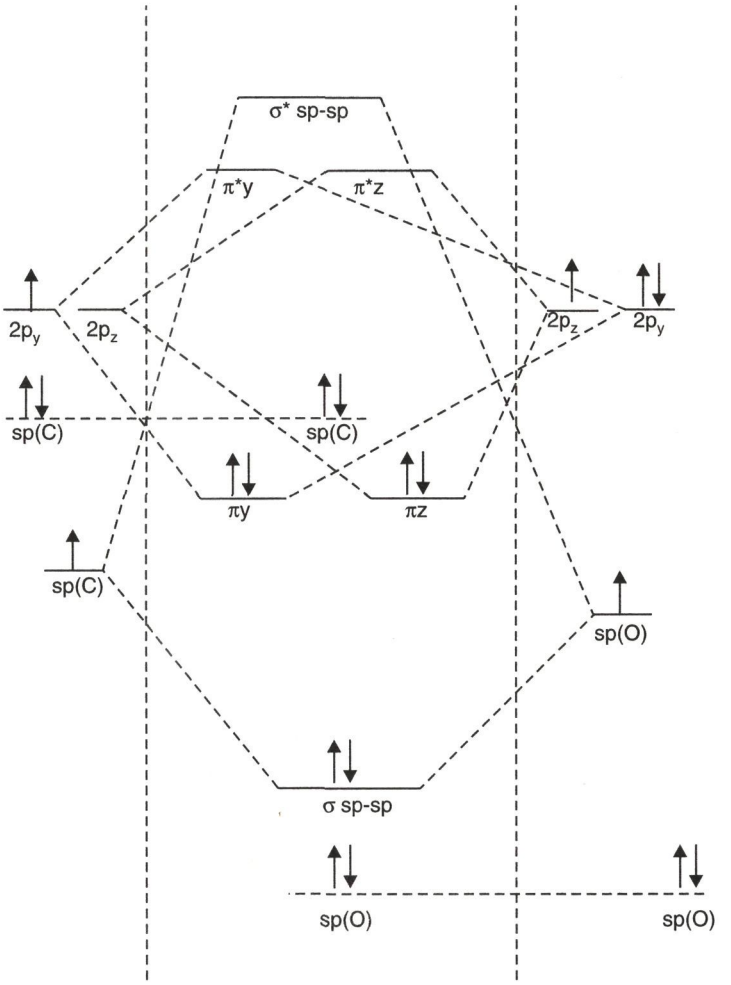


Fig. 1.12: Molecular orbital (MO) diagram of carbon monoxide (CO)

Difference between Atomic Orbitals (AOs) and Molecular Orbitals (MOs)

The *two* major differences between the **AOs** and the **MOs** are as stated under:

(*a*) A **single positive nucleus** is invariably present in an **atomic orbital (AO)**; whereas, in a **Molecular Orbital (MO):** There may be ***two* or *more* nuclei present** actually that solely depends upon the *exact number of atoms* which are involved in the critical formation of a **molecule** ultimately.

(*b*) It has been observed largely that the **Atomic Orbital (AO)** invariably exists in only ***'one type'***; whereas, the respective **Molecular Orbitals (MOs)** usually occur in ***'two types'*** (*viz.*, **Bonding** and **Antibonding**).

Nitric Oxide (NO)

As per the *Periodic Table*, there are **7 electrons in nitrogen (N)** and **8 electrons in oxygen (O) atoms.** Hence, the total number of electrons in the **nitric oxide (NO) molecule** is (8 + 7) = **15.**

Thus, we may have the following **electronic configuration** of **NO molecule:**

$$\sigma 1s^2,\ \sigma^* 1s^2,\ \sigma 2s^2,\ \sigma^* 2s^2,\ \sigma 2p_x^2,\ \begin{Bmatrix}\pi 2p_y^2 \\ \pi 2p_x^2\end{Bmatrix},\ \begin{Bmatrix}\pi 2p_y^0 \\ \pi^* 2p_x^1\end{Bmatrix},\ \sigma^* 2p_x^0$$

Remarks: From above **one may infer:**

- **The 'inner shell'** is found to be *non-bonding* since we have:

  $\sigma^* 2s^2 + \sigma 2s^2$: are duly cancelled;

  σ bond : formed due to $\sigma 2p_x^2$; and

  π bond : formed by $\pi 2pz^2$

- **Formation of a half bond:** Besides, the half-filled $\pi^* 2p_x^1$ - half cancels precisely the $\pi 2p_y^2$— thereby forming a **half bond.**

- **Bond order value for NO:** It is found to be 2.5.

Figure 1.13 illustrates the **molecular orbital (MO)** diagram of **nitric oxide (NO)** as given below:

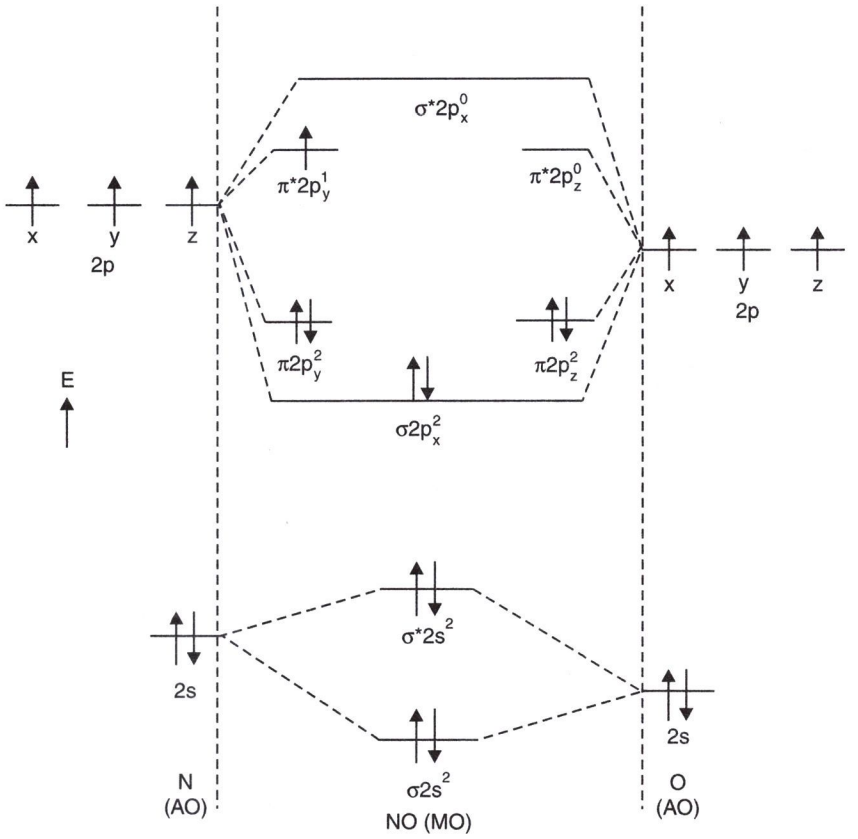


Fig. 1.13: The molecular orbital (MO) diagram of nitric oxide (NO)

Some Cardinal Aspects of Atomic Bonding

The following cardinal aspects of **atomic bonding** are enumerated, such as:

- **Bond Order (or Bond Multiplicity)**
- **Points of Distinction between Molecular Orbital Theory (MOT) and Valence Bond Theory (VBT)**
- **Similarities between MOT and VBT**
- **Similarities between AOs and MOs,** and
- **Points of Distinction between Antibonding Molecular Orbital (ABMO) and Bonding Molecular Orbital (BMO).**

which shall now be treated briefly in the sections that follows:

Bond Order (or Bond Multiplicity): The **bond order (BO)** refers to the precise and exact number of ***covalent bonds*** prevailing critically between the ***two*** **atoms duly combined in a molecule** *viz.,* **CO (Carbon monoxide); NO (nitric oxide).** Alternatively, the **bond order** designates predominantly:

"half of the actual difference existing between the exact number of the *'banding'* and *'antibonding'* electrons".

Thus, we may have the following expression:

$$\text{BO} = \frac{1}{2}(n_b - n_a)$$

where, n_b = Number of *'bonding'* electrons; and

n_a = Number of *'antibonding'* electrons.

Points of Distinction Between Molecular Orbital Theory (MOT) and Valence Bond Theory (VBT)

Molecular Orbital Theory (MOT): Refers to the explanation (using the so-called *'wave-mechanical theory'*) of the respective binding forces between atoms resulting from the overlapping of filled molecular orbitals as opposed to simple binding forces between atoms.

Valence Bond Theory (VBT): Relates to the underlying concept that the power of atoms to bind together to form molecules is based primarily upon the exact number of orbital electrons in their respective outer shells.

The following Table 1.1 shows the points of distinction prevailing between the **MOT** and **VBT** explicitly:

Table 1.1: Points of Distinction between MOT and VBT

S. No.	Molecular Orbital Theory (MOT)	Valence Bond Theory (VBT)
1	*Atoms* usually lose their inherent individual identity.	*Atoms* never lose their individual identity.
2	Obviously, in a **MO** the electrons move critically under the influence of *two* or *even more nuclei.*	In an *atomic orbital* **(AO),** the electrons normally move around a *single nucleus.*
3	**MOT** specifically involves the formation of *bonding orbital (BO)* and *antibonding orbital (AOB).*	Amazingly, **VBT** does *not* involve the *bonding orbitals* **(BOs)** at all.

Contd.

4	**MOT** vividly explains the above *two* characteristic features *viz.*, **BO** and **AOB.**	**VBT** fails to explain both *paramagnetic* and *diamagnetic* character of molecules (*viz.*, B_2 and O_2).
5	**MOT** shows that all the **AOs** (*viz.*, fulfilled, half-filled, or vant) are duly engaged in the formation of **MOs.**	**VBT:** The so-called *half-filled valence shell orbitals* to take part in the **bonding process.**

Similarities between MOT and VBT

Following are the *three* glaring **similarities between MOT and VBT**

1. Interestingly, both the *theories* vehemently suggest the formation of the ***covalent bond*** **(VBT)** or the respective ***molecular orbitals*** **(MOT),** and ***atomic orbitals*** **(AOs)** essentially involving the following ***two*** **properties**:

- **same energy levels, and**
- **possessing symmetry features**

2. Besides, both the **theoretical aspects** are more or less confined to the corresponding ***covalent bond formation.***

3. Furthermore, both the theories (*viz.*, **MOT** and **VBT**) do clearly exhibit an enhanced level of ***'electronic densities'*** existing between the ***two*** **nuclei** stands grossly responsible for these *two* vital features, such as:

- **holding the two atoms together;** and
- **creation of covalent bond(s).**

Similarities between AOs and MOs

There are *four* distinct observed similarities that exist between the **atomic orbitals (AOs)** and **molecular orbitals (MOs)** as enumerated under:

1. In usual practice, an '*electron*' is invariably designated by a **wave function ('ψ').**

2. It has been observed that very much akin to the **AOs,** in **MOs** also, a maximum of 2-electrons may eventually be combined, but obviously both of them must possess just the ***'opposite spins'***.

3. Identical to the **AOs**, in **MOs** also, the *'electrons'* are filled meticulously as per the following *three* recognized and established principles, namely:

- **Hund's Rule**
- **Aufbau Principle,** and
- **Paul's Exclusion Principle,**

as already described under section 1.2, 2.4: Chapter 1.

4. Importantly, very much similar to **AOs**, the **MOs** also essentially bear the following ***two*** **characteristics.**

- **different shapes, and**
- **different energies.**

Points of Distinction between Antibonding Molecular Orbital (ABMO) and Bonding Molecular Orbital (BMO)

The survey of literature would reveal that there are ***four*** **points of distinction between ABMOs and BMOs** that are described as stated under Table: 1.2.

Table 1.2: Points of Distinction between ABMO and BMO

S. No.	Antibonding Molecular Orbital (ABMO)	Bonding Molecular Orbital (BMO)
1	**ABMOs** are duly formed as a consequence of the *'subtractive overlapping'* between the ***two*** **atomic orbitals.**	**BMOs** are formed as a result of the *'additive overlapping'* between the ***two*** **atomic orbitals.**
2	The **'energy amount'** directly linked with **ABMO** is found to be **maximum** *vis-a-vis* to the energies of both the **AOs.**	**'Energy amount'** associated with **BMO** is found to be **minimum** *vis-a-vis* the energies of both **AOs.** Hence, its formation critically leads to the emergence of a **'fairly stable bond'** between the **2-atoms.**
3	**ABMO** essentially involves the *repulsive interaction* between the **AOs.**	**BMO** critically involves the *attractive interaction* between the **AOs.**
4	Probability of finding *electrons* in the *overlapping region* is practically nil. The overall *'electron density'* is apparently concentrated in the ensuing *'exterior region'.*	Probability of locating *electrons* in the *overlapping region* is high.

1.2 THE VALENCE-SHELL ELECTRON-PAIR REPULSION [VSEPR] THEORY

Preamble: Nyholm and Gillespie proposed a *qualitative model* so as to predict the **'geometry of molecules'** usually termed as the **VSEPR-Theory** (*i.e.,* the **Valence-Shell Electron-Pair Repulsion Theory**). Nevertheless, the so-called fundamental assumptions of this theory may be duly summarized as under:

(*a*) The *'electron pairs'* in the valence shell located around the **central atom of a molecule** do have a tendency to:

- **repel each other,** and
- **tend to orient in space**

in order to minimize the respective *'repulsions'* and thus, optimize the actual gap between them.

(*b*) It has been observed that there are ***two*** **types of 'valence shell electron pairs'**, namely:

- **the *'bond pairs'*,** and
- **the *'lone-pairs'*.**

Bond Pairs*:** They are normally shared by ***two **atoms**; and hence, are attracted by ***two*** **nuclei.** Therefore, they do occupy *much lesser space* and causes *lesser repulsion significantly.*

***Lone Pairs*:** These are not at all involved in the process of **'bond formation'** and are usually found to be in *attraction with only one nucleus.* Perhaps that could be the possible reason for the **'lone pairs'** to occupy **more space.** Consequently, the **'lone pairs'** definitely afford **more repulsion.**

Order of Repulsion Between Various Types of Electron Pairs

It may be expressed as under:

Lone Pair – Lone Pair > Lone Pair – Bond Pair > Bond Pair – Bond Pair

NOTE: **It may be observed that the *'bond pairs'* are designated invariably by a solid line (—); whereas, the *'lone pairs'* are represented by a lobe with 2-electrons.**

(*c*) In the **VSEPR-Theory,** the multiple bonds are duly treated, as if they were more *'single bonds'*. However, the *'electron pairs'* in the **multiple bonds** are almost *treated collectively* as a **'single super pair'.**

Inference: Thus, the ultimate *'repulsion'* duly caused by **bonds** enhances predominantly with the *increase in the number of bonded pairs between the atoms i.e.,* a **triple bond (C≡C)** causes definitely **more repulsion** *vis-a-vis* a **double bond,** —which in turn results in **more repulsion** *vis-a-vis* a **single bond.**

(*d*) **Prediction of the Shape of Molecule from Number and Type of Valence Shell Electron Pairs Around the Central Atom:** In a situation when the **valence shell** of the *central atom* specifically comprises only the bond pairs, the molecule does assume ***symmetrical geometry*** by virtue of the **even repulsions** brought about between them.

NOTE: **Obviously, the ensuing *symmetry* gets distorted effectively when there exist the *'lone pairs'* together with the *'bond pairs'* caused due to *uneven repulsion forces.***

(*e*) Primary and Secondary Effects Upon Bond Angles and Shapes: Following are the *cardinal aspects* related to the so-called *primary* and *secondary* effects upon the respective **bond angles** and **shapes:**

(*i*) The **'Bond Angle'** gets reduced proportionately on account of the *critical presence of lone pair of electrons,* that eventually cause *higher repulsion* upon the ensuing **'bond pairs'**; and hence consequently, the **bond pairs** *show a tendency to come closer to each other,* as illustrated in Fig. 1.14.

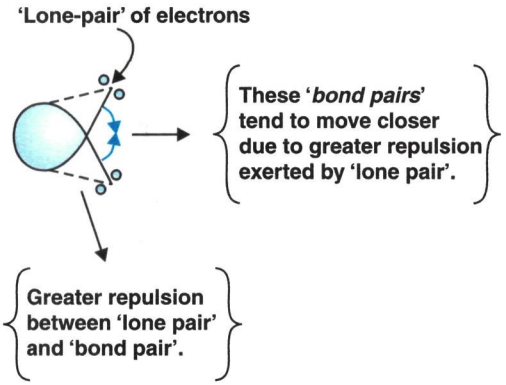
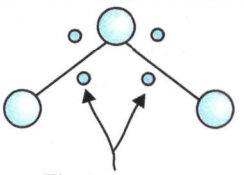


Fig. 1.14: Diagrammatic representation showing decrease in 'bond angle' due to the presence of 'lone pairs'.

(*ii*) **Repulsion between electron pairs enhances with increase in electrogravity of Central Atom: Causes Increment in Bond Angle:** It is known that the ensuing **'bond pairs'** are fairly close to each other; and hence, by shortening the *actual distance between them* one may enhance the **degree of repulsion.** Therefore, the bonds do have a tendency to move away as given under:

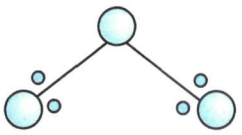


The **'bond pairs'** do tend to move away from each other as the prevailing distance between them is shortened since they are more localized upon *more electronegative central atom.*

Observations: These essentially include:

1. The ensuing **'bond angle'** gets reduced as and when the *electronegativities* of the **ligand (or drug) atoms** are found to be definitely more than that of the *central atom.*

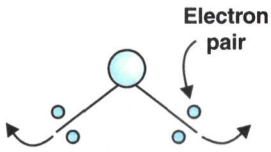
2. Thus, it would ultimately show up an increase in the actual distance between **'bond pairs'**, because they are now closer to the respective **'ligand atoms'.** Obviously, due to this feature, they do have a tendency to *move closer* thereby reducing the **'bond angle'** significantly, as depicted under:



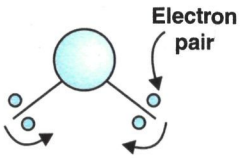
The **'bond pairs'** do have a tendency to come closer because the distance between them gets increased since they are more localized upon the *more electronegative ligand atoms.*

(*iii*) **Decrease in the 'Bond Angle' Commences with Increase in the Size of 'Central Atom'**

Let us look into the following diagrammatic illustrations:

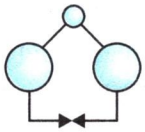
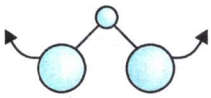


On smaller central atoms the **'bond pairs'** are closer; and hence, tend to move away from each other in oder to *minimize repulsion.* Hence, **bond angle** shall be *more.*



On bigger central atoms the **'bond pairs'** are more apart from each other; and hence, there is *less repulsion.* Hence, they tend to move closer thereby *reducing the bond angle.*

Nevertheless, the **'bond angle'** enhances progressively with an increase in the size of **'ligand atoms'**—that eventually surround the **central atom.**

 There is definitely **less repulsion** between *smaller ligand atoms*; and they may move closer to each other; and thus, decrease critically the resulting **'bond angle'.**	 There is obviously **more repulsion** between *bigger ligand atoms;* and hence, they have a tendency to *move* away from each other thereby the resulting **'bond angle'** increases significantly.

(*iv*) It may be observed that the **'bond angles'** are also altered when the *multiple bonds* are present categorically. Importantly, it is caused due to the **uneven repulsions.**

(*f*) Resonance Structures: When there exists *two* or *more* **'resonance structures'**, one may observe critically the applicability of the **VSEPR-Theory** to any one of the **contributing structures.**

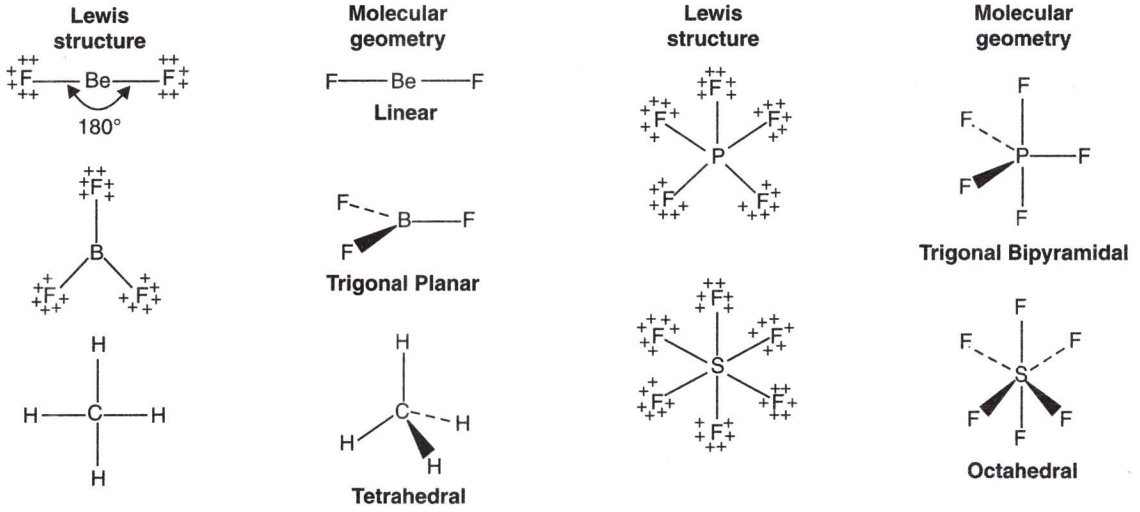
Predicting the Shapes of Molecules

It has been established beyond any reasonable doubt that there exists absolutely no *direct-relationship* between the following ***two*** **entities**, namely:

- **Molecular formula of a compound**, and
- **Shape of the molecules.**

Furthermore, the virtual **shapes** of such ***'molecules'*** may be predicted precisely on the basis of their **Lewis structures***, with the help of a **'model'** almost developed a couple of decades ago invariably termed as the **VSEPR-Theory.**

Amazingly, the foretold **VSEPR-Theory** vehemently ascertains that each and every atom present in a molecule shall achieve a 'geometry' which predominantly reduces the ensuing *repulsion* between the *electrons* in the so-called **'valence shell of that specific atom'.**



* Solomons TWG and Fryhle CB : *Organic Chemistry*, 9th ed., Wiley India (P) Ltd., New Delhi, pp. 7-8, 2008.

The *five* meticulously selected **chemical entities (compounds)** as depicted above may be employed to demonstrate in an absolute vivid manner how the **VSEPR-Theory** could be applied so diligently to such ***simple molecules.***

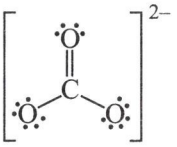
Comments: One may critically take cognizance of the fact that there are **only *two* places in the *valence shell* of the central atom in BeF_2 (*i.e.*, structure 1), wherein the *electrons* may be found.** However, the observed repulsion taking place between these *pair of electrons* may be reduced appreciably by arranging them in such a manner that they point in the **opposite directions.** Therefore, the **VSEPR-Theory** predicts explicitly that **BeF_2** must be a **linear molecule,** having a **180° angle between the 2, Be-F bonds.**

Incorporating Double and Triple Bonds Into the VSEPR-Theory

The organic compounds that essentially contain *double bond* (=C=C=) and *triple bond* (—C≡C—) actually raise an important point. Furthermore, the ***'geometry'*** around an atom is duly determined by the **number of places in the valence shell** of an *atom* where the *electrons* may be found; and certainly not the *number of pairs* **of valence electrons.**

Let us now look at the following *typical* **Lewis structures:**

- **Carbon Dioxide (CO_2),** and
- **Carbonate ion (CO_3^{2-}).**

CO_2:  and CO_3^{2-} : 

Observations

For Carbon Dioxide

1. There exist ***four*** **pairs of the bonding electrons** duly present in **carbon dioxide (CO_2),** but there are only **two places** where one may find these **electrons** (*i.e.*, there are **electrons** in the **(>C=0) double bond** on the left hand side **(LHS)** and similar electrons in the **double bond** on the right hand side **(RHS).**

2. Besides, the **force of repulsion** existing between these electrons get apparently reduced when the ***two*** **(>C=0) double bonds** are placed critically on the **opposite sides of the C-atoms.**

3. The **VSEPR-Theory,** therefore, precisely predicts that CO_2 **molecule** would be a ***linear molecule*** *i.e.,* very much akin to BeF_2 with a **bond angle of 180°.** (as discussed earlier).

For Carbonate Ion

1. The **Lewis structure** of the *carbonate ion* $[CO_3^{2-}]$ also vividly suggests the presence of **8-pairs of valence electrons** located on the central atom, but these electrons are concentrated at ***three*** **different zones** (as shown above) *i.e.,*

- ***two*** **C—O single bonds,** and
- ***one*** **>C=0 double bond**

2. The **repulsions** observed between these electrons are duly reduced when the ***3 O-atoms*** are meticulously arranged **towards the corners of an equilateral triangle.**

3. Hence, the **carbonate (CO_3^{2-}) ion** should essentially have a **trigonal-planar geometry** very much akin to **BF_3** (*with a 120° bond angle*).

Role of Non-Bonding Electrons in a VSEPER Theory

The **valence electrons** located on the *central atom* in the following ***two*** **molecules**:

- **Ammonia (NH_3)** and - **Water (H_2O)**

must be duly distributed toward the corners of a ***'tetrahedron'*** as depicted in Fig. 1.15 below.

At this point in time, our main objective does not centre around the fact—how to **predict the distribution of valence electrons.** But it is pointed towards the precise usage this **distribution of electrons** to **predict the shape of the molecule.** As to date, the ***two*** **aforesaid predicaments** remain virtually the same.

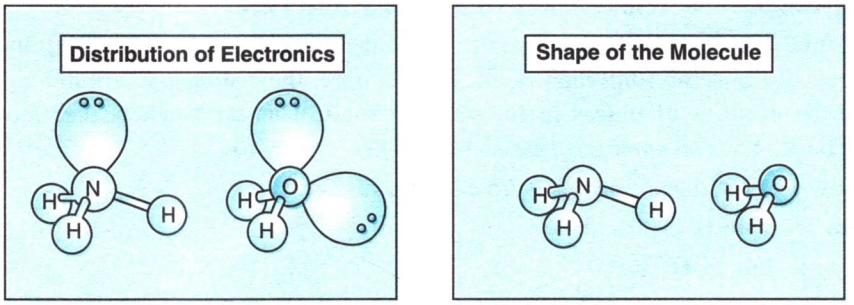


Fig. 1.15: Distribution of electrons and shape of molecules (NH_3) and (H_2O).

Observations: These mainly comprise:

1. **VSEPR-Theory** predicts accurately that the *valence electrons* located on the *central atoms* in both **ammonia (NH_3)** and **water (H_2O)** shall critically point towards the corners of a **tetrahedron.** Since the visual location of the **non-bonding electrons** seems to be not practicable at all; and, therefore, the exact prediction cannot be tested directly.

2. However, the results of the **VSEPR theory** may be employed in order to **predict the exact positions of the nuclei** in the said *two* molecules (*viz.,* **NH_3 and H_2O**) that may be **ascertained experimentally.**

3. Thus, we may have the **shapes of NH_3 and H_2O** as given below:

Ammonia (NH_3)	Water (H_2O)
Its **shape** resembles to that of a **trigonal pyramidal**—with the N-atom located at the top of pyramid.	Its **shape** is found to be either **bent** or **angular.**

Thus, both the aforesaid **predictions** are found to be absolutely true,—that not only reposes our confidence but also reinforces our faith and belief in the **VSEPR theory.**

The Cardinal Postulates of VSEPR-Theory

The survey of literature would reveal that the **VSEPR-Theory** is duly based upon the following vital and important aspects, namely:

- **Effect of electron repulsion upon the bond angles;**

- Shape of *molecule* or *ion* depends upon the following *two* critical factors:
  - **Bonding electron pairs (bps),** and
  - **Non-bonding electron pairs or lone pairs (lps)**

  that are located strategically on the ***'central atom'.***
- **Central atom** is invariably positioned in such a manner that there exists the **bare minimum repulsion* between them**; and
- **Definite shape** of a molecule exclusively based on the fact that there prevails *only one orientation of orbitals* with respect to **minimum energy.**

There are *three* major recognized postulates of the **VSEPR-Theory** as described under:

➢ In a situation, when the so-called ***'central atom'*** in a **molecule** is adequately surrounded by the **bonding electron pairs (bps)** exclusively and also by the **non-bonding electron pairs (lps)**–it would definitely provide: ***Regular Shape*** or ***Regular Geometry***;

➢ In case, the *central atom* in a **molecule,** is enveloped by ***bps*** and ***lps***, it will certainly undergo such **physical changes** as:

▪ **Distortion** ▪ **Change in Shape** **and** ▪ **Irregular Geometry**

Obviously, the ***lps*** has a tendency to cause repulsion to the specific **adjacent electron pairs** rather more intensely than the respective ***bps***; and hence, the repulsion gets enhanced as per the following pattern:

$$(bp—bp) < (bp—lp) < (lp—lp)$$

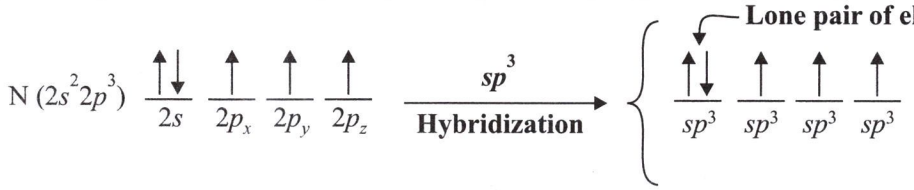
Importantly, the observed *repulsion* taking place between the ensuing **bonded pair of electrons** is predominantly greater provided the so-called **bonded pair of electrons** are located prevalently closer to the *central atom.*

Therefore, bearing in mind the **cardinal postulates of the VSEPR-Theory,** we may carry out an elaborated investigative studies of the structures of ***three*** **selected molecules:**

- **Structure of Ammonia (NH_3) Molecule,**
- **Structure of Water (H_2O) Molecule,** and
- **Structure of Phosphorus Pentachloride (PCl_5) Molecule,**

which shall now be treated individually in the sections that follows:

(*a*) **Structure of Ammonia (NH_3) Molecule:** It has been duly established that in **ammonia (NH_3),** the respective **N-atom** explicitly undergoes the ***sp^3*-hybridization** as given under:



Formation of Ammonia (NH_3) Molecule: From the above description it is evident that out of the ***four*** ***sp^3*** **hybrid orbitals** we have:

- **1 *sp^3*-hybrid orbital** is duly occupied by *one lone pair of electron* (***lp***); and

* That is, having the **maximum stability.**

• **$3sp^3$-hybrid orbitals** are ***half-filled*** and this eventually overlap with **3 half-filled 1*s* orbital** belonging to *3 H-atom* to form **ammonia (NH_3).**

Figure 1.16 depicts the actual structure of the **ammonia (NH_3) molecule** as under:

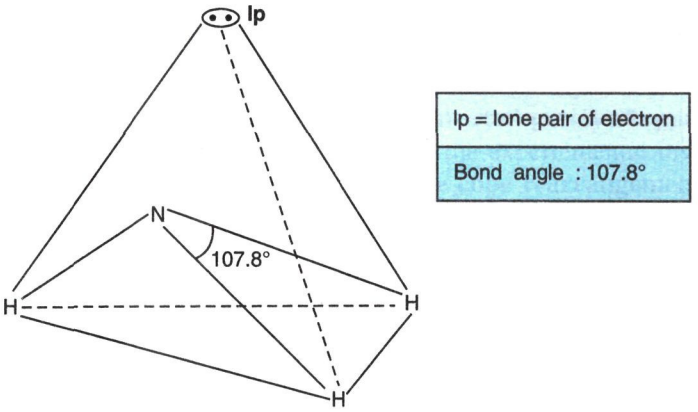


Fig. 1.16: The tetrahedral structure of ammonia (NH_3) molecule

Bond Angle: By virtue of the ***sp^3*-hybridization**, the *bond angle* should be **109.28°** but on account of the ensuing *distortion* (caused critically by ***lp* repulsion**) the said **bond angle gets slightly reduced to 107.8°.**

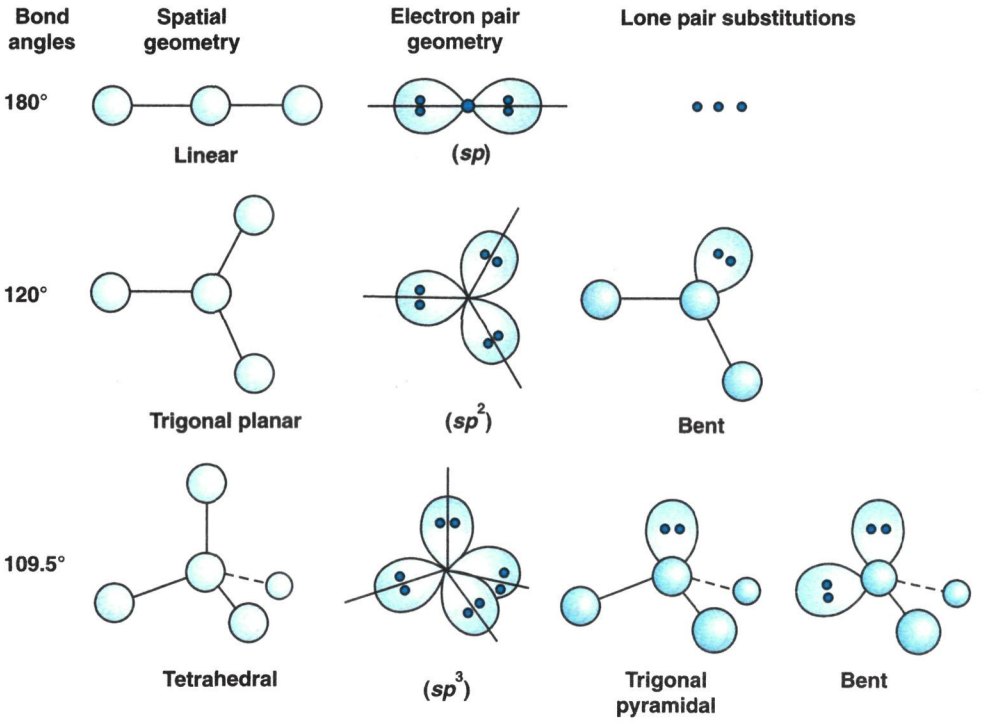


Fig. 1.17: The VSEPR shapes of linear, trigonal planar, and tetrahedral structures

Shape of NH_3: The actual shape of **ammonia (NH_3)** must be that of a ***tetrahedral*** but is found to be ***pyramidal having distinct compressed bond angle.*** However, it would be expected that the ***three*** **covalent bonds** should be directed prominently to the ***three*** **corners of a tetrahedron**; whereas, the *lone pair* is found to be directed towards the **4th corner of the tetrahedron.**

The **VSEPR shapes** in terms of the **bond angles, spatial geometry, electron-pair geometry,** and **lone-pair substitutions** for the respective ***Linear, Trigonal Planar***, and ***Tetrahedral*** structures are depicted explicitly in Fig. 1.17.

Structure of Ammonia (NH_3): Distortion due to Electron Pair Repulsion

VSEPR-Theory suggests vehemently that a **lone pair of electrons** (*lp*) exerts a *greater repulsion profile* upon the ensuing ***bonding pair of electrons*** (*bp*) than that of the ***bonding-pairs*** exert on each other. Consequently, the ***three*** **bonds of ammonia (NH_3) molecules** are forced slightly closer in the **tetrahedral arrangement;** and hence, the ***H—N—H*** **angles** being set at **107.8°** instead of **109.5°** as illustrated in Fig. 1.18.

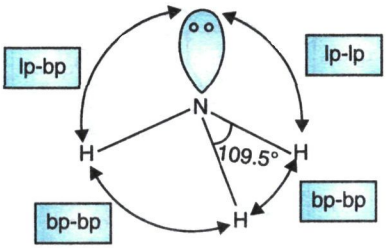


Fig. 1.18: Observed distortion of structure of ammonia (NH_3) caused due to electron pair repulsion

(*b*) **Structure of Water (H_2O) Molecule:** Obviously, in the **structure of water (H_2O) molecule** one may critically notice that the so-called ***central oxygen atom*** of the molecule there exist ***two*** **bonding orbitals,** namely: $2p_y^1$ ***and*** $2p_z^1$ **(of the O-atom)**. Besides, the aforesaid **bonding orbitals** may duly overlap with the ensuing **1*s* orbital** (*belonging to the H-atom*) of the *two* atoms having the ***opposite spins.*** Furthermore, each of these *two* overlapping processes ultimately gives rise to the formation of **σMO** (or σ *molecular orbital*), thereby producing:

"*two* σ-bonds in the water (H_2O) molecule as a whole"

which has been explicitly shown in Fig. 1.19.

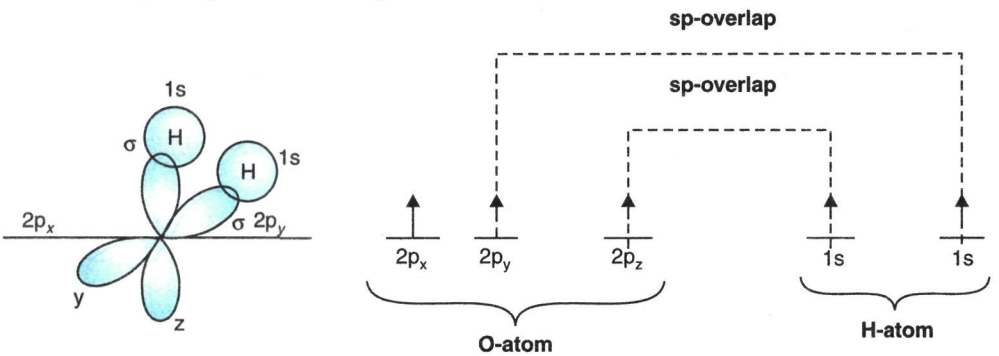


Fig. 1.19: The structure of water (H_2O) molecule

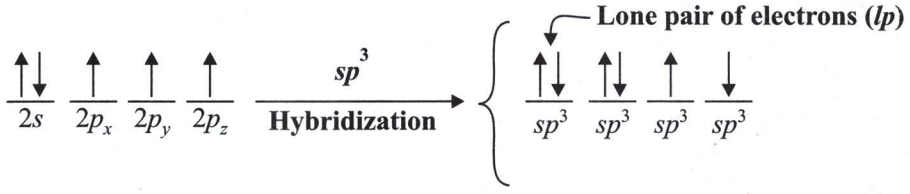
Formation of 4-Tetrahedrally Displaced sp^3 Hybrid Orbitals: The sequential steps involved in the formation of **4-tetrahedrally dispersed sp^3 hybird orbitals** are as given under:

1. The water (H_2O) molecule particularly involves ***two* 2*p* orbitals** located at *right angles*; and hence, the ensuing bond duly produced by an *orbital* does retain the so-called **directional characteristic feature of the bonding orbital.** Thus, it would be fairly logical to express the ensuing ***bond angle*** **to be equal to 90°.**

2. Obviously, the observed difference between the ***two*** **values**, namely:

• **Expected Value** and • **Experimental Value**

pertaining to the ***bond angle*** may be duly explained with the help of the established **hybridization concept.** Thus, one may virtually obtain all the *valence orbitals* belonging to the *second energy shell of the* **oxygen O-atom.** In this manner the phenomenon of ***hybridization*** will occur and give ***four*** **tetrahedrally dispersed sp^2 hybrid orbitals** as shown under:



Observations: These essentially include:

(*i*) **Out of *four* hybrid orbitals—*two*** have **pairs of electrons** having *definite opposite spins;* and are found to be **non-bonding** in character.

(*ii*) However, the remaining ***two*** **hybrid orbitals** do have essentially *one electron,* which is perceptively capable of ***bond formation*** by getting duly **overlapped with the ensuing orbitals belonging to 2 H-atoms.**

Thus, the water (H—O—H) **bond angle would be 109.5°** (see Fig. 1.20).

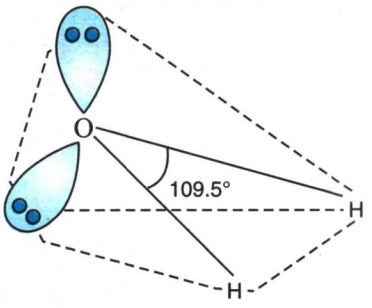


Fig. 1.20: The structure of water (H_2O) molecule

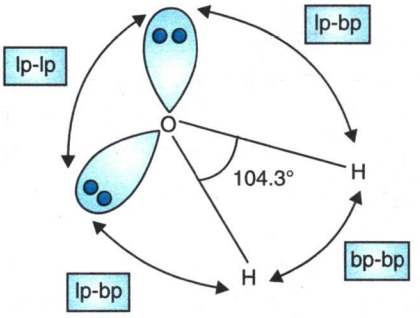


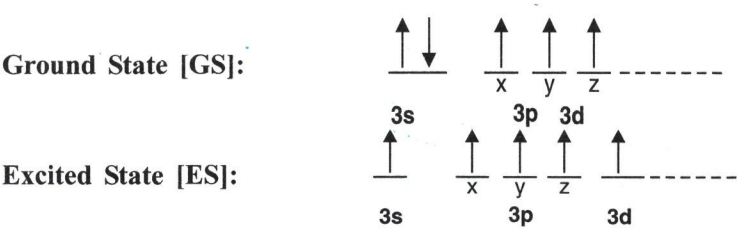
Fig. 1.21: The electron-pair pepulsion in water (H_2O) molecule

According to the **VSEPR-theory** of repulsion the **water (H_2O) molecule** does possess ***two*** **lone pairs of electrons** located in the *vicinity of the centre O-atom* that has *two* **bond pairs of electrons.** The prevailing repulsive forces amongst them is duly depicted in Fig. 1.21. Consequently, the **2 lone-pair of electrons (lp)** in water (H_2O) bring the **2 (O—H) bond pairs of electrons** very much close to each other; and hence, the **H—O—H** angle gets reduced to **104.3°.**

(*c*) **Structure of Phosphorus Pentachloride (PCl_5) Molecule: Phosphorus** occupies the ***'central atom'*** in the **phosphorus pentachloride (PCl_5)** molecule thereby possessing essentially the following ***electronic configuration:***

$$1s^2,\ 2s^2,\ 2p^6,\ 3s^2,\ 3p^3 \text{ and } 3d^0$$

Thus, we may have the **Ground State (GS)** and the **Excited State (ES)** duly expressed as shown below:



Based on the above enumerated configurations one may observe critically that:

- **3 out of 5** ***dsp*^{3}** ***bonding orbitals (BOs) do lie in a plane*** **and also inclined at an angle of 120°**; and

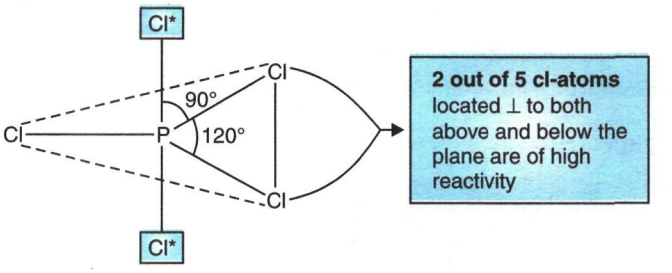


Fig. 1.22: The structure of phosphorus pentachloride (PCl_5) molecule.

- **remaining 2** ***dsp*^{3}** ***are found to be directed almost perpendicularly (⊥) both above and below the plane, thereby taking the ultimate shape of a*** **trigonal bipyramidal** ***(as illustrated above)*** in Fig. 1.22.

It is pertinent to state here that the foretold **orbitals of phosphorus atom** may, in fact, overlap to **3 out of 5 Cl-atoms** thereby forming the **PCl_5 molecule.** However, certain bond angles are of 120° and some are of 90°.

Important Points: The ***trigonal bipyramidal*** geometry of the **phosphorus pentachloride (PCl_5)** molecule explains vividly the supreme reactivity of **2 out of 5 marked Cl-atoms** duly present in the ***PCl_5 molecule.***

1.3 METALLIC CRYSTALS

Crystals: It has been observed invariably that the ***atoms*** do self-organize in the form of **crystals;** and hence, this ensures the **fundamental concepts.** Furthermore, the ***crystalline lattice*** represents the so-called **periodic array of the atoms**. Thus, when the solid substance is not available (or obtained) in a ***'crystalline state'*** it is usually known as **amorphous.**

Examples: Hence, we may have the following *two* typical examples:

- **Crystalline Solids** *e.g.,* **metals** (Sn, Au, Ag, Cu, Fe); **precious stones** (diamond, ruby, emerald, saphire); **ice; graphite** and the like; and
- **Amorphous Solids** *e.g.,* **amorphous carbon (a—C); glass; amorphous silicon (a—Si); various types of 'plastics'.**

Therefore, to facilitate the proper discussion related to the ***crystalline structures,*** it would be worthwhile to assume the atoms as being **'hard spheres'**—having a *well-defined radii*, such as:

- **van der Waal's diameter,**
- **covalent diameter,** and
- **metallic diameter**

as illustrated in Fig. 1.23.

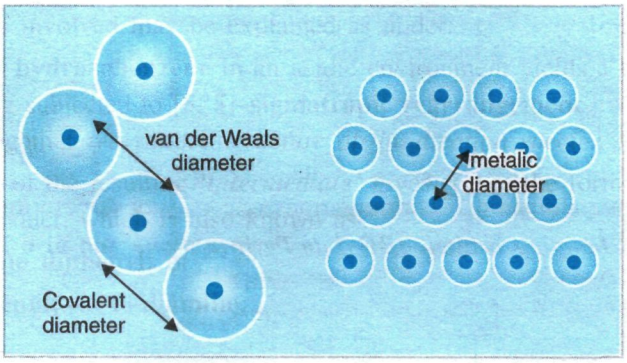


Fig. 1.23: The atoms as hard spheres with well-defined radii

In such an arrangement, the shortest distance between *two* similar atoms is one diameter.

Metallic Crystals: In a broader perspective, a **'metal'** critically comprises a *closely-packed regular arrangement of positive ions,* that are eventually surrounded by a **'sea of delocalized electrons'** which predominantly bind the ions together.

Salient Features: These essentially include:

1. The **metal atoms** have an exceptional characteristic feature whereby their *outermost electrons* could be removed with great ease comparatively.

2. Thus, when ***two* metal atoms** are duly arranged almost side-by-side (as in the particular instance of a **metallic crystal**)—their ***outer-shells overlap each other.***

3. Furthermore, when an array of **'metal atoms'** are arranged closely to one another,—obviously one may observe the critical occurrence of an appreciable quantum of overlapping. Consequently, the ***outer electrons of any one metal atom are no more under the influence of—'just one nucleus'.***

NOTE: **In such a situation, the *'outer-electrons'* are indeed free to move throughout the entire crystal; and hence, are no longer located in the outer shell of any one atom (*i.e.*, they get *delocalized*).**

4. The ensuing movement of the **'electrons'** away from their **original position** renders the so-called ***positive-ions*** to stay behind. Besides, the resulting ***positive ions*** are never pushed apart due to the *repulsion,* which perhaps could be by virtue of the fact that **each cation gets duly attracted to the respective delocalized electron cloud**—*that surrounds them eventually.*

5. **Major Advantages of the Above Arrangement:** These include essentially:

- It usually affords greater strength to a **'metal'**, since all the ensuing particles are held together firmly.
- It critically permits the ultimate structure to change in shape without undergoing any sort of **'fracture'.**
- Hence, most **metals** are found to be ***malleable*** (*i.e.*, may be hammered) and ***ductile*** (*i.e.*, may be drawn into wire).
- **Metals:** Prove to be **good conductor of heat,** since on being subjected to heat—the so-called **'kinetic energy of the electrons'** gets *enhanced significantly;* and the resulting increase gets duly **transmitted *via* the system of the delocalized electrons to the remaining segments of the metal.**

NOTE: **Since, the *outer electrons* may move freely, the *'metals'*, in general, are good conductors of electricity.**

6. Importantly, the **'metallic crystals'** are found to be:
   - **insoluble in polar-covalent solvents,** and
   - **insoluble in non-polar-covalent solvents.**

7. The **'metallic crystals'** are indeed **soluble in mercury (Hg)** (to form *amalgams viz.*, Na—Hg; Ag—Hg etc.)—the **only liquid metal.**

Figure 1.24 depicts the observed deformation of 'metal structure' under stress thereby showing the resulting attraction existing between cation (Hg^{2+}) and delocalized electrons.

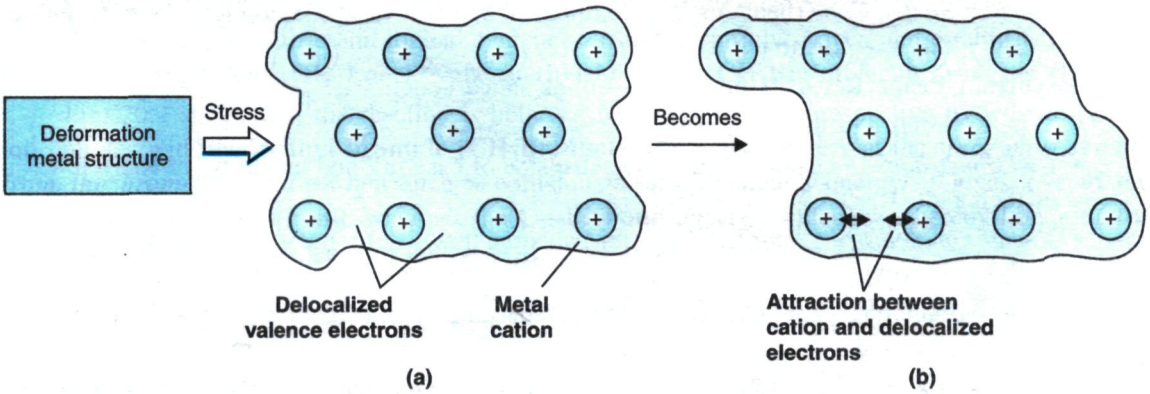


Fig. 1.24: Deformation of metal structure under:
(a) **Stress:** Producing delocalized valence electrons + Metal cation;
(b) **Becomes:** An element of attraction between cation and delocalized electrons.

Table 1.3 records the typical **'type of crystals'** together with their respective: *strength, melting points, electrical conductivity,* and *solubility* profiles.

Table 1.3: Types of Crystals *vis-a-vis* their Physical Characteristics

S.No.	Type of crystal	Strength	Melting point	Electrical conductivity	Solubility
1	**Metallic**	Most are hard, though malleable and ductile.	Variable	Good conductors	Insoluble except in **mercury (Hg)**
2	**Covalent macro-molecular**	Usually hard	High	Unable to conduct	Insoluble
3	**Molecular**	Relatively weak	Low	Unable to conduct	Solely depends on the type of molecules
4	**Ionic**	Hard though brittle	High	Will only conduct in the **molten state or *in solution.***	Invariably soluble in polar solvents

Metallic Crystal Structures: In order to understand the metallic crystal structures elegantly one has to get a clear concept with regard to the **unit cells**.

Unit Cells: The **'unit cell'** designates the smallest structure that critically repeats itself by translation *via* the crystal; and, therefore, these **'symmetrical units'** are duly constructed with the *hard spheres* exclusively.

Following are some of the most commonly encountered variants of the **'Unit Cells'**, namely:

- **FCC** : *Faced-centered cubic;*
- **BCC** : *Body-centered cubic;*
- **HCP** : *Hexagonal close-packed;* and
- **SC** : *Simple Cube* (being used quite often for the *didactical purpose i.e.,* **no material has this specific structure).**

Important Properties of 'Unit Cells'—are as stated under:

- Type of *atoms* and their *radii* **R**;
- *Cell dimensions* [*i.e.,* side **'*a*'** in cubic cells, side of base **'a'**, and height **'c'** in HCP) in terms of their radii **R**;
- *Number of atoms per 'Unit Cell'*, **n**. Thus, an atom that is duly shared with **'m'** adjacent **'Unit Cells'**, one would only count a *fraction of the atom, 1/m;*
- *Coordination number* **'CN',** refers to the number of closest neighbours to which an *'atom'* is bonded duly; and
- *Atomic packing factor* **'APF'**–relates to the *fraction of the volume of the Unit Cell* occupied apparently by the ***hard spheres.*** Thus, we may have:

APF = Sum of atomic volumes/Volume of cell

The *four* types of **'Unit Cells'** *viz.*, **FCC, BCC, HCP,** and **SC** and their corresponding values in terms of *n*, *CN*, *a/R*, and *APF* are duly expressed as under:

S. No.	Unit Cell	*n*	CN	a/R	APF
1	FCC	4	12	$2\sqrt{2}$	0.74
2	BCC	2	8	$4\sqrt{3}$	0.68
3	HCP	6	12	–	0.74
4	SC	1	6	2	0.52

NOTE:

1. **In a *BCC Cell*: the closest packed direction is usually along the diagonal of the *'cube'*.**
2. **In a *FCC Cell*: the closest packed direction is normally along the diagonal of a face of the *'cube'*.**

Crystals Grouped by Properties: There are ***four*** **main categories of crystals,** as grouped by their *physical* and *chemical characteristic features,* such as:

(*a*) **Covalent Crystals:** A *covalent crystal* essentially possess true **covalent bonds** between all the atoms present in the crystal. Thus, one may precisely think of a *covalent crystal* as one **huge molecule.** In fact, quite many **covalent crystals** do have extremely *high melting points.*

Examples: Diamond and Zinc Sulphide (ZnS) crystals.

(*b*) **Metallic Crystals:** The *individual metal atoms* of the **metallic crystals** do reside upon the specific ***lattice sites.*** In this way, it prevalently, leaves the *outer electrons* of such atoms to remain absolutely **'free'**; and hence, *float around the lattice;*

Importantly, the **'metallic crystals'** usually tend to be very dense; and, therefore, have **high melting points.**

Figure 1.25 illustrates the **metallic crystal lattice:**

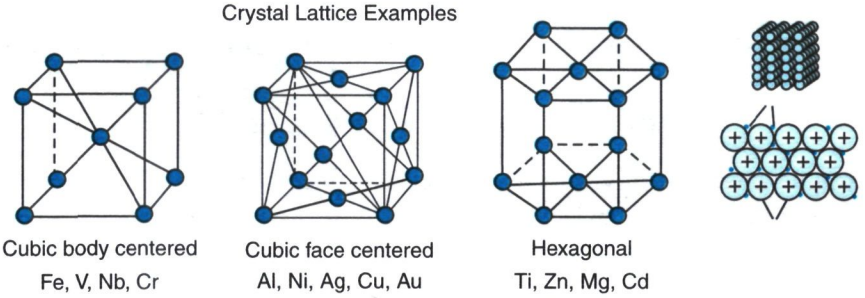


Fig. 1.25: Representation of the metallic crystal lattice

(*c*) **Molecular Crystals:** The **molecular crystals** invariably comprise *recognizable molecules* located strategically within their structures. Thus, a **molecular crystal** is obviously held together by the help of the ***non-volatile interactions,*** such as:

- **van der Waals forces**; or
- **Hydrogen bonding (H-bonding).**

Besides, the **'molecular crystals'** do have a tendency to be soft with relatively *low melting points.*

Example: *Rock Candy* is a beautiful example of a molecular crystal (*i.e.,* crystalline form of Sugar or Sucrose).

Figure 1.26 depicts the diagrammatic representation of **'molecular crystal'.**

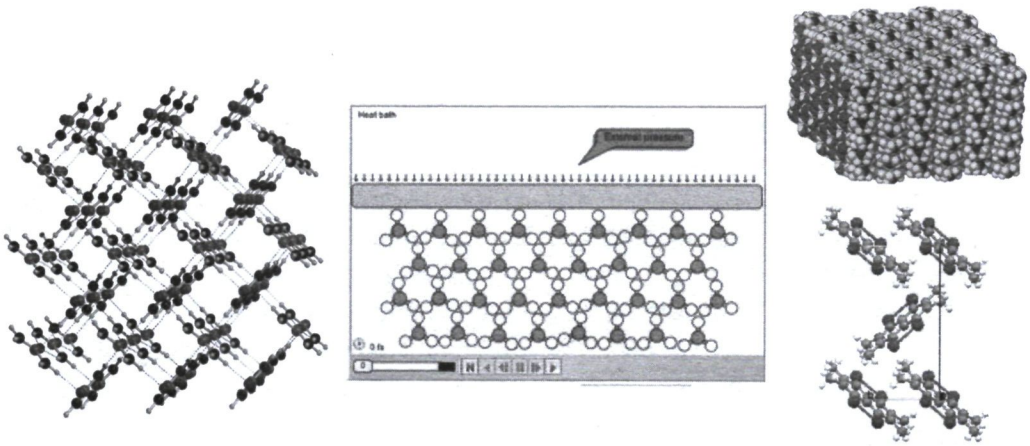


Fig. 1.26: Diagrammatic representation of 'molecular crystal'

(*d*) **Ionic Crystals:** In this particular instance, the atoms present in them are duly held together by the aid of **electrostatic forces** (or the **'ionic bonds'**). Hence, the **'Ionic Crystals'** are comparatively **hard** (*tough*) in texture; and hence, exhibit higher inherent **melting points.**

Example: Table Salt (NaCl): Obtained as the *natural deposit* or obtained otherwise is a befitting example of the so-called **'Ionic Crystals'.**

Figure 1.27 shows the beautiful illustration of the **Ionic Crystal.**

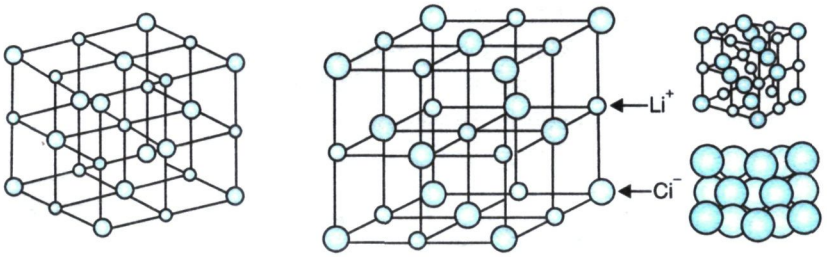


Fig. 1.27: Illustration of an 'ionic crystal'.

Based on the literature survey, we have so far gained sufficient fundamental concept with respect to the **'Metallic Crystals'** duly substantiated with various illustrations, suitable examples, and explanations. Nevertheless, the following *three* critical aspects need to be examined thoroughly so as to have a *better apprehension* of the **'Metallic Crystals'**, namely:

- **Guiding Factors Governing the Formation of Metallic Bond;**
- **Nature of the Metallic Bond;** and
- **Certain Physical Characteristic Features of Metal *vis-a-vis* their Explanations based upon Electron Gas Theory,**

which shall now be discussed briefly in the sections that follows:

1.3.1 Guiding Factors Governing the Formation of Metallic Bond

There are *three* recognized and broadly accepted guiding factors governing the formation of **metallic bond,** namely:

- **Ionization energy** possessed by the ***'metals'*** must be low in order that the correspondingly **valence electrons** of the said ***'metals'*** remain loosely held by the nucleus thereby rendering them absolutely **mobile.**
- Importantly, the respective ***metals*** must inherit **low level of electronegatively** so as to make them incapable of:
  - **accepting electrons**, and
  - **forming *'anions'*.**
- Actual number of the so-called *'vacant orbitals'* present in *metals* must be always more than the actual number of **valence-electrons** duly present in it in order to accomplish the following ***two* cardinal objectives:**
  - **easy movement of *mobile electrons* into the vacant orbitals;** and
  - **prominent characteristics *viz.*, thermal conductivity of the metals could be explained conveniently and easily.**

1.3.2 Nature of the Metallic Bond

In a broader perspective, the precise and exact nature of the **'metallic bond'** could be adequately expatiated and explained based upon the following ***three*** **theories**, namely:

(*i*) **Electron-Sea Theory,**

(*ii*) **Valence Bond Theory,** and

(*iii*) **Molecular Orbital Theory,**

which will now be treated individually in the sections that follows:

1.3.2.1 Electron Sea Theory

It is also known as: **'Electron Gas Theory'** or **'Electron-Cloud Theory'**, which was first and foremost proposed by Lorentz. The **electron-sea theory** suggests vehemently that because the respective **ionization energies of metals** are found to be at their lowest ebb, they do have a tendency to loose promptly their ***valence-electrons;*** and thus, form the **positive metal ions** (*viz.*, Hg^{2+}, Mg^{2+}), usually termed as **'kernels'.**

Interestingly, the *'electrons'* so released by the ensuing **metal atoms** are never found to be **stationary**, but are quite capable of *moving freely* right from **one position to the other *via* the available vacant orbitals.** Perhaps that could be the genuine good reason why these electrons are relatively more **mobile or delocalized.** Therefore, the **electron-sea theory** promulgates strongly that the **'force of attraction'** prevailing between:

- **the metal positive ions (*i.e.*, metal cations),** and
- **the mobile electrons,**

holds firmly the so-called ***metal atoms*** together in the **'metallic crystals'.**

Limitations of Electron-Sea Theory

Following are the *three* vital **limitations of the electron-sea theory,** namely:

- In fact, the above theory fails to explain why **Tungsten (W)** has a *high melting point* (3300°C); whereas, **Mercury (Hg)** has *low melting point (–39°C);*
- The said theory does not fully explain the distinctly *more hardness of* **Osmium (Os) metal**; and
- It also clearly fails to justify and explain why certain **'metals'** do exhibit *more electrical conductivity* in comparison to *other metals* (**elements**).

1.3.2.2 Valence Bond Theory

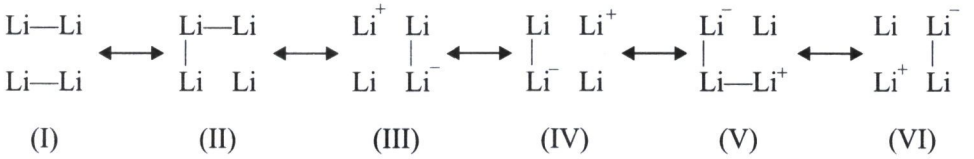
It is also referred to as the **Resonance Theory** and was duly put forward by Pauling. Importantly, the **valence-bond theory** strongly suggests that:

- ***metallic bond*** **is covalent in origin**; and
- **structure of a *metal* involves critically the ensuing electron-pair bonds (*i.e.*, covalent bonds) existing between *each atom* and its *nearest neighbour.***

Example: Let us consider the specific example of **Lithium (Li)-atom,** wherein it has been observed that the said **Li-atom:**

$$\mathbf{Li—1}s^2, 2s^1, 2px^0, 2py^0, 2pz^0$$

is duly surrounded by ***eight*** **neighbouring Li-atoms.** As the **'single-electron'** *i.e.,* the respective **'2*s* orbital'** definitely *cannot form* **electron-pair bonds** along with its ***eight*-neighbouring Li-atoms** which may be duly supported by the assumption that *resonance* comes into play throughout the **entire solid medium.** Thus, one may express the **various resonance forms** as written under:



Remarks: Out of the above ***six*** **contributing structures** only ***four*** **structures** *viz.,* **(III), (IV), (V),** and **(VI)** do contain a ***negatively charged*** **Li-atom,** and that is intimately bound to **2 Li-atoms** by means of ***2 covalent bonds,*** which are commonly known as the **Resonating Covalent Bonds.**

Formation of Resonating Covalent Bonds: The above cited *five* different electronic configurations of the **Li-atoms,** namely: $1s^2$, $2s^1$, $2px^0$, $2py^0$, **and** $2px^0$, vividly depicts that there exists ***three*** **altogether vacant 2*p*-orbitals** *viz.,* $2p_x$, $2p_y$, **and** $2p_z$. Since the inherent energy of three 2*p*-orbitals is not found to be quite different *vis-a-vis* the correspondingly **valence orbital** (*i.e.,* ***2s-orbital***); and, therefore, an ***'electron'*** right from the **2*s*-orbital** *of one particular Li-atom* may get transferred easily to one of the ***three*** **2*p*-vacant orbitals** of the other **Li-atom** in order to convert it into the respective **Li-ion (or Li^+)** having the following *configuration:*

$$1s^2, 2s^1, 2p_x^{\ 1}, 2p_y^{\ 0} \text{ and } 2p_z^{\ 0}.$$

Furthermore, the **Li-atom** that critically provides the electron from its **2*s*-orbitals** gets duly converted into the respective Li^+ **ion** having the configuration $1s^2$. Nevertheless, this particular point may be further expatiated and better understood by clearly affording the marked distinction of the above **Li-atoms** as : Li_a, Li_b, Li_c, **and** Li_d.

NOTE: **It may be understood explicitly that all the *four* Li-atoms do have $1s^2$ and $2s^2$ configuration.**

1.3.2.3 Molecular Orbital Theory (MOT)

MOT is also sometimes referred to as the **'Band Model'**, since the *smallest perceptible piece of a metal* may comprise **nearly 10^{20} atoms.**

Thus, it enables the formation of a *huge quantum* of well-defined **molecular orbitals (MOs)** duly derived from a *large number* of **atomic orbitals (AOs).**

Formation of Molecular Orbitals (MOs): In order to understand reasonably the critical formation of the **molecular orbitals (MOs)** one may have to take into consideration:

'an idealized one-dimensional lattice'.

For this let us assume the sequential formation of a chain of **Li-atoms,** such as : **Li—Li—Li ...Li—Li—Li.** Hence, in the *formation of a chain of Li-atoms* the very first step should be the creation of a **'Li_2-molecule'** out of ***two*** **Li-atom.** Therefore, the formation of **Li_2-molecule** takes place as under:

"the *two* 2s-AOs,* one from each Li-atom, undergo combination to yield *two* MOs."

* That is, each having one electron, $Li \rightarrow 2s^1$.

Remarks: Obviously, the so-called **'lower-energy MO is completely filled with *two* electrons'**; whereas, the *higher-energy MO is found to be absolutely* **empty.** At this particular point in time, if another **Li-atom** is duly attached to the **Li_2-molecule,**—it gives rise to the formation of **Li_3-molecule** (which is certainly regarded to be a **'Hypothetical Molecule'**). Thus, the formation of **Li_3-molecule** takes place as and when:

"*three* 2s-AOs critically combine to yield *three* MOs".

Figure 1.28 illustrates explicitly the formation of **MOs** both from a **Li_2-molecule** and **Li_3-hypothetical molecule.**

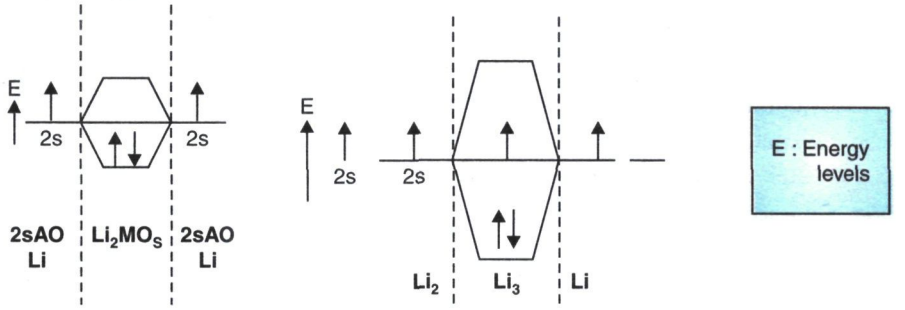


Fig. 1.28: The formation of molecular orbitals (MOs): (*a*) Li_2-Molecule; (*b*) Li_3-Molecule (Hypothetical).

Band Model: It is however, pertinent to state here that as the ensuing length of the chain gets enhanced by a corresponding increment in the number of **Li-atoms,** one may ultimately accomplish a relatively **huge number of MOs spaced together closely and strategically.** Besides, the number of **MOs** (*i.e.,* the emerging *energy levels*) is almost found to be very much akin to that of the respective **AOs** duly responsible for their formation ultimately. Furthermore, since the exact number of the **Li-atoms** gets increased progressively, the accomplished **'energy levels (E)'** become closer gradually to such an extent that they are rendered **'continuous'.** Hence, the actual appearance of a **cluster of continuous energy levels** is invariably called as a **'Band'**; and as a result the ultimate ***molecular orbital theory*** is known as the **'Band Model'.**

Importance of Band Model: Based on various scientific evidences and crucial observations the **band model** may easily expatiate the **different metallic characteristic features of an element** on the Periodic Table. It could be further explained when a ***crystal of Li-metal*** is placed meticulously in the path of an **'electric field',** whereby a small number of electrons do acquire energy; and consequently, get excited to the so-called **'higher vacant MOs'.** In this situation, the ensuing ***higher-energy electrons*** usually carry the *current* with them.

"The observed higher conductivity of '*metals*' is, therefore, solely attributed due to the obvious presence of a huge number of acquired higher-energy vacant MOs."

As the **'bonding electrons'** are not at all localized to any specific atom in the *metal crystal,* the **lattice** may get eventually *'deformed'* with great ease and fervour, that perhaps explains the following ***two* properties of metals,** namely:

- **malleability,** and
- **ductility.**

1.3.3 Certain Physical Characteristic Features of Metals *vis-a-vis* their Explanations Based Upon Electron-Gas Theory

Electron-Gas Theory relates to the concept that the ***'free electrons'*** duly present in a *solid, liquid,* or *gas,* may be treated as a ***'gas'***; and hence, compared with a ***'real gas'*** dissolved in the suitable material. Such an ***electron gas*** strictly obeys a **totally different energy distribution profile** in comparison to a *real gas*, obeying **Fermi-Dirac statistics** rather than the **Boltzmann statistics** obeyed by an ordinary gas. Besides, it also has a **vanishingly small specific heat.**

Following are the ***five*** **important** physical characteristic features of the **'metals'** *vis-a-vis* their most appropriate explanations based upon the **electron-gas theory,** namely:

1. **Metals** are proven to be the **'good conductors of electricity'.**

2. **Metals as Good Conductors of Heat (Thermal Conductivity):** It has been well-established that the metals are **good conductors of electricity** (*i.e.,* **possess an appreciable *thermal conductivity*).** Nevertheless, the elegant **'thermal conductivity of metals'** may be duly expatiated based upon the critical presence of the so-called—**'mobile electrons in the metallic lattice'.**

Example*:** A typical example is that of a *piece of metal* when heated at one end by a naked-flame, the resulting **'mobile electrons'** at this specific end does ***absorb heat energy. Thus, they have a tendency to **move quite fast** *via* the **metallic lattice** toward the ***cooler end***. Obviously, in the course of this phenomenon the so-called **'mobile-electrons'** do *collide with the adjacent electrons*; and hence, transfer their inherent **heat energy** to them. The overall *net impact* being the *mobility of electrons* which eventually permits the **heat transfer to the other end.**

3. **Metals Are Opaque, Exhibit Colour, and Lustre:** As and when the *light rays* fall directly upon the **metallic surface** it gets absorbed more or less completely by virtue of the **electronic transition** duly exhibited by an ***avalanche of electrons.*** Because there is little scope for the light to *pass across the metal*—it is **'opaque'** in character.

Metallic Lustre: Interestingly, a good number of **metals** on being ***scratched*** or ***cut-freshly*** invariably possess a distinct glaring **metallic lustre** (*i.e.,* they *exhibit a shining surface*). The **metallic lustre** may also be explained judiciously based upon the inherent ***mobile electrons*** present in the respective **metal(s).** Thus, when the *light rays* falls upon the **metallic surface**,—the *incident light collides with the mobile electrons* thereby allowing them to get excited. Now, when these **'excited electrons'** ultimately revert to their **'original position'**—they usually *emit energy* in the form of **'light'.** Finally, the ***light*** appears to be *reflected (emitted) from the exclusive surface of the metal*; and therefore, the **metal** appears to inherit the characteristic lustre.

4. **Metals are Malleable and Ductile:** In a broader sense, most **metals** are both *malleable* and *ductile* in nature *i.e.,* when they are:

- **beaten by a *'hammer'*: they are changed into sheets (or malleability);** and
- **drawn through a *'dye-machine'*: they are converted into thin wires (or ductility).**

Mechanism of Malleability and Ductility of Metals: Let us look deep into the actual process, when a **metal** is beaten by the aid of a hammer, whereby *one layer of positive metal ions gets along another layer after passing through a distance*; and finally retains an altogether ***'new position'***. Therefore, the **'sea of electrons'** (also known as the *'valence electrons'*) are duly rendered into the **mobile state.** Consequently, they usually move along with the so-called ***positive metal ions*** (Pb^{2+}); and hence, the ensuing structure of the metal **fails to change** (*i.e.,* retains the *unaltered status*) thereby

restoring the crystal structure predominantly. Perhaps this could be the solid reason that critically results in the reduction.

- **the reduction in the *metal thickness*;** and
- **the metal gets converted into a thin sheet or a thin wire.**

Figure 1.29 illustrates vividly the *malleability* and *ductility* of **metals.**

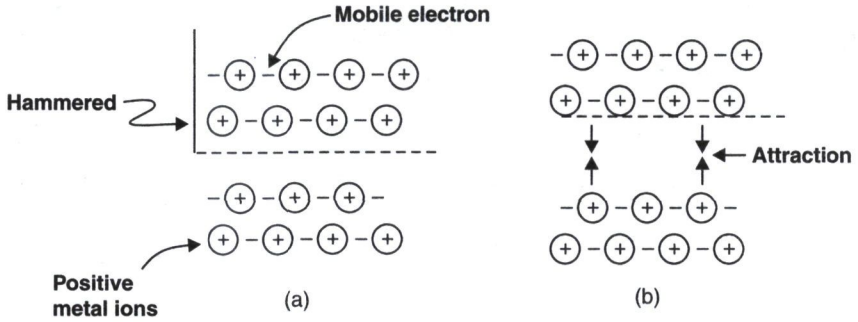


Fig. 1.29: Diagrammatic illustration showing: (a) Malleability; (b) Ductility of metals

NOTE: **The crucial incorporation of an '*alloying metal*' to a *metal* it causes disturbance to the '*structural homogeneity*' of the principal metal; and hence, renders the *newer resulting alloy* both *hard* and *brittle e.g.,* Aluminium Alloy.**

5. **Metals Create Alloy: Alloy** refers to a solution of *two* or more metals or of a metal and a non-metal prepared duly by the careful *'fusion' e.g.,* **an amalgam (Na–Hg).** In other words, the respective **'metallic mixtures'** are invariably termed as **'alloys'.** In fact, the **metals** do form ***alloys*** quite easily and conveniently, such as: **silver and mercury (Ag–Hg); potassium and mercury (K–Hg).**

Importantly, in all such alloys the **spherical ions of various metals** do share prominently the ***same sea of electrons.***

Table 1.4 records the various prevailing differences occurring between the **metallic bonds** and **ionic bonds**; also between the **metallic bonds** and **covalent bonds** in a summarized manner:

Table 1.4: Observed Differences between Metallic Bond and Ionic Bond

S.No.	Metallic Bond	Ionic Bond
1	**Metallic bond** is duly formed due to the simultaneous attractive interaction occurring between the *'kernels'* (*i.e.,* positively charged metal atoms: Na^+), and the *mobile electrons* in a **metal crystal.**	**Ionic bond** is usually formed by the critical transference of the electrons between ***two*** **dissimilar atoms.**
2	**Metals** are malleable/ductile.	Ionic chemical entities (compounds) are brittle.
3	It happens to be a **weak bond.**	It is indeed a **strong bond** (due to the reasonably stronger electrostatic force of attraction.
4	Metals are **good conductors** in the solid state.	These are bad conductors in the solid state.

Table 1.5 summarizes the observed points of differences between the **metallic bond** and **covalent bond** in an explicit manner.

Table 1.5: Observed Differences between Metallic Bond and Covalent Bond

S.No.	Metallic Bond	Covalent Bond
1	**Metallic bond** is duly formed by the simultaneous attractive interaction prevailing between the *'kernels'* and *'mobile electrons'* in a **metal crystal.**	**Covalent bond** is duly formed by the gainful *mutual sharing of electrons* between the similar and dissimilar atoms.
2	**Metallic bond** happens to be a *weak bond* since the **mobile electrons** are attracted simultaneously by a *huge number of nuclei.*	**Covalent bond** is a strong bond since the ensuing *bonded electron pair(s)* gets attracted strongly by nuclei.
3	**Metals** are mostly **solids** (Hg is only *liquid*).	**Covalent compounds** are mostly *liquids* and *gases.*
4	**Metals** prove to be *good conductor of electricity.*	**Covalent bonds** are *bad conductors of electricity* (*graphite* is an exception).
5	**Metallic bond** is *non-directional.*	**Covalent bond** is usually **directional.**

1.4 HYDROGEN BOND

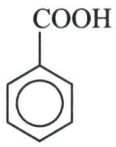
The **Hydrogen Bond** (or **Hydrogen Bonding**) may be defined as **"the electrostatic force of attraction existing between H-atom* and an extremely *electronegative atom* duly present in three different situations:**

- **a molecule of the same substance, or**
- **present in a molecule of different substance, or**
- **present very much within the same molecule."**

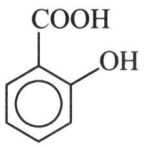
In other words, the so-called **'internal hydrogen bonding'** may influence extensively the ***acid*** or ***base*** **strength** *viz.,*

- **pK_a value of *O*-hydroxy benzoic acid is found to be 2.98;** and
- **pK_a value of *p*-hydroxy benzoic acid is 4.98.**

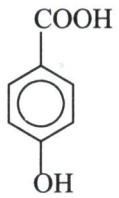
The above disparity could be explained logically based on the fact that the **intramolecular H-bonding** between the **hydroxy (OH^-)** and **carboxy (COO^-) moieties** of the respective *'conjugate base'* of the **'O-isomer'** stabilizes it; and consequently, results in an **increased acidity (*pKa* : 2.98)** as shown below.



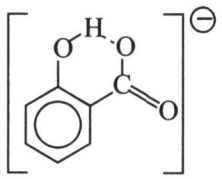
Benzoic acid



***ortho*-Hydroxy benzoic acid**



***para*-Hydroxy benzoic acid**

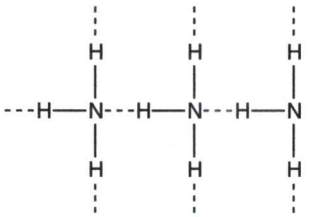


Intramolecular H-bonding between *hydroxy acid* and *carboxy* moities thereby giving an increased acidity

*That is already bound covalently to a highly electronegative atom, such as : **N, O, or F.**

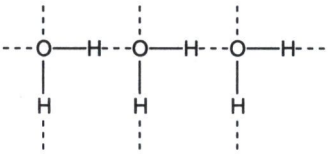
Fig. 1.30 represents the elaborated intramolecular H-bonding taking place between:

- **different molecules of ammonia (NH_3) to give $(NH_3)_x$ cluster;**
- **different molecules of water (H_2O) to yield $(H_2O)_x$ cluster; and**
- **the similar molecules.**



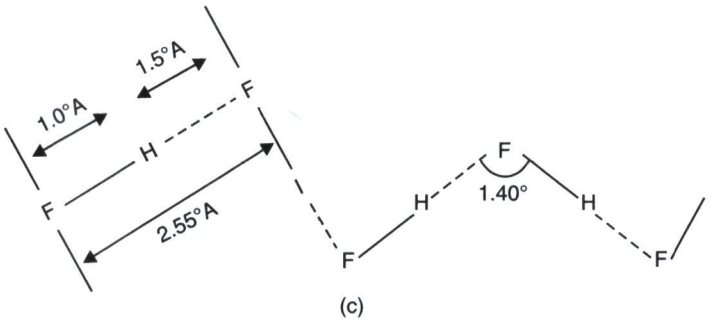
(a)

Representation of *intermolecular H-bonding* between different molecules of ammonia (NH_3) to form *$(NH_3)_x$ cluster*



(b)

Representation of *intermolecular H-bonding* between different molecules of water (H_2O) to form *$(H_2O)_x$ cluster*

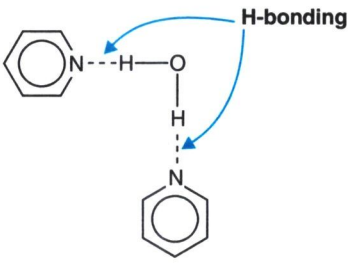


(c)

H-bonding between different molecules of HF to form $(HF)_x$

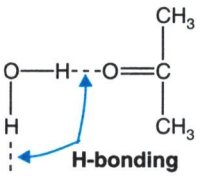
Fig. 1.30: The intermolecular H-bonding between similar molecules only

Likewise, Fig. 1.31 illustrates explicitly the **intermolecular H-bonding** between *two* altogether *different molecules* of **different chemical entities (compounds),** as shown under:



(a)

H-bonding between *two* moles of pyridine and one mole of water

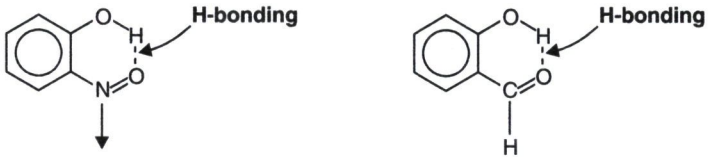


(b)

H-bonding between a mole each of *water* and acetone

Fig. 1.31: Representation of intermolecular H-Bonding between (a) Two moles of Pyridine and one mole of water; and (b) One mole each of water and acetone

Interestingly, Fig. 1.32 depicts clearly the *intramolecular H-bonding* prevailing between ***two* different molecules of the same chemical entity (compound),** as given below:



(a) **Intramolecular H-bonding between *H-atom* and *O-atom***

(b) **Intramolecular H-bonding between *H-atom* and *O-atom***

Fig. 1.32: Illustration of intramolecular H-bonding between: (a) *O*-Hydroxy nitroso benzene; and (b) *O*-Hydroxy benzaldehyde

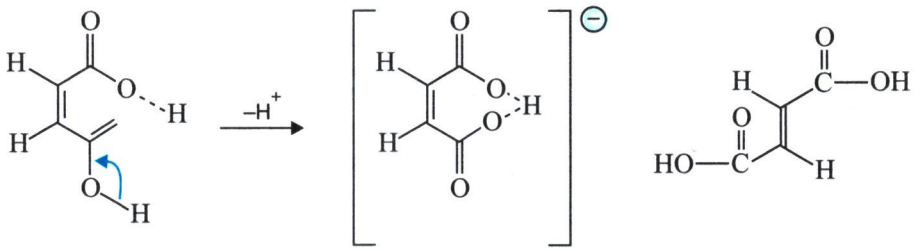
Variants of Hydrogen Bonding: Following are some of the observed **variants of hydrogen bonding,** namely:

(*a*) **Association (or Polymerization) Due to Intramolecular H-Bonding:** It has been amply observed that the *intramolecular H-bonding* usually comes into being either:

- **between several molecules of the same substance,** or
- **between several molecules of altogether different substances.**

Thus, **association** or **polymerization** invariably takes place in such type of *H-bonding* thereby 2 or even more molecules cluster together to yield a relatively **'large agglomerated molecule'.** *Two* typical examples have already been shown above in Figs. 1.31 and 1.32.

(*b*) **Lower pKa Values of *cis*-Maleic Acid than *trans*-Maleic Acid:** It has been duly established that the ***cis*-maleic acid** possesses a ***lower pKa value* (1.92)** due to the so-called *first ionization constant* tenure in comparison to the respective ***trans*-maleic acid* (pKa:3.0),** as shown under:



***cis*-Maleic Acid (pK_a : 1.92)**

An intermediate (with a –ve change)

***trans*-Maleic Acid (or Fumaric acid) (pK_a : 3.0)**

Mechanism: The above **electrostatic transformations** could be explained based upon the **electrostatic effect** caused duly by *one carbonyl dipole* that facilitates critically the following *two* cardinal aspects:

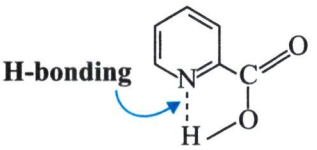
- ❑ apparent departure of the *'first proton'* from the other **carboxyl (—COOH) moiety** which is located strategically in its proximity; and

*Also known as **Fumaric Acid.**

❑ further supported by the fact that the corresponding *singly charged* ***cis*-maleate anion** (the *'intermediate'*) which gets duly stabilized by the *intramolecular H-bonding.*

(*c*) ***ortho*-Substituted Heterocyclic Acids the H—Bond Exerts an Opposite Effect:** In the particular instance of several ***ortho*-substituted heterocyclic acids**—the so-called **H-bonding** does exert an *opposite effect* thereby it predominantly:

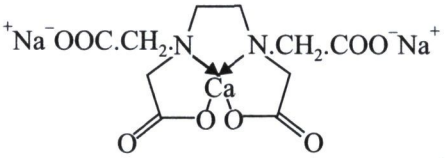
- **retards the strength of the inherent *'acid'*** and
- **stabilizes the acid and lowers the observed dissociation constant significantly.**



***ortho*-Pyridine carboxylic acid**

- stabilization of acid
- lowers dissociation constant (pK_a)

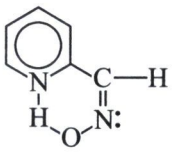
(*d*) **Chelation [or Internal H-Bonding; or Intramolecular H-Bonding]: Chelation** (or **Intramolecular H-Bonding**) relates to the phenomenon whereby a ***'claw'* type of metallic complex (*e.g.*, EDTA–Ca^{2+} complex)** in which a ***meiltiligand molecule*** critically forms a *stable ring* with a **central metallic ion,** thereby rendering the ion *'inactive'*.



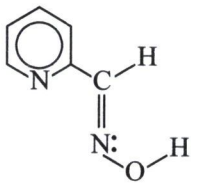
Calcium disodium chelate

EXPLANATION: In this type of **H-bonding** a planar *5-membered chelate ring* is obtained that eventually forms the **intramolecular H-bonding.** Besides, in this type of **H-bonding** the ensuing *interacting atoms* must be positioned in such a manner that there exists a *minimum strain during the closure of the ring.*

Another Classical Example: Let us consider the classical example of **pyridine-2-carboxaldoxime (A)** whose **'*anti*-form'** essentially comprises the **intramolecular H-bonding**; whereas, its corresponding **'*syn*-form' (B)** fails to form the **intramolecular H-bonding** [since the so-called *lone-pair of electrons* residing on the respective N-atom in the ***heterocyclic* pyridine ring** is not oriented towards the respective *hydroxyl (OH) moiety* of the **'oxime'**, as shown below:



(A)
'*anti*-form'
Pyridine-2-carboxaldoxime
(*H-bonding*)



(B)
'*syn*-form'
Pyridine-2-carboxaldoxime
(No *H-bonding*)

(*e*) **Nature and Formation of the Hydrogen Bond:** The exact *nature and formation of the H-bond* may be duly explained by the actual formation of the **H-bonding** in an array of molecules **hydrogen fluoride (HF).** It is an universal fact that the ***F-atom*** has the following *two* important criteria:

- **possesses high electronegativity,** and
- **small dimension of F-atom.**

Thus, the so-called **H—F bond** present in the *HF-molecule* designates a ***'polar covalent bond'***—that could be duly represented as $\mathbf{H^{\delta+}—H^{\delta-}}$. Hence, the resulting *HF-molecule* more or less behaves as a **'dipole'.**

Thus, in a specific instance when a host of such **'dipoles'** *critically come closer to each other* then the respective **H-atom** bearing the *positive charges* (*i.e.*, $H^{\delta+}$) in one $\mathbf{H^{\delta+}—F^{\delta-}}$ **dipole** gets vehemently attracted towards the respective **F-atom** due to the ensuing ***electrostatic force of attraction*** that is termed as the **H-Bond.** Obviously, the final outcome of the **hydrogen-bonding** is that a number of *HF-molecules:*

- **may be combined together**, and
- **ultimately yield of large cluster of molecules,**

that may be eventually represented as $\mathbf{(HF)_x}$. Hence, the formation of the so-called **H-bond** between several ***HF molecules*** (*i.e.*, the creation of $(HF)_x$ cluster] may be expressed as under:

$$\begin{array}{cccccccccc} \delta^+ & \delta^- & \delta^+ & \delta^- & \delta^+ & \delta^- & \delta^+ & \delta^- & \delta^+ & \delta^- \\ \text{---H—} & \text{F---H—} & \text{F---H—} & \text{F---H—} & \text{F---H—} & \text{F---H—} & \text{F---} & & & \end{array}$$

Comment: Based on the aforesaid statement of facts and discussion one may safely conclude that **H-bonding** designates a ***simple*** **dipole-dipole attraction.** Besides, the resulting dipole-dipole attraction is found to be a little more stronger than ***other*** **dipole-dipole attractions.**

(*f*) **Various Determining Parameters for the Formation of H-Bond:** A survey of literature would reveal that the following ***two*** **cardinal determining parameters** are the absolute necessity for the scientific and logical **formation of H-bond,** namely:

- **Critical and Specific Presence of Highly Electronegative Atoms:** The molecules that possess **H-bonds** must essentially comprise **highly electronegative atoms**, for instance: **F, N** or **O** linked directly to **H-atom by a covalent bond.**
- **Presence of Small-Sized Atom:** It is, however pertinent to state here that the respective highly electronegative atom must be essentially of a ***smaller size*** in order that the ensuing **B—H bond** (*viz.*, **B ═ N, or O or F**) could be rendered highly polar ($\mathbf{B^{\delta+}—H^{\delta-}}$); and hence, a strong interaction taking place between several *similar dipoles* may come into being.

Explanation: We know that both **O** and **Cl** do possess electronegativity almost to the same extent **[O = 3.5; Cl = 3.0].** In addition, due to the small size of **O-atom [O = 0.73 Å; Cl = 0.99 Å]** the formation of **H-bonds** takes place; whereas, the corresponding **Cl-atom** fails to do so.

Extending the logical argument further one may easily explain that both **O** and **N** atoms may be able to form **H-bonds;** whereas, the **S** and **P** fails to do so.

NOTE: **Following are the electronegativity values and covalent radii:**
N = 3.0, 0.76 Å; P = 2.1, 1.06 Å; O = 3.5, 0.73 Å; and S = 2.5, 1.02 Å.

(*g*) **Strength of Hydrogen-Bond:** The **hydrogen-bond** is definitely a ***weak bond*** because it simply represents a **feeble electrostatic force of attraction** and **not a chemical bond.** The actual ensuing strength of a **H-bond** gets enhanced with the corresponding increase in the electronegativity of the atom attached with a H-atom by a respective **covalent bond** as could be seen in:

N—H---N and **O—H---F**

Comments: As the *electronegativity* of the atoms **N, O and F** is in the *decreasing order*: **N < O < F**, the ensuing **strength of the H-bond** in the following:

- N—H---N (*viz.*, in NH_3 molecules);
- O—H---O (*viz.*, in H_2O molecules); and
- F—H---F (*viz.*, in HF molecules),

is found to be almost in the same order *i.e.*,

N—H (= 8.37 kJ. mole^{-1}) < O—H---O (= 29.29 kJ. mole^{-1}) < F—H---F (= 41.85 kJ. mole^{-1}).

NOTE:
1. **However, the *H-bond* is found to be much stronger *vis-a-vis* the van der Waal's forces, but definitely weaker in comparison to:**
   - **a covalent bond, and**
   - **an ionic bond**
2. **The order of the strength is as given under: van der Waal's forces < H-bond <covalent bond < ionic bond.**

(*h*) **Effect of H-Bonding on Physical Characteristic Features of Chemical Entities (Compounds) having H-Bonds:** Even though the **hydrogen bonding** (or *H-bond*) is recognized to be a relatively ***'weak bond'***, it predominantly exerts its effect upon a large number of **physical characteristic features** in the typical **H-bonded chemical entities (compounds).** Following are the *five* cardinal properties, namely:

- **BP-Variants in the Binary H-compounds of elements belonging to groups: VA, VIA, and VIIA;**
- **MPs, BPs, Heat of Fusion, and Heat of Vapourisation of the H-bonded compounds and their methyl derivatives;**
- **Comparison amongst the BPs of Methane (CH_4), Ammonia (NH_3), Water (H_2O), and Hydrofluoric Acid (HF);**
- **Solubility profile of organic chemical entities;** and
- **Viscosity of Liquids,**

which shall now be treated individually in the sections that follows:

1. **BP-Variants in the binary H-Compounds of Elements belonging to Groups: VA, VIA, and VIIA:** In a broader perspective, the following ***two*** **criteria,** such as:

- **Molecular Weights (m.w.);** and
- **Boiling Point (°C),**

of the respective **binary hydrogen compounds** belonging to the various elements of **Groups: VA, VIA, VIIA** (as given in **Table 1.6**) invariably record a perceptive increment in the so-called **'molecular weight of hybrids in each group', and also the ensuing *van der Waal's forces of attraction* taking place in the same direction (*i.e., downwards*).**

Table 1.6: Observed variants of the boiling points (°C) of binary hydrogen compounds belonging to the elements of groups: VA, VIA and VIIA.

Group VA			Group VIA			Group VIIA		
Hydride	**m.w.**	**BP (°C)**	**Hydride**	**m.w.**	**BP (°C)**	**Hydride**	**m.w.**	**BP (°C)**
NH_3	17	–34.5	H_2O	18	+100.0	HF	20	+19.4
PH_3	34	–87.5	H_2S	33	–60.7	HCl	36.5	–85.0
AsH_3	78	–62.4	H_2Se	81	–41.5	HBr	81	–67.1
SbH_3	125	–18.4	H_2Te	130	–1.8	HI	128	–35.0

Important Observation: These essentially include: the critical increment in the magnitude of **van der Waal's** forces the **BPs** of the ensuing ***hybrids*** must also **increase downwards,** which means that the **BPs** must be in the following order:

***First* Member < *Second* Member < *Third* Member < *Fourth* Member**

Amazingly, as we observe in the Table 1.6 that:

- **From the *First* member to *Second* member: BPs—instead of *increasing* gets decreased; and**
- **From the *Second* member to *Fourth* member: BPs—do show the expected *increasing trend.***

EXPLANATION: The foretold critical observations may be explained further as detailed under:

- The most probable reason as to why the **BP** of the ***first* member** is found to be **higher** *vis-a-vis* the ***second* member** in each individual group may be explained judiciously based on the fact that:
  - because **N, O** and **F** do possess relatively more degree of electronegativity than **H-atom**; and
  - the observed *electronegativity values* of other elements are found to be *closer to that of the* **H-atom** (*e.g.,* H = 2.1, N = 3.0, P = 2.1, As = 2.0, Sb = 1.9, O = 3.5, S = 2.5, Te = 2.1, F = 4.0, Cl = 3.0, Br = 2.8, and I = 2.5).
- Besides, the **NH_3, H_2O,** and **HF** molecules do undergo critical ***intermolecular* H-bonding**; whereas, the indulgence of this type of **H-bonding** is observed to be almost negligible in other molecules.
- By virtue of the formation of **H-bonding**, such as; **$(NH_3)_x$, $(H_2O)_x$,** and **$(HF)_x$**—the ultimate ***'clusters'*** are duly formed.

- Importantly, the cleavage of the respective **H-bonds** duly attached to the corresponding **NH_3, H_2O and HF molecules** in the form of their **clusters** may be accomplished by the application of **'more heat energy'**; and, therefore, the respective **BPs** of these molecules are found to be higher than those of **PH_3, H_2S, and HCl respectively.**

2. **Melting Points (MPs), Boiling Points (BPs), Heat of Fusion, and Heat of Vapourization of the H-Bonded Compounds and Their Methyl Derivatives:** The sequential replacement of the **H-atom** located strategically in the so-called ***H-bonded compounds*** by the respective **methyl (—CH_3) moieties** one may ultimately obtain the desired **'methyl derivatives'.** However, it is pertinent to state at this point in time that the ***degree of* H-bonding** gets decreased significantly in the **'methyl derivatives'.**

Importantly, a perceptive *decrease in the extent of H-bonding* also goes a long way in affording a definite lowering of the following important parameters, such as:

• MPs • BPs • Heat of Fusion and • Heat of Vapourization

Example: Following is a typical example:

***Heat of Vapourization* of Water [H_2O or H—O—H], methanol [CH_3OH], and dimethyl ether [CH_3—O—CH_3]** are given as under:

- **Melting Points [MPs] (°C):** H_2O = 0.0; CH_3OH = –97.8; CH_3—O—CH_3 = –138.5;
- **Boiling Points [BPs] (°C):** H_2O = 100.0; CH_3OH = 64.7; CH_3—O—CH_3 = –23.7;
- **Heat of Fusion (kJ. mol^{-1}):** H_2O = 3.0; CH_3OH = 2.2; CH_3—O—CH_3 = 4.9; and
- **Heat of Vapourization (kJ. mol^{-1}):** H_2O = 40.6; CH_3OH = 35.6; CH_3—O—CH_3 = 21.5.

Some Exceptional Examples: Following are some exceptional examples, namely:

- The **H-bonded compounds,** such as: **Sulphuric acid (H_2SO_4), Phosphorus acid (H_3PO_3),** and **Phosphoric acid (H_3PO_4)** do not ***boil*** at all, but instead get decomposed at **340°C, 184°C,** and **213°C** respectively (with the critically *loss of a mole of H_2O*).
- Alternatively, the corresponding **methyl derivatives** of these compounds *e.g.,* **dimethyl sulphate [$(CH_3)_2SO_4$], trimethyl phosphate [$(CH_3)_3PO_4$],** and **trimethyl borate [$(CH_3)_3BO_3$],** that are usually the **non-hydrogen-bonded** compounds and *boil at relatively lower temperatures i.e.,* **188°C, 193°C, and 65°C** respectively.
- Besides, there are certain **'exceptional pairs'**, such as:

  HF—CH_3F and H_3N—CH_3—N=N≡N,

  that also exhibit an almost similar trend in their respective boiling points *viz.,* **HF = 19.5°C; CH_3F = –78°C; NH_3 = 37°C; and CH_3—N=N≡N = 20°C.**

3. **Comparison Amongst the BPs of Methane (CH_4), Ammonia (NH_3), Water (H_2O), and Hydrofluoric Acid (HF):** It has been duly established that the respective **BPs** of these ***'hydrides'*** are usually found in the following order:

CH_4 (= – 161°C) < NH_3 (= – 34.5°C) < HF (= + 19.4°C) < H_2O (= + 100°C)

Logical Explanation: It essentially includes:

(*i*) As we know that the **C-atom** possesses an extremely low electronegatively (equal to 2.5), hence the scope of formation of the so-called **methane cluster** $[(CH_4)_x]$ is **almost remote.**

(*ii*) However, ***several*** $\mathbf{CH_4}$ **molecules** are joined together by means of the **van der Waal's forces** that are indeed very weak *i.e.*, even weaker than the respective **H-bonds.**

(*iii*) **Methane** $\mathbf{(CH_4)}$ critically shows the **lowest BP**, because of the presence of ***weak*** **van der Waal's forces.**

(*iv*) Consequently, by virtue of the presence of:

- **relatively high electronegativity,** and
- **smaller size of N, O, and F atoms,**

practically all the ***three*** **molecules** *e.g.,* $\mathbf{NH_3}$, $\mathbf{H_2O}$, and **HF** do have the **H-bonding** obviously.

(*v*) The manner the **H-bonds** are being duly formed in $\mathbf{NH_3}$, $\mathbf{H_2O}$, **and HF,** as depicted in **Fig. 1.30,** suggests explicitly that:

- due to the critical presence of one lone pair of electrons upon the *N-atom*, and
- *3 H-atoms* duly attached covalently with N-atom,

it is possible that **each** $\mathbf{NH_3}$ **molecule** may eventually lead to the formation of **4 H-bonds** with other **4** $\mathbf{NH_3}$ **molecules.**

(*vi*) Likewise, on account of the presence of the *lone pair of electrons* located strategically:

- to an *O-atom,* and
- *2 H-atoms* attached covalently with the respective *O-atom.*

each **water** $\mathbf{(H_2O)}$ **molecule**, very much akin to $\mathbf{NH_3}$ **molecule** may also give rise to the formation of **4 H-bonds** with other **4-**$\mathbf{H_2O}$ **molecules.**

(*vii*) Thus, the formation of **H-bonding** gives: $\mathbf{(NH_3)_x}$, $\mathbf{(H_2O)_x}$, **and** $\mathbf{(HF)_x}$ **in the form of clusters.**

(*viii*) In another specific instance, when it is intended to break the **H-bonds** holding the **F-atom** in the ***HF-molecule***, may actually form only **2 H-bonds with** ***two*** **other HF-molecules.** Hence, the overall net strength of **H-bonding,** which being directly proportional to the *number of H-bonds* formed duly in: $\mathbf{NH_3}$, $\mathbf{H_2O}$ **and HF** molecules must be in the following order:

$$\mathbf{NH_3 > H_2O > HF}$$

(*ix*) As the **N-atom** has the *lowest value of electronegativity* of all the **3-atoms** (*viz.,* N = 3.0, O = 3.5, and F = 4.0); and hence, the ensuing strength of *H-bonding* in the **ammonia** $\mathbf{(NH_3)}$ **molecule** attains a ***bare minimum level*** of all the *3-molecules.*

(*x*) Obviously, the prevailing strength of the **2 H-Bonds** in the **HF molecules** is observed to be far less than the **4 H-Bonds** in **water** $\mathbf{(H_2O)}$ **molecule**; and hence, the *order of the strength of* **H-Bonding** in NH_3, H_2O, and *HF* molecules is as follows:

$$\mathbf{NH_3 < HF < H_2O}$$

(*xi*) In addition, the **BPs of the ensuing *'hybrids'*** are also found to be in the **same order.**

(*xii*) Interestingly, **methane (CH_4)** has the ***lowest BP*** as stated earlier and the order of the so-called **BPs** of all the **'4-hybrids'** is in the order of:

$$CH_4 < NH_3 < HF < H_2O$$

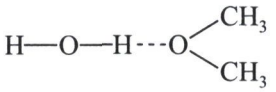
4. **Solubility Profile of Organic Chemical Entities:** It has been duly proven that the solubility profile of **organic chemical entities (or compounds)** in *water (H_2O) molecule* is solely on account of the critical formation of the **H-Bonds** between the:

- **H_2O molecules,** and
- **Organic compounds**

EXAMPLE: One may keenly take cognizance of the underlying fact that the **'alcohols'** are *soluble in water (H_2O)*; whereas, the **'alkanes'** are not. Perhaps this could be the appropriate reason that the **'alkane molecules'** are *incapable of producing the H-Bonds* with the **water (H_2O) molecules**; and, therefore, are **not at all miscible with H_2O.**

Alcohols: with ***three* C-atoms** possessing the *alkyl groups* are indeed found to be *freely soluble in water (H_2O).* Nevertheless, an **increment in the number of C-atoms alcohols** renders the solubility profile to minimize progressively. In other words, only the ***'lower alcohols'*** *viz.*, **CH_3OH, C_2H_5OH, C_3H_7OH** and the like, are found to be **freely water-soluble.**

Amazingly, **dimethyl ether [$(CH_3)_2O$]** duly forms **H-Bonds** with **water (H—O—H)** as shown under:



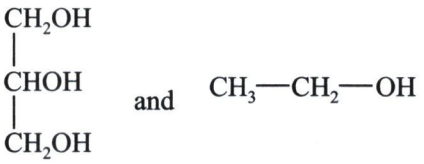
and hence, is found to be completely miscible with water; whereas, the respective sulphural analogue **dimethyl sulphide [$(CH_3)_2S$],** that is incapable of forming **H-Bonds with water,** remains only **partially miscible.**

Another beautiful example is that of **Benzene (C_6H_6)** which being only partially miscible in water (H_2O); whereas, **pyridine** (C_5H_5N) is found to be miscible in *all proportions* by virtue of its **strong H-Bonds** formation *via* the so-called *lone pair of electrons* located on the **N-atom in the pyridine molecule.**

NOTE: **The solubility profile of certain compounds in the specific *non-aqueous solvents e.g.*, chloroform ($CHCl_3$), acetone [$(CH_3)_2CO$], hydrochloric acid (HCl) may also be explained reasonably based on the phenomenon of *hydrogen-bonding.***

5. **Viscosity of Liquids:** Based on the established fact that due to the **H-bonding**—the ensuing attraction taking place between the so-called ***molecules of H-bonded liquids*** also get enhanced appreciably. However, the observed enhancement in the said **'attraction'** helps to lower the tendency of the liquids to *accomplish and maintain the flow in a smooth manner.*

Examples: Let us consider the following ***two*** **compounds:**



Glycerol **Ethanol**

of which the former possesses **3 hydroxy (OH) moieties** and the later only **one hydroxy (OH) group.** Obviously, **glycerol** does form **greater number of H-Bonds** *i.e., more glycerol molecules* are joined together by means of the *intermolecular H-bonding;* and, therefore, its ***observed*** **viscosity** is relatively higher than that of **ethanol** [***Glycerol Viscosity*** = 10^4 **millipoise**; ***Ethanol Viscosity*** = **5.97 millipoise**].

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Chapter 2

Stereochemistry

LESSONS AT A GLANCE

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2.4 Characteristic Features of Enantiomers: Optical Activity
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  2.6.1 Hybridisation
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  2.6.3 Configuration

2.1 INTRODUCTION

Definitions: In order to understand the fundamentals of **'stereochemistry'** one may have to look into the following terminologies along with its brief relevant expatiation:

- ***Stereochemical:*** It relates to the viewing of **3D-molecule** either as such or in a projection.
- ***Stereoconvergence:*** The predominant formation of the same *stereoisomer* or stereoisomer mixture of a reaction product when ***two*** altogether different isomers of the reactant are used in the same reactions. Thus, when that product actually involved in the reaction happens to be *one enantiomer* the ultimate result has been called **enantioconvergence.**

- ***Stereoisomer:*** Two molecules are said to be **'stereoisomers'** of each other when they do have the *exact number* and *kinds of atoms* that are duly bound to each other in the same order, but do differ critically in the *orientation of bonds in space.*
- ***Stereoisomeric:*** It refers to the *isomerism* that takes place due to the *spatial arrangement of atoms* without any variation with respect to the prevailing **bond multiplicity** between the *various isomers.*
- ***Stereomutation:*** It relates to the change of configuration at a **stereogenic *unit*** duly brought about on account of *physical or chemical means.*
- ***Stereospecificity:*** A reaction is said to be stereospecific, if the starting materials actually differ from its product only in terms of the *configuration.*
- ***Stereoselective Synthesis:*** It refers to the chemical reaction in which one or more **newer elements of clurality** are duly formed in a *substrate molecule* and that subsequently gives rise to the formation of either:
  - **enantiomeric**, or
  - **diastereoisomeric,**

  in equal quantities.
- **Historical Evidences:** Following are a few chronological and historical evidences with regard to the *discovery of the phenomenon of the polarization of light.*
  - **Etienne Louis Malus (1808)**—was pioneer in the epoch making discovery of an extremely critical and vital phase of ***'organic chemistry'*** in association with the spectacular phenomenon of the **polarization of light.**
  - **Biot (1815)***—the French physicist (together with Argo), pursued the earlier findings of **Malus (1812);** and observed that a *quartz crystal*:
    - **cut parallel to the axis,** and
    - **traversed by plane-polarized light normal to the surface,**

    helps to rotate the *plane of polarization.* Furthermore, **Biot** vehemently ascertained that certain *quartz crystals* critically *turn the beam of light to the right*; whereas, others *turn it to the left.*
  - **Haiiy**—a renowned **minerologist** (after a couple of years) took cognizance of the fact that certain **typical specimens of quartz crystals** usually exist in:

    '***two* hemihedral forms**'.

    Interestingly, each such **'hemihedral quartz crystal'** was predominantly characterized by the presence of a set of faces arranged in such a manner that either a **right-handed** or **left-handed sense**; and hence, constituting just half of the faces needed to yield a so-called **'symmetrical crystal'.**

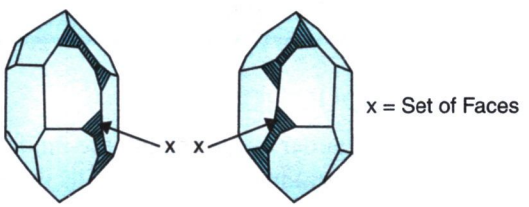


Fig. 2.1: Illustration of hemihedral quartz crystals

Figure 2.1 illustrates explicitly a **hemihedral quartz crystal,** that exhibits an ***enantiomorphous***

* Biot JP: 1774–1862; b Paris; Physicist, College de France.

character,—which is obviously related to each other as the ***right-hand* to the *left-hand.***

- **Sir John Herschel (1820):** Strongly argued that there could prevail an intimate relationship between:
  - **crystallographic properties of quartz,** and
  - **optical properties of quartz**

Comments: Based on the experimental findings it was duly established that crystals having the respective inherent faces inclined to the ***'right'*** and to the ***'left'*** mostly—**'rotate the plane of polarized light in the opposite directions.'**

- **Biot (1815):** further discovered that some *naturally occurring organic chemical entities* (**compounds**) vehemently rotate the *plane polarized light* in either:
  - **liquid form**, or
  - **dissolved state**.

NOTE: **A few such typical substances *viz.*, • oil of turpentine • camphor • sugar solutions and • tartaric acid—were found to show this property prominently; and, therefore, are duly described as having *'optical activity'*.**

2.2 ISOMERISM

In a particular instance, when ***two* or more entirely different compounds** may have the same *'molecular formula'*, they are usually referred to as the **'isomers'** or **'isomerides'**; and this phenomenon is termed as **isomerism.** However, as the said molecules of the so-called **'isomeric compounds'** are duly made up from the **same atoms,** in terms of both:

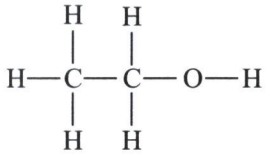
- **with respect to *type***, and
- **with respect to *number***,

it is abundantly clear that the actual prevailing differences in their respective characteristic features should be caused on account of *certain difference in the arrangement* of the **atoms within the molecule.**

Example: The above analogy may be further expatiated by the help of a rather *simple example viz.*,

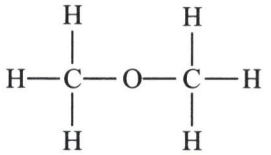
- **Ethanol and** • **Dimethyl Ether**,

which essentially have the ***same* molecular formula—C_2H_6O.** Thus, one may vividly visualize the difference between the aforesaid ***two* compounds** by expresing their ***graphic* or *structural* formulae** as given under:



$CH_3—CH_2—OH$

Ethanol (Ethyl alcohol)



$CH_3—O—CH_3$

Dimethyl Ether

Remarks:

1. The foretold ***two* formulae** have been duly ascertained from a collaborated investigative study of:
   - **methods of formation,** and
   - **chemical behaviour (of *two* compounds)**
2. Besides, such studies are duly aided by the so-called **limitations imposed by considerations of 'valency'.**

NOTE: **In certain specific instances, an organic compound may duly undergo a definite change into a respective *isomeric compound* due to a rearrangement of the various atoms positioned within the molecule.**

Nevertheless, such '*isomeric changes*' invariably come into being:

- ***almost spontaneously*,** or
- **caused by high temperatures,** or
- **due to action of reagents.**

❑ **Tautomerism:** In an event, when ***two* isomers** change very rapidly one into the other so that the compound represented by either formula is or may be regarded as **'equilibrium mixture'** of the two, they are invariably known as:

- ***'dynamic isomers'***, or
- ***'tautomers'***.

Quite often, the change from one form to the other involves the critic transferance of a proton; and hence, the phenomenon is called as **'prototropy'.**

Examples: The most befitting examples are adequately given by such **chemical entities (compounds)** that essentially consist of the ***grouping*** **—CO—CH_2—CO—**, which gets promptly transformed by a ***proton shift*** from *carbon to oxygen* into the respective ***grouping*** —C(OH)=CH—CO—; and hence, it is known as the ***'keto-enol'* tautomerism.**

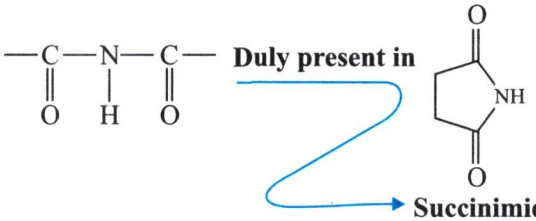
Thus, we may have the expression:



***Keto*-form** ***Enol*-form**

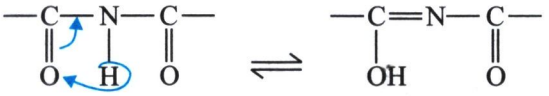
Exception Example: Importantly, one may come across an **exception example** by clearly demonstrating the mixtures of the respective ***'keto'*—and *'enol'*-forms** in an ***equilibrium state,*** *viz.*, **Ethyl acetoacetate** [$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}OC_2H_5$].

❑ **'Lactam-Lactim' Tautomerism:** Amazingly, one may occasionally come across with such chemical entities comprising the following kind of a grouping:



wherein, it essentially involves the transfer of a '**proton**' from ***N-atom*** to ***O*-atom** or ***vice-versa.***

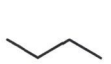
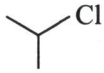
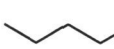
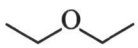
Thus, we may have the expression:



***Lactam*-form** ***Lactim*-form**

Caution: At this point in time, it is very important to **caution** that the readers need not confuse **tautomerism** with the underlying concept of **resonance** at all.

❑ **Constitutional Isomers:** They predominantly differ in their respective *bond connectivities**; and hence, are referred to as the **constitutional isomers.** Following are a few classical examples of the **constitutional isomers.**

Molecular Formula	**Constitutional Isomers**		
C_4H_{10}		and	
	***n*-Butane**		**2-Methylpropane**
C_3H_7Cl		and	
	1-Chloropropane		**2-Chloropropane**
$C_4H_{10}O$		and	
	1-Butanol		**Diethyl Ether**

2.3 STEREOISOMERISM

The **stereoisomers** that critically posses the ***same bond connectivity*** but altogether ***different orientations of atoms* or *groups in space.***

General categories of Stereoisomers: The **stereoisomers** may be sub-divided into ***two* general categories**, namely:

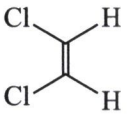
- **Enantiomers,** and
- **Diastereoisomers.**

Enantiomers: The **'enantiomers'** are defined as—**'the stereoisomers whose molecules are non-superimposable mirror images of each other'.**

Diastereoisomers: The **'diastereoisomers'** are referred to as—**'the stereoisomers whose molecules are not mirror image of each other'.**

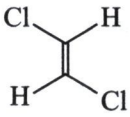
Example I: Following are the typical **alkene isomers,** namely: ***cis*-and *trans*-1,2-dichloroethene,** as shown under, are the **stereoisomers** which are **diastereoisomers.**

* That is, their atoms are connected in an altogether **different order.**



***cis*-1, 2-Dichloroethene**

[Molecular Formula: $C_2H_2Cl_2$]



***trans*-1, 2-Dichloroethene**

[Molecular Formula: $C_2H_2Cl_2$]

Comments: These essentially include:

1. Both compounds do possess critically **2 *central* C-atoms** that are eventually joined by an **olefinic (double) bond.**

2. Both compounds also have **one chlorine atom** and **one hydrogen atom** that are ultimately attached to **each C-atom.**

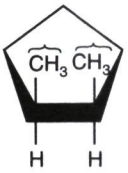
3. Nevertheless, these atoms specifically exhibit a distinct **different arrangement in space** (or **variant *spatial* arrangement**) which is found to be *not at all interconvertible* from one to another*, thereby rendering them **stereoisomers.**

4. Furthermore, these are indeed the **stereoisomers** which are not the so-called *'mirror-images'* of each other; and, therefore, they are **diastereoisomers** and definitely ***not* enantiomers.**

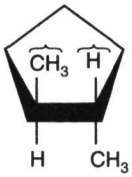
EXAMPLE II. ***cis*-and *trans*-Isomers of Cycloalkanes:** In fact, these *two* compounds critically furnish is with another classical example of the stereoisomers which are diastereoisomers. Thus, we may take into consideration the following ***two* typical organic compounds,** namely:

- ***cis*-1, 2-Dimethylcyclopentane,** and
- ***trans*-1, 2-Dimethylcyclopentane,**

having the following chemical structures:



***Cis*-1,2-Dimethyl cyclopentane**
[Molecular formula : C_7H_{14}]



***trans*-1,2-Dimethylcyclopentane**
[Molecular formula : C_7H_{14}]

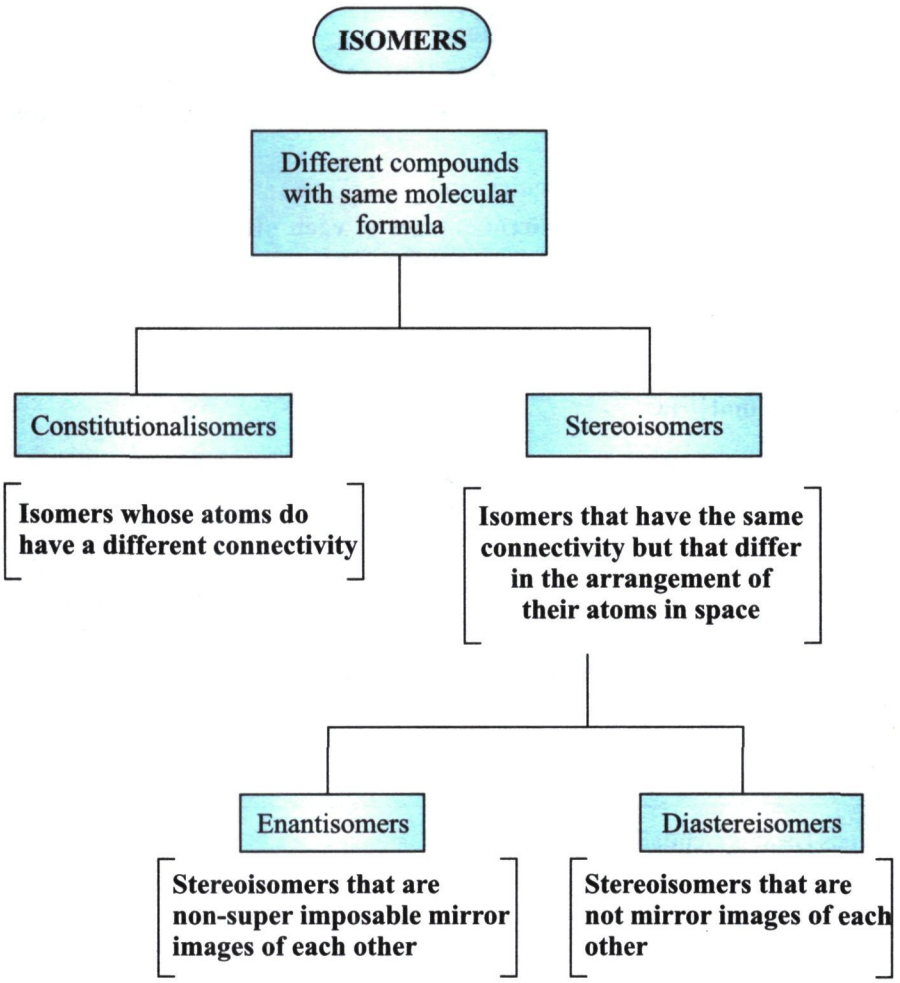
Comments: These essentially comprise:

1. The aforesaid *two* compounds do possess critically:
   - **same molecular formula (C_7H_{14}),** and
   - **same sequence of connections for their respective atoms.**
2. However, they do distinctly show different arrangements of their atoms in space.
3. Obviously, in *one compound*—it shows explicitly that **both methyl (—CH_3) moieties** are duly bonded to the **same face of the ring;** whereas, in the *other compound*—the **2 methyl (—CH_3) moieties** are clearly bonded to the **opposite face of the ring.**
4. Besides, the strategically located positions of the *2 methyl moieties* cannot be at any cost ***interconverted by the ensuing conformational changes.***

*That is, due to the *huge barrier* to permit the usual rotation of the ensuing **carbon-carbon olefinic bond.**

5. Hence, it may be inferred that these ***two*** **compounds** are **stereoisomers**; and since they are **stereoisomers** which are *not mirror images of each other*–they may be further duly classified as **diastereoisomers.**

Sub-Classification of Isomers



2.4 CHARACTERISTIC FEATURES OF ENANTIOMERS: OPTICAL ACTIVITY

For the **'enantiomers'**, one may observe most critically that—*such molecules are not superimposable one on the other end*; and based on this glaring fact it may be concluded vehemently that the so-called **enantiomers** are a *different breed of compounds* (*i.e.,* **chemical entities**).

Important Points of Difference between Enantiomers and Constitutional Isomers/ Diastereoisomers. These essentially include:

1. **Enantiomers** do exhibit *identical* **mp.** and **bp.**

2. **Enantiomers** do not possess *variant physical properties viz.,*
   - **refractive indices (RIs),**
   - **solubility profiles (in common solvents),**
   - **IR-spectral patterns,** and
   - **rates of reaction with *achiral reagents.***
3. A plethora of such **characteristic features** *viz.,*
   - **Melting Points (mp)** • **Boiling Points (bp) and** • **Solubilities,**

   are found to be dependent exclusively upon the *critical magnitude of the intermolecular forces functioning between:*
     - **the prevailing molecules,** and
     - **happen to be the mirror images of each other.**

Table 2.1 illustrates a few typical characterististics of the respective **2-Butanol Enantiomers,** namely:

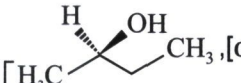
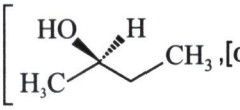
- **(R)-2-Butanol**  , $[\alpha]^{25}_{D} = -13.52°$],
- **(S)-2-Butanol**  , $[\alpha]^{25}_{D} = +13.52°$],

Table 2.1: Physical Characteristic Features of (R)– and (S)–2-Butanol

S. No.	Physical Property	(R)-2-Butanol	(S)-2-Butanol
1	**BP** (1 atm)	99.5°C	99.5°C
2	**Density** [g.mL^{-1} at 20°C]	0.808	0.808
3	**Refractive Index (RI)** at 20°C	1.397	1.397

Comments: These essentially include:

1. Generally, the **enantiomers** exhibit different behavioural pattern as and when they do interact with other **chiral (or asymmetric) compounds.**
2. Besides, the **enantiomers** critically display altogether divergent rates of reaction toward other **chiral molecules *i.e.,***
   - **toward such reagents that essentially comprise a *single enantiomer,*** or
   - **an *excess of a single enantiomer.***
3. **Enantiomers** also show a wide range of *solubility profiles* in various solvents that comprise
   - **a *single enantiomer,*** or
   - **an *excess of a single enantiomer.***

How do the enantiomers vary in their behaviour toward plane polarised light?

It has been duly established that whenever a specific *beam of plane-polarised light* happens to pass *via* an **enantiomer**, the **plane of polarization rotates** perceptively. In addition, ***separate enantiomers*** do help in the rotation of the *plane of plane-polarized light* almost to:

- **an equal extent,** and
- **to the opposite directions.**

Therefore, since their ensuing effect prevailing predominantly upon the so-called **plane-polarized light,** produce **separate enantiomers** that are found to be:

'optically active compounds'.

2.4.1 The Plane-Polarized Light

Light refers to an electromagnetic radiation with wavelengths ranging between **400 nm (*violet*)** and **740 nm (*red*)** that are being:

- **propagated at a velocity of nearly 300,000 km sec^{-1} (*i.e.*, equivalent to 186,000 miles. sec^{-1});** and
- **detected by the normal vision (or human eye) as a visual signal.**

Nevertheless, in the **'laser'** and **'optical communication fields'** the ***'light'*** invariably includes the so-called–*'sufficient broader segment of the electromagnetic spectrum which may be handled by the fundamental optical techniques being employed for the visible spectrum.'* Thus, one may consider it to be duly extended right from the ***near*** **UV-region** of approximately **300 nm** *via* the **visible region,** and penetrating into the ***mid*** **IR-region** varying between **3.0 to 30 μm.**

Another school of thought relates **'light'** as an ***electromagnetic phenomenon.***

Figure 2.2 illustrates the explicit *oscillating electric field* and *oscillating-magnetic field* pertaining to a particular beam of an ordinary light in one plane; and thus, the waves so generated are depicted predominantly here in all possible planes in an ordinary light.

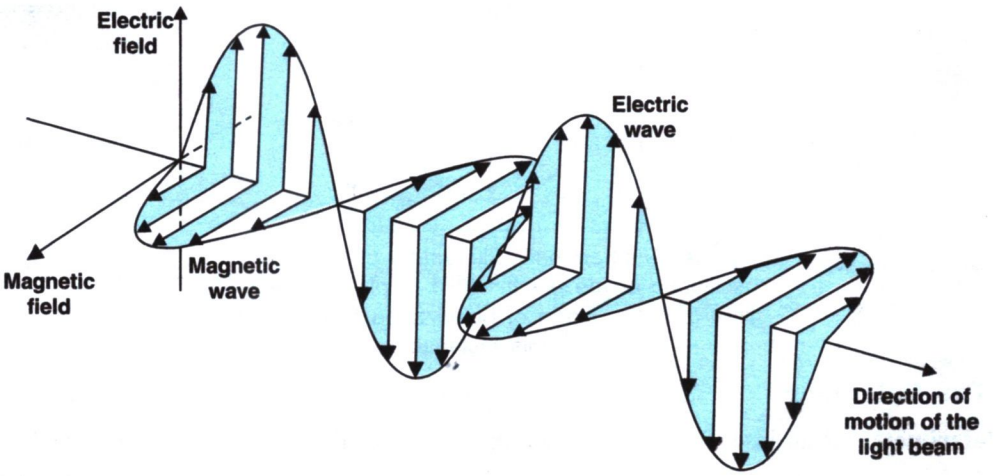


Fig. 2.2: Diagrammatic representation of the oscillating electric and magnetic fields of a beam of light in one specific plane

In Fig. 2.2 the beam of light mostly comprises ***two*** **mutually perpendicular oscillating fields,** namely:

- **an oscillating electric field,** and
- **an oscillating magnetic field.**

Let us now consider the following *two* assumptions:

- **viewing a *beam of ordinary light* from one end;** and
- **actually visualising the planes wherein the *electrical oscillations* were taking place,**

we would keenly observe that the *oscillations of the electric field* were existing duly in practically **all possible planes perpendicular (⊥) to the direction of propagation**, as depicted in Fig. 2.3.*

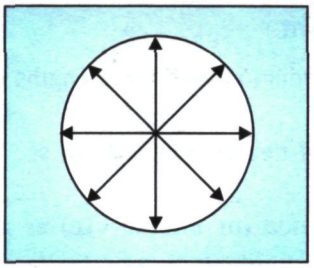


Fig. 2.3: The observed oscillation of ensuing electric field of ordinary light takes place in all possible planes perpendicular (⊥) to the direction of propagation

Likewise, in another situation when an *ordinary light* is made to pass *via* a **'polarizer'**, the latter critically interacts with the ensuing **electric field** in such a manner that the resulting **electric field of the light** which emerges eventually from the **polarizer**** is found to be ***oscillating only in one plane;*** and hence, such light is usually termed as the **'plane-polarized light'** as shown in Fig. 2.4.

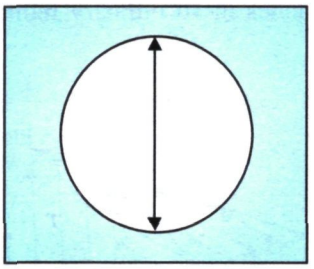


Fig. 2.4: Diagrammatic illustration of the plane of oscillation of the electric field of plane-polarized light [*i.e.*, the plane of polarization being vertical in this instance]

2.4.2 The Polarimeter

The **'Polarimeter'** is an instrument being used exclusively to determine the *direction* and *degree of rotation of the plane-polarized light* as it passes *via* a solution containing an ***optically-active*** **pure compound.**

* That is, the same would also be true for the ensuing magnetic field.

** Besides, the **'magnetic field'** remains **perpendicular (⊥)** to it.

Figure 2.5 explicitly depicts the schematic representation of a **polarimeter** indicating its various vital components.

The 'Polarimeter' essentially consists of the following important parts, namely:

- **Source of Light** : It comprises ***two*** **lenses** [*viz.*, ***Polaroid*** or ***Nicol***].
- **Sample Tube** : It is located between the lenses, a tube to hold the **analyte sample** that is being subjected to examination for its ***'optical activity'***.
- **Polarizer and Analyzer** : All these aforesaid components are arranged in such a manner so as to *allow the passage of the light via one of the lenses* (***polarizer***), followed by the **sample tube**, the second lens (***analyzer***), and reaches our 'eye' ultimately.

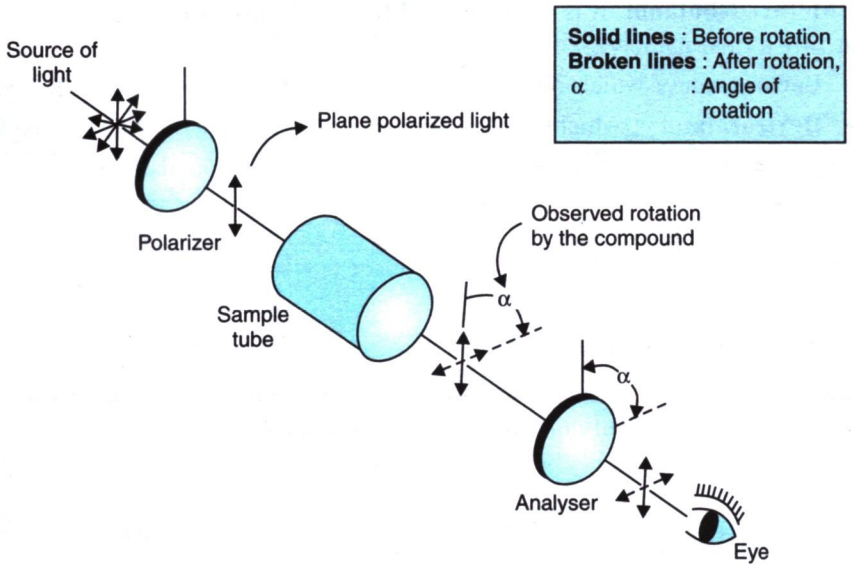


Fig. 2.5: The schematic representation of a polarimeter

***Modus Operandi*:** The various steps involved are as follows:

1. Place the **'analyte sample'** to be tested in the **sample tube.**

2. If the substance *rotates the plane of polarization,* the lens positioned nearer to the **'eye'** (*i.e.,* **analyzer**) should be **rotated to conform with the new plane**; and now if the resulting ***'light transmission attains a maximum value'***—the *analyte sample* is certainly regarded to be **optically active.**

3. At this point in time, one may encounter the following *two* situations, such as:

- In case, the actual *rotation of the plane*; and subsequently, the rotation of the **lens** (*analyzer*) is moved towards the **right-hand side** (*i.e., clockwise*)—the **analyte** is **dextrorotatory** [**Latin:** *dexter*-right]; and
- In case, the observed critical *rotation of the plane* is **left-hand side** (*i.e., anti-clockwise*) the **analyte** is **levorotatory** [**Latin:** *laevus*-left].

NOTE: 1. **Thus, one may virtually determine these *two* vital aspects, namely:**

- **the extent to which the *analyte* has rotated the plane and in which direction (*i.e.*, right or left); and**
- **also precisely to the actual degree.**

2. **In fact, the *extent of rotation* implies simply the number of degrees that one should *rotate the lens (analyzer)* to conform to the light.**
3. **There are *two* symbols *viz.*, (+) and (–) that are being employed commonly so as to indicate the *observed rotations* to:**
   - **the *right* (dextrorotatory), and**
   - **the *left* (levorotatory) respectively.**

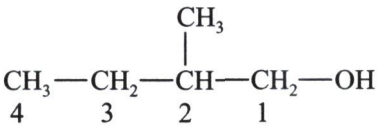
Examples: Following are *two* typical examples:

(*i*) **2-Methyl-1-butanol:** It is duly obtained from the **'fused oil'*** that predominantly occurs in *two* forms, namely:

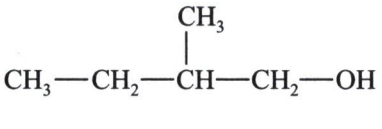
➢ **Levorotatory:** which rotates the *plane of polarized light* to the **'left'**; and

➢ **Dextrorotatory:** which rotates the *plane of polarized light* to the **'right'.**

Thus, we may express these *two* optically active compounds as:

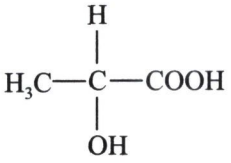


and

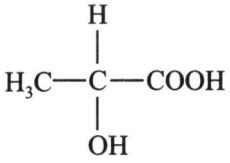


(–)-2-Methyl-1-butanol **(+)-2-Methyl-1-butanol**

(*ii*) **Lactic Acid:** It is obtained usually by the extraction from the **muscle tissues**, and has the following *two* configurations as **optical isomers:**



and



(–)-Lactic acid **(+)-Lactic acid**

2.4.3 Specific Rotation

The **'specific rotation'** refers to the observed optical rotation of a compound duly corrected for such critical and specific parameters, such as:

- **Concentration** • **Temperature** • **Wavelength of light and** • **Specific solvent.**

Alternatively, the **specific rotation** relates to the precise and exact number of degrees of rotation observed duly if a **1-dm (10 cm) sample tube** is used; and the *analyte sample* being examined is present to the extent of **1 g.mL^{-1}** (or **1000 mg.mL^{-1}**). It is usually designated as **[α]** and may be calculated from the respective observations (with *sample tubes* of other lengths) and using *different concentrations* by means of the following relationship:

* That is, a by-product obtained from the fermentation of **starch to ethanol.**

$$[\alpha]_{\lambda}^{t} = \frac{\alpha \times 100}{l \times c} \qquad \ldots(a)$$

i.e., $$\text{Specific rotation} = \frac{\text{Observed rotation (Degrees)}}{\text{Length } (dm) \times \text{Concentration (g / 100 mL)}}$$

We may also express **Eqn. (*a*)** as in **Eqn. (*b*):**

$$[\alpha]_{\lambda}^{t} = \frac{\alpha}{l \times d} \qquad \ldots(b)$$

where, t = Temperature measurement in °C;
λ = Wavelength of polarized light;*
α = Observed angle of rotation in degrees;
l = Sample thickness in decimetre;
d = Density of pure liquid ($g.mL^{-1}$); and
c = Concentration (g per 100 mL)

NOTE: **The specific rotation $[\alpha]_{\lambda}^{t}$ represents as much a property of a chemical entity (compound) as its mp, bp, density, or refractive index (RI).**

Example: Specific rotation of 2-methyl-1-butanol derived from the '*fused oil*' is found to be:

$$[\alpha]_{D}^{20} = -5.90°$$

[Temperature: 20°C; and D designates the wavelength of light used in the measurement (D line of Na: 5893 Å)]

2.4.4 Genesis of Optical Activity

In a broader perspective, most compounds do not actually capable of rotating the so-called **'plane of polarized light'.** Besides, the **'optically active viable chemical entities'** are invariably found in practically *all class of compounds.* Therefore, to observe critically the **specific structural features** that would ultimately give rise to the ensuing **'optical activity'** one may have to examine rather more intensely the particular situation when a **'polarized light'** is made to pass across an *analyte sample* of a **simple pure organic substance.**

Interestingly, a **beam of polarized light** on being passed *via* an individual molecule, one could visualize in each and every instance its plane undergoes rotation even to a *tiny extent* due to the possible interaction with the **charged particles of the organic molecule.** Thus, the *direction* as well as the *degree of rotation* varies with the specific orientation of the ensuing molecule in the beam.

Points to Ponder

- Since the overall random distribution of the large number of molecules which critically comprise even the:
  - **smallest sample of an individual pure chemical entity (compound);** and
  - **each and every molecule being encountered by the light,**

  there prevails another (almost similar) molecule predominantly oriented–***'as the mirror image of the first'***, that precisely cancels its effect. Hence, the *net result* is **total absence of rotation** (*i.e.,* the observed **'optical inactivity'**).

* Usually, sodium D-Line (5893Å)

- Obviously, the **'optical activity'** relates to the property not of individual molecules, but certainly associated with the **"random distribution of molecules which may serve as mirror images of each other perceptively."**
- The virtual requirement of **'optical inactivity'**—being that one particular molecule of a compound necessarily serves as the mirror image of another molecule.
- Nevertheless, in a **pure sample of a *single enantiomer***, no molecule could ever serve as the mirror image of another *i.e.*, **no exact canceling out of the rotations,** thereby the net overall result is **'optical activity'.**

NOTE: **Therefore, the same *non-superimposibility* of mirror images which specifically causes *enantiomerism*—may also be responsible for the ensuing '*optical activity*'.**

2.5 VARIOUS RECOGNIZED PROJECTION STRUCTURES OF STEREOISOMERS

In usual practice, it is not so convenient and easy to designate properly the so-called ***3D-molecules*** either:

- **on a paper,** or
- **on a board.**

Perhaps, that is why a plethora of **2D-formulae** have been duly studied and developed to represent the various molecules having the ***3D-structures.***

Following are the ***four*** **recognized projection structures of stereoisomers,** namely:

- **Fischer's Projection of Enantiomers,**
- **Flying-wedge Representation,**
- **Sawhorse Projection,** and
- **Newman Projection Formula,**

which shall now be discussed with example in the sections that follows:

2.5.1 Fischer's Projection of Enantiomers

The **Fischer's* projection** refers to—*'a specific projection formula in which the vertically drawn bonds are considered to lie very much beneath the projection plane and the respective horizontal bands to lie over that plane'.*

Importantly, this kind of a meaningful representation is invariably done for a ***chiral*** **(asymmetric) C-atom exclusively.**

Assumptions Presumed: These essentially comprise:

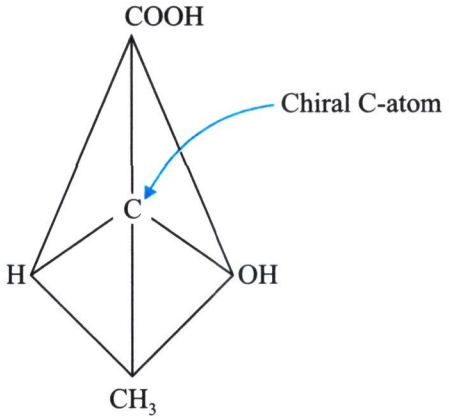
1. The particular ***chiral*** **C-atom** is usually assumed to lie in the *plane of the paper* or *the board.*
2. The inherent **4 C-bonds** are invariably depicted by:
   - ***two*** **vertical straight lines**, and
   - ***two*** **horizontal straight lines.**

Fischer Emil (1852–1919):** a *German chemist,* who received the ***second **Nobel Prize** (in 1902) in **chemistry** for his commendable work on **sugars and purine synthesis.**

3. The precise and exact point of intersection of the aforesaid ***two*** **straight lines** is normally accepted and recognised as the **chiral C-atom.**
4. Importantly, one may prominently visualize the critical presence of the following characteristic features, namely:
   - ➢ *Two* vertical bonds do actually project just beneath the plane of the paper (or board), and
   - ➢ *Two* horizontal lines usually project above the plane.

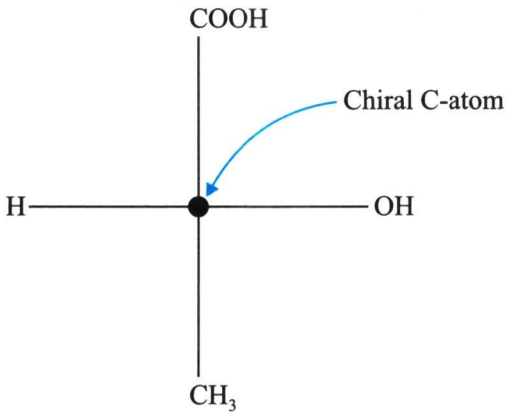
Example: The above statement of facts and conceived thoughts may be exemplified explicitly by the help of the following ***two*** **formulae,** such as:

- **Tetrahedral Formula** **and** - **Fischer's Projection Formula**



Tetrahedral formula

Points to Note
• **Chiral C-atom** (asymmetric C-atom) lies in the plane of paper/board;
• **Carboxyl (—COOH) and methyl ($—CH_3$)** moieties project below the plane of paper/board; and
• **Hydroxyl (—OH)** group project above the plane of the paper/board.



Fischer's Projection Formula

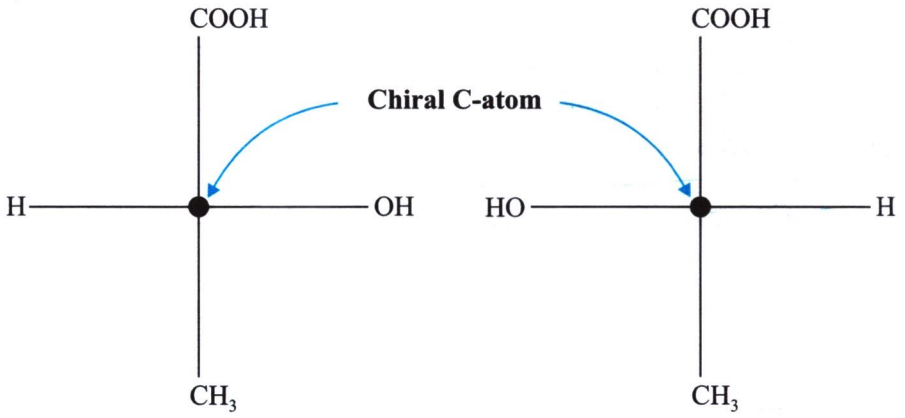
Points to Note
• All the **4-bonds** are depicted by *2-vertical* and *2-horizontal* straight lines.
• Point of *'intersection'* of the 2-straight lines is designated as the **chiral C-atom.**

Comparison between 2-Fischer's Formulae: In order to have a meaningful comparison between the **2-Fischer's formulae** one may take cognizance of the following *two* critical aspects, namely:

- ➢ **allowing the '*rotation*' of the structures in the plane of the paper;** and
- ➢ **permitting the '*sliding*' of the structures in the plane of the paper,**

with a specific restriction imposed that '*no bond*' may be lifted from the plane of the paper.

Example: Enantiomers of Lactic Acid: Serves as a typical example to expatiate the above ideology and concept promulgated: Thus, we may express the ***two*** **Fischer's projection formulae** for the **enantiomers of lactic acid:**



Enantiomers of Lactic Acid

Comment: The above *two* structures of **'lactic acid'** are ***not superimposable*** on each other: provided no bond is permitted to be lifted from the plane of the paper. Therefore, one may safely conclude and infer that these two are **'stereoisomers'.***

NOTES:

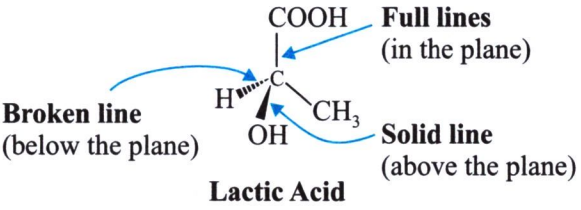
1. **As a '*guiding rule*', the critical exchange of the *two* moieties in the *Fischer's formula* by *odd number of times* gives rise to the respective structure of the '*enantiomer*'.**
2. **However, the crucial exchange of *two* moieties by even number of times fails to *alter the underlying configuration* perceptively.**

2.5.2 Flying-Wedge Representation

In the **flying-wedge formula**, the *two* prevalent bonds located strategically at the **chiral C-atom** are usually shown in the plane of the paper by ***full lines***; whereas, the rest of the *two* bonds are duly present as follows:

- ***first*—shown above the plane of the paper or board by a *solid line*; and**
- ***second*—shown below the plane of the paper (or board) by a *broken line.***

These may be represented explicitly as given under:



Lactic Acid

Remarks: Incidentally, the *flying-wedge representation* invariably occurs in both:

- **Chiral atoms** **and** **Achiral C-atoms**

* That is when 2-molecules do have the same exact numbers and kinds of atoms that are duly bonded to each other in the same order but do differ in the ***bonds orientation in space.***

Salient Features: These essentially include:

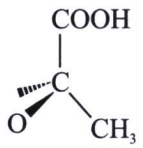
1. In the aforesaid **flying-wedge formula** the *2-full lines* are drawn very much akin to the ***vertical lines*** in the **Fischer's Formula** (see Section 2.5.1).

2. Remaining 2-moieties [*viz.*, hydroxyl (—OH) and H-atom] are duly positioned in the **horizontal lines.**

3. Now, if the ***lower moiety*** with a *full line* present in the **flying-wedge formula** is bent to the ***right-side***, the requisite moiety duly held by the *solid line* is placed on the ***right side*** of the *horizontal line* of the **Fischer's Formula.**

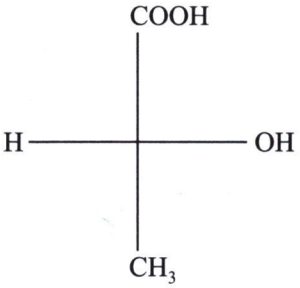
4. Likewise, if it is bent to the left, the functional group duly held by the *solid line* is shown to the *left side* of the *horizontal line* of the **Fischer's Formula.**

Thus, we may have a virtual comparison of both **flying-wedge formula** and **Fischer's Formula** simultaneously as given under:



Flying-wedge formula

The lower functional moity ($-CH_3$) duly held by the *full line* is bent to the *right side*



Fisher's formula

The functional group held by the *solid line* in the **flying-wedge** *formula* is shown on the *right-side* of the **fischer's formula**

2.5.3 Sawhorse Projection

In order to understand vividly the **Sawhorse projection** we may have to fully understand the so-called **'conformational analysis'.**

It is a known fact that the *functional groups* bonded solely by a ***sigma (σ) bond*** (*i.e.*, by a **single bond**) may eventually undergo critical rotation around the said bond with respect to each other. As a result, the *temporary molecular shapes* which emerge due to the **rotation of groups about the *single bonds*** are termed as *conformations of a molecule*; whereas, each possible structure is known as a **'conformer'**. Therefore, the ultimate analysis of the ensuing *energy changes* associated with a molecule involved in the phenomenon of *rotation around single bonds* is invariably called **conformational analysis.**

The **Sawhorse formulae** are very much akin to the ***dash-wedge-3D formulae*** we have examined so far, as shown in the following example of **'ethane':**



Sawhorse formula

In usual practice, whenever a dire need necessity comes into being to know precisely the crucial ***'spatial relationship'*** existing between any **2-adjacent C-atoms** present either:

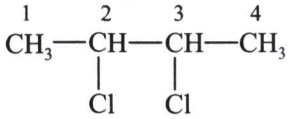
- **as a *chiral* form**, or
- **as an *achiral* form,**

the **Sawhorse projection** seems to be appearing extremely convenient and gainful.

Importantly, in the **Sawhorse projection,** the so-called *2-key-C-atoms* are specifically linked by a **diagonal line** very much in the **plane of the paper (or the board).** However, the rest of the *'bonds'* are duly displayed by rather **smaller lines** projected distinctly both **above and below the plane of the paper (or the board).** Besides, one may predominantly observe the **'free rotation'** around the diagonal line either:

- **in *'clockwise'* state**; or
- **in *'anticlockwise'*** state.

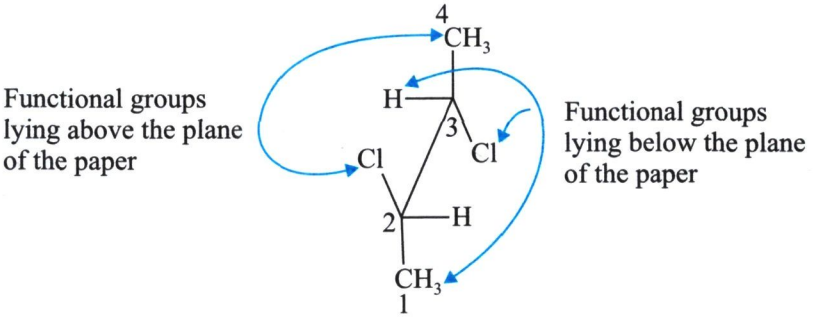
Classical Example: Let us examine the following example of **2, 3-dichloro butane:**



C-2 and C-3 designate as the *'key atoms'* in this molecule.

2,3-Dichloro butane

The **Sawhorse formula** of **2, 3-dichloro butane** may be written as given under:



Sawhorse formula of 2,3-dichloro butane

EXPLANATION

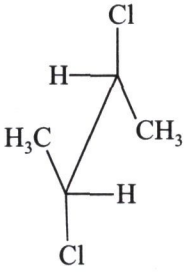
The above configuration of **Sawhorse formula** for 2, 3-dichloro butane may be explained as under:

1. In the aforesaid molecule the ***two* key atoms are C-2 and C-3** respectively (*i.e.,* the C-atoms to which the chloro-groups are duly attached).

2. Therefore, looking along ***C-2, C-3* σ-bond** and then *drawing the respective diagonal in the plane of the paper* (*or the board*), the resulting **Sawhorse structure** may be written as given above.

3. Importantly, *three* different situations arise, namely:

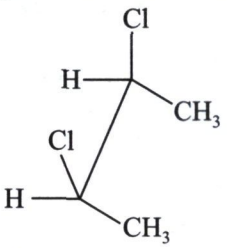
(*a*) Staggered sawhorse formula (θ = 180°) as given below; in



Dihedral angle θ between Cl-atoms = 180°

which the so-called **bulky atoms or groups** (*Cl-atoms* in the case shown above) critically make a ***dihedral angle θ = 180°***. Hence, such a **Sawhorse conformation** of a compound is usually termed as the **staggered conformation.**

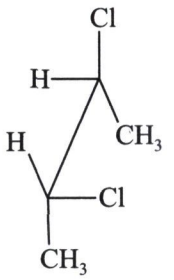
(*b*) Eclipsed Sawhorse formula (θ = 0°): as given under; in



Dihedral angle θ between Cl-atoms = 0°

which the ensuing **free rotation** along the **diagonal *C-2–C-3*** is permissible, other conformations of the compound are also feasible. Here, the **dihedral angle θ** between the **2 Cl-atoms** is equal to 0°, it is called the **eclipsed Sawhorse formula.**

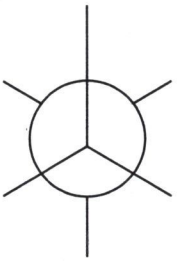
(*c*) Partially eclipsed Sawhorse formula (θ = 120°): as depicted under; in which **θ is equal to 120°** (*i.e.,* the **dihedral angle θ** between the *2 Cl-atoms* is 120°), it is termed as the **partially eclipsed Sawhorse formula.**



Dihedral angle θ between Cl-atoms = 120°

2.5.4 Newman Projection Formula

So far we have seen that the **Sawhorse formulae** are very much akin to the respective—**'dash-wedge-3D-formulae'.** Therefore, in the *conformational analyses* one may make a substantial utilisation of the so-called **Newman projections.** Thus, we may have:



Newman Projection Formula

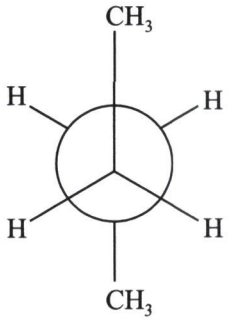
Importantly, in this projection, it is a common practice to visualize the molecule critically along the bond that eventually holds the **2 *key* C-atoms** of the said molecule firmly that could either be ***'chiral'*** or ***'achiral'***; and above all, these atoms are duly represented explicitly as the ***superimposed circles.***

Thus, only **'one circle'** is drawn carefully at the *centre of which* designates prominently the so-called ***front* C-atom**; whereas, the *circumference of the circle* particularly represents the ***rear* C-atom.**

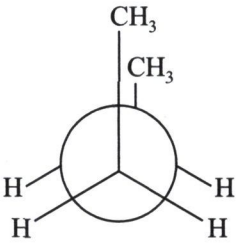
Remarks: In the above **Newman projection formula,** one may observe predominantly that:

- **3 σ-bonds belonging to the *front* C-atom are duly depicted by *3-small lines* drawn right from the *centre of the circle,* thereby giving rise to an angle of *120° with one another;* and**
- **3 σ-bonds of the *rear* C-atom are drawn respectively right from the circumference of the circle.**

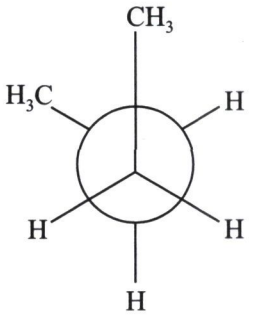
Examples: Following are the *four* distinct possible **conformations** of '***n-butane***', such as:



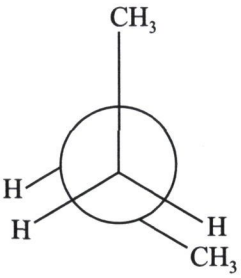
(*a*) Staggered *n*-Butane



(*b*) Eclipsed *n*-Butane



(*c*) Gauche [or Skewed *n*-Butane]



(*d*) Partially eclipsed *n*-Butane

Interconversion of Projection Formulae

Based on the logical and scientific evidences one may lay hands on to certain altogether ***different*** **projection formulae** that may be eventually subjected to *interconversion* by means of some simplified sequential steps.

Examples: The *two* classical examples are as stated under:

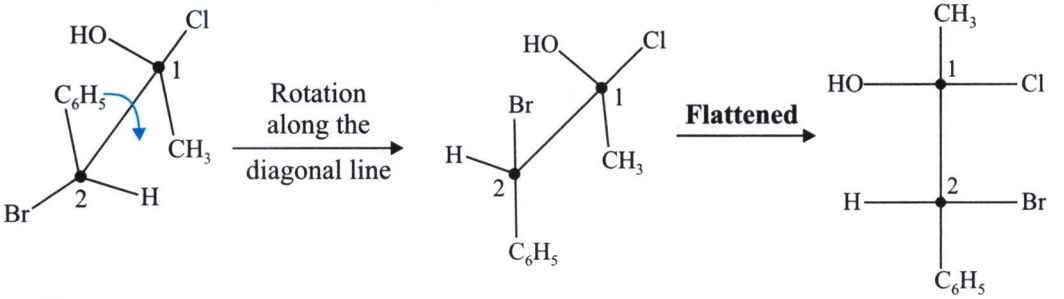
(*i*) Interconversion of Sawhorse Formula to a Fischer's Formula

It essentially involves *three steps:*

Step 1: In this case, the ***front*** **C-atom** in the *Sawhorse formula* is regarded to be the lowest **chiral C-atom** in the respective **Fischer's formula.**

Step 2: Here, the given **Sawhorse conformation** is duly converted to an **eclipsed sawhorse conformation** by critical rotation very much along the *diagonal line* up to the *least number of degrees.*

Step 3: Finally, the resulting **eclipsed Sawhorse conformation**, as obtained in ***step-2*** above, is now flattened to get the desired **Fischer's projection formula,** as illustrated below:



1-Methyl-1-hydroxy-2-bromo-2-phenyl ethyl chloride | **Eclipsed Sawhorse formula** | **Fischer's projection formula**

(ii)* Interconversion of *Fischer's Formula* to a *Sawhorse Formula

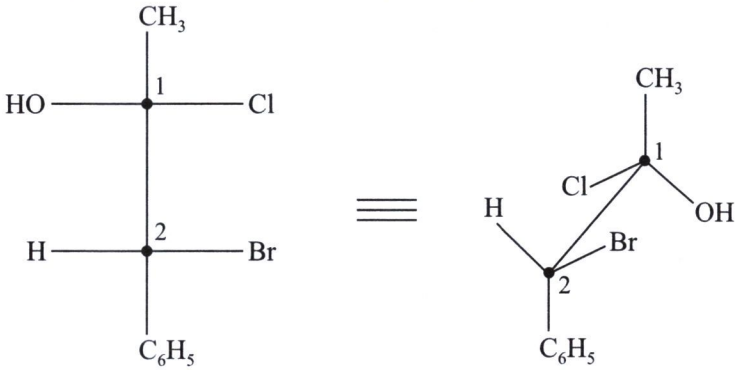
Likewise, we may also carry out the interconversion of a **Fischer's formula** to a **Sawhorse formula** by the aid of the following *two* vital and simplified steps, namely:

Step 1: In this particular instance, the strategically located ***lowest chiral C-atom*** of the **Fischer's formula** undergoes interconversion to the corresponding ***front C-atom*** of the **Sawhorse formula.**

Step 2: All the functional moieties present in the so-called **Fischer's formula** which are drawn critically both in:

- ***anti*-orientation** or - ***trans*-orientation**

with respect to each other are eventually drawn on the **same side of the *diagonal line*** in the respective **Sawhorse formula,** as depicted below:



Fischer's formula | **Sawhorse formula**

Determination of Actual Number of Optical Isomers

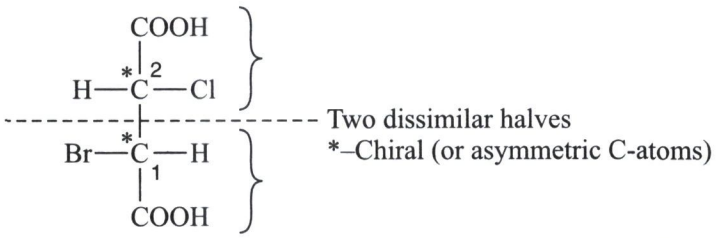
The exact determination of the possible number of ***optical isomers*** for a **'given compound'** may be duly established based upon the precise number of the ***chiral* C-atoms (*n*)** that are present in the *molecule itself.*

Nevertheless, the above objectives may be adequately determined by examining specifically the following *three* **typical examples.**

Example 1: When a particular chemical entity (or compound) essentially comprises '*n*' number of distinctly *different substituted chiral C-atoms*, and that may not be divisible precisely into either *two* equal halves or *two* same halves, then we may have:

- **Number of *Optically Active Forms* = 2^n**
- **Number of *Optically Inactive Forms* = 0**

Solution: Let us take into consideration the typical example of a **compound 'A'** [1-bromo-2-chloro-2-carboxy propionic acid (a *dicarboxylic acid*)] having *two* differently substituted *chiral* C-atoms:



Thus, in the above instance, $n = 2$; and, therefore, the Number of Optical Isomers = $2^n = 2^2 = \mathbf{4}$.

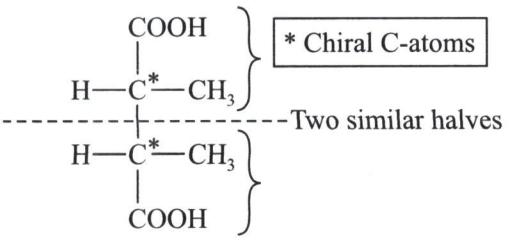
Total number of Stereoisomers = 4 + 0 = **4.**

Example 2: In case, a specific compound contains an *even number of chiral C-atoms (n)*; and the said molecule may be divided into 2 equal and 2 same halves by means of an axis that possess *via* the middle of the compound. In such a typical instance, we may have:

Number of *Optical Isomers* = $2^{(n-1)}$

Number of Optically *Inactive Forms* = $n^{(n-2)/2}$

Solution: The compound **ethane-1, 2-dimethyl-1, 2-dicarboxylate** possesses ***2 chiral C-atoms*** (*i.e.*, '*n*' is *even number*) that are substituted similarly as shown under:



Ethane-1, 2-dimethyl-1, 2-dicarboxylate

Hence, we may have:

(Since there are 2-chiral C-atoms) $n = 2$

Number of *'optically active'* isomers (or forms) $= 2^{(2-1)} = 2$

Number of *'optically inactive'* forms $= 2^{(n-2)/2} = 2^{(0)/2} = 0$

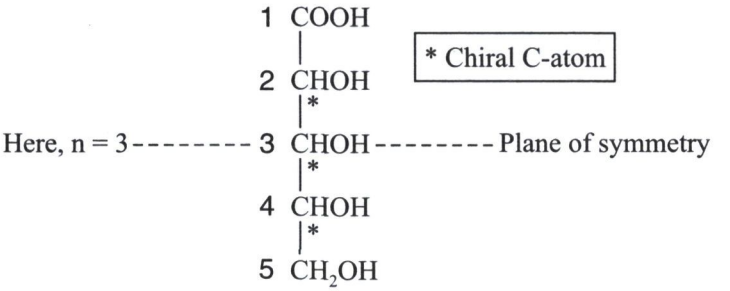
Total number of *'stereoisomers'* $= 2 + 1 = \mathbf{3}$

Example 3: **In another instance, when a compound comprises *odd number of chiral C-atoms* (*n*) and the molecule may be divided into exactly *2 equal halves* or *2 same halves,* then in such a case we have:**

$$\text{Number of 'optically active' forms (or isomers)} = 2^{(n-1)} = 2^{(n-1)/2}$$

$$\text{Number of 'optically inactive forms'} = 2^{(n-1)/2}$$

Solution: Let us consider the typical example of a compound ***viz.,*** **tetrahydroxybutane carboxylate.**



Interestingly, the **middle C-atom** is *not asymetric* in nature; whereas, the ensuing configurations about **2nd** and **4th C-atoms** are either **'R'** or **'S'**, but is certainly found to be **asymmetric** when one of them is **'R'** and the other is **'S'.**

Therefore, in such a typical instance the **3rd (or middle C-atom)** is invariably called as the ***'pseudoasymmetric carbon.'*** Thus, we may have:

$$\text{Number of } \textit{'optically active'} \text{ isomers (or forms)} = 2^{(3-1)} - 2^{(3-1)/2}$$

$$= 2^2 - 2 = 4 - 2 = 2$$

$$\text{Number of } \textit{'optically inactive'} \text{ isomers (or forms)} = 2$$

$$\text{Number of 'geometrical isomers'} = 0$$

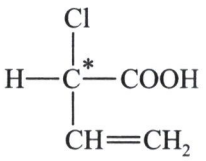
$$\text{Total number of } \textit{'stereoisomers'} = 2 + 0 + 2 = 4$$

Possibility of Obtaining Both Optical and Geometrical Isomers

Importantly, in a critical situation when the so-called **chiral C-atoms** are duly present in a *molecule* in addition to an **olefinic (double) bond** or a **ring-residue,** one may clearly observe the presence of both **optical and geometrical isomers** explicitly. Besides, there are *two* further important conditionalities, namely:

(*a*) When the **chiral C-atom** specifically coincides with the ensuing ***terminals*** that are responsible for the **'geometric isomerism',** then the total **number of 'stereoisomers'** are very much *equal* to the **number of 'optical isomers'.**

Example:



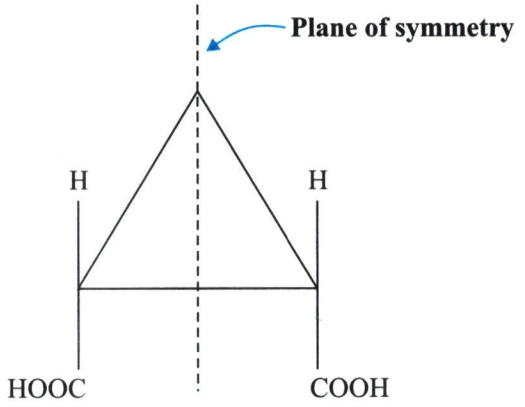
Monochloro ethylene acetic acid

The chiral C-atom (*) is located strategically away from the terminals of olefinic bond; and hence, the number of stereoisomers is double.

NOTE: **Since, the aforesaid compound has both *chiral C-atom* and *olefinic (double) bond*; hence, there prevails the possibility of having both the *'optical'* and *'geometrical'* isomerism.**

(*b*) When the **chiral C-atom** is positioned away from the ***terminals*** that are solely responsible for causing the **'geometrical isomerism'**, then the total number of the ensuing **stereoisomers** are found to be almost **double** the number of the respective **'optical isomers'.**

Example: Let us consider the compound **1, 2-cyclopropane dicarboxylic acid** which essentially contains **2 chiral C-atoms ($n = 2$)**; and hence, may be divided into ***two*** **equal halves** by means of a ***'plane of symmetry'.*** Thus, the resulting **'ring structure'** of the chemical entities associated intimately with the so-called *restricted rotation* allows the emergence of **'geometrical isomerism'** feasible and possible.



1,2-Cyclopropane dicarboxylic acid

2.6 SIMPLE MOLECULES: HYBRIDIZATION, CONFORMATION AND CONFIGURATION

Preamble: Let us consider the ***simplest*** **organic molecule methane (CH_4)** and with particular reference to its:

- **geometry,**
- **2D-representation,** and
- **make-up from the various component atoms.**

Thus, we have in **methane (CH_4)** the following typical features:

➢ **All 4 C—H bonds are equivalent,**

➢ **These bonds are directed toward the corners of a *regular tetrahedron* having the C-atom seated at the centre, and**

➢ **Bond angles [H—C—H] are all *109°.28*.***

Figure 2.6 illustrates the bond formation in CH_4 molecule thereby showing *three* cardinal aspects: (*a*) tetrahedral sp^3 orbitals; (*b*) predicted shape : H nuclei located strategically for maximum overlap; and (*c*) shape and size.

*That is, a value which is found solely in such molecules having a 'tetrahedral' geometry.

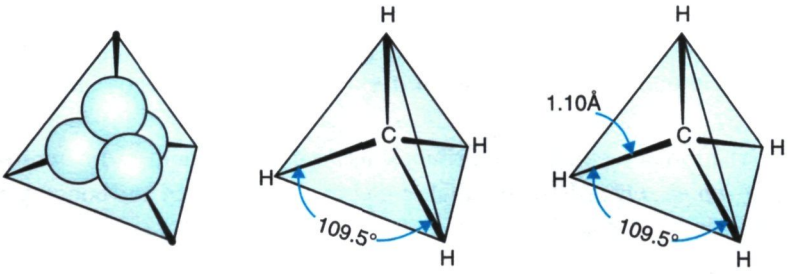


Fig. 2.6 The formation of bond in Methane (CH_4) Molecule: (*a*) Tetrahedral sp^3 orbitals; (*b*) Predicted shape: H nuclei located for maximum overlap; and (*c*) Shape and size.

In true sense, the normal illustration of **methane (CH_4),** as given in Fig. 2.6, and the usual convention that is being applied in a general perspective, relates to the respective representation of **3D-molecules** in **2D-structures.** Therefore, in this scenario we may take cognizance of the following critical and important criteria, such as:

- The *'central C-atom'* is assumed to lie in the plane of the paper along with any 2H-atoms,
- Invariably, these are the *upper* and *left* H-atoms,
- Lines of **'normal thickness'** do designate the bonds that are located between each of these **2 H-atoms** and **C-atom,**
- *Thick 'wedge'* actually represents a bond existing between **'C'** and **'H'** located in **front of the page,** and
- *Dotted lin*e indicated a bond located between **'C'** and **'H' behind the page.**

2.6.1 Hybridization

Hybridisation refers to the phenomenon whereby the *lower energy orbital electrons* are slightly elevated at higher levels; and hence, the corresponding *higher-energy electrons* do assume critically a *lower level* thereby producing an altogether *new energy level* for all electrons that are involved in the shifts *viz.,* the ***'tetravalency'*** **of C-atom.**

Variants in Hybridisation: The phenomenon of **'Hybridisation'** occurs predominantly in a variety of *organic compounds*, namely:

- **Methane,**
- **Ethene and Alkenes,** and
- **Ethyne**

which shall now be treated individually in the sections that follows:

2.6.1.1 Hybridisation: Methane

Interestingly, as and when a **'bond'** is duly established between a **C and H atoms,** one may critically observe these ***two*** **important sequences,** namely:

- **distribution pattern in the orbitals gets disturbed largely,** and
- ***two*** **atomic orbitals which usually contain an *electron each* do become overlapped.**

Bivalency for C-atom: In the particular instance of **methane (CH_4)**, a simple molecule, how one may reconcile the so-called **4 C—H** bonds in it having the outer shell electron configuration, $2s^2 2p^2$, of the **C-atom** specifically in the **'ground state'**—that vehemently indicates the **bivalency for C-atom.**

Furthermore, **H-atom** essentially contributes its **one electron** in a **1*s* orbital**; whereas, the **C-atom** possesses *4 atomic orbitals* with suitable *energy level* utilized for bonding process. In fact, these **4 atomic orbitals** do consist of:

- ***one* 2*s* orbital,** and
- ***three* 2*p* orbitals,**

that are duly designated as $2p_x$, $2p_y$ and $2p_z$—as per their different projections in space *x*, *y* and *z*.*

Salient Features: These essentially include:

1. **The status of 2*s*-orbital** is found to be **spherically symmetrical.** Besides, its **'electron density'** is determined to be the **highest at the nucleus.**

2. **The status of 2*p*-orbital** is established to be **cylindrically symmetrical.** In addition, in contrast to its respective **2*s*-counterpart**, possesses **'zero' electron density** at the nucleus. Thus, in case, ***one* 2*s*** and ***three* 2*p* orbitals,** were duly utilized without the ensuing modification(s) in *bonding formats four* **equivalent covalent bonds** would not ever occurred in the **methane (CH_4) molecules.**

3. **Status at a slightly elevated energy state of C-atom:** is being duly expatiated by the ensuing *electron configuration* $\mathbf{1s^2 2s^1 2p^3}$. Pauling (1930–35) suggested strongly that the prevailing ***four* L-shell** orbitals (*viz.*, 2*s*, $2p_x$, $2p_y$, $2p_z$ with one electron each) available in an *'excited state'* be mixed together *first;* and subsequently, split up into set of **4-equivalent *hybrid orbitals*,** as illustrated in Fig. 2.7, wherein it has been pronouncedly designated as 'sp^3'—a well-known phenomenon invariably known as **'Hybridisation'.** Fig. 2.7 shows the exclusive ***four* equivalent sp^3 orbitals in methane (CH_4)** representing the phenomenon of Hybridisation.

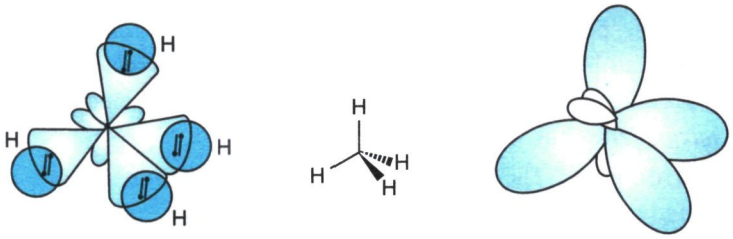


Fig. 2.7: Representation of four equivalent sp^3 orbitals in methane (CH_4) indicating Hybridisation.

Observations: These essentially comprise:

1. In Fig. 2.7, the **4-hybrid orbitals,** under ideal parameters, are critically directed towards the *4 corners* of a **regular tetrahedron.**
2. However, the *C-atom* in **methane** as well as the so-called *'saturated C'* present in most other organic chemical molecules the ensuing ***Hybridisation* process** is described as sp^3.
3. The resulting **'orbitals'** do possess certain inherent characteristic features of the ***component* atomic orbitals.**

* That is, referring to the respective directions of a **Cartesian coordinate system.**

4. Thus, we may have:
   - an sp^3 **orbital** with infinite density of charge located strategically at the *nucleus*, and
   - very much akin to the *2s* (but not the *2p*) orbital exclusively.
5. It possesses **directionality** in common with the **2*p* orbitals,** having the **lobes of unequal dimension.**
6. The observed ***H—C—H*** **bond angles** present in the *methane* molecule are such so that the *H-atoms* could be positioned as far apart as possible.
7. Amazingly, the *same* **bond angles,** as could be seen in the **tetrafluoromethane (CF_4)**—are indeed larger to some extent *e.g.,* **propane (C_3H_8)** having a **bond angle 112°.**

2.6.1.2 Hybridisation: Ethene and Alkenes

Obviously, the logical explanation and evidential analysis pertaining to the ***'geometry of* methane'** fails to justify the *hybridisation phenomenon* encountered **in ethene (C_2H_4)**—that essentially comprises ***2 equivalent C-atoms.*** Importantly, the critical and specific **electron diffraction data**, it has been duly established that **ethene (C_2H_4)** is proved to be an almost **'flat molecule'** having the following *two* cardinal characteristics, namely:

- **all the six atoms (*viz,* 2 C-atom + 4 H-atoms) do lie in a plane, and**
- **bond angles determined to be 120°.**

Rationalisation of Bonding Pattern in Ethene (C_2H_4): It is, however, pertinent to state here that the *bonding pattern in ethene* may be duly rationalized by making use of the **same orbitals**, such as:

- **1-2*s* orbital,** and
- **3-2*p* orbitals ($2p_x$, $2p_y$, $2p_z$).**

Importantly, it shows a distinct difference which critically relates to one of the existing **2*p* orbitals** that never take part actively in the **process of hybridisation.** Consequently, the overall ***'net result'*** elegantly reveals that there are ***three* sp^2 hybrid orbitals in the ethene molecules** plus one separate *p*-orbital per C-atom.

The above observations and findings may be extended to the following aspects overwhelmingly:

- ➢ Presence of an array of appreciable differences with regard to bonding in **ethene *vis-a-vis* methane;**
- ➢ **sp^2-Hybrid orbitals** in *ethene* as well as *all akenes* do possess a major percentage of the **'*s*' character**; and hence, the electrons remain quite closer to the **C-nucleus;**
- ➢ Besides, the respective alteration in the **hybridisation pattern** brings forth a significant change of the **bond angle;**
- ➢ Both in **ethene** and around the **sp^2-hybrid C-atoms** of the *alkenes* the ensuing **bond angles** stand at **120°**—that eventually gives rise to the so-called a **flat-structure;** and
- ➢ Ultimately, the prevalent **'geometrical structural arrangement'** indicates explicitly that the various substituents located strategically around the *alkene C-atoms* usually are as far away from one another as deemed possible.*

* This feature also holds good for **methane** as well.

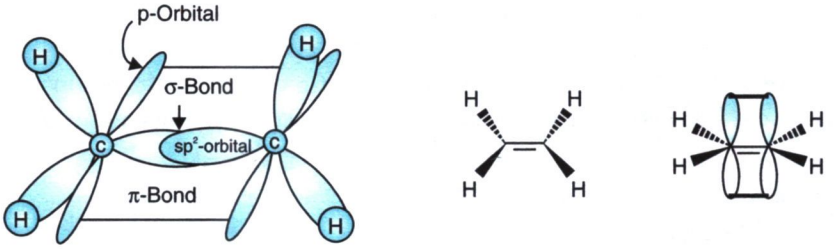
Formation of a π-Bond: Let us look into the fate of the ***p*-orbitals** that failed to take active role in the critical formation of ***sp*²-hybrid orbitals.** In fact, they do remain very much persistent as the ***p*-orbitals** wherein we have:

➢ **remain attached to one at each C-atom**; and

➢ **each *p*-orbital comprises one electron only.**

The combination of the above *two* forms a **'bond'**—usually known as the **'π-bond'** occurring prominently between the respective C-atoms (*i.e.,* the mode of overlap is found to **'sideways on'**).

Formation of a σ-Bond: The particular **'end-on-overlap'** that eventually gives rise to the formation of the **σ-bonds.** In the present foregoing discussion critically involves the so-called **'CH-bonds'** present both in **ethene** and **methane**, plus the other bond existing between the **'C—C bonds'** in ethene.



(*a*) (*b*) (*c*)

Fig. 2.8: (*a*) Orbital structure of Ethene; (*b*) Structure of Ethene; and (*c*) Structure of Ethene showing overlap of p-orbitals of 2 C-Atoms Forming π-Bond.

Figure 2.8 illustrates the ***sp*²-hybrid orbitals** showing **one C—C π bond** and **two C—H π bonds.**

Remarks: These essentially include:

1. The crucial presence of the **π-bond** predominantly refers to the characteristic features of an **'alkene'** which figure it out distinctly from the corresponding **'alkane'.**

2. The respective **π-bond** based upon its typical nature of its ***sideways overlap*** of the *constituent p-orbitals* is found to be definitely weaker than the **σ-bond.**

3. Besides, the inherent electrons of the **π-bond** are exposed duly both *above and below* the plane of the **'alkene'.** Furthermore, these *electrons* do serve as the **major source of reactivity** for the *alkene* towards the ***'electrophiles'*** in particular, such as:

'electrophilic addition of bromine'.

4. The **π-bond** present in **ethene** remains significantly strong so as to prevent the **rotation around the C—C sigma (σ) bond.** However, it endorses the well-established property of the so-called C—C bond present in **ethene.**

5. Bonding between ***sp*²-hybrid C-atoms** of an *alkene* essentially comprises **'1' σ-bond** and **'1' π-bond,** known collectively as the **double bond.**

2.6.1.3 Hybridisation: Ethyne

Let us take into consideration the **triple bond** (or **acetylene bond**) present in **ethylene**, as depicted in Fig. 2.9 (*a*), even though its ensuing *stereochemical significance* is confined significantly. As illustrated in Fig. 2.9 (*b*) the **C-atoms** in **ethylene molecule** critically make use of:

- ***one* σ-orbital,** and
- ***one* π-orbital,**

to give rise to the formation of *two* equivalent ***sp*-hybrid orbitals.** Thus, it predominantly leaves *two* so-called **unhybridized π-orbitals** [Fig. 2.9 (*b*)].

In this manner, the ***sp*-hybrid orbitals** are duly utilized to form the **σ-bonds:**

- ***one* to the other C-atom,** and
- ***one* to the H-atom.**

Furthermore, the ***p*-orbitals** located at each **C-atom** do eventually yield ***two* altogether separate and independent π-bonds**, which are located strategically at *right angles to each other* as may be viewed along the *axis* of the **ethyne molecule** [see Fig. 2.9 (*c*)]. In usual practice, such **π-bonds** are termed as ***'orthogonal'***. However, the 2 C-atoms are duly joined with a **triple bond** (or *acetylenic linkage*), that eventually causes a *further shortening of the usual bond length;* and therefore, an enhancement in the overall **'bond energy'.**

Remarks: In **nitriles** (—C≡N) the bonding is almost similar to the *triple bond* (as seen in *acetylene/ethyne*)—that is made up of **1 σ-bond** and **2 orthogonal π-bonds.**

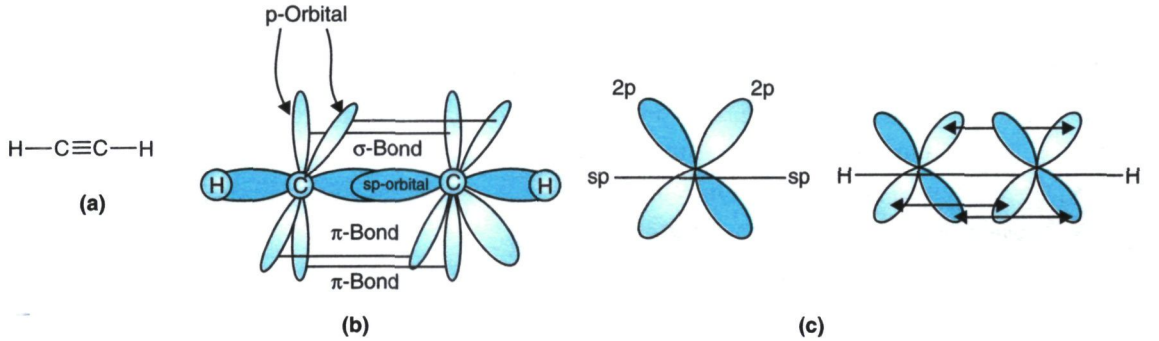


Fig. 2.9: (*a*) Structure of ethyne; (*b*) Orbital structure of ethyne, (*c*) View along the axis of the ethyne molecule.

There is an apparent increase in the *actual percentage* of the **'s' character** related to the particular ***C-hybrid orbitals*** invariably found along the series stated below:

- ***ethane*** [carbons sp^3, tetrahedral];
- ***ethene*** [carbons sp^2, trigonal]; and
- ***ethyne*** [carbons *sp*, linear].

It obviously implies a ***greater electron density*** profile located specifically at the **C-nucleus** as we move along the above series; and this is incomplete agreement with respect to the observed **shorter C—C bond lengths** in a progressive manner as could be seen in the following **average values:**

- **ethane** : 0.154 nm;
- **ethene** : 0.133 nm; and
- **ethyne** : 0.12 nm

NOTE: **Since the crucial presence of the *'radial distribution of the ensuing electron density'* the observed rotation around the *tripple bond* is expected to be absolutely 'free'. However, it never changes the so-called *'original shape of the molecule'* at all.**

2.6.2 Conformation

Preamble: The term **'conformation'** refers to the *spatial arrangements* of various atoms thereby affording the distinction between the **'stereoisomers'** which may be interconverted by rotations about the *single bonds* perceptively.

Following are the various important aspects of the phenomenon of **conformation**, such as:

- **Conformation: Ethane;**
- **Conformation: Butane;**
- ***Chair* Conformation: Cyclohexane;** and
- ***Boat* Conformation: Cyclohexane,**

which shall now be discussed individually in the sections that follows:

2.6.2.1 Conformation: Ethane

In order to expatiate the *dihedral angles* in **ethane (C_2H_6)**, one should make an attempt to define explicitly the ensuing relationship existing between:

- **C—H bonds on one C-atom,** and
- **those present on the other C-atom,**

and to accomplish this objective one may have to view the said molecule in a **Newman projection formula** (as described in *section 4.5.4*). In fact, the **Newman projection** refers to a kind of ***planar projection*** very much along *one specific bond*, that we usually term as the **'projected bond'.**

Figure 2.10 (*a*, *b* and *c*) provides an in-depth view of the **ethane molecule** within the **Newman projection** vividly along the **C—C bond.** Nevertheless, in this projection, one may visualise the **C—C bond** as the ***projected bond.*** In addition, the *Fig. 2.10* illustrates the so-called **Newman projection** (with *'θ'—as the dihedral angle*) that could be attained ***via* two distinct modalities,** such as:

- **ball-and-stick models,** and
- **line-and-wedge formulas.**

Part *'a'*: Ethane molecule being viewed from the end of the bond a person (viewer) wishes to project;

Part '*b*': Resulting end on view as depicted clearly; and

Part '*c*': Representation as the **Newman projection** in the plane of the page (or board).

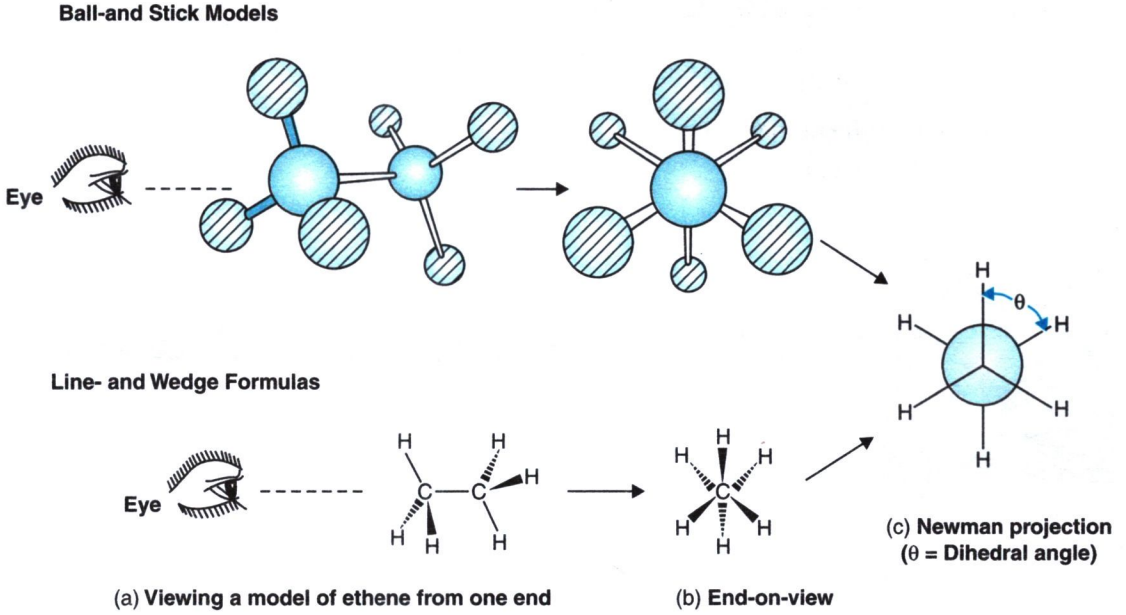


Fig. 2.10: (*a*, *b* and *c*): Representation of a Newman projection of ethane (C_2H_6) using: top—the Ball-and-stick models; and bottom—the Line- and Wedge formulas

Interestingly, in the so-called **Newman projection,** the bonds are usually drawn to the **centre of the circle** are attached to the very **C-atom** located closer to the observer; whereas, the bonds drawn specifically to the **periphery of the circle** (*dark*) are duly linked to the **C-atom** located further from the observer. However, the ***'projected bond'*** (*i.e.,* the *C—C bond*) is **almost hidden.**

Newman projection of ethane (*Fig: 2.10 c*): If one focuses attention upon the **Newman projection of 'ethane'** in the above cited *figure*, one would certainly observe that the ***three*** **C—H bonds** drawn right up to the *centre of the circle* do designate the **bonds to the front C-atom particularly.** Thus, the *three* **C—H bonds drawn to the** respective *periphery of the circle* represent the *bonds to the rear C-atom* specifically.

NOTE: **However, the *Newman projected* bond itself, that being the *fourth* bond attached to each C-atom is hidden.**

Points to Ponder: These essentially include:

1. **Newman projection of ethane** indeed helps to render it a lot easier and convenient to visualize the critical presence of the so-called **dihedral angles θ** existing between its inherent **C—H bonds.**

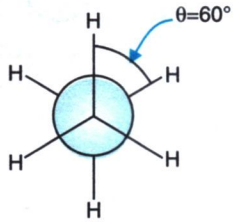
2. Obviously, the overall specification pertaining to all the **dihedral angles** in a particular molecule, justifiably specifies its ***conformation.***

3. Nevertheless, the observed **conformation** of a molecule designates the spatial arrangement of its respective atoms whenever all of its **dihedral angles are duly specified.**

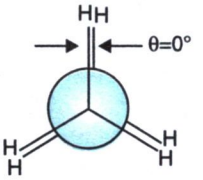
Staggered Conformation and Eclipsed Conformation of Ethane: Based upon scientific and logical evidences one may observe ***two*** **limiting possibilities** related to the ensuing *conformation of ethane* from its **Newman projection,** that are usually recognized as:

- **Staggered conformation,** and
- **Eclipsed conformation,**

which are shown as under:



Staggered conformation of ethern



Eclipsed conformation of ethane

Staggered Conformation: In this case, the **C—H bond** of ***one C-atom*** critically bisects the angle between ***two*** **C—H bonds** of the other. Thus, the *smallest dihedral angle* in the **staggered conformation** is **θ = 60°**; whereas, the other *dihedral angles* are : **θ = 180°**, and **θ = 300°** respectively.

Eclipsed Conformation: Here the **C—H bonds** on the respective *C-atoms* are duly superimposed in the ensuing **Newman projection;** wherein, the *smallest dihedral angle* is **θ = 0°**. Besides, the other *dihedral angles* are: **θ = 120°**, and **θ = 240°** respectively.

Comment: Interestingly, we may come across the presence of the corresponding **'conformation intermediate'** between the **staggered and eclipsed conformations.** However, the foretold ***two*** **conformations** usually known to be of immense *central importance* and *utility*.

Figure 2.11 depicts the variation of energy levels *vis-a-vis* the **dihedral angle** around the *C—C bond in ethane.* In this Fig. 2.11 one may take cognizance of the following ***two*** **cardinal** aspects predominantly:

- **dihedral angle plotted being the one located strategically in between the coloured H-atoms;** and
- **staggered conformations observed at the *energy minima*; and eclipsed conformations seen at the *energy maxima.***

Important Observations: Following *three* ***important observations*** may be derived from Fig. 2.11, such as:

1. The **staggered conformation** is found to be ***more stable conformation*** of **ethane.** Besides, the graphic description clearly depicts that it is certainly more stable in comparison to the respective **eclipsed conformation** by almost about **12 kJ.mol^{-1}** (*i.e.,* approx. **2.9 kcal.mol^{-1}**).

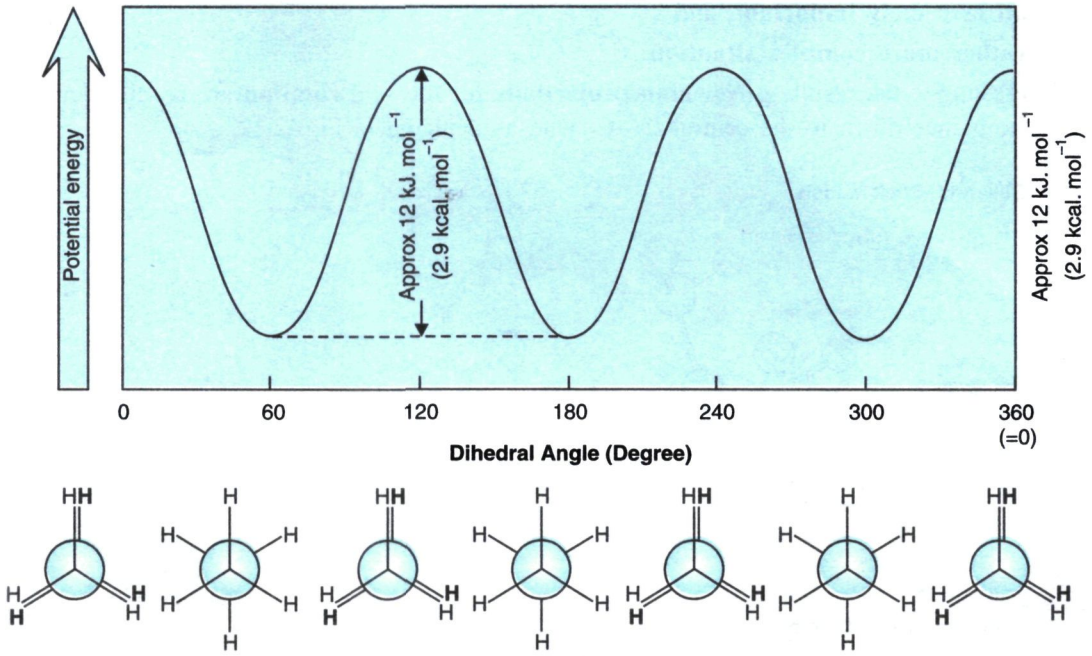


Fig. 2.11: Diagrammatic representation showing the variation of energy levels with respect to the dihedral angle around the C—C bond in ethane molecule [C_2H_6]

NOTE: **Thus, it implies that an energy level of 12 kJ could be consumed in the so-called conversion of *1 mole of staggered ethane* into *1 mole of eclipsed ethane.***

2. The critical *higher-energy level* associated intimately with the **eclipsed conformation phenomenon,** due to the respective *eclipsing of bonds* is invariably termed as **'torsional energy'** (or **torsional strain**). In other words, one may say that the so-called ***eclipsed*** **ethane** is **torsionally strained** to the extent of nearly **12 kJ.mol^{-1}** (or **2.9 kcal.mol^{-1}**) in comparison to the ***staggered*** **ethane.**

3. Internal Rotation: Thus, ***one*** **staggered conformation of ethane** may actually cause the conversion into another by rotation of **either C-atoms** relative to the other around the **C—C bond.** Such a typical observed ***'rotation'*** about a bond is called as an **'internal rotation'.***

NOTE: **It has been duly observed that whenever an *'internal rotation'* comes into play, an *ethane molecule* should pass briefly *via* the *eclipsed conformation i.e.,* initially it must acquire the *additional energy level* for the *eclipsed conformation*; and subsequently, lose it latter.**

2.6.2.2 Conformation: Butane

In an attempt to examine the ***internal rotations*** of **butane** particularly in a **Newman projection** around the ensuing bond between **C-1** and **C-2**, one may observe that almost **'all staggered conformations'** are equivalent. Nevertheless, the critical observed rotation around the ***central*** **C—C bond of butane** virtually designates:

* That is, to differentiate it from a rotation of the entire molecule.

- **an extremely important,** and
- **rather more complex situation.**

Interestingly, the resulting **Newman projections** for the said **rotation** are usually derived by casting the glance down to the central C—C bond as depicted in Fig. 2.12.

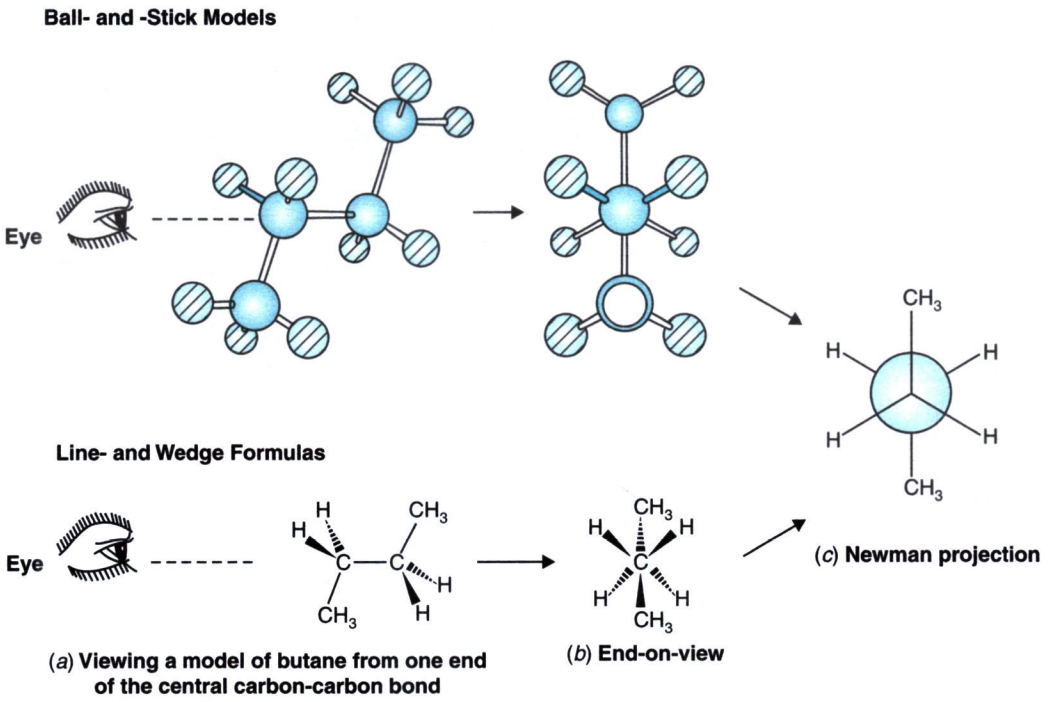


Fig. 2.12: Diagrammatic sequential derivation of the Newman projection of the central C—C Bond in Butane by making use of the Ball-and Stick models (*Top view*); and line and wedge formulas (*Bottom view*).*

In addition, the so-called *'energy-graph'* as the specific **'dihedral angle' (in degrees)** is illustrated explicitly in the Fig. 2.13.

It is, however, pertinent to state here that the ensuing ***different rotational possibilities*** may be generated elegantly by using a model by:

- **holding either of the 2 fixed C-atoms (see Fig. 2.12) *i.e.,* the C-atom away from the observer;** and
- **rotating the other C-atom.**

Salient Features: From Fig. 2.13 one may take cognization of the following important salient features:

1. It shows that the *staggered conformations* of **butane**, very much akin to those of '*ethane*' do occur specially at ***energy minima***; and, therefore, represent explicitly the **'conformations of butane'.**

* That is, only *one* of the **butane conformations** has been shown.

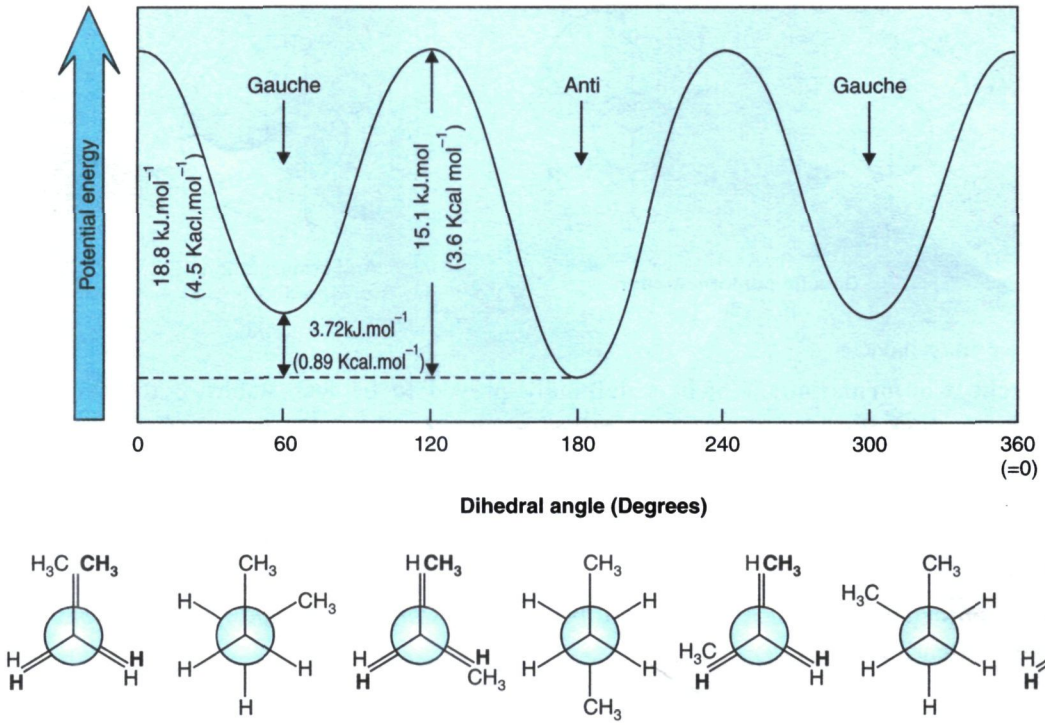


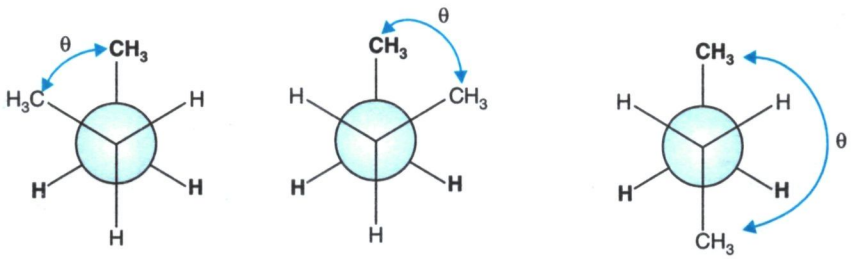
Fig. 2.13: The observed variation of energy level with dihedral angle (degrees) around the central C—C bond of butane. [In the above diagrammatic representation' the dihedral angle plotted happens to be the *'one'* located between *two* CH_3 moieties]

2. Amazingly, not all of the *staggered conformations* (nor the eclipsed conformations) of **butane** are absolutely similar.

3. In fact, **'special names'** have been duly assigned to the **staggered conformation variants** respectively, such as:

- **Conformations with a *'dihedral angle'* of ± 60° (see Fig. 2.13 at 60° and 300°: *'gauche'*) located strategically between the 2 C—CH_3 bonds. These are termed as *'gauche'* conformations (which is duly derived from the *French*: gauchir = 'to turn aside') *i.e.,* the *conformation form* wherein the dihedral angle stands at 180° and is known as the anti-conformation.**
- The aforesaid ***two* conformations** *viz.,* **gauche-** and **anti-conformations** may be illustrated as under:

The above Fig. 2.13 reveals generally that the **'gauche'** and **'anti'**-conformations of ***butane*** do exhibit altogether **different energy levels.**



Gauche conformations
[θ = ±60°°]

Anti confirmation
[θ = 180°]

Thus, we may have:

- **Gauche Conformation:** Which is definitely proved to be less stable of the said ***two*** **conformations.** Besides, it remains ***strained torsionally*** since the **methyl (CH_3)** moieties are *very close together i.e.,* so nearer to each other that the **H-atoms** positioned on the said ***two*** **functional groups** *do occupy each other's space* predominantly. However, it may be observed more critically with the help of the so-called ***space-filling model*** as shown in Fig. 2.14 (a).
- **Anti-conformation:** Which is proved to be the *more stable* of the said ***two*** **conformations** to the extent of:

3.72 kJ.mol (0.89 kcal.mol^{-1})

Important Points: Following are some of the *important points* related to the ***three*** **well-defined conformations in butane:**

(*a*) Gauche Butane: Wherein the **H—H distances** prevailing are found to be much less in comparison to the sum of the **van der Waals radii;**

(*b*) Anti-Butane: The energy required to force the so-called ***two*** **non-bonded atoms** together more closely *vis-a-vis* their **van der Waals' radii.** Since the **van der Waals' radius of a H-atom is ~1.2 Å,** thereby forcing the centres of **2 non bonded H-atoms** to remain closer than 2-folds of this distance needs **extra energy.** Besides, the greater the **2H-atoms** are pushed together—more energy is needed.

Remark: The so-called *'extra energy'* needed to force **2 non-bonded atoms** within the sum of their *van der Waals' radii* is invariably termed as **van der Waals' repulsion.**

- Therefore, to accomplish the said ***gauche*** **conformation** *butane* should require more energy, *i.e.,* one may say that—

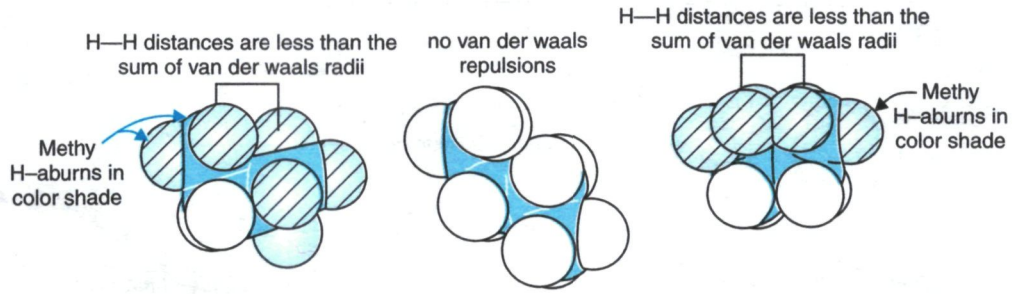
  "gauche-butane is specifically destabilized due to the van der Waals' repulsions existing between the non-bonded H-atoms residing on the two methyl (CH_3) moieties."
- Hence, such **van der Waals' repulsions** are perceptively absent in the ***anti*-butane** (see Fig. 2.14 (*b*).

NOTE: **The *anti*-butane is certainly more stable than the respective *gauche*-butane.**

(*e*) *Eclipsed* Butane: These conformations are proved to be **'unstable'** perhaps based upon the above mentioned logical explanations that the ***eclipsed* conformations** of ethane are unstable. Besides, in the respective **conformation of butane,** wherein the ***two* C—CH_3 bonds** are found to be *eclipsed,* the corresponding **H-atoms** located strategically in the **2 methyl (CH_3) moieties** are even nearer to each other than they are seen in the respective ***Gauche* conformation,** as shown in Fig. 2.14 (*c*).

NOTE:

1. **The *van der Waals repulsions* plus the consequent *'energy cost'* are proportionately greater.**
2. **It may be seen that of *all the eclipsed conformations*—the eclipsed butane happens to be the *most unstable one* [θ = 0° as shown in Fig. 2.13].**



(a) Gauche-butane **(b) Anti-butane** **(c) Butane with C—CH_3 bonds eclipsed**

Fig. 2.14: Representation of space-filling models of different butane conformations
(a) Gauche-Butane with methyl H-atoms shown in colour shade*.
(b) Anti-Butane conformation is most stable since it contains no van der Waals repulsions;
(c) Butane with the C—CH_3 bonds duly eclipsed. In this conformation, the van der Waals repulsions between the H-atoms of two CH_3-moieties are much larger *vis-a-vis* the ones is Gauche-Butane.

2.6.2.3 Chair Conformation: Cyclohexane

Based on the ***stability data*** one may critically observe that the—**'C-atoms present in cyclohexane cannot simply lie in the same plane'.**

In case, we assume that it could happen at all, the ***geometry*** (or the **spatial arrangement of atoms**) does essentially need that the **C—C—C *bond angles*** must be **120°.** Since the observed **'ideal-bond angle'** in the so-called **tetracoordinate C-atom** is found to be **109.5°** (see *Fig. 2.6*), it would obviously be expected that the ensuing *'energy'* duly expended to bring-forth the **larger bond angles** critically needed for the **planar cyclohexane conformation.**

Angle Strain: It relates to the **'extra energy'** which a chemical entity has by virtue of the ***non-ideal* bond angles.** Therefore, due to the existence of **'angle strain'**—the so-called **planar cyclohexane** conformation may not show up to be quite stable as the **'alkanes'** (wherein the bond angles may attain the ***'ideal value'*.**

Points to Ponder: Since it is an established fact that the **'cyclohexane'** is proved to be so *stable*—it must have the following criteria, namely:

*In fact, a **H-atom** from one *methyl (CH_3) moiety* happens to be so close to a **H-atom** of the **other methyl (CH_3) group** that they eventually violate each other's van der Waals radii. The resulting van der Waal's repulsions do cause the **Gauche-Butane** to have a higher energy level than the ***anti*-Butane** in which the interaction is totally absent.

➢ **absolute devoid of the *'angle strain'*,** and

➢ **completely free from *'torsional strain'*.**

Figure 2.15 depicts the highly *sustainable* and *stable conformation* of **cyclohexane.** Thus, it may be observed vividly that in such a ***conformation* of cyclohexane**—the C-atoms may not lie in a **single plane** at all *i.e.,* the unique **C-skeleton** is found to be **'puckered'** (*i.e.,* **gathered no wrinkles**). In fact, such a unique **conformation of cyclohexane** is usually termed as the **'chair comformation'** (as it resembles very much similar to the common *garden chair*).

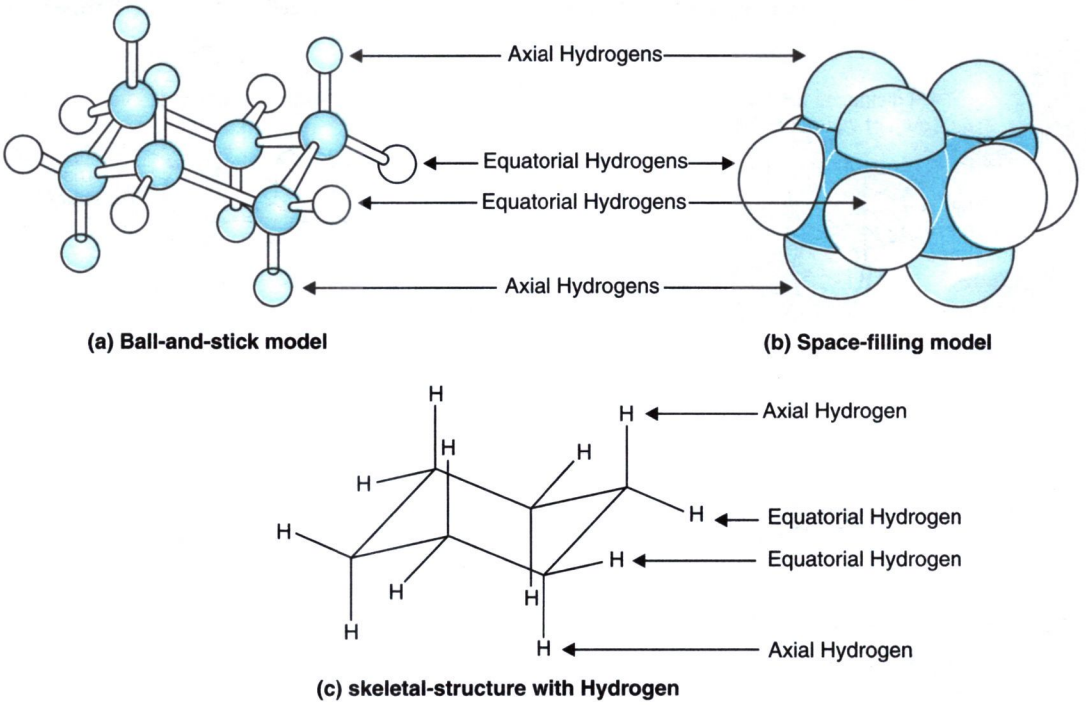


Fig. 2.15: Diagrammatic representation of chair conformation of Cyclohexane as: (a) Ball and Stick model; (b) Space-filling model; and (c) Skeletal structure with H-atoms shown.

In Figs. 2.15 (*a*) and (*b*) the *axial H-atoms* are shown in a gray-shade, whereas in Fig. 2.15 (*c*) these are depicted in a bold face shaded type.

At this point in time, we may look into the following cardinal aspects of the ***chair* conformation of cyclohexane:**

1. While considering the *H-atoms* in **cyclohexane** that are usually of ***two* variants,** such as:

➢ When the **model** (Ball- and Stick model) is duly placed on a *table top*: we may observe that all the ***six* H-bonds** are held **perpendicular (⊥) to the plane of the table;** as shown by the *gray-shaded balls* in Fig. 2.15 (*a*) above;

Besides, the *H-atoms* represented in **gray shading** in Fig. 2.15 (*a*) and (*b*) are known as ***axial* H-atoms;** whereas, the rest of the **C—H bonds** located outward along the *periphery of the ring* as depicted in ***white* balls** in Fig. 2.15 (*a*) and (*b*) are known as the ***equatorial* H-atoms.**

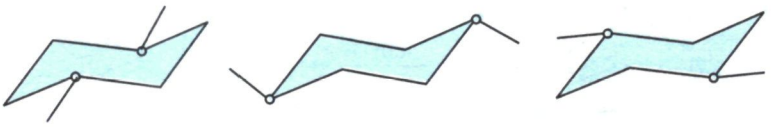
Remarks: It could also be possible that other *functional moieties* be adequately substituted for the H-atoms; and hence, these moieties also may appear critically in either the ***axial*** **format** or ***equatorial*** **arrangement.**

➢ Nevertheless, in the ***chair*** **conformation** all the respective bonds are found to be in a staggered arrangement, which may be duly visualized by carefully looking down any **C—C bond.** Importantly, the ***staggered*** **bonds** are energetically most preferred over the corresponding ***eclipsed*** **bonds.** From Fig. 2.15 one may keenly observe the so-called ***stability*** **of cyclohexane** as a consequence of the underlying fact that all of its inherent bonds may be staggered without compromising, whatsoever, the ensuing **tetrahedral C-geometry.**

Pairs of Equatorial Bonds being Parallel to Pairs of Ring Bonds

The above factual statement may be further proved and expatiated by drawing actually the ***axial bonds*** (*i.e.*, simply done by drawing the **'vertical lines'.** Nevertheless, drawing the respective **'equatorial bonds'** may prove to be certainly a rather tricky and tedious task.

We may have the following ***three*** **different cyclohexane rings having the added C—H bonds:**



(a) (b) (c)

➢ It may be observed explicitly that the so-called **pairs of the 'equatorial bonds'** are set almost parallel to the respective **'pairs of the ring bonds'.**

➢ One may also note the manner of all the **'equatorial bonds'** in Fig. 2.15 (a) do comply with this convention.

Interconversion of Chair Conformations

There are *two* extremely important observations pertaining to the interconversion of ***'chair'*-conformations** which comes into play around the **cyclohexane ring and its respective bonds:**

❑ **First observation:** Here the **3 axial H-atoms** located on **up carbons do point up**; and the respective **3 axial H-atoms** located on **down carbonds do point down** explicitly. However, in contrast, the **three equatorial H-atoms** positioned on *up carbons* do point down, and the *three equatorial H-atoms* positioned on *down carbons* do **point up**, as illustrated in Fig. 2.16 (*a*). Thus, we may have: **'the up and down H-atoms of a given type are completely equivalent'.**

In fact, the **up *equatorial* H-atoms** are found to be *almost equivalent* to the **down *equatorial* H-atoms;** whereas, the **up *axial* H-atoms** are *indeed equivalent* to the **down *axial* H-atoms.** One may observe this by ***turning the ring over:*** as depicted in Fig. 2.16 (*b*).

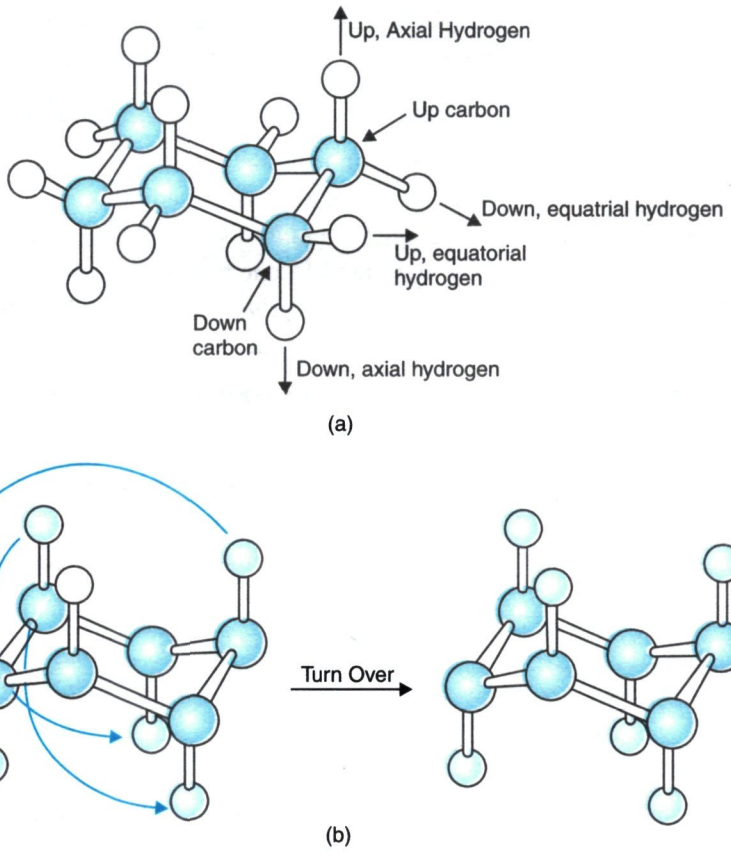


Fig. 2.16: (a) The up and down equatorial and axial H-atoms show that up and axial H-atoms are located on up C-atoms and down axial H-atoms are on down C-atoms. (The contrary stands **'true'** for equatorial H-atoms). (b) The up and down axial H-atoms are equivalent—which may be shown by turning the **ring** over as shown above by the **'coloured arrows'.** The up **axial H-atoms (colour)** become equivalent to the ***down axial* H-atoms (Gray colour).** The same process vividly shows the equivalence of the **up and down equatorial H-atoms.**

Remarks: It essentially causes the **up *axial* H-atoms** to enable exchange their respective positions with the **down *axial* H-atoms** particularly; and hence, everything looks exactly the same. Likewise, turning the ring over renders the **up *equatorial* H-atoms** to replace positions with the respective **down *equatorial* H-atoms.**

- ***Second* observation:** It relates to the underlying fact that in a situation shown an ***axial* H-atoms** is up on ***one* e-atom the *two* close-by *axial* H-atoms** are **down** and ***vice-versa***. The same holds good for the ***equatorial* H-atoms.**

Interconversion of Boat Conformations

It has been observed that when a **cyclohexane molecule** is subjected to undergo *internal rotations,* one may see a certain—**'change in the conformation of the ring itself'** as depicted in Fig. 2.17.

Modus Operandi: The various steps involved sequentially to obtain the **interconversion of *cyclohexane* to the respective boat conformations** are as follows:

1. First of all let us hold in position the **C-atoms 1, 2, and 6 *i.e.*, the rightmost C-atom plus its two adjacent C-atoms**—in order that all the **3 C-atoms** (*viz.*, 1, 2, and 6) fail to move; and thus, able to **raise C–4** as far as it can go up. Consequently, one will lay hands on to a *different conformation* known as the **'boat conformation'.**

2. Besides, one may also take cognizance of the fact that the actual formation of the so-called **'boat conformation'** essentially involve the ***'simultaneous internal rotations'*** around all the rest inherent **C—C bonds,** except those to **C–1.**

3. Now, let us hold the **C-atoms: 3, 4 and 5** of the boat *i.e.*, the **leftmost C-atoms plus its 2 adjacent neighbouring C-atoms (3 and 5)**—in order that they fail to move; and hence, help to bring down C–1 as far as it could go; finally the **ball and stick model** returns to a *chair conformation.* Therefore, in this particular instance, the so-called *simultaneous internal rotations* have come into play around **all C—C bonds,** except those attached to **C–4** specifically.

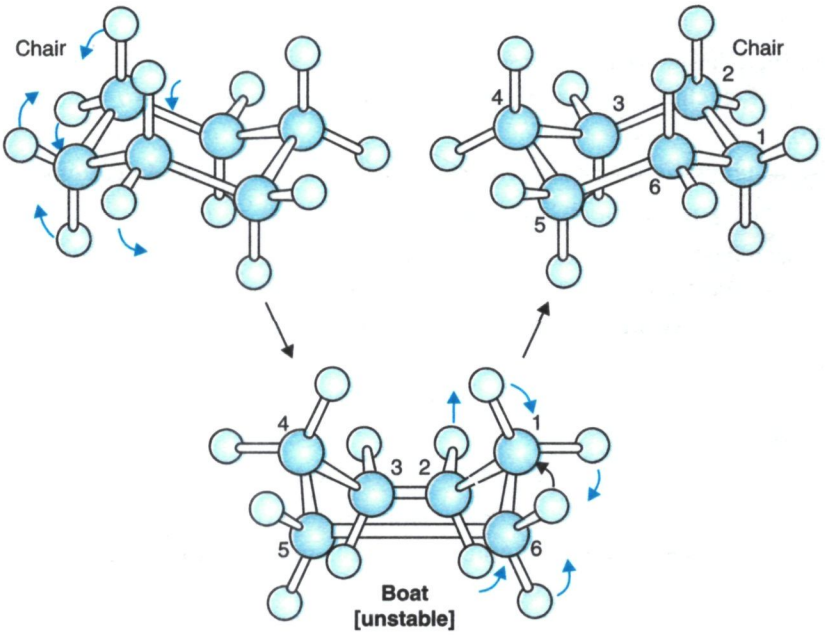
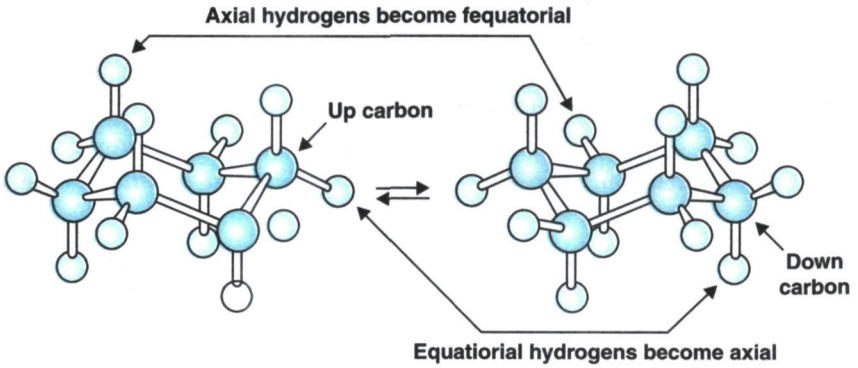


Fig. 2.17: Representation of the interconversion of the two chair conformations of cyclohexane (*i.e.*, the 'chair flip'). The coloured arrows depict explicitly the way the atoms move in each step. The 'Chair Flip' interchanges the respective positions of the H-atoms; the axial H-atoms in one chair conformation turn into the equatorial H-atoms in the other

4. However, the **'upward movement'** of the particular **leftmost C-atom;** and the **'downward movement'** of the **rightmost C-atom** obviously changes ***one chair conformation*** into another *absolutely equivalent chair conformation* (see Fig. 2.17).

Important Points: Keeping in mind the aforesaid interesting phenomena one may observe prominently that:

"The equatorial H-atoms have been rendered axial; and the axial H-atoms have turned into the equatorial ones'.



Besides, in the above diagrammatic representation the so-called ***'up C-atoms'*** have become the ***'down C-atoms'*** and *vice-versa.*

Chair Flip [or Chair-to-Chair Interconversion]: In fact, the prevailing *interconversion* of the ***two* chair forms of cyclohexane** is invariably termed as the **chair flip** (or **the chair-to-chair interconversion).**

Amazingly, the observed **'energy barrier'** for the ***chair flip*** stands at: **45 kJ. mol^{-1} (11 kcal.mol^{-1})**.

2.6.2.4 Boat and Twist Boat Conformations

We have already seen the **'Boat conformation'** of **cyclohexane** as illustrated in Fig. 2.17. Nevertheless, the **'Boat Conformation'** does **not** represent a *fairly stable conformation of cyclohexane,* because it prominently comprises ***two* known sources of instability,** as depicted in Fig. 2.18, and elaborated as under:

- ***First:*** important fact is that *some H-atoms* **(shaded in gray)** are found generally in an ***eclipsed state***; and
- ***Secondly:*** cardinal point being that the ***two* H-atoms** located strategically on the:
  - **'Bow'** and **'Stern'**

  of the respective *boat*, normally termed as the **'Flagpole' H-atoms** do experience the ***van der Waals repulsion*** predominantly.

NOTE: The *'Flagpole' H-atoms* are shown in colour in Fig. 2.18.

Based on the above reasonings one may critically observe that the **boat conformation** virtually undergoes very slight *internal rotations* which could lower the following ***two* vital aspects,** namely:

- **eclipsing interactions [See Fig. 2.18 (*a*)]**; and
- **Flagpole van der Waals repulsions [Fig. 2.18 (*b*)],**

thereby giving rise to another, *stable form of the cyclohexane* termed as a **'twist-boat conformation'.**

Furthermore, one may vividly have a view of the ensuing conversion of a **'boat'** into a **'twisted-boat'**; and this could be seen when observing a model of the ***boat-conformation*** from the top of the ***flagpole H-atoms*** (as illustrated in *Fig. 2.18 (b)*). Now, holding the said model of the ***boat conformation*** by means of its **flagpole H-atoms** poke slightly one of the **flagpole H-atoms *up*** and the other ***down*** so as to lay hands on the ***twist-boat conformation*** ultimately.

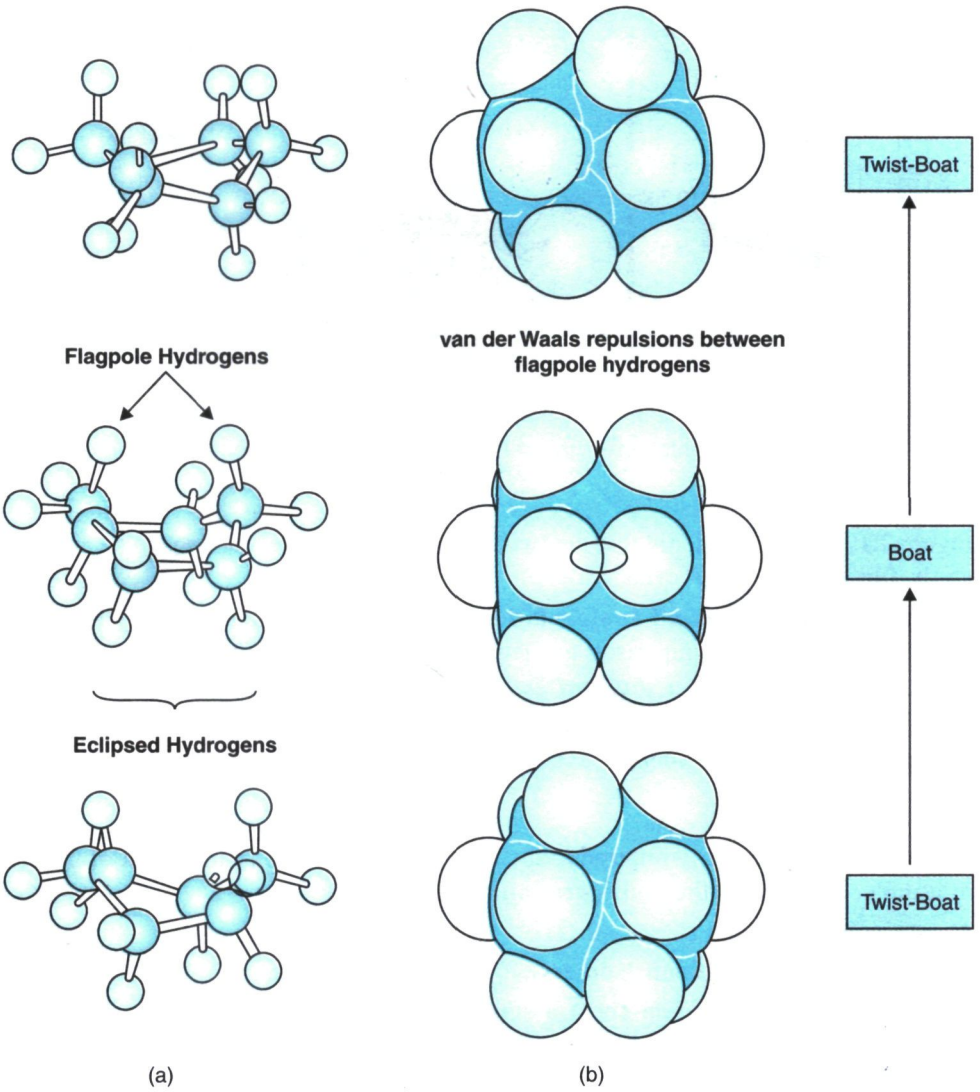


Fig. 2.18: Representation of boat cyclohexane (Centre) and its two related twist-boat conformations (top and bottom). The flagpole H-atoms are shown in colour; whereas, the eclipsed H-atoms in the boat conformation are shaded gray. (a) Ball- and -stick models; and (b) Space-filling models viewed from the top of flagpole H-atoms.

Figure 2.18 clearly depicts this motion that may actually take place in either of the ***two*** **ways** (*i.e.,* **'up'** and **'down'**); and thus, the ***two*** **twist-boat conformations** are assumed to be **related virtually to any one boat conformation.**

However, Fig. 2.19 illustrates the ensuing ***enthalpy relationships*** occurring amongst the **conformations of cyclohexane:**

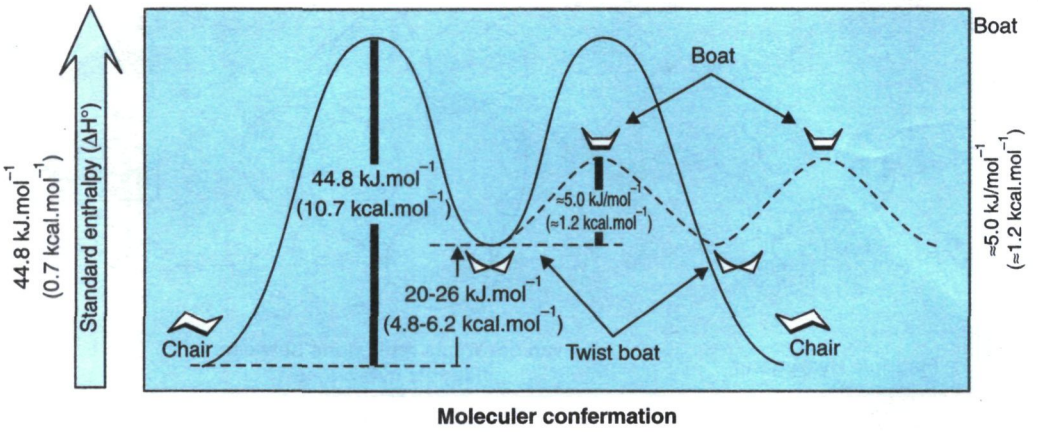


Fig. 2.19: Graphic representation of the relative enthalpies of cyclohexane conformations

Important Points:

1. Figure 2.19 reveals explicitly that the **twist-boat conformation** happens to be an ***intermediate* in the 'chair flip'.**

2. Even though the **twist-boat conformation** lies at a bare minimum energy level, it is found to be relatively *less stable* in comparison to the respective **chair conformation** up to the extent of **23 kJ.mol^{-1} (5.5 kcal.mol^{-1})** in a *standard enthalpy.*

3. However, the observed ***standard* free-energy difference [15.9 kJ.mol^{-1} (3.8 kcal.mol^{-1})]** is also within the *considerable limits.*

2.6.3 Configuration

The term **configuration** is usually referred to the fixed relative spatial arrangement of the atoms duly present in a molecule. Hence, the **configurational isomers** *viz.,*

- **Diastereoisomers,** and
- **Enantiomers (or Inversion Isomers),**

cannot be interconverted by rotation about a single bond and also they are found to be *non-super imposable upon their mirror images* (see under *section 3*).

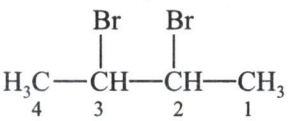
Configuration for Chemical Entities Comprising More than One Chiral Centre

In a broader perspective, all such *chemical entities* (or **compounds**) comprising *more than one chiral centres*, the ensuing configuration around ***each* chiral C-atom** is usually determined individually by making specific usage of:

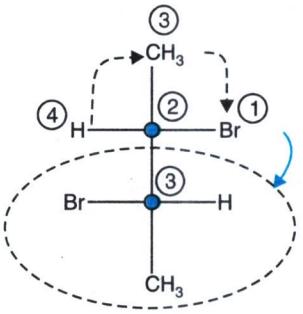
- **sequence rules**, and
- **actual numbers,**

that are being used to specify **each chiral C-atom.**

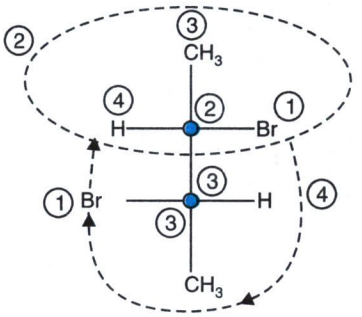
Example: Let us consider the particular example of **2, 3-dibromobutane:**



Thus, one may critically draw the configuration with respect to C–2 as 'R'; and also the configuration with respect to C–3 as 'R' as given under:



2,3-Dibromobutane
['R' wrt e-2]



2,3-Dibromobutane
['R' wrt e-2]

● Chiral centre

At C–2: the *four* moieties and their respective inherent ***'priority order'*** is as expressed below:

Br > the C-chain CH (Br) CH_3 > CH_3 > H

At C–3: the ***'priority order'*** of various functional groups is as given under:

Br > CH (Br) CH_3 > CH_3 > H

Remarks: However, the overall configuration of the compound **2, 3-dibromobutane** may be expressed as: **(2R, 3R)**, wherein the *numerals* **2** and **3** categorically specify the ***exact number of C-atoms*** along which the ensuing *configuration* of that **specfic C-atom is written explicitly.**

Suggested Reading

Bassendale A.: **The Third Dimension in Organic Chemistry,** Wiley, New York, 1984.

Eliel EL: **Stereochemistry of Carbon Compounds,** McGraw Hill, New York, 1963.

Kagan H.: **Organic Stereochemistry,** Wiley, New York, 1979.

Klyne W and Buckingham J.: **Atlas of Stereochemistry,** 2nd ed. Chapman and Hall, London (UK), 1978.

Mislow K.: **Introduction to Stereochemistry,** WA Benjamin, New York, 1965.

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Chapter 3

Reaction Intermediates and Factors Governing Reactivity

LESSONS AT A GLANCE

3.1 Introduction
3.2 Carbocations [or Carbonium Ion]
  3.2.1 Classification of Carbocations
  3.2.2 Formation of Carbocations
  3.2.3 Stability Profile of Carbocations
  3.2.4 Actual Structure of Carbocation
3.3 Carbanions
  3.3.1 Classification of Carbanions
3.4 Free Redicals
  3.4.1 Structure of Free Radicals
  3.4.2 Formation of Free Radicals
3.5 Stereochemistry of Radical Substitution Reactions
3.6 Carbenes
3.7 Nitrenes [Imidogenes]
3.8 Arynes [Benzynes]
3.9 Factors Governing The Reactivity Profile
  3.9.1 Electronic Effect
  3.9.2 Inductive Effect [or Transmission Effect or I-Effect]
  3.9.3 Mesomeric Effect
3.10 Hyperconjugation
  3.10.1 Theories of Hyperconjugation
  3.10.2 Variants in Hyperconjugation

3.1 INTRODUCTION

It has been broadly studied and duly established that the *mechanism of various chemical reactions* do invariably imply the different actual series of distinct as well as discrete sequential steps that are involved in the specific intended transformation(s) of the ensuing reactants into a host of desired products. Hence, the underlying mechanism of an **organic reaction** involves most frequently the *crucial cleavage* of the **'covalent bond'** in the following *two* ways, namely:

- **Homolytically**, and
- **Heterolytically**

Homolytic Bond Fission: It relates to the cleavage of a bond by the process known as **homolytic fission** or **homolytic cleavage** in such a manner that each of the molecular fragments between which the bond is duly broken virtually retains one of the so-called ***'bonding electrons'***. Finally, it leads to the formation of a **'Free Radical'.**

Heterolytic Bond Fission: In true sense, it leads to the formation of **'carbanions'** (or **'carbonium ions'**).

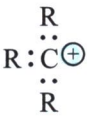
In the light of the foregoing brief discussion it would be worthwhile to study the various arms of **'reaction intermediates'** one-by-one in the sections that follows:

3.2 CARBOCATIONS [or CARBONIUM ION]

The **carbocations** refer to a cation containing an even number of electrons with a significant portion of the excess positive charge located strategically either on one or more C-atoms.

Another school of thought describe the **carbonium ions** as

"the positively charged species comprising a C-atom with only six electrons in the form of 3 sigma (σ) bonds and a positive (+) charge on it": (see below)



Nomenclature: The **carbocations** (or **carbonium ions)** are so-called based upon ***two* conventions**, such as:

- **the positively charged C-atom *i.e., carbocation*;** and
- **the names of the bonded functional groups appear as a** *'prefix'*.

3.2.1 Classification of Carbocations

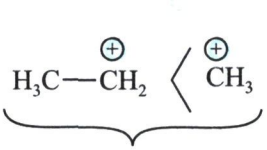
In general, the **carbocations** may be characterized due to their such cardinal aspects as:

- ➢ **transient (short) life-span;**
- ➢ **tendency to attach completion of the *octet of the C-atom* by means of:**
  - ❑ **an available anionic species,**
  - ❑ **an electron-rich species,**
  - ❑ **specific molecules *viz.*, H_2O, NH_3,** and
  - ❑ **loss of an atom or group.***

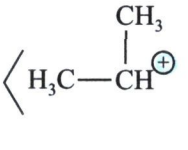
* That is, usually H-atom derived from the adjacent C-atom.

Thus, one may classify the **carbonium ions** conveniently in terms of: *primary, secondary* and *tertiary* that solely depends on the precise nature of the **C-atom** bearing the **positive charge.**

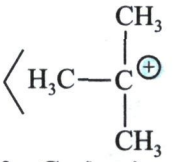
Examples: Following are the typical examples of ***pri-, sec-***, and ***tert*-carbocations:**



1° – Carbonium Ion (Primary)

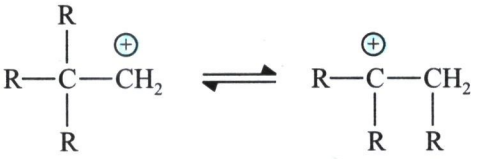


2° – Carbonium Ion (Secondary)



3° – Carbonium Ion (Tertiary)

Comment: It has been observed that quite a few **carbocations** may eventually undergo **molecular rearrangement** to yield the corresponding ***more stable*** **carbonium ion** as depicted under:



Carbonium Ion (*less stable*) **Carbonium Ion (*More stable*)**

3.2.2 Formation of Carbocations

In a broader perspective, the **carbocations** are duly formed as a consequence of articulated **heterocyclic bond fission.** Following are a few proven methods that usually help to form the **carbocations (or carbonium ions),** namely:

3.2.2.1 Heterolytic Fission (or Direct Ionisation)

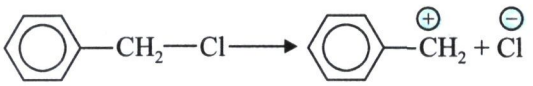
In this particular instance the typical presence of a ***highly polar organic entity*** do go a long way to produce the so-called **carbocations.**

Examples: These essentially include

Generalized example:



Benzyl chloride:



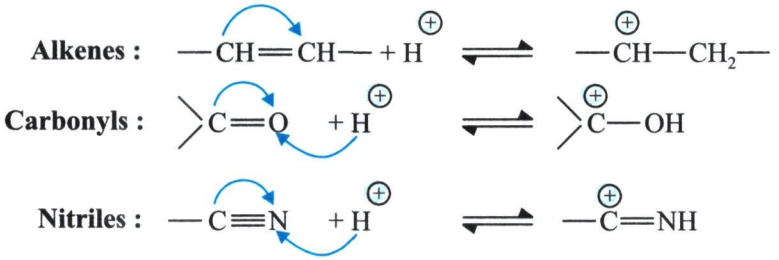
Benzyl chloride Benzyl carbocation

3.2.2.2 Protonation of Unsaturated Compounds

It has been duly proven that the following *three* types of chemical entities on protonation give rise to the formation of **carbocations** *viz.,*

- **Alkenes** • **Carbonyls** and • **Nitriles**

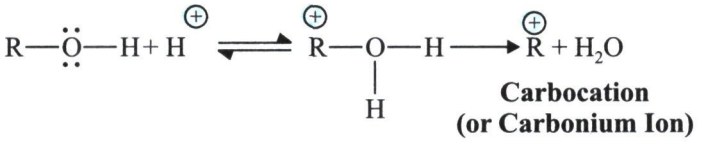
Examples:



3.2.2.3 Addition of Proton to C-Atom Bearing Lone Pair of Electrons

The *organic compounds* essentially bearing a ***lone-pair of electrons*** do have a tendency to yield a **carbocation** (or **carbonium ion**) when subjected to *protonation*.

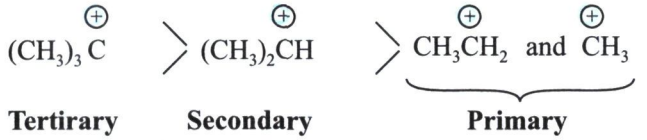
Examples: Alcohol (R—OH) serves as a typical example:



Carbocation (or Carbonium Ion)

3.2.3 Stability Profile of Carbocations

The **carbocations** do exhibit predominantly the following ***proven stability***:



Tertirary **Secondary** **Primary**

Nevertheless, the overall observed **stability of the charged system** is duly enhanced by the aid of the *dispersal of charge.* In other words, any ***specific*** **factor** that either:

- **disperses,** or
- **spread out the positive charge,**

located strategically over the ***electron-deficient C-atom*** *vis-a-vis* to the rest of the neighbouring C-atoms, is usually assumed to help in the **stabilisation of the prevailing charged system.**

It is worthwhile to mention at this material time there are ***three*** **cardinal effects**—that are solely responsible for bringing about the critical *dispersal of the ensuing charge duly held by the* **carbocation**; and, therefore, are being the crucial cause of displaying the above mentioned **'order of stability'.**

3.2.3.1 Hyperconjugation

Hyperconjugation, in fact, relates to the phenomenon of ***electron delocalisation*** (*via* **orbital overlap**) right from a *filled bonding orbital* to an *adjacent unfilled orbital.* Besides, **hyperconjugation** involves the so-called **sigma (σ) electrons**; and hence, accounts for the following *two* aspects:

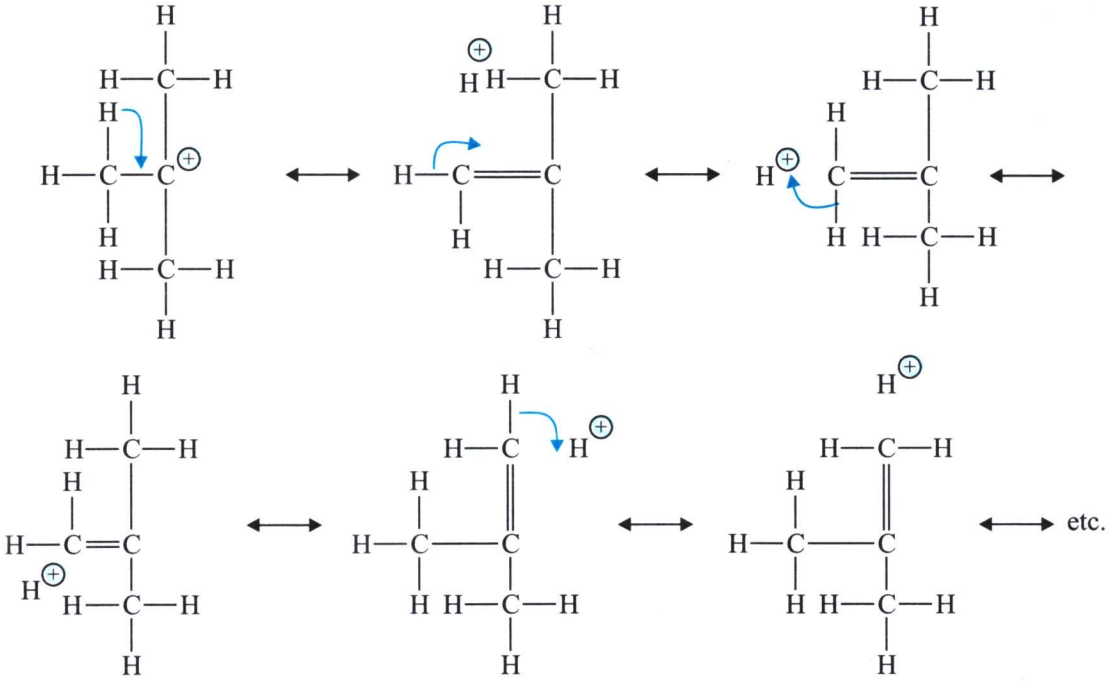
- **stabilising effect of a group**; and
- **electron donating effect of a group**.

In doing so, the **hyperconjugation** phenomenon does involve critically the so-called *delocalization of electrons* (with respect to the **C—H bond**) into an adjacent '***π-system***' between the **C—C bond.**

Obviously, **hyperconjugation** may largely expatiate the overall greater extent of stability for the ***tertiary*** **carbocation.**

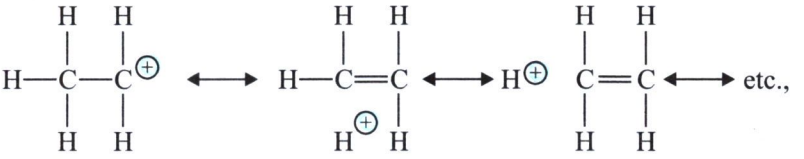
Following are some of the possible recognised **canonical structures** of the ***tertiary*** **carbocation** and the ***primary*** **carbocation:**

➢ ***Tertiary*** **Carbocation (or Carbonium Ion)**



NOTE: **Thus there are *nine* possible canonical forms of *tertiary* carbocation.**

➢ **Primary Carbocation (or Carbonium Ion)**



NOTE: **In fact, there are *five* possible canonical forms of *primary* carbocation.**

Comments: It has been established reasonably that there lies an ample scope and possibility for many more canonical forms particularly for the **tertiary carbocation** *vis-a-vis* the ***primary*** **carbocation.**

In addition, *all the canonical forms* (*i.e.,* for the ***tert*-and *pri*-carbocation**) fail to contribute to the same extent to the **'true molecule'**, which indicates explicitly that each structure almost contributes both proportionately and legitimately into the overall stability of the **end-product(s).** Thus, more stable forms would be contributing greater degree *vis-a-vis* the less stable forms; and hence, the actual number of the **canonical forms** shall always remain greater pertaining to their contribution towards the **stability of the ion.**

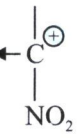
3.2.3.2 Positive Inductive Effect (or Field Effect)

The **positive inductive effect** (or **field effect**) refers to the specific electron-donating effect of the *alkyl moieties* that critically enhance these *two* important aspects, namely:

- electron density at the charge bearing C-atoms thereby during the overall net positive charge upon the carbon of carbocation; and
- subsequently the ensuing positive charge is duly being spread over:
  - **the α-C atoms,**
  - **adjacent alkyl moiety,** and
  - **according to the law any such effect that eventually brings about the dispersal or spreading of charge thereby stabilising the system.**

Examples: Let us examine the following examples:

- $R_3C^{\oplus}$: In this case, '**R**' designates an *alkyl moiety* which being an **electron releasing entity** (*i.e., **exhibiting a positive inductive effect***). Besides, it helps to **release the electrons** towards the *electron deficient C-atom* (*i.e., **the C-atom bearing the +ve charge***). **It minimises the +ve charge by enhancing the ensuing electron density over the C-atom**; and, therefore, the observed stability of the carbonium ion (or carbocation) gets increased significantly. Thus, greater the number of the **electron-releasing moieties or electron-donating groups** (*viz.,* R, Ar, F, Cl, I, Br, SH, SR, O^-, S^-, NR_2, NHR, NH_2, NHCOR, OR, OH, OCOR) over the C-atom **bearing a +ve charge,** greater would be the prevailing stability of **carbonium ion** (or **carbocation**).

- Alternatively, in the specific case,  if '**X**' represents an *electron-withdrawing moiety* (*viz.,* NO_2, CN, COOH, COOR, $CONH_2$, CONHR, $CONR_2$, CHO, COR, SO_2R, SO_2OR, NO), it would perceptively lower the so-called **electron density** over the C-atom **bearing the +ve charge.** Subsequently, intensifying the **overall +ve charge** over the **C-atom**; and hence, shall minimise the stability of the **carbonium ion** (or **carbocation**).

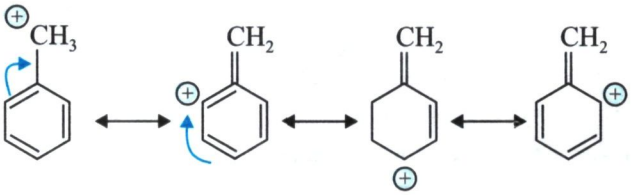
3.2.3.3 Resonance

Resonance broadly explains the *stability* profile of the following ***two* carbocations**, namely:

- **allylic carbocation**, and
- **benzylic carbocation**.

Importantly, the positive charge borne by the **carbocation** (or **carbonium ion**) gets duly delocalized over the adjacent atoms which causes the former to exhibit the phenomenon of **resonance.**

Examples: The **benzylic carbonium ion** are found to be rather more stable *vis-a-vis* those wherein **resonance** is virtually absent *viz.*, **alkyl carbocation**, as shown under:



Benzylic carbocations

Likewise, in the so-called **allylic carbocations** one may visualise vividly the presence of the *positively charged carbocation* in perfect conjugation with an olefinic bond (or **double bond**) whereby the stability seems to be certainly more prominent due to the **phenomenon of resonance**—that ultimately causes the *delocalization* of the **+ve charge,** as shown under:



Allylic carbocation

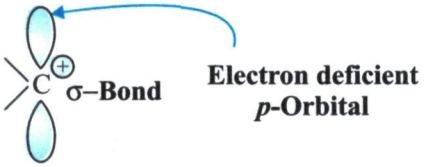
3.2.4 Actual Structure of Carbocation

It has been duly established that the **C-atom of a carbocation** has prominently the following *two* characteristic features:

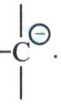
- sp^2**-hybridization**, and
- **presence of** $3sp^2$ **orbitals,**

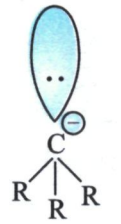
that are duly engaged in the formation of **covalent bonds** to the ***three*** **alkyl substituents.** Thus, ***one*** ***p*-orbital** of the **carbocation** having the **+ve charge** dwelling on it is found to be unoccupied.

Interestingly, the **carbocation** has the actual **planar structure** having **all the 3-covalent bonds** lying in the same plane with a ***bond angle*** **of 120°,** as shown below:



3.3 CARBANIONS

The carbanion designates the *intermediate reaction* wherein the **C-atom** virtually carries a **–ve charge** on it *i.e.*,  . Besides, the **C-atom** is sp^3**-hybridized**; and, therefore, a *tetrahedral* could be represented duly as shown:



Carbanion

3.3.1 Classification of Carbanions

In general, the **carbanions** are of *two* **types,** such as:

- **Non-classical carbanions**, and
- **Classical carbanions**

which shall now be treated separately in the sections that follows:

3.3.1.1 Non-Classical Carbanions

In these specific **carbanions** the so-called *negative charge* residing on the **C-atom** gets duly delocalized over a number of such atoms. Thus, the said **carbanions** is stabilized meticulously on account of the **phenomenon of resonance.**

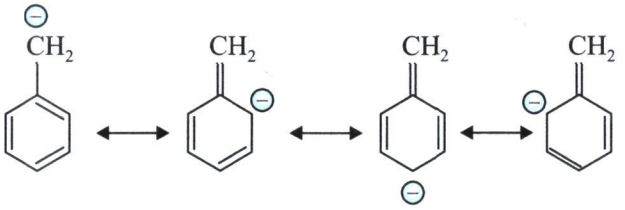
Examples: Following are *two* **classical examples:**

(*a*) Allyl Carbanion



A carbocation **An allyl carbanion**

(*b*) Benzyl Carbanion



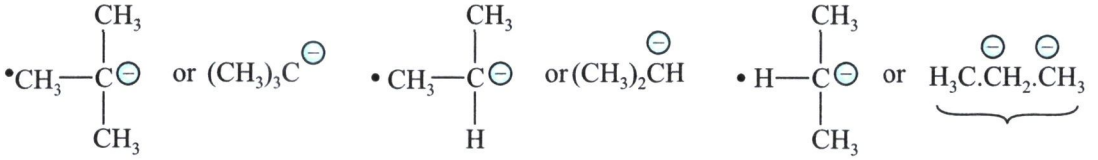
Various Configurations of Benzyl Carbanion

3.3.1.2 Classical Carbanions

Interestingly, the **classical carbanions** possessing the **–ve charge** gets duly localized upon a **C-atom.** However, these **classical carbanions** have been duly classified in *three* altogether different categories, namely:

- **Tertiary carbanion**,
- **Secondary carbanion**, and
- **Primary carbanion**,

which are depicted as under:



Tertiary **Secondary** **Primary**

Remarks: In reality, whenever certain organic chemical entities (compounds) are duly treated with the strong **Lewis Bases** (*i.e.*, **reducing agents**) they invariably *lose a H-atom* to produce a ***'C—H Bond'***—as a **proton** to form the so-called **anionic species 'carbanion'.**

3.3.1.3 Structure of Carbanions



Tetrahedral Carbanion

It may be observed clearly that in the **'carbanion'** the ***central* C-atom** bearing the *– ve charge* is ***sp*³ hybridized** having typical ***unshared pair of electrons located duly at one apex of the tetrahedron.*** Thus, one would see the ***pyramidal structure* of the tetrahedral carbanion**—as illustrated here:

Furthermore, the ***three sp*³-hybrid orbitals** present on the *central C-atom* do form the **covalent bond** having *3 atoms or moieties*; whereas, the ***Fourth sp*³-hybrid orbital** possess a distinct *non-bonding pair of electrons.* Nevertheless, the **pyramidal** or **tetrahedral** structures of the ensuing **carbanion** normally explains the loss of the **inherent optical activity** perhaps due to the causation of either:

- **an asymmetric C-atom (or *Chiral centre*),** or
- **substitution of central C-atom by different substituents,**

since there prevails a rather ***rapid* inversion of the configuration** by virtue of ***rapid* interconversion phenomenon** existing between the said **'*two* forms'.**

Thus, we may have the following expressions:



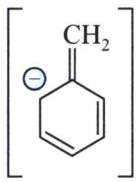
Remarks: The central carbanion designates the *sp²-hybridized* as observed in the conjugated anions.

3.3.1.4 Stability Profile of Carbanions

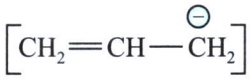
The formation and stability of the **carbanions** is increased potentially as and when the critical **negative charge** residing and concentrated on the **central C-atom** gets adequately dispersed upon the other strategically located adjacent atoms.

Following are stability profile of **'carbanions'** pertaining to the:

Benzylic Carbanion



Allylic Carbanion





Primary Secondary Tertiary-C-atoms

3.3.1.5 Scientific Explanations with Respect to the Order of Stability of Carbanions

There are *three* vital and important factors that solely affect the ***stability profile* of carbanion variants,** namely:

- **Inductive Effect [or Field Effect],**
- ***s*-Character of Carbanion C-atom,** and
- **Resonance**

which will now be treated individually in the sections that follows:

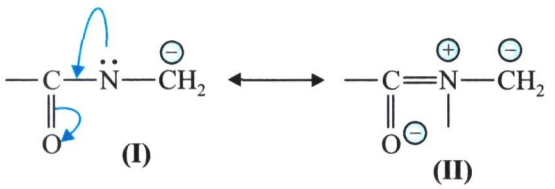
3.3.1.5.1 Inductive Effect [or Field Effect]

One may observe critically that the presence of the **electron-withdrawing groups** help to stabilize the **carbanion** predominantly by causing the ***dispersion* of the –ve charge** over the adjacent **atoms or moieties.** Likewise, the presence of the **electron-releasing groups** (*viz.,* alkyl groups) actually tend to afford the intensification of the *negative charge* upon the *central C-atom* thereby stabilizing the **carbanion** squarely.

In this manner, it provides a scientific explanation to justify the so-called **'least stability profile by the tertiary carbanion'** *vis-a-vis* the corresponding ***secondary* and *primary*-carbanions.**

In addition, the **carbanions** are found to get duly stabilized due to the **'Field Effect'**, in case there exists any hetero-atom (*viz.,* **O, N, S, etc.**) located precisely in the viccinity of the C-atom bearing the negative charge, only when the **hetero-atom** bears a **+ve charge** on it *i.e., the electron deficiency seen in any of the canonical structures.*

Examples: Obviously, one may find the following structure definitely **more stable:**



NOTE: **The *structure (II)* appears to be more stable by virtue of the critical presence of the *electron deficient N-atom* located adjacent to the *anionic C-atom.***

3.3.1.5.2 s-Character of Carbanion C-Atom

It has been observed that the stability profile of the **carbanion** enhances prominently with the enhancement of the **s-character*** of the ensuing **carbanionic C-atom.** However, the underlying fact could be evident based upon the following **'order of stability'.**

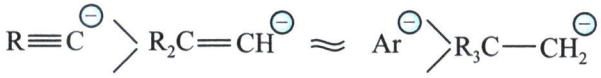


Table 3.1 records the hybridization of carbanionic C-atom and the percentage of s-character for *three* different carbanions:

Table 3.1: Various carbanions with their hybridization of carbanionic C-atom and percentage of s-Character

S. No.	Carbanion	Hybridization of carbanionic C-atom	Percentage of *s*-Character
1	$RC\equiv C^{\ominus}$	*sp*	50
2	$R_2C(^{\ominus})-CH/Ar^{\ominus}$	sp^2	33
3	$R_3C-CH_2^{\ominus}$	sp^3	25

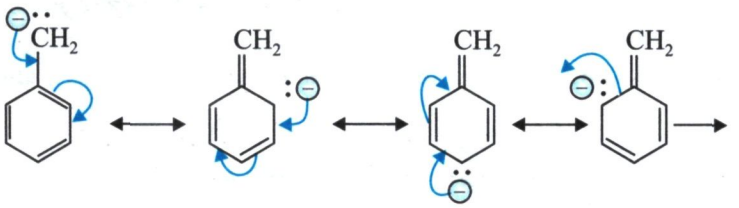
* ***s*-character:** It refers to the α-tendency of the electrons to attract electrons thereby enhancing the so-called *negative inductive effect.*

Comment: The percentage of *s*-character is found to be *maximum* in **sp-orbitals** and *minimum* in sp^3**-orbitals.**

3.3.1.5.3 Resonance

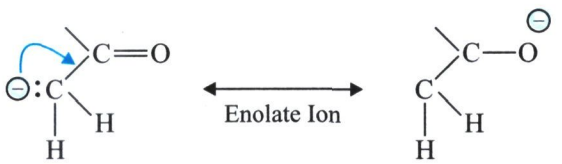
The stability profile of the **benzylic carbanions** as well as the **allylic carbanion** (*viz.*, **enolate anion**) may be duly expatiated based upon the ***resonance phenomenon***, since the resonance causes the *dispersion* of the ensuing **negative charge** located on the **carbanionic C-atom** thereby rendering the **carbanion** fairly stable.

Examples: Resonance profile in the **'benzyllic carbanion'** is shown as under:



NOTE: **However, one may further extend the** *resonance* **quite easily and conveniently towards the overall stability of the** *carbanion* **having a carbonyl (>C=O) moiety in the viccinity of the** *carbanion*.

Resonance profile in the **'allylic carbanion'** is given as below:



Remarks: Thus, one may broadly interpret from the **stability pattern** that the **carbanions** which invariably come into being as the ***'intermediates in organic reactions'*** are found to be usually bound to the various available **stabilizing moieties** that are supposed to be deficient in electrons.

3.3.1.6 Reactions Involving Carbanion

The **'carbanions'** being the so-called ***electron-rich nucleophiles*** that are ***basic in character*** do serve as the potent and powerful base.

Following are the few classical reactions which preferentially involve the **carbanions**—as the so-called ***reaction intermediates.***

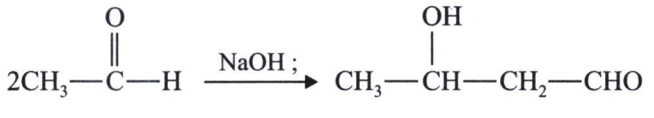
- **Addition Reactions** *e.g.*, **Aldol Condensation, Claisen Condensation**;
- **Elimination Reactions** *e.g.*, **Decarboxylation**; and
- **Substitution Reactions** *e.g.*, **Reimer-Tiemann Reaction, Carbanion as a Nucleophile**

3.3.1.6.1 Addition Reactions

These include the following reactions:

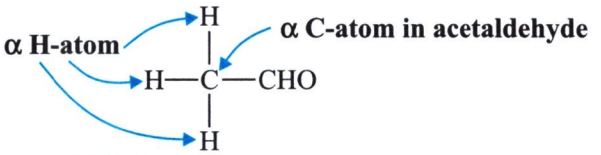
➢ **Aldol Condensation:** Let us take into consideration the typical examples of ***two*** **aliphatic aldehydes** *viz.*, **Formaldehyde** and **Acetaldehyde.** Since, the *former* (*i.e.*, ***formaldehyde***) bears **no alpha (α) H-atom**; whereas, the *latter* (*i.e.*, **acetaldehyde**) has **3α H-atoms** (because it has **one α-C-atom* bearing 3–H atoms**).

Examples: Aldol Condensation with Acetaldehyde



Acetaldehyde — **An Aldol**

Aldol Condensation with Formaldehyde

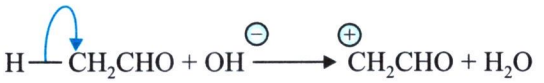


HCHO
Formaldehyde

Mechanism of Aldol Condensation: This involves the **carbanion** as the *reaction intermediates* and the various steps that come into play are as follows:

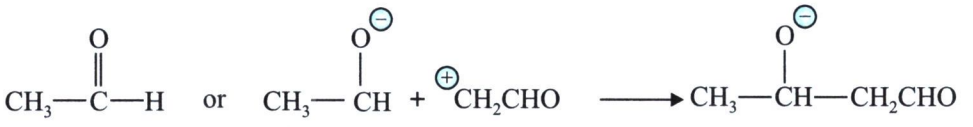
Acetaldehyde: It incurs *two* steps:

Step - 1:



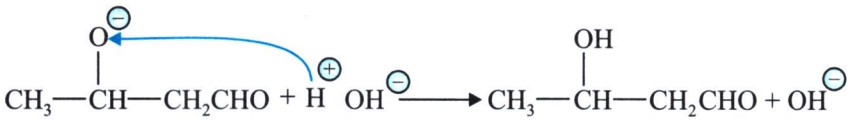
Acetaldehyde — **A carbanion**

Step - 2:



Acetaldehyde — **Acetaldehyde [*in Ionic form*]** — **Carbanion** — **Aldol Anion**

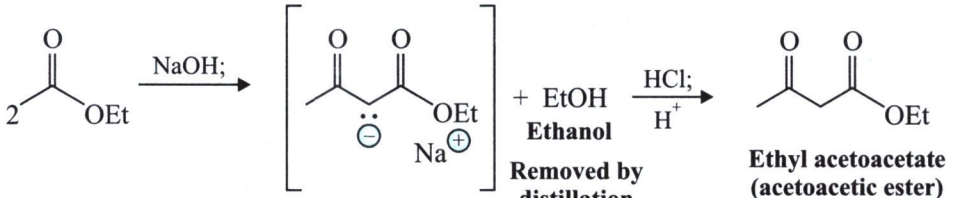
Step - 3:



Aldol Anion — **An Aldol**

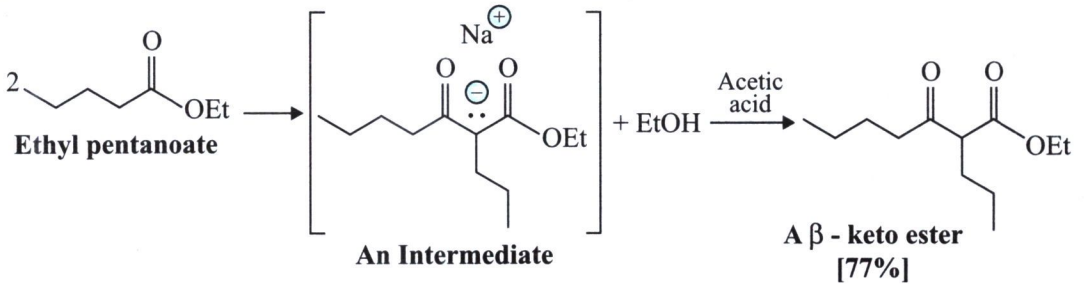
* **Alpha (α) C-atom:** It refers to the **C-atom** which is duly attached to the *functional moiety.*

➢ **Claisen Condensation [Synthesis of β-Keto Esters]:** It also represents another kind of an **'addition reaction'** *i.e.,* when *ethyl acetate* is made to react with (freshly prepared) *sodium ethoxide* **($NaOC_2H_5$)**, it rapidly undergoes a **condensation reaction.** However, after careful *acidification* one gets the product known as a **β-ketoester**, ***ethyl acetoacetate*** (commonly termed as **acetoacetic ester**):



Explanation: A *condensation* of this particular nature often takes place with several *other esters* and are invariably called as the **Claisen condensations.*** Very much similar to the **'aldol condensation'** (see section 3.1.6.1), the **Claisen condensations** do critically involve the **'α C-atom'** of one molecule and the respective **carbonyl (>C=O) moiety** of another.

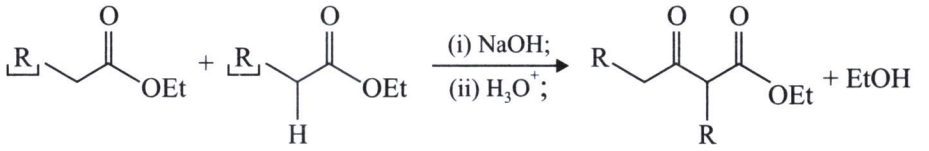
Examples: Reaction between Ethyl pentanoate and sodium ethoxide yields the **β-keto ester** as given under:



Remarks: In case, we may have a close look at the *two* aforesaid examples, it would be quite evident that the overall ***two*** **reactions** intimately involve a condensation wherein:

- **one *'ester'* loses an α H-atom**; and
- **second loses an *'ethoxide ion'*.**

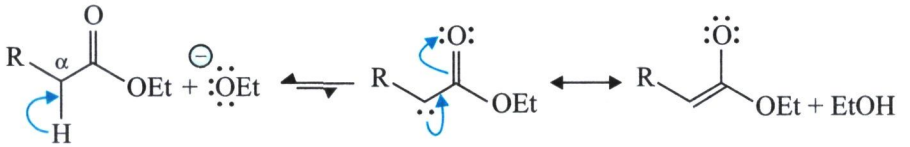
Thus, we may have the following expressions:



* Claisen L and Lowman O: *Ber*, **20** : 651 (1887)

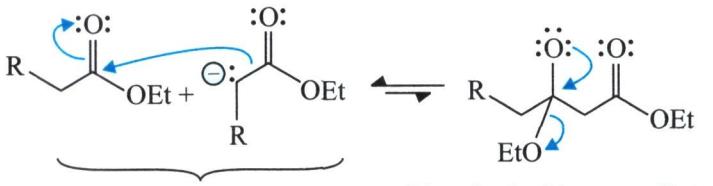
Mechanism of Claisen Condensation: It essentially involves *four* sequential steps which shall be briefly discussed in the sections that follow:

Step-1:

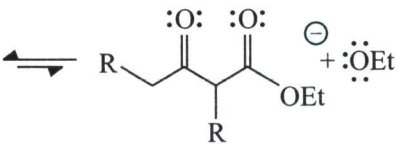


EXPLANATION: Obviously, an **alkoxide base** eliminates an **α-proton** from the *ester* thereby resulting into the formation a **nucleophilic phenolate ion.** Though the so-called **α-protons** of an *ester* are not found to be as *acidic* as those of the **aldehydes** and **ketones** the resulting **enolate ion** gets duly stabilised due to the phenomenon of resonance in an identical manner.

Step-2:



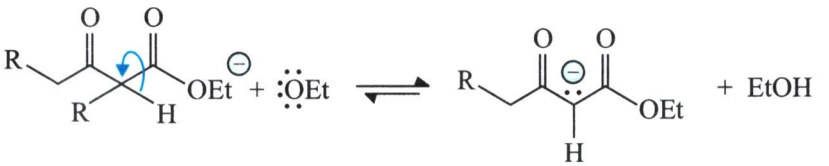
Nucleophilic addition **Tetrahedral intermediate and elimination**



β-Dicarbonyl system

EXPLANATION: In the above instance the **enolate ion** attacks specifically the **carbonyl (>C═O) C-atom** of *another ester molecule,* thereby forming a **tetrahedral intermediate.** This intermediate in turn expels an **alkoxide ion,** resulting in the substitution of the **alkoxide ion** by the moiety derived from the **enolate.** Hence, the overall net result is the ***nucleophilic addition—elimination*** at the respective ester *carbonyl (>C═O) moiety.* Importantly, the **overall equilibrium** for the ensuing process remains quite unfavourable so far; and hence, it is drawn towards the **'final product'** by the precise removal of the so-called ***acidic α H-atom*** right from the **new β-dicarbonyl system.**

Step-3:

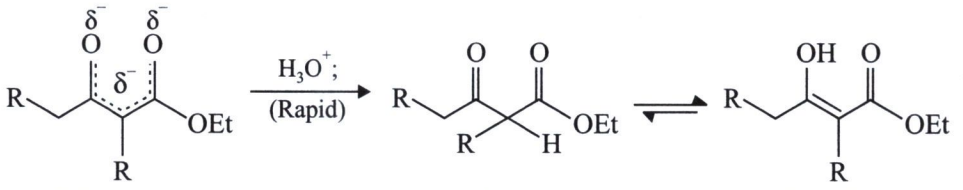


β-*keto* Ester [pKa~I; Stronger Acid] **Ethoxide ion [Stronger Base]** **β-keto ester anion [Weaker Base]** **Ethanol [pKa = 16; Weaker Acid]**

EXPLANATION: In this particular case, an **alkoxide ion** helps to remove an ***alpha*-proton** from the *newly formed condensation product*, thereby indulging in the ***resonance stabilized* β-*keto* ester ion.** However, this step is found to be extremely favourable and is solely responsible for establishing

the *overall equilibrium* towards the ultimate **product formation.** Hence, the **alcohol by product** (ethanol in this instance) may be distilled from the reaction mixture as and when it is generated, which further aid in *drawing the equilibrium towards the desired product.*

Step-4:



β–*Keto* ester [in equilibrium mixture of its *keto* and *enol* forms] ***Keto*-form** ***Enol*-form**

EXPLANATION: In fact, the addition of an acid (hydronium ion) quenches the reaction by affording these ***two*** **critical steps**:

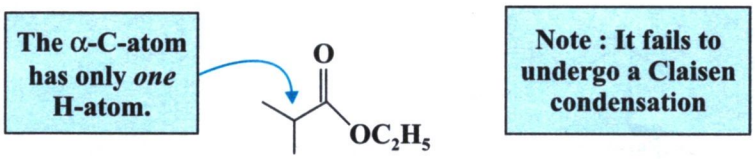
- **neutralisation of the base,** and
- **protonation of the Claisen condensation product.**

Besides, the so-called **β-*keto* ester** predominantly exists as an *equilibrium mixture* of its ***keto*** **and *enol* forms** respectively.

How do we avoid *'transesterification'* between a reaction of an ester with an alkoxide ion? It has been observed that an intended reaction between an *ester* and an *alkoxide ion*—one should use with extreme care an **'alkoxide'** that essentially possess the ***same alkyl moiety*** as that of the **alkoxyl group of the ester.** Amazingly, this particular critical step does avoid the **transesterification phenomenon.*** The resulting *methyl and ethyl esters* are proved to be the most prevalent as well as common **'ester-reactants'** in such *synthesis.* Perhaps this could be the most probable reason one makes use of **sodium ethoxide** (C_2H_5–ONa) as and when the so-called **'ethyl esters'** are duly involved; whereas, the usage of **sodium methoxide (CH_3ONa)** are prevalent when the **'methyl esters'** are involved.

Limitations of Claisen Condensation: It has been proved beyond any reasonable doubt that there are certain highly specific instances whereby the **'esters'** which have only ***one*** **α H-atom** do not undergo the usual **Claisen condensation** effectively.

Example: Ethyl 2-methyl propanoate provides a befitting example:



Ethyl 2-methyl propanoate

* That eventually comes into play with the **alkoxides** almost by the same mechanism as the **base-promoted ester hydrolysis.**

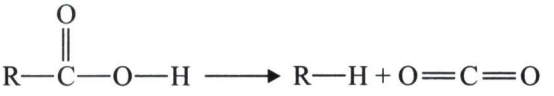
Remarks: An introspection of the **'mechanism'** just provided shall render it abundantly clear that an ***ester*** having specifically only **one α H-atom** will not possess an **acidic H-atom** when ***step-3*** has been obtained. Thus, the aforesaid ***step-3*** does cater for an appropriate favourable equilibrium that eventually ensures the success of the on-going reaction.

3.3.1.6.2 Elimination Reactions

There exist a host of **elimination reactions** and ***decarboxylation*** is a typical example where it predominantly involves the **carbanion** as a vital ***intermediate.***

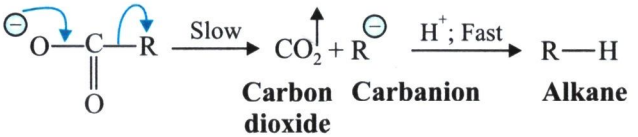
Decarboxylation: The loss of a **carbon dioxide (CO_2)** from a *carboxylic acid molecule* is termed as **'decarboxylation'.**

Examples:



A carboxylic acid **Alkane** **Carbon dioxide**

The above reaction may be further expatiated as under:



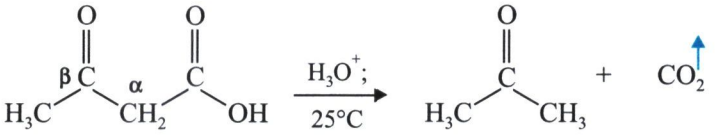
Carbon dioxide **Carbanion** **Alkane**

In a broader perspective, **decarboxylation** may ***not*** prove to be an **important reaction** for **most carboxylic acids**; however, there are some types of **carboxylic acids** that are ***decarboxylated*** readily, such as:

- **β-*keto* acids**
- **Malonic acid derivatives**, and
- **Carbonic acid derivatives,**

which shall now be exemplified individually as under:

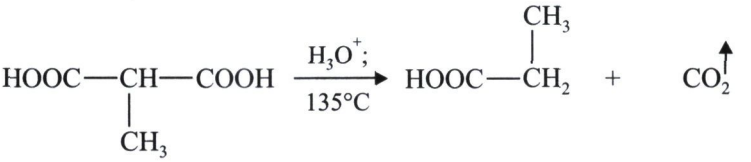
(*a*) **β-*keto* Acids:** The carboxylic acids having a ***keto*-group** located at the **β-position**—gets rapidly decarboxylated at the room temperature in an ***acidic solution.***



Acetoacetic acid [a β-*keto*acid] **Acetone** **Carbon dioxide**

Comments: The decarboxylation of a **β-keto acid** involves particularly an ***enol intermediate*** which is formed duly by an **internal proton** transfer from the *carboxylic acid moiety (—COOH)* to the respective *carbonyl oxygen atom (>C=O)* present in the ***ketone.*** Hence, the **'enol'** gets transformed almost spontaneously right into the corresponding ***'ketone'*** ultimately.

(*b*) **Malonic acid derivatives:** They usually get readily decarboxylated on heating in an acidic environment (H_3O^+) as shown under:



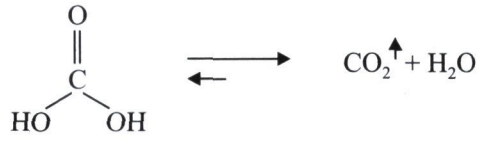
Methyl malonic acid **Propionic acid** **Carbon dioxide**

Comments: The above reaction that also fails to take place in a *basic medium*, bears a close resemblance to the *decarboxylation* of the respective **β-keto acids** since both ***malonic acid*** and ***β-keto acids*** do have a *carbonyl (>C=O) moiety* to the **carboxyl group.**

(*c*) **Carbonic acid derivatives:** It has been duly established that the **carbonic acid** is fairly **unstable** and **decarboxylates** almost spontaneously in an acidic environment to **carbon dioxide (CO_2) and water (H_2O).**

Remarks: The **carbonic acid** is produced reversibly when CO_2 is slowly bubbled into water; and thus, the **carbonic acid** renders the ensuing ***'Carbonated beverages'*** their desired acidity, while the **CO_2** provides them their excellent ***'fizz'***.

We may have the following expression:

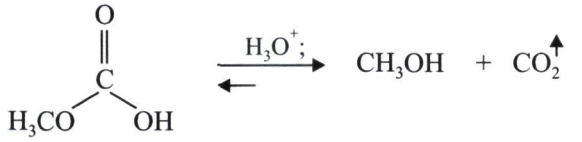


Carbonic acid **Carbon dioxide** **Water**

Likewise, any ***'carbonic acid derivative'*** having a ***free*** **carboxylic acid (—COOH) moiety** shall also, **decarboxylate** under the influence of the prevailing **'acidic conditions'.**

Thus, one may express the following reactions:

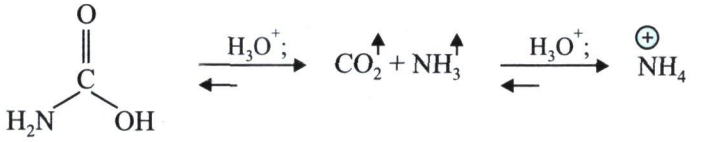
(*i*)



Methyl carbonate **Methanol** **Carbon dioxide**

i.e., **methyl carbonate** in an *acidic environment* gives a mole each of **methanol** and **carbon dioxide.**

(*ii*)



Carbonic acid **Ammonium ion**

i.e., **carbonic acid** in an acidic condition gives a mole each of **carbon dioxide (CO_2)** and **ammonia (NH_3)**, which under environment further yields the so-called **ammonium ion (NH_4^+).**

Special Notes

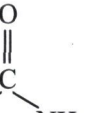
1. It has been proven beyond any reasonable doubt that under the ensuing **'basic conditions'**—the respective *carbonic acid* (*HOCOOH*) and its *derivatives* do exist as:

   'Carboxylate salts and fail to undergo decarboxylation'.

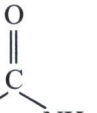
   Example: The **Na-salts** of carbonic acid [*viz.,* **sodium bicarbonate ($NaHCO_3$)**], and **sodium carbonate (Na_2CO_3)**], are recognised to be quite ***"familiar stable compounds"***.

2. **Carbonic acid diesters and diamides:** These are **fairly stable** in character.

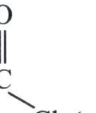
   Example: These essentially comprise:



❑ **Dimethyl carbonate :** H_3C NH_2 (– a **diester of carbonic acid**);



❑ **Urea :** H_2N NH_2 (– a **diamide of carbonic acid**); and



❑ **Phosgene :** Cl Cl (– an **acid chloride**).

3.4 FREE RADICALS

The **'free radical'** refers to a *C-centered radical* having the following *two* specific criteria:

- **an *'unpaired electron'* (·) located on a C-atom**; and
- **a *'formal charge'* of zero.**

In a more generalized version, a **free radical** relates to:

➢ **an atom,** or

➢ **a group of atoms,**

possessing an ***'unpaired electron'***.

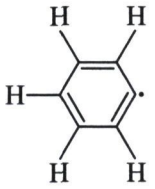
Nevertheless, the aforesaid specific *'definition'* critically embraces certain such entities, for instance:

- **stable inorganic molecules,** and
- **stable atoms,**

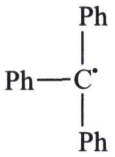
including **NO, NO_2, NR** and **Cl**; besides, **O_2** may also be included since it possesses ***two*** **unpaired electrons [:O:].**

Examples: A few typical examples are enumerated as under:

- **Methyl radical** : $\dot{C}H_3$
- **Vinyl radical** : $CH_2{=}\dot{C}H$
- **Phenyl radical** :



- **Triphenylmethyl radical** :



Interestingly, the **'radicals'** are most prevalently termed as **'Free Radicals'.** Perhaps the actual *genesis* of this terminology arose right from the ***earlier*** **nomenclature systems** prevailing wherein it was duly designated as a ***substituent moiety*** which was indeed preserved as the—

'specific typical *'unit' via* a chemical transformation'.

Comments: In true sense, the **methyl (CH_3) moiety** does serve as a *substituent* which was known categorically as the **'methyl radical'**; and hence, a so-called **neutral CH_3 moiety** eventually turned into a ***'free radical'***.

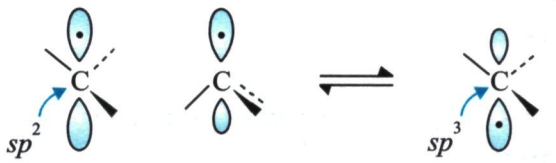
NOTE: **As to date, the *two* common terminologies *viz., 'radical'* and *'free radical'* are now being used almost *interchangeably.***

3.4.1 Structure of Free Radicals

It has been duly established that the **'alkyl free radical'** do possess a *planar* (*i.e., trigonal*) structure having ***sp*^{2}-bonding** with the so-called strategic location of an ***odd electron*** **in a *p*-orbital.** However, if the bonding is ***sp*^{3}** only then the following ***two*** **sequential critical events** are possible, namely:

- **rapid inversion of the *'pyramidal structures'*, and**
- **location of the *'odd electron'* in *sp*^{3}-orbital,**

as shown explicitly as under:



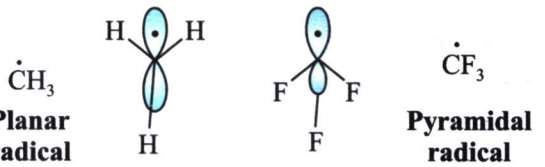
Planar **Pyramidal**

Remarks: Therefore, there are only ***two*** **possible structures** meant for the ***simple alkyl radicals***, for instance:

- ***planar*** **with an *'odd electron'* in a *p*-orbital, or**
- ***pyramidal*** **with an *'odd electron'* in a *sp*^{3}-orbital.**

Based on the **'electron-spin resonance (ESR)'** studies the ensuing spectra of *methyl* (CH_3) as well as other similar *simple alkyl radicals* indicate predominantly that all such ***'radicals'*** do critically exhibit the **'planar structures'**.

Thus, we may have:



Experimental Evidence: It has been duly established that there prevails an ample **experimental evidence** suggesting that the so-called **'alkyl radicals'** invariably possess either:

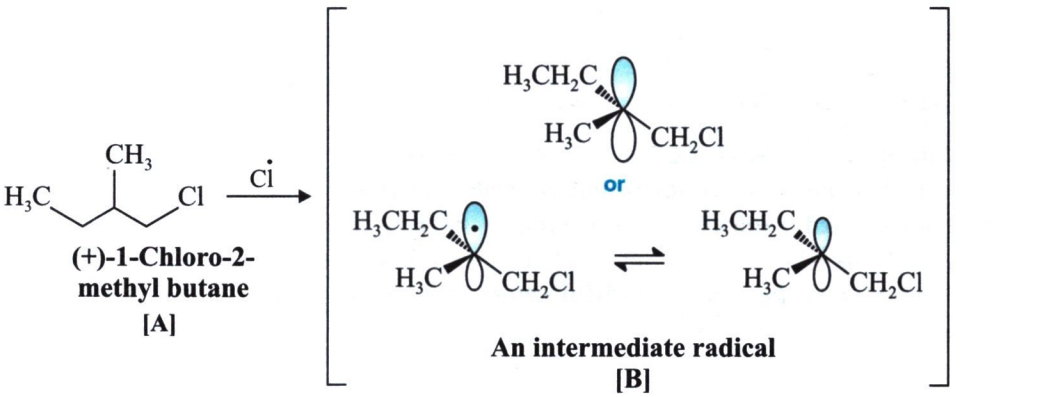
- **planar structures,** or
- **pyramidal structures,**

and obviously, they may become ***planar via inversion*** (*viz.,* ammonia, NH_3).

Examples: The careful *chlorination* of **(+)-1-chloro-2-methyl butane (A)** ultimately gave rise to the formation of a ***racemic*** **(±) 1,2-dichloro-2-methyl butane (C).** However, the overall net results seem to be extremely ***consistent*** with a specific **intermediate radical (B).** Amazingly, the **product (B)** has been shown to be **planar** or that crucially retains only a *small barrier to inversion,* in order to afford the ensuing *reaction of (B)* may take place almost to the same extent from either ***'face'*** **of the radical centre.**

Comments: The observed critical *loss of optical activity profile* elegantly demonstrates that probably the ***'free radical'*** happens to be **planar** in nature.

The above sequence of reactions may be shown as under:



Salient Features of Free Radical Reactions

There are *three* cardinal salient features of **'free radical reactions'**, such as:

- **Distinguishing between Planar and Non-planar compounds by spectroscopic data,**
- **Estimates of the geometry of substituted radicals,** and
- **Stabilization *'Ethyl Radical' via* Pyramidalization.**

(a)* Distinguishing between Planar and Non-planar Compounds by Spectroscopic Data:** It has been ascertained duly that the spectroscopic data has been used meticulously to distinguish between the **'planar'** and **'non-planar'** compounds by inverting readily the ***specific* radical centres.** However, the respective ***hyperfine* coupling constant (a_α) present in the **methyl radical ($\dot{C}H_3$)** is found to be **23.0 G**, that eventually designates a typical value for the splitting of an **EPR-signal** by the protons duly attached to a ***'radical centre'*.**

***(b)* Estimates of the Geometry of Substituted Radicals:** These estimates may be accomplished adequately from the analysis of such *species* that are labelled with ^{13}C exclusively.

Interestingly, *two* renowned organic chemists, Fessenden and Schüler, specifically determined that the ***angle* F—C—F** duly present in the so-called **'trifluoromethyl radical'** is found to be **111.1°** (*i.e.*, almost close to the **sp^3 hybridization).** In addition, the ever enhancing level of **'F-substitution profile'** renders the radicals to go from:

"planar sp^2 hybridization for $\dot{C}H_3$ (methyl radical) to nearly sp^3 hybridization for $\dot{C}F_3$ (trifluoromethyl radical)."

Amazingly, the aforesaid conclusion quite fall in line with the consistent results of the **INDO-calculations;** and hence, the geometrics of the **fluoromethyl radicals [$\dot{C}F_3$]** duly calculated by this procedure may be depicted as in Fig. 3.1 under:

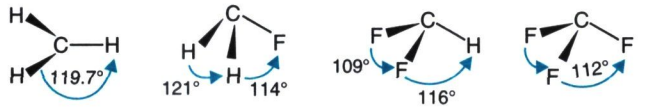


Fig. 3.1: The calculated geometrics from INDO calculations of fluoro-substituted methyl radicals.

(c)* Stabilization of 'Ethyl Radical' *via* Pyramidalization:** An elaborated progressive study not only reveals that the **'fluoro-substituted radicals'** are ***non-planar in nature, but also the so-called **'alkyl-substituted radicals'** are observed to be ***non-planar*** in character. In fact, it was Paddon-Row and Houk who primarily put forward quite explicitly the ensuing **hydrocarbon radicals** affecting the ***pyramidalization*** of the **radical centre** due to ***two* major effects,** namely:

- **enhanced staggering of bonds to the particular *radical centre* that critically *gets bound to the adjacent atoms*;** and
- **marked and pronounced increase in the *hyperconjugation* profile of the *p-orbital* along with one of the *adjacent* σ-*bonds*.**

Figure 3.2 shows evidently the stabilization pattern of the ethyl radical *via* the pyramidalization phenomenon:

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* **Coupling Constant:** It recognizes the splitting pattern in **NMR—spectroscopy;** and are determined by measuring the separation in hertz between each peak of a signal.

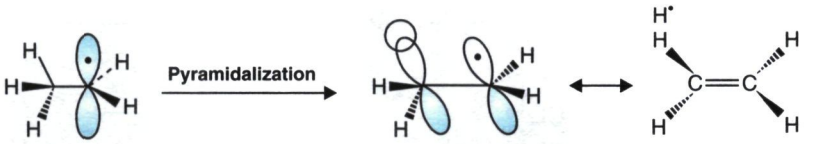


Fig. 3.2: Illustration of the stabilization incurred in ethyl radical *via* pyramidalisation.

Remarks: As depicted in Fig. 3.2 the **pyramidalization** of the **ethyl radical** [$\dot{C}_2H_5$] clearly renders the *C—H bonds* located strategically upon the *methylene group* (—CH_2—) is found to be more ***staggered*** with respect to the **2 of the C—H bonds** on the CH_3 **moiety.** However, simultaneously the ***p*-orbital** located on the **methylene** (—CH_2—) **group** actually turns out to be more parallel with respective orbitals forming the 3rd **C—H bond**; and thereby helps in the stabilization of the ensuing ***unfilled*** **orbital systems** of the said radical.

3.4.2 Formation of Free Radicals

In a situation when the ***'bonds'*** undergo cleavage; and thereby one atom gets hold of both the ***bonding electrons,*** the phenomenon is termed as **'heterolysis'** and the resulting products are known as **'ions'.**

Homolysis: It relates to the process when the bonds undergo cleavage and the atoms do retain **one bonding electron each** and the emergent products are invariably known as **'radicals'.**

General methods to form 'Free Radicals': There are *three* known **general methods** which may be used prevalently to form the **'Free Radicals',** namely:

***First* method:** In this case the radicals may be formed almost directly by any of the following *three* processes:

- **thermal technique,** or
- **photochemical method,** or
- **redox processes,**

which eventually accomplish the ***homolytic dissolution*** of a **2-electron bond.**

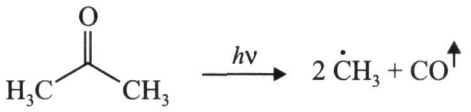
***Second* method:** In this instance, the *two* specific breeds of chemical entities (compounds), such as:

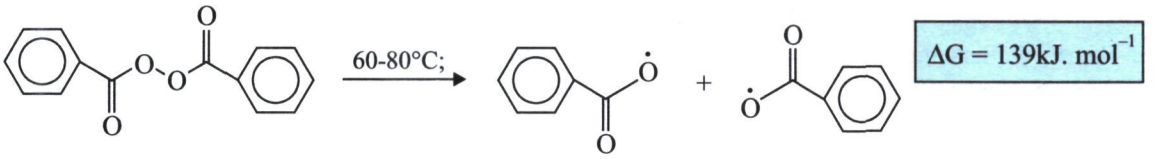
- **organic peroxides,** and
- **azo compounds** [***viz.,*** **azo-bis-isobutyronitrile (AIBN)**],

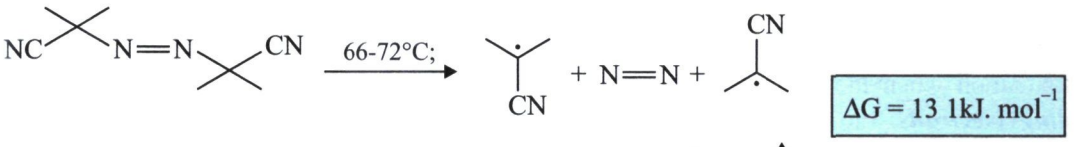
that critically possess rather ***weaker bonds*** which ultimately dissociate to form the **radicals.**

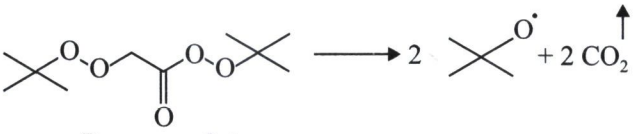
Third* method:** In this typical example the respective **'halogens'** seem to be ***homolyzed quite rapidly in the presence of light (UV).

Following are a few specific examples to expatiate the above statement of facts:









Peroxyoxalate

Special Features for Free Radicals

The following specific and typical, examples do represent fully the special features for the **'free-radicals'** often encountered in the domain of ***organic chemistry,*** such as:

(*a*) **Organometallic Compounds:** One may invariably come across certain highly specific **organometallic compounds,** such as:

- **organomercuries**, or
- **organocobitals**,

that often exhibit reasonably *feeble C-metal bonds;* and hence, are *homolyzed* most easily to yield the **carbon-centred radicals.**

$$R—Hg—R \longrightarrow 2R\bullet + Hg$$

(*b*) **Emergence of Radicals from Chemical/Electrochemical/Reduction of Stable Molecules:** First and foremost let us examine the status of the **'single electron-transfer'** phenomena whereby one may obtain primarily the generated following ***two*** **species:**

➢ **cations (for *oxidation*)**, or

➢ **anions (for *reduction*)**,

that may finally undergo *fragmentation* to produce both **radicals** and **ions.**

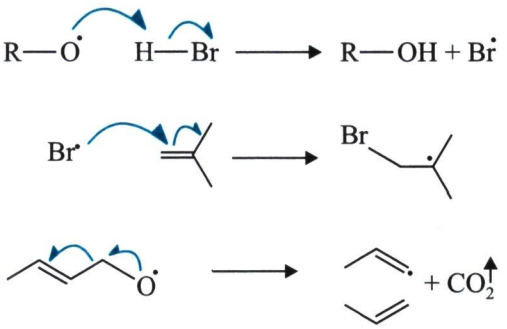
Example: Sargent *et al,* found out that in the solutions of **1, 2-dimethoxyethane, the** *radical anion of naphthalene [i.e., sodium naphthalenide* (*viz.,* **Na^+ and Ar^-**) helped in the transferance of an electron to the corresponding **'propyl iodide'.** However, the follow up loss of an **iodide ion**

$[I^-]$ from the respective **iodide ion** from the incumbent **'propyl iodide radical anion'** duly generated from the **'propyl radical'.**

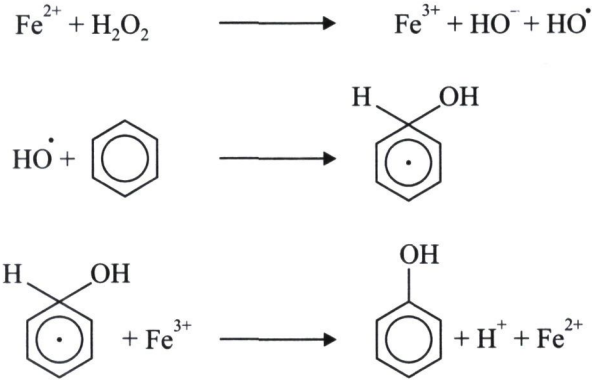
In addition, the **radicals** may also be produced right from *other radicals* by such known procedures:

- **substitution** (*i.e.*, **abstraction**),
- **addition,** or
- **elimination.**

Thus, we may have the following expressions:



(*c*) **Fenton's Reagent*:** It has been demonstrated exclusively that the **Fenton's reagent** usually produced by the interaction of $\mathbf{H_2O_2}$ with $\mathbf{Fe^{2+}}$ (ferrous ion) oxidises the *organic chemical substances* as shown under:



Comments: In an exactly similar manner the Fe^{2+} *(ferrous ions)* are made use of in the production of **'radicals'** right from the following ***two*** **chemical entities,** namely:

- **Chloramines [R_2NCl],** and
- **Hydroperoxides [ROOH]** (also called **'superoxide dismutase'**)**.

* **Fenton's Reagent:** It is an admixture of *hydrogen peroxide* (H_2O_2) and *ferrous salts.*

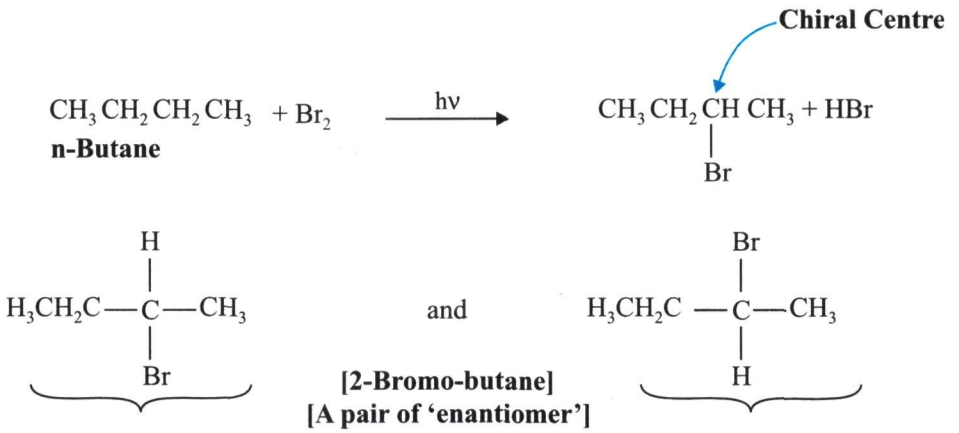
** **Superoxide Dismutase:** An enzyme that catalyses the **dismutation reaction of superoxide anion to dihydrogen peroxide;** and dioxygen to protect us by catalyzing the destruction of the toxic superoxide radical.

Thus, the critical transference of ***one* electron** to or from a species comprising only the ***paired* electrons** finally gives rise to the formation of the desired **'free-radicals'.** Obviously, the **'electron transfer'** may actually take place from both ***charged*** and ***neutral molecules.***

$$Fe^{2+} + R_2NCl \longrightarrow Fe^{3+} + Cl^- + R_2N^\bullet$$
$$Fe^{2+} + ROOH \longrightarrow Fe^{3+} + OH^- + RO^\bullet$$

3.5 STEREOCHEMISTRY OF RADICAL SUBSTITUTION REACTIONS

It would be worthwhile to mention at the very outset that if a **radical substitution reaction** forms a ***chirality*** (or an ***asymmetric carbon centre***) in the final chemical entity (compound), we may expect the formation of both the **R** and **S** ***enantiomers,*** as given under:



Remarks: These essentially include:

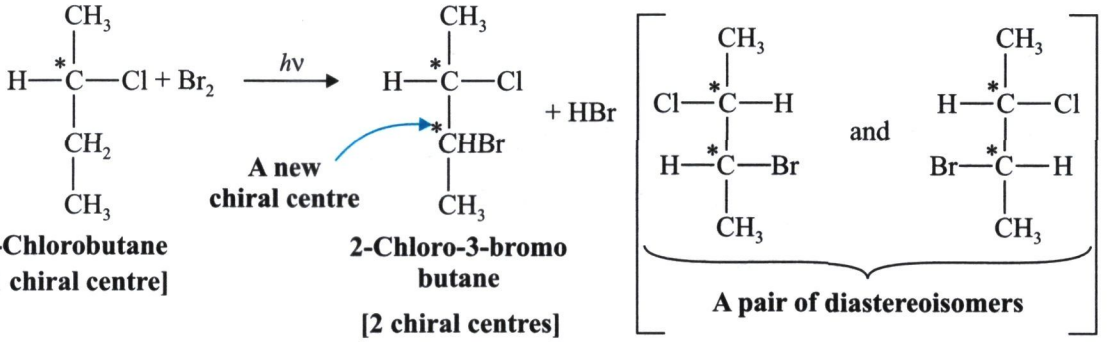
- The **C-atom** holding the *unpaired electron* is found to be the ***sp*²-hybridized** *i.e.,* the ***three* functional moieties** to which it is duly bonded **lie in a plane** exclusively:
- However, the ***incoming*** **halogen atom** predominantly bears an almost equal access to both sides of the plane; and
- Consequently, both the ***R and S enantiomers*** are duly accomplished in **equal quantum.**

Importantly, one may further expatiate the *stereochemistry of radical substitution reactions* with the help of the following ***two* classical examples,** namely:

Examples: Let us examine a reactant already having a ***chiral centre***; whereas the *radical substitution reaction* forms a ***second* chirality centre**—in such a manner so as to form a **pair of diastereoisomers usually in unequal quantum.**

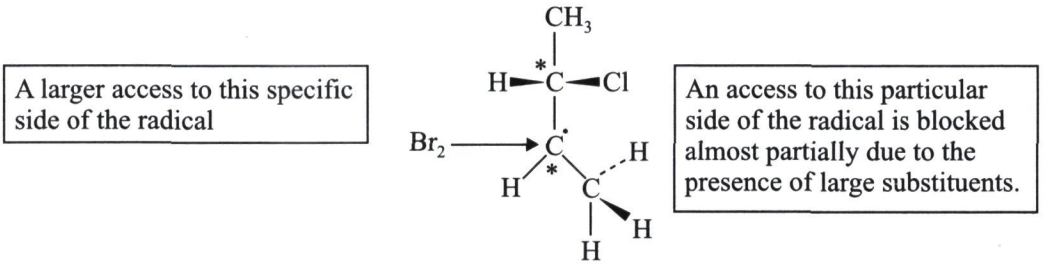
Why do we obtain the 'diastereoisomers'? The **diastereoisomers** may come into being by virtue of the fact that the ***new chirality centre*** so created in the **'newer product'** should have either the **'R' or the 'S' configuration.** Nevertheless, it may be observed that since none of the bonds engaged to the creation of the so-called **'chirality centre'** gets cleaved in the course of the on-going reaction.

Thus, we may have the following expression:



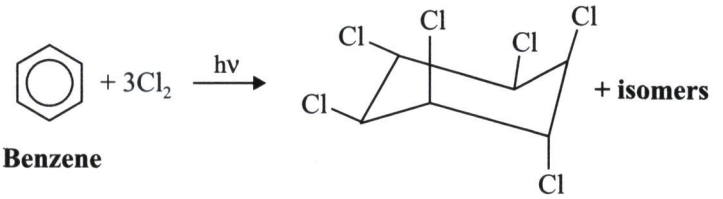
Comments: Obviously, one of the ***two*** **diastereoisomers** thus obtained should be available in **greater quantum** *vis-a-vis* the other species. Since the incoming **Bromine (Br_2)** will definitely exhibit a distinct greater access to one side of the so-called **'radical intermediate'** in comparison to the other perhaps on account of the presence of the ***original chirality centre.***

Thus, we may have the following revelations:



Status of Benzenoid Compounds: Importantly, the **benzenoid compounds** may also react elegantly by the careful addition of the **chlorine atoms.**

EXAMPLE: The critical *irradiation* of **benzene** and **chlorine** provides the production of a mixture of the ***stereoisomeric*** **hexachlorocyclohexanes** as shown below:



3.6 CARBENES

The **carbenes** represent the *neutral reaction intermediates* comprising essentially a bivalent **C-atom** wherein the **C-atom** is:

- **bonded covalently to 2 other atoms or moieties,** and

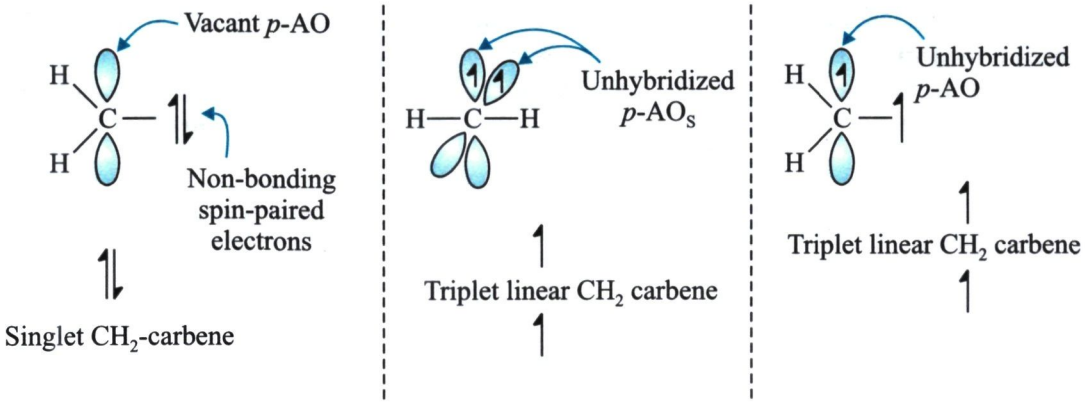
- **possesses 2 other valence electrons distributed evenly between the two non-bonding orbitals.**

Singlet Carbene: In this case, the electrons do exist in a ***spin-paired* state.**

Triplet Carbene: In this instance, the *spins of electrons* remain **parallel** to one another prevalently.

Explanations: In ture sense, the **C-atom** present duly in a **singlet carbene** is specifically ***sp*^{2}-hybridized** wherein the *spin-paired electrons* do retain an ***sp*^{2}-orbital**; and hence, the overall shape of such **carbene** happens to be **planar.** However, when the *C-atom* present in several **triplet carbenes** is *sp*-hybridized particularly with one electron each having **parallel spin** in the remaining *two* unhybridized ***p*-atomic orbitals** (*i.e.*, ***p*-AOs**). In fact, these resulting **carbenes** do exhibit a **linear shape.** Besides, the so-called ***bent* triplet carbenes** are also encountered frequently wherein the *C-atom* is ***sp*^{2}-hybridized**, and the ***two* non-bonding electrons** that occupy an ***sp*^{2}-atomic orbital** (or ***sp*^{2}-AO**); and an **unhybridized *p*-AO** having a parallel spin.

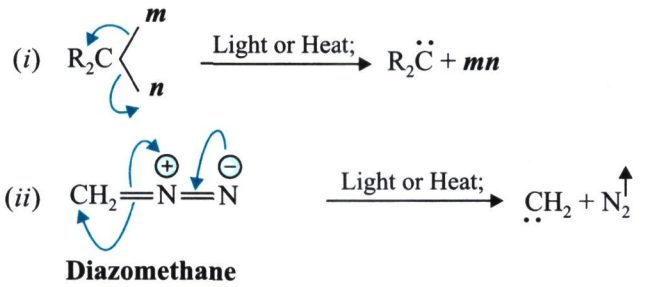
Thus, we may express the various **carbene transformations** as given under:



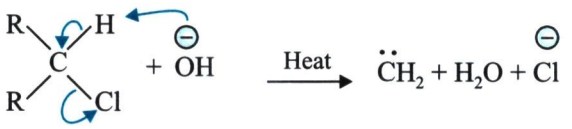
Generation of Carbenes: In general, the **carbenes** do designate as the ***'endothermic* species'***; and, therefore, for their formation energy (heat) is supplied in the form of *light* or *heat.*

There are *two* common methods that are usually adopted for the **generation of carbenes,** namely:

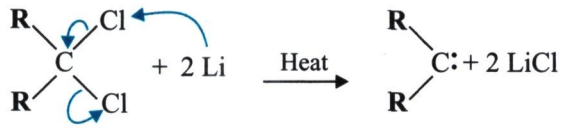
***(a)* Thermal or Photolytic α-Elimination Reactions:** Following are a few frequently employed methods to generate **carbenes** using **thermal or photolytic α-elimination reaction:**



* **Endothermic:** It refers to a process in which the system under study absorbs ***heat*** from its surrounding *i.e.*, a process in which ***heat*** is required.

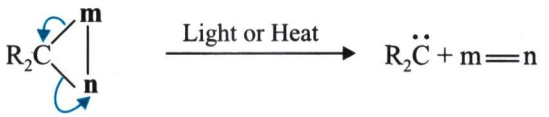
(*iii*) 

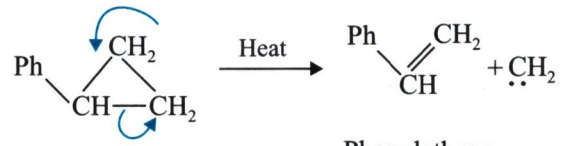
Chloroform

(*iv*) 

***gem* -Dichloro alkane**

(*b*) Thermal or Photolytic Cycloelimination Reactions: The **carbenes** may also be generated by making use of **thermal or photolytic cycloelimination reactions** as exemplified below:

(*i*) 

(*ii*) 

Phenylcyclopropane Phenylethene

Common Reactions of Carbenes

It has been duly ascertained that the **'singlet carbenes'** are invariably much more reactive than the **'triplet carbenes'.** Obviously, one could reasonably expatiate such a variation in reactivity perhaps due to the ensuing **electron repulsion energy** which should be duly overcome to ***pair* 2-electrons in an orbital.** Therefore, the ground state of a **carbene** is the ***triplet state*** precisely. In fact, it leads one to believe that both **singlet and triplet carbenes** do designate the **highly reactive known carbene species.**

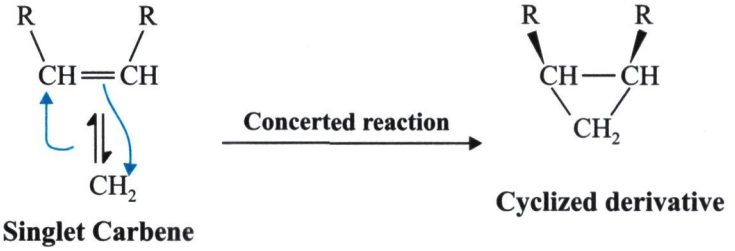
NOTE: **Interestingly, their reactivity may be largely moderated by making use of the *Cu-powder* in their reactions as and when needed.**

Following are a few synthetically viable and important variety of reactions that **carbenes** usually undergo, namely:

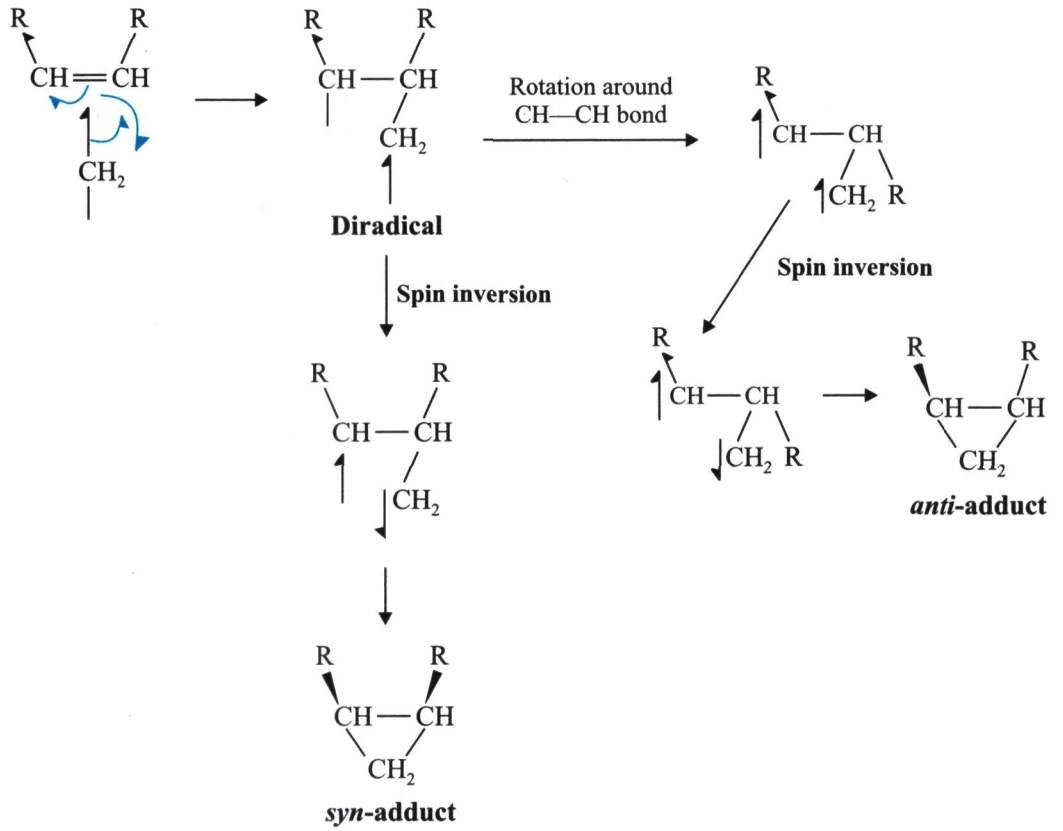
(*a*) π-Insertion Reaction: It has been shown that **carbenes** do undergo ***'cycloaddition'*** with **C=C (olefinic) bond** to yield the **cyclopropanes.** Thus, we may have the following *two* typical examples, such as

- **Singlet carbenes**—they usually undergo ***cis*-stereospecific** insertion with the respective ***cis*-alkenes** thereby producing the so-called ***thermodynamically less stable syn*-products.**
- **Triplet carbenes**—which eventually yield an admixture of both ***syn*-and *anti*-adducts.**

Hence, we may have the following expression:



Remarks: Amazingly, the afforesaid **'cycloaddition'** of the *singlet carbenes* happens to be a ***concerted phenomenon***, the *triplet carbenes* normally react, in various steps involving a ***'diradical intermediate'*** as shown below:



(*b*) σ-Insertion Reactions: Very much akin to the **π-insertions,** the **carbenes** do have a tendency to take part in the so-called **π-insertion reactions;** however, the reactions are of a little *synthetic importance* because they mostly occur indiscriminately.

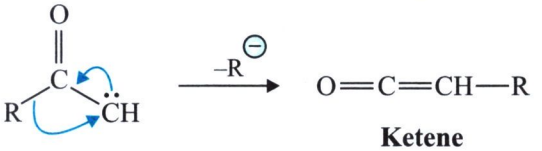
Example: $R_2\ddot{C} + X{-}Y \longrightarrow X{-}CR_2{-}Y$

(*c*) Reaction of Carbenes with Nucleophiles: The interaction of **carbenes** with the *nucleophiles* give rise to the formation of altogether different classes of chemical entities (compounds).

Example: $Ph_2\ddot{C} + \ddot{O}(H){-}R \xrightarrow{\sigma\text{-Insertion}} H{-}CPh_2{-}\ddot{O}R$

Carbene **Alcohol** **Ether**

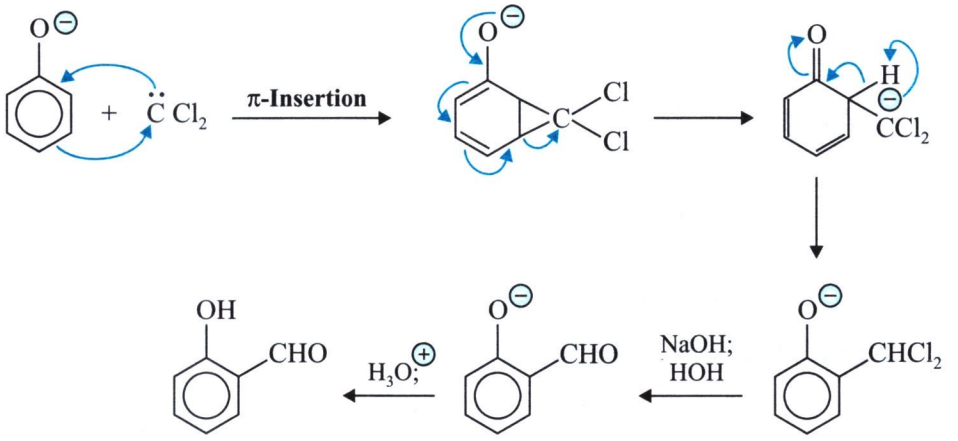
(*d*) Skeletal Rearrangements: ***Acyl carbenes*** normally, undergo an ***anionotropic* 1, 2-shift** so to yield the **'ketenes'** in the **Wolff-rearrangement*** as depicted under:



An acyl carbene **Ketene**

(*e*) Carbenes in Electrophilic Aromatic Substitution Reactions: Interestingly, the **carbenes** representing the electron-deficient species, would essentially take part in the typical **electrophilic aromatic substitution reactions *viz.*, Reimer-Tiemann Reaction.****

Example:



Salicylaldehyde
[*O*-Hydroxy benzaldehyde]

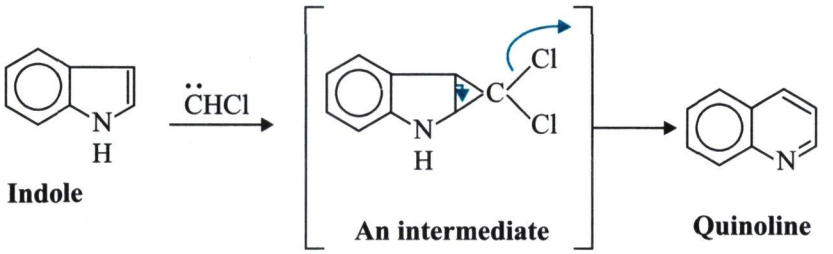
* Wolff L: *Ann.*, **394,** 25 (1912).

** Reimer K and Tiemann F: *Ber,* **9** : 824, 1268, 1285 (1876).

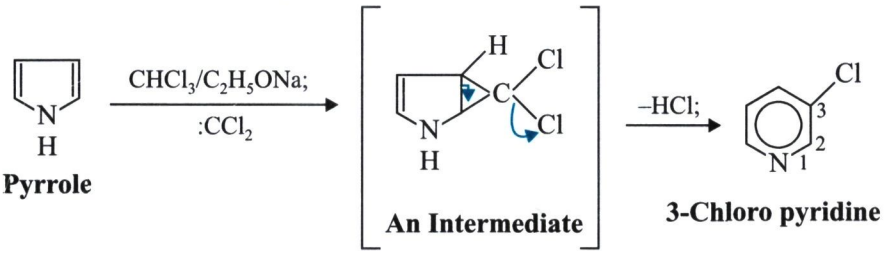
(*f*) Ring Expansion Reaction: It essentially involves the addition of a *halogenocarbene* across a **double bond (or olefinic bond).**

EXAMPLES: Following are *two* classical examples:

(*i*) Indole to Quinoline



(*ii*) Pyrrole to 3-Chloropyridine



Detection of Carbenes: The presence of even traces of **carbenes** in a mixture may be detected 100% by adopting any *one* of the following methods:

- **Electron Paramagnetic Resonance (EPR) Spectroscopy:** It may be employed effectively to detect the formation of the ***triplet carbenes*** exclusively. Obviously, these **carbenes** are absolutely *paramagnetic in nature* by virtue of the critical presence of **2 unpaired electrons** present in them.
- **UV and Visible Spectra:** The *rotational five structure* of the respective **UV and visible spectra** may specifically detect the formation of the following *two* types of the **carbenes:**
  - **singlet (*bent form*) carbene**; and
  - **triplet (*linear form*) carbene.**
- **π-Insertion Reactions:** These may also help in the *detection* and *distinguishing* the generation of **singlet and triplet carbenes.**

3.7 NITRENES (IMIDOGENES)

In a broader perspective, the **nitrenes** (or **imidogenes**) are invariably termed as the so-called ***nitrogen analogue of carbenes*** *i.e.,* **R—N.** Alternatively, it may be defined as the **electron deficient species** wherein the *N-atom* essentially bears a **sextet of electrons.**

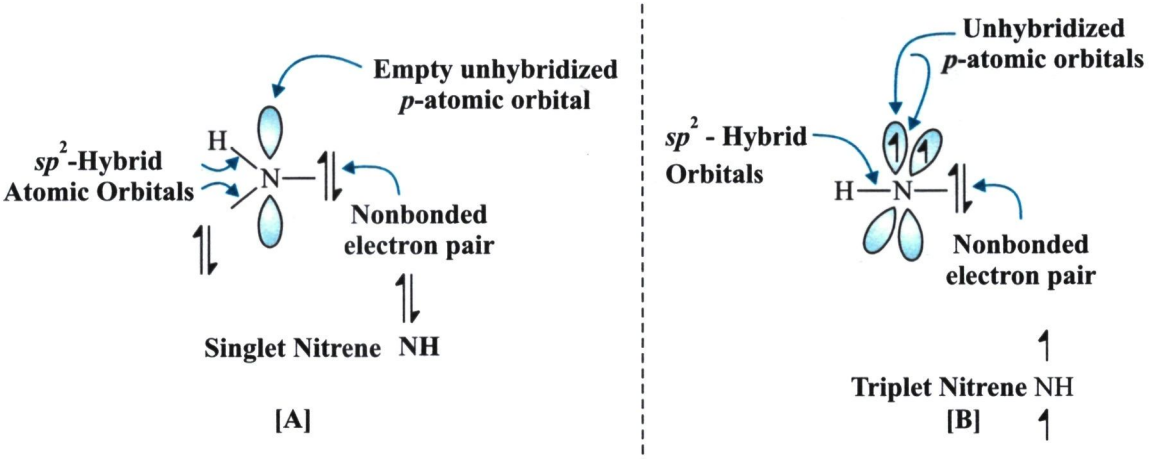
In other words, the **nitrenes** designate the specific ***neutral reaction intermediates.*** There are certain highly crucial criteria that are solely confined to the **nitrenes**, such as:

- Very much akin to the **'carbenes'**, the **nitrenes** do also may occur in the form of a **'singlet nitrene'** wherein the **N-atom** is particularly ***sp^2-hybridized.***
- Thus, the ***two*** **of the** ***three*** **hybrid atomic orbitals** prominently accomodate ***two*** **non-bonded electron pairs;** whereas, the ***third*** **hybrid atomic orbital (AO)** is engaged almost entirely in a **σ-bond formation.**

- It renders the so-called ***unhybridized p*-atomic orbital almost empty**; and the *shape* of such type of **nitrenes** happens to be **planar** in character.
- The **'nitrenes'** can also be formed in a typical ***triplet diradical state***, wherein the N-atom is ***sp*-hybridized.**
- Thus, ***one* of the *two* hybrid atomic orbitals (AOs)** does accomodate specifically a *non bonded electron pair*; whereas, the **other hybrid atomic orbital** is intimately engaged in a so-called **σ-bond formation.**
- Each and every ***unhybridized p*-atomic orbital** essentially accomodates an **electron with a parallel spin.**
- Ultimately, it imparts predominantly a typical ***diradical characteristic feature*** particularly to the respective **triplet nitrenes** which are eventually found to be *linear in shape.*

Thus, we may have the following expressions pertaining to the following *two* different **atomic orbitals (AOs)**, such as:

- **Empty unhybridized *p*-atomic orbital (A)**; and
- **Unhybridized *p*-orbitals (B).**

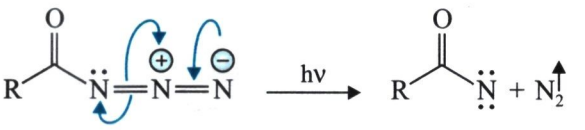


Generation of the 'Nitrenes': Following are the *two* distinct procedures adopted for the **generation of the 'nitrenes'**, such as:

***(a)* By Photolytic, Thermal or Base-catalyzed α-Elimination Reactions:** It has been amply proven that the **nitrenes** are duly generated by means of the **photolytic, thermal, or base-catalyzed α-elimination reactions.**

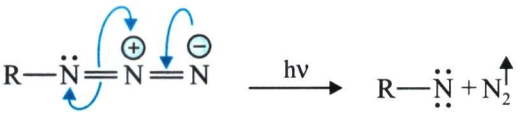
Examples: A few classical examples are as stated under:

- **Acyl azides to Acyl nitrene**



Acyl azides **Acyl nitrene**

- **Alkyl azides to Alkyl nitrene**



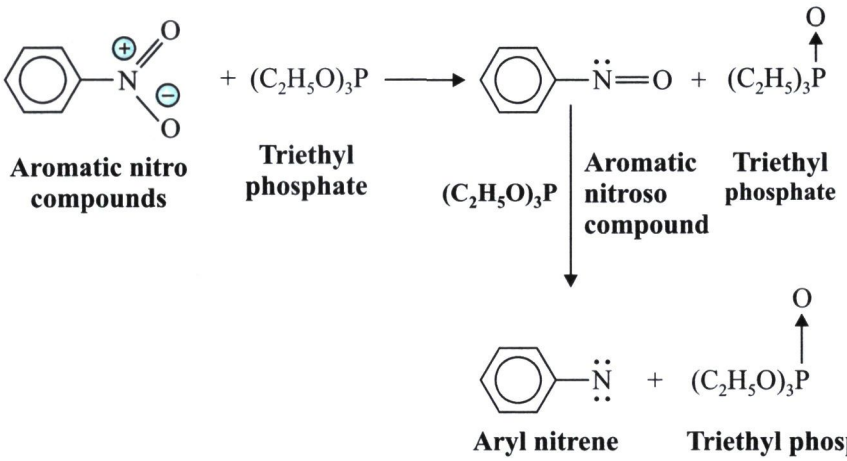
Alkyl azides **Alkyl nitrene**



N-Bromo amides **Acyl nitrene**

(*b*) By Reduction of Nitro Compounds with Trialkyl Phosphites: The usual critical reduction of the *nitro compounds* with *trialkyl phosphites* can be suitably exemplified by the help of the underlying sequence of reactions:

- **interaction of the aromatic nitro compounds with triethyl phosphate to yield an *aromatic nitroso compound*,** and
- **the resulting product on further treatment with triethyl phosphite to give an *aryl nitrene*.**



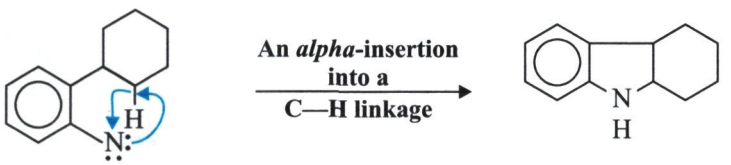
Aromatic nitro compounds **Triethyl phosphate** $(C_2H_5O)_3P$ **Aromatic nitroso compound** **Triethyl phosphate**

Aryl nitrene **Triethyl phosphate**

Reactions of Nitrenes: We normally come across *three* types of **reactions of nitrenes** which shall be discussed briefly in the sections that follows:

1. **Singlet Nitrene undergoes an *alpha*-insertion to yield the *secondary* amines.**

Example:

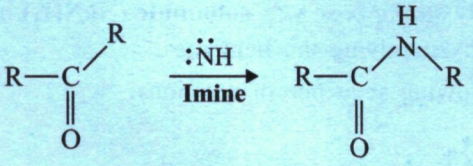


A singlet nitrene **A *secondary*-amine**

Remarks: Importantly, the **α-insertion** taking place into either

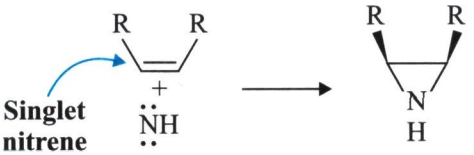
- **a C—C bond** or
- **a carbonyl (>C=O) moiety,**

of the **ketones** give **amides:**



A ketone **Amides**

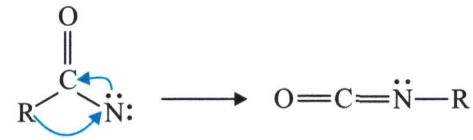
2. The π-Insertion of Nitrenes into a C=C bond yields Aziridines: Thus, the **C=C bond** present in a **singlet nitrene** when reacted with an **imine (:NH)** it results into the formation of an **aziridine** as shown below:



Imine **Aziridine**

3. An Acyl Nitrene undergoes the skeletal rearrangement to yield an Alkyl isocyanate.

Example: Skeletal rearrangement of an **acyl nitrene** into an **alkyl isocyanate.**



Acyl nitrene **Alkyl isocyanate**

Remarks:

(*i*) The aforesaid *skeletal rearrangement* is duly involved in the **Curtius and Hoffmann rearrangements.***

(*ii*) Interestingly, the so-called **'triplet nitrenes'** may also be detected and distinguished conveniently right from the *singlet nitrenes viz.*, **carbenes by Electron Paramagnetic Resonance (EPR) spectroscopy.**

3.8 ARYNES (BENZYNES)

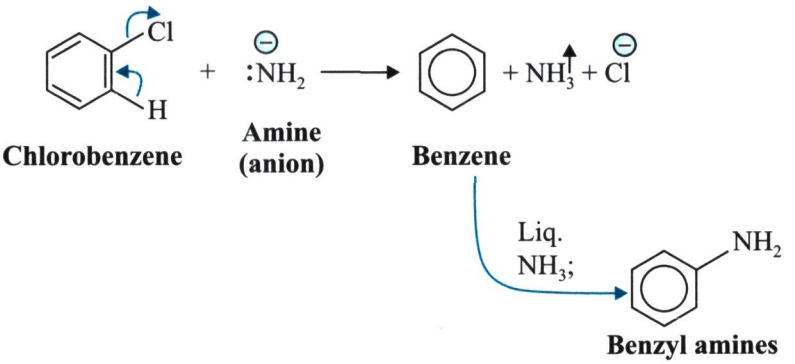
The **aryne (benzyne)** may be broadly defined as **'a neutral highly reactive intermediate wherein the usual inherent aromatic character of a chemical entity is not distributed pronounceneedly'**

* Curtis T: *Ber.*, **23** : 2023, (1890); Shioiri T. *Comp. Org. Syn*, **6** : 795–82, 1991.

Another school of thought relates the **arynes** as the ***aromatic reaction intermediates*** possessing a **formal C≡bond.** Thus, the *general nomenclature* of the ensuing intermediate is known as **'aryne'**; whereas, the new *emerging structure* with respect to the *benzene ring system* is termed as **'benzyne'.**

In true sense, the **arynes (*e.g.*, benzyl amine)** may be duly obtained when the so-called *aryl halides* **(chlorobenzene)** do undergo the successive ***elimination-addition* reactions** on being subjected to treatment with a reasonably *strong base viz.*, **sodamide ($NaNH_2$)** or **metal alkoxides (potassium butoxide: (Me_3COK)** thereby involving the **benzynes.**

Thus, we have the following sequence of reactions:

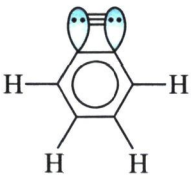


Important Observations

Following are certain vital and important observations pertaining to the **benzynes (arynes),** namely:

- In the particular instance for the presence of ***tripple bond*** in **acetylene (HC≡CH)** in which one may observe critically the following glaring facts:
  - ***two* C-atoms do form a σ-bond using the *sp*-atomic orbitals (AOs),** and
  - **remaining *p*-atomic orbitals (AOs),**

  are being utilized to form **2π-bonds** as well as the **tripple bond of benzyne.** Nevertheless, these are not found to be the same eventually since the inherent *benzene ring* is intimately associated with the established **'hexagonal chemistry'** to an appreciable extent.
- Besides, the **bonds** in ***'benzyne'*** **(aryne)** are formed actually in a sideways profile thereby overlapping the ***sp*^{2}-atomic orbitals (AOs)** located strategically to the ***two* adjacent C-atoms** precisely.
- Finally, the ***new bond* atomic orbital** lies very much along the *side of the benzene ring* having an almost **negligible interaction** taking place with **π-electron cloud** placed both above and below the **flat benzene (hexagonal) ring system** as depicted under:



NOTE: **Importantly, the prevalent weak sideways overlapping of the particular *sp^2-atomic orbitals (AOs)* that forms π-bond outside the benzene ring and also *out-of-the plane* of π-system of the benzene ring; and thus, renders the *benzyne* (*aryne*) extremely reactive in nature.**

Formation of Aryne (Benzyne) Based on an Elimination Addition Reaction

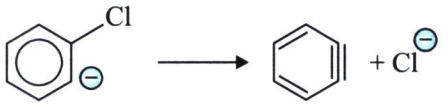
The actual formation of **aryne (benzyne)** is exclusively based upon an ***elimination-addition*** **reaction** that essentially involves the following **two cardinal steps,** such as:

Step 1: It relates to the **elimination step** that crucially involves the abstraction of a proton by amide to form the respective ***carbanion*** as given below:



Chlorobenzene **Carbanion** **Ammonia**

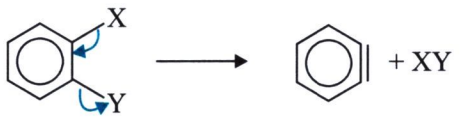
Step 2: It specifically concerns with the loss of the **halide ion** right from the ***carbanion*** (in *Step-1*) to yield the desired **aryne (benzyne)**, as depicted under:



Carbanion **Benzyne (Aryne)** **Chloride ion**

Generation of Benzyne: In a broader perspective the **benzynes (arynes)** are generated duly by the elimination of **2 *ortho* moieties** into a ***benzene*** **ring system.**

EXAMPLE:

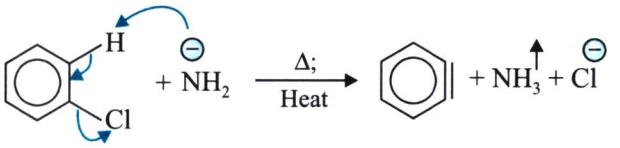


A Benzene ring system with 2-ortho moieties (X and Y) **Benzyne**

Four Different Methods to Obtain the 'Benzynes': There are indeed *four* distinct and different methods to obtain the desired ***'benzynes'*** which shall now be discussed briefly in the sections that follows:

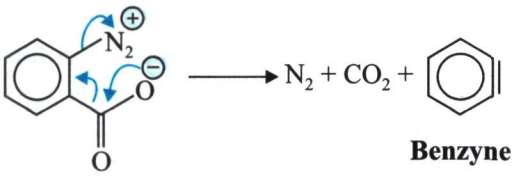
(*a*) Due to a base-induced elimination of HCl from Chlorobenzene:

Thus, we may have the following expressions:



***O*-Chlorobenzene** **Benzyne**

(*b*) Due to spontaneous decomposition of Benzene diazonium-2-carboxylate (with violence) to yield *Benzyne*—as given under:

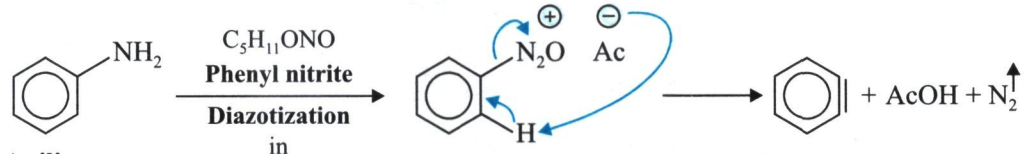


Benzyne

Benzene diazonium-2-carboxylate
[A diazonium salt of anthranilic acid]

(*c*) Diazotisation of Aniline gives Benzene diazonium acetate that undergoes ion-promoted elimination to form Benzyne

Thus, we may have the following reactions:

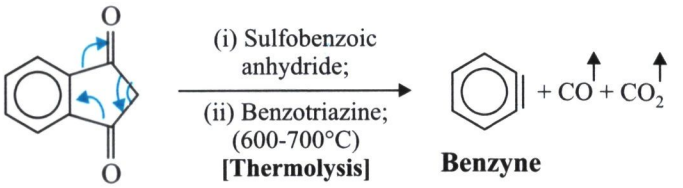


Aniline Benzene diazonium acetate **Benzyne**

EXPLANATION: Aniline on being subjected to *diazotisation* with phenyl nitrite in the presence of acetic anhydride yields **benzene diazonium acetate** which subsequently undergoes an acetate *ion-promoted elimination* of the specific ***ortho*-H-atom** to give **benzyne.**

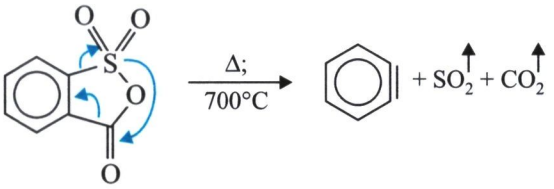
(*d*) Thermolysis of Phthalic anhydride at 600–700°C forms Benzyne

Thus, we may have the following reaction:

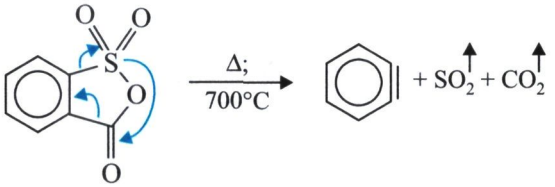


Phthalic anhydride **Benzyne**

That is, the **benzyne** may be obtained in a gaseous phase, by the **high-temperature thermolysis** (600–700°C) of *phthalic anhydride* in the presence of *sulfobenzoic anhydride* and *benzotriazine.*



Sulfobenzoic anhydride **Benzyne**



Sulfobenzoic anhydride **Benzyne**

Common Reactions of Benzyne

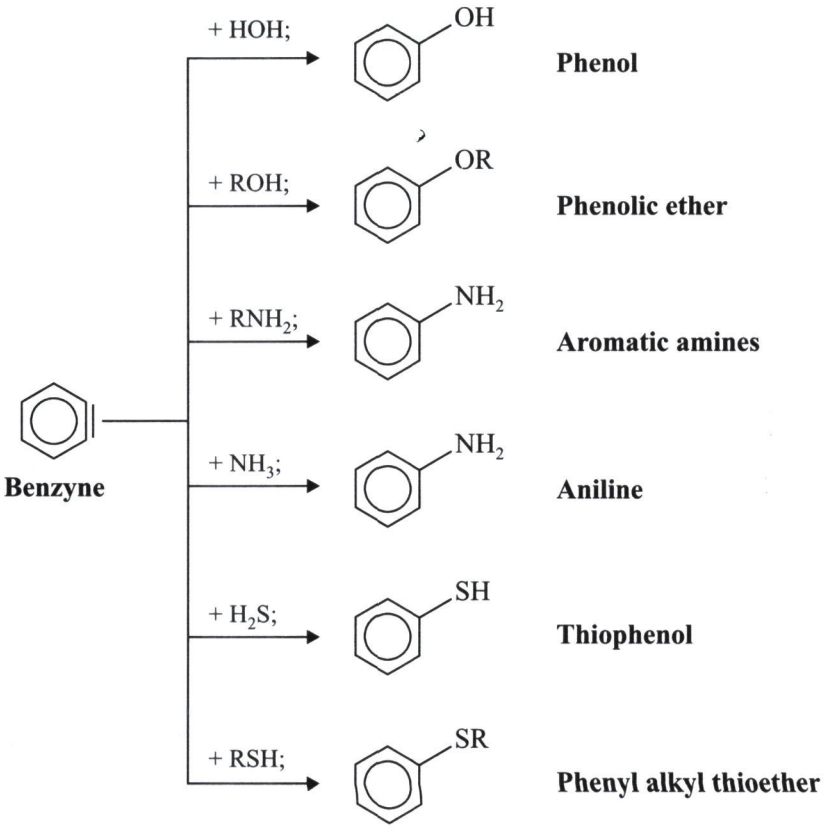
It has been duly proven and ascertained that the **benzyne** does react with an array of:

- ***mono-***, and
- ***poly*-olefins,**

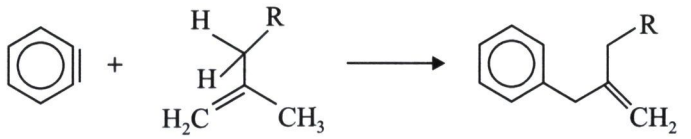
heteroatoms that essentially comprise the so-called *unsaturated chemical entities (compounds)* and also with each other to produce **dimers.**

Examples: Following are a few classical examples:

(*i*) **Benzyne** interacts with a host of ***nucleophiles*** to yield *various classes of organic compounds*, such as:



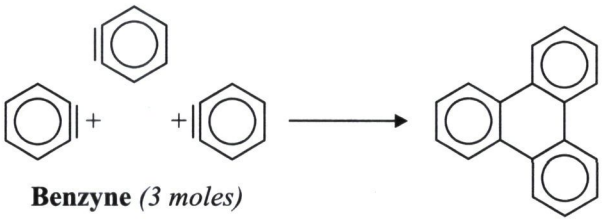
(*ii*) **Benzyne** undergoes *'ene'* reaction as shown under:



Benzyne **2-Propene derivative**

That is, **2-propene derivative** is duly obtained by the reaction of **benzyne** with **2-ene substituted (alkyl) propene.**

(*iii*) **Benzyne undergoes self-reaction to yield *triphenylene* as shown under:**



Benzyne *(3 moles)* **Triphenylene**

3.9 FACTORS GOVERNING THE REACTIVITY PROFILE

It has been duly established that there are a plethora of critical factors that essentially govern the reactivity profile of a molecule by affording the so-called absolute ***'electronic imbalance'*** in a **specific bond.** In addition, the said **specific bond** is attacked exclusively by a ***charged species*** only if there exists an **imbalance in the electronic density** that is invariably termed as **'polarity'.**

In a broader perspective, one may take cognizance of the following ***three*** **cardinal factors** which would actually govern the *reactivity profile*, namely:

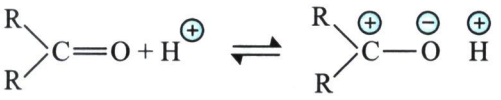
- **Electromeric Effect,**
- **Inductive Effect,** and
- **Mesomeric Effect**

that shall be treated individually in the sections that follows:

3.9.1 Electronic Effect

It may be regarded as a totally *temporary effect* invariably exhibited by the so-called **multiple bonded moieties** in the crucial presence of a *reagent.* Hence, quite unlike the *inductive effect (I-effect)*, one may observe in an **electromeric effect** the bonded electron pair of mostly a **π-bond** that gets eventually shifted *forever* to the respective ***more*** **electromagnetic side** ultimately resulting into the formation of an altogether never **charge-separated structure.**

Examples:



A ketone **An alcohol**

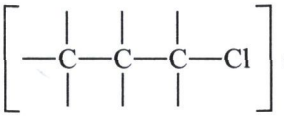
Comments: It evidently suggests that such an effect seems to be operative only in the ***excited form* of the molecule.** It always acts in the direction wherein the *specific reaction* involving the **multiple bonds** is duly *increased.* However, the ensuing effect is absolutely *temporary* since it disappears when the **reagent is withdrawn abruptly.**

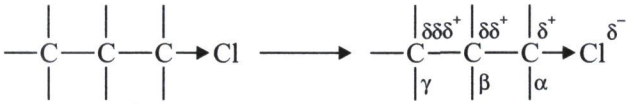
3.9.2 Inductive Effect [or Transmission Effect or I-Effect]

The **inductive effect [I-effect]** relates to the electronic repulsions or attractions caused duly by the *bound atoms and moieties* present very much within the molecules.

Examples: **Chloroacetic acid [Cl·CH_2—COOH]** is found to be relatively stronger than **acetic acid**; whereas, the **lactic acid [$CH_3CH(OH)COOH$]** and **alanine [CH_3·$CH(NH_2)COOH$]** are observed to be stronger than the **propionic acid [CH_3—CH_2—COOH]** due to the *electron-withdrawing* effects by certain groups substituted strategically adjacent to the **carboxyl (—COOH) moiety.**

In other words, the **inductive effect** designates an *electron delocalization* effect as could be seen in a **σ-bond** of the *respective species* where ***two* σ-bonded atoms** do differ appreciably in their corresponding **electronegativities.**

Example: In the **σ-bonded chain**  called terminal ***Cl-atom*** is much **more electronegative** *vis-a-vis* the **C-atom** to which it is attached. Besides, the ***Cl-atom*** eventually pulls the *σ-bonded electron pair* of the C_α—*Cl* bond towards itself that renders the **C_α-atom** positive marginally. Thus, the ensuing **C-atom** is rendered rather *more electronegative* in comparison to the next corresponding **C_β-atom** of the chain to which is linked eventually. In this way, it critically pulls the **σ-bonded electron pair** of the respective **C_β—C_α—Cl bond** towards itself perceptively thereby making the **C_β-atom +ve fractionally.** In other words, the so-called ***electron-withdrawing* effect of Cl-atom** is duly transmitted *via* the **chain of C-atoms.** Nevertheless, this particular transmission gets reduced readily with the distance; and hence, may be ignored almost beyond the **β-C atom** of a chain as shown below:



(–)-I-Effect

Comments: The aforesaid **I-effect** is exhibited explicitly by an ***'arrow'*** drawn at the middle of the *σ-bond* having the **arrowhead** pointing towards the comparatively more **electro-negative atom.** Thus, when a specific *moiety* happens to withdraw ***electron density*** towards itself, that eventually *lowers the electron density* at the **C-end by the I-effect,** then such moieties are designated exclusively by the **– I groups** and the overall effect as a **(–) I-effect** (*e.g.,* Cl, Br, CN and NO_2 moieties are the **(–) I-groups.**

(+) I-Groups: Such *groups* which actually release electron from them to the respective **C-end** are duly known as **(+) I-groups;** whereas, the observed effect as the **(+) I-effect.**

Example: **The methyl (CH_3), ethyl (C_2H_5) groups** etc., do represent the **(+)-I-groups.** Importantly, the **I-effect** affords a **'permanent effect'**, and it operates in the specific **'ground energy state'** of the given molecule.



(+)-I-Effect

NOTE: **Amazingly, in the *I-effect* the so-called *bonded σ-electron pair* gets shifted for ever to the more electronegative side, yet the *electron pair* remains strategically in the bonded molecular orbital (BMO). Thus, it categorically suggests that by virtue of the ensuing *I-effect* the corresponding *σ-bond* fails to undergo cleavage, but gets weakened to a certain extent.**

3.9.3 Mesomeric Effect

The **mesomeric effect** refers to the *reaction rates, ionization equilibria* etc., attributed to a substituent due to overlap of its ***p* or *pi*-orbitals** with the respective ***p*- or *pi*-orbitals** of the rest of the molecular entity.

Alternatively, the **mesomeric effect** relates to a ***permanent* polarization effect** on account of a particular moiety that is duly conjugated with a **π-bond.** Besides, this effect is *transmitted via* the **π-electrons of the system** thereby giving rise to an **uneven distribution of electrons** in the ***unsaturated chain.*** The particular moiety duly attached to the *unsaturated chain* could be either:

- **electron-releasing groups,** or
- **electron-withdrawing groups.**

Obviously, the **mesomeric effect (M-effect)** prevalently gives rise to **canonical structure*** that provided ***stability to the ion.*** Perhaps based upon the underlying cardinal reason the observed **'electron transfer'** is invariably termed as either:

- **resonance effect,** or
- **conjugative effect,**

whereas in the *ground state* the same is vividly indicated by the ***'dipole moment'.***

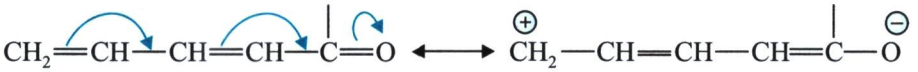
Example: The **mesomeric effect (M-effect)** may be depicted by the **polarization of the carbonyl (>C═O) moiety** as shown under:



❑ Furthermore, when the **carbonyl (>C═O) group** is conjugated progressively with the usual chain of **'alternate single and double bonds'**—the so-called ***positively charged carbonyl C-atom*** does exert critically an *electron transfer* towards itself. Therefore, the **carbonyl (>C═O) moiety** gets polarized crucially with the *transferance of actual polarization via* the **π-electrons of the C-chain** ultimately.

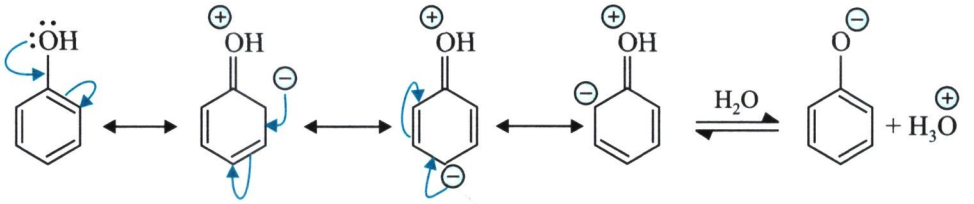
* That is, a set of *structures* or *writings* accepted as **'genuine'.**

Thus, we may have the following expression:



- It solely depends upon whether the *unsaturated chain* is either:
  - **adjoined to electron-releasing,** or
  - **adjoined to electron withdrawing moieties,**

  the resulting *mesomeric effect (M-effect)* are usually of ***two* types,** namely:
  - ➢ **(+) M-Effect:** *e.g.,* Groups include are: —NH_2, —OH, —NHR, —NR, —OR; and
  - ➢ **(–) M-Effect:** *e.g.,* Groups include are: $>C{=}O$, $C{\equiv}N$; —NO_2, —CHO, etc.
- **Acidity of Phenols:** The **acidity of phenols** may be duly expatiated by the so-called **(+) M-effect of the OH moiety** as shown under:



EXPLANATION: The *loan pair of electrons* located on the **O-atom** gets duly transformed to the respective **π-electrons** of the **benzene molecule** thereby resulting in ***several* resonating structures** (as shown above) having the ***+ve charge* seated on the O-atom.** It finally causes the easy removal of the **H-atom** from the **phenolic (OH) moiety.**

NOTE: **Interestingly, the respective *phenoxide ion*, the respective separation of charge takes place in the *canonical structures*; and obviously, due to this reason the phenoxide ion [C_6H_5—$O^{\ominus}$] becomes highly stable in character.**

3.10 HYPERCONJUGATION

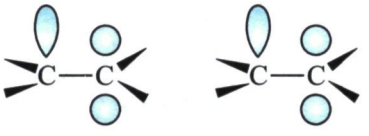
In true sense, the observed *relative stabilities* of:

- **tertiary** • **secondary** and • **primary-*alkyl radicals***

are duly justified for on precisely the same basis as that of the stability of the ***allyl radical*: delocalization of electrons.** However, it occurs *via* the overlap between the ***p*-orbital** occupied by:

- **an odd electron,** and
- **a σ-orbital,**

pertaining to the respective **alkyl moiety** as illustrated under:



(a) (b)

Hyperconjugation in an alkyl free radical : (*a*) **separate σ and *p*-orbitals**; and (*b*) **overlapping orbitals.**

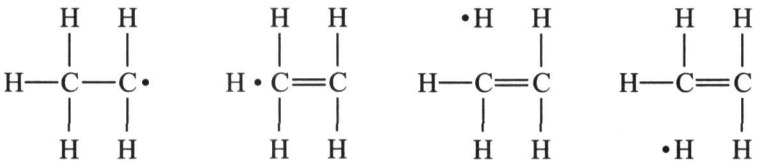
Comments: Importantly, *via* this overlap, the so-called *individual electrons* may help to a certain degree ***bind together intimately*:**

- ***three* nuclei** • ***two* C-atoms** and • ***one* H-atom**

This kind of *delocalization* involving the typical **σ bond orbital** is termed as **hyperconjugation.**

Besides, in terms of the **'resonance language'** one may pronounce that the ***ethyl radical*** **[C_2H_5•]** as an example designates

- **a hybrid of the usual 'structure-I',**
- *three* **additional structures *viz.*, II, III and IV***, and
- **an *odd electron* is held in position by a H-atom.**



I **II** **III** **IV**

Hyperconjugation (or 'no-bond resonance'): Interestingly, each of these **'no-bond resonance'** structures invariably appears to be quite strange, but when taken together, they do implicate that the ensuing **'C—H bond'** is definitely:

- **less than a single-bond,**
- **C—C exhibits some sort of double-bond characteristic feature,** and
- **odd electron is partially accommodated by H-atoms.**

Observations: These essentially include:

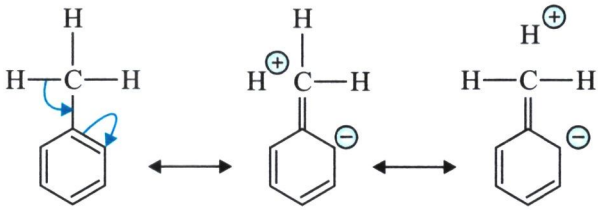
(*i*) The contribution grossly made by these unstable structures does seem to be not so important *vis-a-vis* the **equivalent structures** for the ***allyl radical*** **[CH_2=CH·CH_2•],** and

(*ii*) the overall resulting *stabilization* never turns out to be so large.

NOTE: **Hence, to stabilize the so-called *ethyl radical* (C_2H_5•) up to the degree of 6 kcal *vis-a-vis* to *methyl radical* (CH_3•) (104.98) for which such a resonance is not possible at all.**

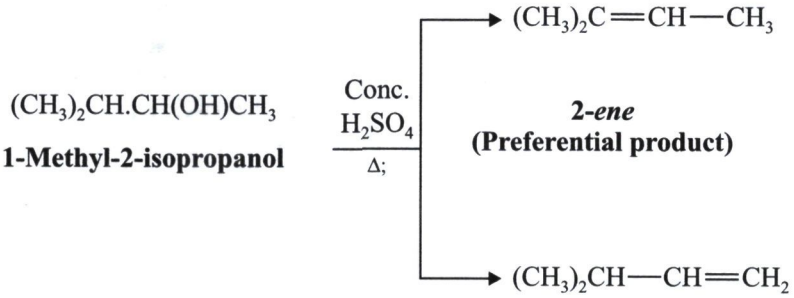
Examples: Following are *two* classical examples to explain the phenomenon of *hyperconjugation,* namely:

(*a*) Effect of *o*- and *p*-directing Methyl (—CH_3) moiety which attributes genuinely to *release of electron* by **hyperconjugation** as shown under:



* That is, in which an olefinic (double) bond joins the **2 C-atoms.**

(*b*) **Formation of 1-*ene* and 2-*ene* by Dehydration of Alcohol:** The **2-*ene*** formation is definitely preferential to that of **1-*ene***, as shown below:



EXPLANATION: The above preferential formation of **2-*ene*** *vis-a-vis* **1-*ene*** could be explained by the phenomenon of **hyperconjugation** since there exists **9 α-H-atoms** that eventually help to stabilize the **2-*ene*** over **1-*ene*** which only possesses **1 α-H-atom** as depicted above.

3.10.1 Theories of Hyperconjugation

The various recognised **theories of hyperconjugation** are broadly classified under the following *three* heads, namely:

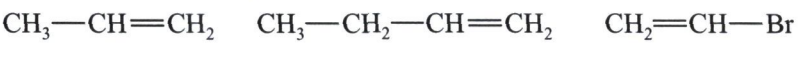
- **Valence Bond Theory [Resonance Theory],**
- **Molecular Orbital (MO) Theory,** and
- **Coulson's Theory of Group Orbitals,**

which shall now be discussed individually in the sections that follows:

3.10.1.1 Valence Bond Theory [Resonance Theory]

Theoretically, the phenomenon of **hyperconjugation** may also be considered in terms of ***resonance.***

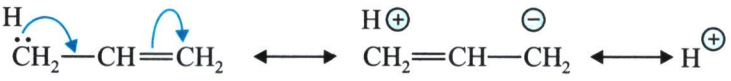
Example: A few typical examples are:



1-Propene **1-Butene** **Vinyl bromide**

Let us now examine **1-propene** and **vinyl bromide** more critically as stated under:

(*a*) **Hyperconjugation Profile Observed in 1-Propene**



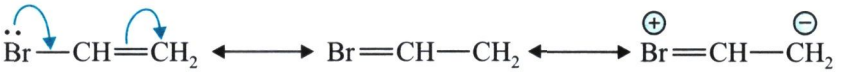
(a) **(b)**



(c) **(d)**

Thus, one may lay hands on *four* different ***hyperconjugation profiles*** of **1-propene.** Besides, in the **resonating structures** (*'a' through 'd'*) there exists **no definite bond between** *1 C-atom* and *1 H-atom*. Hence, **hyperconjugation** is also known as the **No-Bond Resonance.**

(*b*) Electromeric Effect in Vinyl Bromide



Comments: In addition, one may also take cognizance of the fact that the phenomenon of **'hyperconjugation'** is a *resonance* critically engaging the **σ-electrons.** However, the said phenomenon may also be described as the *conjugation* taking place between:

- **single and double bonds,** or
- **an intimate interaction of *a-electrons* of C—H bonds with the *p-electrons* of the ensuing *unsaturated system* to which it remains conjugated.**

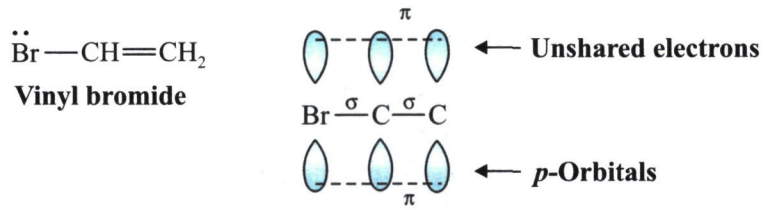
Remarks: Therefore, the above phenomenon is usually referred to as the **'Sacrificial Hyperconjugation'.** Nevertheless, in this specific instance **No-Bond Contributing Structures** do comprise one bond less than the ***normal contributing structures.***

3.10.1.2 Molecular Orbital (MO) Theory

In a broader perspective, one may explain *hyperconjugation* by having the assumption that the overlapping of the ***s-orbital*** or the ***sp^2-hybrid orbitals*** invariably comes into play with the ***p-orbital*** of the **adjacent C-atom** thereby giving rise to the formation of a ***non-localized orbital.*** Thus, alternatively it may be added that the phenomenon of *hyperconjugation* occurs perhaps due to the respective **overlapping of C—H σ-bonding electrons** of the ***alkyl moieties with the π-electrons of the double bond.***

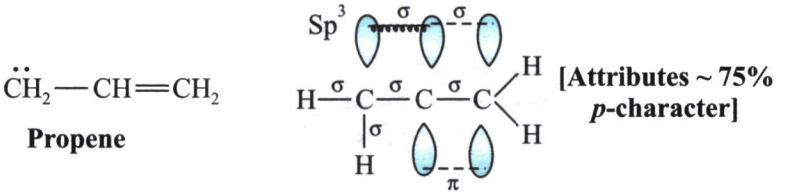
Importantly, the **MO-theory** may be further expatiated by the help of the following ***two*** **specific examples,** such as:

- **Vinyl Bromide**



Comments: In the aforesaid molecule there exists ***three*** **parallel *p*-orbitals** (*i.e.,* one each on *2 C-atoms* plus one on *Cl-atom*) that would ultimately interact to form **'delocalized π-orbitals'.**

- **Propene**

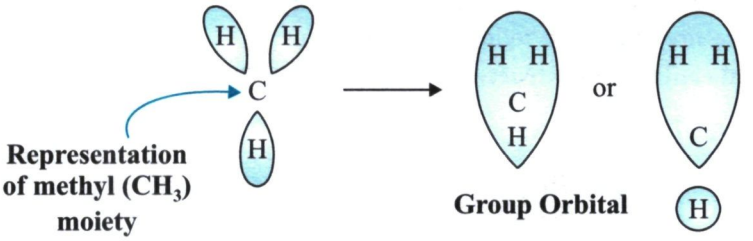


Comments: These essentially include:

1. There exists no ***p*-orbital** located upon the —CH_3 (methyl) moiety for the interaction with the ***p*-orbitals** of the ***C=C olefinic (double) bond*** *i.e.,* **—CH=CH_2.**
2. It has been duly proposed that a few of the so-called **σ-orbitals** present specifically in the —CH_3 (methyl) moiety may eventually overlap to a certain degree only with the ***p*-orbitals** located strategically upon the **adjacent C-atom** to give rise to the formation of the **delocalised π-orbital.**
3. Finally, the significant presence of the ***p*-character** belonging to the ***sp^3*-orbital** of —CH_3 (methyl) moiety, in fact, critically enables it to **interact with the *p*-orbitals located duly upon the adjacent C-atom as in vinyl bromide.**

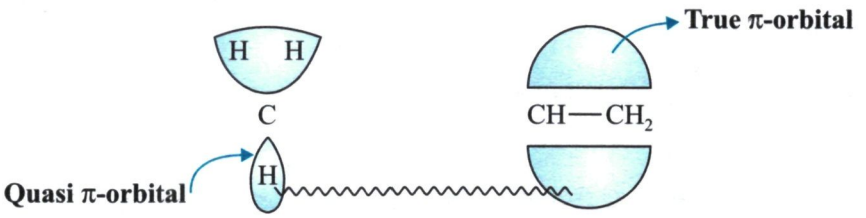
3.10.1.3 Coulson's Theory of Group Orbitals

Coulson* intelligently applied the underlying concept of ***'group orbital'*** in order to explain the phenomenon of **hyperconjugation** in another manner. In fact, he considered the *methyl* (CH_3) *moiety* as an **'atom'** that essentially do possess a *'group orbital'* as illustrated below:



'Group Orbital' formation as depicted by Coulson for methyl (CH_3) group.

Remarks: In actual practice, the aforesaid **'group orbital' (σ-orbital)** is now baptised as **'Quasi π-orbitals'** by Coulson. However, these **group orbitals ion** do overlap to a certain degree with the ***true* π-orbitals** of the ensuing molecule to produce an ***extended orbital*** thereby causing *delocalization* in the above **conjugation system** almost vividly.



'Group Orbital' represented as Quasi π-orbital of $CH_3CH=CH_2$.

NOTE: **It may be observed explicitly that the Quasi *π-electrons* that are comparatively found to be bonded more strongly *vis-a-vis* the *two* π-electrons. Therefore, the phenomenon of *hyperconjugation* exerts a weaker effect in comparison to the *conjugation effect* (*i.e.,* almost recorded to be only 1/10th of the *conjugation effect).***

* Coulson CA: Developed the method at the Oxford University, London (UK).

3.10.2 Variants in Hyperconjugation

Based on the scientific evidences and logical explanations there are ***three*** **variants in hyperconjugation**, namely:

- **Sacrificial Hyperconjugation,**
- **Isovalent Hyperconjugation,** and
- **Reverse Hyperconjugation,**

which shall now be treated separately in the sections that follows:

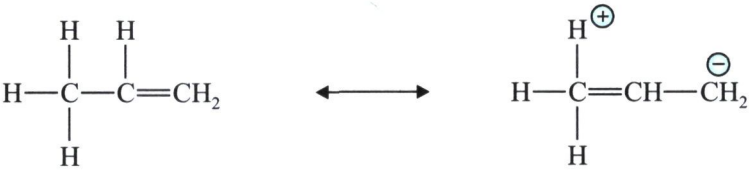
3.10.2.1 Sacrificial Hyperconjugation*

It may be stated at the very outset that the **sacrificial hyperconjugation** has not gained enough popularity and recognition.

In fact, it relates to the phenomenon of **hyperconjugation** specifically in the *ground state* (*i.e.,* low energy level) of a molecule (usually *neutral*); whereas the respective **canonical forms** are duly represented by the so-called ***'charge-separation'*** that is not truly inherited by the main form.

Example: Let us consider the typical example of **'Propene'.** Importantly, in the ensuing **No-Bond Contributing Structure** it is found to contain **one-bond less than the *normal contributing structure.*** Thus, we may have the following expressions:

Normal contributing structure **No bond contributing structure**



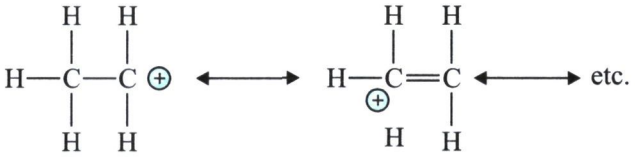
Propene **Propene**

[Showing 6 C-H bonds] **[Showing 5 C-H bonds]**

3.10.2.2 Isovalent Hyperconjugation

At present the evidence is crucially against **hyperconjugation** in the **ground states of neutral molecules.**** Nevertheless, for the ***carbocations***** and ***free radicals,***** and also for the ***excited states of molecules,***** one may encounter several evidences that ascertains **hyperconjugation** is important.

Thus, we may have the following expressions:



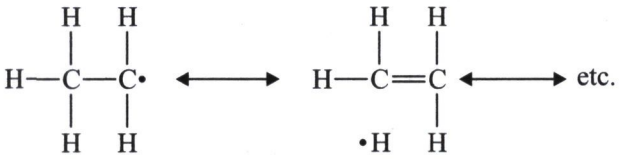
* Muller and Muliken: *J. Am. Chem. Soc.,* **80** : 3489, 1958.

** For some evidence in favour see: Cooney and Happer: *Aust. J. Chem.,* **40** : 1537, 1987.

*** Symons: *Tetrahedron,* **18** : 333, 1962.

**** Rao *et al.: Can. J. Chem.,* **38** : 2508, 1960.

***** Muller and Muliken : *J. Am. Chem. Soc.,* **80** : 3489, 1958.



Remarks: Even here the *main form* does contribute more to the **hybrid form** *vis-a-vis* the other forms.

3.10.2.3 Reverse Hyperconjugation

It has been duly established that the **C—F bond distance** invariably gets decreased with the corresponding increase in the ***number*** **of F-atoms** residing on the **C-atom.**

Examples:

Compound	C—F Bond Length (Å)
Methane [CH_4]	1.54
Fluoromethane [CH_3F]	1.39
Difluoromethane [CH_2F_2]	1.36
Trifluoromethane [CHF_3]	1.33
Tetrafluoromethane [CF_4]	1.32

Comments: The critically observed ***'bond-shortening'*** phenomenon of the **C—F bond** may be duly explained by the so-called **reverse hyperconjugation.**

Suggested Reading

Bethel D and Gold V : **Carbonium Ions: An Introduction,** Academic Press, New York, 1967.
Buncel E and Durst T : **Comprehensive Carbanion Chemistry,** Elsevier, New York, 1980.
Gram DJ : **Fundamentals of Carbanion Chemistry,** Academic, New York, 1965.
March J : **Advanced Organic Chemistry,** 4th edn, John Viley and Sons, New York, 2001.
Nonhebel DC *et al.* : **Radicals,** Cambridge University, Cambridge. 1979.
Olah GA : **Carbocations and Electrophilic Reactions,** Wiley, New York, 1974.
Pryos WA : **Free Radicals,** McGraw Hill, New York, 1965.
Walling C : **Free Radicals in Solution,** Wiley, New York, 1970.

❑❑❑

Section 2

Name Reactions Based on Product Formed

Chapter 4. Reactions Giving Carbonyl Compounds

Chapter 5. Reactions Giving Alcohol—Hydroxy Carboxylic Acid and Phenols

Chapter 6. Reactions Giving Arenes

Chapter 7. Reactions Giving Saturated and Unsaturated Hydrocarbons

Chapter 8. Reactions Giving Carboxylic Acids and its Derivatives

Chapter 9. Reactions Giving Heterocyclic Compounds and its Derivatives

Chapter 10. Reactions Giving Halogen Derivatives

Chapter 11. Miscellaneous Organic Reactions

Chapter 4

Reactions Giving Carbonyl Compounds

LESSONS AT A GLANCE

4.1 Introduction
- 4.1.1 Aldol Condensation
- 4.1.2 Gattermann Synthesis
- 4.1.3 Rosenmund Reduction
- 4.1.4 Sommelet Reaction
- 4.1.5 Baker; Mahal *et al.* Reaction
- 4.1.6 Carroll Rearrangement
- 4.1.7 Nef Reaction
- 4.1.8 Robinson Annulation
- 4.1.9 Friedel-Craft's Acylation
- 4.1.10 Mannich Reaction
- 4.1.11 Dieckmann Condensation Reaction

4.1 INTRODUCTION

In the domain of '*organic chemistry*' there exists a variety of **reactions giving carbonyl (>C═O) compounds**, such as:

- **Aldol Condensation,**
- **Gattermann Synthesis**
- **Rosenmund Reduction**
- **Sommelet Reaction**
- **Baker; Mahal *et al.* Reaction**
- **Carroll Rearrangement**
- **Nef Reaction**

- **Robinson Annulation**
- **Friedel-Craft's Acylation**
- **Mannich Reaction**
- **Dieckmann Condensation Reaction**

which shall now be discussed individually in the sections that follows:

4.1.1 Aldol Condensation

Preamble: The *nucleophilic reactivity* of the '**carbanions**' duly accomplished from either:

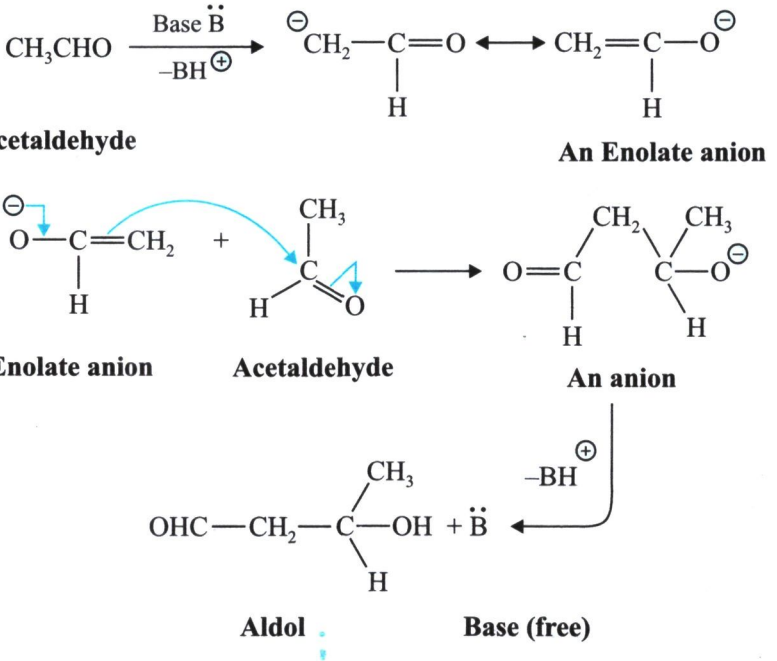
- **Ketones** or - **Related Chemical Entities (compounds),**

matches almost squarely with the *electrophilic reactivity profile* of a ***carbonyl* (>C=O) moiety**; and for which a plethora of *C—C bond formation reactions* involving intimately these *species* are well-known. In fact, these aforesaid reactions are invariably termed as per the *respective partners* which have actually reacted as well as the *type of the products* generated duly in the perspective reaction.

Example: A few typical examples are as stated under:

(*a*) In reality, the so-called ***stabilized carbanions***, more correctly known as '**enolates**'—are duly obtained from either **aldehydes (-CHO)** or **ketones (>C=O)**; and subsequently, react with the C=O of *aldehydes* or *ketones* to yield categorically the **β-hydroxy carbonyl compounds** termed as **'aldols'**. This particular reaction is known as **'aldol condensation'.**

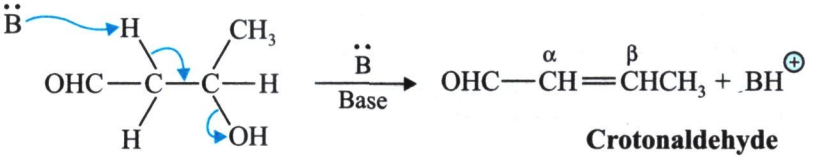
These reactions may be expressed as under:



IMPORTANT OBSERVATIONS:

These essentially include:

1. When the **'aldol'** contains an ***active* α-H atom** under the crucial influence of the **base [$\ddot{B}$],** it predominantly undergoes *β-elimination reaction* to eliminate a mole of H_2O to yield an **α, β-unsaturated aldehyde or ketone** as shown under:



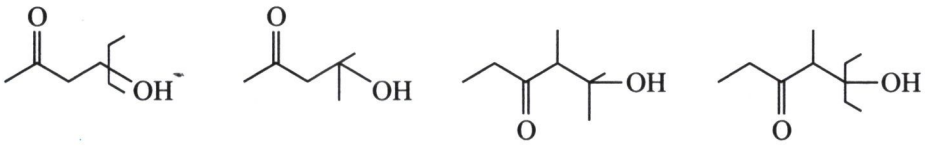
Crotonaldehyde

[An α, β-unsaturated aldehyde]

2. In a specific instance, when the *electrophilic* and *nucleophilic* pairs of the **aldol condensation** are duly obtained from the same *carbonyl* (*>C=O*) *compound* (as in the foretold case) both could be accomplished from ***acetaldehyde*** *i.e.,* a **single aldol** is obtained. Hence, this type of **aldol condensations** are usually called as the ***simple aldol condensation***. Nevertheless, when the said *pairs (partners)* are altogether different, it is normally termed as the ***cross-aldol condensation***. Interestingly, in the **cross-aldol condensation** one may lay hands on ***four*** **possible aldols** that are duly formed.

Remarks: Amazingly, of the ***two*** **carbonyl (>C=O) chemical entities** the **one specific species** which is found to be *more electrophilic in nature* tries to exist as the **'*electrophile*'**. Hence, it implies vehemently that the other *'partner'* is definitely **more enolized**; and perhaps it solemnly dictates the emergence of the ***most*** **predominant aldol.**

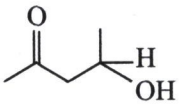
Example: In the so-called, **cross-aldol condensation** occurring between **acetone [CH_3COCH_3]** and **3-pentanone [$CH_3CH_2COCH_2CH_3$]**, the former **(acetone)** is found to be more electrophilic in nature (since the electron-releasing effect of the **ethyl (CH_3CH_2–)** moiety is proved to be greater than that of the **methyl (CH_3–) moiety** for which the following ***four*** **aldols** are quite possible, and (III) is generously obtained as the **major compound.**



[I] **[II]** **[III]** **[IV]**

3. Lastly, as the *aldehydes* are definitely much stronger **electrophiles** *vis-a-vis* the *ketones*; hence, the **aldolization** of a mixture comprising: • **aldehyde** and • **ketone**, gives rise to the formation of only a **'*single aldol*'**—wherein the **'aldehyde molecule'** serves critically as the **electrophile.**

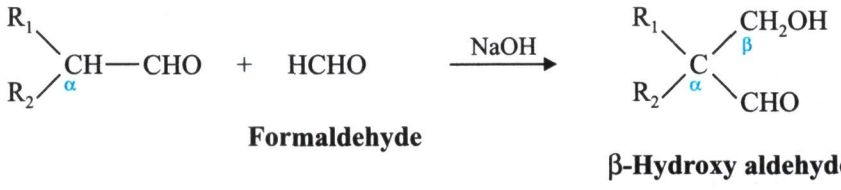
Example: The crucial **aldolization** of an **acetaldehyde** and **ketone** admixture fails to yield the so-called **cross-products.** Hence, the **single aldol** is shown to be (V):



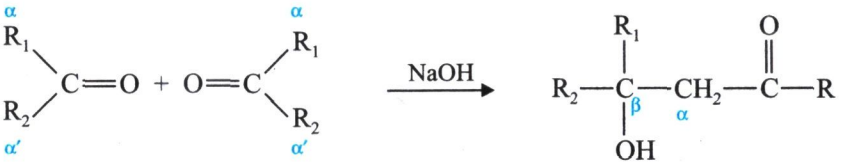
[V]

Aldol Condensation

In a broader perspective, the **'aldol condensation'** critically takes cognizance of the involvement related to the addition of an **'aldehyde'** to the respective *carboxyl (—COOH) moiety* of the **parent compound** (*i.e.,* a molecule of **aldehyde** or **ketone**). In this manner, the ***'carbanion'*** is added on to a second molecule so as to yield a product in which the **α C-atom** gets attached directly to the **carbonyl (>C=O) C-atom** of the **chemical entity (compound),** as shown under:



Formaldehyde **β-Hydroxy aldehyde**



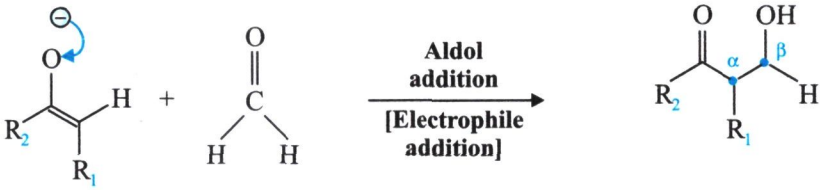
2, Moles of α, α′-disubstituted ketone **β-Hydroxy ketone**

A good number of *organic researchers** have rightly pronounced the **'aldol condensation'** as the excellent ***bond-forming reaction.***

Reaction Variants: It has been duly demonstrated that the **'aldol condensation'** essentially involves the eventful conversion of the *nucleophile aldehyde* to yield *β-hydroxy ketone* or ***'aldol'.***

i.e., **Ald+ol** or a unique combination of an **aldehyde functional moiety** and an **alcoholic moiety****, as shown under:

We may have the following expressions:



Ketone enolate [Nucleophile] **Aldehyde [Electrophile]** **'Aldol' [C-C Bond formation takes place]**

*Heathcock CH: *Comp Org. Syn.,* pp 133–179, 1991; Mahrwald R: **Modern Aldol Reactions, Vols. 1** and **2,** Wiley-VCH, Verlag GmbH and Co., KGaA, 1218–1223, 2004; Smith MB and March J, **Advanced Organic Chemistry,** 6th edn, Wiley Interscience, New York, 1218–1223, 2007.

Mukaiyama T: The Direct Aldol Reaction, *Org. React.,* **28**: 203, 1982; Peterson L: **New Asymmetric Aldol Methodology,** *Chem. Ind.,* **12**: 390, 1988.

Remarks: An array of nucleophiles may be employed for the aforesaid purpose that essentially includes:

• **Enols** • **Enolates** • **Aldehydes** • **Enol Ethers of '*ketones*' and** • **Carboxyl (COOH) compounds having '*Aldehydes*' as *Electrophilic Partners.***

Mechanism of Reaction: Importantly, the ensuing **mechanism of reaction** causing the '***aldol condensation***' critically involves *two* cardinal steps, namely:

❑ ***First Step*** relates to the **aldol reaction** *i.e.,* a typical **nucleophilic addition**; and

❑ ***Second Step*** refers to the phenomenon of *dehydration i.e.,* an **elimination reaction.**

Furthermore, the ultimate **'aldol addition product'** thus obtained in the first-step gets duly dehydrated by ***two*** **different mechanisms** that depend solely upon the critical formation of either:

• **Enol** or • **Enolate**

specifically in the course of the ***two*** **following reaction mechanisms,** namely:

• **Enol Mechanism**, and

• **Enolate Mechanism.**

Besides, the *aldehydes* and *ketones* get converted into the respective 'enols' or 'enol ethers'—that are:

• **nucleophilic (*i.e., electron deficient*) at the α-position; and**

• **promptly react with the '*protonated aldehydes*' *via* the ensuing '*enol mechanism*'.**

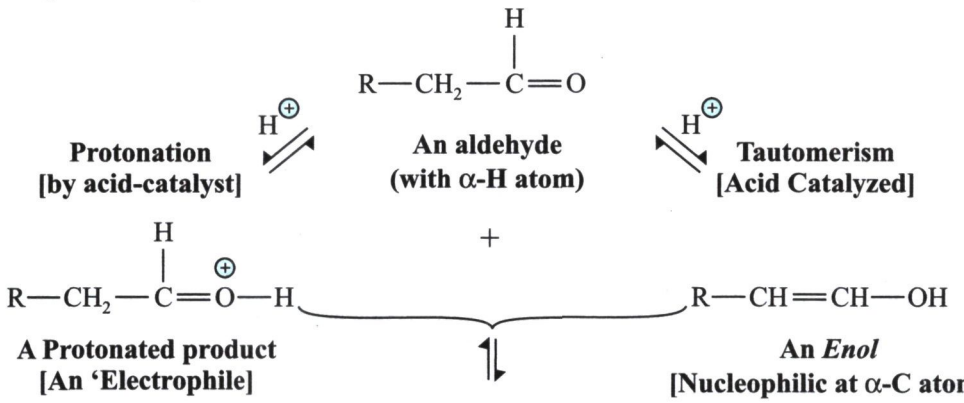
Simultaneously, the **carboxylic acids (—COOH)** are duly '*deprotonated*' to give the respective *enolates* (which are indeed more *nucleophilic* in comparison to either **'*enols*'** or **'*enol ethers*'**) thereby in a position to **attack the electrophiles directly.**

At this point in time, let us look into the critical aspects of the *Enol-Mechanism* and *Enolate Mechanism* individually with regard to the undergoing interaction pertaining to the respective **carboxyl compound** or **carboxyl (—COOH) moiety** as stated under:

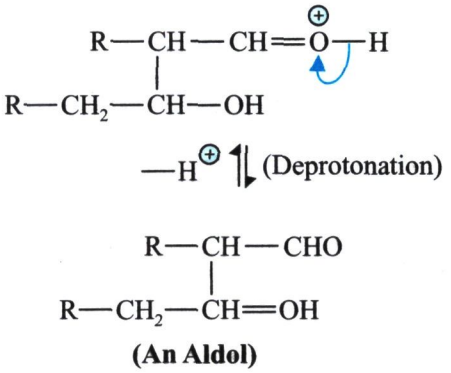
❑ **Enol Mechanism:** In this particular instance the first and foremost segment of the *on-going reaction* relates to the so-called **nucleophilic addition reaction.** It essentially follows the ***aldol-reaction*** (as explained earlier) which is predominantly accompanied by a *dehydration* (or an **elimination** reaction) usually being **acid-catalyzed.**

The **'enol-mechanism'** essentially involves the following ***two*** **cardinal steps,** namely:

• **Step 1: Nucleophilic Additions**



(Contd...)

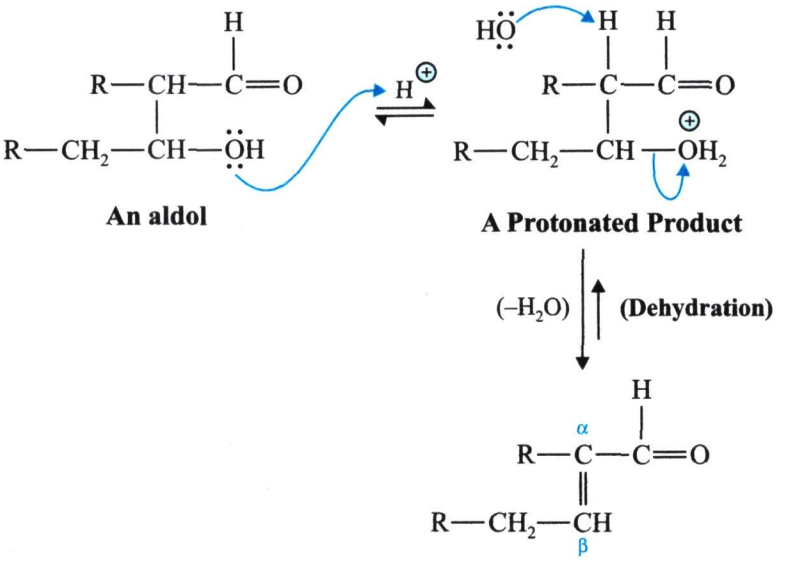


EXPLANATION

The various steps involved may be explained as under:

1. An **aldehyde** with a *α-H atom* on being subjected to **protonation** by an *acid-catalyst* yields a **protonated product** (*i.e.*, an *electrophile*); whereas, the respective **aldehyde** undergoes the phenomenon of **tautomerism** in an *acid-catalyzed medium* gives an ***enol*** (being **nucleophilic** at α-C atom).
2. The *two* aforesaid products (*viz.*, **electrophile** and **enol**) give rise to a ***reversible*** **protonated intermediate product**, which subsequently upon *deprotonation* (**—H⊕**) yield a **'aldol'** as the final product.

- **Step 2: The Acid-Catalyzed Dehydration Reaction (*i.e.*, an Elimination Reaction)**



EXPLANATION

An **'aldol'** on being protonated yields a protonated product, which on *dehydration* duly forms the desired **α, β-unsaturated aldehyde.**

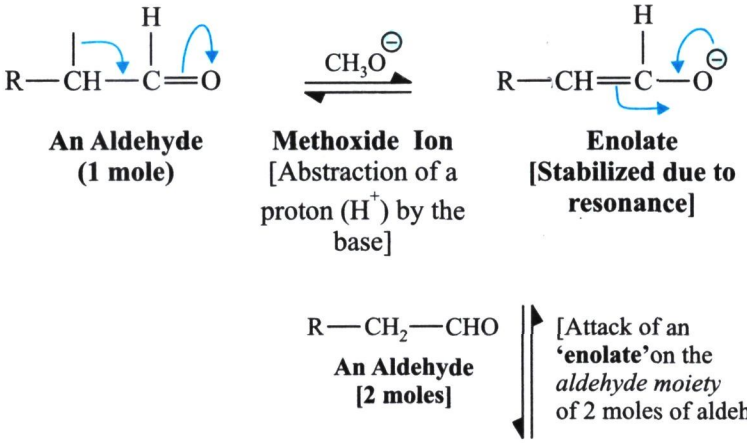
Remarks: The above cited mechanism illustrates explicitly the mechanism of a ***typical* acid-catalyzed self-condensation** of an ***'aldehyde'***.

❑ **Enolate Mechanism:** In reality, the **enolate mechanism** critically involves a particular **moderate base,** such as:

• **Hydroxide Ion (—OH^-)** or • **Alkoxide Ion** (CH_3O^-),

which invariably serves as a '***catalyst***'. Very much akin to the **'Enol Mechanism'** (discussed earlier)—the **Enolate Mechanism** also do possess *two* important steps, namely:

• **Step 1: Base-Catalyzed Nucleophilic Addition**

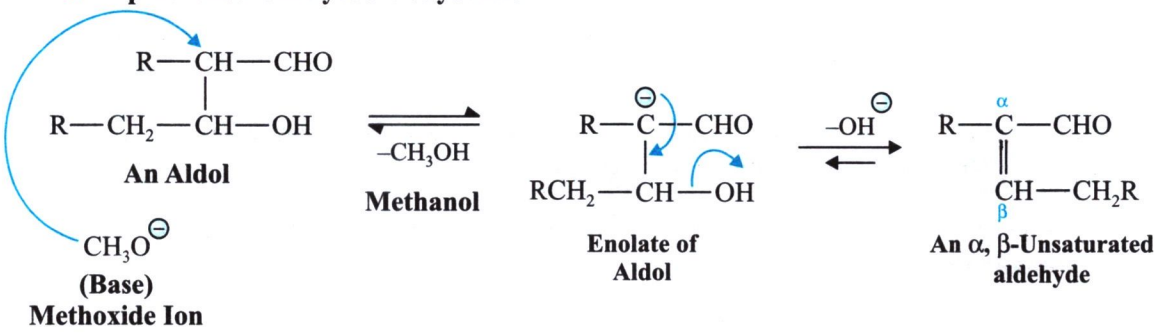


EXPLANATION

The various steps involved in the above sequence of reactions may be explained as under:

1. An **aldehyde** (1 mole) when treated with a *methoxide ion* [$\mathbf{CH_3O^{\ominus}}$] it affords the abstraction of a **proton ($\mathbf{H^+}$)** by the ***base*** to yield an **'Enolate'** that eventually gets duly **stabilized due to resonance effect.**
2. The resulting **'Enolate'** on interaction with an *aldehyde* **(2 moles)** gives an **'Alkoxide-Salt'** of *Aldol* due to an attack of an **'enolate'** aldehyde moiety of 2 moles of aldehyde.
3. The **'Alkoxide-Salt'** of *aldol* reacts with *methanol* to produce an **'Aldol'.**

- **Step 2: Base-Catalyzed Dehydration**



EXPLANATION

The **'aldol'** on being treated with an *alkoxide ion* **(base)** loses a mole of methanol to yield the **enolate of aldol**, which on abstraction of a *hydroxide (OH^-) ion* gives rise to the formation of an **α, β-unsaturated aldehyde.**

Remarks: However, in this specific instance the **'enolate formation'** is found to be absolutely ***irreversible***; and hence, the resulting ***aldol product*** is not generated at all unless and until the ***metal alkoxide*** of the said ***aldol product*** is duly *protonated* in an **altogether different step.**

NOTES: Certain extremely pertinent observations are as follows:

1. **Knoevenagel Condensation* suggests that when an *amine (base)* and an *active hydrogen compound* gets suitably activated usually yields a condensed new product.**
2. **Perkin Reaction relates that an *enolate* is produced from an *aldehyde.***
3. **Claisen Condensation** occurs when *two* ester compounds interact with each other.**
4. **Cannizzaro's Reaction*** takes place when *two* aldehydes (any α-Hydrogen atoms are involved.**
5. **Aldol Condensation comes into play when *two* different *carbonyl* (>C=O) *compounds* and α *H-atom* are involved.**
6. **Dieckmann Condensation**** takes place when the *two* ester groups present in the same molecule are involved to give a *cyclic compound.***

EXEMPLIFICATION OF ALDOL CONDENSATION

Following are the *two* glaring examples to elaborate the **aldol condensation** phenomenon appropriately:

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*Knoevenagel E. *Ber.*, **31**: 2596, 1898.

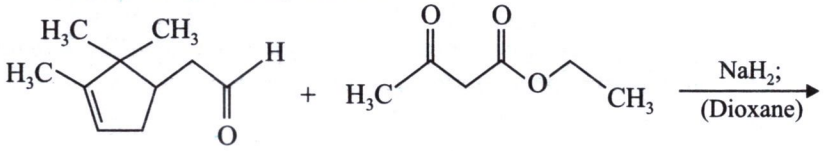
Claisen L and Lowman O, *Ber*, **20: 651, 1887.

***Cannizzaro S., *Ann.*, **88**: 129, 1853.

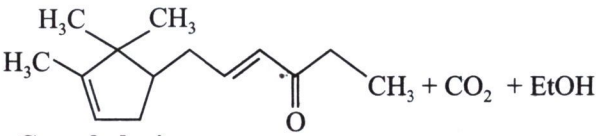
****Dieckmann W, *Ber*, **27** (102), 965, 1894.

(a) Aldol Condensation of Campholenic Aldehyde and Ethyl 2-Methyl Acetoacetate.

Let us look into the following reaction:



Canpholenic aldehyde (1) **Ethyl - 2 - methyl acetoacetate (2)**



Campholenic ethylacetate (3)

MODUS OPERANDI

The various steps involved in the above reactions are as follows:

(*i*) To a constantly stored solution of NaH_2 *in dioxane* add slowly to **ethyl-2-methyl acetoacetate (2).**

(*ii*) Now, **campholenic aldehyde (1)** is incorporated to the resulting mixture and refluxed gently for 15 hours at a stretch.

(*iii*) Neutralization is done by adding **HCl (2M)** and the mixture extracted with solvent ether successively.

(*iv*) The combined ethereal layers are duly washed sequentially with **HCl (2M), saturated solution of $NaHCO_3$ and NaCl solution (brine).**

(*v*) The resulting **organic-phase** is dried over **anhydrous sodium sulphate (Na_2SO_4)** and the solvent evaporated *under reduced pressure* to give a **residue (crude).**

(*vi*) Finally, the **crude residue** was further purified by **vacuum distillation** to yield **campholenic ethylacetate (3)** upto **58% of yield.**

EXPLANATION

Campholenic aldehyde (1) When treated with **ethyl-2-methyl acetoacetate (2)** in an alkaline medium in dioxane yields **campholenic ethylacetate (3)** with the elimination of one mole each of carbon dioxide and ethanol.

(b) Stereoselectivity of Aldol Reaction

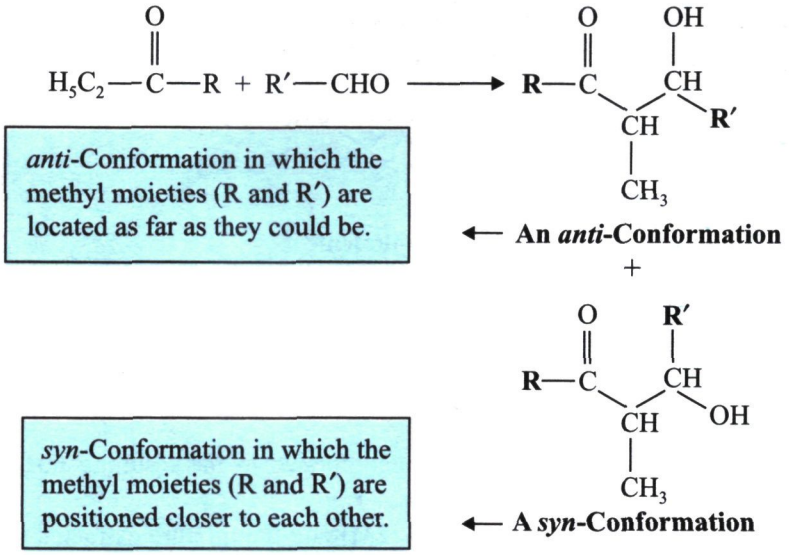
The study of **stereoselectivity of the aldol reaction** may be carried out by the effective formation of ***two* stereogenic centres** into a ***single reaction.*** Thus, to represent the so-called **relative stereochemistry** specifically at the **α- and β-carbon atoms**—the '***syn***'/'***anti***' prefix are being employed. It is, however, pertinent to state here that whenever a *high order nucleophiles* are duly incorporated right to the **aldehydes**—one would ultimately lay hands upon either:

- **'*syn*'-convention**, or
- **'*anti*'-convention,**

which solely depends upon the exact position of the ***stereocentres***.

Remarks: Nevertheless, earlier we have been making use of the so-called ***erythro-/threo-*** nomenclature frequently.

Example: Obviously, one may expatiate the aforesaid *stereoselectivity of aldol reaction* by citing the typical example of the addition of a ***'propionate nucleophile'*** to the aldehyde judiciously—as shown under:

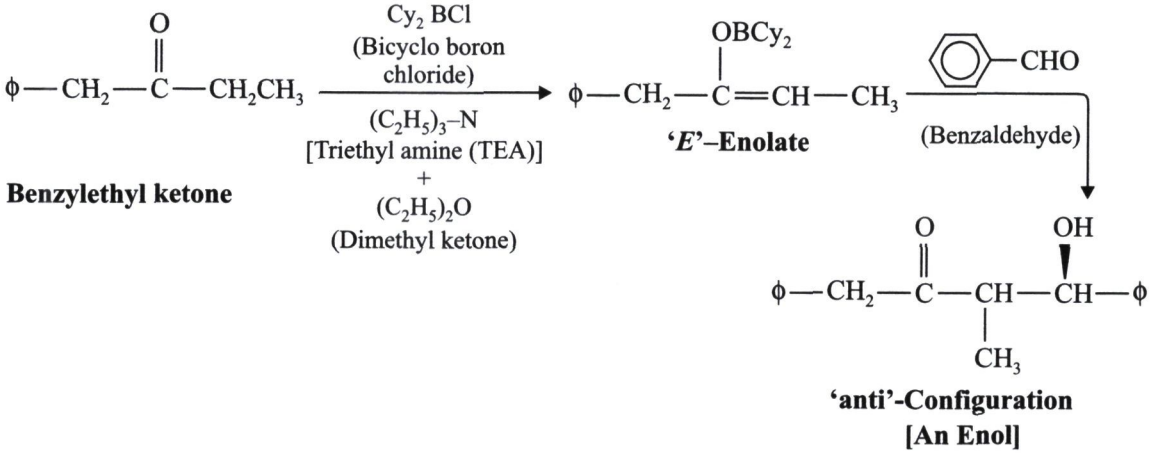


ABSENCE OF SIGNIFICANT DIFFERENCE BETWEEN THE STEREOINDUCTION LEVELS OF '*E*' AND '*Z*' ENOLATES

Brown *et al.* (1989)* reported the absolute absence of the significant difference between the **stereoinduction levels of '*E*' and '*Z*' enolates** as given under:

❑ **Stereoinduction of '*E*' Enolate Showing anti-Conformation:**

(*i*)

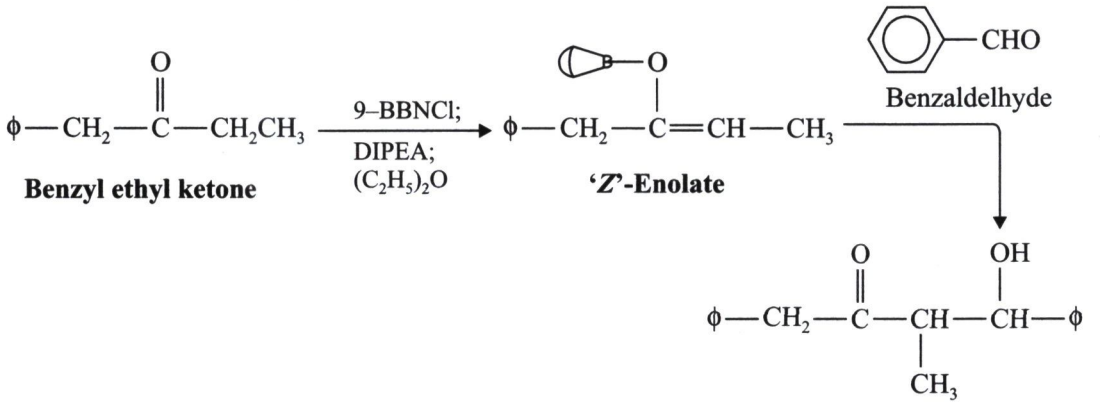


*Brown HC, *et al.*: *J Am Chem Soc*, **111**: 3441–42, 1989.

Thus, the ***ketone*** (**benzyl ethyl ketone**) when treated with bicyclo boron chloride and triethyl amine (TEA) followed by dimethyl ketone yields the **'E'–enolate**, which on further interaction with *benzaldehyde* gives rise to the formation of an '***anti*-Configuration'** (an *enol*).

❑ **Stereoinduction of '*Z*' Enolate Showing *syn*-Conformation**

(*ii*)



Benzyl ethyl ketone **'*Z*'-Enolate**

'*syn*'-Configuration
[An Enol]

Benzyl ethyl ketone on reaction with *IBBNCl* and **DIPEA** followed by *diethylether* gives the **'*Z*'-enolate**, which on treatment with *benzaldehyde* yields the respective '*syn*'-Configuration (an *enol*).

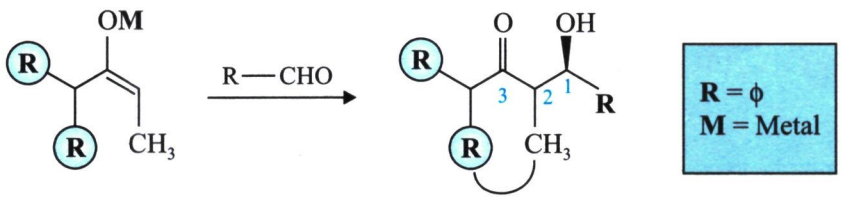
Stereocontrol: Based on Substrate and Chirality

It has been duly proven and established that the ***aldol reaction*** is specially controlled and monitored by *two* important aspects, namely:

- **precise nature of the substrate,** and
- **prevailing chirality,**

present strategically on any of the *two* aforesaid *reactants* thereby making a positive influence upon the overall outcome of the said **aldol reaction.** Nevertheless, the critical presence of the ***'stereocentre'*** particularly at the α-*position* grossly affords a significant **stereocontrol of the reaction** as depicted under:

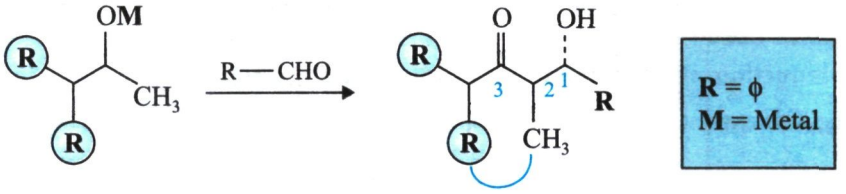
❑ ***'E'-Enolate Configuration*:** gives the respective **1,3-*anti*-product** as given below:



'E'-Enolate **1, 3-*anti*-configuration**

i.e., interaction of an *'E'-enolate* with benzaldehyde yields the corresponding **1,3-*anti*-Configuration.**

❑ **'Z'-Enolate Configuration:** yields the corresponding **1,3-*syn*-product** as shown under:



'*Z*'-Enolate **1, 3-*syn*-Configuration**

i.e., interaction of '*Z-enolate*' with benzaldehyde gives rise to the formation of **1, 3-*syn*-Configuration.**

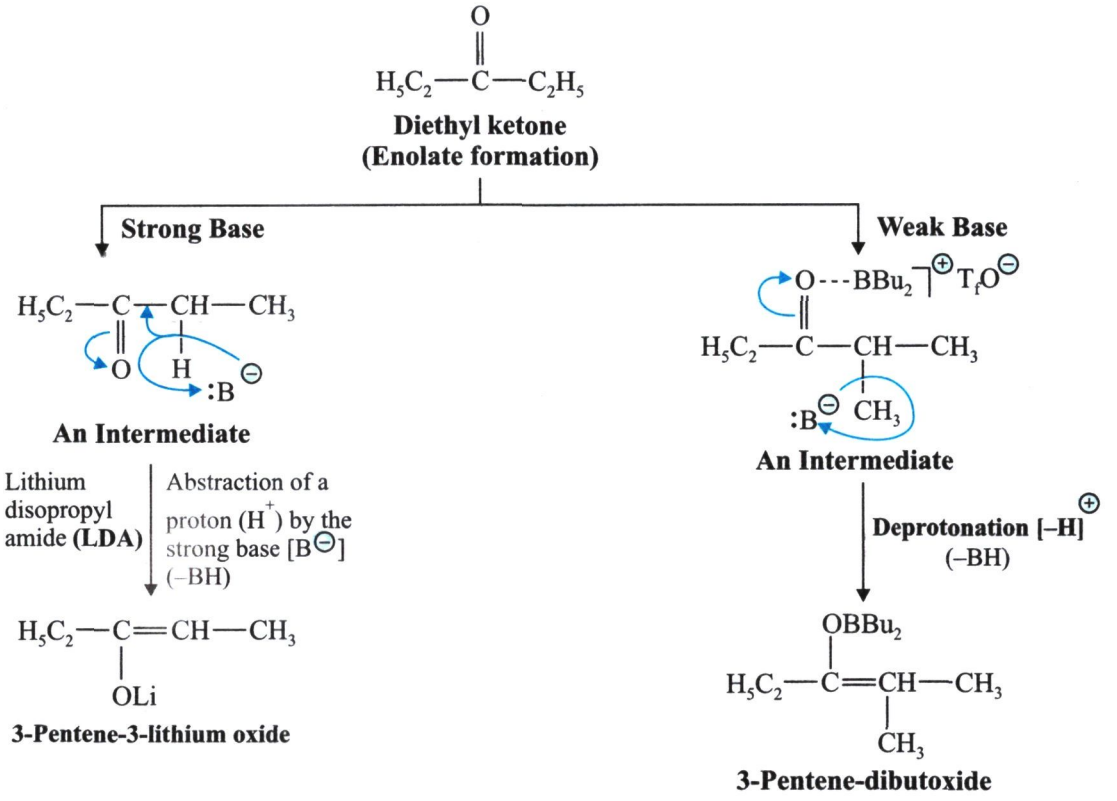
Formation of Enolates: The Stereochemical Characteristic Feature

In order to facilitate the formation of an **'enolate'** the following ***two* conditionalities** seem to be extremely vital and important *viz.,*

(*i*) **specific *'hard conditions'* consisting of a strong base**; and

(*ii*) **specific *'soft conditions'* comprising a *Lewis acid** plus a *weak base.***

Example: It may be further expatiated with the following example of **diethyl ketone [Et. CO. Et].**



* **Lewis acid:** It refers to an **oxidizing agent** *i.e.,* a substance that usually *accepts electrons in a chemical reaction.*

Brown *et al.* (1989)* carried out an array of investigative reactions leading ultimately to the ***formation of enolates***—under a wide range of experimental parameters thereby accomplishing the so-called **desired geometry.**

***Stereoselective Formation of the Enolates* [Ireland Model]**

Interestingly, the **stereoselective formation of the enolates** has undergone virtually a thorough **rationalization process** based on the so-called **Ireland Model.****

Certain assumptions in the Ireland Model

These essentially comprise the following important aspects:

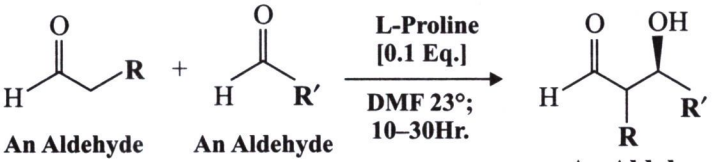
- ***deprotonation* phenomenon invariably comes into being *via* a 6-membered transition state,** and
- **electrophile having relatively bigger substituents usually take the course of an *equatorial-oriented disposition* towards the *favoured transition state,***

which ultimately gears to the generation of the **'E'-enolate.**

NOTE: **However, the *Ireland Model* fails to attain absolute success and accomplishment in majority of the instances.**

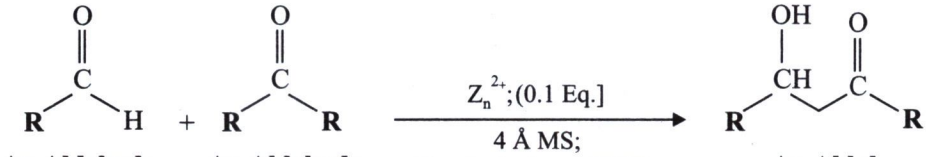
Enantioselective Direct Cross-Aldol Reaction Pertaining to Aldehydes

(*a*) Northrop *et al.* (2002)*** were pioneer in reporting the **direct enantioselective cross-Aldol reaction** with the *aldehydes* as given under:



An Aldehyde **An Aldehyde** **An Aldol**

(*b*) Trost *et al.* (2001)**** exhaustively studied the direct ***asymmetrical* aldol reactions** of acetone by making use of a **bimetallic zinc catalyst**—as shown below:



An Aldehyde **An Aldehyde** **An Aldol**

(*c*) Ooi *et al.* (2004)***** carried out the remarkable development of the highly ***diastereo*-and enantioselective *direct asymmetric aldol condensation*** reaction pertaining to the **aldehydes duly** catalyzed by means of the so-called ***chiral* quarternary ammonium salt**—as given under:

---

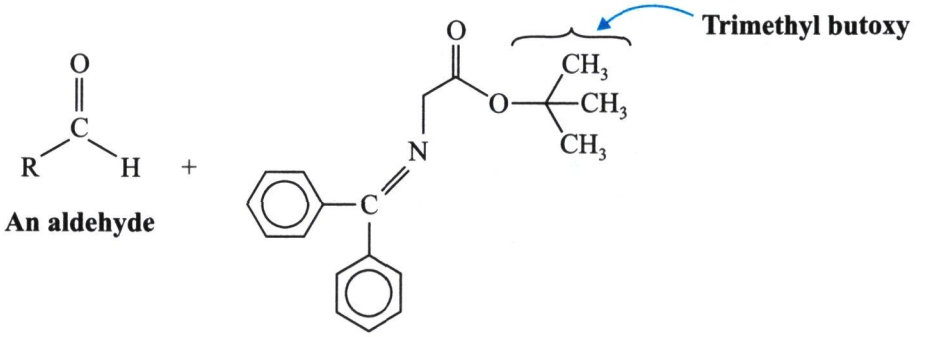
*Brown HC *et al.* : *J Am Chem. Soc*, **111**: 3441–42, 1989.

Ireland *et al.* : *J Org. Chem.*, **56: 650–657, 1991; Xie L *et. al.* : *J Org. Chem.*, **62**: 7516–19, 1997.

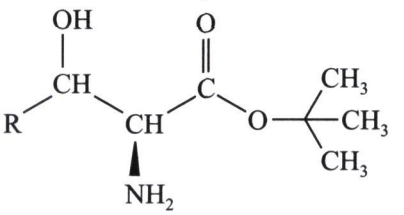
***Northrop AB *et. al.*: *J Am Chem. Soc.*, **124**: 6798–99, 2002.

****Trost EM *et. al.* : *Org. Lett*, **3**: 2497–2500, 2001.

*****Ooi T *et al.* : *J Am Chem. Soc.*, **126**: 5685, 2004.



(i) 2 Moles-Catalyst (%);
NH_4Cl (0.1 Eq.); NaOH (0.15 Eq);
Toluene (1% Eq.); 1.5-10 Hr;
(ii) Successive Extractive Workup;
(iii) Tetrahydrofuran (THF): 1 M
HCl (81); 0°C; 1 Hr;



An Aldol

Comments: 1. The aforesaid **direct asymmetric aldol condensation** is promoted apparently by the respective ***negative inductive*** effect; and hence, reduced adequately by the so-called ***positive inductive effect.***

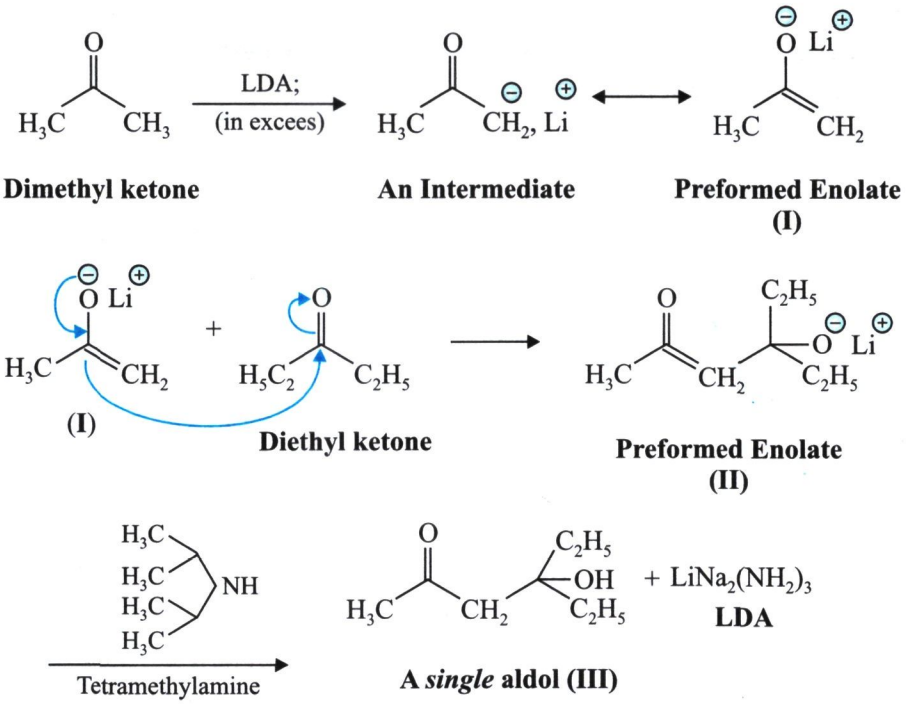
2. It is, however, pertinent to state here that overall ***reaction equilibrium*** is found to be extremely favourable for the **'aldehydes'** *vis-a-vis* the **'ketones'.**
3. Nevertheless, in the critical presence of a *strong alkali* (*viz.,* NaOH); whereas, the successive **aldol condensation** occurs thereby causing the ***formation of resins*** perceptively.

Critical Check on the Cross-Aldolization of Mixture of Two Carbonyl (>C=O) Compound Variants

Importantly, the **'cross-aldolization'** of *two* variant carbonyl (>C=O) chemical entities may be checked gainfully by adopting either of the following procedures of performing the aforesaid reactions, namely:

(*a*) **Making use of a reformed '*Enolate*' of a component carbonyl compound in the presence of an excess of a *strong base e.g.*, lithium diisopropylamide (LDA)**—which is duly expatiated as under:

Examples:



EXPLANATION

The various steps involved in the above sequence of chemical reactions may be explained as under:

1. **Dimethyl ketone** interacts with an excess of *lithium diisopropyl amide (LDA)* to form an intermediate Li-salt, which undergoes a reversible reaction to give the **preformed enolate (I).**
2. **Preformed enolate (I)** subsequently on treatment with *diethyl ketone* (a higher homologue of aliphatic ketone) to produce the **preformed enolate (II),** which on treatment with *tetramethylamine* yields *two* products *i.e.,* **the single aldol (III)** and **LDA (1 mole)** is liberated.

(*b*) **Mukaiyama's Aldolization:** Mukaiyama and Kobayashi (1987)* suggested that the **silylated enol ether** of the ***nucleophilic carbonyl* (>C=O) *component*** is duly prepared; and subsequently, allowed to interact with the so-called ***electropholic carbonyl* (>C=O) *partner***, of course, in the critical presence of *titanium tetrachloride* ($TiCl_4$) in **dichloromethane (DCM)** as the respective solvent.

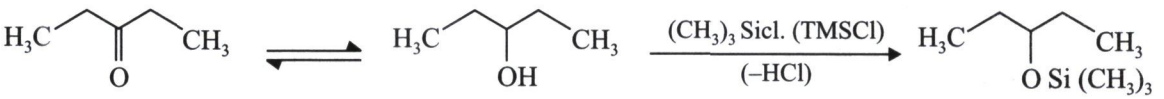
*Mukaiyama T and Kobayashi S: *Heterocycles*, **25**: 245, 1987.

Amazingly, the **Mukaiyama's aldolization** procedure essentially possesses the following ***two* vital meritorious advantages**, namely:

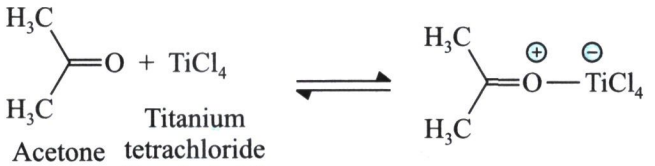
(*i*) Total absence of the **'cross-aldol condensation'** phenomenon occurs.

(*ii*) Because the prevailing **'reaction parameter'** is found to be of an *acidic nature* solely on account of the crucial presence of the *Lewis Acid* **($TiCl_4$)**—that ultimately leads to total absence of the ensuing ***spontaneous* dehydration of the 'aldol'.**

Thus, we may have the following expressions:

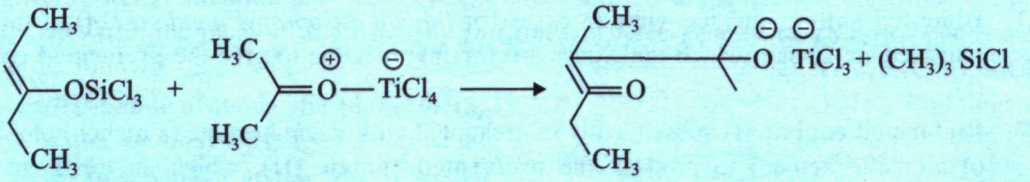


Diethyl ketone — 3-Hydroxy pentane — **[Trimethyl siloxane derivative] Silylated enol ether**

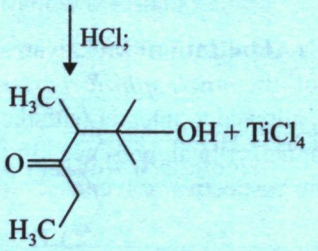


Acetone — Titanium tetrachloride **(Lewis Acid)** — **Acetone titanium chloride (Salt)** [*ie*, absence of spontaneous of dehydration of 6 aldol']

Comment: Dimethyl ketone undergoes a reversible reaction to form **3-hydroxy pentane,** which on treatment with *trimethylsilane chloride* yields the desired **silylated enol ether** (*i.e.,* a *trimethyl siloxane derivative*). Besides, the corresponding *acetone* when reacted with **$TiCl_4$ (Lewis acid)** also undergoes a reversible reaction to give **acetone titanium chloride** (salt)—thereby showing the total absence of **spontaneous dehydration of 'aldol'.**



Diethyl ketone silane trichloride — Acetone litanium chloride (salt) — **An Intermediate salt** — **Trimethyl silane chloride**



An 'Aldol

Comment: Interaction between *diethylketone silane trichloride* and *acetone titanium chloride (salt)* yields an **intermediate salt** plus a mole of *trimethylsilane chloride* gets knocked out. Thus, the respective **intermediate salt** when treated in an *acidic medium* (HCl) gives rise to the formation of an **'aldol'** with the elimination of a mole of *titanium tetrachloride* **(Lewis acid).**

Cardinal Factors Governing The Aldol Reaction

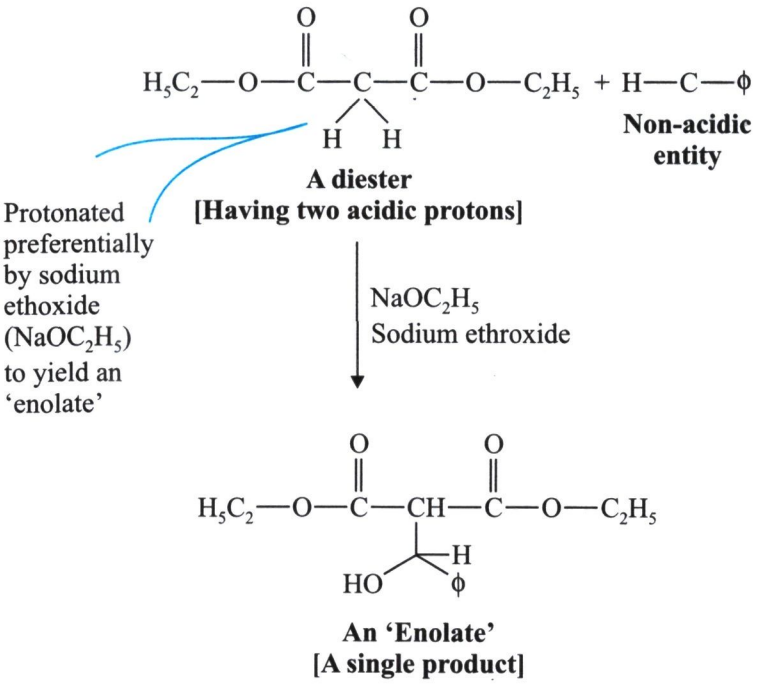
There are *two* cardinal factors that largely govern the **'aldol reaction'**, such as:

- **Acidity,** and
- **Kinetics of Reaction,**

which shall now be treated individually in the sections that follows:

(*a*) **Acidity:** Let us consider a typical instance when one of the *reactants* appears to be **more acidic** in comparison to the other, then the most prevalent **acidic protein** gets duly abstracted by the respective '*base*' thereby giving rise to the critical formation of an **'enolate'** by such a *reactant molecule* which certainly possess ***greater*** **acidic protons.**

Example: The above factual statements may be exemplified by the following conversion of the ***acidic protons*** present in a *diester* to the corresponding **'enolate'**:



Remarks: In the aforesaid reaction one would take cognizance of the fact that the overall reaction is duly **controlled** and **modulated** by the ensuing *acidity of a reactant*; and, hence, comprises the following ***two*** **vital and important *elements of control,*** namely:

- **Electrophile is *devoid of* α *H-atoms*;** and
- **Nucleophile *possesses acidic* α *H-atoms.***

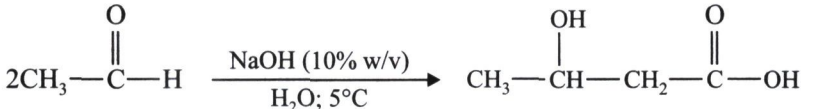
(*b*) **Kinetics of Reaction:** Bal *et al.* (1985)* studied intensively the precise order of the **Aldol Reaction**, whereby the following *two* sequential steps come into play:

- **formation of '*enolate*' from one mole of the reactant; and**
- **incorporation of the '*enolate*' to the other one under kinetically controlled parameters.**

Examples: Let us examine the following specific reactions:

(*a*) **The Aldol Reaction: The Addition of Enolate Anions to the Aldehydes and Ketones** **Acetaldehyde** when subjected to reaction with *dilute NaOH* at normal *room temperature (20 ± 2°C)* or even below—a **dimerization reaction.**** comes into play thereby producing **3-hydroxybutanol.** Because **3-hydroxybutanol** shows the dual feature of an **aldehyde** and an **alcohol**; hence, it has been suitably assigned the common name **'aldol'**. Therefore, the reaction of this type are invariably termed as **'aldol additions'** or **aldol reactions.**

Example:



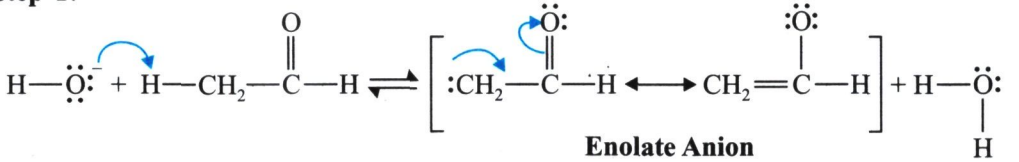
3-Hydroxybutanol
[An **'Aldol'**] **(50%)**

Remarks: The underlying mechanism for the **aldol addition** depicts clearly the following *two* cardinal characteristic features of the **carbonyl (>C═O) compounds,** namely:

- **inherent acidity of their α H-atoms,** and
- **critical tendency of their *carbonyl moieties* to undergo *nucleophilic addition*.**

The **Aldol Addition** reaction has *three* important sequential steps as given below:

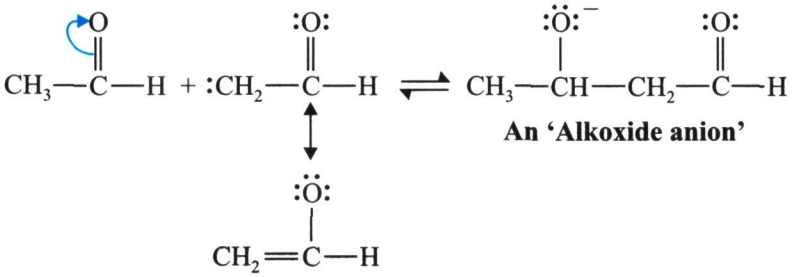
Step 1:



Enolate Anion

In the above step the **base** (a *hydroxide ion*) helps to remove a *proton* from the *α C-atom of the molecule* of acetaldehyde to yield a **resonance-stabilized enolate anion** finally:

Step 2:



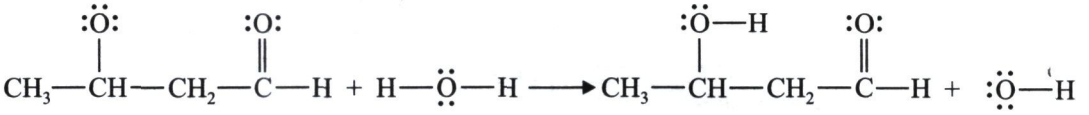
An 'Alkoxide anion'

* Bal B *et al.*: **Organic Synthesis Coll.** Vols. 7 and 63, (1985, 1990).

** **Dimerization Reaction:** It relates to such reaction that forms **'dimers'** (*di* = two; *mer* = part).

The **enolate anion** subsequently acts as a **nucleophile** and attacks the **carbonyl C-atom** of a second molecule of acetaldehyde thereby producing an **alkoxide anion.**

Step 3:



A Stronger base **An Aldol** **Weaker base**

The **alkoxide anion** eliminates a ***proton*** from a mole of water to yield the respective **aldol.**

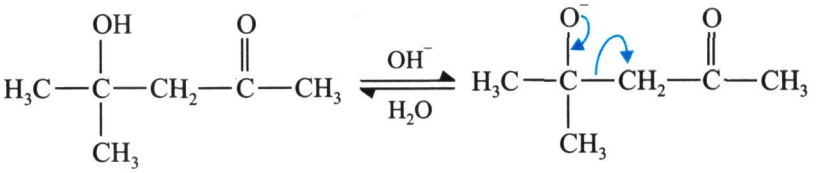
(*b*) **The Retro-Aldol Reaction [or The Reversibility of Aldol Additions]**

Importantly, the **'aldol addition'** (see section '*a*' above) is found to be reversible. Let us consider the typical example of the so-called **'aldol addition product'** duly obtained from ***acetone*** and heated subsequently with a ***strong base***,—it reverts to a definite **equilibrium mixture** which mostly comprises:

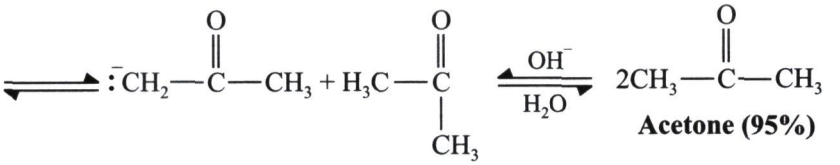
'nearly 95% of acetone (a *ketone*)'.

Amazingly, such type of a chemical reaction is invariably termed as—***'retro-aldol-reaction'.***

Example:



2-Dimethyl hydroxy methane acetone (5%) **An Intermediate**



Acetone (95%)

Thus, from **2-dimethylhydroxymethane acetone** on treatment within alkali yields an **intermediate**, which on further hydrolysis gives **acetone** up to **95%.**

Remarks: Following are the *six* cardinal critical observations:

1. The *condensation reaction* involving two moles of either an **aldehyde** or **ketone** with ***α-H atoms*** under the influence of a diluted base gives rise to the formation of :

   'a β-hydroxy aldehyde or ketone'.

2. Interestingly, the mechanism of the said reaction critically involves the so-called **'nucleophilic addition'** immediately followed by **dehydration** (*i.e.*, loss of a mole of H_2O).
3. However, based on the inherent reactivity of the **aldehydes** or **ketones**—there exists ***two*** **distinct mechanisms**, namely:

- **'*enol*' mechanism**; and
- **'*enolate*' mechanism.**

4. Importantly, the creation of ***two*** **prominent stereogenic centres** in one of the reaction reveals the ***stereoselectivity*** of the reaction which solely rests on the strategic positions of the respective ***stereocentres*** being used:
   - **'*syn*' convention; or**
   - **'*anti*' convention.**
5. It has been established beyond any reasonable doubt that the **'aldol reaction'** is largely controlled stereochemically by means of the *substrate* (*i.e.*, the substance on which the enzyme acts).
6. The **crossed-aldol condensation** is invariably performed between ***two*** **different 'aldehydes'** with the respective **H-atoms.**

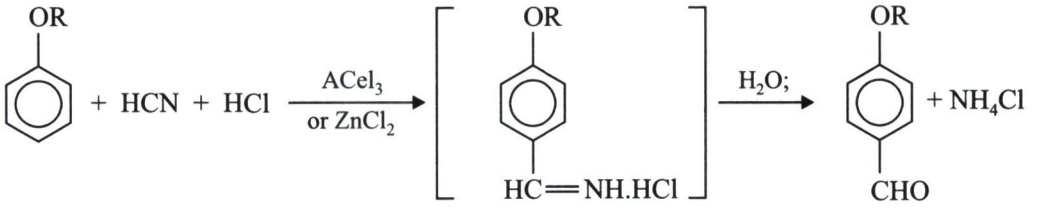
4.1.2 Gattermann Synthesis [or Gattermann Aldehyde Synthesis]

Gattermann (1907)* proposed the preparation of:

- **phenolic aldehydes** • **phenol ethers** or • **heterocyclic compounds**

by the treatment of the ***aromatic substrate*** with *hydrogen cyanide* **(HCN)** and *hydrogen chloride* **(HCl)** in the presence of the **Lewis acid catalysts:**

Thus, we may have the following reactions:



A *p* - Methylimine hydrochloride derivative **A *p* - Aldehyde derivative**

Comments: The usual variation comprises in the usage of ***liquid*** **hydrogen cyanide (HCN)** in place of **carbon monoxide (CO)** as a source of the **'formyl (—CHO) substituent'**; and of course, **hydrogen chloride (HCl)** is essentially required, invariably in combination with *aluminium chloride* ($AlCl_3$) or *zinc chloride* ($ZnCl_2$), but *Cuprous chloride (CuCl)* is omitted.

Explanation

The aforesaid reaction formerly was duly regarded to proceed *via* a ***transient*** **addition product of hydrogen cyanide (HCN)** and **hydrogen chloride (HCl)** thereby forming:

'formimino chloride (Cl. CH = NH)'

but now ascertained to follow the more complicated course.

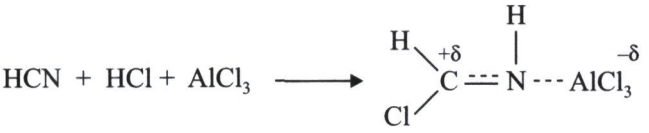
*Gattermann L., *Ber*, **31**: 1149, 1983; *Ann.*, **313**, 1907.

Nevertheless, in the total absence of the *hydrocarbon component*—the other reagents usually combine to yield a specific *molecular complex*, **$AlCl_3 \cdot 2HCN \cdot HCl$**, possibly by careful incorporation of the ***intermediate*** **formimino chloride to hydrogen cyanide (HCN).**

Mechanism of Reaction

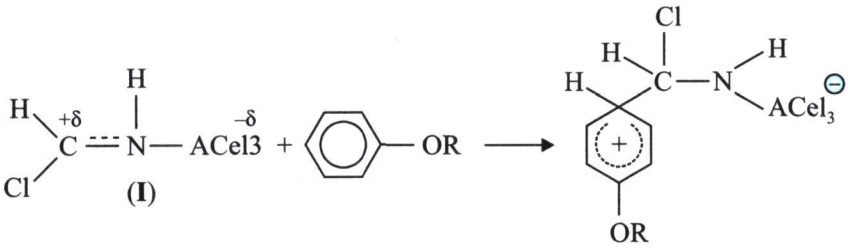
There are ***four*** **important steps** that are intimately involved to explain the **mechanism of reaction** in the ***Gattermann synthesis***, namely:

Step 1: It specifically involves the generation of an ***electrophilic species*** **(I)** from *hydrogen cyanide (HCN)* and *hydrogen chloride (HCl) gas* and a **Lewis acid**—as given under:



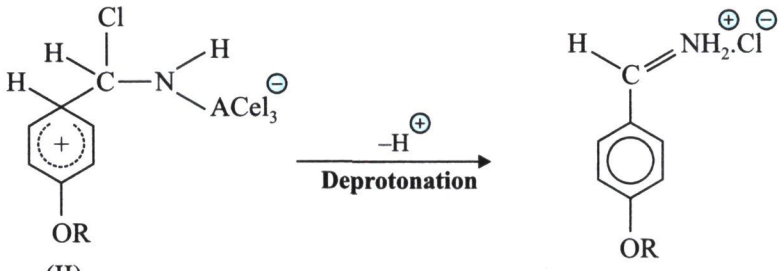
Electrophilic species
I

Step 2: Further addition of an *electrophile* to the corresponding ***aromatic ring*** gives rise to the formation of a typical **cationic intermediate** as shown below:



A Cationic Intermediate
(II)

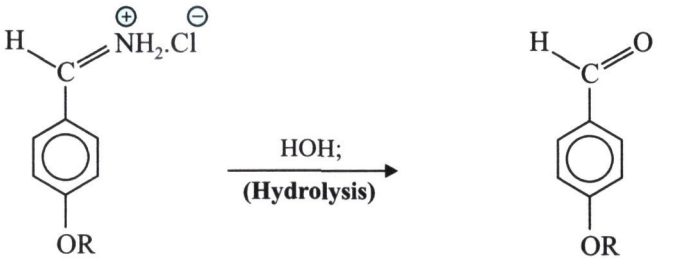
Step 3: The subsequent ***deprotonation*** of **(II)** and a follow up ***concomitant*** **rearomatization** helps to complete the **substitution**—as given under:



Iminium species (III)

Step 4: The ultimate *hydrolysis* of the **iminium species (III)** yields **formylated aromatic product**—as shown below:

(Contd...)



(III) **Formylated aromatic product (IV)**

Comments: It may, however, be observed that the so-called **formyl (—CHO) moiety** is introduced particularly to the ***'para'*-position** to the respective ***activating substituent;*** but in such an instance when the ***'para*-position'** is duly pre-occupied—then one would obtain the corresponding ***'ortho'*-derivative.**

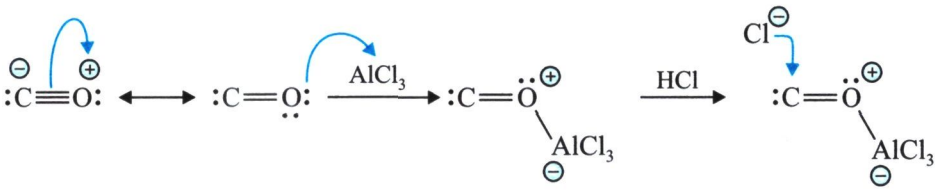
Progressive Extension of Gattermann Reaction

A critical survey of literature reveals that the **Gattermann reaction** may be extended progressively in terms of the following ***two*** **typical reactions**, such as:

- **Gattermann-Koch Reaction**; and
- **Houben-Hoesch Reaction,**

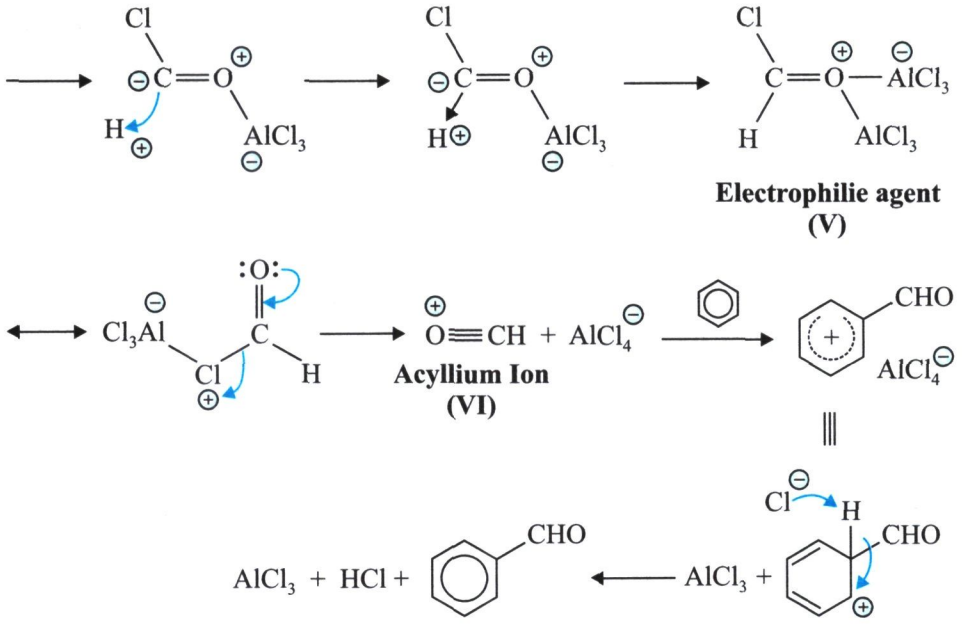
which shall now be treated individually in the sections that follows:

(*a*) **Gatterman-Koch Reaction***—Importantly, it also duly designates a **formylation reaction** known as the ***Gattermann reaction***, essentially involving the formylation of the '**arenes**' by making use of *carbon monoxide (CO)* and *hydrogen chloride (HCl)* in the presence of $AlCl_3$ (aluminium trichloride) **under high pressure.** However, it also represents the reaction of an ***'aromatic substrate'*** with *CO* and *HCl (gas)* specifically in the presence of a **Lewis acid catalyst.** Besides, closely analogous to the **Gattermann reaction** it essentially involves the formation of the so-called **electrophilic agent (V)**—that eventually undergoes reaction with the **aromatic substrate** (*i.e.,* ***aromatic electrophilic substitution***) to produce the respective **formylated aromatic compound** *via* the **acylium ion O≡CH (VI)** as depicted in the following **sequential reactions:**



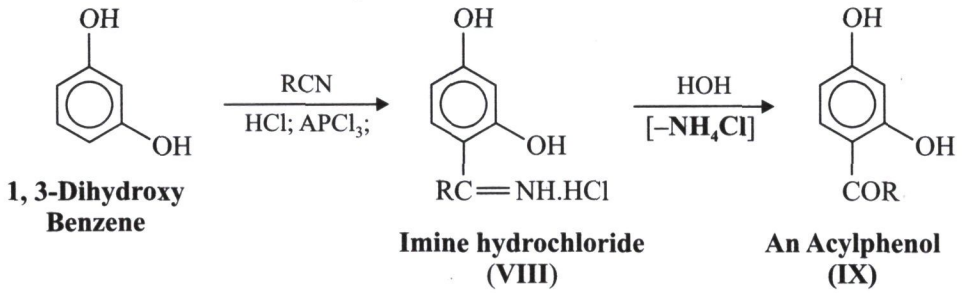
(Contd.)

* Olah GA *et al.*: *Chem, Rev.*, **87**: 671–686, 1987;
Gattermann L and Koch JA : *Ber Dtsch Chem Ges*, **30**: 1622–1624, 1897.
Kantlehner W *et al.*: *J Prakt Chem*, **342**: 297, 2000.
Donna MJ *et al.* : *Rev Roum Chem.*, **46**: 345, 2002.



(*b*) **Houben-Hoesch Reaction [or the Acylation with Nitriles]:** It is a reaction which proves to be analogous to **Gattermann-Koch reaction,** wherein the ***aryl ketones*** are critically produced from the respective **'nitriles'** by making use of the **Lewis acids**—as the **catalysts.***

The **Houben-Hoesch reaction** relates to the synthesis of the **acylphenols** either from ***phenols*** or ***phenolic ethers*** by the action of *organic nitriles* (**R—CN**) in the presence of **hydrochloric acid (HCl)** and **aluminium chloride ($AlCl_3$)** as the catalyst:

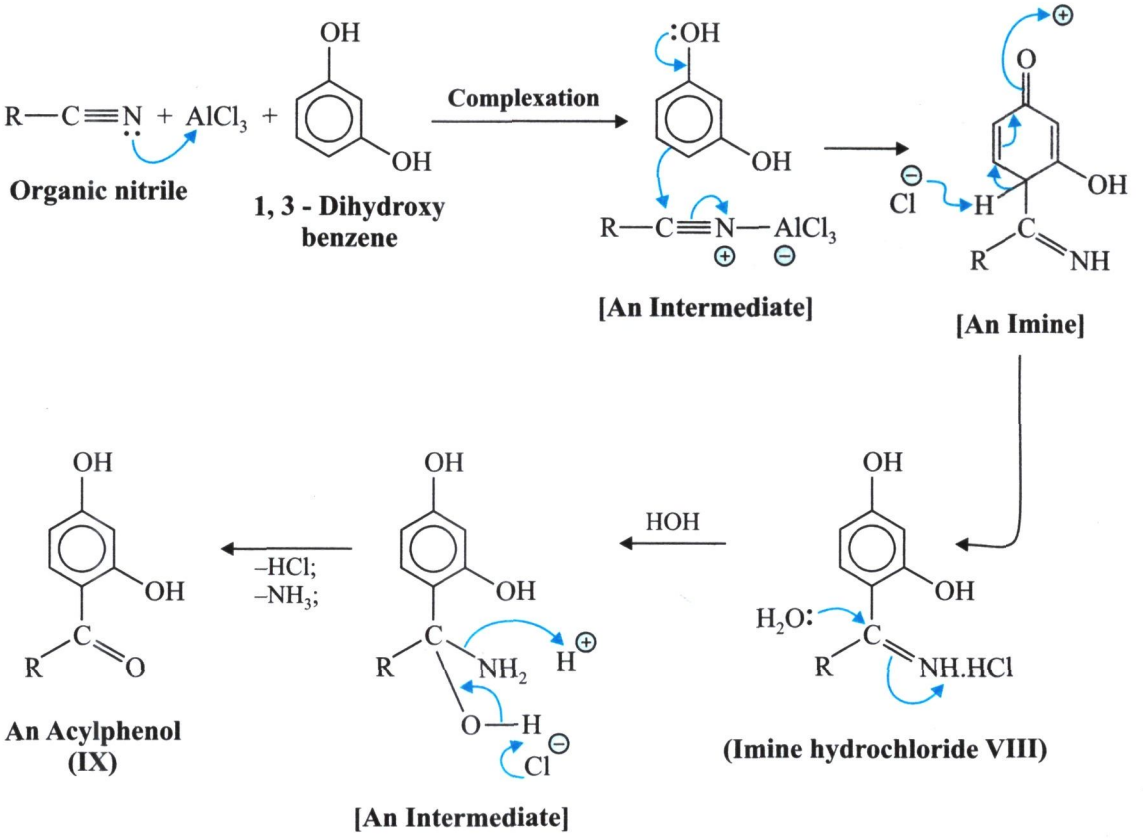


Mechanism of Reaction

Thus, the complex mechanism of the reaction critically involves first the formation of the **imine salt (VII)** obtained from the so-called *attacking species,* **imine hydrochloride (VIII),** which on subsequent *hydrolysis* give the product' **acylphenol' (IX).**

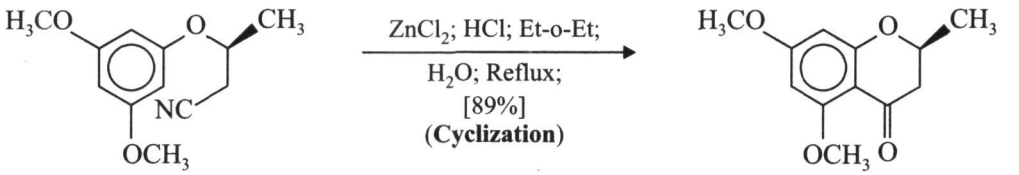
* Houben J: *Ber Dtsch Chem Gen,* **59**: 2878–2891, 1926.
Hoesch K: *Ber Dtsch Chem Gen,* **48**: 1122–1133, 1915.

Following are the various steps involved in the *sequential reactions:*



Intramolecular Houben—Hoesch Reaction

Rao *et al.* (1994)* first and foremost carried out the extensive studies related to the **intramolecular Houben-Hoesch reaction,** which may be expatiated by the following reaction:



3, 5-Dimethoxy-2-methyl ethane nitrile ether

2-Methyl-benzopyron-5, 7-dimethoxy-4-one

Thus, it helps in the conversion of an *open-chain nitrile* into the corresponding cyclized **benzopyran derivative** with the elimination of a mole of H_2O.

*Rao AVR *et al.* : *Tetrahedron Lett.*, **35**: 6347, 1994.

Remarks: These essentially include:

1. The **Houben-Hoesch reaction** takes place successfully with the so-called **polyhydroxy phenols** *viz.*, the ***m*-hydroxyphenols.**
2. It has been proven that the aforesaid reaction is not quite successful with **phenol** perhaps due to the formation of the ***amino-ether hydrochloride*** as a product.
3. Both ***aliphatic*** **and** ***aromatic*** **nitriles** may be employed effectively for this purpose.
4. However, the **ketones** may also be obtained by heating **phenols** or the **phenolic ethers** having specifically a **nitrile (CN)** in the presence of Fe_3CSO_2OH* with an altogether different mechanism.
5. **Fries rearrangement** is found to be absolutely *not suitable* for the **monoacylation of the polyhydroxy phenol** perhaps due to the formation of the **polymeric aluminium phenoxide;** and hence, **Houben-Hoesch reaction** is employed.

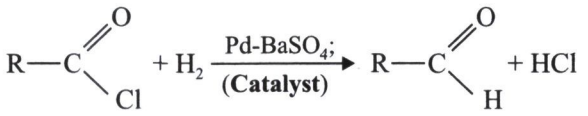
4.1.3 Rosenmund Reduction**

The **Rosenmund reduction** refers to the specific **catalytic hydrogenation** of either:

- **acid chlorides** [R-COO-Cl]; or
- **acyl chlorides** [R-CO-Cl],

into the corresponding ***aldehydes*** **[R-CHO]** by making use of **Pd-$BaSO_4$** (*i.e.*, **Pd-poisoned catalyst)*****. Thus, it serves as an useful method of transforming an ***acid*** into an **aldehyde (R-CHO)** having the same **C-chain** *i.e.*, enables the **catalytic hydrogenation** of the respective **acid chloride.**

We may express the reaction as stated under:



An Acyl chloride **An Aldehyde**

However, the overall *success of the method* solely depends upon the ensuing **differentiation profile** existing between these ***two*** **aspects**, namely:

- **speed of replacement of *Halogen* by *Hydrogen***; and
- ***hydrogenation*** **of the resulting *aldehyde*.**

Mechanism of Reaction

The actual mechanism of the technique introduced by **Rosenmund** essentially consists in adding a small quantum of a ***'poisoning agent'*** containing **sulphur**—that fails to inhibit articulately the so-called **desired reduction of the highly reactive acid chloride,** but stops quite effectively the possible ***hydrogenation*** of the **'aldehyde'.**

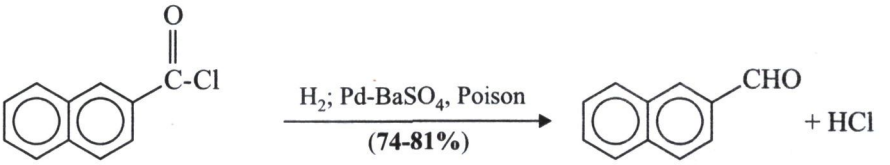
---

*Booth and Noori : *J Chem. Soc.*, 2894 (1980); 1075 (1983).

Rosenmund KW: *Ber Dtsch Chem Gen,* **51: 585–593, 1918.

***Saytzeff M : *J Prakt Chem.*, **6**: 128–135, 1873.

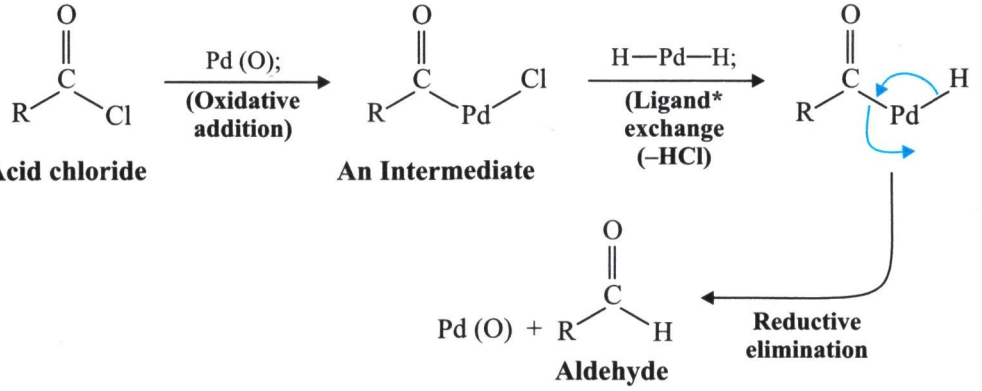
Thus, we may have the following expression:



β-Naphthoyl chloride **β-Naphthaldelhyde**

A stream of *hydrogen gas* (H_2) is passed *via* a boiling solution of the **acid chloride** (β-naphthoyl chloride) in a *hydrocarbon solvent* (*viz.*, *n*-Hexane; Benzene), and **exist gas** is passed into a **standard alkali,**—the actual course of the reaction is followed from the amount of **hydrogen chloride (HCl)** duly absorbed.

Another school of thought, explains the above mechanism of reaction based on the critical formation of an **organopalladium species** as a probable **'intermediate'** which upon reaction with **hydrogen (H_2)** gives rise to the formation of the desired product—**'aldehyde'**,—as shown below:



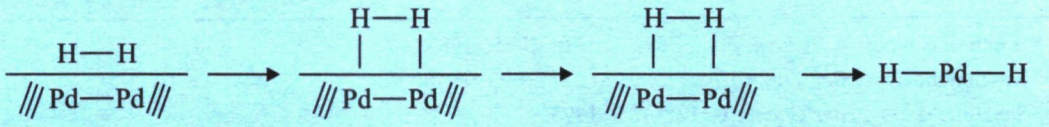
Acid chloride **An Intermediate** **Aldehyde**

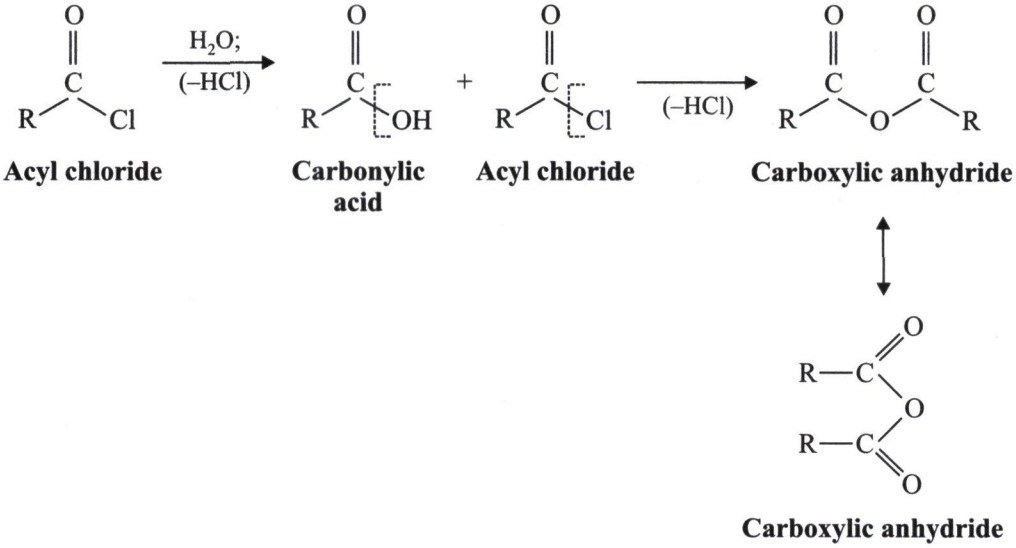
Comment: Amazingly, one may usually encounter a plethora of **side reactions** that are possible with the **Rosenmund reduction**; however, these probable ***side-reactions*** may be prevented as far as possible by making use of the appropriate **reaction parameters.**

NOTE: **The crucial need of *'poisoning'* arises prevalently to check the further reduction of the *'aldehyde'* into an *'alcohol'*, since a reasonably *poor deactivated catalyst* may ultimately lead to the reduction of aldehydes to alcohols.**

In another particular instance, if a small quantum of H_2O is present inadvertently,—a **partial hydrolysis** of the respective **acyl chloride** occurs into the corresponding **carboxylic acid (—COOH),** that would further react with the **acyl chloride** to yield a **carboxylic anhydride**—as shown below:

***Ligand Exchange** is as shown below:



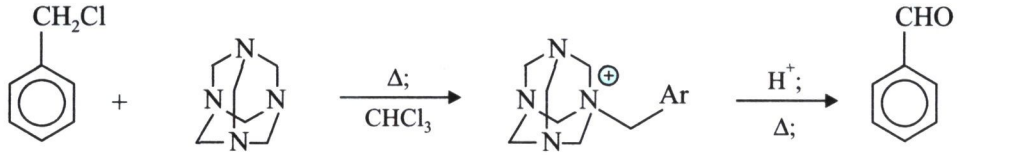


Remarks: The major application of the **Rosenmund reduction** relates to the critical conversion of the **carboxylic acid** into the respective ***aldehyde*** *via* the **acid chloride.** Besides, the **carboxylic acid** may conveniently get reduced to the corresponding ***alcohol*** *via* **$LiAlH_4$** (lithium-aluminium hydride) which gets duly **oxidized** to the **aldehyde.**

4.1.4 Sommelet Reaction

Sommelet (1913)* proposed a reaction that involves the specific *transformation* of the ***benzyl halides*** into the respective **benzaldehydes** by the treatment with *hexa-methylenetetramine* **[$C_6H_{12}N_4$]**, whereby the specific **chloromethyl moiety** gets duly *oxidized* to the **aldehyde (-CHO) group.** The resulting product, **quarternary ammonium salt****, yields the **benzaldehyde** ultimately in an acidic medium.***

Thus, we may have the following expression:



Mechanism of Reaction

The precise mechanism of the **Sommelet reaction** is not well known. However, according to the overall *accepted mechanism* the said reaction is supposed to be initiated by the ensuing *interaction* between:

---

* Sommelet M: *Compt Rend*, **157**: 852, 1913.

** $[C_6H_{12}N_4CH_2Ar]^+ . Cl^-$

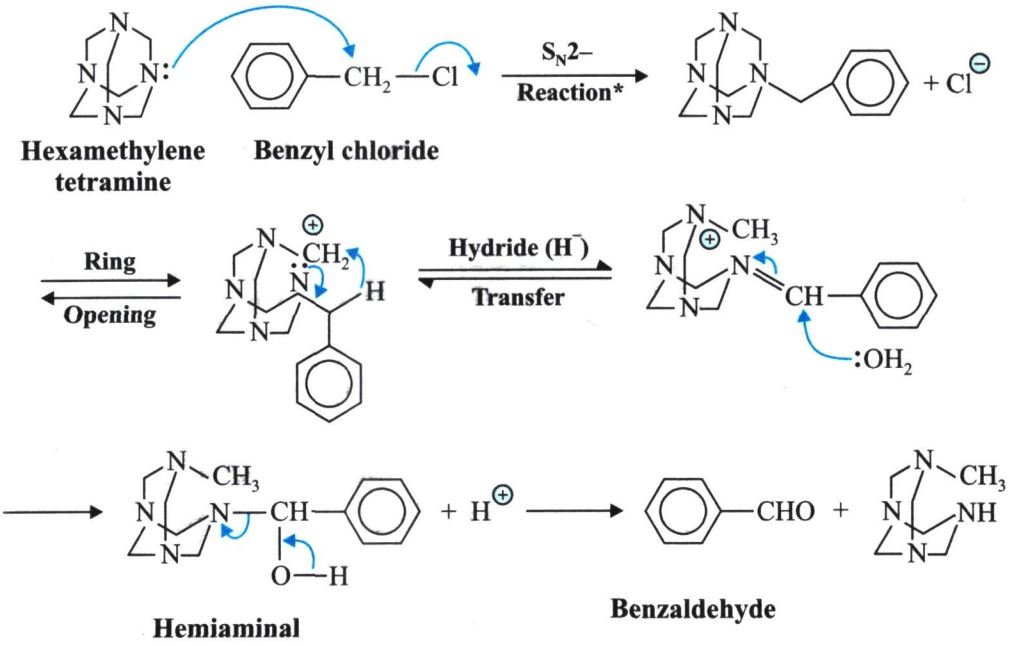
*** Le Henaff P: *Annals Chem Phys*, 367, 1962.

- **benzyl halide,** and
- **hexamethyltetramine,**

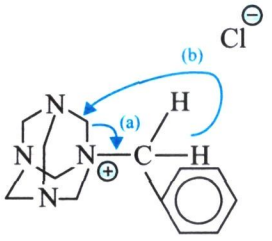
thereby exerting the so-called ***Bimolecular Nucleophile Substitution*** to yield a **quarternary ammonium salt** $[C_6H_{12}N_4CH_2Ar]^+ \cdot Cl^-$, which is subsequently *hydrolyzed* to the respective **amine.** Thus, the **quarternary ammonium salt** elegantly undergoes the following *two* transformations:

- **ring cessation (or ring opening);** and
- **hydride transfer,**

whereby the resulting species on being subjected to *hydrolysis* (in an **acidic medium**) yields ***'benzaldehyde'*** as given under:



Comments: The *ring opening* and *hydride (H^-) transfer* in the respective *hexamethylenetetramine* molecule may come into play in an ***absolute synchronized manner*** as depicted under:



Hexamethylene tetramine Benzyl salt

(*a*) : Ring Opening
(*b*) : Hydride (H^-) Transfer

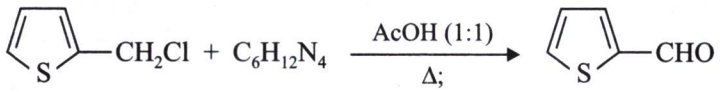
* **S_N2 Reaction:** The reaction between **methyl bromide** and **hydroxide ion** to give *methanol* follows the second-order kinetics *i.e.,* the rate depends solely upon the concentrations of both reactants:

$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^- \| \text{ rate} = k\,[(CH_3Br)\,(OH^-)].$$

Importantly, the critical presence of the ***strong* deactivating moieties** (*i.e.*, the so-called ***O*-substituents**) helps to lower the yield appreciably. In a particular instance, when both the ***ortho*-positions** are fully occupied, the reaction fails to take off at all.

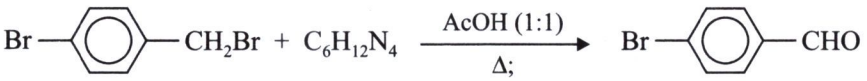
Examples: The **Sommelet Reaction** is of ***synthetic importance*** mostly for the **'aldehydes'**-derived from *amines* and *halides* as given under:

(*a*)



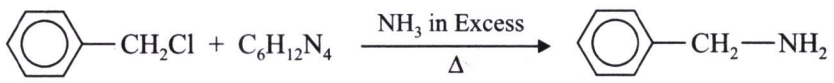
Thiophene-2-methyl chloride Hexamethylene tetramine **Thiophene-2-aldehyde**

(*b*)



***p*-Bromo-benzyl bromide** ***p*-Bromobenzaldehyde**

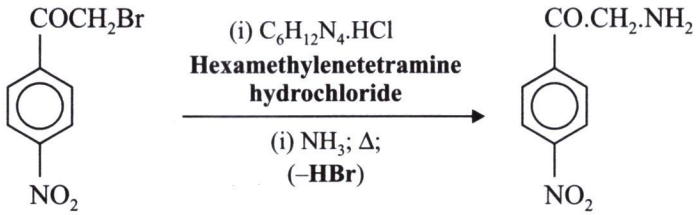
(*c*)



Benzyl chloride **Benzyl amine**

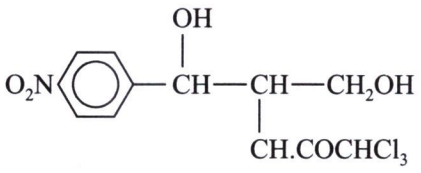
NOTE: **The said reaction may also be employed for the synthesis of a *aminoketone intermediate* needed critically for the synthesis of chloromycetin.**

The Intermediate for chloromycetin (an antibiotic)*—Thus, the treatment



p*-Bromo acetate nitro benzene (I)** **α-Bromo acetate *p*-nitro benzene

*** An '*intermediate*' for chloromycetin**



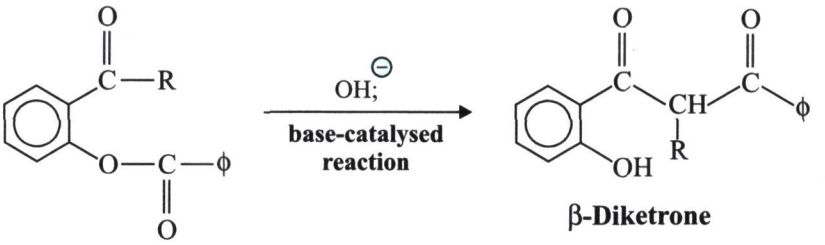
Chloromyectin

* Malykhin EV and Steingans VD: *J Fluorine Chem.*, **91** : 19, 1998, Lin X and HuW : *Huaxue Shiji*, **23:** 237, 2001.

of **compound (I)** with *hexamethylenetetracycline HCl* followed by *ammonia* (NH_3) and heating leads to the formation of **α-amino-acetyl-*p*-nitrobenzene**—as an ***intermediate*** for the synthesis of **chloromycetin.**

1.5 Baker*; Mahal *et al.* Reaction**

It represents a typical ***base-catalyzed*** **chemical reaction** that critically involves the underlying conversion of the **α-acyloxy ketones** into the corresponding **1,3-diketones** as given under:

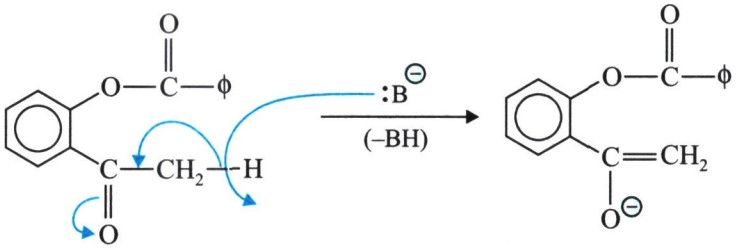


α-Acyloxy ketone

β-Diketrone

Mechanism of Reaction: The precise mechanism of **Baker; and Mahal *et al.* reaction** essentially involves the following ***two*** **important steps,** namely:

Step 1: Crucial abstraction of a *proton* (H^+) by the *base* to result into the formation of an **'Enolate'** as given under:



α-Acyloxy ketone

Enolate

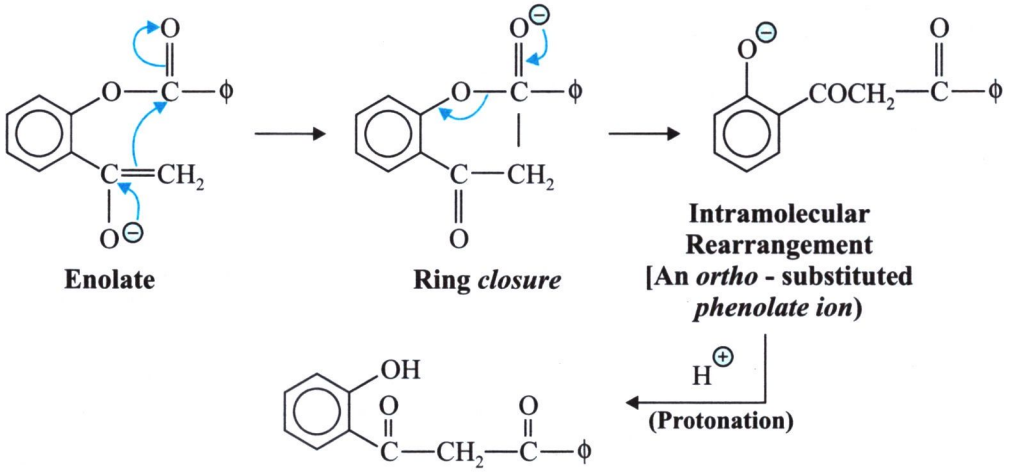
Thus, **α-acyloxy ketone** abstracts a **proton** (H^+) in the form of a ***base*** **'BH'** as shown above to yield an ***'enolate'***.

Step 2: Acyl transfer from the 'Enolate' to form β-Diketone *via* Intramolecular Rearrangement

Let us examine the following *sequence of reactions*:

* Baker W: *J Chem. Soc.*, 1380–1389, 1933

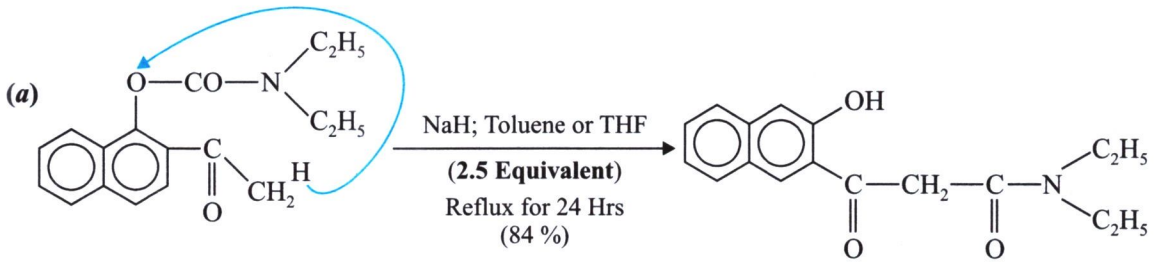
** Mahal HS and Venkataraman K., *J Chem., Soc.*, 1767, 1934.



EXPLANATION

Thus, the **'enolate'** undergoes *intramolecular rearrangement* to form a **bicyclic compound,** which further upon ***cleavage of*** **the second ring** yields an ***ortho*-substituted phenolate ion.** The ***resulting product*** on being subjected to ***protonation*** gives the desired product **β-diketone.**

Kalinin *et al.* (1998)* put forward further illustration of the Intramolecular Rearrangement—They exemplified the **intramolecular rearrangement** in ***diketones*** with the help of following *two* examples:



1-Diethyl amino carbonyl oxy-2-acetyl naphthalene (I)

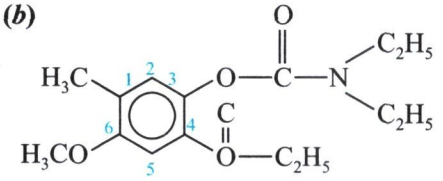
[Intramolecular Rearrangement]

3-Diethyl amide acetyl-2-naphthol (II)

In this particular example a *diketone* : **1-diethyl amino-carbonyloxy-2-acetyl naphthalene (I)** when treated with sodium hydride (NaH) (2.5 equivalent) in either *toluene* or *tetrahydrofuran* and refluxed for **24 hrs** yields **3-diethylamide acetyl-2-naphthol (II)** due to the so-called ***intramolecular rearrangement*** as shown above.

*Kalinin AV *et al.* : *Tetrahedron Lett.*, **39** : 4999, 1998.

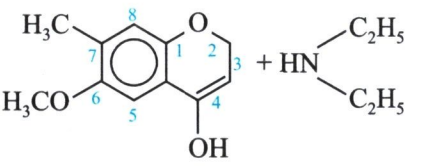
(b)



A Diketone

3-Diethyl oxyamide-4-propyl-6-methoxy toluene
(III)

[Cyclization]
NaH [2.5 Equivalent] in tolune; Reflex for 2Hrs; Add THF (2.0 Equivalent); Reflux for 1 Hr.; **(93%)**
[Intramolecular Rearrangement]

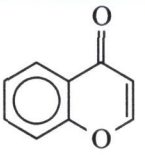


4-Hydroxy-6-methyoxy-7-methyl coumarin
(IV)

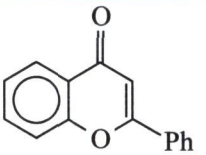
Thus, the ***diketone***, **3-diethyl oxyamide-4-propyl-6-methoxy-toluene (III)** undergoes *intramolecular rearrangement* (causing **cyclization**) to yield **4-hydroxy-6-methoxy-7-methyl coumarin (IV)** up to a yield of **93%** (using the aforesaid experimental parameters).

Special Remarks: Wheeler (1952)* strongly recommended that the reaction (see *Section 1.5*) may be candidly applicable to the synthesis of the following ***two*** **classes of compounds:**

• Chromones, and • Flavones.



Chromone
[4H-1 Benzopyron-4-one]

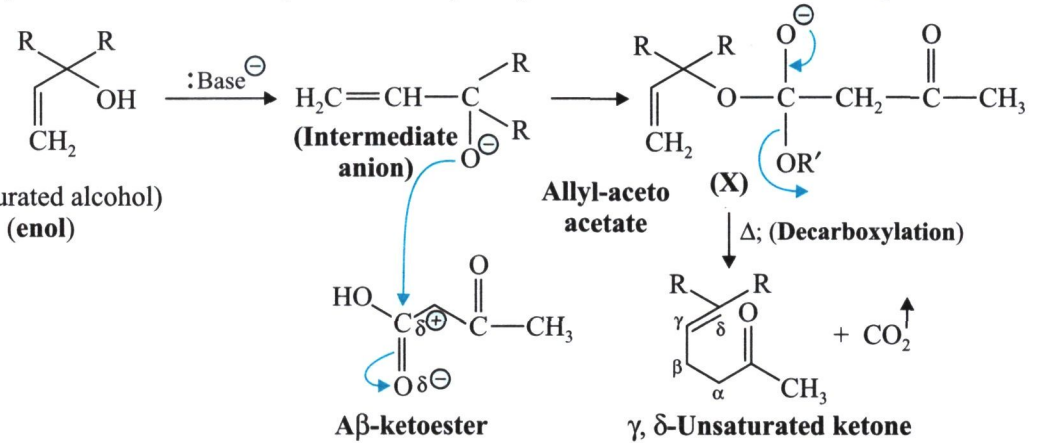


Flavone

4.1.6 Carroll Rearrangement**

The **Carroll rearrangement** refers to the **thermal rearrangement** of the ***allyl acetoacetates*** or the **base-catalyzed reactions** of the ***allyl alcohols*** to yield **γ, δ-unsaturated ketones,** as depicted below:

Part 'a'



(Unsaturated alcohol)
(enol)

(Intermediate anion)

Allyl-aceto acetate

(X)

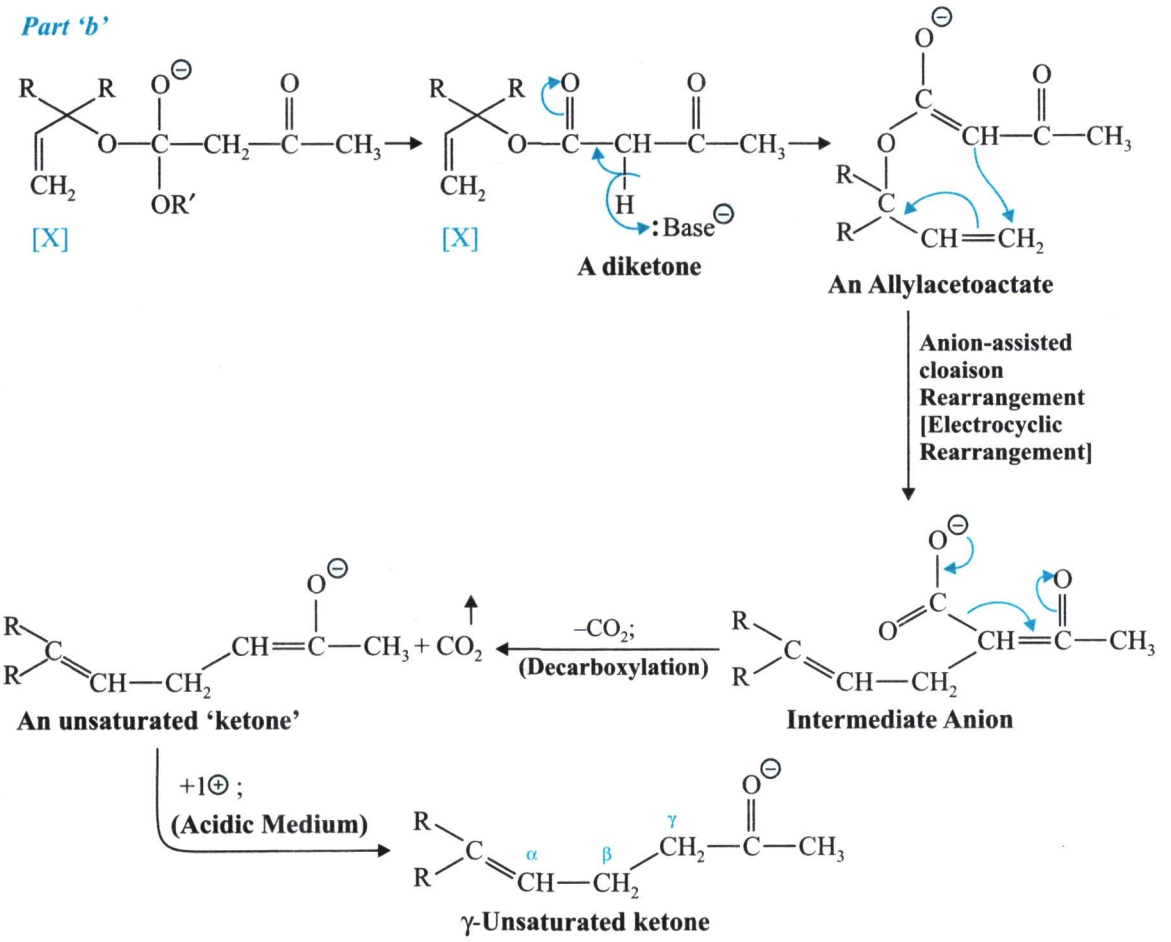
Δ; **(Decarboxylation)**

Aβ-ketoester

γ, δ-Unsaturated ketone

* Wheeler TS: **Flavone,** *Org. Syn.* **32:** 72, 1952; Laurent M *et al.*: *J. Org. Chem.*, **69**: 3194, 2004; Reetz MT *et al.*, *Angew Chem. Int.* Ed. **43**: 4076, 2004.

** Carroll MF : *J. Chem Soc.* 704, 1940.



EXPLANATION

Part '*a*': Various steps may be expatiated as under:

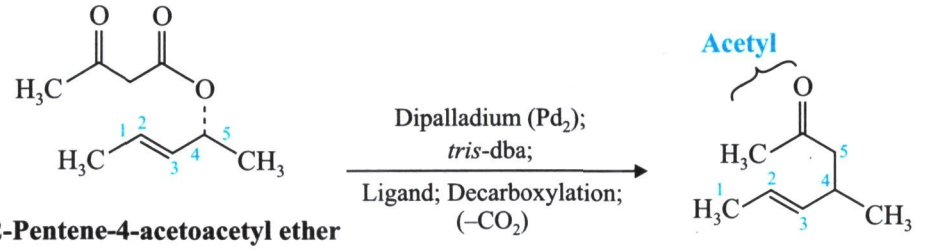
1. The '***enol***' (an **unsaturated alcohol**) on treatment with a *base* [: **Base**$^{\ominus}$] yields a **β-keto- ester** (bearing $\delta^{\oplus}$ and $\delta^{\ominus}$ atoms) *via* an ***intermediate*** **anion.**
2. The resulting ***intermediate*** **ion** gives rise to the formation of an **allyl acetoacetate [X]**, which on heating undergoes *decarboxylation* to produce the desired product **γ, δ-unsaturated ketone** and a mole of CO_2 gets eliminated.

Part '*b*': The sequential steps involved in the reaction are explained as under:

1. The **product [X]** undergoes intramolecular rearrangement to give a **diketone**, which on treatment with a **base [:Base$^{\ominus}$]** yields an **allyl acetoacetate.**
2. The resulting product undergoes an ***anion-catalyzed Claisen Rearrangement*** (or **electrocyclic rearrangement**) to produce an ***intermediate*** **anion.**
3. The **intermediate anion** on *decarboxylation* gives an **unsaturated ketone,** which on *protonation* ($H^{\oplus}$), in an acidic medium, yields the respective **γ-unsaturated ketone.**

The Enantioselective Reactions with Suitable '*Chiral Ligands*'*

In the recent past various organic chemistry scientists: Hatcher *et al.* (2002)** and Jung *et al.* (2004)*** vehemently explored and reported the so-called enantioselective reactions using suitable ***'chiral ligands'*** *i.e.,* chiral drug substances. Burger *et al.* (2004)**** showed elegantly the aforesaid **enantioselective** reaction by means of the ***asymmetric rearrangement*** duly catalyzed by ***tris*-(dibenzylidene acetone) dipalladium (Pd_2)** which may be expressed as under:



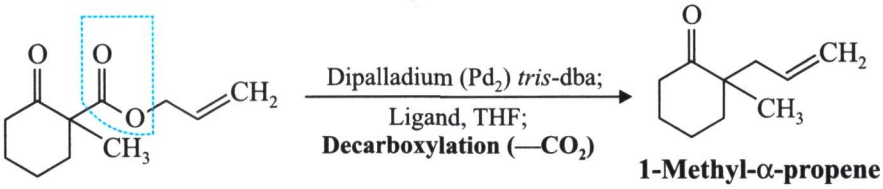
tris-dba: *tris* (Dibenzylidene acetone)

2-Pentene-4-acetoacetyl ether (A)

5-Acetyl-4-methyl-2-pentene (B) (82%)

Thus, **compound (A)** upon enantioselective reaction using the aforesaid experimental parameters yields **82%** of **compound (B)** *i.e.,* a **diketone** chemical entity provides a **monoketone compound.**

Interestingly, Mohr and Behenna (2005)***** strongly supported the **enantioconvergent reaction.**



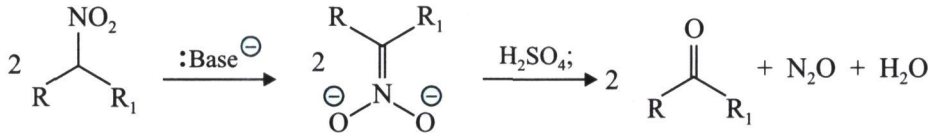
1-Methyl-α-propene ester Cyclohexanone (C)

1-Methyl-α-propene cyclohexanone (D)

Thus, **compound (C)** on being subjected to the so-called **enantioconvergent reaction** in the presence of the ligand and THF undergoes *decarboxylation* to give **compound (D)**.

4.1.7 Nef Reaction

Nef (1894)* reported that the formation of **aldehydes** and **ketones** from ***primary* and *secondary* nitroalkanes**—respectively by treatment of their salts with *sulphuric acid* (H_2SO_4) as given below:



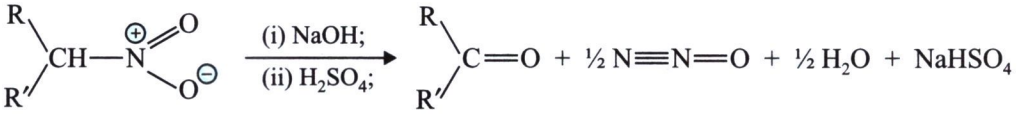
***pri*-or-*sec*-Nitro alkene**

A *ketone*

N_2O:N≡N═O

* You-shu-Li and Dai Xi Lin: *Angew Chem.* (Int. Edn.), **45**: 4246–48, 2006.
** Hatcher MA and Posner GH: *Tetrahedron Lett.*, **43**: 5009, 2002.
*** Jung ME and Duclos BA: *Tetrahedron Lett.*, **45**: 107, 2004.
**** Burger CE and Tunge JA., *Org Lett,* **6** (22): 4113–16, 2004.
***** Mohr JT and Behenna DC: *Angew Chem.*, (Int. Edn), **44**: 6924–27, 2005.
****** Nef Ju: *Ann.*, **280**: 263, 1894.

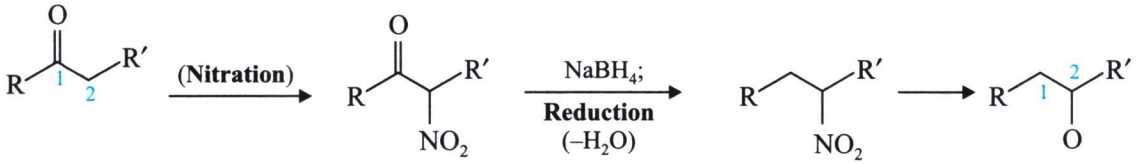
In other words, the **Nef reaction** relates to the *acid hydrolysis* of a salt of ***pri*-or *sec*-nitroalkanes** into the respective **carbonyl compounds** (*viz.*, **aldehydes** or **ketones**).*



1° or 2°-Nitro alkane **A Ketone**

1,2-Transposition of the Carbonyl (>C=O) moiety

Hassner *et al.* (1968)** skillfully extended the **Nef reaction** for the critical **1,2-transposition of the carbonyl (>C=O) moiety** as given under:

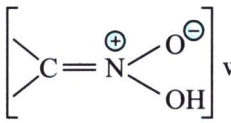


1-ketone (I) **A nitro ketone** **A nitro compound** **2-ketone (II)**

Comments: The **1-ketone (I)** on nitration gives the respective **nitro ketone,** which upon controlled reduction with **sodium borohydride ($NaBH_4$)** yields a **nitro compound.** The resulting product on further treatment produces a **2-ketone (II)**, thereby indicating explicitly that the desired **1,2-transposition of the carbonyl (>C=O)** moiety has taken place finally.

Mechanism of Nef Reaction

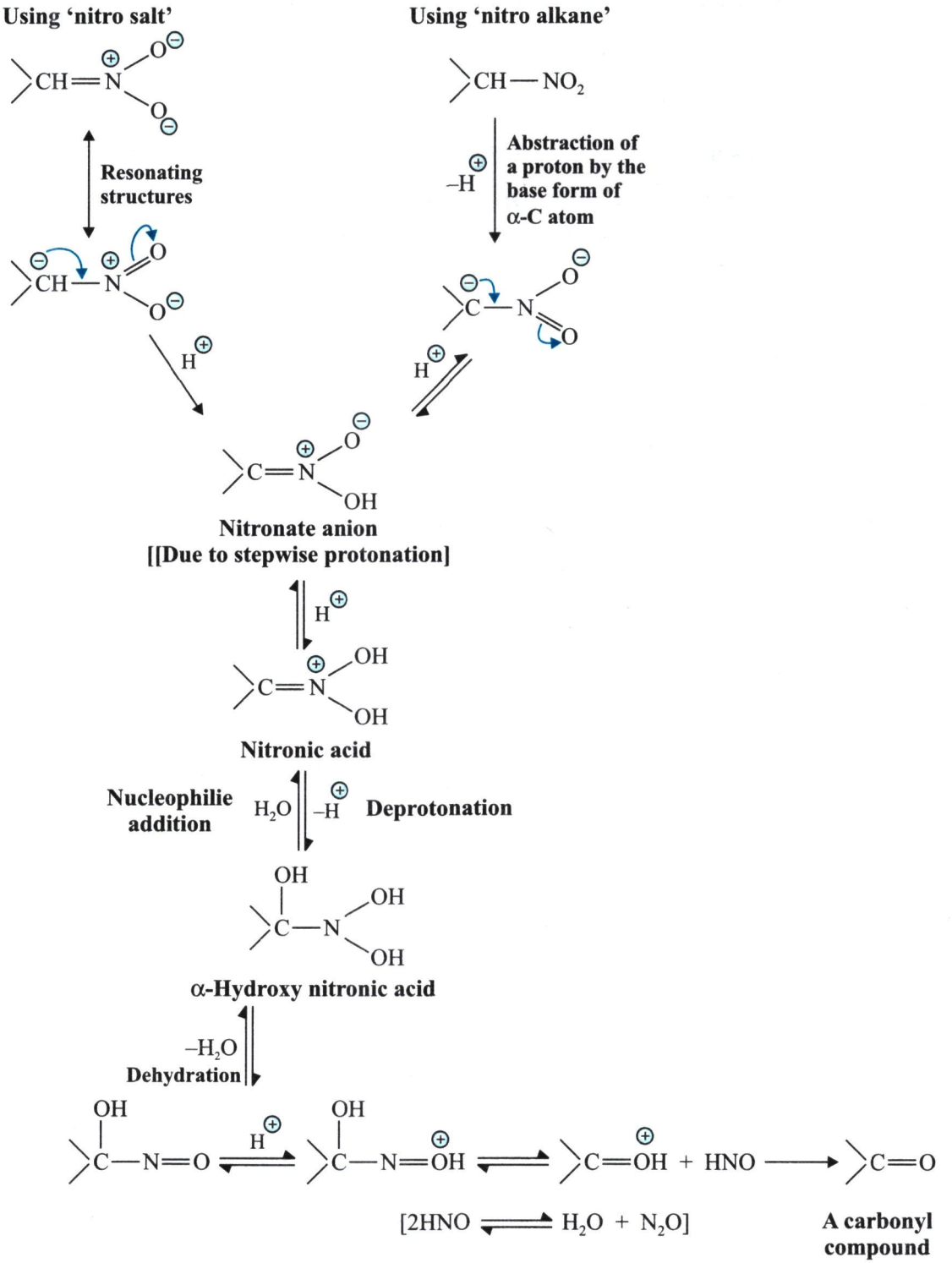
The **mechanism of Nef reaction** essentially comprises the following *important steps:*

- an observed variation to the initial ***nitro* salt** or ***nitro* alkane substrates**—that eventually aims towards the critical formation of a ***'nitronate anion'***  which further undergoes a sequential **protonation (H^+) phenomenon**; and
- subsequently it undergoes a ***hydrolytic cleavage*** to give rise to the formation of a **carbonyl (>C=O) compound** with **dinitrogentrioxide (N_2O_3)** and a mole of H_2O.

** Pinnick HW: *Organic React*, **38**: 655–792, 1990.

*** Hassner A *et al.*: *J Org. Chem.*, **33**: 1733–1739, 1968.

The various reactions involved above may be expressed as under:



Explanation

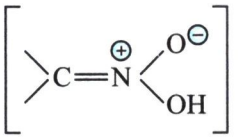
The various steps involved may be explained as under:

1. *First*, **'nitro salt'** exhibits the corresponding *resonating structures*, which upon **protonation (H^+)** yields the ***nitronate anion*** (due to the *stepwise protonation*).
2. *Secondly*, **'nitro alkane'** involves the abstraction of a **proton (H^+)** by the ***base form of α-C-atom*** to give an intermediate that on subsequent **protonation (H^+)** yields the same ***nitronate anion.***
3. The resulting **nitronate anion** derived from either of the *two* aforesaid steps on **protonation (H^+)** produces the **nitronic acid.**
4. The **nitronic acid** acts on ***two* ways**, namely:
   - **deprotonation ($-H^+$)**—to yield ***α-hydroxy nitronic acid,***
   - **nucleophilic addition ($+H_2O$)**—affords a reversible reaction to give **nitronic acid.**
5. Finally, **α-hydroxy nitronic acid** on *dehydration* yields a *hydroxy nitroso product* which on being subjected to a series of reactions *viz.*, **protonation (H^+), reversible reaction** etc., gives a **'carbonyl compound'.**

Limitations of Nef Reaction

There are *two* serious **limitations of *Nef Reaction***, namely:

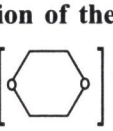
1. It specifically undergoes the ***'side reactions'*** based on the fact that the critical presence of the so-called **delocalized negative charge** located strategically on the ***'nitronate anion'***

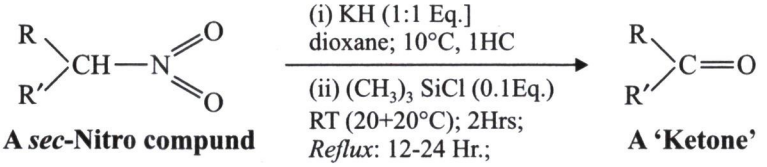


may eventually react at **various positions** with an ***'electrophile'.***

2. In a particular instance, when a **proton (H^+)** is incorporated at an ***α-C-atom***, the ***substrate*** **'nitro alkane'** gets reconstituted eventually. Thus, the **'nitronate anion'** may now act as the ***leaving group***; and, therefore, ultimately leads to a **elimination product** *i.e.*, the desired **carbonyl compound.**

Reduction of *sec*-Nitro compounds with Potassium Hydride [KH]

Hwu *et al.* (2006)* thoroughly investigated the **reaction of the *secondary* nitro compounds** with *KH (potassium hydride)* in a medium of *1,4-dioxane,*  by making use of **chlorotrimethylsilane [$(CH_3)_3SiCl$]**, finally leading to the formation of the desired **'ketones'** as depicted below:



A *sec*-Nitro compund **A 'Ketone'**

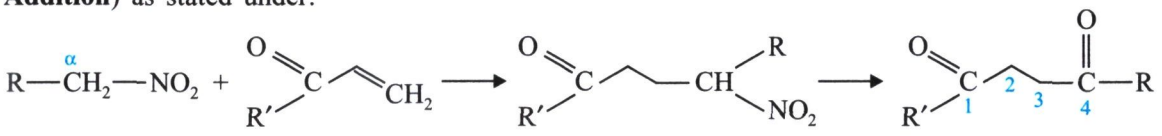
* Hwu JR *et al.*: *Synthesis*, 3305–08, 2006.

Comment: The crucial usage of a ***sec*-nitro group (>CH—NO_2)** serves predominantly as an **unpoled carbonyl (>C=O) function,** which may be importantly recognized as an ***unique* feature of the Nef Reaction.**

Besides, the **α-H atom** attached to the ***nitro (—NO_2) group* (I)** is found to be ***acidic*** in nature; and hence, may be abstracted easily by the incumbent **base**. Now, the, ***anion*** thus obtained does possess a **'nucleophilic C-atom'** that may be duly attacked by the so-called **'electrophiles'.**

Amazingly, unlike the *C-atom* present in the **carbonyl (>C=O) function (II)** behaves as an *electrophilic* entity; and, therefore, possesses affinity for the **nucleophiles.**

Example: Lever *et al.* (1976)* reported the preparation of the compounds, **1,4-diketones,** starting from the **α-acidic nitro** compounds by **Nef Reaction** sequential reaction (or using a **Michael Addition**) as stated under:



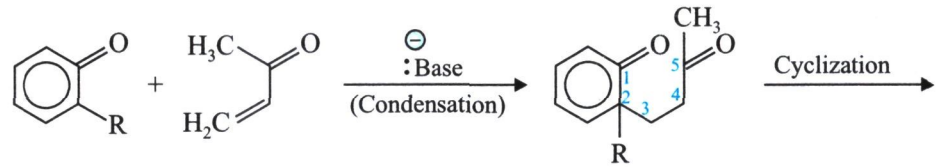
(I) **(II)** **(Intermediate)** **1,4-Diketone**

4.1.8 Robinson Annulation

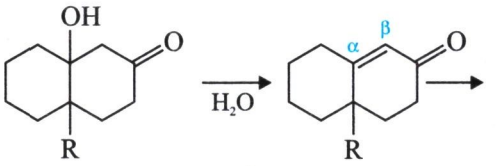
Robinson and Rapson (1935)** reported primarily the formation of a **6-membered ring system** having **α,β-*unsaturated ketones*** by the strategic incorporation of the **cyclohexanones** to the respective:

- **methyl vinyl ketone**, or
- **simple structural analogues of methyl-vinyl ketones**, or
- **its equivalents**,

which is duly followed by an ***'intramolecular aldol condensation'*** as shown under:



***O*-Substituted cyclohexanone** **Methyl-vinyl ketone** **1, 5 Diketone**



Bicyclical β unsaturated ketone

Robinson annulation can also be explained based upon the **Michael additions** pertaining to the ***cyclic ketone*** (*viz.*, **cyclohexane**) with *methyl-vinyl ketone*, and followed immediately by the

* Lever OW (Jr.): *Tetrahedron*, **32**: 1943–1971, 1976.

** Robinson R and Rapson WS: *J Chem. Soc.*, 1285, 1935.

intramolecular aldol condensation to result into the formation of:

'bicyclic α, β-unsaturated ketone due to ring closure'.*

NOTE: **The *Robinson annulation* essentially comprises *two* cardinal and consecutive reactions, such as:**

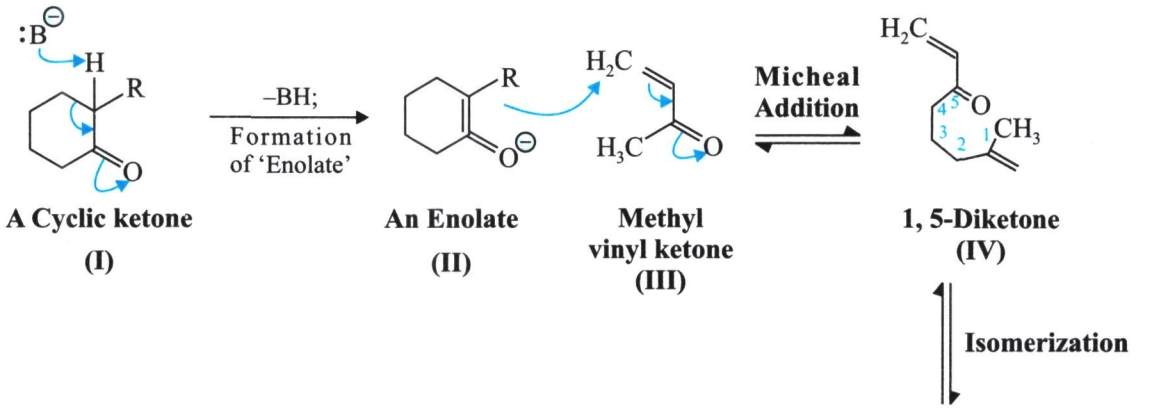
- **Michael Addition and**
- **Aldol Condensation**

Special Remarks: It is worthwhile to state at this point in time that an *'annulated 6-membered carbocycle system'* designates crucially a common structural unit of most ***naturally occurring products.*** Hence, the so-called **Robinson annulation** may be used intelligently in an ***'organic synthesis'*** of the *two* important classes of **natural products** *viz.*, **Terpenes** and **Steroids.** However, it has been observed overwhelmingly that the ensuing domain of the **asymmetric synthesis** of such chemical entities has enormously augmented and enhanced their **synthetic applications** (Hajos and Parrish, 1974).**

Mechanism of Robinson Annulation***:** In true sense, the proposed *reaction mechanism* of **Robinson annulation** has been duly substantiated by the **enolate (II)** formation starting from the reaction of the cyclic ketone (I) with the **base (-BH)** (*i.e., via* **deprotonation**). The resulting **enolate (II)** undergoes the **Michael addition** to entail the *conjugate addition* to the corresponding **methyl-vinyl ketone (III)** to produce the desired **1, 5-diketone (IV).** Thus, the unique ***isomerization*** of the ***substituted*** **cyclohexane pyran (IV)** subsequently followed by:

- **intramolecular aldol addition;** and
- **dehydration ($-H_2O$),**

to give rise to the formation of the ***'bicyclic enone'*** **(V)**, as stated below:



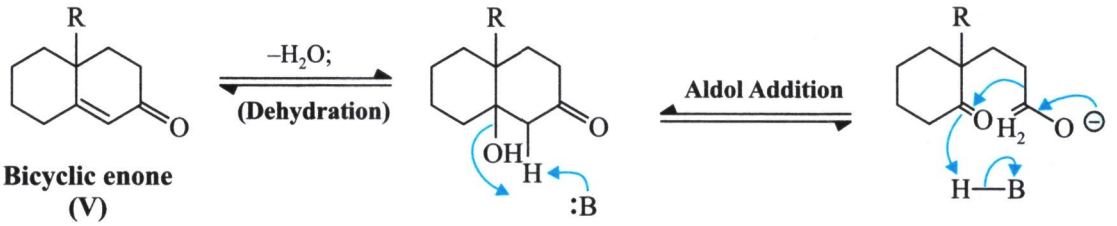
A Cyclic ketone (I) | **An Enolate (II)** | **Methyl vinyl ketone (III)** | **1, 5-Diketone (IV)**

(Contd.)

* Gawley RE: *Synthesis,* 777–794, 1976.

** Hajos ZG and Parrish DE, *J Org Chem.*, **39** (12): 1615–1621, 1974.

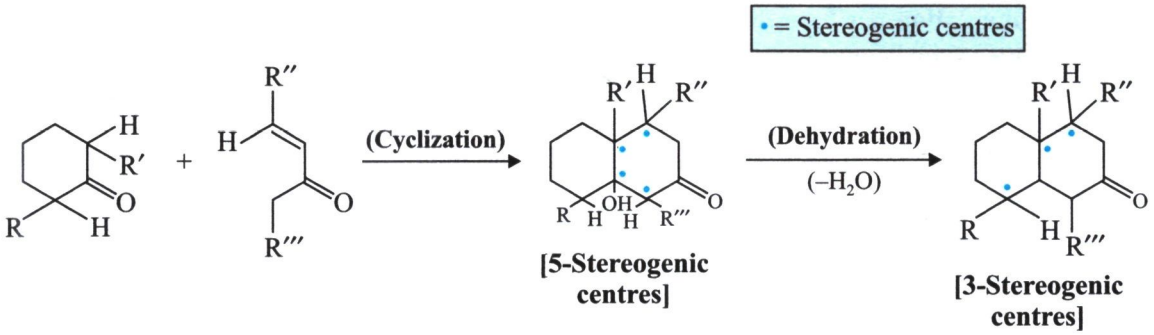
*** **Annulation:** It is **ring forming reaction** from the **Latin annulus,** meaning **'ring'.**



Highlights of Robinson Annulation Reaction

Following are a few noteworthy highlights of **Robinson annulation reaction,** namely:

➢ **Extremely complex inherent nature of reaction:** It has been duly observed that the **Robinson annulation reaction** is of an *extremely complex nature* **stereochemically**—since the *precise configuration*, as could be seen, at **'the 5-stereogenic sp^3-C centres'**, is found to be largely influenced in the course of its formation of the ***first*** **annulation product**; whereas, a subsequent *dehydration* (—H_2O) step lowers critically the so-called ***stereogenic centres*** categorically from **5 to 3**, as illustrated under:



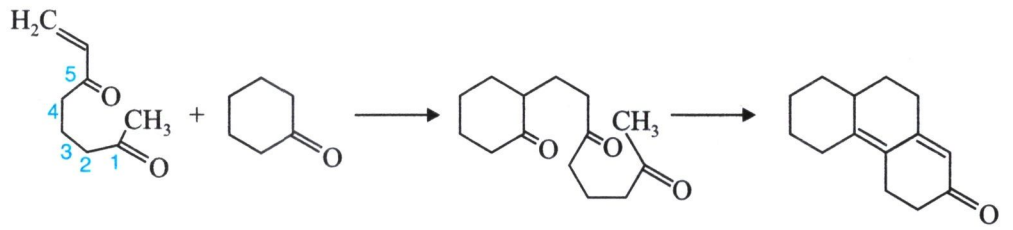
Thus, we may lay hands on ***two*** **distinct** products of **reaction** *viz.*, having **5 and 3-stereogenic centres** duly after **cyclization** and **dehydration** respectively.

➢ **Aldol Reaction in a Chiral Base:** Obviously, the so-called **aldol reaction** may be conveniently performed in the critical presence of a ***chiral base*** (*i.e.*, a compound having an *asymmetric C-atom*) to give rise to the formation of such a new product that predominantly possesses an ***enantiomeric access***. In addition, the aforesaid statement of facts may be further substantiated by the interaction of **2-methylcyclopenta-1, 3-diene** with **methyl-vinyl ketone (III)** in the presence of **α-amino acid.**

➢ **Higher Regioselectivity by the 'Preformed Enolates':** Interestingly, the judicious usage of the ***'preformed enolates'*** may eventually yield **higher regioselectivity**, which could be further expatiated by the following typical example:

Example: A ***diketone*** on being subjected to a **double Robinson annulation reaction**—the final reaction product so obtained immediately after the **Michael addition** critically undergoes subsequently ***two*** **times** the **aldol condensation reaction** to produce ultimately, the **tricyclic dienone (Z)** (Gawley,1976)* as expressed under:

* Gawley RE: *Synthesis*, 777–794, 1976.

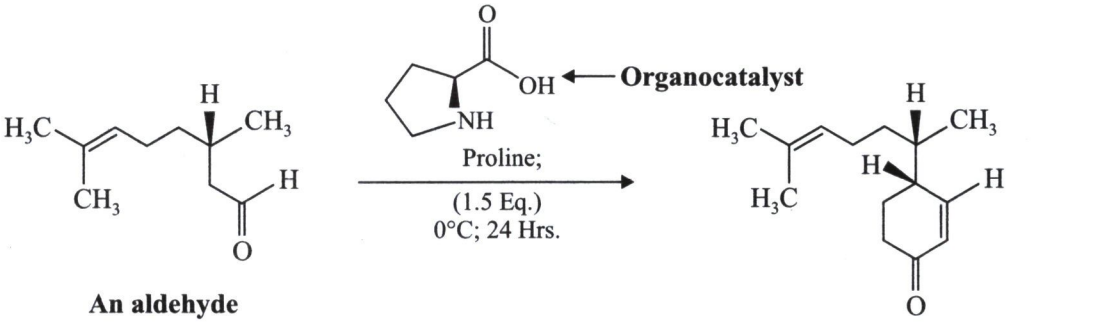


1, 5-Diketone **Cyclophenone** **A triketone** **A Tricyclic dienone (Z)**

Asymmetric Robinson Annulation

"Sir Robert Robinson, won the Nobel Prize in chemistry in 1947 for his remarkable research on the naturally occurring compounds."

The asymmetric **Robinson annulation reaction** may be accomplished by making use of '***proline***'— a **organocatalyst** so as to resolve specifically the so-called **enantiomeric isomers** related to **Robinson annulations** (Robinson, 1990)* as given under:

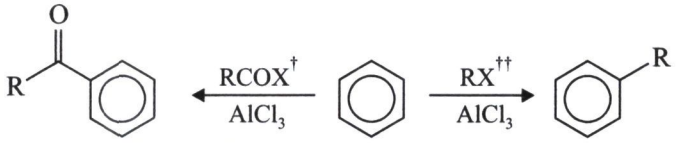


An aldehyde **Cyclohexone-2-exe derivative**

4.1.9 Friedel-Craft's Acylation

The **Friedel-Craft's acylation**** refers to the *acylation* of aromatic compounds catalyzed by *aluminium chloride* ($AlCl_3$) or other *Lewis acids.*

It may be expressed as under:



†	**RCOX** = Acyl Halides, Anhydrides;
††	**RX** = Alkyl Halides, Alkenes, Alkynes, Alcohols.

In a broader perspective, the **Friedel-Craft's reaction** partially designate the ***aromatic electrophilic substitution*** specifically involving the following *two* reactions, namely:

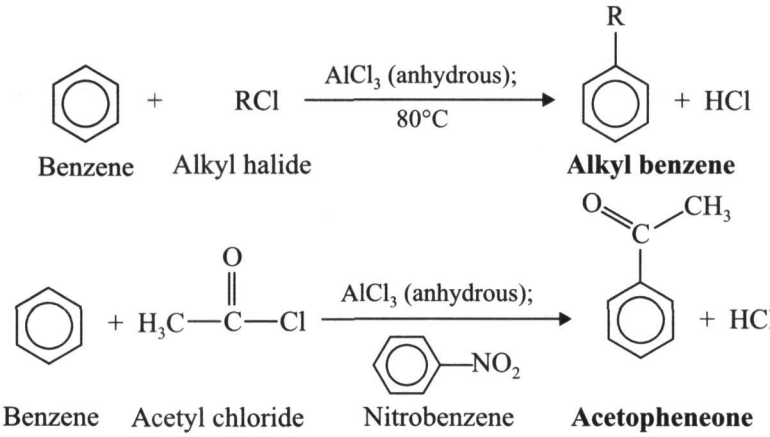
* Robinson R: *Org Syn. Coll, Vol.* **7**, p.368, 1990.

* Friedel C and Craft JM: *Compt Rend,* **84**: 1392 and 1450, 1877.

- **alkylation reaction**, and
- **acylation reaction**

pertaining to the respective **aromatic chemical entities** with either the ***alkyl halides*** or ***acid halides*** or ***anhydrides*** in the very presence of a **metal halide catalyst (Lewis acid)** *viz.*, **aluminium chloride ($AlCl_3$).**

These sequential reactions may be expressed as under:



Comments: Both **acid chlorides** and **anhydrides** do cater for as the useful ***acylating agents***; whereas, the respective **alkyl halides, olefins, esters, alcohols** and the like do serve as the **alkylating agents.**

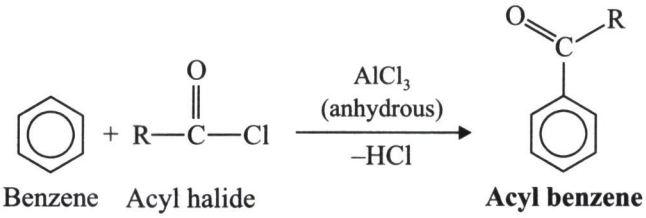
Variants in Friedel-Crafts Reaction: There are ***two*** **major variants** in the **Friedel-Crafts reaction,** namely:

- **Friedel-Crafts Alkylation Reaction,** and
- **Friedel-Crafts Acylation Reaction,**

which shall now be discussed separately in the sections that follows:

4.1.9.1 Friedel-Craft Acylation Reaction

In this particular instance, an **acyl moiety [CH_3—CO—]** is introduced meticulously into an ***aromatic compound*** by interaction with either an *acyl halide* or *anhydride* in the presence of a **Lewis acid catalyst**—as depicted below:



Comment: Obviously, it designates an important procedure for the synthesis of many ***aromatic ketones*** (Taylor, 1990)*.

* Taylor R: *Electrophilic Aromatic Substitution*, Wiley, NewYork, pp. 232–238, 1990.

Mechanism of Friedel-Crafts Acylation Reaction

Interestingly, we may explain the probable mechanism of the **Friedel-Crafts acylation reaction** by the following ***two* major steps:**

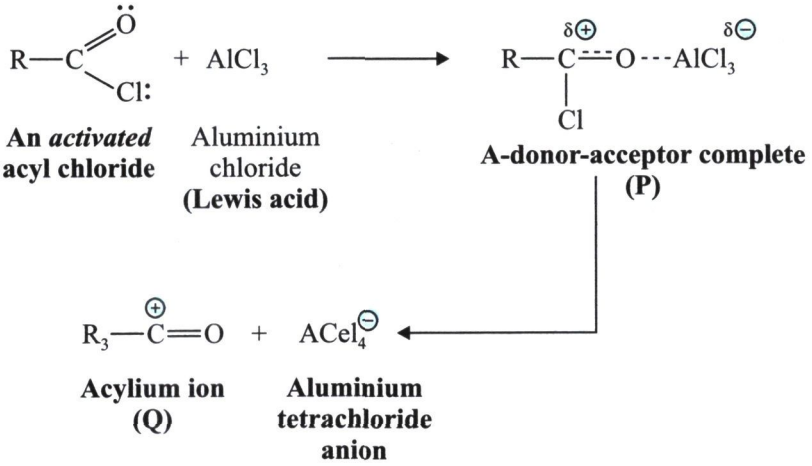
***Step 1:* Generation of Acylium Ion** $[R-\overset{\oplus}{C}=O]$**:** The **acylium ion** is *attacking specie*, which is duly formed by the interaction of:

- **an activated acyl chloride** $[R-C\ddot{O}-Cl:]$, and
- **Lewis acid** $(AlCl_3)$

to yield a **donor-acceptor complex (P):** To serve critically as the *initiation step.* Subsequently, the **complex (P)** gets explicitly dissociated into the following *two* distinct entities:

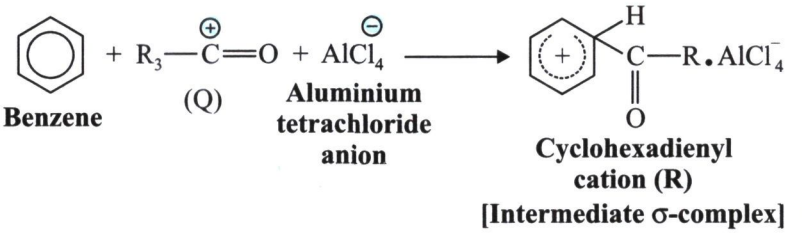
- **acylium ion (Q);** and
- **aluminium tetrachloride anion.**

The above reactions may be expressed as under:



Step 2: Electrophilic aromatic substitution of (P) and (Q) to benzene ring yielding the *cyclohexadienyl cation* (R).

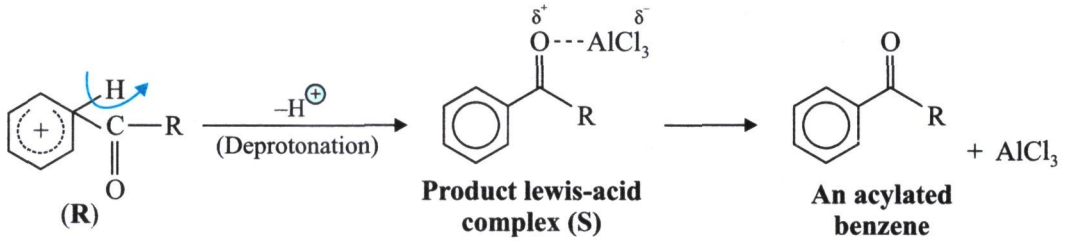
The careful electrophilic aromatic substitution of the **donor-acceptor complex (P)** and the **acylium ion (Q)** to the *benzene ring* ultimately gives rise to the formation of an ***intermediate σ-complex* (R)** *i.e.,* the **cyclohexadienyl cation (R)** plus the aluminium tetrachloride anion as depicted below:



Remarks: It has been adequately proven and established that eventually **a proton (H^+)** gets lost from the aforesaid **intermediate σ-complex (R);** and in this way helps to restore the ***'aromaticity'*** of the compound largely. Furthermore, an ***arylketone*** particularly coordinated to the ***Lewis acid*** **[$AlCl_3$]** together with *carbonyl* (>C═O) *oxygen* forms a new chemical entity usually termed as:

'product Lewis-acid complex (S)'.

These reactions may be depicted as under:



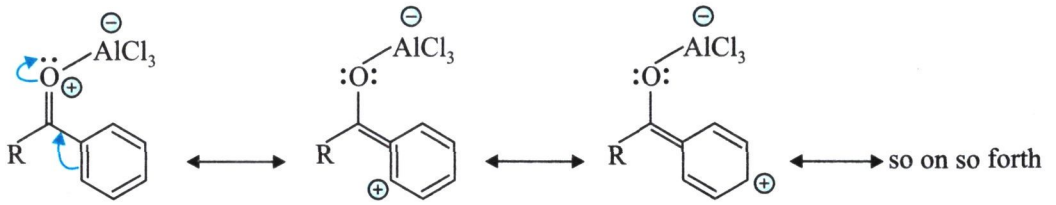
Special Note: Based on the scientific evidences one may take cognizance of the fact that—

"as and when one or more *non-deactivating substituents* are duly present in the so-called starting compound itself, the attained *direction of acylation* may be mostly predicted by the overall generalized guidelines meant for the aromatic substitution."

Salient Features of Friedel-Crafts Acylation

Following are some of the noticeable **salient features of Friedel-Crafts acylation** phenomenon—that would be discussed briefly in the present context:

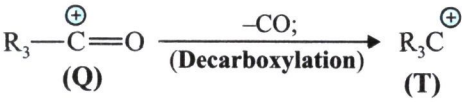
(a) **Absence of Carbocation Rearrangements:** Since the **carbonium ion** (S) gets duly stabilized by ***resonance*** according to the following *sequence of reactions:*



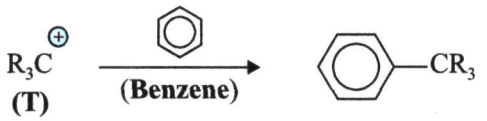
(S) **(i)** **(ii)**

Thus, the **+ve charge** located on the **O-atom** in (**S**) above gets adopted to the *resonating structures* (in the **benzene ring**) to (**i**) and (**ii**) respectively—and so on so forth.

(b) **Decarboxylation (—CO_2) from the Acylium Ion (Q):** In this particular instance one may critically observe the so-called **side-reaction in (Q)** thereby resulting into the formation of the **carbonium ion (T)** as shown under:



Furthermore, (**T**) on being subjected to treatment with an **aromatic chemical entity** (compound) yields an alkylated ***aromatic compound*** (**U**) as given below:

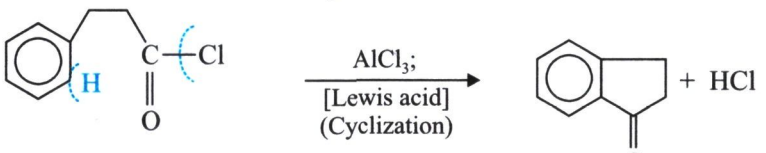


An alkylated aromatic compound (U)

Comment: Obviously, a plethora of *organic compounds* bearing certain **'activating moieties'** *viz.*, **alkoxy, alkyl, acetamide** and the like may be ***acylated*** conveniently specifically at the ***para*-position only** based on the **steric reasons.**

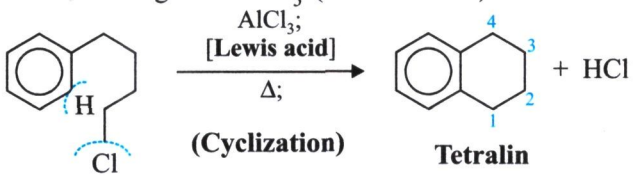
(*c*) **Friedel-Crafts Acylation Serves as Intramolecular Reaction:** In reality, the **Friedel-Crafts acylation** is found to be solely applicable in carrying out the *cyclization* phenomenon (*i.e.*, **ring-closure**) particularly to the **6-membered ring systems, 5-membered ring systems,** and the **heterocycles** (Cheug *et al.* 2001)*. Let us examine the following *two* classical examples, namely:

(*i*) **Benzopropyl chloride:** Thus, **benzopropyl chloride** yields the **1-hydrindone** upon *cyclization* with a *Lewis acid* ($AlCl_3$).



Benzopropyl chloride [An aromatic acid chloride] **1-Hydrindone**

(*ii*) **Benzobutyl chloride:** The **benzobutyl chloride** gives the **tetralin** on being subjected to *cyclization* on heating with $AlCl_3$ (a **Lewis acid**) as stated under:



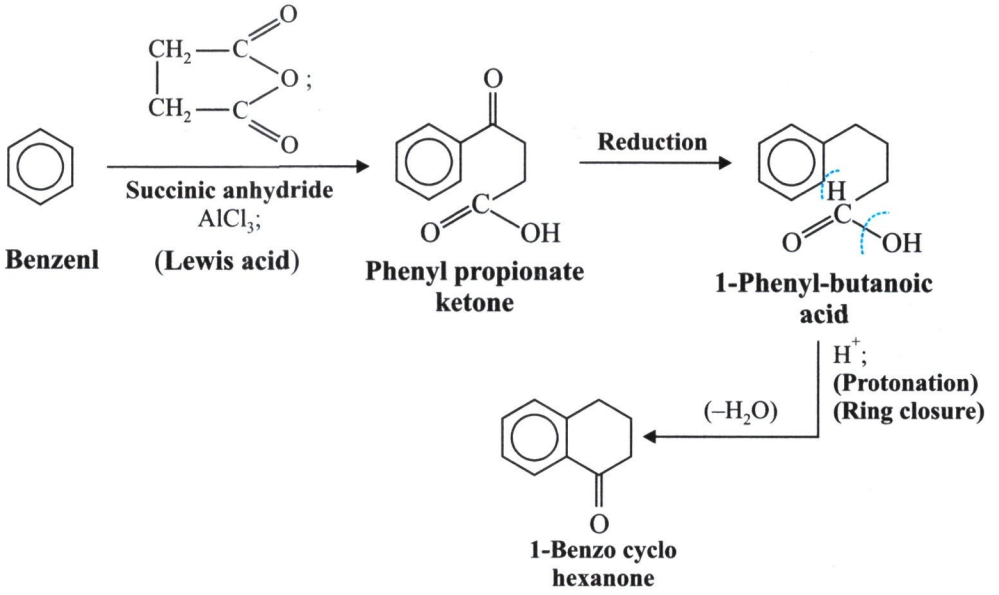
(Cyclization) **Tetralin**

Comment: In actual practice, the above **Friedel-Crafts acylation reaction(s)** *via* the **intramolecular mechanism** [*see (i) and (ii) above*] virtually give rise to the formation of an array of so-called **'fused-ring-systems'** *viz., cyclopentane, cyclohexane* etc.

(*d*) **Friedel-Crafts Acylation using Cyclic or Open-chain Anhydrides:** It is, however pertinent to state here that the **Friedel-Crafts acylation** may come into play in ***two* distinct** ways, namely:

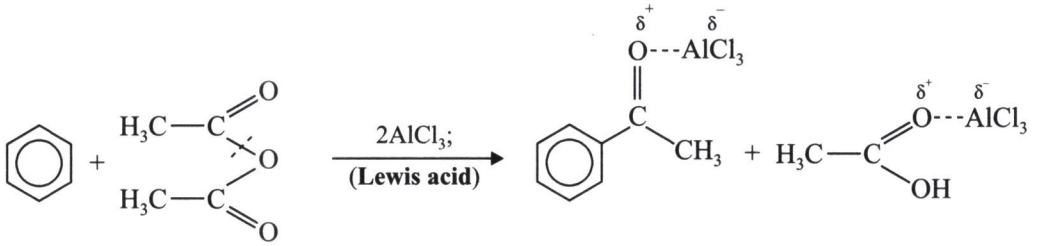
- **With a Cyclic Anhydride:** Let us examine the reaction of *benzene* with *succinic anhydride* (an **aliphatic 'cyclic anhydride'**) to yield **1-benzo cyclohexanone** *via* ***two* sequential steps** *e.g., reduction* and *protonation* as given under:

* Cheug Y *et al.*: *Synthesis*, pp 804–808, 2001.



Thus, one may finally obtain a ***bicyclic* compound** from a ***monocyclic* compound.**

➢ **With an Open-Chain Anhydride:** One may look into the specific instance when **benzene** (a *monocyclic compound*) is made to react with **acetic anhydride** (an *open-chain anhydride*) or a *carboxylic anhydride*) instead of an **acyl halide [R—CO—Cl], arylketone** (*cyclohexanone*), and **carboxylic acid** (*benzoic acid, succinic acid*) and ultimately forms a complex with a **Lewis acid ($AlCl_3$)** as stated below:



NOTE: **Thus, one may eventually obtain *two* altogether *'divergent ketones' viz., arylketone* and *alkyl-ketone* due to the interaction of benzene and acetic anhydride in the presence of a Lewis acid ($AlCl_3$).**

4.1.10 Mannich Reaction

Mannich (1917)* proposed first and foremost a **3-component aminomethylation** process commencing duly from a ***primary* or *secondary* amine (1), formaldehyde**(2)**, and a **chemical entity possessing an acidic methylene group (3).** Interestingly, it has been duly established the so-called ***'iminium'* structural analogue'** of the *aldehyde* critically serves as the ***potential* acceptor** in the **Mannich**

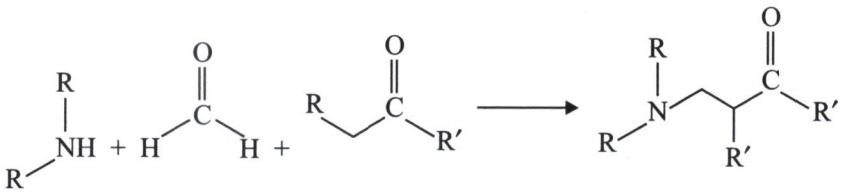
* Mannich C: *Arch Pharm.*, **255**: 271–276, 1917.

** Usually obtained as a **'non-enolizable aldehyde'**.

reaction. Nevertheless, in the recent past various **organic scientists*** related justifiably the **Mannich reaction** as the:

'aminomethylation of the CH–acidic compounds of a ketone'.

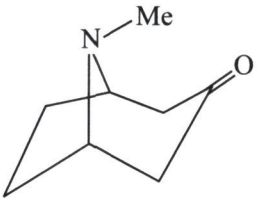
We may have the following expressions:



A Secondary amine (1) **Formaldehyde (2)** **An 'enolizable' carbonyl compound [Acidic methylene moity] (3)** **A mannich base (4)**

Comment: It is worthwhile to mention here that both *pri-* and *sec*-amines are employed preferentially for the *activation of formaldehyde* predominantly in the **Mannich reaction.** Obviously, the so-called **'aryl amines'** as well as the ***tertiary*-amines** are used scarcely for the **Mannich reaction** since these particularly come to a *standstill status* (or **stop**) at the ***Schiff base***, since it invariably is devoid of a **proton (H^+)** to give rise to the formation of an ***'intermediate imine'***.

Besides, the ensuing *reaction products* derived from the **Mannich reaction** are usually known as the **Mannich Base (4)** *i.e.*, they are commonly designated as the **β-amino carbonyl compound**, such as: **Tropinone.**



Tropinone

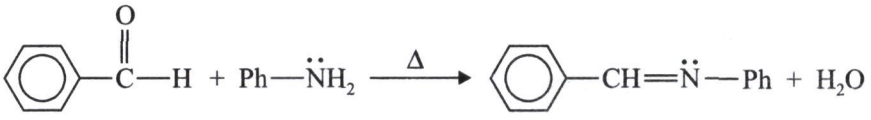
Mechanism of Mannich Reaction

Importantly, one may explain the **Mannich reaction** in terms of:

'a *nucleophilic addition of an amine* to the respective *carbonyl moiety* with the subsequent *elimination* of a hydroxyl anion [OH^-] to the corresponding Schiff's base'.

The **Schiff's bases** are also known as **'imines'**—and may be prepared by the interaction of *aldehydes* or *ketones* with the **1°-amines**, as given under:

* Tramoutini M and Angiolini L: *tetrahedron*, **46:** 1791–1837, 1990; Overman L, *Aldrichim Acta*, 28: 107–110, 1995.



Benzal dehyde A1°-amine **An Imine (84-87%)** **Separates from the reaction mixture**

Remarks: Thus, an ***electrophile*** (*i.e.*, **a substance that accepts electrons in a chemical reaction**) invariably reacts with a **carbanion** in a ***second*** **nucleophilic addition.** Therefore, the **Mannich reaction** prominently possesses the **dual-characteristic features,** *viz.*,

• Electrophilic and • Nucleophilic.

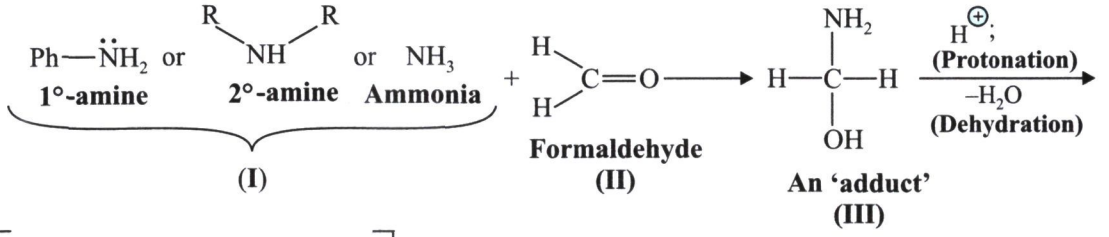
In a broader perspective, Cummings and Shelton (1960)* and Thompson *et al.* (1968)** studied exhaustively the following ***three*** **cardinal steps** which are intimately involved in the **mechanism of Mannich reaction**, namely:

Step 1: The **Mannich reaction** gets a kick off by the initial ***nucleophilic addition*** of either a **1°-amine** or **2°-amine** or **NH_3 (ammonia)** (**I**) with **formaldehyde (II)** to result into the formation of an ***'adduct'*** **(III)**;

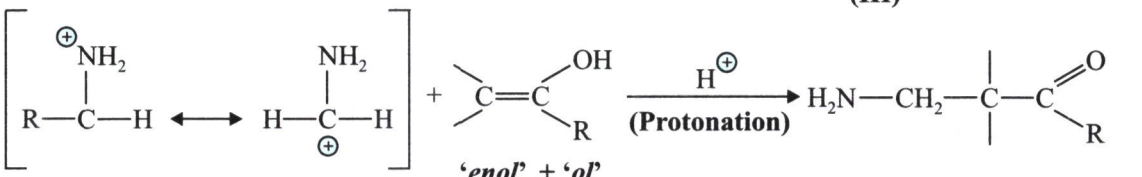
Step 2: The resulting **adduct (III)** on being subjected to *protonation* **(H^+)** and *dehydration* ($-H_2O$) given an altogether *new specie* **(IV)** due to the formation of a **resonance stabilized iminium ion** (*i.e.*, **structure, IV**); and

Step 3: The resulting **iminium ion specie (IV)** interacts specifically with the **'enol' (V)** belonging to the corresponding ***CH–acidic substrate*** due to the elimination of a **proton (H^+)**—thereby yielding **Mannich reaction product (VI).**

We may now express the various reactions involved in **step–1** through **step–3** as stated below:



1°-amine **2°-amine** **Ammonia** **(I)** **Formaldehyde (II)** **An 'adduct' (III)**



Resonance-stabilized iminium Ion (IV) ***'enol'*** **+** ***'ol'*** **(V)** **Mannich Reaction Product (VI)**

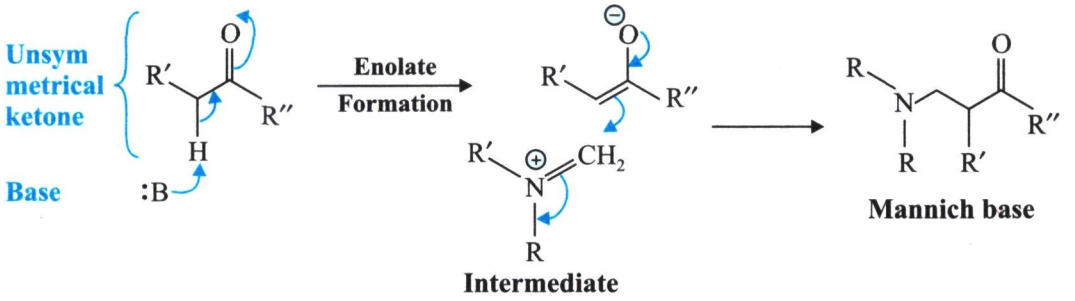
* Cummings TF and Shelton JR: *J Org. Chem.*, **25**: 419–423, 1960.

** Thompson B *et al.*: *J Pharm Sci*, **57**: 715–733, 1968.

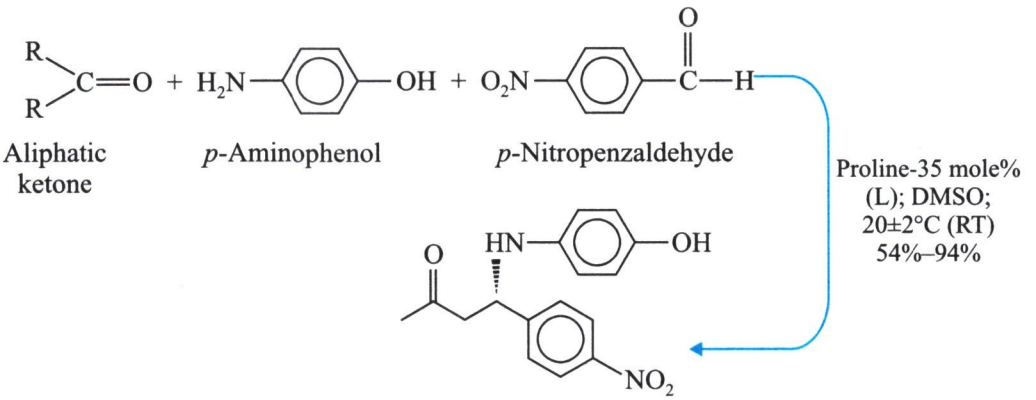
Highlights of Mannich Reaction

A few remarkable highlights of the Mannich reaction are enumerated as under:

1. **Regioselective Reaction*:** It may be accomplished by means of an *unsymmetrical ketone* as **CH–acidic substrate** so as to form ***two*** **regioisomeric products.**
2. **Mannich Reaction under Basic Experimental Parameters:** It can be successfully performed also under the influence of ***basic*** **experimental parameters,** and may be expressed as under:



3. List (2000)** reported the ***asymmetric*** **Mannich reaction** using an **aliphatic ketone**, ***p*-amino phenol**, and ***p*–nitro benzaldehyde** to yield a **Mannich base (X)** as given under:



Mannich Base (X)

[From Asymmetric mannich reaction]

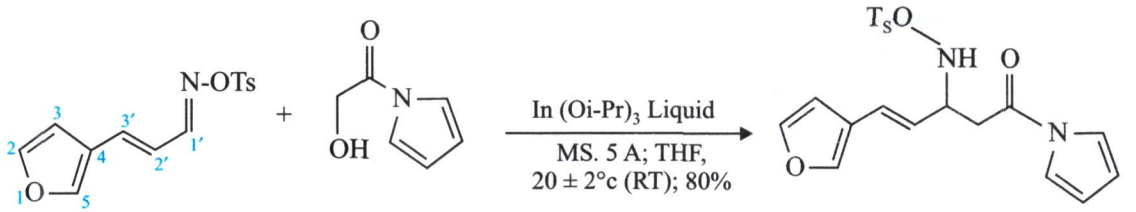
4. **Asymmetric *Aza*-Mannich Reaction:** Harda *et al.* (2005)*** showed the **asymmetric *aza*–Mannich reaction** by the interaction of

---

* **Regioselective Reaction:** It refer to such reactions that from the standpoint of orientation, give either nearly exclusively or exclusively one of several possible isomeric products. [From the *Latin*–**regio**, direction and pronounced "**rejio**".]

** List B: *J Am Chem Soc*, **122**: 9336, 2000.

*** Harda R *et al.*: *Angew Chem.*, Int. Edn., **44**: 4365, 2005.



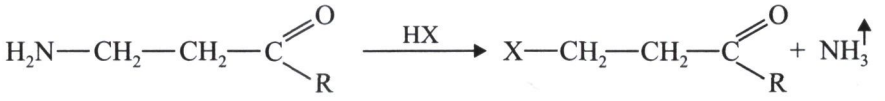
1'-Imino-*p*-toluene-sulphate-2, 4- dienefuran + 1-Indole-hydroxy methyl ketone → **An asymmetric-*aza*-Mannich Base**

Thus, one may obtain a ***para*-toluene sulphonate-asymmetric *aza*-Mannich base** from *two* different *substituted heterocyclic components* (with **'furan'** and **'indole'** ring systems).

Uses of Mannich Reaction in Organic Synthesis

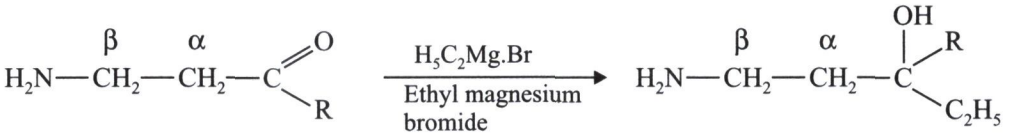
The **Mannich reaction** can be intelligently employed to accomplish gainfully and successfully certain typical **organic synthesis**, which shall be discussed briefly in the sections that follows:

1. **Use of the Mannich base: As Alkylating Agents***—An *aliphatic amino ester* yields an *aliphatic halide ester* duly in the presence of a **halogen acid (HX)** as stated under:



Aliphatic amino ester → Aliphatic haloester + Ammonia

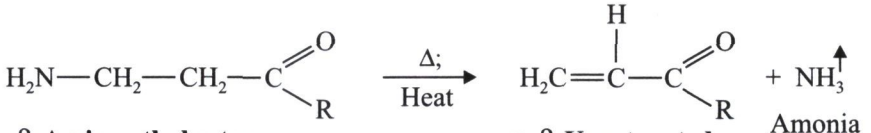
2. **Formation of β-Aminoalcohols with Grignard Reagents (*i.e.*, organo-magnesium reagents):** The interaction of a **β-amino ester** with **ethyl-magnesium bromide** (*Grignard Reagent*) gives rise to the formation of the corresponding **β-amino alcohol.**



A β-Amino ester → **[Grignard peagents]** → **A β-Amino alcohol**

3. **Mannich Bases: As an Intermediate in Most Organic Synthesis**—It has been amply proven and established that **Mannich bases** do serve critically as an ***excellent* 'intermediate'** in **most organic synthesis**, such as:
"formation of an α, β-unsaturated carbonyl (>C=O) chemical entity from the elimination of an '*amine*'."

The above statement of facts may be expressed as under:



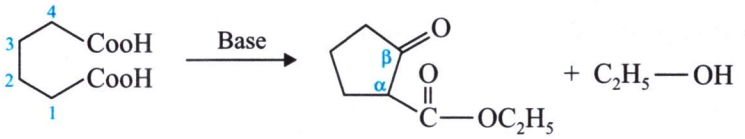
β-Amino ethyl ester → **α, β-Unsaturated carbonyl** + Amonia

* Matsunaga S *et al.*: *Agnew Chem.*, Int. Edn., **37**: 1004, 1998.

4.1.11 Dickmann Condensation Reaction*

It relates to the **base-catalyzed cyclization** of the ***dicarboxylic acid esters*** to yield the respective **β-ketoesters** *i.e.*, it essentially represents an **intramolecular equivalent** of the **Claisen-condensation**** (or the **acetoacetic ester condensation**).

It may be expressed as under:



1, 4-Butane-dicarboxylate — **β-*keto*-ethyl-carboxylate** — Ethanol

Thus, from 1,4-butane dicarboxylate after the base-catalyzed reaction undergoes **cyclization** to give a **β-*keto*-ethyl carboxylate** plus a mole of *ethanol* gets duly eliminated.

Besides, the **Dieckmann condensation reaction** has been extensively exploited in the formation of:

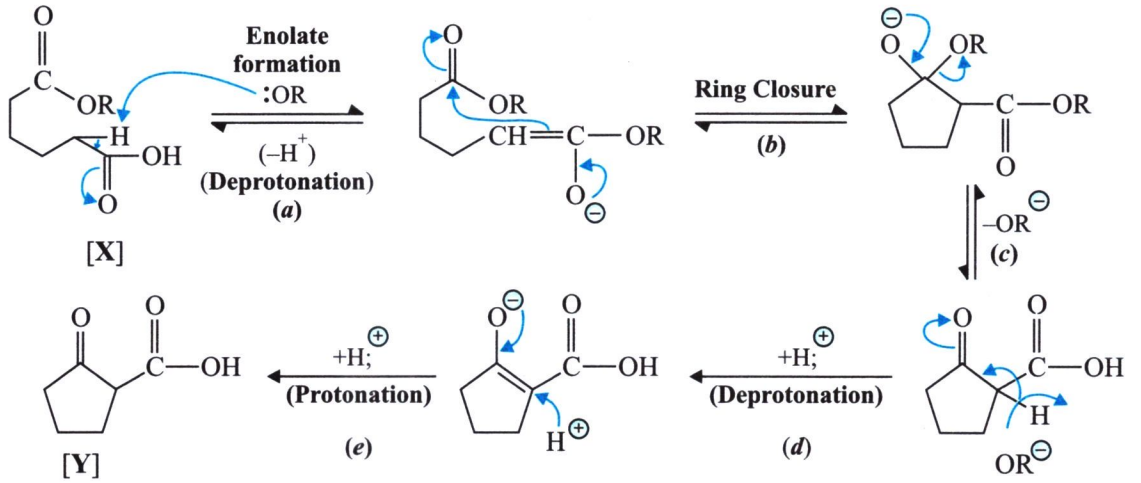
'5-, 6-, and 7-membered cyclic β-ketoesters'

Mechanism of Dieckmann Condensation Reaction

Ashby *et al.* (1983)*** reported that the precise mechanism of **Dieckmann condensation reaction** appears to have a close similarity to **Claisen condensation reaction**; and hence, specifically endorses the so-called **tetrahedral mechanism.**

Importantly, the **Dieckmann condensation reaction** is usually initiated by the so-called ***'enolate formation'***—followed immediately by **ring-closure**—thereby ultimately leading to the formation of the desired product.

The various important sequential steps that are involved in the **Dieckmann condensation reaction** may be detailed as under:



* Dieckmann W: *Ber.* **27**: 102, 965, 1894.

** Claisen L and Lowman O: *Ber,* **20**: 651, 1887.

*** Ashby *et al.*: *Tetrahedron Lett.* 1667, 1983.

- Above *sequential reactions* involve in all ***five*** **steps.**
- **Deprotonation** ($-H^{\oplus}$) takes place at **steps (*a*) and (*d*).**
- **Ring closure** comes into play at **step (*b*).**
- **Protonation** ($+H^{\oplus}$) occurs at last **step (*e*).**
- Starting from **compound [X]** *i.e.,* 1-carboxylate-4-butyl ester, one may ultimately lay hands on the final **product [Y]** *i.e., 5-membered chemical entity* known as **Cyclopentane ketone 1-carboxylate.**

Suggested Reading

Loudon GM: **Organic Chemistry**, 4th edn., Oxford University Press, New York, 2002.

March, J: **Advanced Organic Chemistry**, 4th edn., Wiley Interscience Publications, New Delhi, 1992.

Morrison, RT, Boyd, RN and Bhattachariya SK: **Organic Chemistry**, 7th edn., Pearson Education Inc., New Delhi, 2012.

Singh, MS: **Advanced Organic Chemistry**, Pearson Education (Singapore) Pvt. Ltd., 2005.

Sharma, D: **Advanced Organic Chemistry**, New Age International Publishers, New Delhi, 2010.

Smith, JC: **Organic Chemistry**, 2nd edn., Prentice Hall, NY, 2008.

Solomons, TWG and Fryhle, CB: **Organic Chemistry**, 9th edn., Wiley India (P) Ltd., New Delhi, 2008.



Chapter 5

Reactions Giving Alcohol—Hydroxy Carboxylic Acid and Phenols

LESSONS AT A GLANCE

5.1 Introduction

5.2 Detailed Treatment of Various Name Reactions and Rearrangements

- 5.2.1 Meerwein-Ponndorf-Verley Reduction [Aluminium Alkoxide Reduction]
- 5.2.2 Blanc Chloromethylation [Blanc Reaction]
- 5.2.3 Brown Hydroboration
- 5.2.4 Cannizzaro Reaction
- 5.2.5 Nozaki-Hiyama-Kishi Reaction [Nozaki-Hiyama Coupling Reaction]
- 5.2.6 Oppenauer Oxidation
- 5.2.7 Grignard Reaction
- 5.2.8 Evans-Aldol Reaction
- 5.2.9 Dienone–Phenol Rearrangement
- 5.2.10 Bomberger Rearrangement

5.1 INTRODUCTION

The host of ***organic reactions*** that specifically give rise to the production of **alcohol-hydroxy carboxylic acid and phenols** are not only highly useful but also prove to be quite meritorious in the pursuit of knowledge and the ever-expanding ***base of*** **organic chemistry research** across the globe.

There is always a dire need of meaningful scientific research, duly supported by concrete evidences, which largely carries the **'cart of-wisdom'** gracefully with a quantum leap forward.

Importantly, this particular chapter entails solely the reactions that yield the aforesaid products of interest through various **Name Reactions** or certain **Classical Rearrangements** as listed under, namely:

(*i*) **Meerwein-Ponndorf-Verley Reduction [Aluminium Alkoxide Reduction].**

(*ii*) **Blanc Chloromethylation (Blanc Reaction);**

(*iii*) **Brown Hydroboration;**
(*iv*) **Cannizzaro Reaction;**
(*v*) **Nozaki-Hiyama-Kishi Reaction;**
(*vi*) **Oppenauer Oxidation;**
(*vii*) **Grignard Reaction;**
(*viii*) **Evans-Aldol Reaction;**
(*ix*) **Dienone-Phenol Rearrangement; and**
(*x*) **Bamberger Rearrangement,**

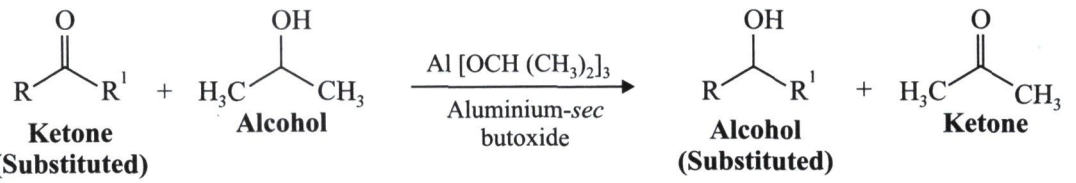
which shall now be discussed individually in the sections that follows:

5.2 DETAILED TREATMENT OF VARIOUS NAME REACTIONS AND REARRANGEMENTS

5.2.1 Meerwein-Ponndorf-Verley Reduction [Aluminium Alkoxide Reduction]*

The *reduction* of **aldehydes (—CHO)** and **ketones (>C=O)** to the respective **alcohols** using the ***aluminium alkoxides*** *e.g.*, **aluminium *sec*-butoxide Al [OCH-$(CH_3)_2]_3$** (*i.e.*, just *reverse* of the **Oppenauer oxidation**).

The reactions may be shown as given under:



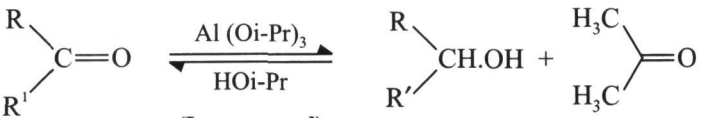
Ketone (Substituted) **Alcohol** **Alcohol (Substituted)** **Ketone**

In other words, the **aluminium alkoxide reaction** essentially involves the crucial *reduction* of either:

- **Ketones** or - **Aldehydes**

in the presence of **aluminium isopropoxide**, Al [OCH-$(CH_3)_2]_3$**, in excess of isopropanol—to produce the corresponding alcohols.

The reaction may be expressed as under:



A ketone **(Isopropanol)** **An alcohol** **Acetone**

* Meerwein H and Schmidt R: *Ann.* **444** : 221, (1925); Ponndorf W, *Agnew Chem.*, **39**: 138 (1926); Verley A, *Bull Soc Chem. Fr*, **37**: 537, 871, (1925);

Comment: Interestingly, the **Meerwein-Ponndorf-Verley reduction** is indeed highly specific for the **carbonyl (>C=O) moiety.** However, in a typical instance when the ***two*** **carbonyl moieties** are present concurrently:

- **one group gets reduced;** and
- **second group (a ketonic moiety) remains duly protected.***

Mechanism of Aluminium Alkoxide Reduction

Importantly, the underlying mechanism of the **aluminium–alkoxide reduction** critically involves the following sequential reaction path:

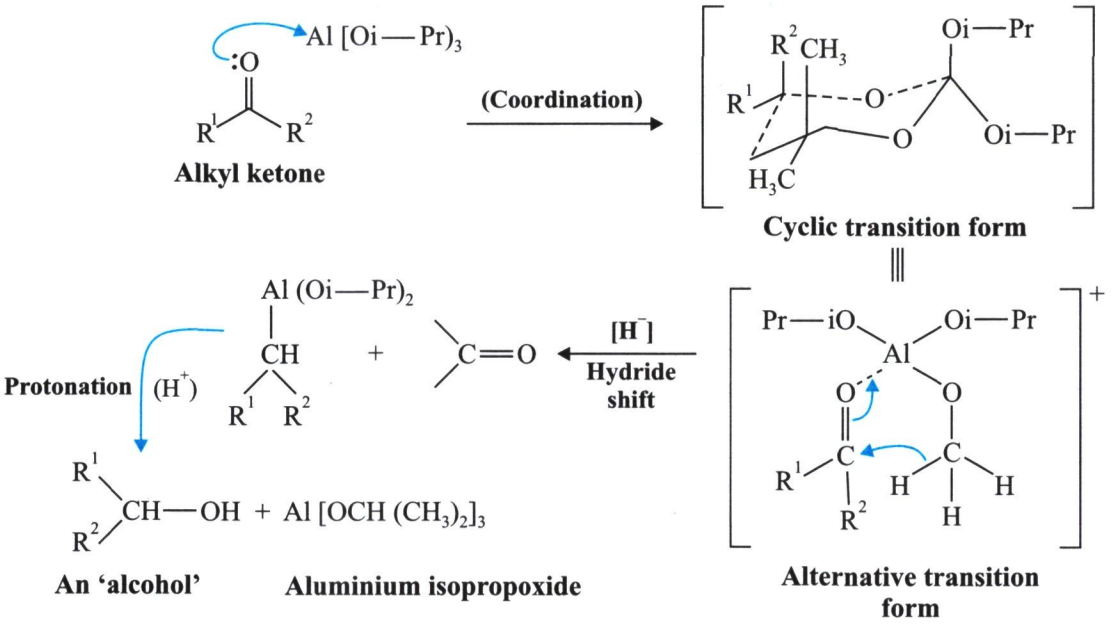
"perfect tangible coordination of aluminium isopropoxide, Al $[OCH{\cdot}(CH_3)_2]_3$, with a ketone to result into the formation of a *'transition-state'* that predominantly undergoes the hydride (H^-) shift right from an *α-CH bond* of the alkoxide to the respective *carbonyl* (>C=O) *carbon* of the ketone to yield the mixed alkoxide."

Besides, one may certainly make use of an **excess of isopropanol $[(CH_3)_2{\cdot}CHOH]$** that categorically gets exchanged with the ***mixed alkoxide*** to yield the desired **'alcohol'.**

NOTE: **Amazingly, all the H-atoms duly employed in the above reduction are generously provided by:**

- **Catalyst** **and** - **Solvent**

We may express the aforesaid reactions as stated under:



* Due to the **'acetal formation'** for getting reduced.

Remarks: These essentially include:

1. The **aluminium isopropoxide in isopropanol** is usually written as: **Al (O-iPr)$_3$ in HOi-Pr.**
2. The ***reverse reaction*** is invariably termed as the **Oppenauer oxidation***.
3. Importantly, both **β-diketones** and **β-keto esters** (*i.e., ketones* having relatively **high *enol*-content**) fail to undergo this reaction.

Besides, the above cited mechanism *via* a **6-membered *cyclic-transition form*** (as shown earlier) another equally *probable mechanism* has also been put forward for certain **important substrates.****

Points to Ponder: They usually comprise:

1. The actual *reaction rate* is prominently influenced by the **temperature** (a *physical characteristic*), provided the ***reaction mixture*** is duly maintained at a *temperature* little above the **bp of acetone (56.5°C)**; and hence, the reaction proceeds smoothly towards the **completion stage.**
2. Now, if it is so desired to **tilt the equilibrium of the reaction** towards the ***'forward direction'***, whereby the so-called *low-boiling reaction product* (***i.e.,* acetone**) needs to be removed almost instantly from the ensuing **reaction mixture.**
3. When an excess of **acetone** is utilized the *shift of the equilibrium could be critically shifted* in such a direction so as to give *two* products: **ketone (X)** and **isopropanol (Y)** as given below:



A *sec*-Alcohol **Acetone** **[X]** **[Y]**

Special Notes

1. The *Meerwein-Ponndorf-Verley reduction* as of late has been duly replaced by more *effective* and *potent* **reducing agents** *viz.,* **Lithium aluminium hydride [LiAlH$_4$], Sodium borohydride [NaBH$_4$]** etc.; however, the former is known for its:

   • **Mildness** and • **Selectivity,**

   since it categorically affects the C—C double bond or tripple bonds of the substrate.
2. **Lanthan Compounds [Okano *et al.* (1987)]*****: They reported overwhelmingly the application of the **'lanthan compounds'** *viz.,* ***lanthan isopropoxide*** and showed them to be immensely useful in comparison to the **aluminium propoxide** already discussed earlier.

---

* Oppenauer EV: *Recl Trav Chim Pays-Bas*, **56**: 137–144, 1937.

** Srettas CG and Caziania CT, *Tetrahedron*, **34**: 933–949, 1978.

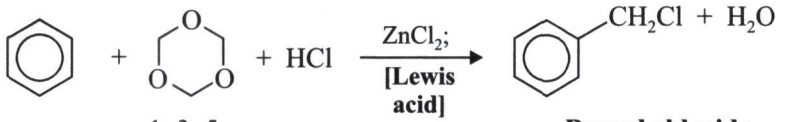
*** Okano T *et al.*: *J Chem Lett.*, 181–184, 1987.

5.2.2 Blanc Chloromethylation [Blanc Reaction]

Blanc (1928)* proposed specifically a chloromethylation process using:

- Lewis-acid promoted chloromethyl moiety's due installation upon the so-called aromatic ring systems having 1,3,5-trioxane; and
- Hydrochloric acid (HCl) in the presence of a catalyst.**

The reaction may be expressed as under:



1, 3, 5 - Trioxane

Benzyl chloride
[A chloromethylated product]

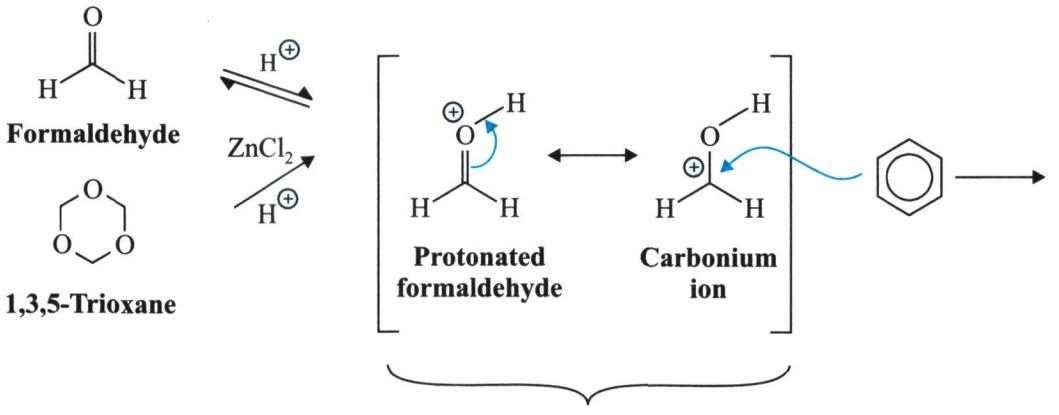
Comment*:** Interestingly, one may very well compare the **Blanc reaction** *vis-a-vis* **Friedel-Crafts acylation** since the critical 'rate-determining step***' happens to be an **electrophile 'S_{Ar}'.**

Mechanism of Blanc Reaction

In reality, the **Blanc reaction** is invariably triggered off due to:

"the *protonation* of formalin (HCHO) or 1,3,5-trioxane that eventually augments its inherent reactivity towards the '*electrophilic-aromatic substitution*' of the benzene ring."

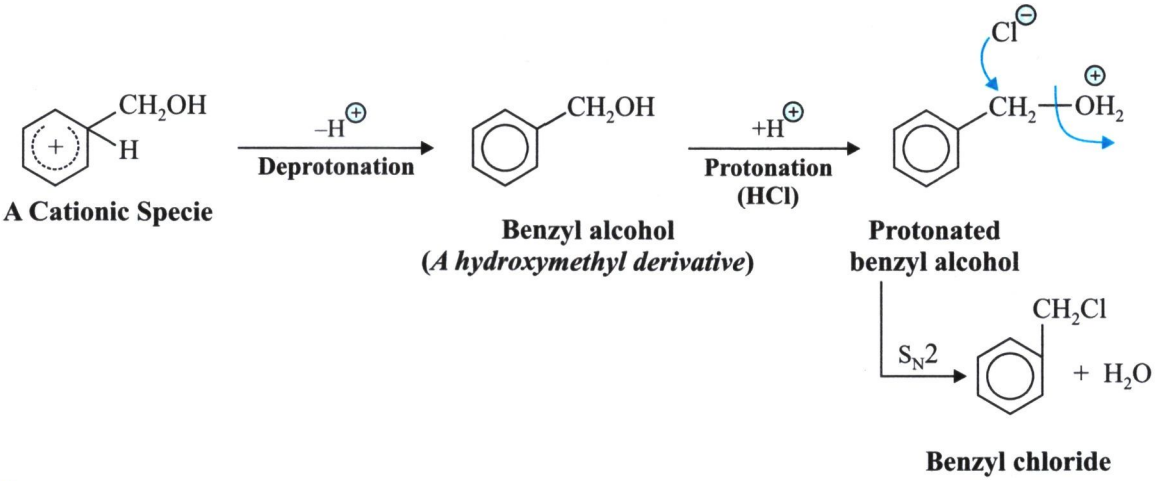
The aforesaid interaction with **formalin (formaldehyde)** and **proton (H^+)** or a **reverse reaction of formalin and $ZnCl_2$ (Lewis-acid catalyst) or protonation of 1,3,5-trioxane** gives the following *sequence of reactions:*



(Contd...)

* Blanc MG: *Bull Soc. Chem. Pr.*, **33**: 318–319, 1928.

** Fuson RC and McKeever CH: *Org React*, **1**: 63–90, 1942.



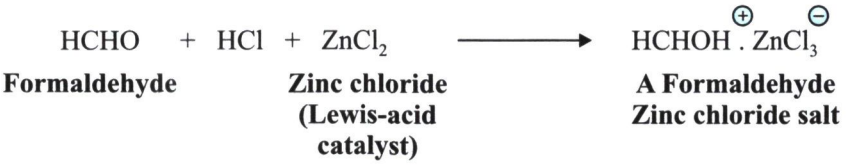
Explanation

The above sequential reactions may be duly explained as under:

1. **Protonation** of *formaldehyde* gives the respective **protonated formaldehyde** that subsequently yields the **carbonium ion** (bearing a *positive charge on the C-atom*) then it attacks the *aromatic* **benzene ring** to produce a **cationic specie** (see above).
2. The resulting **cationic specie** on *deprotonation* yields an **aromatic hydroxymethyl derivative** (or **benzyl alcohol**), which on further *protonation* with **HCl** gives rise to the formation of a **chloromethylated product** (or **benzyl chloride**) with the loss of a mole of **water** (Belenkii *et al.*, 1977).*

Lewis-acid Catalyst Zinc Chloride ($ZnCl_2$)

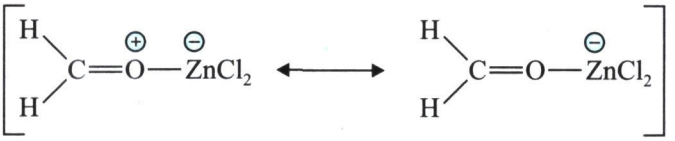
Fuson and McKeever (1942)** successfully made use of the **Lewis-acid catalyst $ZnCl_2$** in the **Blanc Reaction** as shown below:



Formaldehyde | **Zinc chloride (Lewis-acid catalyst)** | **A Formaldehyde Zinc chloride salt**

Mechanism of Reaction

The most probable mechanism of the above reaction critically entails the formation of an ***electrophilic specie*** as expressed under:



A Formaldehyde-Zinc chloride-'SALT' ⟷ **A Formaldehyde-Zinc chloride-'ANION'**

* Belenkii LL *et al.*: *Russ Chem Res*, **46**: 891–903, 1977.

** Fuson EC and McKeever CH: *Org. React*, **1**: 63–90, 1942.

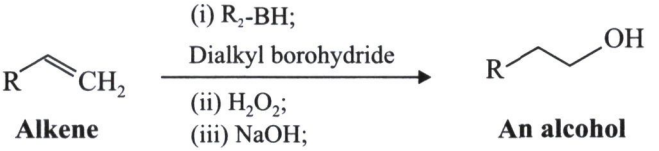
NOTE: **According to McKilloq *et al.* (1983)* the presence of a *'catalyst'* may not even be required particularly for the so-called *'electron-rich aromatic chemical entities'*. Thus, one can gainfully use the following *two* catalysts, namely:**

- ***methoxy acetyl chloride*** **[$CH_3O—CH_2—COCl$]; and**
- ***chloromethyl methyl ether*** **[$H_3C—O—CH_2Cl$].**

5.2.3 Brown Hydroboration

"Brown's epoch making discovery of *'hydroboration'* led to his being named as a co-winner of the *1979 Nobel Prize in Chemistry.*"

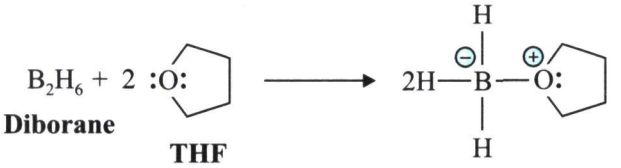
Hydroboration of an ***alkene*** *viz.*, **propene** [] is obviously the starting point for a host of extremely useful and intrigue **synthetic procedures**, such as: ***anti-Markovnikov syn Hydration.*** However, **hydroboration** was first and foremost discovered by **Herbert C Brown** (at the *University of Purdue*, **USA**), which may be represented explicitly as stated below:



Alkene **An alcohol**

Alternative Method

Hydroboration may also be accomplished by means of ***'diborane'*** [B_2H_6] that categorically designates a ***gaseous dimer of borane*** [BH_3] or rather achieved still easily and conveniently by making use of a special reagent normally prepared by the careful dissolution of **diborane in THF.** Importantly, the introduction of **diborane** in **THF** promptly forms the **Lewis acid-base complex of borane** (*i.e., Lewis-acid*) plus **THF.** The aforesaid ***'complex'*** is invariably represented as: **BH_3: THF**; and the reaction involved as given under:



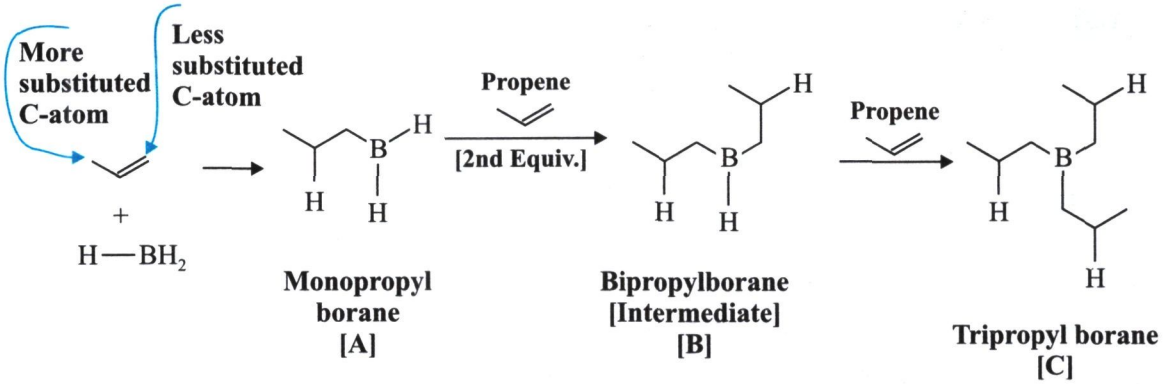
Diborane **THF** **[Tetrahydrofuran]** **BH_3: THF** **[A 'Complex']**

NOTE: **Solutions containing *BH_3 : THF complex* is available commercially. Besides, the *hydroboration* reactions are invariably carried out in ethers, *viz., diethylether [Et—O—Et]*; and also in higher m.w. ether *viz.*, "*diglyme*" [$(CH_3OCH_2CH_2)_2O$].**

Mechanism of Hydroboration

The precise **mechanism of hydroboration** may be explained by taking the typical example of a ***terminal*** **alkene** *e.g.*, **propene** [], which on being treated with a solution containing **BH_3: THF** (*complex*),—whereby the **boron hydride (BH_3)** adds on successively and strategically on to the **double bonds of 3-moles of the alkene (propene)** to yield the respective chemical entity—***'trialkylborane'***, as shown below:

* McKilloq A *et al.* : *Tetrahedron Lett.*, **24**: 1933–36, 1983.



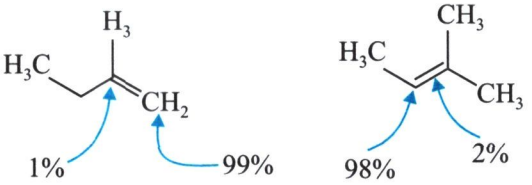
Comments: Interestingly, in each and every **'addition step'** one may observe that:

"the Boron atom becomes intimately attached to the *less substituted C–atom* of the double-bond",

and hence, a **H-atom** gets transferred right from the **Boron-atom** to the other **C-atom** of the double-bond. In this manner, the phenomenon of **hydroboration** is predominantly rendered ***'regioselective'***; and, therefore, it is an ***anti*-Markovnikov (*i.e.*, the H-atom eventually gets attached to the C-atom having few H-atoms).**

Examples: Obviously, there are quite a few other examples which vividly display this *tendency* for the **Boron-atom** to get attached eventually to the **less substituted C-atom** as given below. Nevertheless, the ***percentages*** do designate clearly the **particular C–atom** where the **Boron-atom** becomes attached ultimately.

Thus, we may have the following expressions:



Remarks:

1. The above cited **percentages** do indicate specifically the point where the **Boron** is precisely attached in the reactions using the aforesaid ***starting materials***,—thereby brings forth the actual inherent tendency for **Boron** to bond at the ***less substituted C–atom*** of the **double bond.**
2. Amazingly, the ***observed attachment*** of the so-called **Boron-atom** to the ***less-substituted C–atom of the double-bond*** appears to result to a certain extent from the **'steric factors'** (*i.e.*, the *bulkiness of the atoms*) or the **bulky Boron-containing moieties** that may have an ***easy access to the less-substituted C–atom.****

* Clay JM *et al.*: *J Am Soc*, **127**: 5766–67, 2005; Hirano K *et al.*: *Org. Lett.*, **9**: 1541–44, 2007.

5.2.4 Cannizzaro Reaction

Cannizzaro (1853)* reported the **base-catalyzed disproportionation** reaction of either:

- **aromatic aldehydes**; or
- **aliphatic aldehydes,**

having absolutely devoid of an **α-H atom** attached to the corresponding **'acid'** and **'alcohol'**, as shown below:

$$2\,RCHO \xrightarrow{\text{Base;}} RCOO^- + RCH_2OH$$

2 moles of an aldehyde — **Acid** — **Alcohol**

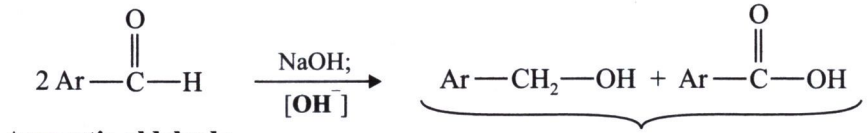
Comment: In case, the **aldehydes** are altogether different, the reaction is termed as the—**"Crossed Cannizzaro Reaction."**

In other words, the **Cannizzaro reaction** may be referred to a ***'redox reaction'*** that critically involves disproportionation of the **'aldehydes'** without the **α-hydrogen atoms**, usually in the presence of a ***strong base*** (*viz.*, **NaOH, KOH**)** into the respective

- **carboxylic acid salts**; and
- **an alcohol.*****

Examples: Let us examine a few classical examples pertaining to the **Cannizzaro reaction**:

1. **Conversion of *two* moles of an Aromatic Aldehyde in the presence of a *strong base***



Aromatic aldehyde [2-moles]

One mole each of the corresponding 'alcohol' and 'carboxylic acid'

Thus, the *disproportionation* of an **aromatic aldehyde (2 moles)** in the presence of a *strong base (NaOH)* essentially involves:

- **reduction of one mole of the aromatic aldehyde [having *no* α-*H atom* into an alcohol (benzyl alcohol];** and
- ***oxidation* of second mole of the aromatic aldehyde into a carboxylic acid (benzoic acid).**

2. **Conversion of α-*keto* aldehyde into an α-hydroxy carboxylate due to *Intramolecular disproportionation.***

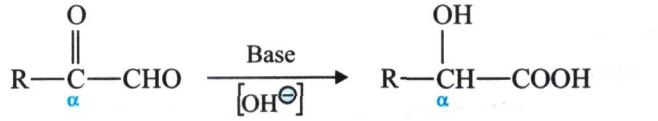
* Cannizzaro S: *Ann.*, **88**: 129, 1853.

** Geissman TA: *Org. React.*, **2**: 94–113, 1944.

*** List K *et al.*: *Liebigs Annalen*, **80**: 190–210, 1854.

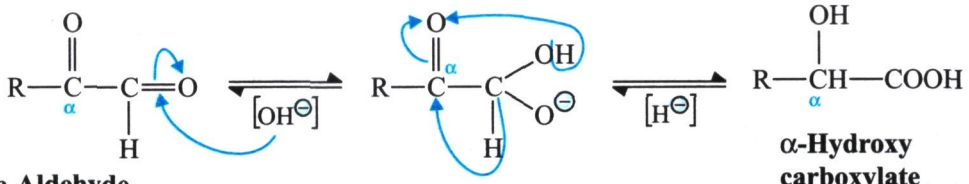
The various reactions involved sequentially may be expressed as under:

Simple Expression



α-*keto*-Aldehyde **α - Hydroxy carboxylate**

Detailed Expression



α-*keto*-Aldehyde **α-Hydroxy carboxylate**

Salient Features

These essentially comprise:

1. The **'key-step'** involved in the aforesaid *two*-step series of reactions from **α-*keto*-aldehyde** to the final product **α-hydroxy carboxylate** are as follows:
   - **hydride ion (H^-) shift**; and
   - **proton (H^+) shift.**
2. The above cited reaction gets a *kick off* predominantly due to the:
   "nucleophilic addition of a hydroxide anion [OH^-] to the corresponding *carboxyl (-COOH) C–atom of the aldehyde* (*i.e.*, without having any α-*H-atom*) thereby giving rise to the formation of an 'anion' (A)".
3. Besides, in the critical presence of the base [OH^-], the resulting **anion (A)** get deprotonated eventually to give a **di-anion specie (B)** in a rather ***strongly* basic environment.**
4. However, the *two* aforesaid potential intermediates **(A)** and **(B)** may interact with the ***second*-molecule of aldehyde** confirming to the **(H^-) shift** and **(H^+) shift** yielding ***newer breeds of products.***

Mechanism of Cannizzaro Reaction

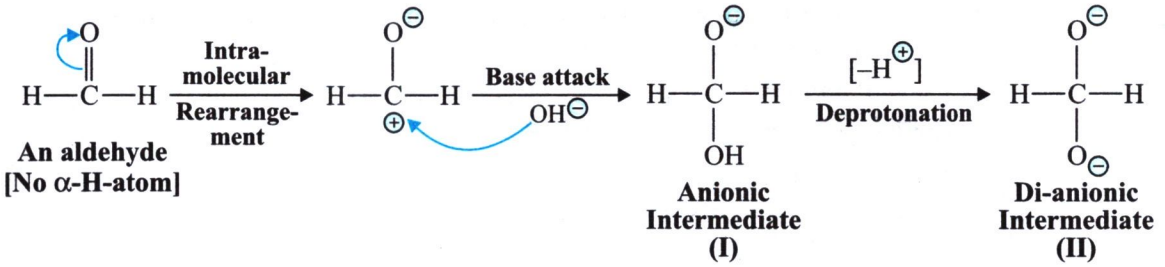
The underlying mechanism of the **Cannizzaro reaction** may be adequately explained based on the following ***two* distinct steps:**

Step 1: Critical Formation of Anionic and Di-anionic Intermediates:

In this particular instance, one would obtain from ***one* mole of an *aldehyde* devoid of any α-H atom** *two* intermediates, namely:

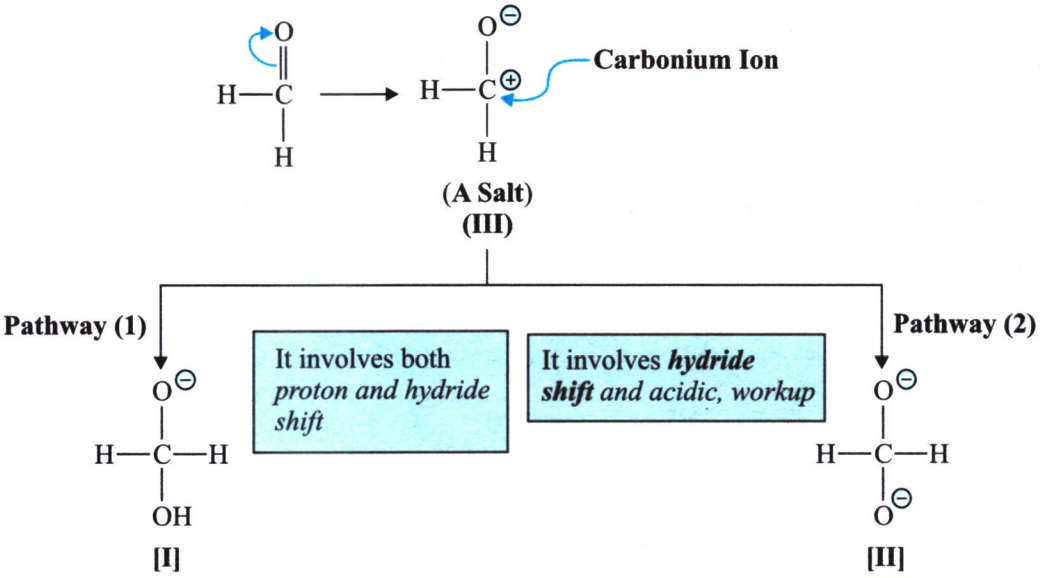
- **Anionic intermediate (I);** and
- **Di-anionic intermediate (II),**

as expressed under:



Step 2: Hydride and Proton Shift:

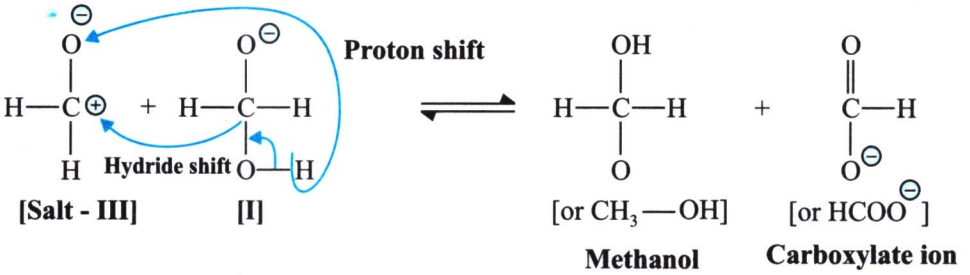
(*a*) Formation of Anionic Intermediate (I) and Di-anionic Intermediate (II)



Comment: Obviously, the **electron donating effect** of either *one* or *two* O^-, permits for the transfer of a **hydride ion** ($H^{\ominus}$) on to another molecule duly.

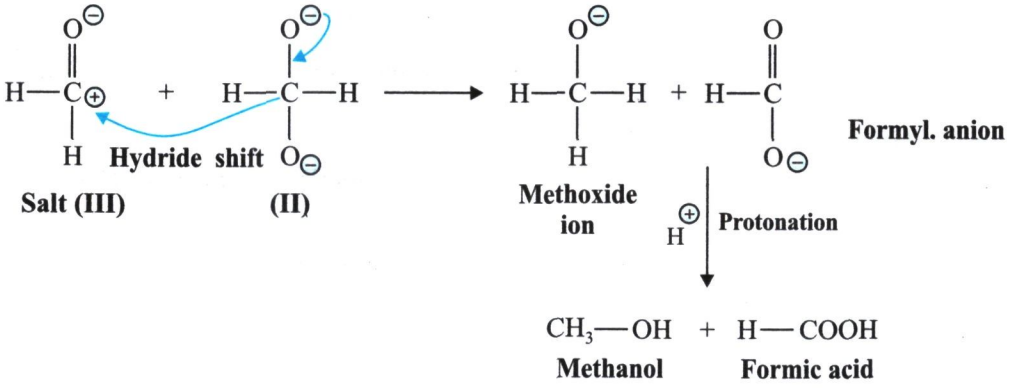
(*b*) Interaction of Salt (III) with Anionic Intermediate (I); and Salt (III) with Di-anionic Intermediate (II)

Part 1: Interaction of **Salt (III)** with **anionic intermediate (I)** yields *methanol* and *carboxylate* (1 mole each) *via* a **reversible reaction** as shown under:



Thus, an **anionic intermediate (I)** produces one mole each of **methanol** and **carboxylate ion** *via* **hydride shift** and **proton shift.**

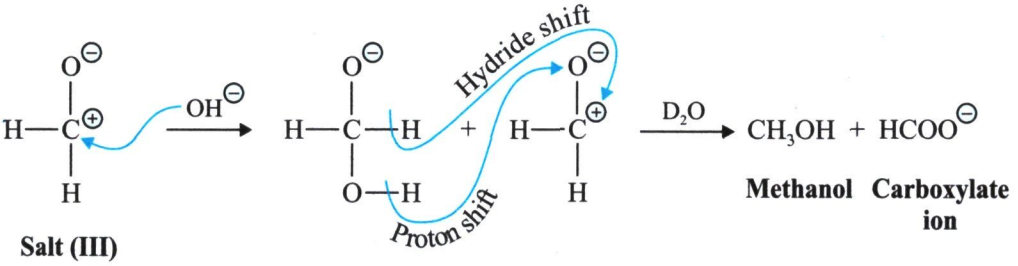
Part 2: Reaction of **Salt-(III)** with **di-anionic intermediate (II)** gives a mole each of *methanol* and *formic acid via* ***two*-stage reaction** as depicted below:



Concrete Scientific Evidence for the Mechanism of Cannizzaro Reaction

Importantly, the so-called **concrete scientific evidences** for the **mechanism of Cannizzaro reaction** are solely based upon the particular experiments carried out with ***deuteriated water*** **(D_2O)** as the solvent.

It may be expressed as under:

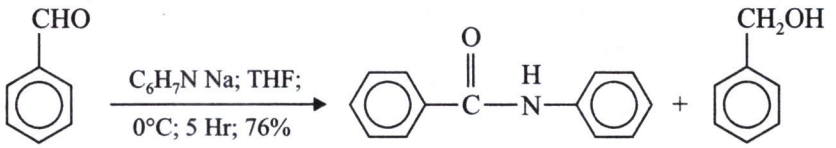


Remarks: The **methanol** (*alcohol*) fails to contain the **C-bonded deuterium** thereby ascertaining the fact that the so-called *shifted hydride* ($H^{\ominus}$) *ion* is given by a ***second*-substrate mole**; and certainly not from the **solvent** (***i.e.*, D_2O**).

Further Supporting Illustrations of Cannizzaro Reaction

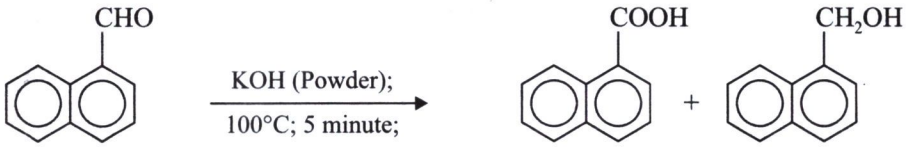
A survey of literature reveals the presence of ***two*** **logical illustrations** in support of the **Cannizzaro reaction:**

First **Illustration:** The reaction between an *aromatic aldehyde* (*viz.*, **Benzaldehyde**) and C_6H_7N *Na* in THF at 0°C for 5 hours yields **phenyl benzamide (~76%)** and **benzyl alcohol** as shown under:



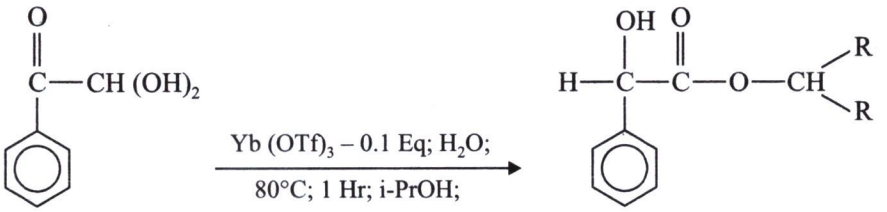
Benzaldehyde **Phenyl benzamide** **Benzyl alcohol**

***Second* Illustration:** It relates to the interaction of **α-naphthyl aldehyde** with KOH (powder) and heating at 100°C for a duration of 5 minutes in a *solvent free medium* to yield a mole each of **α-naphthyl carboxylate** and **α-naphthyl methyl hydroxide** as given below:



α-Naphthyl aldehyde **[Solvent-free medium]** **α-Naphthyl carboxylate** **α-Naphthyl methyl hydroxide**

Curini *et al.* (2005)* extended the **Cannizzaro's reaction** by treating *dihydroxy methoxy benzene* (I) with 0.1 Eq. of **Ytterbium** $(OTf)_3$ in water at 80°C for 1 hour in the presence of **iso-propanol [i-PrOH]** to yield **phenyl-hydroxymethyl-dialkyl methyl carboxylate (II)** as shown under:

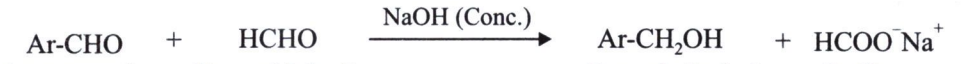


[I] **[II]**

Crossed Cannizzaro's Reaction

In general, an admixture of ***two* aldehydes** undergoes a **Cannizzaro reaction** to produce an array of all possible products. Now, if one of the aldehydes is **formaldehyde (HCHO)**; nevertheless, the reaction gives almost exclusively **sodium formate (HCOONa)** and the resulting *alcohol* corresponding to the other **'aldehyde'.**

Thus, we may have the following expression:



An aromatic aldehyde **Formaldehyde** **Benzyl alcohol** **Sodium formate**

such a reaction is invariably termed as **Crossed Cannizzaro Reaction.**

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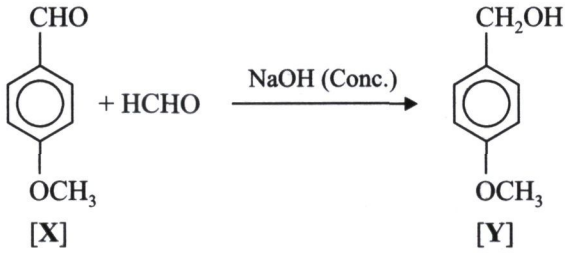
* Curini *et. al.*: *M Curini, F Epifano, S Genovese, MC Marcotullio, O Rosati,* ***Org Lett.*** *7: pp. 1331-1333,* 2005

Example: Conversion of Anisaldehyde (X) into *p*-Methoxy benzyl alcohol (Y)



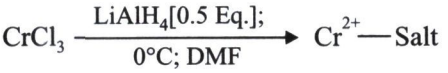
[X] [Y]

5.2.5 Nozaki-Hiyama-Kishi Reaction [Nozaki-Hiyama Coupling Reaction]*

The **Nozaki-Hiyama-Kishi reaction (1977–1986)** refers to a ***Ni–Cr bimetallic catalyst promoted coupling interaction*** critically involving either:

- **redox addition of vinyl,** or
- **allyl halides to aldehydes,**

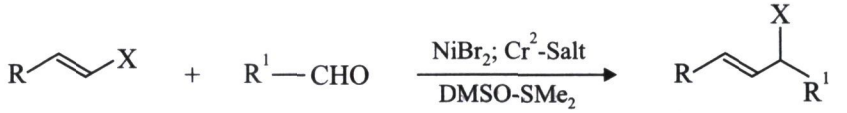
in order to form an ***alcohol*** as shown under:



Chromium trichloride **Chromous salt**

Thus, *chromium trichloride* undergoes the reduction in the presence of *lithium-aluminium hydride (LiAlH$_4$)* in 0.5 equivalent at 0°C in *dimethyl formamide (DMF)* to yield a corresponding **chromous (Cr^{2+}) salt.**

Furthermore, **1-propene halide [CH_3—CH=CH—X]** reacts with an *alkyl aldehyde* **(R—CHO)** in the presence of *nickel dibromide (NiBr$_2$)* and a *chromous salt* **[Cr^{2+}–salt]** in a mixture of **dimethyl sulphoxide (DMSO)** and **dimethyl sulphide (SMe_2)** to produce a **substituted alcohol** as shown below:



1-Propene halide **Alkyl aldehyde** **Substituted 2-butene alcohol**

R^1 = Aryl; Alkynyl; Alkenyl, Allyl, Propargyl

Remarks: These essentially include:

1. The *solvents* that are normally employed in the **Nozaki-Hiyama coupling reaction** are:
   - **N, N Dimethyl formamide (DMF) [H·CO·N $(CH_3)_2$];** and
   - **Dimethyl sulphoxide (DMSO) [H_3C·SO·CH_3].**

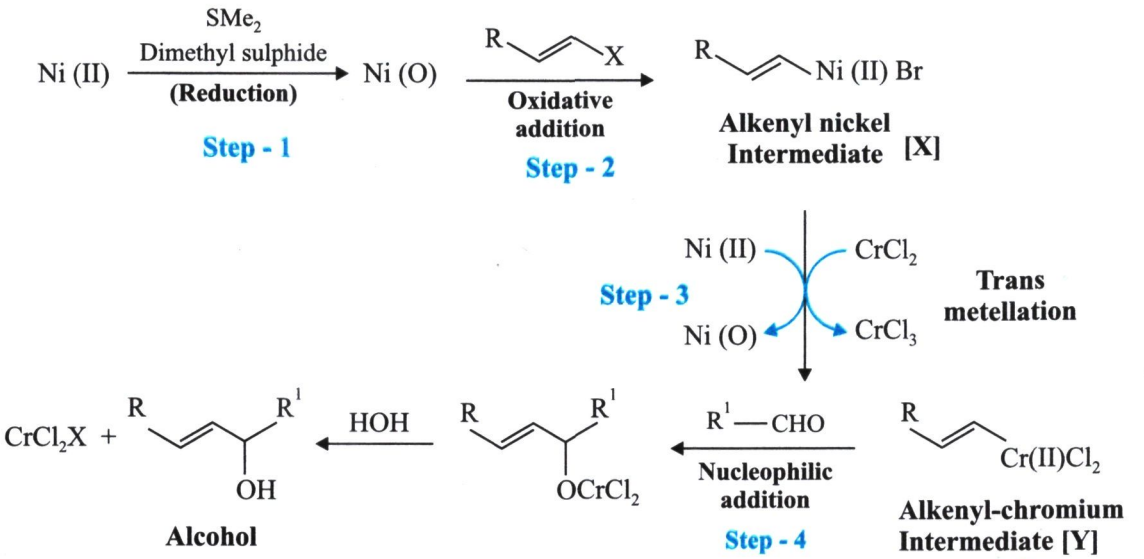
   Besides, there is another dire requirement of a **Cr^{2+}-salt** that must be soluble in either of the above *two* solvents.

* Okude Y *et. al.*: *J Am Chem Soc.*, **99**: 3179, 1977; Takai K *et al.*, *Tetrahedron Lett.*, **24**: 5281, 1983; Takai K *et al.*: *J Am Chem Soc.*, **108**: 6048–6050, 1986.

2. Initially, the underlying overall probability of the **NHC–reaction** to commence solely depended upon the actual source of **chromium (II) chloride** (salt); however, Takai *et al.* (1986) thoroughly studied the critical and vital importance of **Ni** in the aforesaid reaction. Since, then **Nickel (II) chloride** [$Ni^{2+}\cdot 2Cl^-$] is being employed as an ***adjunct catalyst*** (with [$Cr^{2+}\cdot 2Cl^-$].
3. Yoshita *et al.* (1986)* reported exhaustively the inherent *catalytic effect* of **Ni (II) chloride** while studying the **'total synthesis'** of **polytoxin.**

Mechanism of Nozaki–Hiyama Coupling Reduction

The **NHC–reduction** reaction may be expatiated through a ***four*-step** sequential reaction as given under:



Explanation

Step 1 : It relates to the *reduction* of **Ni (II)–chloride** to **nickel (O)** by means of **Cr (II)–chloride** (*i.e.,* the so-called *sacrificial catalyst*) thereby resulting into the formation of **Cr (III)–chloride.**

Step 2 : It deals with the *oxidative addition* of **Ni** to the *C–atom* located just adjacent to the *halide*; and thus, yields an **alkenyl-nickel intermediate (X).**

Step 3 : It is the most critical and important **transmetellation step** that eventually helps in the exchange of **NiX** with a **Cr (III) moiety** into the **alkenyl chromium intermediate (Y)** along with the specific regeneration of **Ni(II).**

Step 4 : The final step being the **nucleophilic addition** of [Y] with the carbonyl (>C═O) moiety by *hydrolysis.*

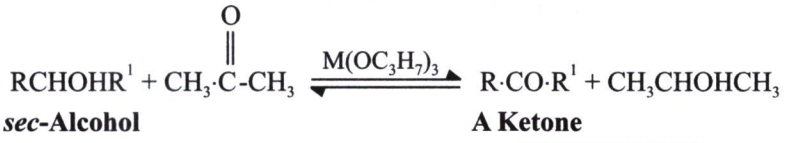
* Yoshita K *et al.*: *J Am Chem Soc.*, **108**: 5644, 1986.

NOTE: **It is pertinent to state here that the quantum of Ni being used in the aforesaid reaction(s) must be quite *reasonably low* since the possibility of indulgence of a *'side-reaction'* pertaining to *direct coupling with alkene* to yield a 'diene' is noticed.***

5.2.6 Oppenauer Oxidation

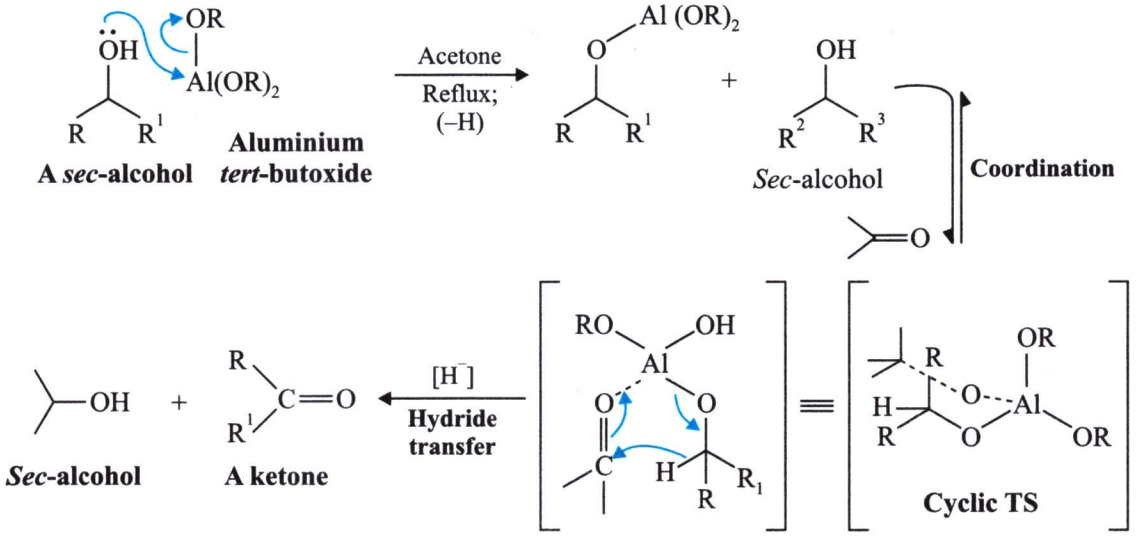
Oppenauer (1937)** first and foremost reported the **Al-or K-alkoxide catalyzed oxidation** of a ***'secondary* alcohol'** to the corresponding ***ketone*** (*i.e.*, the reverse of the **Meerwein-Ponndorf-Verley reduction:** see section 5.2.1).

It may be expressed as given below:



Mechanism of Oppenauer Oxidation

The mechanism of the so-called *chemoselective oxidation reaction i.e.*, **Oppenauer oxidation** essentially involves a ***cyclic* transition state** as illustrated under:



EXPLANATION

1. When a *sec*-alcohol in either **acetone** or **cyclic ketone** is duly refluxed with **aluminium *tert*-butoxide** in benzene or toluene, the alcohol gets *dehydrogenated* to form a **ketone.**
2. Furthermore, the **H-atoms** so eliminated by the *alcohol* are duly transferred to:
   - **cyclic ketone**; or • **acetone,**

   to yield the corresponding **alcohols.**

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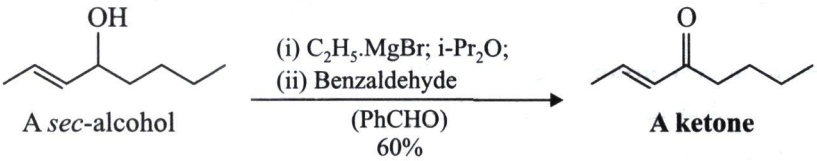
* Takai K: *Org. React.*, **64**: 253–612, 2004 **(Review).**

** Oppenauer RV: *Rev Tran Chim.*, **56**: 137, 1937.

Oppenauer Oxidation by Grignard Reagent

Byrne and Karras (1987)* used a **Grignard reagent** *e.g., ethyl magnesium bromide* **(EtMgBr)** to perform the **Oppenauer oxidation** as shown under:



A *sec*-alcohol — **A ketone**

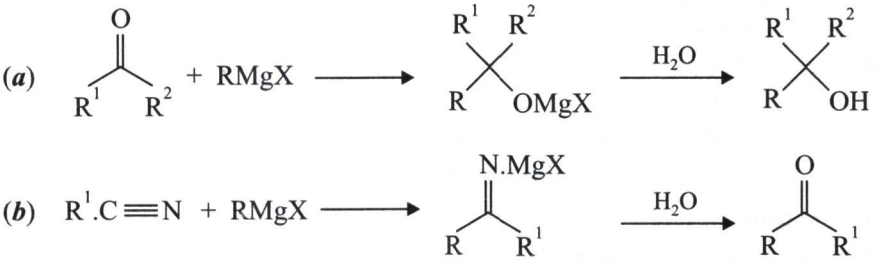
The **Oppenauer Oxidation** invariably makes use of the following commonly used **'ketones'** and **'bases'**, namely:

- ***Ketones:*** **Acetone; Methyl ethyl ketone; Cyclohexanone;**
- ***Bases:*** **Aluminium isopropoxide; Aluminium *tert*–butoxide; Potassium *tert*-butoxide.**

5.2.7 Grignard Reaction

The **Grignard reaction*** refers to the critical addition of organomagnesium compounds (***Grignard Reagents***) to the *carbonyl* (>C=O) *compounds* to generate **alcohols.** Nevertheless, a rather more recent interpretation does extend the scope of the reaction to include the thoughtful addition of the **Grignard reagents** to a broad-spectrum of the ***electrophilic substrates.***

It may be expressed through the following two typical examples, namely:



In true sense, the substrate for the reaction are those comprising the so-called ***polar functional moieties,*** namely:

- **Aldehydes (—CHO)** • **Ketones (>C=O)** • **Nitriles (—C ≡ N)** • **Esters (—COOR)** and • **Carbon dioxide (CO_2).**

Why is the Grignard Reaction so *'important'*?

The **Grignard reaction** is extremely important in **organic chemistry** because of the following ***cardinal reasons***, such as:

1. It really enables us to take *two* organic molecules and convert them easily into a **'bigger molecule'.**
2. To accomplish the aforesaid objective an attempt is made to ***'form a C—C bond'***; and thus, once again one may join them together, that is:
   - **electrophilic carbon,** and
   - **nucleophilic carbon.**

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* Byrne B and Karras M: *Tetrahedron Lett*, **28**: 769, 1987.

** Grignard V: *Compt Rend*, **130**: 1322, 1900.

3. Obviously, the so-called **electrophilic C–atom** is duly provided by the respective ***carbonyl*** **(>C═O)** ***moiety***.

4. Alternatively, for the **nucleophilic C–atom** one may take the advantage of the ***'carbanion'*** for instance:
   - **Organic moiety of an *'organometallic chemical entity'*.**
     - **Grignard reagent [*viz.*, R—Mg—X]; or**
     - **an organolithium [*viz.*, $R_2Cu^-Li^+$].**

Comment: Hence, the **Grignard reaction** predominantly serves as the most vivid example of:

- **aldehydes** [—CHO]; and
- ketones $\left[\begin{matrix} \diagdown \\ \diagup \end{matrix}\!\!>C{=}O\right]$; and

there by giving rise to the ***nucleophilic addition.***

5. **Extension of *Grignard reaction* for building still Bigger and More Complicated Organic Structures:**

   It may be quite necessary and equally pertinent to mention at this point in time that the **Grignard reaction** is not only confined to the synthesis of a pre-determined **C—C bond** in an *organic* compound but also goes a long way in the preparation of such products that essentially comprise:

   'the extremely versatile hydroxyl (—OH) moiety'.

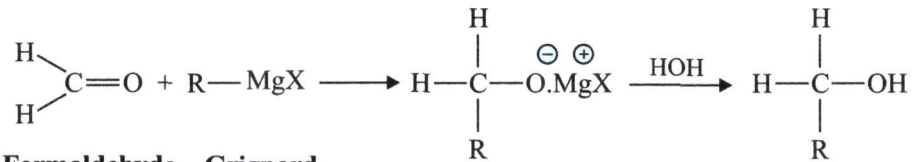
Interestingly, the aforesaid ***'dictum and analogy'*** have been extended intelligently to accomplish:

- **further synthesis,** and
- **critical constitution, of *'still bigger'* and 'more *complicated structures'*.**

Classical Examples: The exemplary class of *organic compounds viz.,* **Alcohols** as obtained by means of a **Grignard reaction** rests exclusively upon the exact and precise nature of the respective **carbonyl (>C═O) compound** being used:

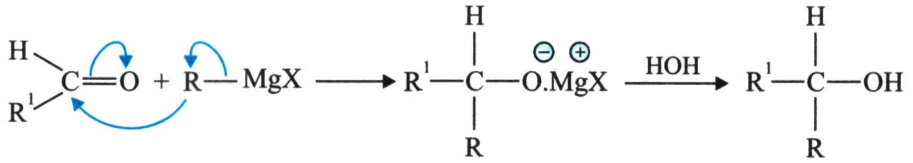
- **Formaldehyde [HCHO]:** that gives only the ***primary*** **alcohols**;
- **Higher Aldehydes [RCHO]:** which yields mostly the ***secondary*-alcohols**; and
- **Ketones [R_2C = O]:** that produces the *tertiary* **alcohols.**

EXAMPLE OF FORMALDEHYDE



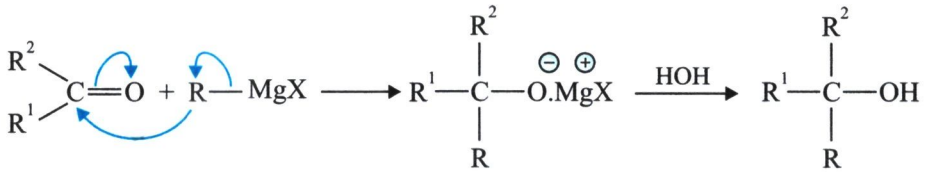
Formaldehyde **Grignard reagent** **An Intermediate [Aldehyde - GR complex]** ***Pri*-alcohol**

Example of Higher Aldehydes

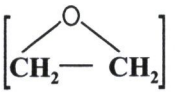


Higher aldehyde **Grignard reagent** **An Intermediate [Aldehyde - GR complex]** ***sec*-alcohol**

Example of Ketones



Ketones **Grignard reagent** **An Intermediate [*tert*-butyl-GR complex]** ***tert*-alcohol**

Allied Synthesis Using Ethylene Oxide  **to Obtain Primary-Alcohols Comprising *two* Additional C–Atoms**

It is not only feasible but also quite convenient to bring forth an ***allied synthesis*** which eventually makes use of **ethylene oxide** to yield specifically:

"*primary*-alcohols comprising *two* additional C–atoms",

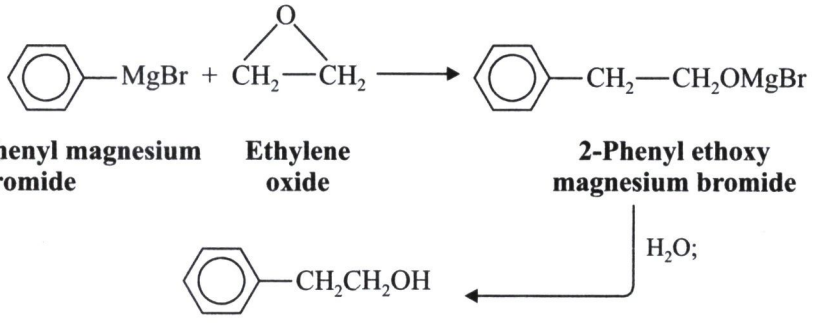
in comparison to the one obtained from the **Grignard Reagent.** Nevertheless, in this particular instance too the so-called ***'organic entity'*** becomes duly attached to both:

• **Carbon** and • **Magnesium.**

and ultimately to **Oxygen** owing to the meticulous cleavage of a specific.

'Carbon-Oxygen σ bond'

located strategically in a **reasonably high-strained *three*-membered ring system** as shown below:



Phenyl magnesium bromide **Ethylene oxide** **2-Phenyl ethoxy magnesium bromide**

2-Phenylethanol

Limitations of the Grignard Reaction

Points to Ponder

1. The major cardinal reason to ascertain the actual inherent ***'reactivity'*** that renders a **Grignard reagent** so immensely beneficial critically limits how one may use it in a particular synthesis. Therefore, it would be absolutely important to bear-in-mind the ***intended reactivity*** as and when one chalks out the *experimental parameters of the synthesis* being undertaken, such as:
   - **proper and meticulous selection of the *halide (X)* in the making of the *Grignard reagent*;** and
   - **to select the *probable compound* that is intended to react with ultimately.**
2. **Grignard reagent** when react with *water*—it yields an **'alkane'** (*i.e.,* a stronger acid relatively); and hence, the former duly helped in the displacement of the **extremely weak acid (*alkane*)** from its salt. Thus, in the same vein, any chemical entity having **H–atom** attached to the ***electromagnetic element*** *viz.,* **O,S,** or **N,** or **triply bonded carbon** (—C≡N; —C≡C—) — is found to be: **'acidic enough to decompose the Grignard reagent R—Mg—X'.**

   Eventually, it would certainly render a **Grignard reagent** to interact rather swiftly with:
   - **O–atom,**
   - **Carbon dioxide (CO_2),** and
   - **with almost each *organic molecule* having either a *C—O* or *C–N* multiple bond.**
3. Absolute scrupulously *'dried'* and free of *'alcohol'* (*e.g., aldehyde, alkyl, halide, ether*—being used as **solvent in the Grignard reagent**) are genuinely required:
   - ➢ **$CaCl_2$—Guard Tube** is used to check and prevent water vapour, CO_2, and oxygen (present in the air);
   - ➢ **Dry N_2–gas** a slow constant passage of **dry N_2–gas** throughout the on-going reaction shall give a *good yield* of the **final product**; and
   - ➢ **Duly selected halide and Aldehyde** it also plays a pivotal role in the *good overall yield of the product.*
4. **Preparation of Aryl-Magnesium-Halide [Ar—Mg—X]** One must be extremely vigilant and cautious in the critical preparation of the so-called **arylmagnesium halide** bearing in mind the *naked truth* that a wide-spectrum of **substituents** which may be present in the **'Benzene-Ring-System'** commonly, such as:

   • **Carboxyl (—COOH)** • **Hydroxyl (—OH)** • **Amino ($—NH_2$)** and

   • **Sulphuric Acid ($—SO_3H$),**

   that vehemently contain at **H–atom** duly attached to **O, N,** and **S** atoms; and hence, prove to be *highly acidic in nature* thereby decomposing the **Grignard reagent** perceptively.

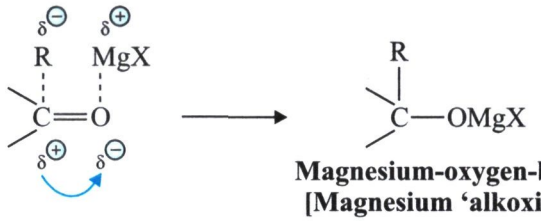
Mechanism of Grignard Reaction

Based on the available evidences scanned from the scientific literatures it may not be quite practicable to lay hands on to a ***'uniform reaction mechanism'*** that could possibly describe judiciously the so-called intricacies of the underlying **mechanisms of Grignard reaction.** In general, one may encounter the following *two* suggested **mechanisms** of **Grignard reaction,** namely:

- **Polar Mechanism,** and
- **Radical Mechanism,**

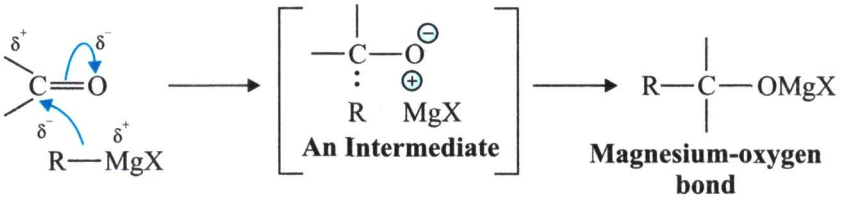
which shall now be discussed individually in the sections that follows:

(*a*) **Polar Mechanism:** It refers to the **group 'R'** very much along with the respective **electron pair** precisely on to the corresponding ***carbonyl* (>C═O)** ***carbon centre***—thereby ultimately leading to the crucial generation of a **'magnesium–oxygen–bond'** in the ***magnesium alkoxide*** of a ***tert*-alcohol*** as shown under:



Magnesium-oxygen-bond
[Magnesium 'alkoxide']

(*b*) **Radical Mechanism:** It relates to the particular inclusion of the ***transfer of a single-electron*** right from the **Grignard reagent** into the respective ***carbonyl moiety* (>C═O),** invariably termed as the **'single-electron-transfer (SET) system'** thereby the *pair-of-radicals* so generated upon due combination give rise to the formation of the **desired product**—as depicted beow:



Magnesium-oxygen bond
[Magnesium 'alkoxide']

Remarks: It is, however, pertinent to state here that the exact nature of the ***'organomagnesium reagent'*** virtually decides the **mechanism** by which the **Grignard reaction** would follow the *ultimate course.*

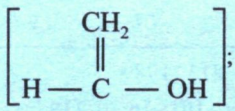
Example

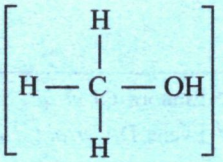
- Interaction of *Benzophenone* with **Grignard reagent** *viz.,* **Methyl magnesium bromide [CH_3—Mg—Br]** where the ***tert*-butyl magnesium chloride** is employed as the perspective **Grignard reagent** (to cater for as the *radical mechanism*).

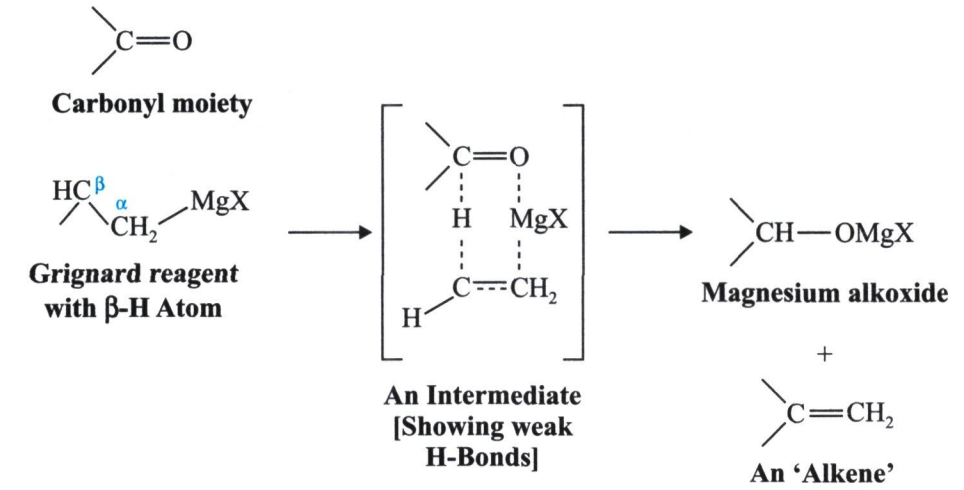
Grignard Reduction

In actual practice, the so-called **Grignard reagents** which specifically comprise a **β—*H* atom** may undergo virtual transfer of **β—H atom** to cause an effective reduction of a **carbonyl (>C═O) substrate** as shown under:

---

* *tert*–Alcohol [HC ≡ C–OH]; *sec*-Alcohol 

; ***pri*-Alcohol** 

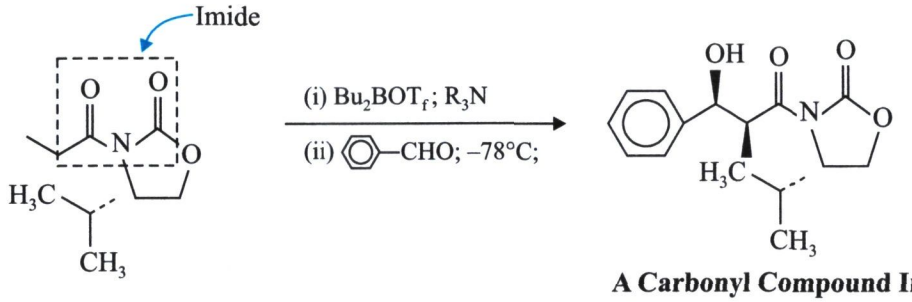


NOTES:

1. **The *Grignard reaction* is regarded to be one of the most vital and important reactions perhaps on account of the inherent inbuilt versatlality due to the *C—C bond formation.***
2. **Einhorn *et al.* (1989)* advocated one of the most advanced applications of the *Grignard's reagent* duly obtained *via* the *slow-reacting alkyl/aryl halides* (as pointed out in the *'ultrasound'* devices.**

5.2.8 Evans-Aldol Reaction

Evans (1979, 1981)** reported the ***highly*** **enantioselective Aldol condensation** of the ***chiral*** **N-acyl-oxazolidinone** *via* its **dibutylboryl enolate** with an *appropriate aldehyde,* as shown under:



A Carbonyl Compound Imide

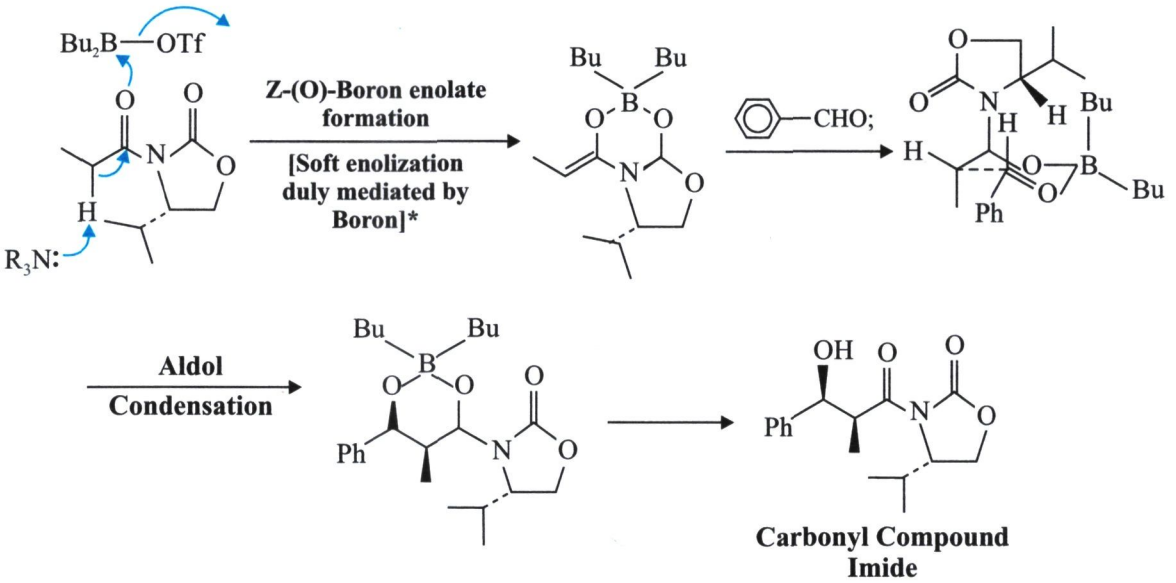
In fact, the **Evan's Aldol reaction** specifically creates temporarily—**'a *chiral enolated* by appending critically a chiral auxiliary (oxazolidinone)'.** Therefore, the already *pre-existing chirality* duly emanated from the ***'auxiliary'*** get subsequently ***transferred*** to the so-called **'Aldol Adduct'** *via* a **diastereoselective aldol reaction.** Hence, the actual desired **'Aldol stereoisomer'** is observed prominently—as and when the *auxiliary is removed* articulately. Thus, the *ultimate product* as obtained from the **Evan's Aldol reaction method** is termed as the—***'carbonyl compound imide'.***

* Einhorn CJ *et al.*: *Synthesis,* 787–813, 1989.

** Evans DA *et al.*: *J Am Chem. Soc.* **101**: 16/20, (1979); **103**: 2127 (1981).

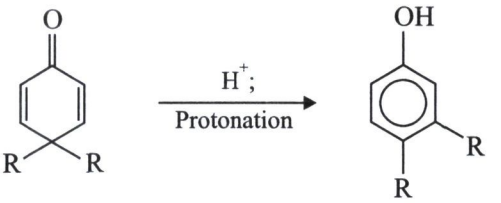
Mechanism of Evan's Aldol Reaction

The following *four* sequential steps are involved to elaborate the mechanism of **Evan's Aldol Reaction:**



5.2.9 Dienone-Phenol Rearrangement

Von Auwers and Zeigler (1921)* reported the most crucial *transformation* of a **4,4–disubstituted cyclohexadienone** into the respective **3,4–disubstituted phenol** due to an *acid treatment*, as shown under:



4,4-Disubstituted cyclohexadienone (A) **3,4-Disubstituted phenol (B)**

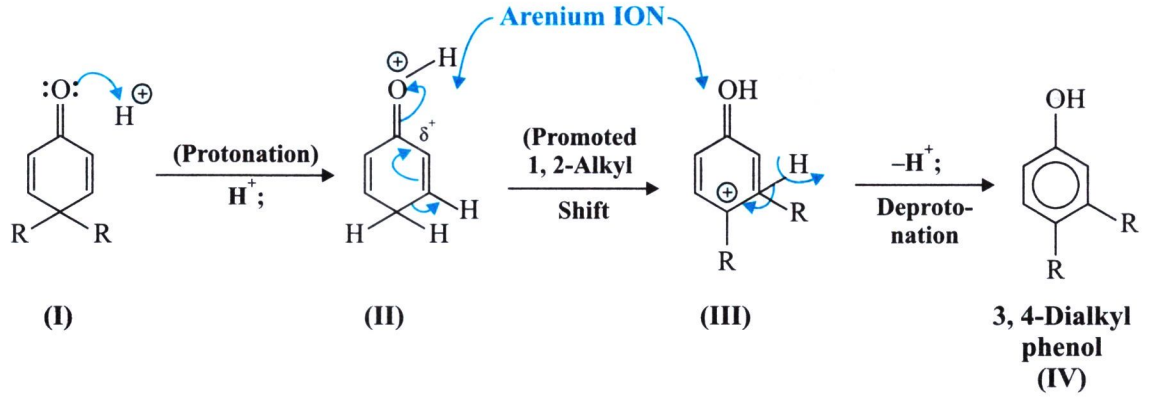
In other words, it relates to an–**'acid-promoted rearrangement'**, whereby the initial **compound (A)** gets duly *transformed* into **compound (B)** *via* protonation. Besides, such a rearrangement largely involves the critical formation of an **aromatic system** (Perkins *et al.*, 1971).** Importantly, one of the **alkyl moieties** located strategically at **C—4** undergoes the **1, 2-shift.**

* von Auwers K and Zeigler E: *Ann*, **425**: 217, 1921.

** Perkins *et al.*: *Mech Mol Migr.*, **4**: 56–112, 1971.

Mechanism of Dienone-Phenol Rearrangement

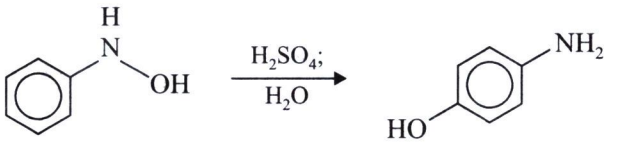
Based on the scientific evidences one may expatiate the underlying mechanism of the **Dienone–Phenol rearrangement** *via* the following *three* sequential steps, as given under:



Comment: The **compounds (II) and (III)** in the above reactions do bear a prominent **positive charge on them**; and hence, these are usually known as the ***'arenium ions'***.

5.2.10 Bomberger Rearrangement

Bomberger (1894)* proposed a *intermolecular* rearrangement of **N-phenylhydroxylamines** in an aqueous acid to yield the corresponding **4-aminophenols**, as given under:

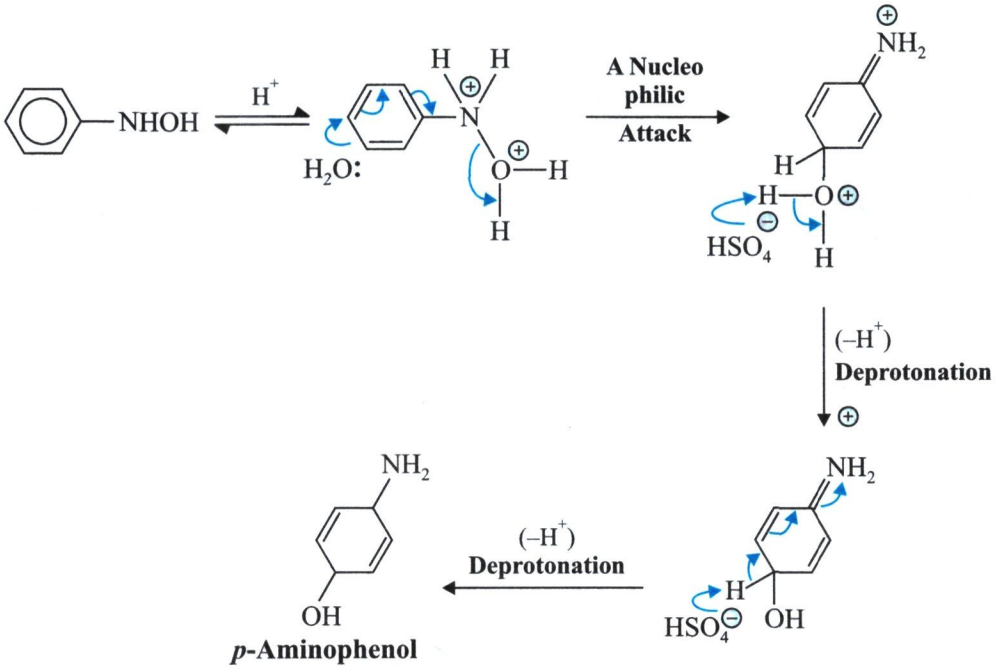


N-Phenylhydroxyl-amine — ***p*-Aminophenol**

MECHANISM OF BOMBERGER REARRANGEMENT

Following are the *four* distinct sequential steps to explain the mechanism of the **Bomberger rearrangement.**

* Bomberger E: *Ber*, **27**: 1347, 1958 (1894).



The various steps involved in the above reaction steps are quite easy and self-explanatory.

Suggested Reading

Loudon, GM: **Organic Chemistry**, 4th Ed., Oxford University Press, Oxford, 2002.

Morrison, RT, Boyd, RN and Bhattacharjee, SK: **Organic Chemistry**, 7th Ed., Pearson, India, 2011.

Solomons, TWG and Tryhle, CB: **Organic Chemistry,** 9th Ed., Wiley, India, 2008.

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Chapter 6

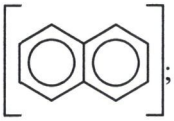
Reactions Giving Arenes

LESSONS AT A GLANCE

6.1 Introduction
6.2 Friedel-Crafts Alkylation Reaction
6.3 Benzoin Condensation

6.1 INTRODUCTION

The **'arenes'** designate the class name for *unsaturated cyclic aromatic compounds*, of which **'benzene'** represents a typical example. Besides, there may also exist *several rings* that could be invariably observed in the following *two* classical examples:

- **bonded chemically** *e.g.,* diphenyl  ; or
- **fused together** *e.g.,* anthracene 

In a broader perspective the organic reactions giving rise to the formation of **'arenes'** may be categorised perceptively into the following ***two*** **aspects**, namely:

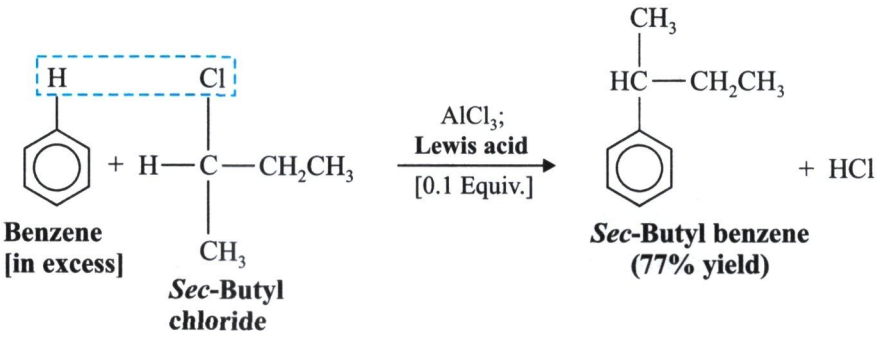
(*a*) **Friedel-Crafts Alkylation Reaction;** and

(*b*) **Benzoin Condensation,**

which shall now be discussed separately in the sections that follows:

6.2 FRIEDEL-CRAFTS ALKYLATION REACTION

The **Friedel-Crafts alkylation reaction** relates to the reaction of an **alkyl-halide with benzene** in the specific pressure of a ***Lewis acid catalyst*** yields an **alkylbenzene** as given below:



EXPLANATION

The above reaction represents a classical example of the **Friedel-Crafts alkylation**. As we are aware that an **'alkylation'** obviously designates a reaction that ultimately results in the ***'transfer of an alkyl moiety'***. Therefore, in a **Friedel-Crafts alkylation reaction**—an ***'alkyl moiety'*** gets duly transferred to an aromatic ring in the critical presence of an acid-catalyst.*

Comment: However, one may critically observe in the **previous example,** the **alkyl moiety** hails from an ***'alkyl halide'***; whereas, the *'catalyst'* being the **Lewis acid aluminium trichloride ($AlCl_3$).**

Formation of an 'Electrophile' in a Friedel-Crafts Alkylation Reaction

Interestingly, the ***electrophile*** in a **Friedel-Crafts alkylation reaction** is duly formed due to the actual:

'Complexation of the Lewis acid ($AlCl_3$) together with the halogen of an *alkyl halide* (RX)—almost in the same manner as the *electrophile in bromination of benzene* gets duly generated by the specific complexation of ferric bromide ($FeBr_3$) with bromine (Br_2).'

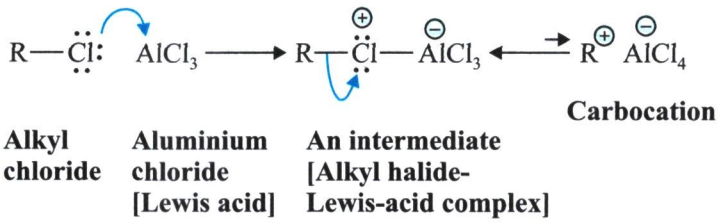
In a situation, when the **alkyl halide** happens to be either

- ***secondary*** **[R_2CHX]**; or
- ***tertiary*** **[R_3CX]**,

the ensuing complex may even react further to result into the formation of the so-called:

'carbocation intermediates'.

Thus, we may have the following expression:



* That is, a **Lewis acid** ($AlCl_3$) serving as a **'catalyst'.**

EXPLANATION

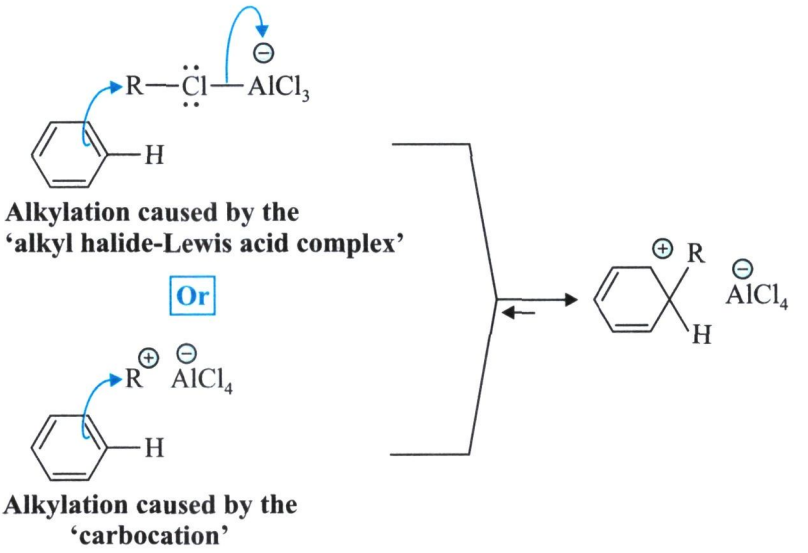
It is, however, pertinent to state here that the formation of an *'electrophile'* in a **Friedel-Crafts alkylation reaction** would either:

- **form the *'Alkyl-halide Lewis-acid complex'*, or**
- **form the *'Carbocation derived from it'*,**

that may eventually cater as the intended ***'electrophile'*** in a **Friedel-Crafts alkylation reaction.**

Benzene π-Cloud Electrons Invariably attack an '*Electrophile*'

The above concept and analogy may be expatiated based on the following typical example:

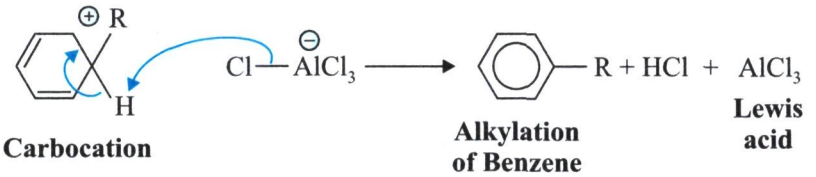


Remarks: Thus, the actual attack of the **benzene π electrons** or **π clouds** strategically onto a corresponding **carbocation** designates clearly altogether another aspect duly listed in the ***'carbocation reactions'***—that would usually comprise the following:

- **specific reaction with the *'nucleophiles'*,**
- **rearrangement to *other carbocations*,**
- **elimination of a *β-proton* to yield an *'alkene'*, or an *'aromatic ring'*, and**
- **specific reaction(s) with the *π electrons* of an olefinic bond (double bond) or an *aromatic ring system.***

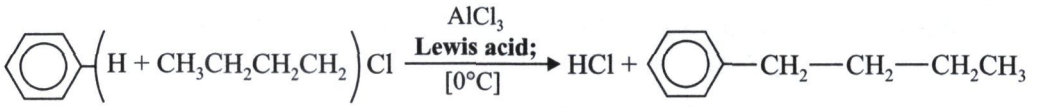
Loss of a Proton (H^+) to Chloride Ion (Cl^-) Virtually Ensures the Completion of Alkylation Phenomenon

The above facts may be exemplified with the following example:

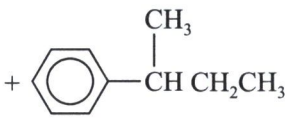


Remarks: Since, there are certain **'carbocations'** that may possess the ability to rearrange, it is not quite surprising that the corresponding *rearrangements* of the **alkyl moieties** are duly observed in certain **Friedel-Crafts alkylation.**

Let us look into the following sequence of reactions:



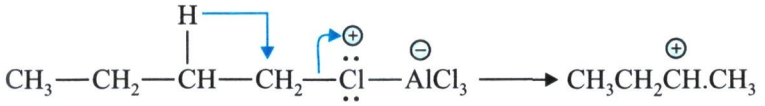
Benzene **1-Chlorobutane** **Butyl benzene (I)**
[Yield = 27%]



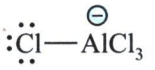
***Sec*-Butyl benzene (II)**
[Yield = 49%]

Remarks: Obviously, the **alkyl moiety** present in the ***secondary-butyl benzene (II)*** has been rearranged meticulously. As we know that the so-called **carbocations** are generally found to *quite unstable*; and hence, found not to be involved as the probable ***intermediates.*** Thus, the resulting complex of the **alkyl halide** and **$AlCl_3$** ***(Lewis acid)*** undergoes a **rearrangement.**

Amazingly, this **specific complex** does have enough carbocation characteristic feature that it virtually behaves more or less like a **'carbocation'**.



***Sec* - Butyl cation**
[Alkylates 'benzene' to yield *sec*-Butyl benzene (II)

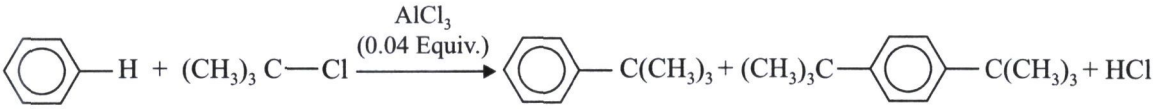


See the previous reaction

Special Observations: It is, however, pertinent to state here that there would be no **feasible rearrangement** in the typical **Friedel-Craft's alkylation** in such critical circumstances when the ***carbocation intermediate*** is found to be:

'Not Prone to Rearrangement Phenomenon'.

In order to expatiate the above statement of facts let us consider the following reaction:



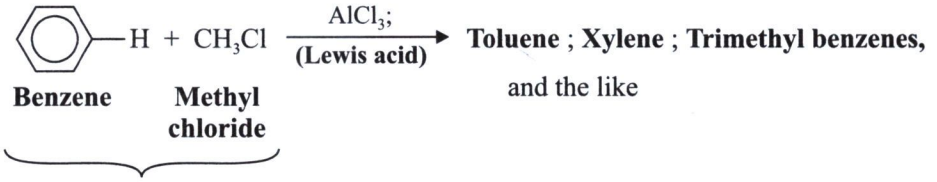
Benzene [3 Times in Excess] **Trimethyl methane chloride** ***tert*-Butylbenzene [Yield 66%]** **1,4-Di-*tert* Butylbenzene [Yield small % only]**

Comments: These essentially include:

1. The ***tert*-butyl cation [$(CH_3)_3C^{\oplus}$]** behaves as the *alkylating agent;* since, it is *tertiary* in nature, the **carbocation** fails to *undergo rearrangement.*
2. Besides, the **alkylbenzenes** *viz.,* **butylbenzene [C_6H_5—$(CH_2)_3CH_3$],** as shown in the earlier equation, which are duly derived from the respective ***rearrangement prove* alkyl halides** are **not** usually prepared by the **Friedel-Craft's alkylation,** but by any one of the following ***three* reactions,** namely:
   - **Clemmensen Reduction*—*of aryl ketones*;** or
   - **Wolff-Kishner Reduction**—*of aryl ketones*;** or
   - **Stille Reaction*** *i.e.,*** Pd-catalyzed cross-coupling reaction of organostannanes with organic halides, acetates etc.

Another Complication in Friedel-Crafts Alkylation

It has been duly observed that the **alkylbenzene products** are definitely *more reactive* in comparison to **benzene**; which clearly implies that the said product may probably undergo ***further alkylation*** and yields an **admixture of products duly alkylated to various extents,** as given under:

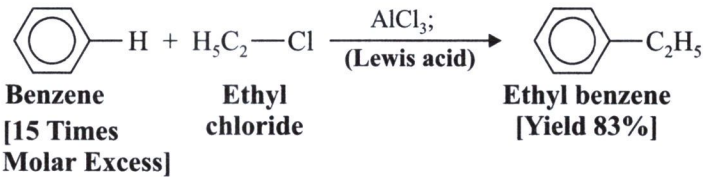


Comments: Nevertheless, one may usually lay hands on to a respective **monoalkylation product** that may be obtained in **good yield** (provided one has an access to the **aromatic starting material** abundantly).

Example: The reaction between **benzene** and **ethyl chloride** yields **ethyl benzene** in the presence of $AlCl_3$ (**Lewis acid**). Importantly, in such a reaction almost the **15 times molar excess of benzene** ascertains that in usual process:

"a molecule of alkylating agent is much more likely to encounter a molecule of *benzene* in the reaction mixture *vis-a-vis* a molecule of the *ethylbenzene product.*"

Thus, we may have the following expression:



* Clemmensen E, *Ber.,* **46**: 1837, 1913.

** Kishner N, *J Russ Phy S Chem Soc.,* **43**: 582, 1911; Wolff L, *Ann.,* **394**: 86, 1912.

*** Stille JK *et al.*: *J Am Chem Soc.,* **100**: 3636, 1978.

Friedel-Crafts Alkylation Reaction: A Reversible Reaction

Unlike the *'acylation reaction'* the **Friedel-Crafts alkylation** reaction behaves predominantly as a ***reversible reaction***. Amazingly, the aforesaid characteristic feature attributes the reaction to be exploited and employed generously for:

"the particular regioselective synthesis of substituted aromatic structural analogues (congeners)".*

Demerits

1. One of the most glaring **demerits** of the **Friedel-Crafts alkylation** being observed is:
   "the electron indicating *'alkyl chain'* renders the end product rather more *nucleophilic in character* in comparison to the ensuing *reactant* thereby leading the same to:
   - ***overalkylation of the aromatic ring;*** and
   - **resulting into a *polyalkylated product.*"**

Therefore, the above mentioned undesirable characteristic feature restricts mostly the *vast synthesis uses* of the **FC–alkylation.**

NOTE: **Thus, advantageously a large degree of suitable *aromatic substrate* are being utilized to retard progressively the *polyalkylation* phenomenon.**

2. The second prominent **demerit** of the **FC–alkylation reaction** being the ***carbocation rearrangement*** that comes into play by virtue of the **relative stability** of the respective ***tert*–carbonium ion** *vis-a-vis* **any other carbonium ion** (*viz.*, ***pri*-or *sec*–carbonium ion**).

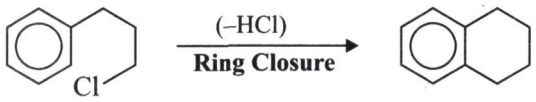
Salient Features of Friedel-Crafts Alkylation Reaction

There are *five* glaring examples that essentially highlights the **salient-features** of the **Friedel-Crafts alkylation reaction,** namely:

(*a*) **Ring Closure:** It largely helps to affect the ***ring closure*** phenomenon especially in the ***six*-membered ring system**; however, the same may even be extended to either:

- ***five*-membered ring** and - ***seven*-membered ring**

Thus, we may accomplish the specific ***intramolecular*** **variant** of the **Friedel-Crafts reaction,** as shown under:



Propylchloro benzene **Cyclohexyl benzene**

Comments: It has been shown that the following ***two*** **chemical entities** (compounds), namely:

- **naphthalenes;** and
- **polycyclic aromatics.**

may eventually generate **'side products'** perhaps due to their exceptionally **high reactivity profile** towards the **catalysist (Lewis acid)** *i.e.*, $AlCl_3$.

* Effenberger F, *Chem Unserver Zeit.*, **13**: 67–94, 1978.

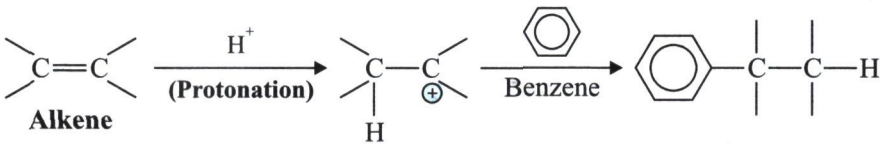
NOTE: **Besides, several *aromatic heterocycles* fail to undergo the Friedel-Crafts alkylation reaction perceptively.**

(*b*) **Electron withdrawing Moieties Inhibit Friedel-Crafts Alkylation Reaction:** It has been observed that the very presence of the ***activating*** **functional moieties**, for instance:

• **Hydroxyl (—OH)** • **Amino ($—NH_2$)** and • **Alkoxy (—OR),**

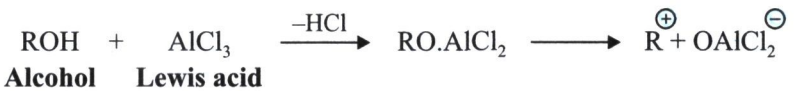
if located strategically upon the **aromatic ring**, they usually get coordinated with the particular **Lewis acid catalyst** ($AlCl_3$); and thus, helps to retard the alkylation reaction significantly.

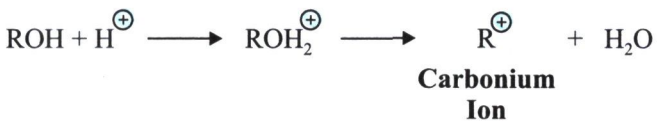
(*c*) **Friedel-Crafts Alkylation with Alkenes (*viz.*, Ethene) Being Catalyzed by Protons (H^+):** In this instance, the **proton (H^+)** is duly incorporated to the **carbon-carbon double bond (C=C)** (*i.e.*, the **olefinic bond**) strictly according to the **Markownikoff's Rule*** so as to give a **carbonium ion.** This on further reaction by the above cited mechanism gives rise to the formation of an ***alkylated aromatic compound***, as shown under:



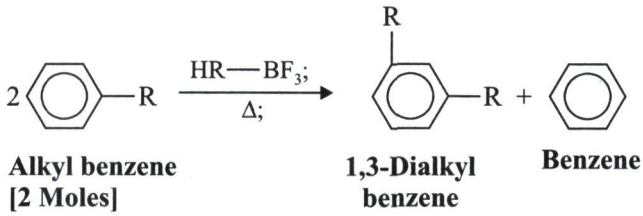
(*d*) **Alcohols as an Alkylating Agent:** Based on the scientific evidences it has been duly established that the **alcohols** may also be employed as an **alkylating agent.** Thus, the **alcohols** do have a tendency to react with the **Lewis acid** ($AlCl_3$) and get ***protonated*** first, which on being subjected to *dehydration* gives the desired **carbonium ion.**

Thus, we may have the following expressions:





(*e*) **Isomerization and Disproportionation:** It has also been observed that in the presence of an *excess quantum of a catalyst* and at an **elevated temperature**—the prevailing ***reactant*** undergoes both **isomerization and disproportionation** phenomena critically, as illustrated explicitly in the following example:



* **Markownikoff Vladimir:** A Russian Chemist (1838–1904)–Doctoral dissertation in 1869–proposed a **"rule"** for the regioselective addition of **hydrogen halides (HX)** to the **alkenes.**

NOTE:

- **Bearing in mind the above mentioned *serious drawbacks* of the so-called Friedel-Crafts alkylation reactions, such as:**
  - **Polyalkylation**
  - **Rearrangement and**
  - **Isomerization**

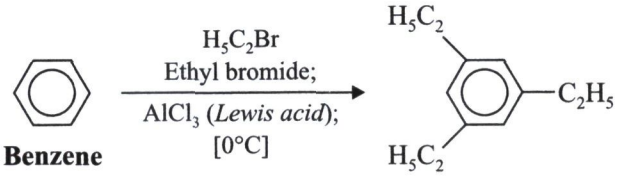
  it is always advisable to produce an—*'alkylated aromatic compound'* by means of the Friedel-Crafts Acylation immediately followed by careful reduction of the keto (>C=O) moiety to the respective methylene (—CH_2—) moiety to accomplish the intended *'alkyl side-chain'*.
- **In addition, quite recently the use of the *'acidic resins' viz.,* Nafion–H, are being employed extensively as the catalysts for carrying out the said *alkylation reactions.**
- **As-on-date, even one may successfully use the *'chiral catalysts'* (or asymmetric catalysts) in the aforesaid alkylation reactions.****

Friedel-Crafts Dealkylation Reaction

It is also referred to as the **'reversible Friedel-Crafts alkylation reaction'**, that essentially involves the meticulous elimination of the ***alkyl moieties*** in the presence of **protons (H^+)** and **Lewis acid ($AlCl_3$)**, such as:

"multiple addition of ethyl bromide to the benzene ring system under the critical influence of controlled temperature-parameters."

Let us consider the following conversion of *benzene* into **1,3,5-triethyl benzene:**



Benzene **1,3,5-Triethyl benzene (A)**

Explanation

The product **1,3,5-triethyl benzene (A)** is duly formed by virtue of the *successive reactions,* namely:

- **alkylations,** and
- **dealkylations.**

It is worthwhile to state here that almost all **ethyl moieties** are basically ***metasubstituted*** in the above **product (A)**, which is perhaps due to the underlying fact that:

"the controlled thermal parameters predominantly causes a drastic reduction in the possible steric hindrance; and, therefore, the *meta*-substitution is mostly favoured; otherwise, soon after the mono-substitution of the alkyl (C_2H_5) group (*i.e.,* the activating moiety), further incoming *two* alkyl (*i.e.,* ethyl) groups must obviously move on to the respective *ortho*-and *para*-position (Wallace *et al.*, 2005).*"**

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* Olah GA *et al.*: *Synthesis*, 513–531, 1986.

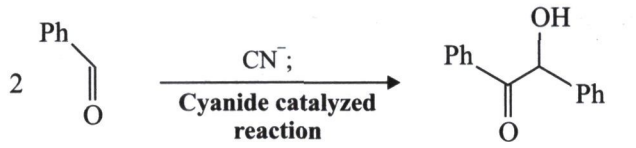
** Jorgensen KA: *Synthesis*, **10:** 1117–1125, 2003.

*** Wallace K *et al.*: *Synthesis*, **12**: 2080–83, 2005.

6.3 BENZOIN CONDENSATION

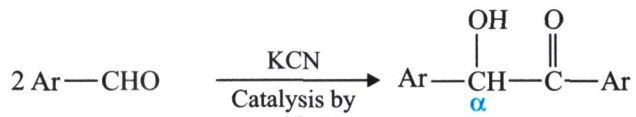
The **benzoin condensation** relates to the respective ***cyanide-catalyzed condensation reaction*** of *two* moles of the **same aromatic aldehydes.**

Example: *Benzaldehyde* (2 moles) reacts with *potassium cyanide (KCN)* to yield an ***α-hydroxy ketone*** called **benzoin** as given under:



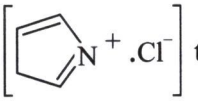
Benzaldehyde **Benzoin (α-Hydroxy ketone)**

The above *cyanide-catalyzed condensation reaction* may also be represented as below:



Aromatic aldehyde (2 moles) **A α-Hydroxy ketone (Benzoin)**

Comments: Benzaldehyde is obviously devoid of any **α–H atom** which on interaction with a **cyanide ion (CN⁻)** gives rise to the formation of **benzoin** *i.e.*, an **α-hydroxyketone.***

Besides, the aforesaid reaction is invariably applicable to the so-called **aromatic aldehydes** exclusively; however, it can also be duly extended to the ***aliphatic aldehydes*** a **base** as a **catalyst** and in the critical presence of the **thiozolium salts**  thereby forming the product **'acryloin'** instead of *benzoin.* Therefore, this particular reaction bears an immense importance for the crucial synthesis of a host of **heterocyclic chemical entities.****

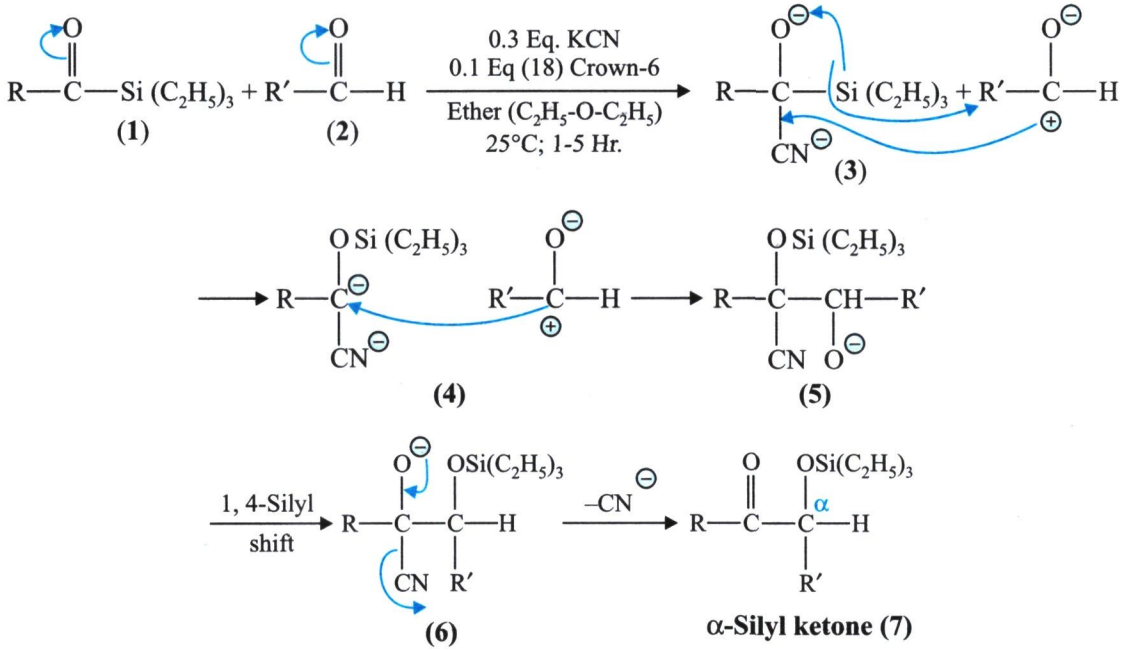
Cross-Coupling Benzoin Condensation***

In this particular instance, *two* altogether different aldehydes usually undergo the desired condensation reaction known as **Cross-Coupling Benzoin Condensation,** whereby one would ultimately lay hands onto ***two*** **different products** in a mixture, as depicted under:

* Ide WS and Buck JS: *Org React*, **4**: 269–304, 1948; Staudinger H, *Ber Dtsch Chem Ges*, **46**: 13535–38, 1913.

** Stetter H and Kühlmann H: *Org React.*, **40**: 407–496, 1991.

*** Dünkelmann P *et al.*: *J Am Chem Soc.*, **125**: 8432, 2003.



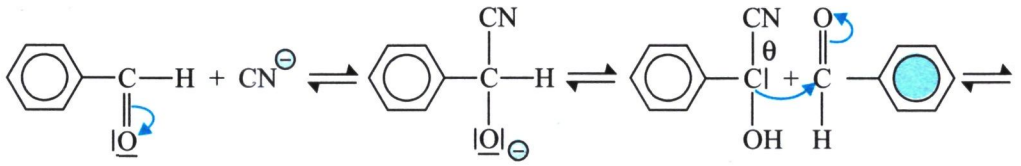
Explanation

The various steps involved may be explained as under:

1. Interaction between an **alkyl triethyl silicon ketone (1)** and an **alkyl aldehyde (2)** gives an **intermediate (3)** in the presence of KCN (0.3 Eq.) and crown-6 (0.1 Eq.), diethylether, 25°C for 1 hr.
2. The resulting **product (3)** subsequently gives another **intermediate (4)**, which yields an **anion (5).**
3. The **anion (5)** undergoes **1,4–Silyl shift** to produce another **anion (6)** note the shift of *triethyl silicon oxide* from the C–atom having **R** to the C–atom having **R′.**
4. Finally, the treatment with **KCN** gives the **α-silyl ketone (7).**

Mechanism of Benzoin Condensation

The following sequence of ***five* reversible reactions** is the *accepted mechanism**, which was originally proposed by Lapworth in 1903.**

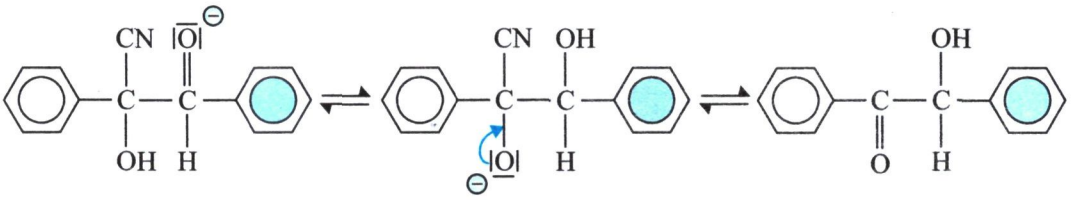


Donor **Acceptor**

(Contd...)

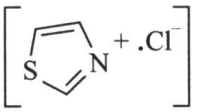
* Kuebrich *et al.*: *J Am Chem Soc.*, **93**: 1214, 1971.

** Lapworth, *J Chem Soc.*, **83**: 995, 1903; **85**: 1206, 1904.



EXPLANATION

These essentially include:

1. The reaction is **reversible** entirely.
2. **Key step** *i.e.,* the critical loss of the **aldehydic proton (H^+)**, may occur since the ***acidity of C—H bond is enhanced particularly by the electron withdrawing power of the cyano (CN) moiety.***
3. Thus, **CN^-** designates a **highly specific catalyst** for the aforesaid reaction, since practically in an exceptional manner, it may essentially carry out the following ***three*** **cardial functions,** namely:
   - **it serves as a *nucleophile*;**
   - **its electron withdrawing ability profile allows the loss of the aldehyde proton (H^+);** and
   - **finally, it acts as a *leaving group.***
4. Besides, there are certain **thiazolium salts**  that can also **catalyze the reaction effectively.***
5. However, in this specific instance an *aliphatic aldehyde* may also be employed** (the products are invariably termed as the **'acyloins'**); and thus, the *mixtures* of **aliphatic and aromatic aldehydes** do yield the so-called mixed **α-hydroxy ketones.*****
6. Interestingly, the aforesaid reaction has also been performed successfully **without the cyanide ion (CN^-)** *i.e.,* by making use of the ***benzoylated cyanohydrin*** as one of the components in a **phase-transfer catalyzed phenomena.** Hence, by such means one may also obtain products from the ***'aldehydes'*** that usually do not undergo ***self-condense.******

Suggested Reading

Jack Jie: **A collection of Detailed Reaction Mechanisms,** Springer-Verlag, 2007.

Loudon GM: **Organic Chemistry,** 4th edn., Oxford University Press, New York, 2002.

March J: **Advanced Organic Chemistry**, 4th edn., John Wiley and Sons, New York, 2001.

Olah GA: **Friedel-Crafts and Related Reactions,** Vols. 1 & 2, Wiley, New York, 1963–64.

Taylor R: **Electrophilic Aromatic Substitution,** Wiley, New York, 1990.

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* Diederich and Lutter, *J Am Chem Soc.*, **111**: 8438, 1989.

** Matsumoto and Ohishi, *J Org Chem.*, **50**: 603, 1985.

*** Stetter and Dämbkes, *Synthesis*, 403, 1977.

**** Rozwadowska, *Tetrahedron,* **41**: 3135, 1985.

Chapter 7

Reactions Giving Saturated and Unsaturated Hydrocarbons

LESSONS AT A GLANCE

7.1 Introduction
7.2 Divergent Reactions Giving Saturated and Unsaturated Hydrocarbons
- 7.2.1 Birch Reduction
- 7.2.2 Clemmensen Reduction
- 7.2.3 The Chugaev Reaction [Tschugaeff Olefin Synthesis]
- 7.2.4 Cope Elimination Reaction [Cope Reaction]
- 7.2.5 Hoffmann Elimination Reaction [Hoffmann Degradation]
- 7.2.6 Kolbe Electrolytic Reaction [Kolbe's Electrooxidation]
- 7.2.7 McMurry Coupling [McMurry Reaction; De-Oxygen-Coupling]
- 7.2.8 The Peterson Olefination Reaction
- 7.2.9 Shapiro Reaction
- 7.2.10 Wolff-Kishner Reduction (Huang-Minlon Modification)
- 7.2.11 Ziemmermann Rearrangement (Di-π-Methane Rearrangement)

7.1 INTRODUCTION

In general, the **organic compounds** all comprise *carbon (C)*; however, they may also contain a wide spectrum of other elements. The extent of the prevailing ***chemical diversity*** has reached such a copious volume that one would appreciate to commence the humble beginning right from the so-called ***simplest organic compounds***, the **'hydrocarbons'**. The **hydrocarbons** are usually the **organic chemical entities** (*compounds*) that contain exclusively the *elements*: **Carbon** and **Hydrogen.**

In a broader sense, the **hydrocarbons** are invariably regarded as the ***parent substances*** from which a host of other **'organic compounds'** may be considered to be derived intelligently by the **organic chemists.** Besides, the **hydrocarbons** are duly categorized into *three* recognized forms, namely:

- **saturated hydrocarbons *viz.*, paraffins;**
- **unsaturated hydrocarbons *viz.*, olefins** and **acetylenes**; and
- **aliphatic-aromatic hydrocarbons *viz.*, benzene** and **toluene.**

7.2 DIVERGENT REACTIONS GIVING SATURATED AND UNSATURATED HYDROCARBONS

An attempt has been duly made to elaborate and discuss at length the following divergent types of reactions, appropriate examples, and mechanism of reaction, wherever possible, namely:

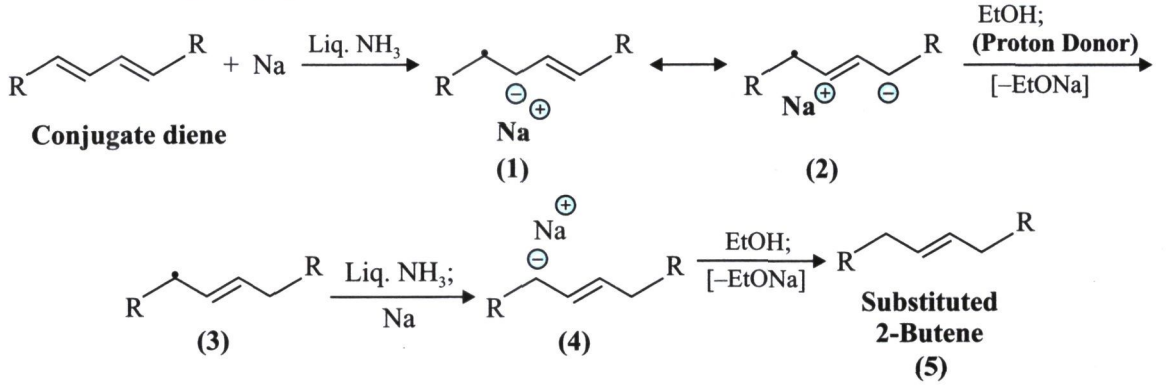
(*i*) **Birch Reduction,**
(*ii*) **Clemmensen Reduction,**
(*iii*) **The Chugaev Reaction,**
(*iv*) **Cope Elimination Reaction,**
(*v*) **Hoffmann Elimination Reaction** (Hoffmann **Degradation**),
(*vi*) **Kolbe Electrolytic Reaction,**
(*vii*) **McMurray Coupling,**
(*viii*) **The Peterson Olifination,**
(*ix*) **Shapiro Reaction,**
(*x*) **Wolf-Kischner Reduction,** and
(*xi*) **Ziemmermann Rearrangement (Di-π-methane Rearrangement),**

which shall now be treated individually in the sections that follows:

7.2.1 Birch Reduction*

The **Birch reduction** related to the **dienes** that undergo ***1,4-addition***; whereas, the **arenes** yield the ***unconjugated*** **cyclohexadienes** by *alkali metals* (*viz.*, **Na** or **Li**). Thus, this type of reactions are usually termed as **Birch reduction** that eventually occurs through the critical generation of an ***anion radical*** due to a **single electron transfer** from the *alkali metal* to the corresponding *substrate* as depicted under:

(a) Reduction of Conjugated Dienes



* Birch AJ: *J Chem Soc.*, 430–436, 1944.

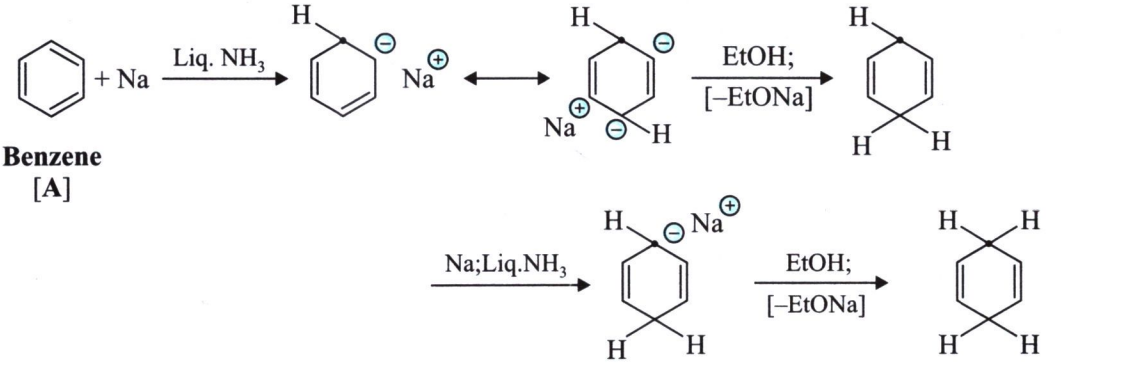
EXPLANATION

The various steps involved may be explained as under:

1. The reaction between a **conjugated diene** and **Na-metal** in the presence of liquified ammonia gives an intermediate (1) which gets interchanged to the **intermediate (2)**.
2. The resulting **intermediate (2)** on being treated with *ethanol* (a **proton donor**) eliminates a mole of *sodium ethoxide* (EtONa) thereby forming **2-butene-3-radical derivative (3)**, which on further treatment with liquified ammonia and Na-metal gives rise to the formation of **2-butene-3-sodium salt derivative (4).**
3. Finally, the **product (4)** on reaction with *EtOH* loses a mole of *sodium ethoxide* to give the desired product **substituted 2-butene (5).**

(b) Reduction of Arenes

Let us consider the following sequence of reactions starting from **benzene (A)** to yield **1,4-dihydrobenzene (B):**



EXPLANATION

The various sequential steps engaged in the above reactions may be explained as below:

1. **Benzene (A)** reacts with freshly cut/squeezed *Na-metal* pieces in the presence of *liquified ammonia* gives the **benzene-1-radical-2-anion sodium salt.**
2. The resulting product undergoes a reversible reaction to form **benzene-1-radical-4-anion-sodium salt,** which on being subjected to treatment with EtOH (ethanol) loses a mole of sodium ethoxide (EtONa) to form **1-radical-4-dihydrobenzene**.
3. The above product further reacts with a *Na-metal* and *liquified ammonia* to form **1-anion-sodium salt-4-dihydrobenzene,** which on treatment with EtOH (ethanol) gives the desired product **(B)** with the loss of a mole of sodium ethoxide (EtONa).

Salient Features of Birch Reduction

Following are the ***four*** **salient features** of the **Birch Reduction:**

1. **Birch reduction** is found to be extremely useful owing to its ***small steric requirement*** of the intended **reducing agents** *i.e.*, ***electrons***, that critically allow such reactions that are rather difficult and tedious to accomplish with other available reducing agents.

2. Interestingly, as the said reaction is usually performed in liquid ammonia (NH_3) **(bp–33°C),** the prevalent solubility profile of the **organic substrates** in *liquid–NH_3* at this low temperature is certainly *very negligible*. Hence, the particular usage of cosolvents, such as:

   • **Ether** • **Tetra-hydrofuran (THF) and** • **Dimethylethane (DME)**

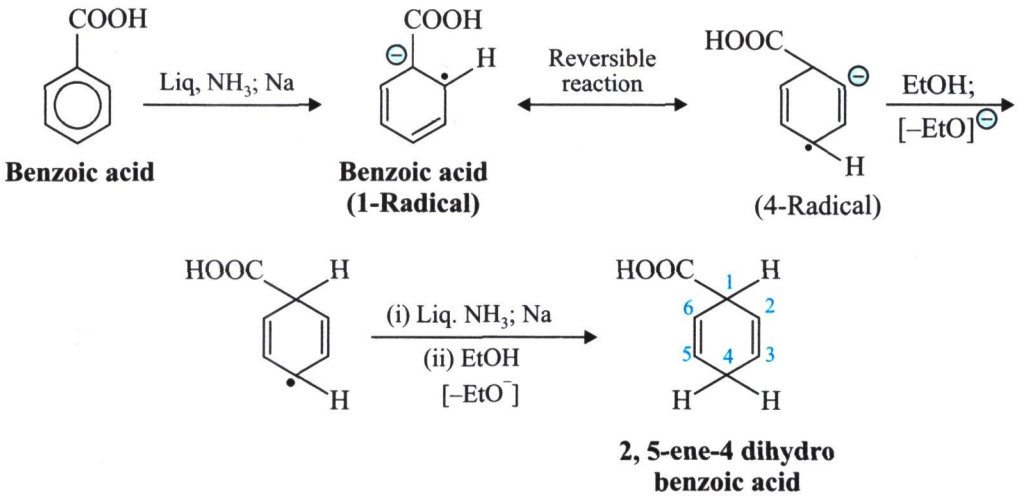
   are invariably made use of along with *liquid-ammonia* so as to improve upon the overall solubility of the substrate.

3. Amazingly, for the so-called *monosubstituted benzenes*, the ensuing ***reduction*** **is extremely stereoselective**; and, therefore, the observed selectivity is critically controlled by the **polar nature** of the *substituent(s)*. One may come across *two* different situations, namely:

   - **Substituent Being Electron Withdrawing in Character**—It helps to ***stabilize*** **the negative charge** of the inherent ***'anion' radical intermediate'***; and
   - **Substituent Being Electron Releasing in Character**—It aids in the ***destabilization*** of the ***'negative charge of the anion radical'.***

Thus, it governs overwhelmingly the ***regioselectivity*** of the reaction:

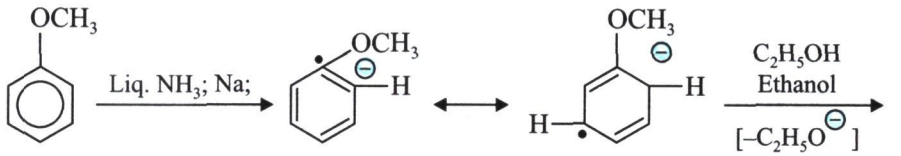
Example: 1. Benzoic Acid: having an ***electron withdrawing*** **—COOH moiety:**



Benzoic acid | **Benzoic acid (1-Radical)** | (4-Radical)

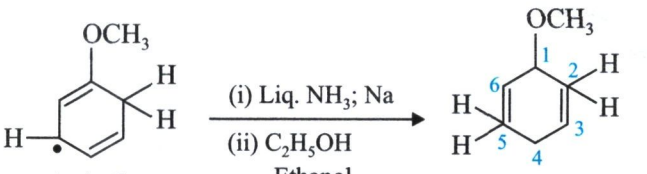
2, 5-ene-4 dihydro benzoic acid

2. Anisole: having an ***electron releasing*** **(—OCH_3) moiety:**



Anisole [Methoxy benzene] | **Anisole anion** (1-Radical) | **Anisole anion** (5-Radical) | **Ethoxide anion**

(Contd...)

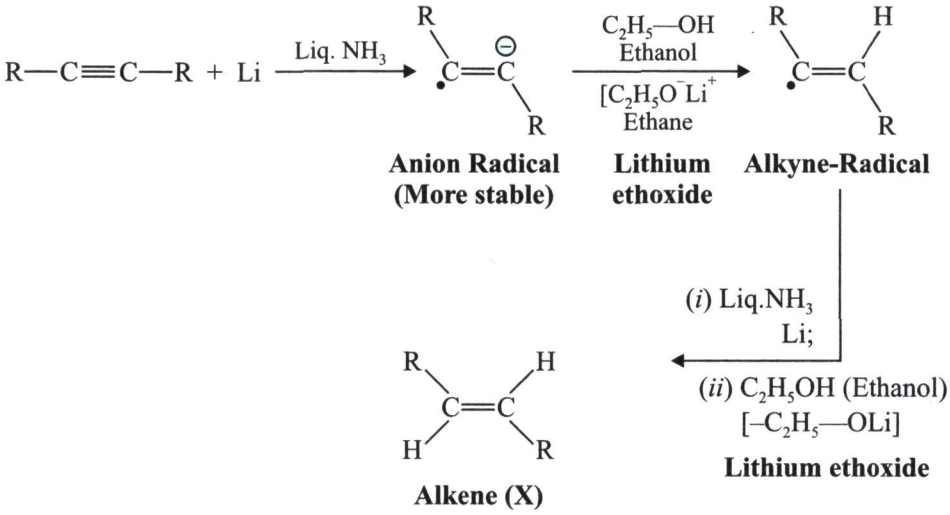


Anisole (5-Radical)

Ethoxide anion

3,6-ene-2,5-Tetra-hydroanisole

4. **Conversion of Internal Alkyne to form Alkene:** ***Birch reduction*** helps emphatically to **reduce the C≡C of an internal alkyne** to yield an **alkene (X)**, as given under:



Anion Radical (More stable)

Lithium ethoxide

Alkyne-Radical

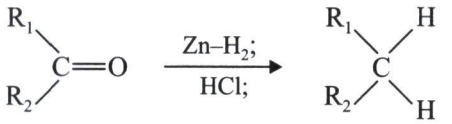
Lithium ethoxide

Alkene (X)

NOTE: **The Birch Reduction proves to be an extremely useful reaction in Organic Chemistry.**

7.2.2 Clemmensen Reduction

It essentially relates to the *reduction* of both **'aldehydes (-CHO)'** and **'ketones (⟩C═O)'** to the respective **methylene (-CH_2–) chemical entities** (*compounds*) in the presence of **Zn–Hg** (*amalgamated zinc*) and *hydrochloride acid (HCl)* as given under*



A ketone (Substituted)

Methylene substituted

* Clemmensen E: *Ber Dtsch Chem Gen,* **46**: 1837–43, 1913; Martin EL, *Org. Res.,* **1**: 155–209, 1942.

Remarks: The reducing agent comprising Zn–Hg and concentrated HCl or HCl–gas converts critically the ketoness (>C═O) and aldehydes (—CHO) into their respective hydrocarbons. Interestingly, the above cited reduction is of immense use for ketones containing either:

- Phenolic (Ar—OH) or • Carboxylic (—$CO^{-}OH$) moieties that usually remain absolutely unaffected during the process.

Points to Ponder: These essentially comprise:

(*i*) Obviously, the *ketones* **(>C═O)** are observed to be rather more susceptible and prone to undergo *reduction vis-a-vis* the **aldehydes.**

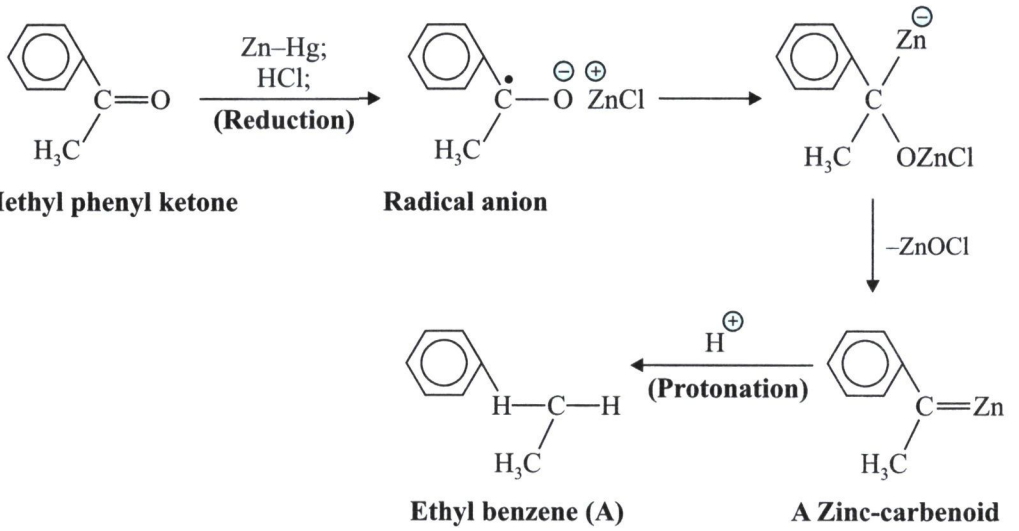
(*ii*) The status of **alcohols (R—OH)** are altogether different and **not** regarded to be the ***intermediates*** in the **Clemmensen reduction** since they prove to be *quite resistant to undergo* **any sort of reduction** under the above experimental parameters (*i.e.,* **using Na–Hg/HCl**); and, therefore, may be carried out in an independently generated **'alcohols'** in respect to the said **carbonyl (>C═O) substrates** (*organic compounds*).*

Mechanisms of Clemmensen Reduction

A survey of literature would reveal that the **mechanism of Clemmensen reduction** may be expatiated vividly under the following ***two*** **different ways,** namely:

- **By a sequence of one-electron and one-proton transfer reaction;** and
- **By transfer of an electron from metal (Zn) to carbonyl ( )CO) moiety of ketones yielding radical specie reacting finally to a zinc-carbenoid specie, which shall now be discussed individually in the sections that follows:**

(*a*) **By using a sequence of one-electron and one-proton transfer reaction:** Starting from **methyl phenyl ketone** and by making use of a sequence of ***one-electron*** **and** ***one-proton*** **transfer reaction** may finally obtain **ethyl benzene (A)** (*i.e., a higher homologue of the phenyl alkyl derivative*) as shown under:



Methyl phenyl ketone **Radical anion**

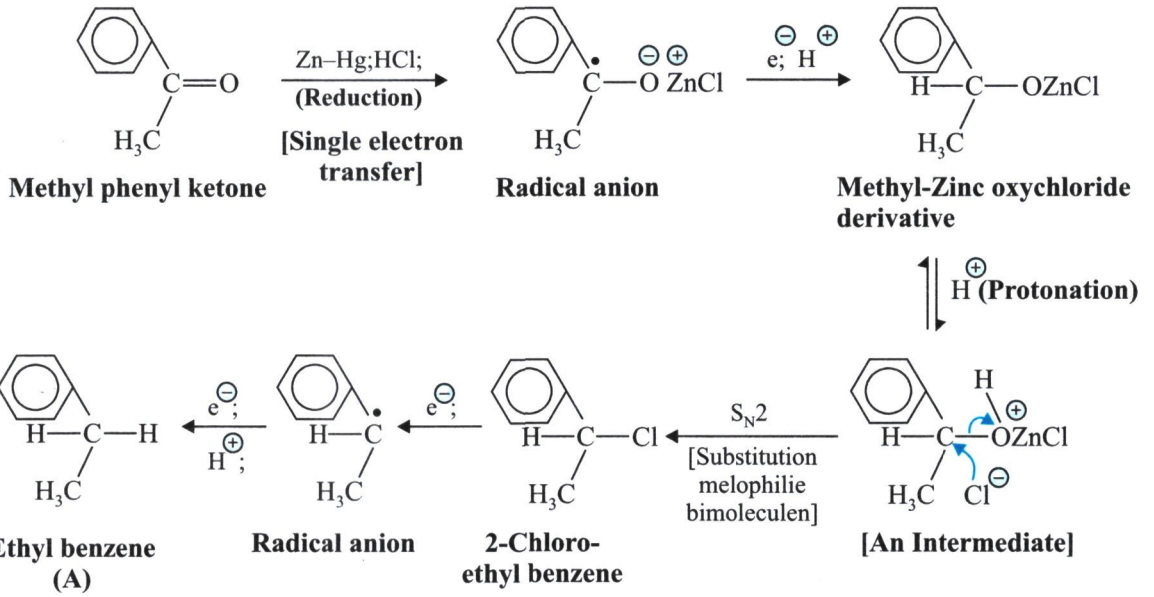
Ethyl benzene (A) **A Zinc-carbenoid**

* Burden J and Price RC, *J Chem. Soc. Commun,* 893–894, 1986.

EXPLANATION

1. *Reduction* of **methyl phenyl ketone** in the presence of Zn–Hg and HCl–gas yields the corresponding **radical anion**, which upon *one-electron* and *one-proton transfer reaction* gives the **zinc anion product.**
2. The resulting product eliminates a mole of **ZnOCl** (zinc oxychloride) to produce the desired **zinc carbenoid.**
3. **Protonation** (H^+) of **zinc carbenoid** gives rise to the formation of a higher homologue of the *phenyl-alkyl derivative i.e.,* **ethyl benzene (A).**

(*b*) **By Transfer of an Electron from Zn to Carbonyl (>C=O) moiety of ketone giving a radical specie reacting finally to a zinc-carbenoid specie:** It provides an *alternate mechanism* to produce the **ethyl benzene (A)** commencing from **methyl phenyl ketone** by transfer of an electron from Zn to carbonyl moiety of ketone giving a **radical specie** reacting ultimately to a zinc-carbenoid specie, as given below:



EXPLANATION

The various steps in the above sequential reactions may be explained as under:

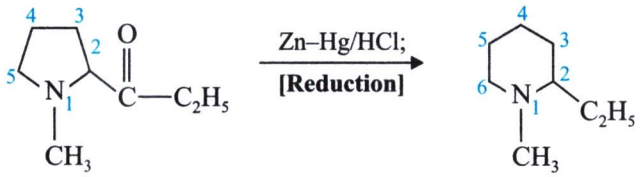
1. Reduction of **methyl phenyl ketone** with *Zn–Hg/HCl* gives the **radical anion,** which on addition of an **electron (e^-)** and **protonation (H^+)** yields **methyl zinc oxychloride derivative.**
2. The **resulting product** on further **protonation (H^+)** gives an intermediate (which being a *reversible reaction*); and undergoes the **S_N2–reaction mechanism** to produce **2-chloro ethyl benzene.**
3. The **end-product** obtained in *step (2)* on addition of an **electron (e^-)** gives a **radical**, which finally with an **electron (e^-)** addition followed by **protonation (H^+)** gives rise to the formation of **ethyl benzene (A).**

SPECIAL NOTE: **The Clemmensen reduction** specifically helps in the

- **expansion of a ring system;** and
- **contraction of a ring system,**

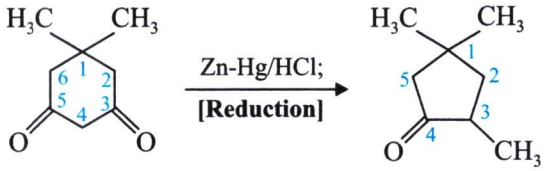
which may be further expatiated as under:

❑ **Expansion of a Ring System:** *Reduction* of **2-ethyl carbonyl–N–methyl pyrrole** with Zn–Hg/HCl gives **2-ethyl–N–methyl piperidine** *i.e.,* the **5-membered pyrrole ring** gets expanded to the **6-membered piperidine ring system.**



2-Ethyl carboxyl-N-methyl pyrrole **2-Ethyl-N-methyl piperidine**

❑ **Contraction of a Ring System:** *Reduction* of 1-dimethyl–3, 5-diketo-**cyclohexane** with Na–Hg/HCl yields the corresponding 5-membered product known as **1-dimethyl-3-methyl-4-keto-cyclopentane,** as given under:



1-Dimethyl-3,5-diketo cyclohexane **1-Dimethyl-3-methyl-4-keto-cyclopentane**

Thus, the *6-membered* **cyclohexane** ring system gets duly contracted to the *5-membered* **cyclopentane** ring system.*

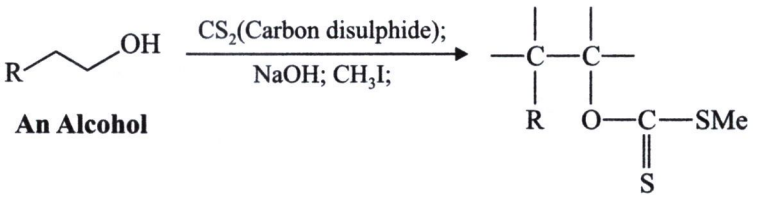
7.2.3 The Chugaev Reaction** [Tschugaeff Olefin Synthesis]

The Chugaev Reaction essentially involves the so-called ***thermal elimination*** of the **Xanthates** (*viz., methyl xanthates*) to the corresponding **'Olefins'** together with the formation of ***gaseous*** **carbon oxysulphide (COS)** and **thiol (R—SH)** as the by products.

[The above Reaction is named after the *Russian Organic Chemist*: Lev Aleksandrovich Chugaev [Tschugaeff)].

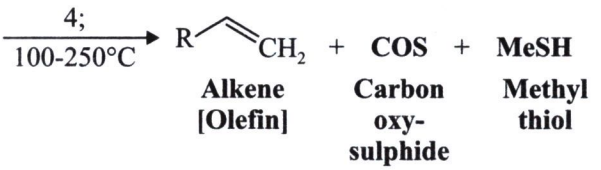
* Alessandrini L *et. al.*: *Steroids,* **69**: 789, 2004; Kohara T *et al., Synthesis,* 355, 2002.

** Chugaev (Tschugaeff) L, *Ber,* **32**: 3332, 1899; NaeeHR, *Org React.*, **12**: 57–100, 1962.



An Alcohol

R-Xanthate
[R = CH_3; Methyl xanthate]



Alkene [Olefin] | **Carbon oxy-sulphide** | **Methyl thiol**

EXPLANATION

1. An **alcohol** on being treated with *CS_2*, *NaOH*, and *methyl iodide* **(CH_3I)** yields a ***substituted* xanthate** (*R-xanthate*).
2. The **xanthate** when heated between **100–250°C** gives rise to the formation of one mole each of an **olefin** (*alkene*), **carbonoxy sulphide**, an **methyl thiol.***

Comments: These essentially include:

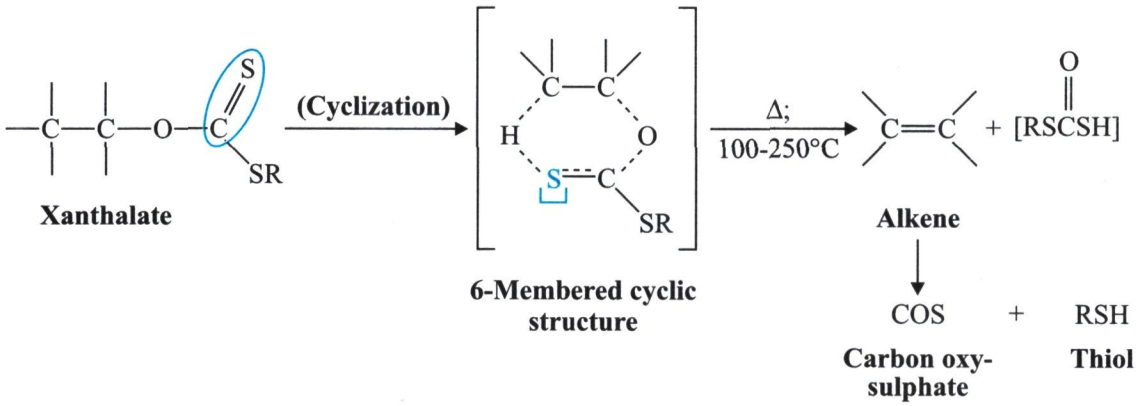
1. **Pyrolysis** (*i.e., thermolysis associated with exposure to a high temperature*) of the xanthalate to produce the *olefin*, *COS*, and *thiol* is called the ***Chugaev Reaction.***
2. It may be very much akin to the **pyrolysis of esters of carboxylic acids** (*e.g., hydro-acyloxy elimination*), an indiret method of accomplishing **dehydration of alcohols** (*e.g., hydro-hydroxy elimination*).
3. The temperatures needed with the **'xanthalates'** are definitely lower than with the ***indirect esters***, which is quite advantageous since the so-called:
   "possible isomerisation of the resulting *olefin* gets minimized."

Mechanism of Chugaev Reaction

It has been duly prover and ascertained that the underlying mechanism of *Chugaev Reaction* is **Ei-Type** (*i.e., **syn*-elimination**), critically involving a **6-membered cyclization state**, as evidenced by particular labelling of the ***xanthalate*** (starting material) by **34S′** and **^{13}C.**** Thus, we may have the following expression:

* For a method of preparing **xanthates** from **alcohols** in a *single-laboratory step*–see–Chan, Wong, Wong, *Synth Commun*, **19**: 547, 1989.

** Bader RFW and Bowns AN, *Cau J Chem.*, **39**: 346-358, 1961.



Remarks:

1. The **Xanthalate** undergoes *cyclization* to form an **intermediate** having a ***6-membered cyclic structure*** (with several *H-bonds* in it).
2. The resulting *intermediate* cyclized structure on heating yields:
   - **Alkene** and - **Substituted-sulpho thiocarboxylate.**

   i.e., one mole each.
3. The **'alkene'** (*olefin*) subsequently gives rise to the formation of one mole each of **carbon oxysulphate** and **substituted thiol.**

NOTE: **Initially, there was quite a bit of doubt as to which *'S–atom'* helped in the closure of the *6-membered ring*; however, now, it is amply proved and established (based on evidences) that as per the exhaustive investigative study of $^{34}S'$ and ^{13}C *isotope effects*—confirmed beyond any reasonable doubt that it is the *'C=S'* sulphur atom.**

Some More Cardinal Considerations of Chugaev Reaction

Following are a few more cardinal considerations of the **Chugaev Reaction,** such as

1. **Nature of the End-Product:** Obviously, the precise nature of the so-called **end-product** obtained *via* the **Chugaev Reaction** solely depends upon:

   "the exact nature of *'alcohol'* from which *'xanthalate'* has been derived".

   Example: There are *three* typical examples of **'alcohol variants'** that are being used in the **Chugaev Reaction:**

   (*a*) **Primary (1°) Alcohol**

   Primary Alcohol → Xanthate → Single Olefin

   (*b*) **Secondary (2°) Alcohol (Acyclic and Alicyclic)**

   Secondary Alcohol → Xanthate → Regioisomeric product and E/Z-Isomers

   (*c*) **Acyclic Substrate (compound)**

   Acyclic substrate → Xanthate → Olefin Mixtures

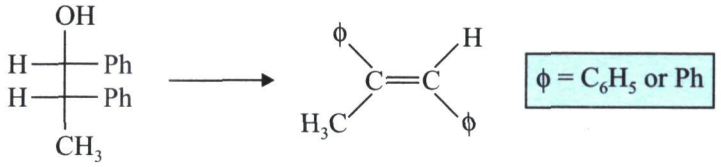
2. **Alicyclic Substrate (Organic Compounds):** Amazingly, in the specific instance of an **alicyclic substrate** (*compound*), the generation of the ***end-product*** is virtually determined by the **actual stereochemical requirement,** which means that:

   "the Xanthate moiety and the 3-H atom must by '*syn*' to each other"

3. Importantly, one may explicitly illustrate the *effect of the stereochemistry* upon the so called **elimination phenomenon** by performing the ***thermolysis of xanthates*** right from:

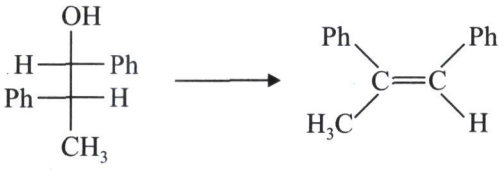
   '*Erythro*–and *Threo*–secondary alcohols'.*

(*a*)



***Erythro* - Alcohol** **E-Isomer**

(*b*)



***Threo* - Alcohol** **Z-Isomer**

NOTE:

1. **It has been duly observed that the *Chugaev Reaction* (*elimination*) fails to indulge in any sort of a rearrangement in its *C-skeleton.*****
2. **Besides, if the *Chugaev Elimination* comes into effect in more than one direction and on more than one H-atom duly present on the β-C-atom, the said reaction certainly proves to have *limited applicability.***

7.2.4 Cope Elimination Reaction [Cope Reaction]

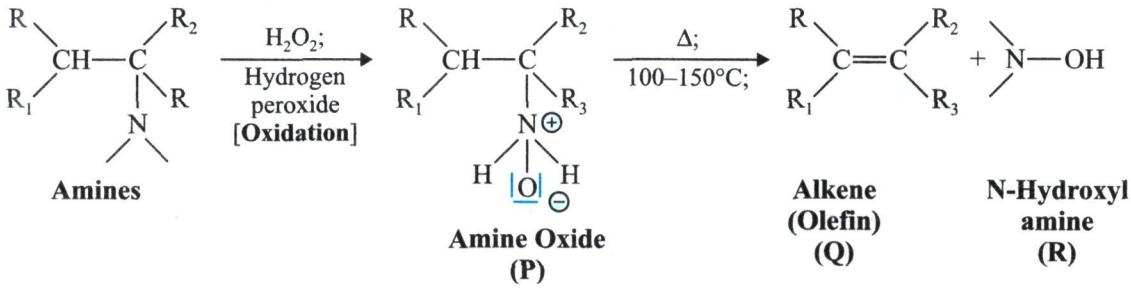
The **Cope elimination reaction** accounts for the specific **'cleavage of amine oxides'** *i.e.*, invariably referred to as the:

"hydro-(Dialkyloxidoammonio)–elimination."

In other words, it vividly represents the ***thermal elimination*** of the ensuing **amino oxides (P)** to the respective **alkenes (olefins) (Q),** and the **N-hydroxylamines (R),** as expressed under:

* Cram DF and Elhafez FAA, *J Am Chem Soc.*, **74**: 5828–35, 1952.

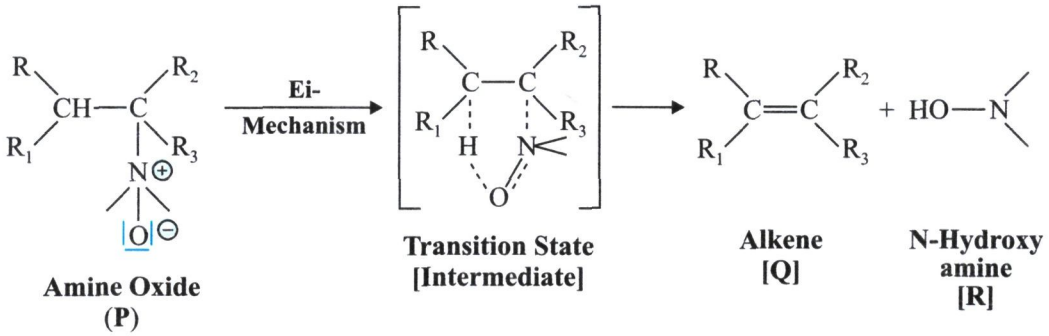
** Cops AC and Trumbull AR, *Org React,* **11**: 317–493, 1960.



Cleavage of amine oxide to yield an alkene and hydroxyl amine is seen

Mechanism of Cope Reaction

The **Cope reaction** critically proceeds *via* the **Ei-mechanism***,–thereby involving a **5-membered transition state (S)** according to the following sequence of reactions:



Explanation

1. The **amine oxide (P)** undergoes **Ei mechanism** to retain the **transition state** (an *intermediate)*.
2. The resulting **intermediate** gives *two* different products:
   - **an alkene (Q)**; and
   - **a N-hydroxy amine (R)**.

Points to Ponder: These essentially include:

1. **Cope reaction** is largely applicable for the preparation of the **'olefins'** since the prevailing ***mild reaction parameters*** helps to minimize drastically the following ***two*** **specific and cardinal** aspects, namely:
   - **ensuing side-reactions,** and
   - **Rearrangement of olefins.**

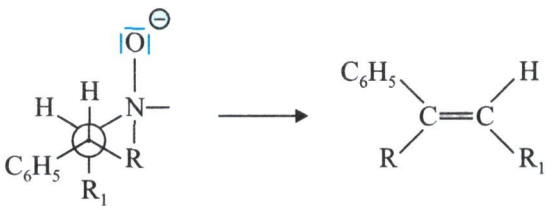
* That is, when *two* groups leave at about the same time and bond to each other, the designation is **Ei** in the **Ingold terminology**; and cyclo–D_E–D_NA_n is the *IUPAC system.*

2. **Cope reaction** predominantly designates the so-called–***'ring opening reaction'*** for **5 to 10 membered ring systems** (but the 6-membered ring systems as the exceptions).*

Stereochemistry of the Cope Reaction

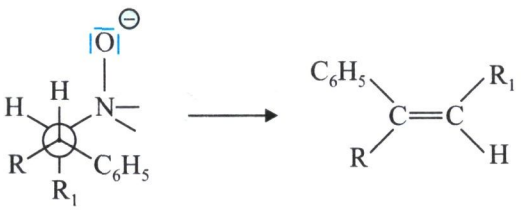
Based on the scientific evidences and logical explanations the **Cope reaction** (or **Cope elimination reaction**) does represent categorically the ***'stereoselective syn process'.***** However, the precise evidence originated right from the decomposition of the **amine oxides** duly derived from ***threo*-and *erythro*-2-amino-3-phenyl butane**, as given under:

(*i*)



***Threo* - Amine oxide (S)** **E- Isomer (T) (or *E-Olefin*)**

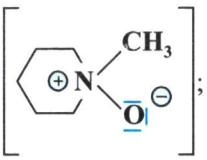
(*ii*)



***Erythro*-Amine Oxide** **Z- Isomer (V) (or Z-Olefin)**

EXPLANATION

1. **Reaction (*i*)** definitely exhibits *higher degree of selectivity* perhaps on account of the fact that the ***5-membered*** **transition state** certainly possesses ***less extent*** **of steric hindrance** *vis-a-vis* the *lesser selectivity* in the **Reaction (*ii*).**
2. Besides, the **Cope elimination reaction** may not prove to be successful by making use of the **amine oxides** duly obtained from the ***6-membered*** **heterocyclic amines,** such as:

N-methyl piperidine oxide  ; as it fails to proceed even *via* a ***5-membered*** **planar transition form** effectively.

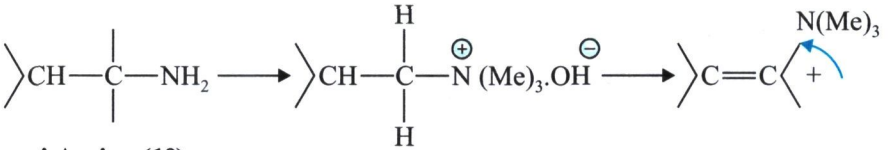
7.2.5 Hoffmann Elimination Reaction [Hoffmann Degradation]

It is also known as: **Hoffmann Elimination of Quaternary Ammonium Hydroxides.** Interestingly, when a quaternary ammonium **hydroxide** [$—\overset{\oplus}{N}(Me)_3 \cdot OH^{\ominus}$] is subjected to careful heating

* Cope AC *et al.*: *J Am Chem Soc.*, **82**: 4656, 1960; Cope AC *et al.*: *J Am Chem Soc.*, **82**: 4663, 1960.

** Gravestock MB *et al.* : *J Chem Soc Perkin*, **1**: 3292, 2000.

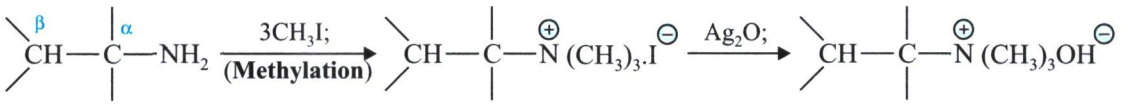
(100–200°C), a **β-elimination reaction*** comes into play to yield an ***'alkene'***—that may be subsequently ***distilled from the reaction mixture.*** Thus, one may use **primary (1°), secondary (2°), and tertiary (3°) amines** for carrying out the **Hoffmann Elimination Reaction**—as shown under:



***pri*-Amine (1°)** **Quaternary-Ammonium Hydroxide** **Alkene**

It is, however, pertinent to state here that the aforesaid reaction is duly initiated by the specific and critical generation of a ***'quaternary ammonium iodide*** **(II)** by successive methylation of **1°, 2°,** and **3° amines (I)** with *methyl iodide* **(CH_3I).** A follow-up treatment of **(II)** with *silver oxide (AgO)* in an aqueous medium gives **quaternary ammonium hydroxide (III),** as stated below:

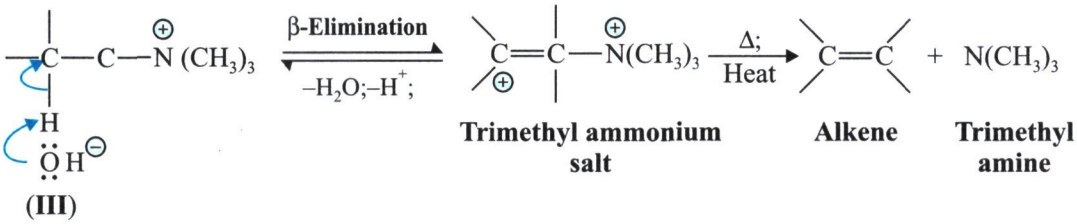
Thus we may have the following sequence of reactions:



1°-Amine (with β-H atom) (I) **Quaternary Ammonium Iodide (II)** **Quaternary Ammonium hydroxide (III)**

β–Elimination: The **β-elimination** of **quaternary ammonium hydroxide (III)** loses a mole each of *water* and *proton* (H^+) to yield the *trimethylammonium salt*, which upon careful heating gives a mole each of an ***alkene*** and ***trimethyl amine.***

We may express the reactions as shown under:



(III) **Trimethyl ammonium salt** **Alkene** **Trimethyl amine**

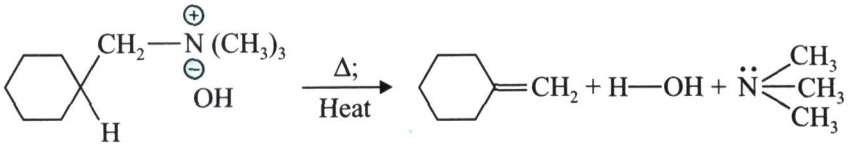
Another Classical Example of β-Elimination

In a particular instance, when a *quaternary ammonium hydroxide* is subjected to heat, a **β-elimination reaction** comes into play to produce an **alkene**—that may be distilled from the **reaction mixture.****

---

* Hoffmann AW: *Justus Liebigs Ann Chem.*, **78**: 253–286, 1851.

** Amazingly, this kind of *elimination* is termed as **Hoffmann Elimination,** after **August Wilheim Hoffmann (1818–1895)**—a renowned *German Chemist,* who became Professor at the Royal College of Chemistry in London (UK). Hoffmann was specifically noted for his excellent work on **'amines'.**

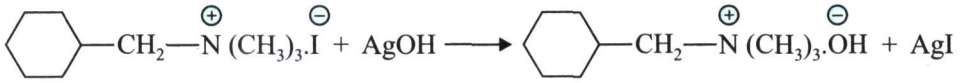


Quaternary ammonium hydroxide | **Methylene cyclohexane (Yield:74%)** | **Trimethyl amine**

Formation of Quaternary Ammonium Hydroxide: It has been duly ascertained that the critical usage of a **quaternary ammonium hydroxide** [$—\overset{\oplus}{N}(CH_3)_3 \cdot \overset{\ominus}{OH}$] as the *starting material* in the **Hoffmann elimination reactions** is being generated by the treatment of:

- **a quaternary ammonium salt**; and
- **silver hydroxide (AgOH)***,

as shown under:



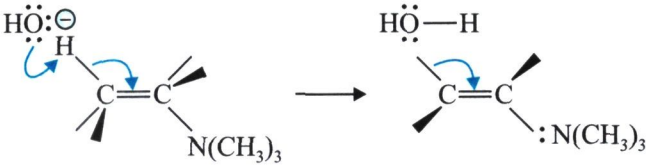
Quaternary ammonium iodide | **Silver hydroxide** | **Quaternary ammonium hydroxide** | **Silver iodide**

Comments:

1. Importantly, the **Hoffmann elimination reaction** is conceptually analogous to the E_2 *reaction* of the **alkyl halides** whereby a *proton* (**H^+**) and a *halide ion* (**X^-**) are duly knocked out; whereas, in the so-called **Hoffmann elimination**–a *proton* and a *tertiary amine* are duly eliminated.
2. Since the ***amine (—NH_2)*** **leaving moiety** happens to be extremely basic in nature; and, therefore, a relatively ***poor*** **leaving moiety,** the conditionalities of the **Hoffmann elimination reaction** are definitely found to be **typically harsh** in character.

Hoffmann Elimination: Occurs as an *Anti*-Elimination Reaction

In a broader perspective, very much akin to the *analogous E2-reaction* of the **alkyl halides** the so-called **Hoffmann elimination** invariably takes place as an ***anti*-elimination reaction,** as given below:



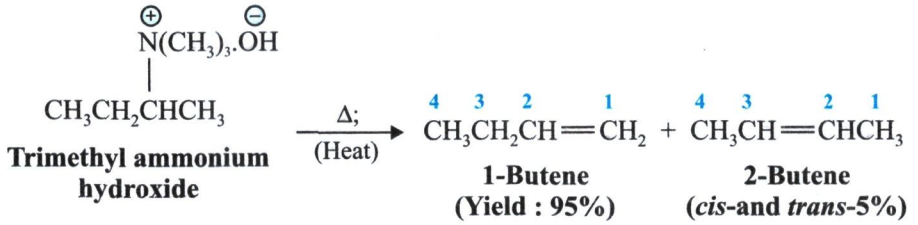
* **Silve Hydroxide (AgOH):** It may be formed by the interaction of *water* and *silver oxide (AgO)*.

Examples of Hoffmann Elimination Reaction

Let us examine the following ***three*** **cardinal examples** of **Hoffmann elimination reaction:**

(*a*) The **Hoffmann elimination,** quite in contrast to the respective **trimethylammonium salt** yields usually the **1-butene**:

We may have the following expression:

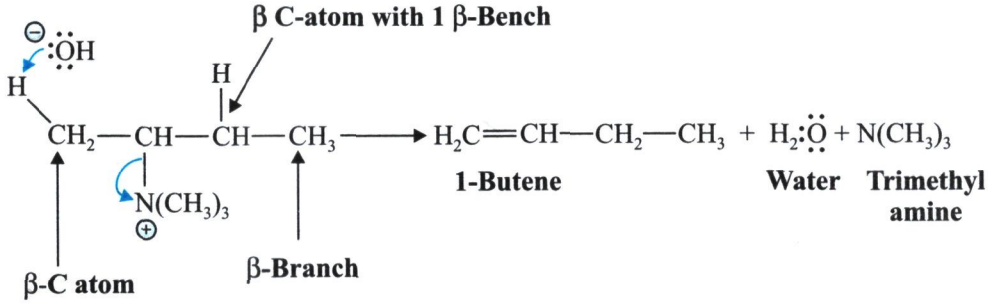


Trimethyl ammonium hydroxide

1-Butene (Yield : 95%)

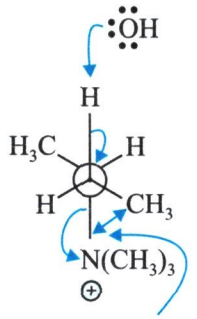
2-Butene (*cis*-and *trans*-5%)

(*b*) Generally, one may encounter the so-called **elimination of a trialkylammonium hydroxide taking place in order that the ensuing *base* duly abstracts a proton (H^+) from the β C–atom having virtually the least observed branching,** as depicted under:

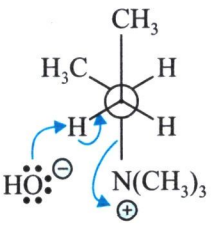


(*c*) **Regiochemistry of the Hoffmann Elimination Reaction:** To a certain degree of an acceptable explanation pertaining to the **regiochemistry of the Hoffmann elimination reaction** actually originates right from the critical and specific examination of the *possible transition states* for the said reaction.

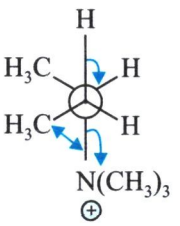
Let us look into the following *three* individual configurations showing the **regiochemistry** of the **Hoffmann Elimination reactions** *viz.,* **I, II and III.**



Severe van der Waals repulsion (I)

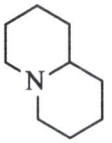


Not an *anti*-elimination (II)

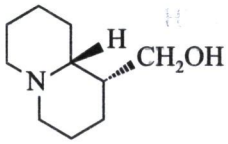


Severe van der Waals repulsion (III)

Mechanism of Hoffmann Elimination Reaction: In a typical situation when the **N–atom** is holding a common status to ***two*** **rings** *viz.*, **quinolizidine** then a **3rd series of elimination reaction** is required essentially in order to get rid of **N–atom** from the **olefin (double)** bond; and hence, the resultant product is observed to be a **'triene'.**



Quinolizidine

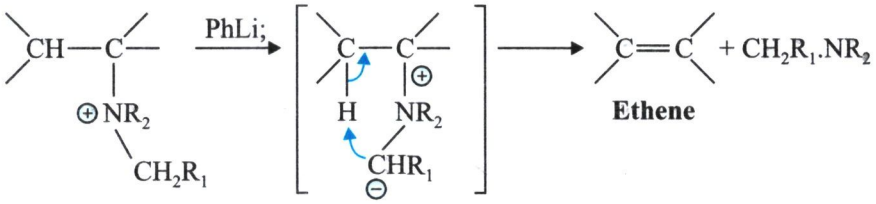


Lupinine (an '*alkaloid*')

In addition, there are quite a few examples wherein the molecule is being hindered largely, such as:

'a classical 5-membered E1-mechanism'

Thus, we may have the following expression.



Ethene

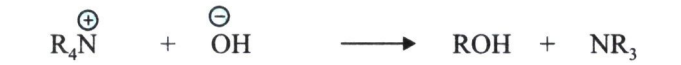
5-Membered
E_1-mechanism

NOTE: **The above mechanism is also called as 'α, β-Elimination'.**

Side-Reaction Associated with Elimination Reaction

It has been amply proven and established that a **side-reaction** gets invariably associated with the **Hoffmann elimination reaction.**

***Example*:** **Nucleophilic substitution** yields an **alcohol.**



Ammonium ion **Hydroxide ion** **Alcohol** **Trimethyl amine**

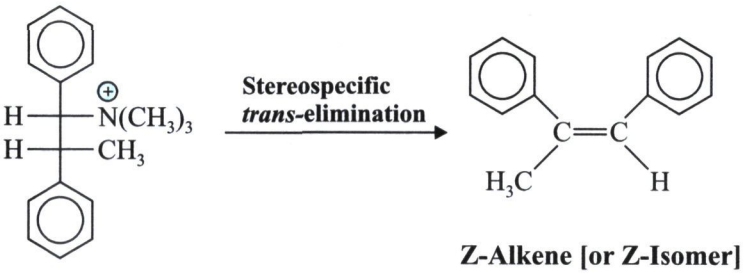
Thus, the series of reactions that are essentially required for the specific generation of **trimethylamine [$N(CH_3)_3$]** throws a sufficient light with respect to the **extent of addition of a particular *N–atom*** *i.e.*, an important application pertaining to the so-called *structural analysis of the various naturally occurring alkaloids.*

Stereochemistry of Hoffmann Elimination Reaction

It is also called the **'evidence for E_2-Reaction'**, and it relates to a **stereospecific *trans*-elimination** usually observed to take place when the **trimethylamine [$N(CH_3)_3$]** and **water (H_2O)** are eliminated duly right from:

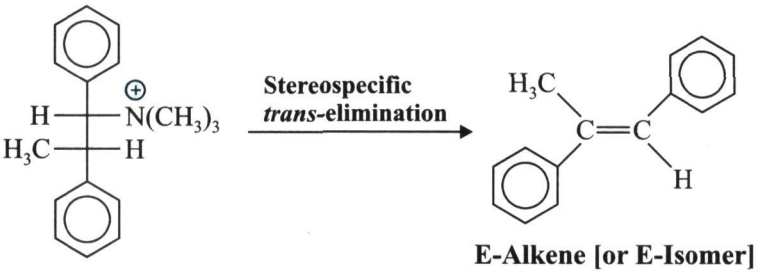
"*erythro*-and *erythro*-forms of trimethyl–1, 2-diphenyl propyl, ammonium iodide on being reacted with sodium ethoxide [EtONa]."

Thus, we may have the following expressions:



Trimethyl-1,2-diphenyl-propyl ammonium ion [*Erytho*-form]

Z-Alkene [or Z-Isomer]



Trimethyl-1,2-diphenyl-propyl ammonium ion [*Erytho*-form]

E-Alkene [or E-Isomer]

Thus, the above explicit illustration does provide an evidence very much favouring the **E_2-mechanism.**

Two Important Rules Governing the Hoffmann Elimination Reaction

There are *two* extremely vital and important rules that predominantly govern the **Hoffmann elimination reaction,** namely:

- **Zaitsev's Rule,** and
- **Hoffmann Rule,**

which shall now be discussed separately as under:

(*a*) Zaitsev's Rule

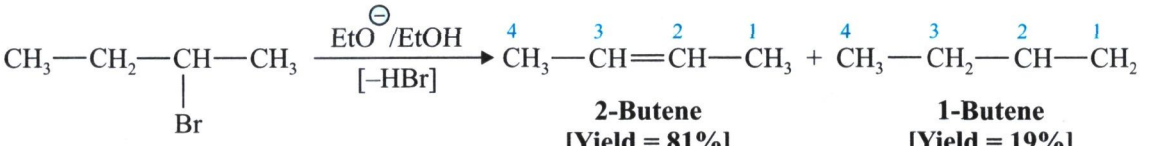
Based on the scientific evidences and logical explanations it has been duly observed that:

"Using an array of substrates—the elimination reaction can occur in more than one ways".

Besides, the path of direction duly adapted by the **'new olefinic (double) bond'** invariably being decided precisely by the so-called ***'relative stabilities'*** of the resultant ***'alkene products'*** *i.e.,* by the **Zaitsev's Rule.**

Hence, according to the **Zaitsev's Rule**—when *two* **β-and β′-C atoms** happen to be present in the *substrate (*or organic compound),–the **β-elimination** comes into play in ***two* possible products**; of which the ***'alkene'*** having comparatively more substituents located strategically at the **olefinic C-atoms** (or *double bonded carbons*) is found to be **more stable** in nature.

Thus, we may have the following expressions:



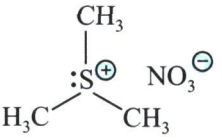
(*b*) Hoffmann Rule

A survey of literature reveals that the **Hoffmann Rule** is considered to be an exception to:

- **Saytzeff's Rule**; or
- **Zaitsev's Rule**

❑ **Saytzeff's Rule** (or **Zaitsev's Rule**) relates to the critical observations that one may have an access to a ***less substituted*** **alkene product** (as a *major component*) right from the **base-induced elimination:**

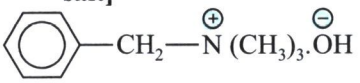
- **Sulphonium salts** *e.g.*,



Trimethyl sulphonium nitrate

[A sulphonium salt]

- **Quaternary ammonium salts** *e.g.*,

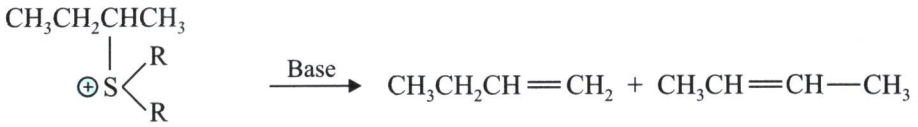


Benzyltri-methyl ammonium hydroxide

[A Quaternary ammonium salt]

Examples: Let us consider the following *two* typical examples:

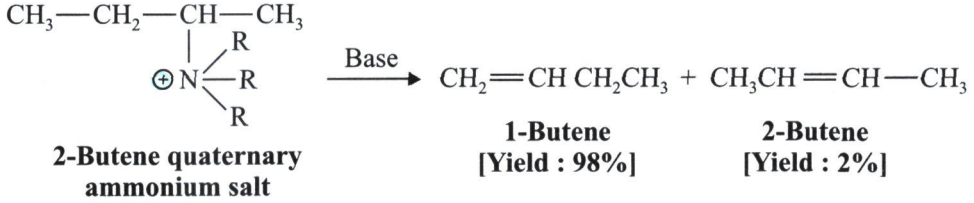
(*i*)



That is the conversion of 2-butane sulphonium salt in the presence of a suitable *base* yields a mole each of:

- **1-butene (Yield : 74%)**; and
- **2-butene (Yield : 26%)**.

(*ii*)



Thus, the actual conversion of **2-butene quaternary ammonium salt** in the presence of an appropriate base gives one mole each of:

- **1-butene (Yield : 98%)**; and
- **2-butene (Yield : 2%).**

NOTE: **The most plausible explanation for the observed differences between the above *two* elimination reactions [(*a*) and (*b*)] from an *alkyl bromide* (*i.e.*, 2-bromobutane) [according to the *Saytzeff or Zaitsev's Rule*); and also from a *quaternary ammonium ion* (*i.e.*, 2-butane quaternary ammonium salt) [as per the *Hoffmann's Rule*] has emerged to be the 'poor leaving moiety profile of the amino (—NH_2), functional group *vis-a-vis* the bromide (Br) group'.**

7.2.6 Kolbe Electrolytic Reaction [Kolbe's Electrooxidation]

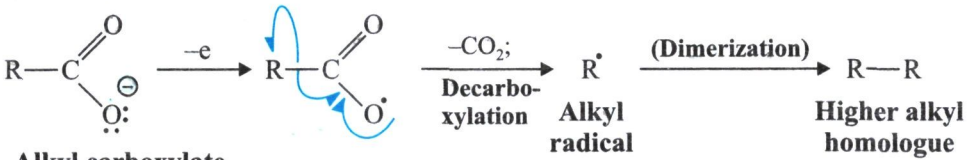
In reality, the **carboxylates** (or **carboxylic acid salts**) do possess reasonably **high electron densities** since the —**$COD^{\ominus}$ moiety** is responsible for attributing a relatively low ***oxidation potential***. Perhaps this could be the *valid reason* why the **carboxylic acid salts** invariably undergo a rapid and convenient **electrooxidation phenomenon.** Nevertheless, these *oxidative reactions* may ultimately give rise to the production of **altogether different products** *i.e.*, solely dependent upon the *reaction conditionalities.*

Example: In a particular instance, when an extremely concentrated ***acidic solution of*** **$RCOO^{\ominus}$** (*alkyl carboxylate anion*) is being carefully **oxidized** specifically at an ***'inert anode'*** *viz.*, **Pt-under high-current density** and also in the virtual absence of other host of ***nucleopiles***, the *major product* being the **hydrocarbon [R—R];** and hence, the reaction is usually termed as **Kolbe's Electro-oxidation [or Kolbe Electrolytic Reaction].**

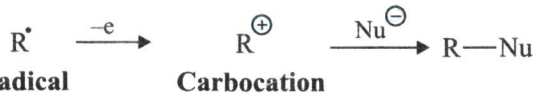
❑ Kolbe's Electrooxidation Under High-Current Density

In a specific instance when the *oxidation* is performed meticulously under **high potential** and also in the presence of a **strong nucleophile** ($Nu^{\ominus}$)—one may eventually accomplish **R—Nu** as the **major end-product.**

We may express the various sequential reactions as under:

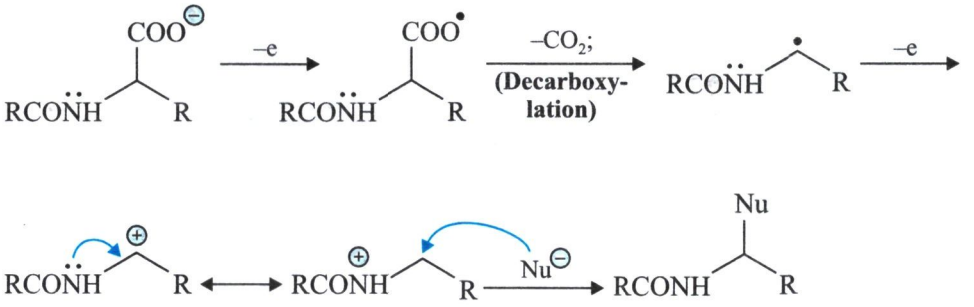


In another situation, when the ***oxidation*** is performed duly under the influence of **high potential,** the **radical 'R'** gets further *oxidized* to the corresponding **carbocation $R^{\oplus}$**, as given under:



Nevertheless, the critical generation of the products **R—Nu** may be further favoured and influenced by the definite presence of a ***'carbocation stabilizing substituent'*** in the respective **carboxylate ion [—COO^{-}].**

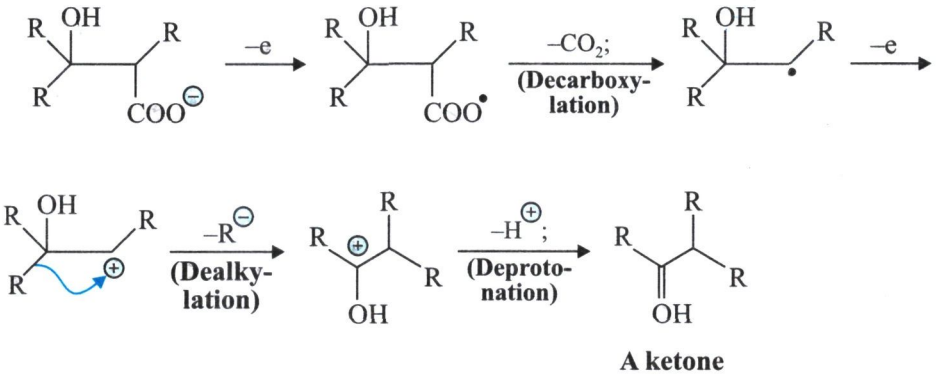
Example:



Carbocation
[Intermediate]

Thus, when a **carbocation intermediate** is duly formed, there exists a greater chances of **Wagner-Meerwin rearrangement** to get *enhanced significantly*.

Example:



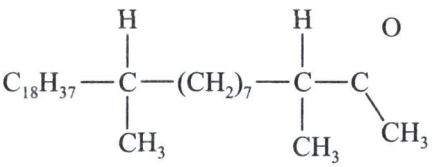
A ketone

Comments: The various aforesaid sequence of reactions actually do provide an ample evidence in support of the so-called **'radical mechanism'**—that are virtually based upon a good number of scientific and logical findings.

Kolbe's Electrolytic Synthesis

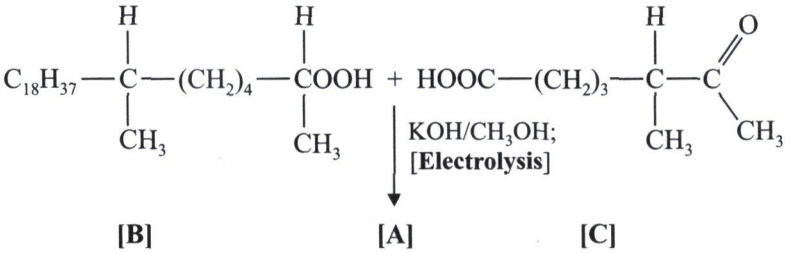
Importantly, the **Kolbe's electrolytic synthesis** may be illustrated intelligently by studying the synthesis of:

"3,11-dimethyl-2-nanocosanone (A)"



[A]

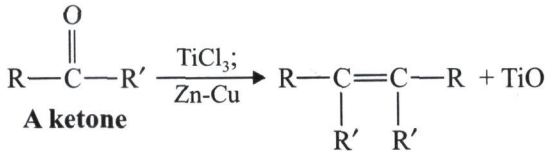
Product [A] represents a ***'sex-pheromone'**** for the German Cockroach, duly obtained from **6-methyl tetra cosanoic acid (B)** having *three* equivalents of 5-methyl-6-heptanoic acid (C) to yield **42%** of the desired product,** as given under:



7.2.7 McMurry Coupling*** [McMurry Reaction; De-Oxygen-Coupling]

The **McMurry coupling** (or **McMurry reaction**) refers to a ***reductive coupling*** critically involving the **olefination** of *carbonyls* (>C=O) with ***covalent*** **titanium ($TiCl_3$, titanium trichloride)** and a **Zn–Cu couple.**

We may have the following expression:



In other words, both **aldehydes (-CHO)** and **ketones (>C=O)** either *aromatic* and *aliphatic* (also includes the **'cyclic ketones'**) may be converted in reasonably high yields to the respective: **dimeric alkenes** by careful treatment with a **Zn–Cu couple.****

NOTE:

1. **The reagent produced in this manner is known as—'low-valent titanium Reagent'.**
2. **Other allied reagents can also be used effectively *e.g.*,**
   - **From Mg and a $TiCl_3$—THF complex;**
   - **From $TiCl_4$ and Zn or Mg;**
   - **From $TiCl_3$ and $LiAlH_4$;**
   - **From $TiCl_3$ and lamellar potassium graphite;**
   - **From $TiCl_3$ and K or Li; and**
   - **From $TiCl_3$ and Zn-Me_3SiCl.**

* **Pheromone:** A substance secreted by an organism to affect the behaviour or development of other members of the same species, **sex-pheromones**—which attract the opposite sex formating are used in monitoring certain insects.

** Seidel W and Schafer HJ: *Chem Ber.*, **113**: 451–56, 1981.

*** McMurry: *Chem Rev.*, **89**: 1513–1524, 1989.

**** McMurry JE *et al.* : *J Org Chem.*, **43**: 3225, 1978.

Mechanisms of McCurry Coupling

A good number of mechanisms of **McCurry coupling** have been reported; however, the ***single-electron transfer***—crucially induced by the so-called **'low-valent titanium specie'** does put forward a logical explanation for the mechanism of the said reaction.

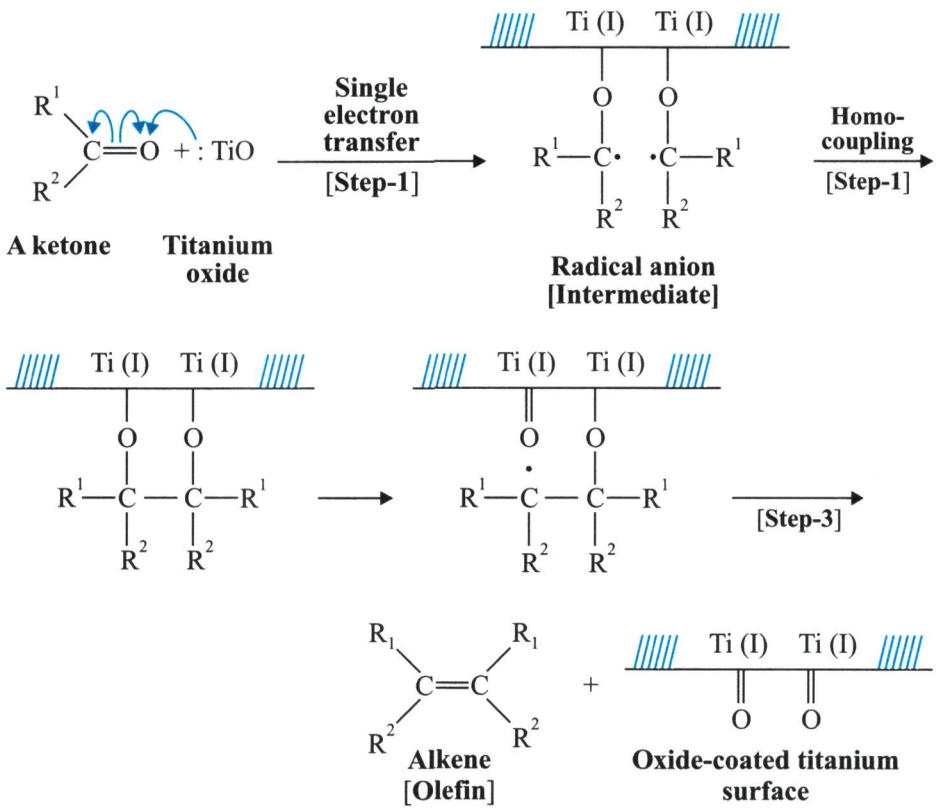
Let us examine the *three* sequential steps involved individually:

Step 1: The very first step of the **McCurry coupling reaction** relates to the binding of the **carbonyl (>C=O) substrate** to the available *titanium surface* exclusively. Thus, the **single electron** gets duly transferred right from **Titanium** (*i.e.,* **low-valent specie**) to the corresponding **carbonyl (>C=O)** moiety;

Step 2: Reduction of the **carbonyl (>C=O) moiety** to a *radical species* and subsequent oxidation of **titanium.** In this way the *two* **radical species** get *dimerised* solely to give rise to the formation of a **titanium pinacolate** like intermediate duly **coordinated to titanium**; and

Step 3: Formation of an **alkene** (*olefin*) and a **titanium oxide (TiO)** obtained by the cessation of the **C—O bonds.**

The various reactions involved in the above *three* sequential steps may be shown as under:



Comments: Amazingly, the ***intermolecular*** **McMurry coupling reaction** eventually produces either:

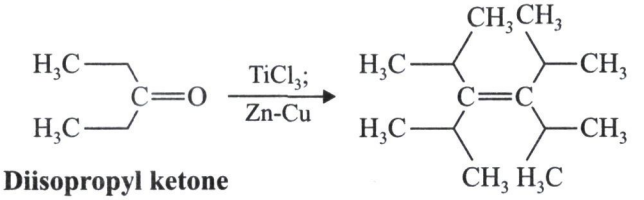
- **symmetric products**; or
- **ring systems.**

Nevertheless, it has been observed that under the influence of most suitable experimental parameters, preferentially at **low temperatures,** the ***C—O bond*** fails to undergo any sort of cleavage; and hence, the product is found to be a **'vicinal diol'.***

Besides, the extremely ***strained and substituted*** **alkenes** are duly synthesized by means of the **McCurry coupling reaction** efficaciously.

Example: Following is a classical example of wherein *two* moles of **diisopropyl ketone (I)** on being subjected to **McCurry reaction** yields **tetra-isopropylethene (II)** up to an yield of 78%.**

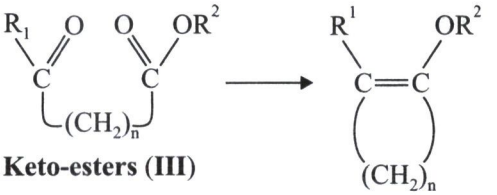
Thus, we may have the expression as stated below:



Diisopropyl ketone (I)

Tetra isopropyl ethene (II)

Likewise, the **enol ethers (IV)** may also be accomplished by the **McCurry coupling reaction** starting from the **ketoesters (III)**, as depicted under:



Keto-esters (III)

Enol ethers (IV)

NOTE: **In general, the importance of the *McCurry coupling reaction* in the domain of *'Organic Chemistry'* is of great help towards the synthesis of an array of useful chemical entities (*compounds*).*****

7.2.8 The Peterson Olefination Reaction

It is also known as the **'Alkylidene–de–oxo–bisubstitution'** reaction. In the **Peterson Olefination reaction******** the *lithio* **(Li)** [or sometimes *magnetio* **(Mg)**] derivative of a *trialkylsilane* adds on to an:

* Corey EJ *et al.*: *J Org Chem.*, **41**: 260–65, 1976.

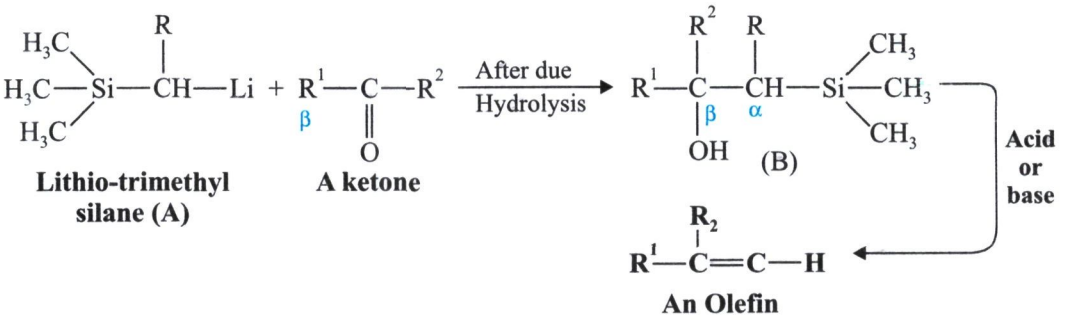
** McMurry JE *et al.*: *J Org. Chem.*, **54**: 3748–3749, 1989.

*** Duan XF *et al.*: *J Org Chem.*, **71**: 9873–76, 2006.

**** Peterson: *J Org Chem.*, **33**: 780, 1968.

• **Aldehyde (—CHO)** **or** • **Ketone (>C=O)**

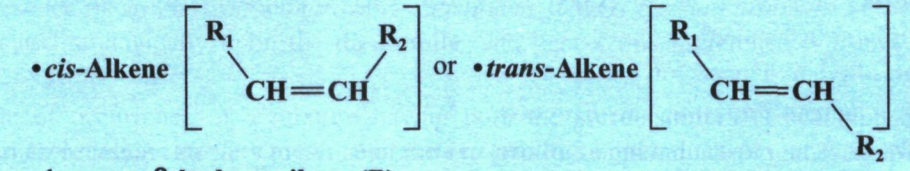
to produce a **β-hydroxysilane**, that eventually knocks out a mole of water, or may be made to do so by subjecting it to the treatment with *acid* or *base*, to yield an **olefin** (or **double bond**), as shown below:



Lithio-trimethyl silane (A) **A ketone** **An Olefin**

Thus, the interaction of **lithio-trimethyl silane (A)** and a *ketone* after careful *hydrolysis* gives rise to the formation of a **β-hydroxysilane (B),** which on further treatment with an **acid** or **base** yields an **olefin** (*i.e.*, a *substituted olefin*).

Remarks: In general, one may make use of the **Peterson Olefination reaction** to obtain either:



duly from the same β-hydroxysilane (B).

It is, however pertinent to state here that when the so-called **β-hydroxysilane (B)** is carefully subjected to treatment within an ***acidic*** **environment**, an ***alkene*** is produced, but if the same is treated under a ***basic*** **environment**, an ***alkene*** having **opposite stereochemistry** is obtained.

Mechanisms of Peterson Olefination Reactions

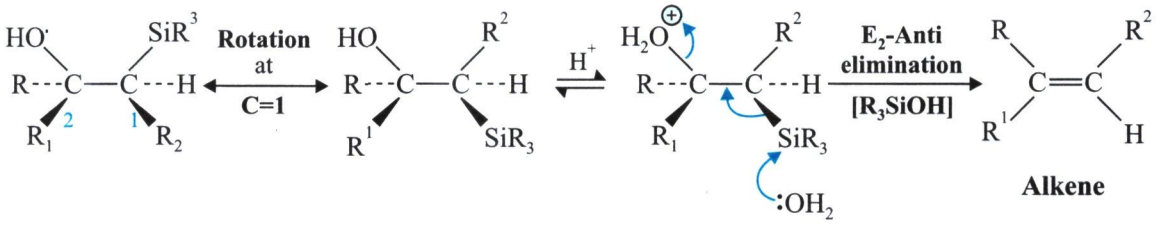
In true sense, it is absolutely relevant and justifiable to show the precise and exact mechanisms involved in the **Peterson olefination reaction** under:

- **Acidic elimination (Scheme–1)**; and
- **Basic elimination (Scheme–2),**

as given under:

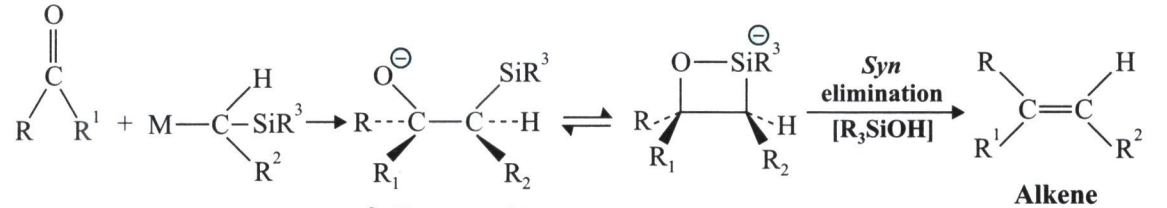
Elimination Under Acidic Environment

When **β-hydroxysilane** is carefully treated with **protonation (H^+)** in an *acidic medium*, it gives rise to the formation of an 'alkene' as shown under:



Elimination Under Basic Environment

When **β-hydroxysilane** is being treated with a **base**, the critical formation of **β-silyl alkoxide** as an intermediate that eventually undergoes the typical ***syn*-elimination** to yield the desired product **'alkene'**, as given below:



β-Silylalkoxide
[An intermediate]

Remarks: Based on the aforesaid sequential reaction steps involved one may observe explicitly that when either:

- **the alkyl hydrogen**; or
- **the electron-donating substituents,**

are found to be present having an **α-silyl carbanions,** the overall **stereochemical outcome** of the **Peterson Olefination reaction** may be controlled effectively by virtue of the fact that:

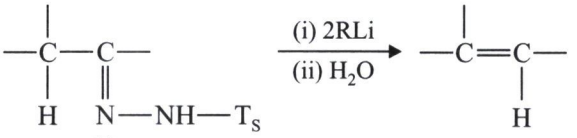
"at a low temperature regimen the elimination phenomenon is markedly slow and sluggish in nature."

Contrarily, when an **α-silyl carbanion** does contain the so-called **electron withdrawing substituents**, the ***'alkene'*** is duly formed readily (directly) by means of the Peterson **Olefination reaction** predominantly.

7.2.9 Shapiro Reaction

It represents the decomposition of **toluene-*p*-sulphonyl hydrazones (I)** and thus, we may have the following expressions:

(*a*)



(I) **Alkene**

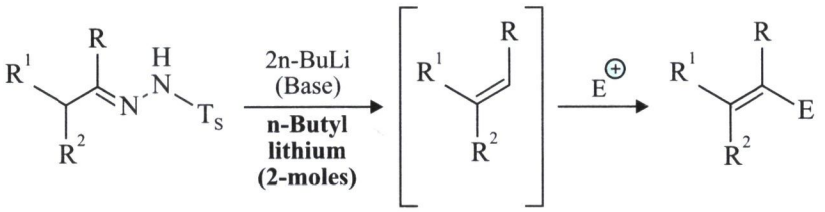
Comments: Treatment of the **tosylhydrazone** with either an **aldehyde** or a **ketone** in the presence of a strong base precisely leads to the formation of an **'alkene'** (or *olefin*),—the reaction being predominantly an *elimination reaction* accompanied by a **Hydrogen Shift.***

The aforesaid reaction has been successfully applied to **tosylhydrazones** of an array of *'aldehydes'* and *'ketones'*. The most useful procedure involves synthetically the critical treatment of the *substrate* with a minimum of **2-equivalents** of an ***organolithium*** *compound* (invariably **methyl lithium, CH_3Li**) dissolved in ***hexane*** or ***tetramethylenediamine.***

NOTE: **The aforesaid method provides good yields of *alkenes* without any sort of *side reactions*; and where a choice is possible, mostly gives the less highly substituted 'olefin.'**

(*b*) The **Shapiro Reaction** essentially involves the critical conversion of either a ***'ketone* (>C=O),** or an ***'aldehyde (—CHO)'*** respectively into an **'alkene'** *via* an ***intermediate*** **hydrazone** in the presence of ***two*** **equivalents of a strong base.*****

Thus, we may have the following expression:



Intermediate

Remarks: Evidence from the literature reveals that the **Shapiro reaction**† represents a variant of the so-called **Bamford-Stevens reaction.******** Importantly, the **Shapiro reaction**† makes use of such *bases* as:

- **Alkyl Lithium (*n*-BuLi) and**
- **Grignard Reagents (CH_3–Mg–I);**

whereas, the corresponding **Bamford-Stevens reaction** uses an altogether different kind of *bases* as:

- **Na**
- **$NaOCH_3$**
- **LiH** and
- **$NaNH_2$.**

Important Observations

These essentially include:

- **Shapiro Reaction** takes care of the **less substituted olefins** yielding the so-called ***'kinetic products'***; and

* Adlington and Baviett: *Acc Chem Res,* **16**: 55–59, 1983.

** Stenker and Bond, *Tetrahedron Lett.,* 1815, 1975.

*** Shapiro RH *et al.*: *J Am Chem Soc.,* **89**: 471, 1967; Shapiro RH and Health MJ, *JAm Chem Soc,* **89**: 5734, 1967.

**** Bamford WR and Stevens TS: *J Chem Soc.,* 4735, 1952.

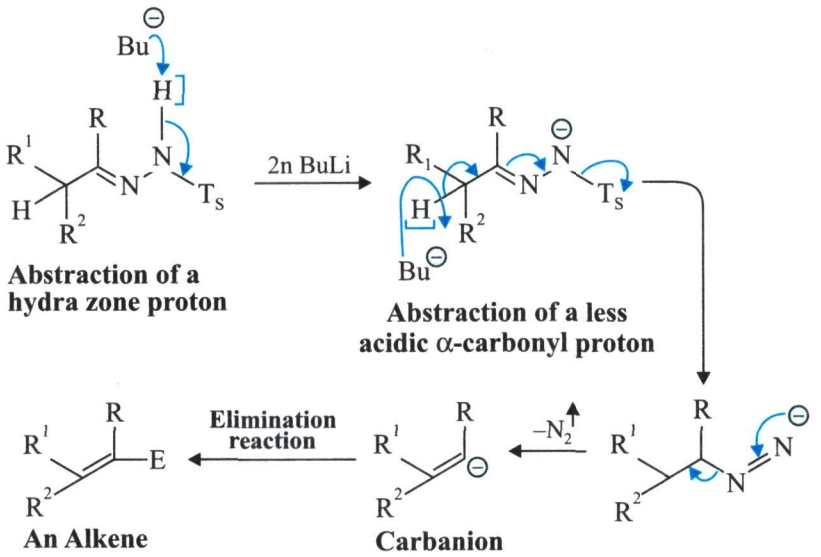
† Shapiro RH *et al.*: *J Am Chem Soc.,* **89**: 471, 1967; Shapiro RH and Health MJ, *JAm Chem Soc.,* **89**: 5734, 1967.

❑ **Bamford-Stevens Reaction** entails the **more substituted olefins** giving rise to the formation of the ***'theromodynamic product'***.

Mechanism of Shapiro-Reaction

Based on the scientific evidences and supported by logical explanations we may explain the **mechanism of the shapira reaction** that essentially involves the interaction taking place between a **ketone/ aldehyde** and ***p*-toluene sulphonyl-hydrazide*** to yield the respective ***p*-toluene sulphonyl hydrazone** [*i.e.*, either **imine** (—NH—) or **hydrazone** $\left(\text{>CH—}\overset{|}{\text{C}}\text{=N—NH—Ts}\right)$] aptly followed by the *abstraction* of a **hydrazone proton** primarily; and subsequently, the so-called availability of a ***less acidic* α-carbonyl proton** by the aid of ***two* equivalents of a strong base *viz.*, *n*-butyllithium (*n*-BuLi)** thereby yielding a ***carbanion*** that eventually undergoes a further **elimination reaction** to produce an **olefinic (C=C) bond.** Thus, leading to the ultimate conversion of the respective **(I) into (II)****.

Hydrazone Moiety (I) ⟶ Lithium Diazonium Moiety (II) we may express the various sequential steps involved in the entire episode as given under:



7.2.10 Wolff-Kishner Reduction*** (Huang-Minlon Modification)

The **semicarbazones** of *carbonyl* (>C=O) *chemical entities* (*viz.*, [**aldehydes** (—CHO) or **ketones** (>C=O)] on being subjected to heat with $NaOC_2H_5$ *(sodium ethoxide)* or other *strong bases* in a sealed tube get duly converted to the respective **methylene ($-CH_2-$) moiety** at *200°C*; and hence,

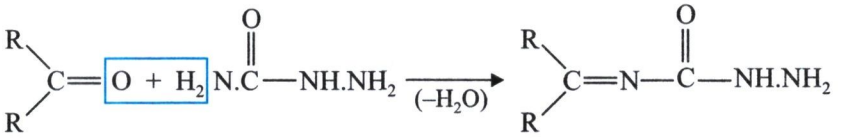
---

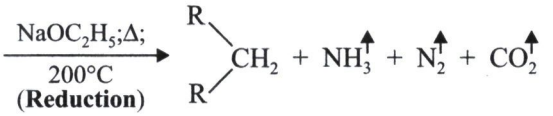
* **Organic Synthesis,** *Coll. Vol. 5,* 1055, 1973; *ibid*; **40**: 93, 1960.

** Girard N *et al.* : *Eur J Org Chem.*, 2269, 2005; Alvarez R *et al.*: *Chem Eur J.*, **9**: 5821, 2003.

*** Kishner N : *J Russ Chem Soc.*, **43**: 582, 1911; Wolff : *Ann.*, **86**: 394, 1912; Huang Minlon; *J Am Chem soc.*, **68**: 2487, 1946.

such a **reduction** is termed as **Wolff-Kishner reduction.** In other words, it also relates to the *reduction* of **semicarbazones** with ***low-valent N-compounds.*** We may express the reactions as given under:





EXPLANATION

Various steps involved in the above sequential reactions may be explained as under:

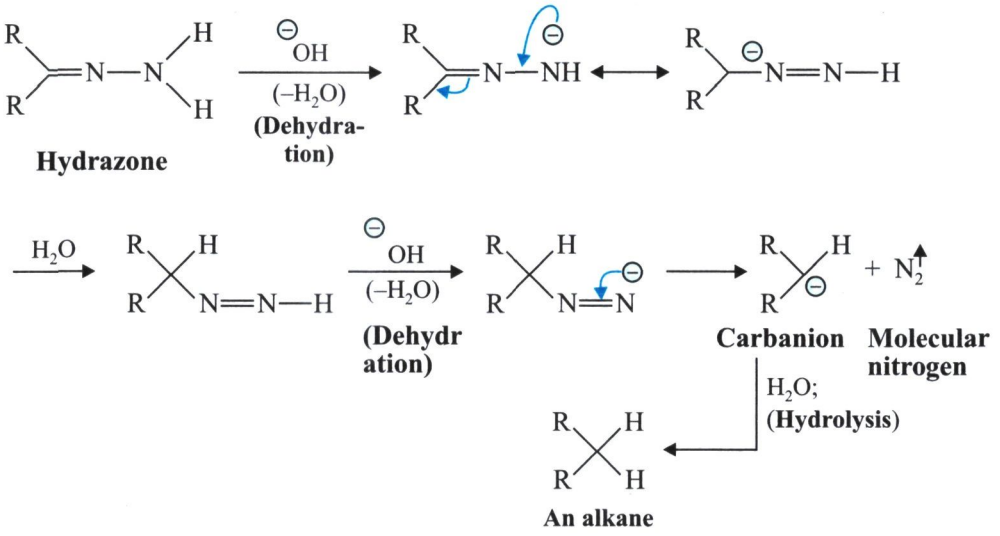
1. Interaction between a **ketone** and **hydrazine ketoamine** loses a mole of water to yield a **semicarbazone.**
2. The *resulting product* (**semicarbazone**) on being subjected to heating at 200°C in the presence of *freshly prepared* **sodium ethoxide** ($NaOC_2H_5$) undergoes ***reduction*** to produce a *methylene group* (*—CH_2—*) *i.e.,* the **carbonyl (>C=O) function** changes to **methylene (>CH_2) function** with a mole each of ammonia, molecular nitrogen and CO_2.

At this point in time, it is indeed worthwhile to have a glimpse (a brief view) the following allied versions of the **Wolff-Kishner reduction**, namely:

- **Huang-Minlon Modified Wolff-Kishner's Method**; and
- **Cram, Sahyum, and Knox Method,**

in the sections that follows:

- ***Huang-Minlon Modified Wolff-Kishner's Method:*** In this particular instance the hydrazone of the respective carbonyl (>C=O) compound together with a strong base (NaOH) in the critical presence of a ***high boiling point*** **organic solvent** *viz.,* **Ethylene Glycol** (HO/\/OH) at an elevated temperature ranging between **180–200°C.**
- ***Cram, Sahyum, and Knox Method:*** They used intelligently **potassium tertiary butoxide [*tert*-BuOK]** dissolved in *dimethyl sulphoxide* **(DMSO)** in order to enable the conversion of the **hydrazones** into the respective **alkanes** at the *room temperature (RT)* only, as given under:

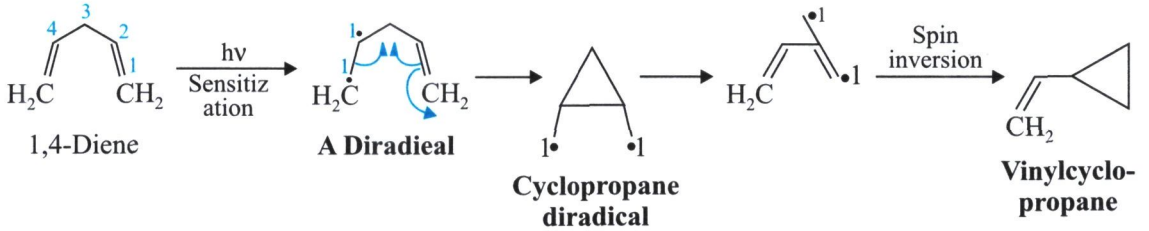


EXPLANATION

Importantly, the **Cram, Sehyum, and COX reduction** invariably comes into play *via* the formation of a **carbanion** and simultaneous evolution of **molecular nitrogen** (that eventually escapes as a gas from the reaction mixture).

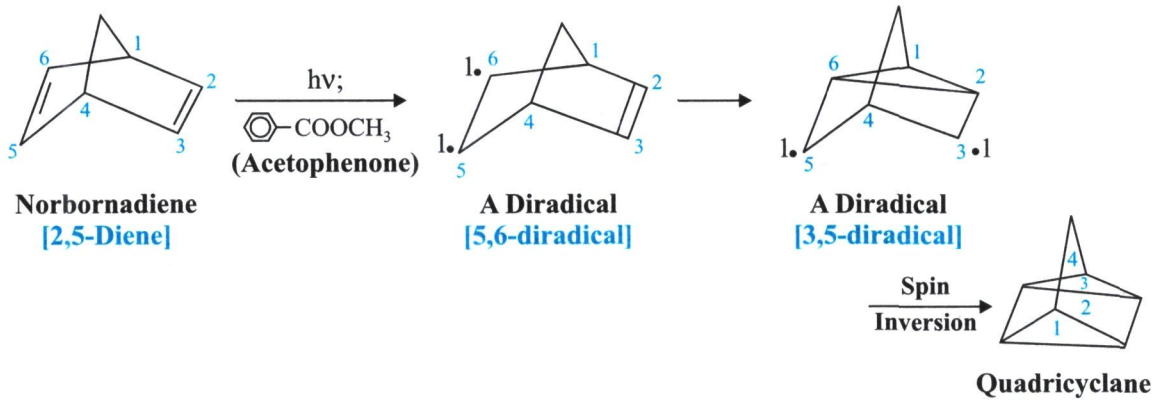
7.1.11. Ziemmermann Rearrangement (Di-π-Methane Rearrangement)

When a **conjugating substituent** (*viz.*, **1, 4-diene**) or an **aryl moiety** is present, the absolute need for a ***triplet*** **sensitization** always prevails; and the ensuing reaction is termed as **Ziemmermann rearrangement**, that ultimately results into the formation of a ***vinylcyclopropane***, as shown under:



Example: Formation of **Quadricyclane** from **Norbornadiene** upto an yield of 70–80% using acetophenone as the sensitizer, as given below:

* Ziemmermann W: *Z Physiol Chem.*, **233**: 257, 1935.
Ziemmerman W *et al.*: *J Am Chem Soc.*, **88**: 183–84, 1966.
Ziemmermann W *et al.*: *J Am Chem Soc.*, **92**: 6259–67, 1970.
Ziemmermann W *et al.*: *J Am Chem Soc.*, **93**: 3646, 1971.
Ziemmermann W *et al.*: *Chem Rev.*, **73**: 531–51, 1973.
Ziemmermann W *et al.*: *J Am Chem Soc.*, **100**: 4131, 1978.



EXPLANATION

The 2,5-diene known as **norbornadiene** on being subjected to **sensitizer (hv)** in the presence of *acetophenone* yields a **5, 6-diradical**, which undergoes further *intramolecular rearrangement* called the **Ziemmermann rearrangement** to give the respective **3,5-diradical.** This resulting product undergoes **spin inversion** to produce the desired **quadricyclane** *i.e.*, ***comprising four*** **distinct cyclic rings (numbered 1, 2, 3 and 4).**

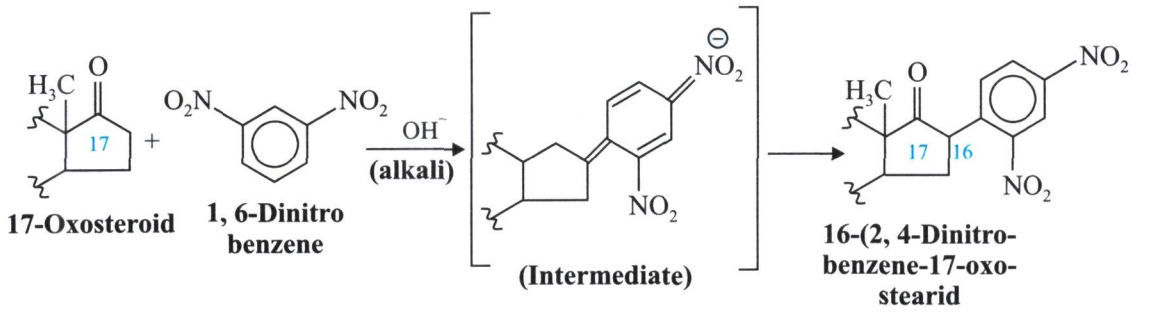
Quantitative Determination of 17–oxosteroids

Alternatively, the **Ziemmermann reaction** essentially takes place between:

- **methylene ketones**; and
- **aromatic polynitro compounds**,

in the presence of an *alkali*. Thus, when it is applied to the respective **17–oxosteroids**, the ***coloured compounds*** so obtained may be employed exclusively for the specific estimation of **17–oxosteroids.**

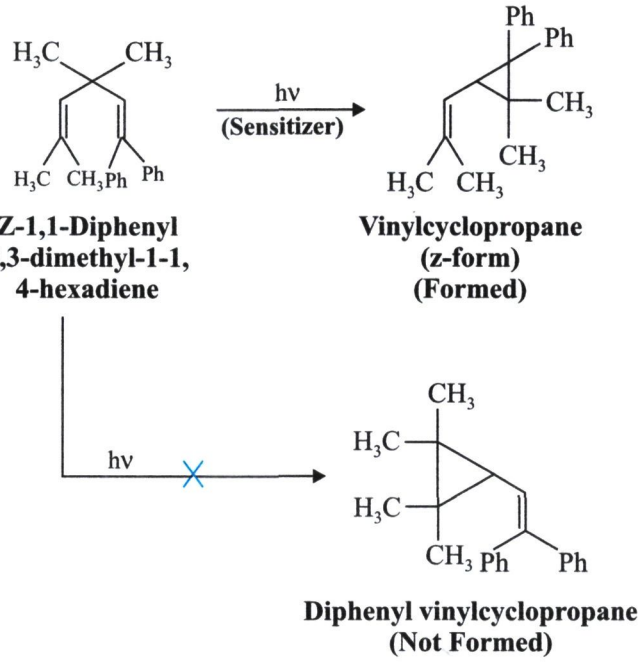
The various steps involved in the above mentioned reactions maybe expressed as under:



Regioselectivity for Unsymmetrical Dienes

Another school of thought considers the **Ziemmermann reaction (Di-π-methane rearrangement)** represents a **regioselective interaction** particularly for the ***unsymmetrical dienes*** as shown below*:

* Paquette LA *et al.* : *J Org Chem.*, **47**: 423–28, 1982.

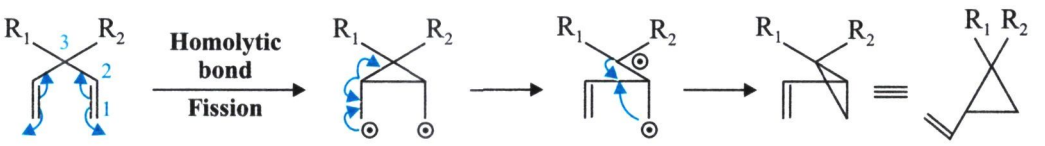


Remarks: These essentially include:

1. In a situation when the substituents present in the substrate at positions **C–1** and **C–5** are *not at all different in structure*; and hence, one certainly ends up in obtaining an admixture of **regioisomers.**
2. Amazingly, the **sensitizer** treatment with **hν** to the same **starting material (X)** may not yield the **diphenyl vinylcyclopropane** at all.

Mechanism of Ziemmermann Rearrangement

The underlying *mechanism* of the **Ziemmermann reaction** critically involves the formation of the ***diradicals* (III) and (IV)**. Obviously, the same could be mostly feasible only when the cleavage takes place exclusively between the **C–2 and C–3 bond,** —that may be facilitated generously due to the crucial presence of the substituent located strategically at **C–3** so as to **'stabilize'** the **diradicals (III) and (IV)** respectively.*



[I] [III] Diradical [at C-1 & C-5] [IV] Diradical [at C-1 & C-3] [II]

* Hixon SS *et al.*: *Chem Rev.*, **73**: 531–551, 1973.

Besides, **(III)** and **(IV)** *i.e.*, the ***two* variant diradicals** may actually designate the ***transition states***. However, for some typical *substituted substrates*, the corresponding **configuration** is duly:

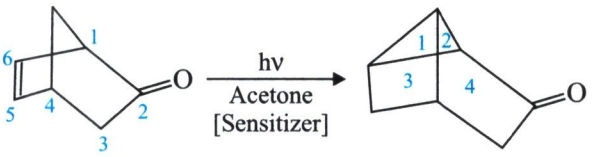
- **inverted at C–3;** and
- **retained at C–1 and C–5.***

NOTE: **Interestingly, the so-called *Ziemmermann rearrangement reaction* may be extended gainfully to the *allylic benzenes.*****

The Oxa-Di-π-Methane Rearrangement

It is nothing but an extension to the **Di–π–Methane Rearrangement** (or the **Ziemmermann Rearrangement**). In this particular instance, the ensuing reaction is very much akin to **di-π-methane rearrangement**; however, the **C=C olefinic bond** is duly replaced by a **carbonyl (>C=O) bond.** Thus, it proceeds prevalently with β, γ-unsaturated ketones *via* the so-called ***triplet excited* conditionalities.*****

We may express the aforesaid reaction as under:



Norborn-5-ene-2-one **Qudricyclane-2-one**

NOTE: **The aforesaid reaction provides a convenient access to *highly strained structures* having *smaller rings* perceptively. Hence, starting from *norborn-5-ene–2-one* using acetone as the sensitizer one would ultimately obtain the *quadricyclane*-2-one with an additional cyclic ring system.**

Suggested Reading

Banthorpe DV: **Elimination Reactions,** Elsevier, New York, 1963.

de Mayo P (Ed.): **Molecular Rearrangemets,** Interscience, New York, 1963.

Gutsche CD: **The Chemistry of Carbonyl Compounds,** Prentice-Hall, Englewood Cliffs NJ., 1967.

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Norman R and Coxon JM: **Principles of Organic Synthesis,** 3rd edn., Nelson Thomes, Cheltenkam (UK), 2005.

Rylander PN: **Hydrogenation Methods,** Academic: Oriando FL., 1985.

Saunders WH and Cockerill AF: **Mechanisms of Elimination Reactions,** Wiley, New York, 1973.

Stewatt R: **Oxidation Mechanisms,** WA Benjamin, New York, 1964.

Wiberg KB (Ed.): **Oxidation in Organic Chemistry,** Academic, New York, 1965.

Zollinger H: **Azo and Diazo Chemistry,** Interscience, New York, 1961.

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* Ziemmermann W *et al.*: *J Am Chem Soc.*, **96**: 4630, 1974.

** Ziemmermann W *et al.*: *J Org Chem.*, **49**: 3069, 1984.

*** Hixon SS *et al.*: Chem Rev., **73**: 531–551, 1973.
Demuth M and Mikhail G: *Synthesis.*, 145–162, 1989.

Chapter 8

Reactions Giving Carboxylic Acids and its Derivatives

LESSONS AT A GLANCE

8.1 Introduction

8.2 Name Reactions: Giving Carboxylic Acids and its Derivatives

- 8.2.1 Darzen Condensation [or Darzen-Glycidic Ester Condensation]
- 8.2.2 Kolbe-Schmitt Reaction
- 8.2.3 Knoevenagel Condensation Reaction [Conjugated Carboxylic Acid]
- 8.2.4 Michael Addition Reaction [Michael Condensation]
- 8.2.5 Perkin Reaction
- 8.2.6 Reformatsky Reaction [Reformatskii Reaction]
- 8.2.7 Stobbe Condensation
- 8.2.8 Yamaguchi Esterification [Yamaguchi Macrolactonization]

8.1 INTRODUCTION

In **'organic chemistry'** quite a few specific reactions do give not only the **carboxylic acids (-COOH)** but also their respective **derivatives** as well. Interestingly, such **organic reactions** categorically involve an array of highly typical interactions, namely:

- **Ester Condensation,**
- **Carboxylate Condensation,**
- **Addition Reaction,**
- **Esterification, and**
- **Condensation.**

Based on the kopious volume of information from the *literature* and the *scientific journals* one may come across a variety of specialized **name reactions**—that eventually broaden the horizon and scope of ***organic chemistry*** elegantly in the design of **newer organic compounds** every moment across the globe.

Therefore, it would be indeed a very gainful exercise if we intend to have a look at the creative genius and scientific outputs of research in this direction of **organic chemistry.**

8.2 NAME REACTIONS: GIVING CARBOXYLIC ACIDS AND ITS DERIVATIVES

Following are the list of some important and typical **name reactions** that give *carboxylic acids* and its *respective derivatives*, such as:

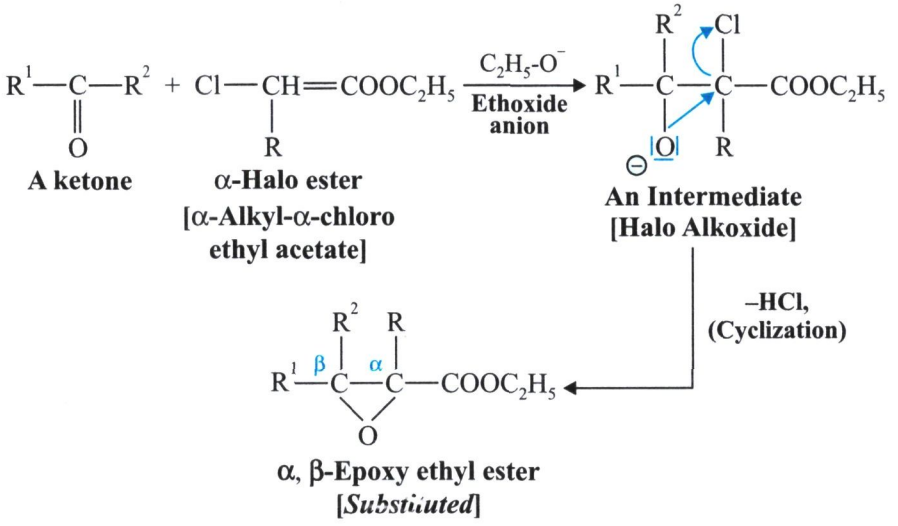
- **Darzen Condensation [or Darzen-Glycidic Ester Condensation],**
- **Kolbe-Schmitt Reaction,**
- **Knoevenagel Condensation [or Conjugated Carboxylic Acid Condensation],**
- **Michael Addition Reaction,**
- **Perkin Reaction,**
- **Reformatsky Reaction,**
- **Stobbe Condensation,** and
- **Yamaguchi Esterification,**

which shall now be discussed individually in the sections that follows together with typical examples, explanations, and mechanism of reaction (wherever possible).

8.2.1 Darzen Condensation [or Darzen-Glycidic Ester Condensation]

The **Darzen Condensation** is also recognized as **Darzen-glycidic ester condensation.** It designates a typical: **"base-catalyzed condensation of an α-haloester with a carbonyl (>C=O) compound [*viz.*, aldehyde (-CHO) and ketone (>C=O)] to give:**

- **α, β-Epoxy esters or Glycidic esters***; or
- **[2 + 1] OC, CC–Cyclo-α-Alkoxycarbonyl methylene–addition."**



Explanation

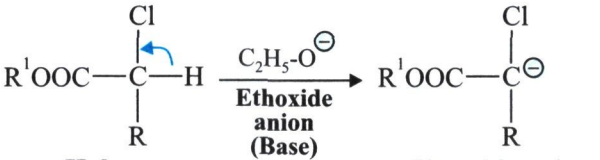
Although the **intermediate halo alkoxide** obtained by the interaction of a *ketone* and an *α-haloester*, it is usually **not isolated** [*i.e.*, the **α-chloro esters** being a *poor leaving group* in the *nucleophilic* substitution].*

Mechanism of Darzen Condensation

In true sense, the underlying mechanism of **Darzen condensation** essentially consists of the following ***three* sequential steps,** namely:

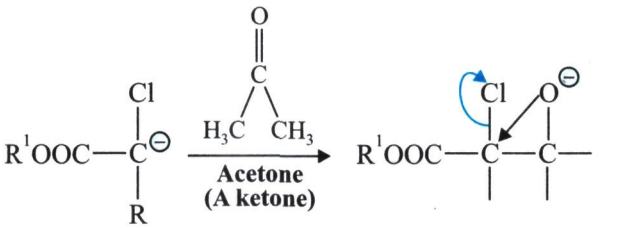
- **Deprotonation of *α-haloester* to *α-halo alkoxide* to obtain an *unstable anion* (I);**
- **Condensation of (I) with a *ketone* or *aldehyde* to obtain α-halo alkoxide (II); and**
- **Intramolecular nucleophilic substitution of (II) to give the respective 'Epoxide' (III).**

(*a*) Deprotonation of α-Haloester by the base [$C_2H_5O^{\ominus}$]



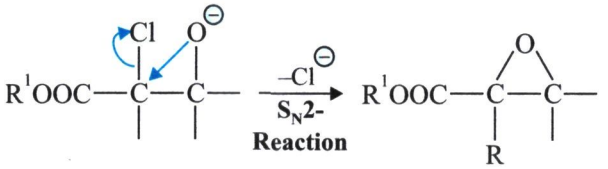
α-Halo ester — An Unstable anion (I)

(*b*) Condensation of (I) with a *ketone* or *aldehyde* to obtain α-halo-alkoxide (II)



(I) — α-Halo alkoxide (II)

(*c*) Intramolecular nucleophilic substitution of (II) to give the respective *'Epoxide'*.



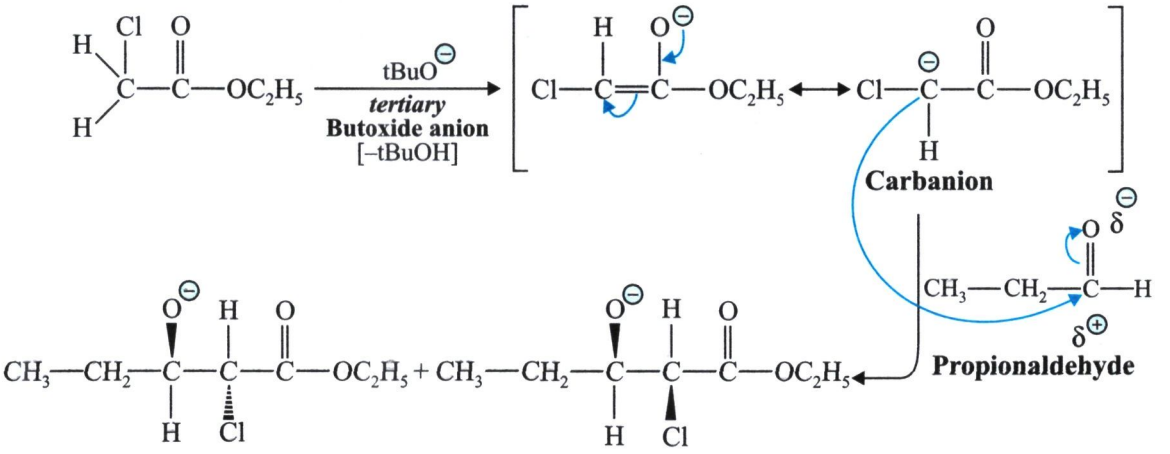
α-Halo alkoxide (II) — An Epoxide (III)

* Newman MS and Magerlein BJ: *Org. React.*, **5**: 413–440, 1949; Berti G : *Top stereochem.*, **7**: 210–218, 1973.

* Ballester and Blaneo P: J *Org. Chem.*, **23**: 652, 1958.

Stereochemical Aspect of Darzen Condensation Reaction

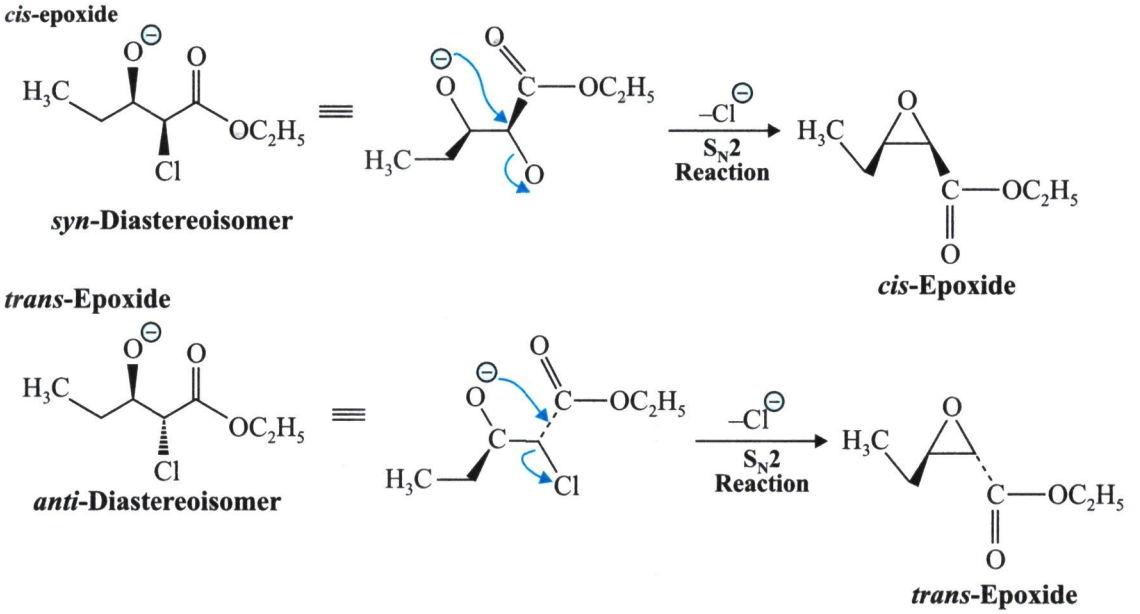
The stereochemical aspect of the **Darzen condensation reaction** may be carried out by the formation of ***syn*-and *anti*-diastereoisomers** after the **deprotonation** phenomenon, as given under:



NOTE: **It may be noted that in the *anti*-diastereoisomer the orientations of *oxide anion* and *chloride ion* are on the opposite direction; whereas, in the *syn*-diastereoisomer the orientation of both *oxide anion* and *chloride ion* are in the same direction.**

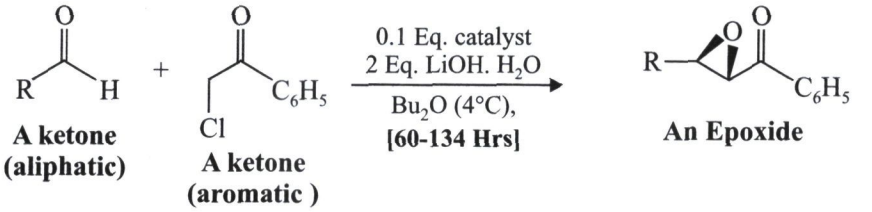
syn- and *anti*- Distereoisomers Undergo Intramolecular S_N2 Reaction to Produce *cis*-and *trans*-Epoxides

The critical formation of *cis*-and *trans*-epoxides from the **intramolecular S_N2 reaction** of *syn*- and *anti*-diastereoisomers may be shown as under:

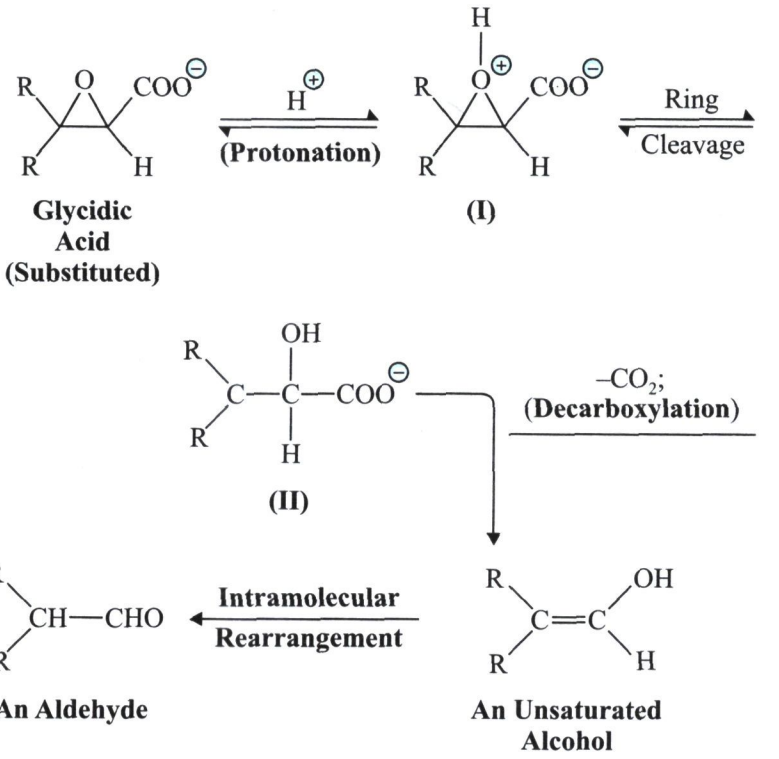


Underlying Concept for Highly Diastereoselective and Enantioselective Transformation to form Epoxides

Arai *et al.* (1999)* reported primarily the concept for the critical formation of the **epoxides** commencing from **highly diastereoselective** and **enantioselective transformation** of the ***ketones,*** as shown under:



Successive Conversion of Glycidic Acid  **into the Next Higher Homologous of Original Aldehyde/Branched Aldehyde.****



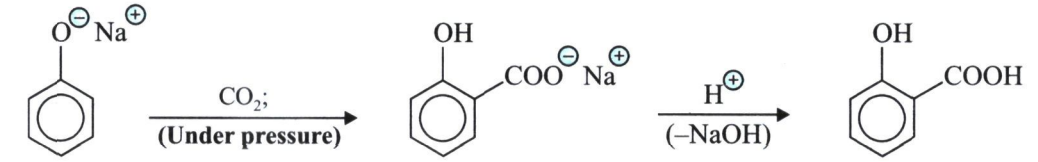
* Arai S *et al.* : *Tetrahedron*, **55**: 6375–86, 1999.

** de Souza AL and Pillai RA: *Org Lett*, **7**: 1617, 2005; Rapoport J : *J Org. Chem.*, **68**: 109, 2003.

Comments: Protonation of a *substituted glycidic acid* yields a **glycidic carboxylate salt (I)**, which on being subjected to *ring cleavage* gives an ***open-chain* carboxylate (II).** The resulting **product (II)** on *decarboxylation* gives an unsaturated alcohol, which on further *intramolecular rearrangement* yields an **aldehyde.**

8.2.2 Kolbe-Schmitt Reaction*

The **Kolbe-Schmitt reaction** relates to the formation of **aromatic hydroxy acids** by *carboxylation of the* **phenolates**, preferentially at the *ortho*-position by using **carbon dioxide (CO_2)** under pressure, as shown below:

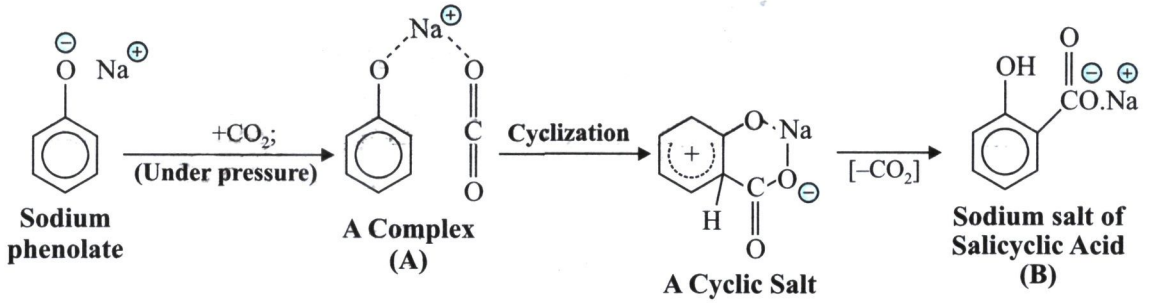


Sodium phenolate | **Sodium salt of salicyclic acid [*ortho* - Hydroxy sodium benzoate]** | **Salicyclic acid [*O*-Hydroxy-benzoic acid]**

NOTE:
1. **Necessity of high pressure of CO_2 may be an absolute must to accomplish higher yields.**
2. **The above intermediate *O*-hydroxy sodium benzoate serves as a potential precursor of *'aspirin'* (*i.e.*, acetylsalicyclic acid)—an antipyretic drug.**

Mechanism of Kolbe-Schmitt Reaction

Let us look into the following sequential reactions starting from **sodium phenolate:**



Sodium phenolate | **A Complex (A)** | **A Cyclic Salt** | **Sodium salt of Salicyclic Acid (B)**

Explanation

Various steps involved in the above reactions may be explained as under:

1. **Sodium phenolate** on being subjected to *carbonation* with CO_2 under pressure yields an ***ortho*-substituted product** that may be duly expatiated by the formation of a **complex (A)** (**an open-chain cyclic compound**).

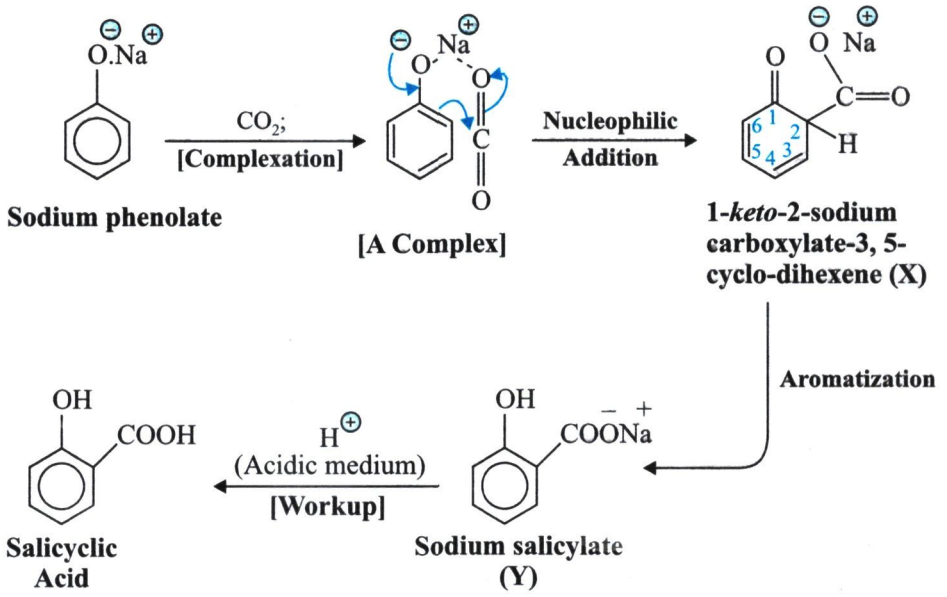
*Kolbe H: *Ann.*, **113:** 125, 1860; Schmitt R., *J. Prakt Chem.*, [2], **31:** 397, 1885.

2. The resulting **complex (A)** undergoes *cyclization* to give a **cyclic salt** (*i.e.*, **benzene** bears the **+ve charge** in it and the **additional cyclic ring** has a **–ve charge** upon the **O–atom** located in between the H–bond with Na and carbonyl (>C=O) group).
3. The resulting product undergoes *decarboxylation* to lose a mole of CO_2 and the respective **sodium salt of salicyclic acid (B)** is obtained duly.

   In other words, the CO_2 gets duly **polarized**; and hence, its inherent **electrophilic character** gets increased significantly. Thus, the ultimate complex so obtained possesses an appropriate ***geometrical relationship with the so-called activated C–centre.****

Kolbe-Schmitt Reaction *via* Nucleophilic Addition

It has also been scientifically established that the **Kolbe-Schmitt reaction** may also be accomplished *via* the **nucleophilic addition** of a **phenolate** (*sodium phenolate*) to **molecular CO_2** (*under pressure*), to initiate the complexation phenomenon, and immediately followed up by an appropriate *aromatization*, finally an **acidic (H^+)** workup to obtain the desired **salicyclic acid.** Let us examine the various sequential steps involved in the aforesaid reaction:



Explanation

1. Sodium phenolate undergoes complexation with CO_2, which on being subjected to **nucleophilic addition** yields the **1-*keto*-2-sodium carboxylate-3,5-cyclodihexene (X).**

NOTE: **In *'organic chemistry'*–an attracting reagent that shows an affinity for *electron-sparse* or *positively charged centres* in a molecule.**

2. The resulting **product (X)** upon *aromatization* gives the respective salt, **sodium salicylate (Y)**, which on **acidic (H^+) workup** yields the desired product **salicyclic acid.**

*Hirao I and Kito T : *Bull Chem Soc.* **Jpn., 46:** 3470–74, 1973.

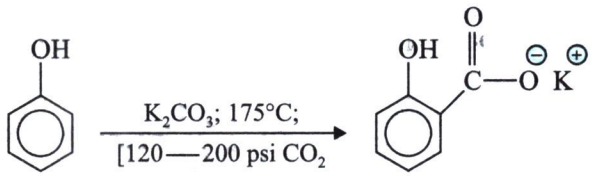
Comments: Henecka (1952)* pointed out that the **Kolbe-Schmitt reaction** is solely confined to such reagents only as:

- **Phenol**
- **Substituted Phenols and**
- **Heteroaromatics**

❑ Marasse's Modification**of Kolbe-Schmitt Reaction

The suggested modification by **Marasse** essentially make use of an excess of ***anhydrous*** **potassium carbonate (K_2CO_3)** to replace *carbon dioxide* (CO_2) [as used in **Kolbe-Schmitt reaction**].

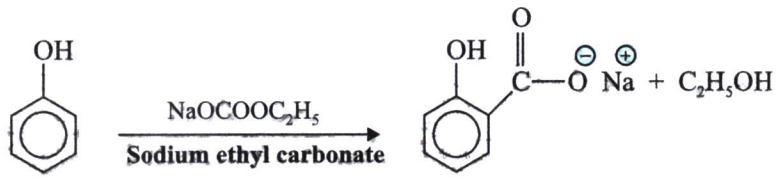
Thus, we may have the following expression:



Phenol **Potassium salicylate**

❑ Jone's Modification*** of Kolbe-Schmitt Reaction

Jone's modification of the Kolbe-Schmitt reaction advocates the use of **sodium ethyl carbonate [NaOCOOEt]** in place of **carbon dioxide (CO_2),** as given under:



Phenol **Sodium salicylate** **Ethanol**

SPECIAL NOTE: These essentially include:

1. **Sodium or Potassium Phenoxide** may be subjected to the phenomenon of ***carboxylation*** **regioselectively** at the ***para-position*** in relatively **high yield** by careful treatment with:
   - **Sodium carbonate**
   - **Potassium Carbonate and**
   - **Carbon Monoxide.****
2. Nevertheless, the meticulous ^{14}**C–labeling** (*radioisotope*) vehemently showed that:
   "it is the carbonate C–atom which virtually appears in the so-called *p*-hydroxy benzoic acid product

   (*i.e.*, HOOC  **OH)".***
3. Eventually, the **carbon monoxide (CO)** gets converted to either **sodium or potassium formate** (salt).

---

*Henecka H: *Methods Org. Chem.*, **8**: 372–77, 1952.

Marasse S: *German Patent*, **73: 279, 1893.

***Jones JI: *Chem Indus.*, 889, 1957.

****Yashura and Nogi: *J Org. Chem.*, **33**: 4512, 1968.

4. Besides, **carbon monoxide (CO)** has also been employed to carry out the ***carboxylation*** **of aromatic ring systems** using: **"palladium (Pd) compounds as the preferred catalysts".***
5. Amazingly, a particular **Pd–catalyzed reaction** has also been employed successfully to carry out the preparation of **'Acyl Fluorides'** as shown below:

$$\boxed{\text{ArH} \longrightarrow \text{ArCOF}}\ **$$

8.2.3 Knoevenagel Condensation Reaction*** [Conjugated Carboxylic Acid]

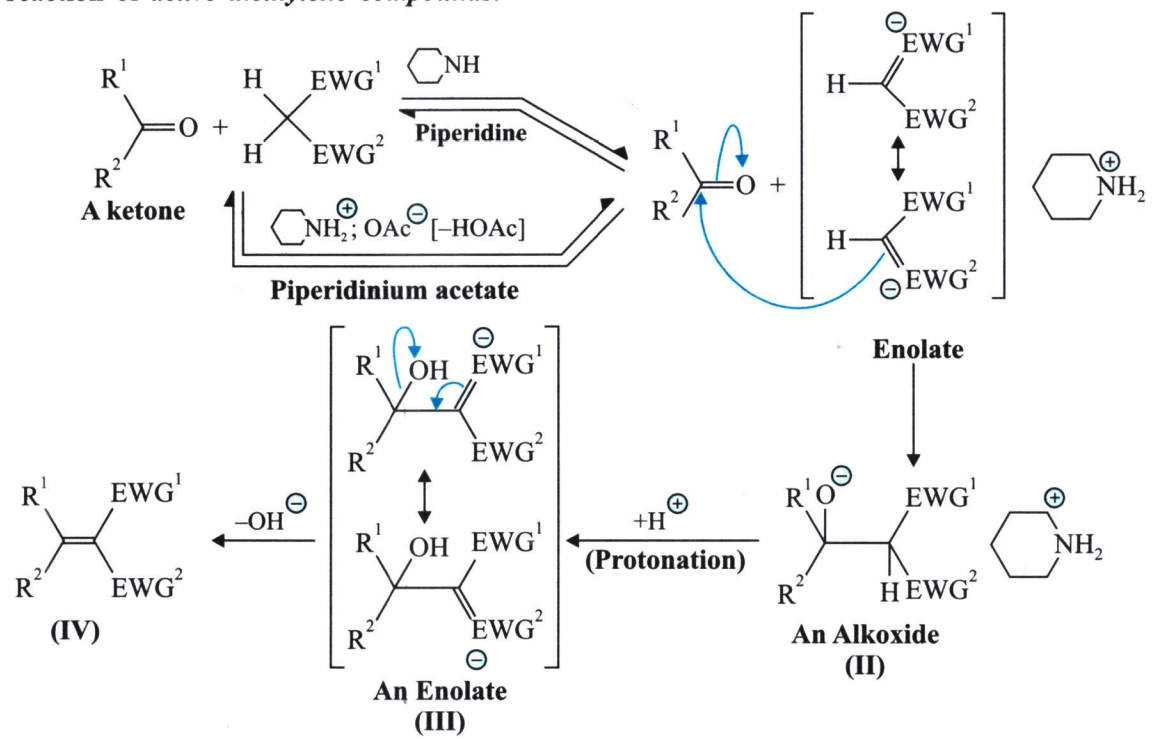
The **Knoevenagel condensation reaction** is also commonly known as **Doebner Modification.****

A **Knoevenagel reaction** refers to a *condensation* occurring between following *two* organic entities, namely:

- **an '*active*' methylene compound or the comparably C, H–acidic nitromethane;** and
- **a carbonyl (>C═O) compound (*aldehyde or ketone*).**

Interestingly, the end-product of a **Knoevenagel reaction** is an ***'alkene'*** which critically comprises ***two*** **geminal***** **acceptor moiety.**

Let us look into the following sequential reactions involving the mechanism of the **Knoevenagel reaction** of ***active methylene compounds:***



* Ugo and Chiesa: *J Chem Perkin Trans.*, **1**: 2625, 1987.

** Sakakura *et al.*: *J Organomet Chem.*, **334**: 205, 1987.

*** Knoevenagel E: *Ber.*, **31**: 2596, 1898.

**** Doebner O: *Ber.*, **33** : 2140, 1900.

***** **Geminal selectivity:** Many functional moieties present in an allylic position usually cause the hydrogen to be removed from the side-chain than the other [Chennan *et al.*: *J Am Chem. Soc.*, 112: 5193, 1990].

[EWG = Electron Withdrawing Group; Presence of *two* geminal acceptor groups *viz.*, EWG^1 and EWG^2 in (IV) above.]

EXPLANATION

1. The **Knoevenagel reactions** are invariably performed in a **mildly basic media,** such as:
   - **in piperidine**; or
   - **in a neutral solution**; or
   - **catalyzed by piperidinium acetate.**
2. Amazingly, the so-called inherent **'basicity'** of *piperidine* or of *acetate ions*, respectively, practically suffices to produce an appreciably high *equilibrium concentration* of the **ammonium enolate** of the ***active-methylene*** **compound (I).**
3. The **enolate (I)** subsequently adds on to the **carbonyl (>C═O) olefinic bond** present in the ***ketone*** or ***aldehyde***. Thus, the primary resulting product happens to be an **alkoxide (II),** which eventually consists of the ***structural motif*** of a reasonably strong **C, H–acid,** – namely, of an **active-methylene compound.**
4. Therefore, the **intermediate (II)** gets duly **protonated (H^+)** particularly at the **alkoxide oxygen**; and thereby the **C–β atom** gets *deprotonated* **(almost to the same extent as that of the starting material).**
5. The formation of an **OH–substituted enolate (III)** is obtained, which then undergoes an **$E1_{cb}$-elimination** thereby leading to the so-called *condensation* of **product (IV).**

Points to Ponder: It would be worthwhile to state at this point in time that there prevails a common aspect in both:

- **Knoevenagel condensation;** and
- **Aldol condensation,**

with respect to having a **sequence of an enolate hydroxy-alkylation** and an **$E1_{cb}$-elimination.**

NOTE: **The *Knoevenagel condensation reaction* may be used extensively for the critical synthesis of a broad-spectrum of vital *'condensation products'* since the *carbonyl* (>C═O) *component* plus the *active-methylene component* may be varied easily and conveniently.**

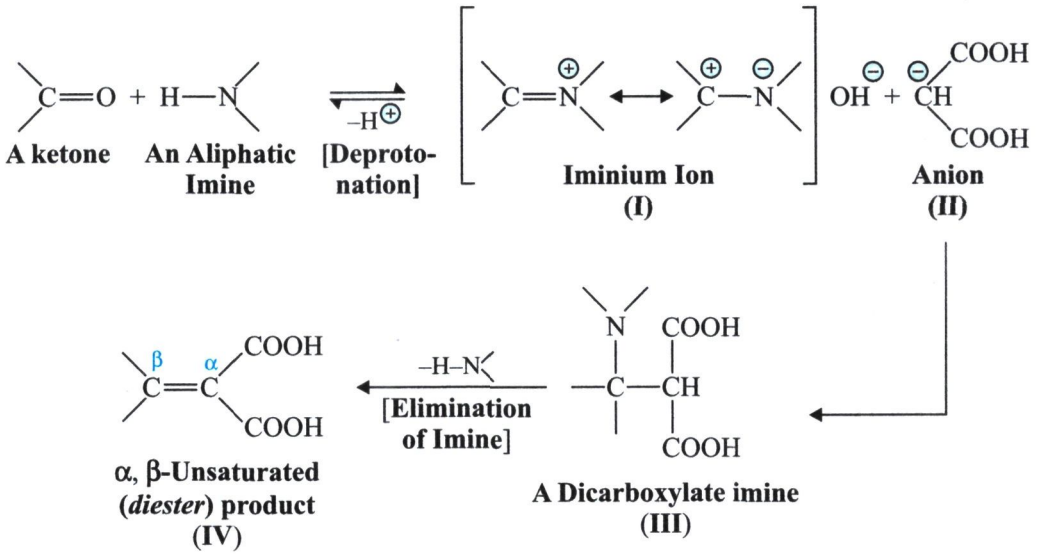
Mechanism of Knoevenagel Condensation Reaction

The underlying ***mechanism*** of the **Knoevenagel condensation reaction** essentially involves the generation of:

- **iminium ion** $\left[\rangle C{=}\overset{\oplus}{N}\langle\right]$ from the carbonyl (>C═O) substrate; and
- **amine ($—NH_2$).**

Thus, the **iminium ion** so obtained gets duly condensed with the respective **anion** to give rise to the formation of the desired product, **α, β-unsaturated diester**, as given under:

Example 1: For Aliphatic Imines

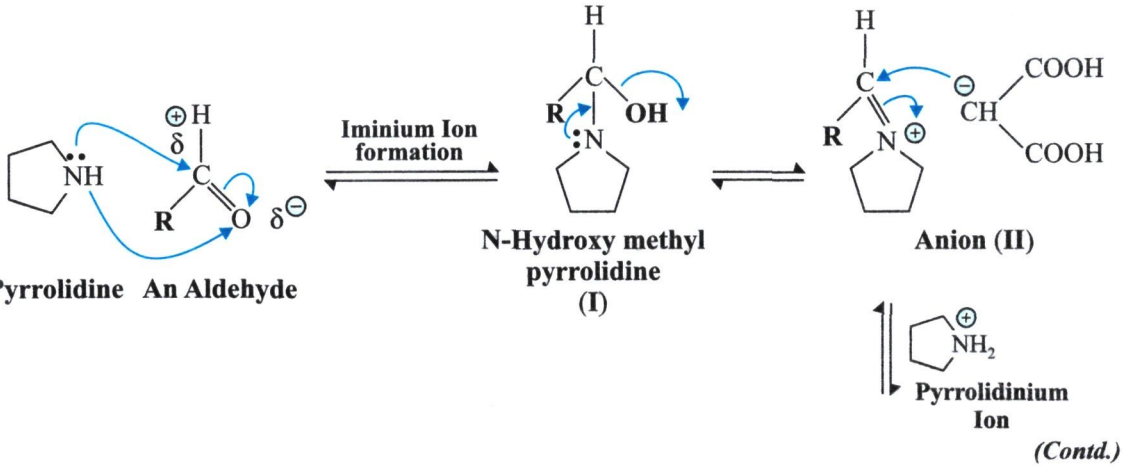


EXPLANATION

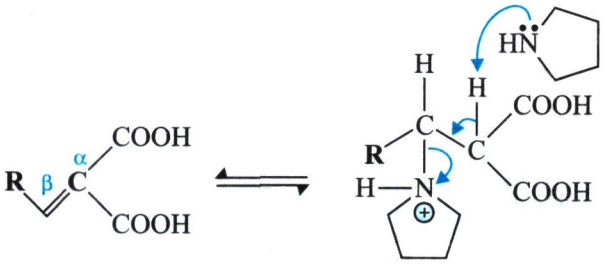
The various steps involved may be explained as under:

1. Interaction of a **carbonyl (>C=O) [ketone]** with an *aliphatic imine* undergoes *deprotonation* to yield the ***iminium ion*** **(I)** plus an **anion (II)** (*i.e.,* a *dicarboxylate anion*).
2. The resulting **anion (II)** undergoes complexation with the respective **iminium ion (I)** to form the corresponding **dicarboxylate imine (III).**
3. The resulting **dicarboxylate imine (III)** eliminates an *imine* to yield the desired **α, β-unsaturated (diester) product (IV).**

Example 2: For Aromatic Imines



(Contd.)



α, β-Unsaturated (diester) product (IV)

A Dicarboxylate pyrrolidine imine (III)

EXPLANATION

The various steps involved in the above reaction may be explained as under:

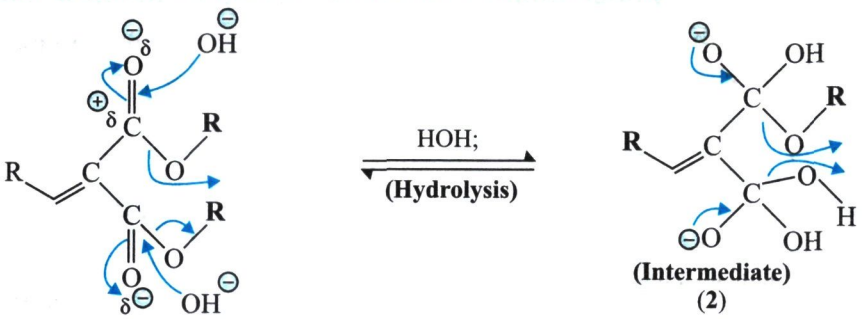
1. The reaction between **pyrrolidine** (an *aromatic heterocyclic imine*) and an **aldehyde** undergoes the *imminium ion formation* to yield **N-hydroxy methyl pyrrolidine (I)**, which further registers a typical *reversible reaction* to give the corresponding **anion (II).**
2. The resulting **anion (II)** on being subjected to treatment with the **pyrrolidinium ion** gives rise to the formation of a **dicarboxylate pyrrolidine imine (III),** which undergoes a reversible reaction to produce the desired **α, β-unsaturated (diester) product (IV).**

Production of α, β-unsaturated Carboxylic Acid from the α, β-unsaturated Diester Product

The further sequential reactions starting from **α, β-unsaturated diester product** (as obtained earlier) when subjected to the following *three* stepwise reactions, such as:

- **hydrolysis**
- **acid (H^+) workup,** and
- **decarboxylation ($-CO_2$).**

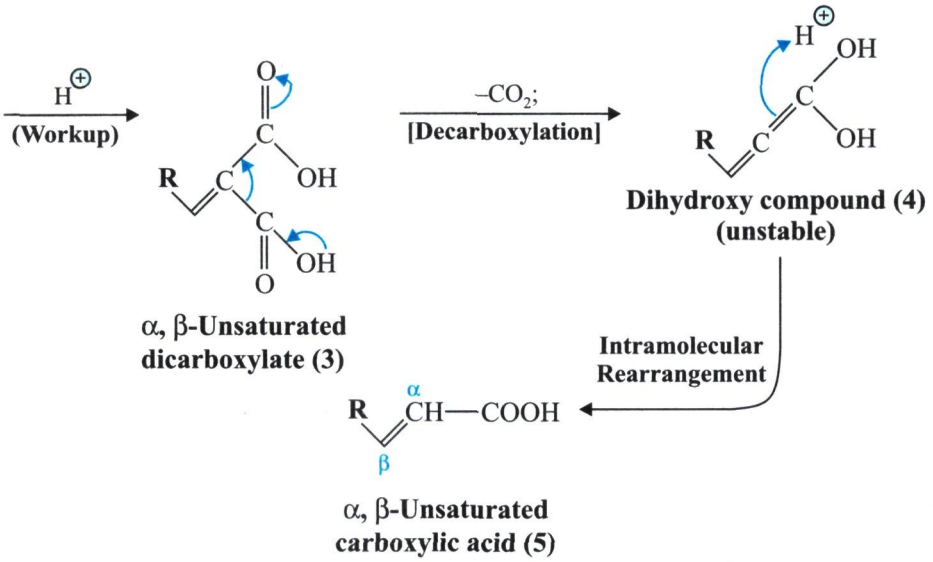
gives rise to the formation of **α, β-unsaturated carboxylic acid,** as stated under:



α, β-Unsaturated diester (1)

(Intermediate) (2)

(Contd.)



NOTE: **The aforesaid pathway has been duly endorsed by the observations of Charles (1968)* and Crowell *et al.* (1953).****

Explanation

The various steps engaged the aforesaid pathway may be explained as under:

1. The **α, β-unsaturated diester (1)** undergoes *hydrolysis* to give an **intermediate (2)**, which upon **acid (H^+) workup** yields an **α,β-unsaturated dicarboxylate (3).**
2. The resulting **product (3)** on being subjected to *decarboxylation* gives a **dihydroxy compound (4)** which being unstable undergoes **intramolecular rearrangement** to yield the desired **α,β-unsaturated carboxylic acid (5)**.

Domino Reaction***

The **Domino reaction** clearly illustrates the rather a recent usage of **Knoevenagel reaction**; and it evidently involves either two or *more than two* simultaneous **transformations** wherein the ***next follow-up step*** solely depends upon the functionality thus evolved in the ***preceeding step***. In true sense, this type of reactions are invariably termed as:

- **Tandem Reactions;** or
- **Cascade Reactions.**

Knoevenagel Condensation Reaction and a Subsequent Hetero Diels-Alder Reaction

Tietze and Beifuss (1993)**** put forward a befitting example involving the underlying sequence comprising:

*Charles G: *Bull Soc. Chem., France,* 1576–83, 1968.

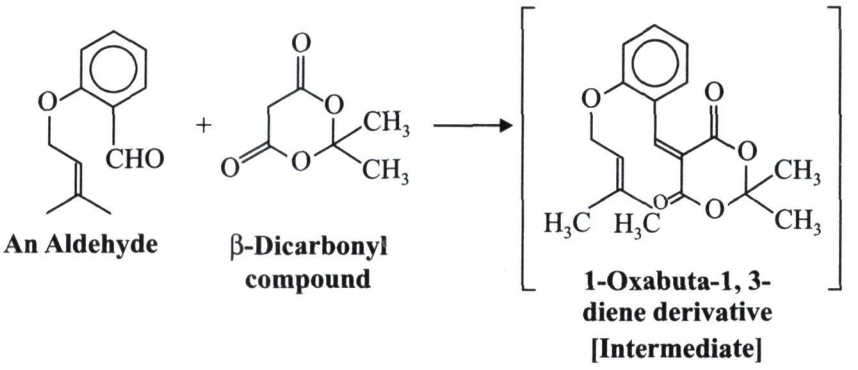
Crowell TI and Peck DW: *J Am Chem Soc.,* **75: 1075–77, 1953.

***Waldmann H: *Nachr Chem Tech Lab.,* **40**: 1133–40, 1992.

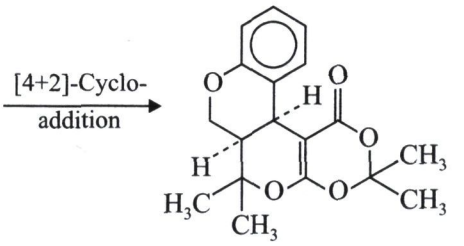
****Tietze LF and Beifuss U: *Angew Chem.,* **105**: 137–70, 1993.

- **Knoevenagel Condensation;** and
- **Diels-Alder Reaction,**

which may be expressed as under:



An Aldehyde **β-Dicarbonyl compound** **1-Oxabuta-1, 3-diene derivative [Intermediate]**

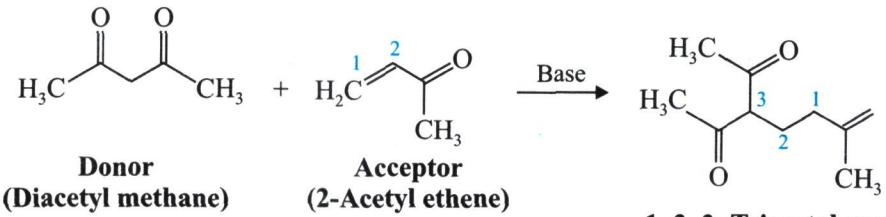


A Cycloadditive derivative

It comprises the condensation of an *aromatic aldehyde in situ* with a *β-dicarbonyl compound* (also known as : **Meldrum's Acid**) to give rise to the formation of **1-oxabuta-1, 3-diene derivative,** which ultimately undergoes further **intramolecular rearrangement** [*i.e.,* **(4 + 2)–Cycloaddition**] with a *dienophile* to produce the desired **cycloadditive derivative.**

8.2.4 Michael Addition Reaction* [Michael Condensation]

The **Michael addition** relates to a **base-promoted conjugate addition** of the ***carbon nucleophiles*** **(donors)** to the respective ***activated unsaturated systems*** **(acceptors)**; and hence, may expressed as under:



Donor (Diacetyl methane) **Acceptor (2-Acetyl ethene)** **1, 3, 3- Triacetyl propane [A 'activated' unsaturated system]**

* Michael A: *J Prakt Chem.*, [2] **35**: 349, 1887.

Following are some of the commonly encountered **donors, acceptors,** and **bases** being used in **organic chemistry:**

Donor : Malonates; Cyanoacetates; Acetoacetates; Carboxylic esters; Ketones; Aldehydes; Nitriles; Sulphones; and Nitro compounds.

Acceptor : α, β-Unsaturated ketones; Esters; Aldehydes; Amides; Carboxylic acids; Nitriles; Sulphoxides; Sulphones; Nitro compounds; Phosphonates; and Phosphoranes;

Base : $NaOCH_2CH_3$ [Sodium ethoxide]; NH $(CH_2CH_3)_2$ [Triethyl amine]; KOH [Potassium hydroxide]; KOC $(CH_3)_3$ [Potassium *tert*-butoxide]; N $(CH_2CH_3)_3$ [Triethyl amine]; NaH [Sodium hydride]; BuLi [Lithium butane]; and LDA [Lithium diisopropylamide].

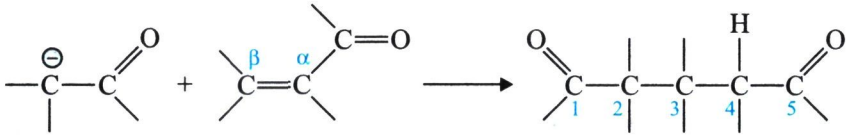
The **Michael addition** is of special importance in such synthesis that essentially entails the so-called **nucleophilic addition of carbanions** to the corresponding **α, β-unsaturated carbonyl (>C=O) chemical entities** (*compounds*). Therefore, in a rather more elaborated fashion it is invariably defined as:

"1, 4-addition of an enolate anion to an α, β-unsaturated carbonyl (>C=O) compound to give rise to the critical formation of a 1, 5-dicarbonyl compound."

Thus, we may consider the following *generalized reaction* between:

- **a carbanion;** and
- **an α, β-unsaturated carbonyl compound,**

to yield the ***1,5-dicarbonyl compound:***



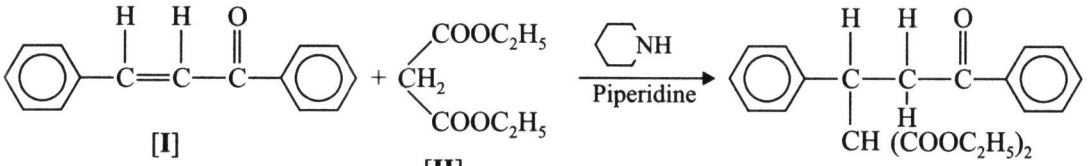
Carbanion **α, β-Unsaturated carbonyl compound** **1, 5-Dicarbonyl compound**

Comments: The **Michael addition** is found to be an exceptionally good reaction specifically with the so-called **β-dicarbonyl chemical entities(compounds).**

Typical Examples of the Michael Addition

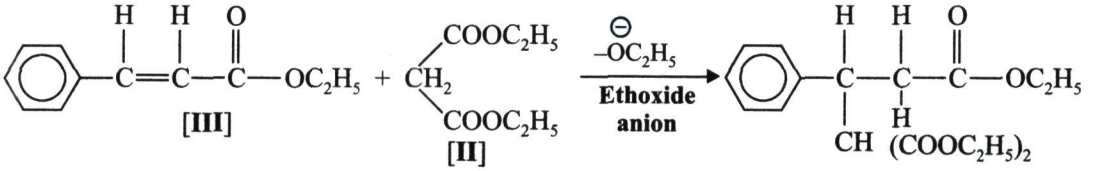
Following are *four* typical examples exhibiting the **Michael addition reaction**, namely:

***(a)* Reaction between Benzalacetophenone (I) and Ethyl Malonate (II)**



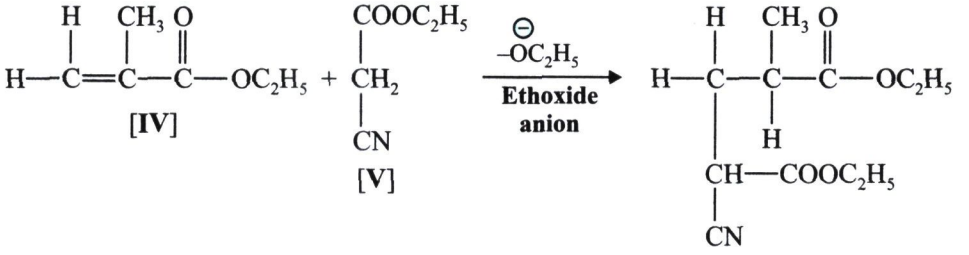
[I] **[II]** **Benzyl acetophenone ethyl malonate**

(*b*) Reaction between Ethyl Cinnamate (III) and Ethyl Malonate (II)



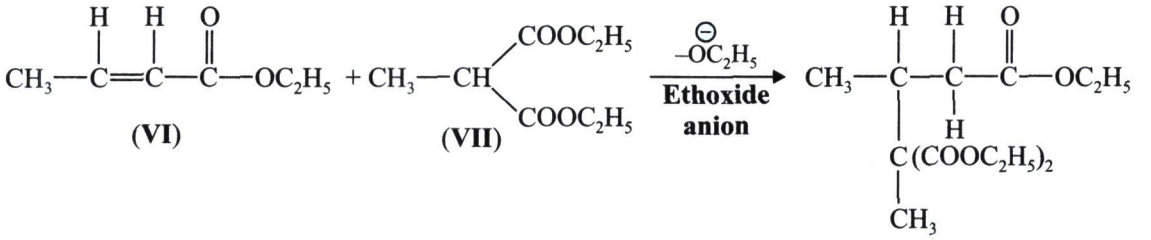
Cinnamyl ethyl malonate ethyl

(*c*) Reaction between Ethyl α-methyl acrylate (IV) and Ethyl Cyanoacetate (V)



Ethyl cyanoacetyl ethyl-α- methyl acrylate

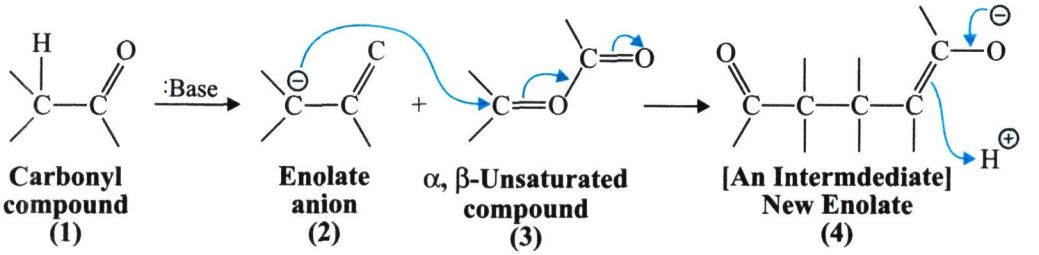
(*d*) Reaction between Ethyl Crotonate (VI) and Ethyl methyl malonate (VII)

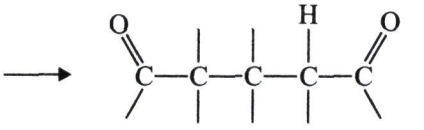


Ethyl methyl malonate ethyl crotonate

Mechanism of Michael Addition

The underlying mechanism of **Michael addition** may be given as stated under:





1, 5-Dicarbonyl compound (5)

Explanation

The various steps involved may be explained as under:

1. Carbonyl compound (1) on treatment with a **base** gives *two* products of reaction, namely:
   - **an enolate anion (2)**; and
   - **an α, β-unsaturated compound (3).**
2. The said *two* products **(2)** and **(3)** combines to form an ***intermediate* (4)** *i.e.,* an altogether **'new enolate' (4)**, which on **protonation (H^+)** yields the desired **1, 5-dicarbonyl compound (5).**

NOTE: **The sequence of the aforesaid reaction is preferentially carried out in a *protic organic solvent viz.,* an alcohol (ethanol) or even by the usage of an *'alkoxide'* as a base, such as:**

sodium ethoxide $\left[-\overset{\ominus}{O}\,C_2H_5\right]$ **or potassium *tert*-butoxide [*t*-BuK].**

Another Mechanism of Michael Addition

The **Michael addition** is believed to take place by the following alternative mechanism *i.e.,* as illustrated for the particular ***'Malonic Ester'.***

(*i*) $H-CH(COOC_2H_5)_2 + :Base \xrightarrow[\text{Abstraction}]{-H^{\oplus}} H:Base^{\oplus} + CH(COOC_2H_5)_2^{\ominus}$

Diethyl malonate (A) **Nucleophilic reagent carbanion (B)**

(*ii*) $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O + CH(COOC_2H_5)_2^{\ominus} \longrightarrow -\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}=\overset{|}{C}=O}_{\ominus}$

A Conjugated System (C) **(B)** **Diethyl malonate carbanion (D)**

(*iii*) $-\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}=\overset{|}{C}=O}_{\ominus} + H:Base^{\oplus} \longrightarrow -\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underset{\underset{H}{|}}{\overset{|}{C}}-\overset{|}{C}=O + :Base$

(D) Protonated base **Conjugated diethyl malonate (E) [Michael addition]**

Explanation

The *three* sequential steps involved in the above reactions may be explained as under:

1. The very first step involves the interaction between a **diethyl malonate (A)** with a *base* to yield a **carbanion** (or *nucleophilic reagent*) **(B)** plus a *protonated base* (*via* abstraction of a proton from the base).

2. The resulting **carbanion (B)** interacts with a **conjugated system (C)** to yield **diethyl malonate carbanion (D)**, which on further reaction with a *protonated base* gives rise to the formation of a **conjugated diethyl malonate (E)** (*i.e.*, a **Michael addition**) and the free base is liberated.

Comments: In a broader perspective, the *chemical entity* (compound) from which the respective **carbanion** (*viz.*, **B** or **D**) should by all means be a ***fairly acidic entity*** in order that a significant concentration of the **carbanion** may be obtained satisfactorily. In fact, such type of *chemical entity* is invariably one which essentially comprises:

"a $—CH_2—$ or —CH-moiety duly flanked by *two* electron withdrawing groups (EWGs),— that may virtually help to accommodate the negative charge of the anion (B) or (D)."

NOTE: **Instead of *diethyl malonate,* –one may also make use of such similar type of esters as:**

• ***Ethyl cyanoacetate*** ***and*** • ***Ethyl acetoacetate***



Stereochemical Features of Michael Addition

The *stereochemical features* of **Michael addition reaction** exclusively rests upon the following ***two* cardinal factors**, namely:

- **geometry of the α, β-unsaturated carbonyl (>C═O) chemical entity;** and
- **the enolate.***

Stereogenic Centre

Let us look into a ***tetrahedral* 3D–structure** of an **sp^3–C–compound**, wherein the respective ***four* corners** of the respective *tetrahedron* are duly occupied by **4-different atoms or moieties.** In other words, provided the **4 σ-bonds** duly formed by an **sp^3–C–atom** are obtained with altogether **4-divergent atoms,** in such a situation one may eventually:

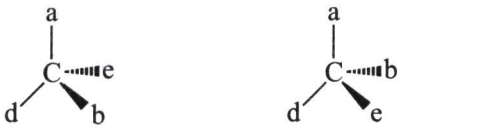
"retain a 3D-configuration which fails to possess any sort symmetry element except C–1 in it."

Therefore, in such a typical environment, one may critically observe the presence of **4-moieties or atoms in C_{abde}** which may be arranged particularly around the **sp^3-C-atom** in the following *two* manners, such as:

- **a right-handed manner;** and
- **a left-handed manner [from *a* → *b* → *d* → *e*].**

Besides, the aforesaid *two* arrangements are found to be related to each other as the so-called **non-superimposable images.** Thus, we may have the following ***two* orientations:**

* Oare DA and Heathcock CH: *Topics Stereochem.*, **19**: 227–407, 1989; Heathcock CH: In: **Modern Synthetic Methods** [Ed., R Scheffold, VHCA, Basel, pp, 1–103, 1992.

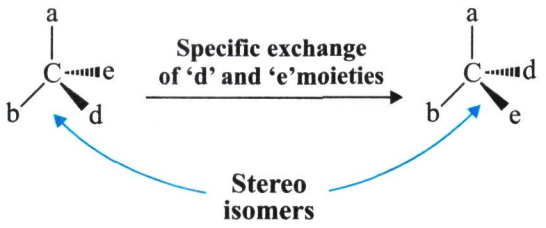


Left-handed way (a→b→d→e) **Right-handed way** (a→b→d→e)

Hence, based on the above example of a **stereogenic centre** duly present in the ***sp*^{3}-C-atom** in C_{abde} ***molecule***,–the definition of the **stereogenic centre** may be stated as:

"an atom with moieties or atoms of such nature than an exchange of any *two* moieties or atoms yield a *'stereoisomer'*."

Example: The above conceived expression of thought may be exemplified as under:



Now, if both the reactants do essentially contain a **'stereogenic centre'**, it could be both possible and feasible to accomplish the so-called phenomenon of ***'diastereoselectivity'*** *i.e.*, an obvious similarity pertaining to the **'aldol reaction'.**

Diastereoselective Reactions

In order to understand the intricacies of the **diastereoselective reactions** we may have to consider ***four* different cases,** namely:

(*a*) Since both **'enolate'** and ***'α, β-unsaturated carbonyl compound'*** invariably occur in ***'E'*** and ***'Z'*** isomeric forms;

(*b*) In a situation, when the ***Z*-enolate** interacts with the corresponding ***E*-enolate of α, β-unsaturated carbonyl compound**, one may virtually obtain ***two* staggered conformations*** (or *transition states*), whereby the observed coordination with the *'metal centre'* is solely responsible to bring together the ensuing ***reactants***; and this is also termed as ***'chelation control phenomenon'.***

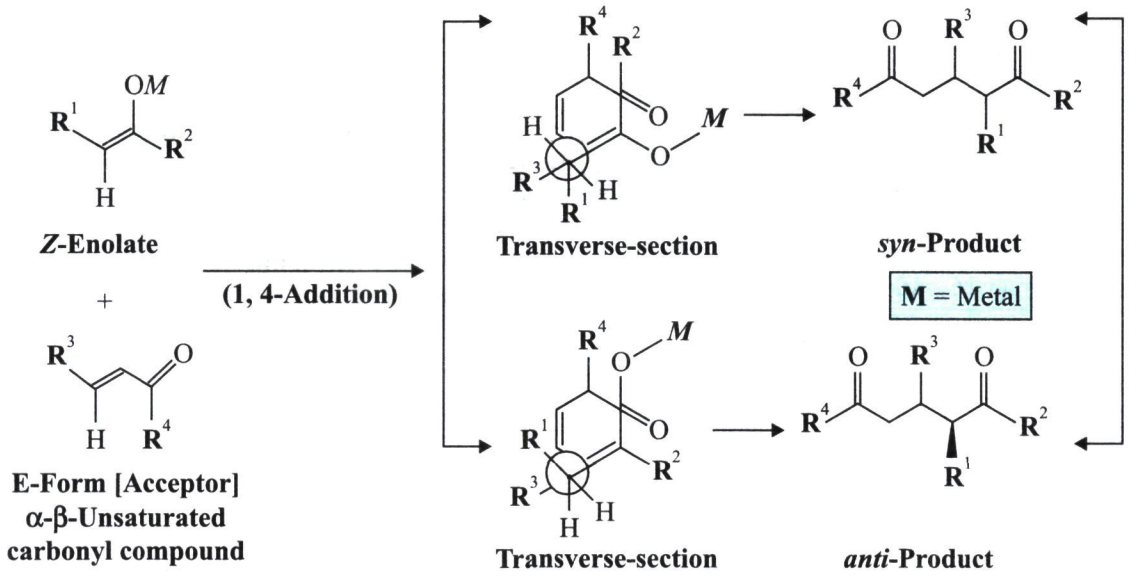
(*c*) Importantly, the ***two* transition states** ultimately lead to the generation of both ***syn*-and *anti*-products;** of which the ***anti*-form** usually to be seen abundantly since the ***syn*-product** remains **unfavourable thermodynamically** perhaps by virtue of the prevailing ***mutual steric hindrance*** between **R^3 and R^4 groups.**

(*d*) Amazingly, the observed ***steric hindrance*** between **R^3** and **R^4** is mostly held responsible for causing the actual **diastereoselectivity** predominantly.

---

* **Staggered Conformation:** It refers to the conformation of moieties (groups) attached strategically to ***two* adjacent atoms**; and hence, said to be *staggered* if the *torsion angles* are such that the moieties are as far away as possible from an eclipsed arrangement.

The various reactions may be expressed as under:



Remarks: In addition, the following classical *combinations* are also possible and feasible, namely:

- ***E*–Form of Enolate**
  + ⟶ ***syn*-Product**
  ***E*–Form of α, β-unsaturated carbonyl (>C═O) compound [Acceptor]**
- ***Z*-Form of Enolate**
  + ⟶ ***anti*-Product**
  ***E*–Form of α, β-unsaturated carbonyl (>C═O) compound [Acceptor]**

Tandem Reactions Comprising the Michael Addition and the Consecutive Reactions

Now let us take into consideration a typical instance when a **Michael addition** of a ***enolate*** does give rise to the formation of a ***ketone enolate*** as:

"its most preferred *reaction product.*"

Obviously, in such a situation the ensuing ***'enolate'*** shall be **protonated** practically to the maximum extent to yield the respective ***'ketone'***. However, the *reaction medium* remains still ***'basic'*** in character because it still contains enough of the so-called **hydroxy** *[$HO^{\ominus}$]* or **alkoxy** *[$RO^{\ominus}$]* **ions.**

Therefore, the *Michael adduct*, a ketone (>C═O) is, therefore, gets *deprotonated* ($-H^{\oplus}$) reversibly only to a small degree.

Effect of Deprotonation

It has been duly observed that the overall **effect of deprotonation** may actually afford to reform specifically the ***ketone enolate*** which was eventually formed as:

"an *intermediate* ex-route to the respective *Michael product.*"

Importantly, the so-called ***'regioisomeric ketone enolate'*** may also be generated skillfully and intelligently in altogether ***three*** **different ways**, such as:

(*i*) **1, 5-Diketone [Michael Adduct 'C']** : Fig. 8.1 (*a*);

(*ii*) **δ-*Keto* aldehyde** : Fig. 8.1 (*b*); and

(*iii*) **δ-Ketoester** : Fig. 8.1 (*c*),

which may now be discussed in details separately in the sections that follows:

(*a*) 1, 5-Diketone: The formation of **1,5-diketone** *i.e.,* the **Michael adduct 'C'** may be explained explicitly based on the following sequence of reactions:

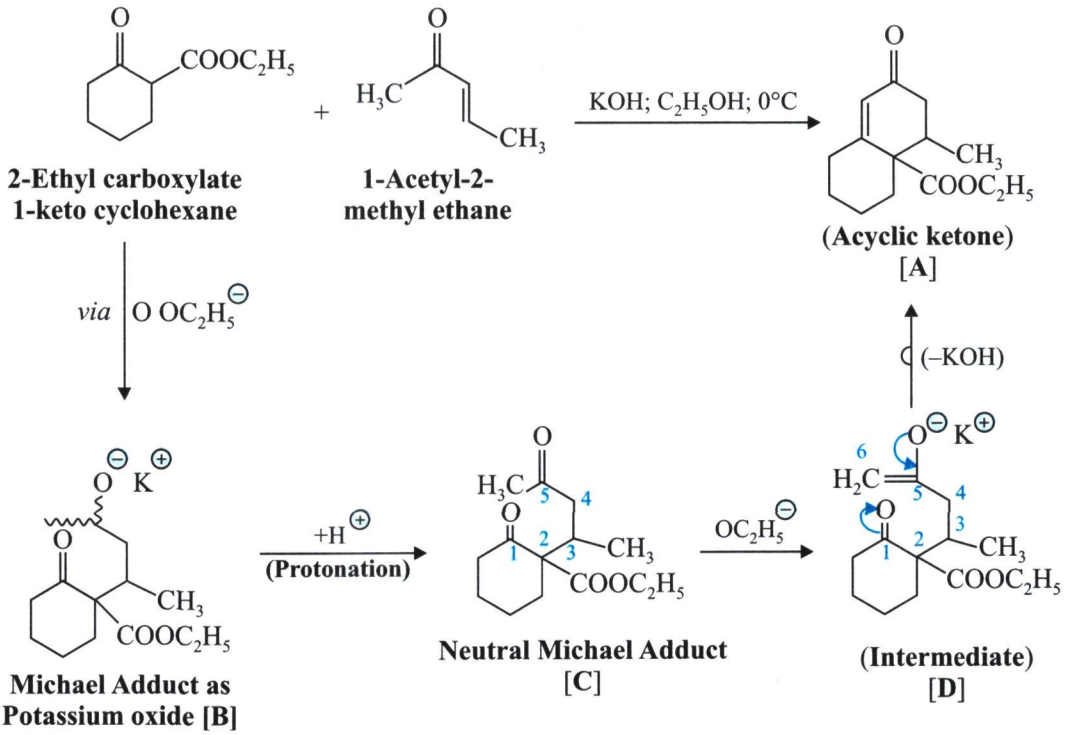


Fig. 8.1 (a) The Tandem Reaction comprising a Michael addition and an aldol condensation: Robinson annulation reaction of the 6–membered rings that are virtually condensed to an existing ring.

EXPLANATION

1. Reaction between **2-ethyl carboxylate-1-*keto*-cyclohexane** and **1-acetyl-2-methyl ethane** in the presence of an alkali (KOH) and ethanol at 0°C yields a **cyclic ketone (A).**
2. Also the interaction amongst the ***two*** **reactants** [mentioned in, (1) above] *via* the **ethoxide anion** gives **Michael adduct (B)** as the *potassium oxide*, which on being subjected to *protonation* yield a ***neutral*** **Michael adduct (C)** (which is a **1, 5-diketone**).

NOTE: **Nevertheless, the *'regioisomeric ketone enolate'* may also be generated as shown in Fig. 8.1 (*a*) through 8.1 (*c*).**

3. The resulting **product (C)**, in the presence of *ethoxide anion* gives an **intermediate (D)**, wherein the newly evolved **enolate carbon** is located strategically at ***position 6*** in **(D)** above.

4. Interestingly, the ***numbering scheme*** in the **intermediate (D)** we may observe: *"position one is being held by the* C=O *double bond of the kets* (>C=O) *moiety. [see Fig. 8.1(a)]"*
5. The resulting **intermediate (D)** loses a mole of KOH to produce a **cyclic ketone (A).**

General Remarks: Considering Fig. 8.1 (*a*) once again the **enolate (D)** may eventually undergo an ***'aldol reaction'*** having the **carbonyl (C=O) double bond** of the *ketone*. Thus, it gives rise to the formation of the **'bicyclic compound (A)'**–as the ***condensation product.*** However, it is also possible to combine the *formation* as well as the *consecutive reaction* of the so-called **Michael adduct** preferentially by means of:

"a one-spot reaction."

In true sense, the overall course of the undergoing reaction may be represented as an:

"annulation of a cyclohexanone to an enolizable ketone."

Therefore, the sequence of various reactions [as *given in Fig. 1.8 (a)*] is invariably termed as the **'Robinson Annulation'*** *i.e.*, regarded to be the most versatile and important synthesis of the ***6-membered ring systems.***

(*b*) δ-Keto-aldehyde: It usually represents the **tendem reaction II**, that essentially comprises a **Michael addition reaction** and an **aldol condensation reaction,** as given under in Fig. 8.1 (*b*).

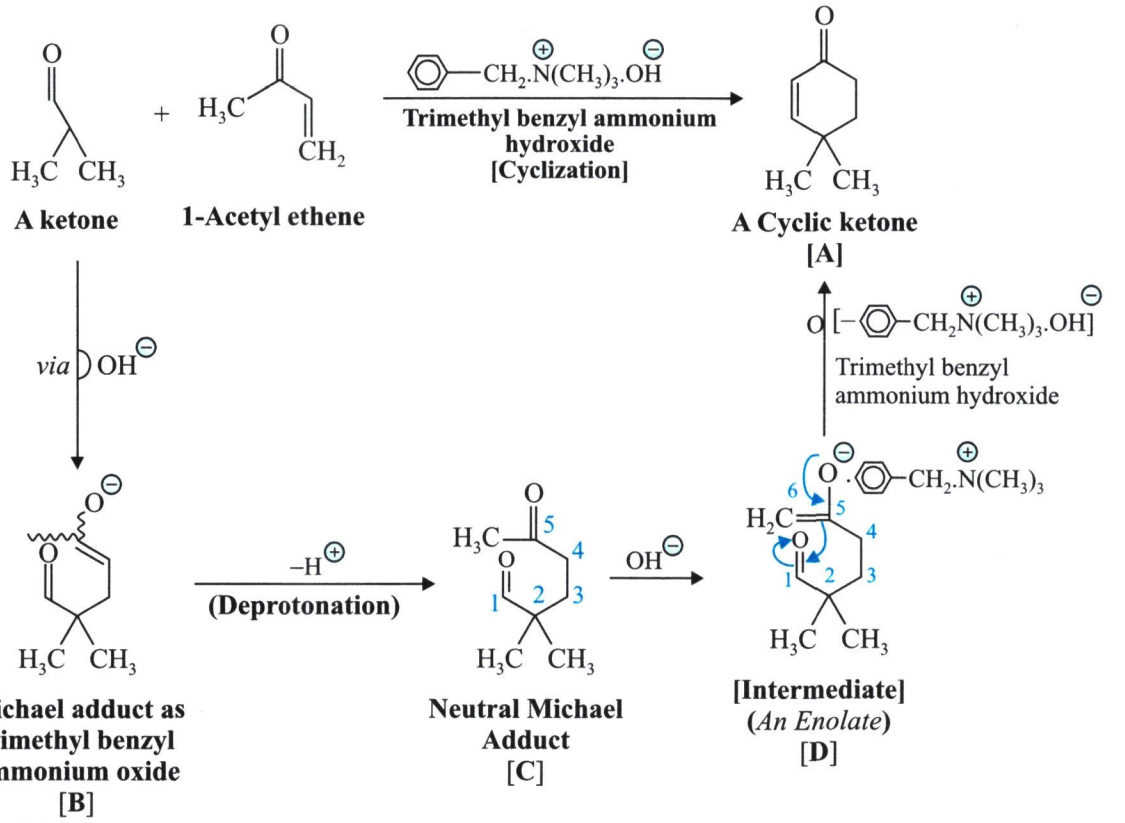


Fig. 8.1 (b) The Tandem Reaction II consisting of a Michael Addition and an Aldol Condensation.

*Rapson WS and Robinson R: *J Chem Soc.*, 1285, 1935.

EXPLANATION

1. The interaction between an **alkyl ketone** and **1-acetyl ethene** in the presence of **trimethyl benzyl ammonium hydroxide** (a *base*) causes *cyclization* to yield a **cyclic ketone (A).**
2. However, the reaction between the same *two* reactants [as in *(1) above*] in the presence of a *base* gives rise to the formation of **Michael adduct** as the corresponding **trimethyl benzyl ammonium oxide (B),** which on *deprotonation* yields **neutral Michael adduct (C).**
3. The resulting **product (C)** gives the **enolate (D),** –that eventually undergoes an ***'aldol condensation'*** with the **C=O double bond.**
4. The **enolate (D)** knocks out a mole of **trimethyl benzyl ammonium hydroxide** to yield a **cyclic ketone (A).**

NOTE: The reaction represent a *6-membered ring synthesis* even though it is not a six-ring annulation.

(*c*) δ-Keto ester: It explicitly designates a **Tandem Reaction** that essentially comprises a **Michael addition** and an **Enolate acylation** [as depicted in *Fig. 8.1 (c)*]. However, the so-called *major tautomer* of the reaction product is not shown in the said figure.

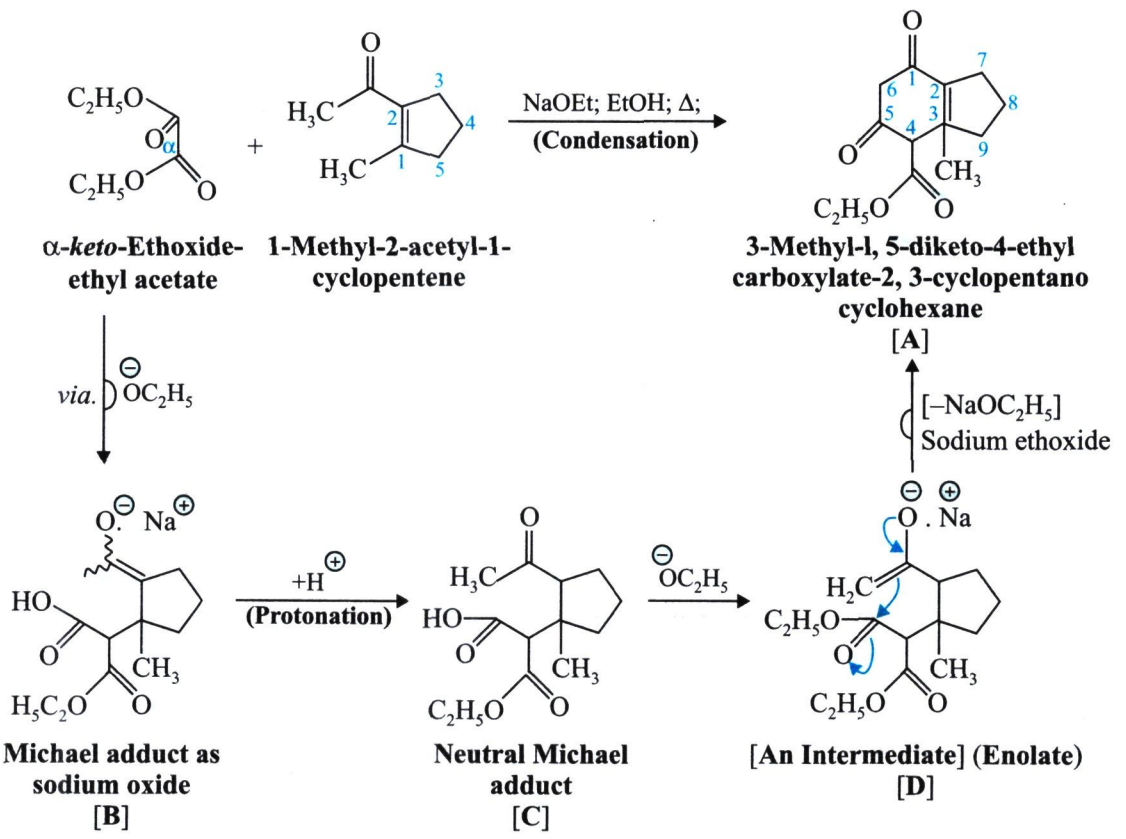


Fig. 8.1 (c) The Tandem Reaction comprising a Michael Addition and an Enolate Acylation. [The major tautomer of the reaction product is not shown].

EXPLANATION

1. The reaction between **α-*keto*-ethoxide ethyl acetate** and **1-methyl-2-acetyl-1-cyclopentane** undergoes *condensation* in the presence of sodium ethoxide, *ethanol*, and *mild heating* to give **3-methyl-1,5-diketo-4-ethyl carboxylate-2,3-cyclopentano cyclohexene (A).**
2. Besides, the interaction of the said ***two* reactants** [as in (1) above] in the presence of *sodium ethoxide* (freshly prepared) yields the **Michael adduct as its sodium oxide (B)**, which on subsequent *protonation* gives a ***neutral* Michael adduct (C).**
3. The resulting **product (C)** on further treatment with *ethoxide anion* ($\overset{\ominus}{O}C_2H_5$) gives rise to the formation of an **enolate (D)** as an **intermediate product.**
4. The **enolate (D)** when subjected to treatment with *sodium ethoxide* (freshly prepared) gives the *bicyclic compound*: **3-methyl-1,5-diketo-4-ethyl carboxylate-2,3-cyclopentano cyclohexene (A).**

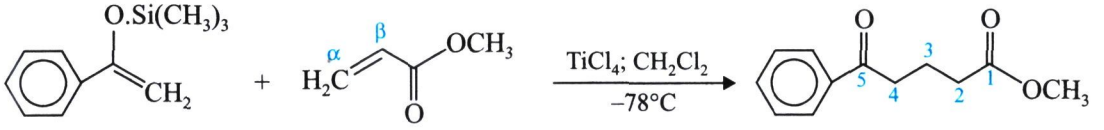
Comments: Enolate (D) [See *Fig. 8.1 (c)*] gets duly acylated by the respective ester following the usual mechanism. The **bicyclic compound (A)** designates a product, that critically contains a **new 6-membered ring system** which has been ***annulated* to an existing ring.**

Mukaiyama Michael Reaction*

It relates to the formation of **1,5-dicarbonyl compounds** by the interaction of:

- **ketone silyl acetals,** and
- **α,β-unsaturated ketones and esters.**

We may have the following expression:



A Ketone silyl acetal (I) | **α, β-Unsaturated ketone (II)** | **1, 5-Dicarbonyl compound (III)**

Thus, the reaction between **(I)** and **(II)** comes into play in the presence of *titanium tetrachloride* ($TiCl_4$) and *methylene dichloride* (CH_2Cl_2) at **–78°C** to produce the desired **1,5-dicarbonyl compound (III).**

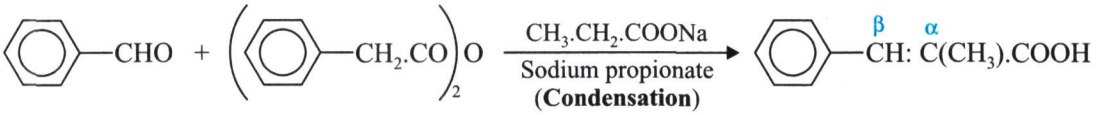
8.2.5 Perkin Reaction

The **Perkin reaction** essentially involves the *condensation* of **aryl aldehydes** (*viz.*, benzaldehyde or any other aromatic aldehyde) on being subjected to heating with the *anhydride of an aliphatic acid* (**containing *two* active H–atoms**) *e.g.*, **acetic anhydride** in the presence of its *sodium salt* (CH_3COONa, sodium acetate) to yield a **β-arylacrylic acid**, such as:

"benzaldehyde, acetic anhydride, and sodium acetate gives a mole of cinnamic acid."

*Mukaiyama T and Kobayashi S: *Heterocycles,* **25**: 245, 1967; Narsaka K *et al. Bull Chem Soc. Jpn.,* **49**: 779, 1976.

Thus, we may have the following expression:



Benzaldehyde **Propionic anhydride** **α-Methyl cinnamic acid**

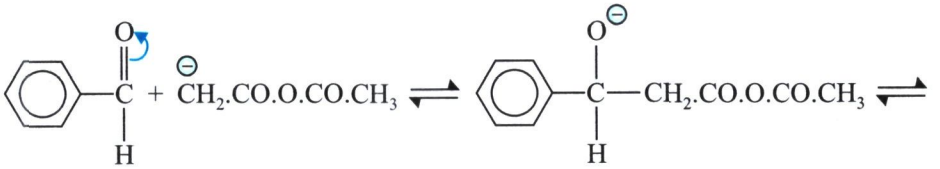
Mechanism of Perkin Reaction

Infact, the underlying **mechanism of Perkin reaction** has long been the subject of *contradictions* and *discussions.* Initially, **Perkin** have had the notion that the ***anhydride*** was duly engaged in the aforesaid reaction itself; however, fitting strongly opined it was indeed the ***salt***. The overall present generalized concept being that it is the particular ***'anhydride'*** which serves as the respective **'addendum'**. Nevertheless, the actual steps involved are found to be **'quite uncertain'.**

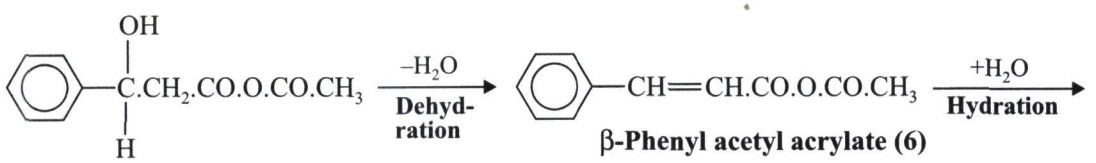
Hence, the **mechanism of Perkin reaction** may be expressed as follows (*i.e.,* based on the *Aldol Condensation phenomenon*):



Dimethoxy ether (1) **Acetate ion (2)** **An Anion (3)**



Benzaldehyde **An Aryl oxide ion (4)**



Aldol (5) **β-Phenyl acetyl acrylate (6)**



β-Phenyl acrylic acid (7) **Acetic acid**

Explanation

1. The interchangeable (reversible) reaction between *dimethoxy ether* **(1)** and an *acetate ion* **(2)** yields an ***anion*** **(3)** plus a mole of acetic acid.
2. The resulting **anion (3)** interacts with *benzaldehyde* to give an **aryl oxide ion (4)** by a reversible reaction, which further yields an **aldol (5).**

3. The **aldol (5)** on being subjected to *dehydration* gives **β-phenyl acetyl acrylate (6)**, which on *hydration* produces the **β-phenyl acrylic acid (7)** with the elimination of a mole of *acetic acid.*

Points to Ponder: These essentially include:

1. Preferentially the so-called **α-H-atoms** of the *anhydride* are intimately in the *condensation* process.
2. The **acyloxyl ion** (or the **acetate ion**) more or less behaves as the base (whereas, in certain specific instances **triethylamine**, $N(CHCH_3)_3$, as the base even yields better overall results).
3. Evidences based on the experimental observations reveals that the **Perkin reaction** invariably proceeds on a much faster mode when the respective **'aldehyde (-CHO)'** does contain either:
   - **a halogen (X) atom,** or
   - **a nitro ($-NO_2$) group** (in ***the ring system***).

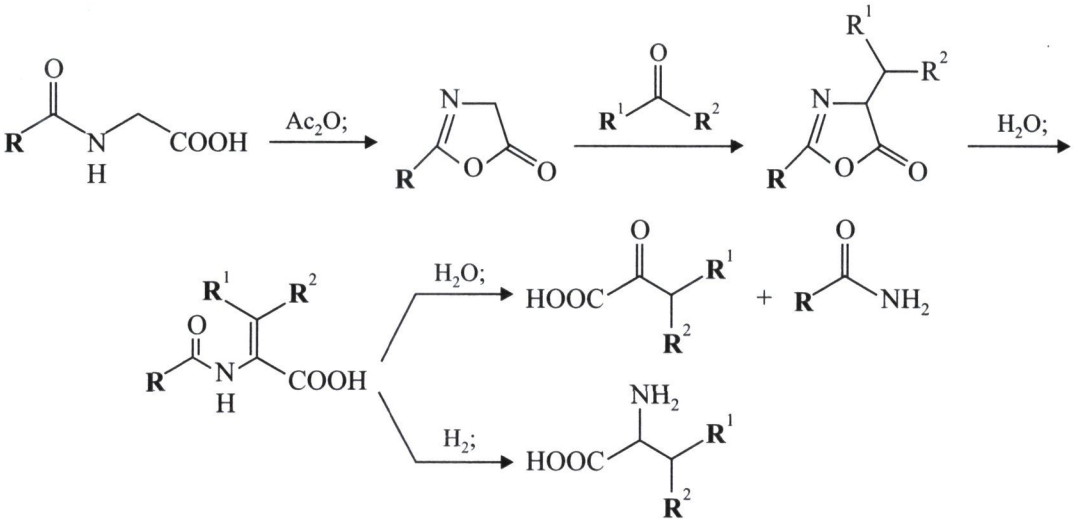
NOTE: **It is worthwhile to state here that the *Perkin*, reaction fails to proceed with *'aliphatic aldehydes'*; however, it may eventually take place if the incumbent *'anhydride'* happens to be *p*-nitrophenylacetic anhydride (Crawford *et al.*, 1959).**

Erlenmeyer-Plöchl Azlactone and Amino Acid Synthesis*

In a broader sense, it relates to the formation of: ***"azlactones* by intramolecular condensation of the acylglycines in the critical presence of acetic anhydride."**

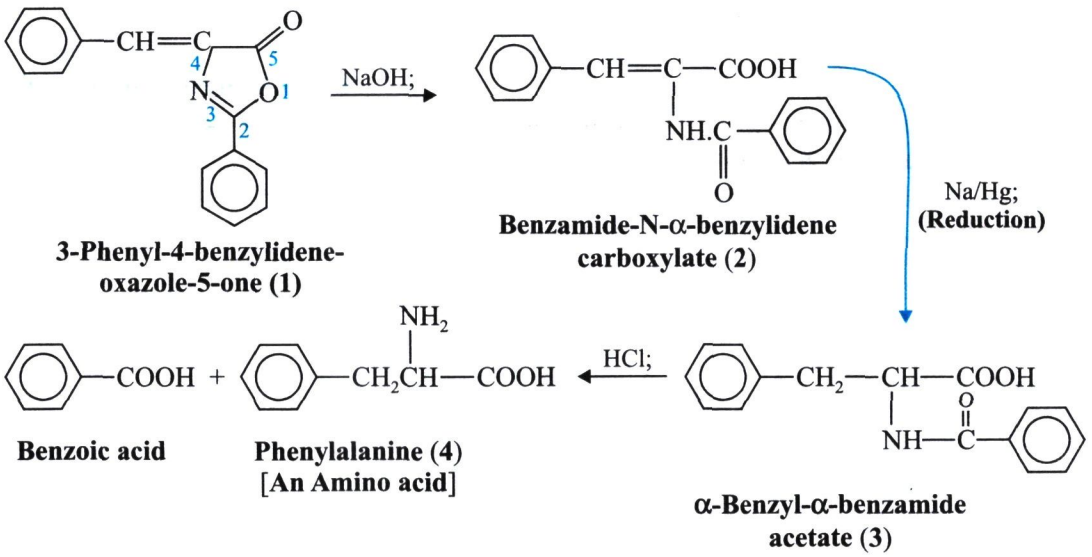
Hence, the reaction of **azlactones** with *carbonyl* **(>C=O)** *chemical entities* immediately followed by hydrolysis to the corresponding unsaturated *α-acylamino acid* and also by *reduction* gives the ***amino acid***; whereas, the *drastic* (*vigorous*) *hydrolysis* gives rise to the formation of the desired ***α-oxo acid.***

The various sequential reactions may be shown as under:



*Erlenmeyer E: *Ann.*, **275**: 1, 1893; Plöchl J: *Ber*, **17**: 1616, 1884.

Another school of thought believes vehemently that the **azlactones** are regarded to be extremely important as the **'intermediates'** in the preparation of ***amino*-and *keto*-acids** *viz.*, the amino acid **phenylalanine** may be synthesized from the **benzoyl-α-aminocinnamic azlactone** (or **3-phenyl-4-benzylidene oxazol-5-one**) as stated under:



EXPLANATION

The various steps involved in the above sequence of reactions may be explained as under:

1. The alkaline treatment of **3-phenyl-4-benzylidene oxazole-5-one (1)** brings forth the cleavage of the *heterocyclic oxazole* ring to yield **benzamide-N-α-benzylidene carboxylate (2).**
2. The resulting **product (2)** on being subjected to *reduction* with *sodium amalgam (Na/Hg)* yields **α-benzoyl-α-benzamide acetate (3),** which upon acidic treatment gives **phenylalanine** (4) plus a mole of benzoic acid.

8.2.6 Reformatsky Reaction* [Reformatskii Reaction]

In order to understand the fundamentals of **Reformatsky reaction** we may have to be apprised ourselves adequately with the so-called **Organozinc Compounds.**

The **electronegativity difference** observed broadly between **C** and **Zn** stands at **0.8** for which the respective **C–Zn bond** must be approximately **30% ionic** in nature; and, therefore, such kind of the **organometallic chemical entities** may be prepared conveniently and easily by means of the prevalent **'transmetallation reaction'.**

Example:

$2RLi$	+	$ZnCl_2$	⟶	R_2Zn	+	$2\ LiCl$
Alkyl lithium		Zinc chloride		**Dialkyl zinc**		Lithium chloride

*Reformatskii S: *Rev.*, **20**: 2010, 1887.; *J Russ Phys Chem Soc.*, **22**: 44, 1890.

Comments: Amazingly, the **dialkyl zinc (R_2Zn)** is found to be quite ***'unstable'*** as well as ***'explosive in character'***; and also is readily attacked by either:

- **H_2O_2/HCl [hydrogen peroxide in HCl]**; or
- **C_2H_5OH [ethonolic medium].**

Besides, Zn^{2+} (being a divalent metal like Mg^{2+}) is prone to form the **Grignard type chemical entities** (*compounds*) eventually. However, such kind of ***'organozinc compounds'*** do undergo the phenomenon of disproportionation quite easily.

Example:

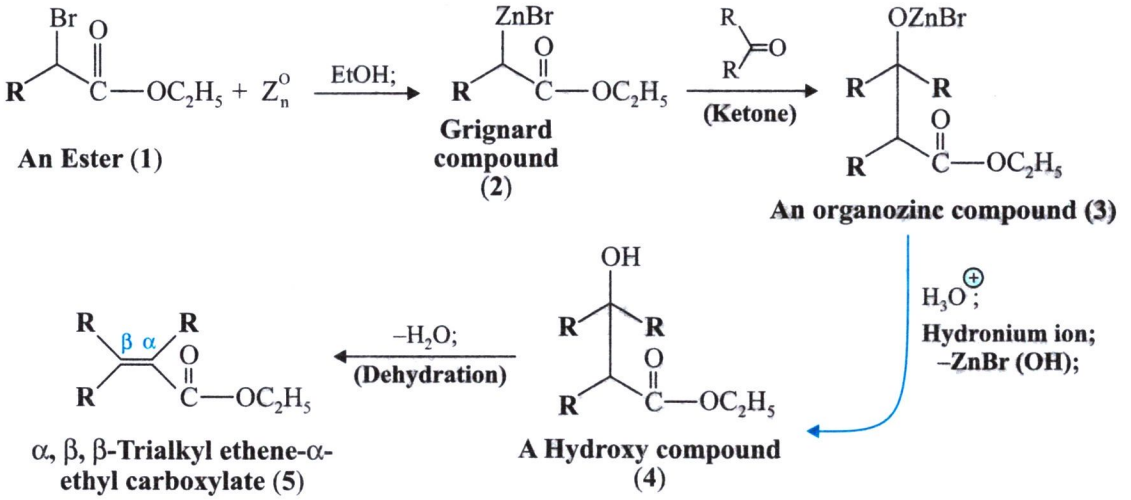
$$\underset{\substack{\textbf{Alkyl-zinc halide}\\ \textbf{(Grignard compound)}}}{2R\ ZnX} \longrightarrow \underset{\textbf{Dialkyl-zinc}}{R_2Zn} + \underset{\text{Zinc halide}}{ZnX_2}$$

Remarks: Interestingly, when an *electron-withdrawing group (EWG) viz.*, an **ester moiety (—COOR)** is located strategically in the vicinity of a typical **'C–Zn'** bond, the overall observed stability of the ***'zinc-organyls'*** gets improved substantially.

NOTE: **In reality, this kind of *'organozinc compounds'* gets duly formed as an intermediate in the *Reformatsky reaction* perceptively.**

Reformatsky Reaction

We may often encounter an array of common types of ***'nucleophilic reactions'*** invariably undergone by the so-called **organozinc chemical entities** could be exemplified by the following **Reformatsky reaction:**



Explanation

1. An **ester (1)** reacts with Z_n^o in the presence of absolute ethanol yields a **Grignard compound (2)**, which on being treated with a *ketone* forms an **organozinc compound (3).**

NOTE: **Because the so-called organozinc chemical entities are found to be much less reactive *vis-a-vis* either the Grignard reagent or the alkyl lithium (ELi)—they virtually attack 'chemoselectively' the keto (>C═O) carbonyl moiety and certainly not the ester (—COOR) moiety. Besides, these organozinc compounds also fail to attach such functional groups as:**

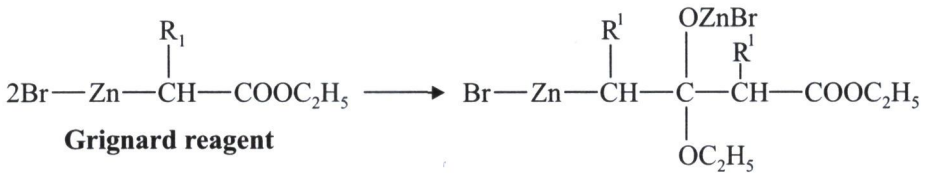
—C≡N (Nitrile); >C═N—; or CO_2.

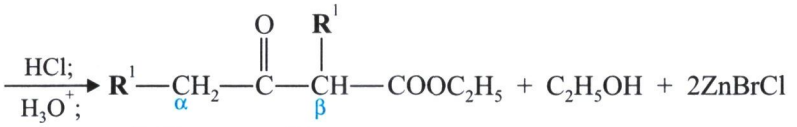
2. The resulting **compound (3)** when subjected to treatment with the **hydronium ion** eliminates a mole of *zinc bromo hydroxide* to form a **hydroxy compound (4).**
3. The resulting **compound (4)** upon dehydration forms an **unsaturated product (5)** known as: **α, β, β-trialkyl ethene-α-ethyl-carboxylate** (which being an *ester derivative*).

- Importantly, another school of thought recognizes the **Reformatsky (Reformatskii) reaction** to have a close relationship with the so-called **Grignard reaction (GR)**—whereby the initial intermediate so formed bears a close similarity to that of **GR.** It is, however, important to mention here that **GR** could not be possibly derived from the ***'β-ketoesters'*** because it reacts critically with the ***active halogen atoms*** instantly. Since the **organiczinc chemical entities** are certainly prove to be **much less reactive** *vis-a-vis* the **GR**; and also fail to react with their ***inherent*** **ester (—COOR)moiety** at all.
- In a typical instance, when the **'ketone (>C═O)'** is *too densely substituted* the **organic-zinc chemical entity** *(compound)* may not be added to it easily perhaps due to the prevailing **steric hindrance.** Therefore, in such a crucial instance the reaction generally proceeds by virtue of its:

"own ester (—COOR) moiety yielding the β-ketoester".

Thus, we may have the following sequence of reactions:

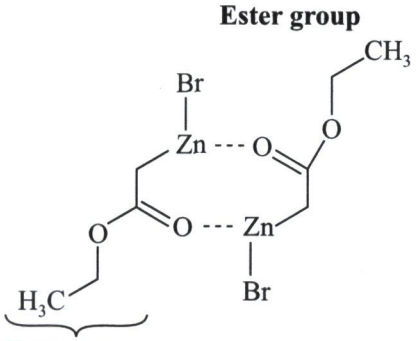




EXPLANATION

Thus, *two* moles of a **Grignard reagent** (*with Zn*) yields an **organozinc compound (A)** due to *condensation*, which eventually on further treatment with *HCl* and *hydronium ion* (H_3O^+) gives rise to the formation of a **β-ketoester (B)** plus a mole of *ethanol* and *two* moles of *zinc bromo chloride.*

Special Note on Organozinc Reagent: A survey of literature rightly suggests that the **organic reagent** is also invariably termed as **'Reformatskii enolate'**. Thus, one may prepare conveniently the **organozinc compounds** from the respective ***α-halogenesters*** [*i.e.,* quite akin to Grignard reagent (GR)], as stated under:



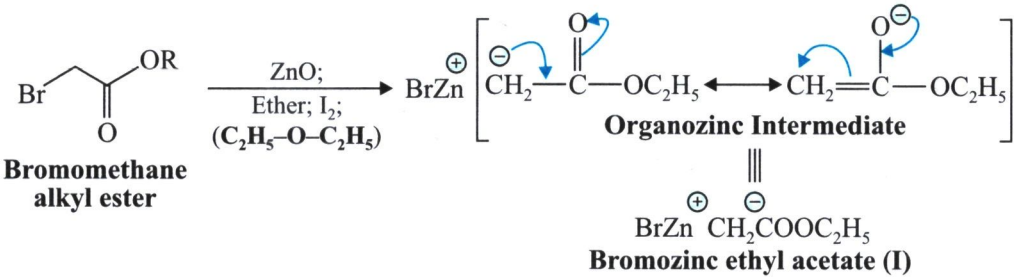
An ester stabilized organozinc reagent

Mechanism of Reformatsky Reaction

In order to have an in-depth understanding with regard to the probable **mechanism of the reformatsky reaction**, we may have to examine the following ***two*** **sequential steps involved:**

Step 1: Formation of an Organozinc Intermediate from Zn and an α-Bromoester

The following reactions are involved:



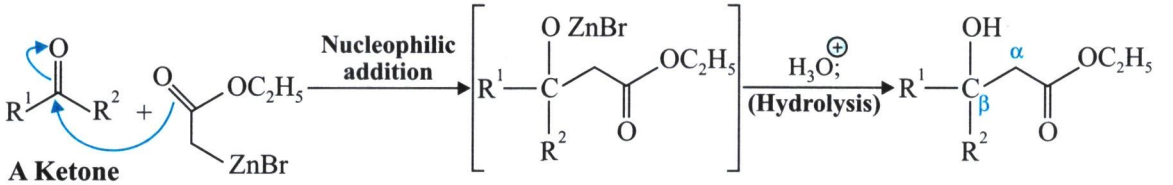
Bromomethane alkyl ester

Bromozinc ethyl acetate (I)

Thus, **bromomethane alkyl ester** when treated with pure *ZnO*, solvent ether and iodine gives the **organozinc intermediate**, which is equivalent to the so-called **benzozinc ethyl acetate (I).**

Step 2: Oxidative Addition of Zinc-salt of 'Enol-ester' to carbonyl (>C=O) Moiety of Aldehyde (–CHO) or ketone (>C=O) and subsequent Hydrolysis to produce β-Hydroxyester.

Thus, we may have the following expressions:



A Ketone

Zinc salt of enol ester (I)

Organozinc intermediate

β-Hydroxy ester (II)

Remarks: In general, the **Reformatski reaction** proceeds most efficaciously with such **carbonyl (>C=O) reactants:**

- **Aldehydes (—CHO)**
- **Methyl ketones** $\left(-CH_2-C(=O)\right)$ **and**
- **Cyclic ketones** $\left(\text{C}_6\text{H}_4(=O)\right)$.

Reactivity Profile of the α-Haloesters

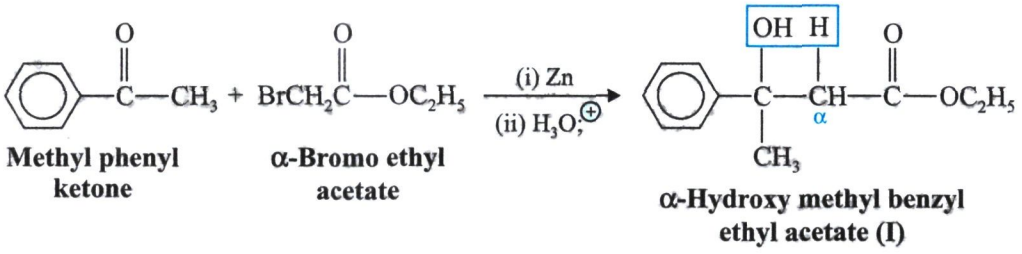
Amazingly, the reactivity order of the **α-haloesters** is as given below:

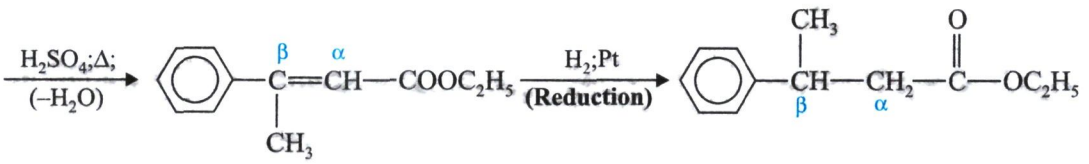
- **Iodo (I)** • **Bromo (Br) and** • **Chloro (Cl).**

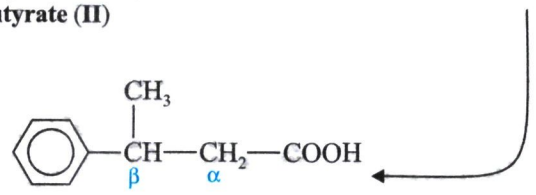
In reality, such a reaction is indeed found to be extremely useful for the **'lengthening' of the C–chain'** *viz.*,

- **saturated or unsaturated organic acids**; or
- **saturated or unsaturated organic esters,**

with critical ***branching*** taking place at **α– and β–carbon atoms**, which may be synthesized as stated under:



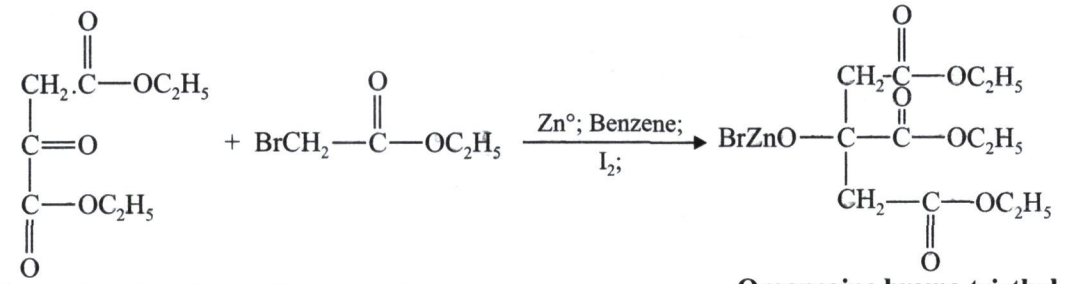




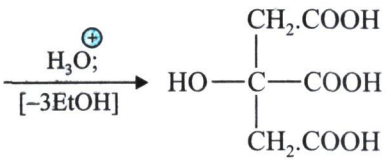
The various steps involved in the above sequential reactions are *self-explanatory.*

Usefulness of Reformatsky Reaction in the Synthesis of Drug Substances [Citric Acid; Citral; Vitamin A Alcohol]

(a) Synthesis of Citric Acid



Diethyl oxalacetic acid (1) **α-Bromoethyl acetate (2)** **Organozinc bromo triethyl citrate (3)**

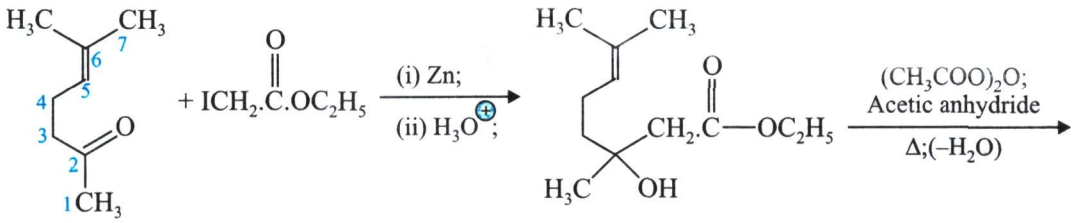


Citric acid (4)

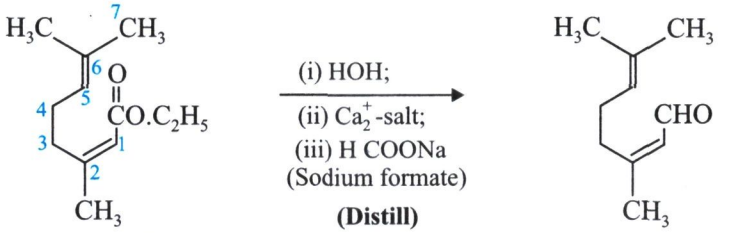
EXPLANATION

The interaction of **diethyl oxalacetic acid (1)** and **α-bromo-ethyl acetate (2)** in the presence of Zn, benzene and iodine yields the **organozinc bromo triethyl citrate (3)**, which upon hydrolysis with ($H_3O^{\oplus}$) gives **citric acid (4)** with the loss of 3 moles of **ethanol.**

(b) Synthesis of Citral



6-Methylhept-5-ene-2-one (A) **α-Iodo ethyl acetate (B)** **6-Methylhept-5-ene-2-hydroxy-2-ethyl acetate (C)**

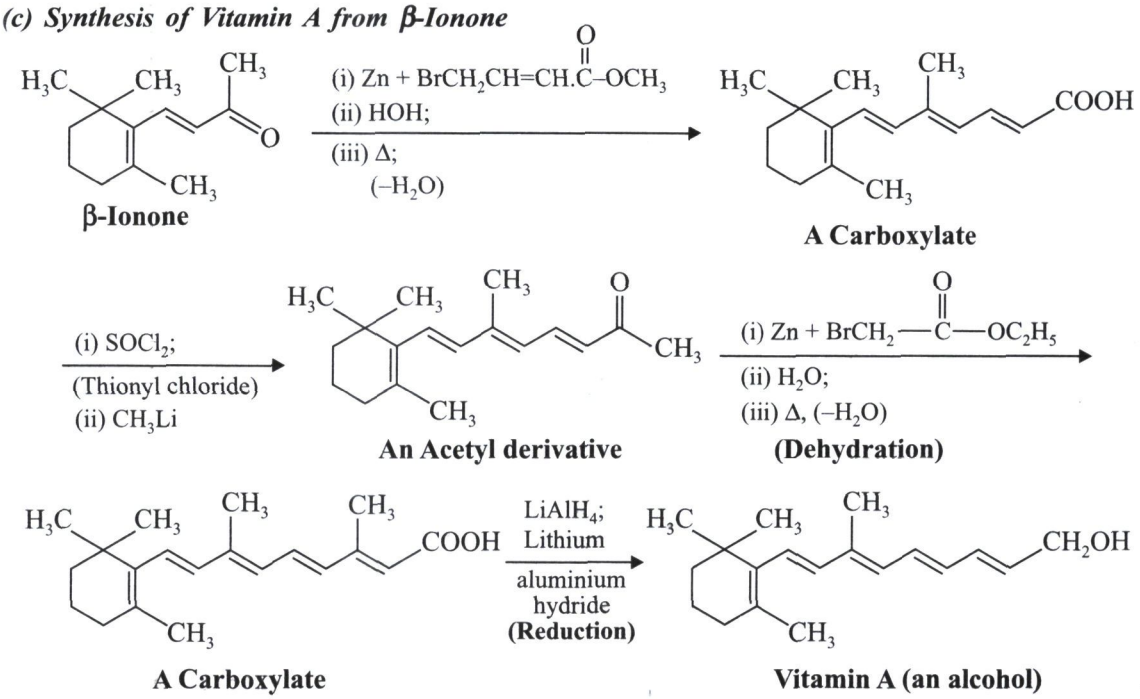


2, 6-Dimethylhept 1, 5-diene-1-ethyl carboxylate (D) **Citral (E) [An aldehyde]**

EXPLANATION

1. The reaction between **6-methylhept-5-ene-2-one (A)** and **α-iodo ethyl acetate (B)** in the presence of Zn and $H_3O^{\oplus}$ gives **6-methylhept-5-ene-2-hydroxy-2-ethyl acetate (C).**
2. The resulting **product (C)** when treated with acetic anhydride and heated mildly loses a mole of water to yield **2,6-dimethylhept-1,5-diene-1-ethyl carboxylate (D).**
3. **Product (D)** on hydrolysis, followed by treatment with a Ca^{2+}-salt and then with sodium formate and distilled under reduced pressure gives rise to the formation of **Citral (E).**

(c) Synthesis of Vitamin A from β-Ionone

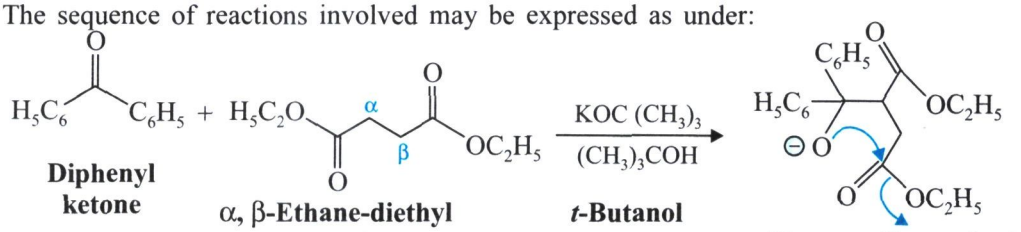


The various steps involved in the above synthesis of **Vitamin A** from **β-ionone** are self-explanatory.

8.2.7 Stobbe Condensation*

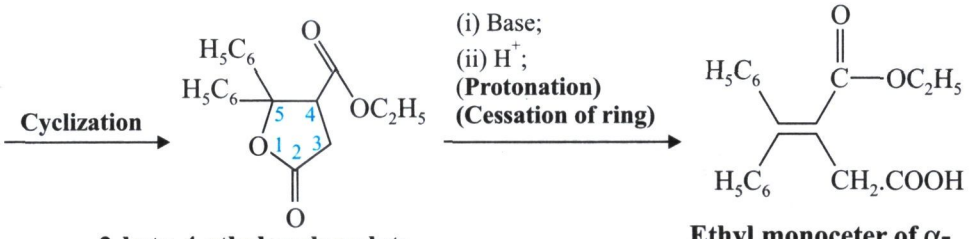
The **Stobbe condensation** relates to **"the condensation of *aldehydes* or *ketones* with diethyl succinate in the presence of a reasonably strong base to form the so-called *monoesters of α-alkylidene* (or *arylidene*) succinic acids."**

The sequence of reactions involved may be expressed as under:



(Contd.)

*Stobbe H., *Ber,* **2b**: 2312, 1893; *Ann.*, **282**: 280, 1894.



2-keto-4-ethyl carboxylate -5-diphenyl furan (II)

Ethyl monoceter of α-arylidene succinic acid (III)

EXPLANATION

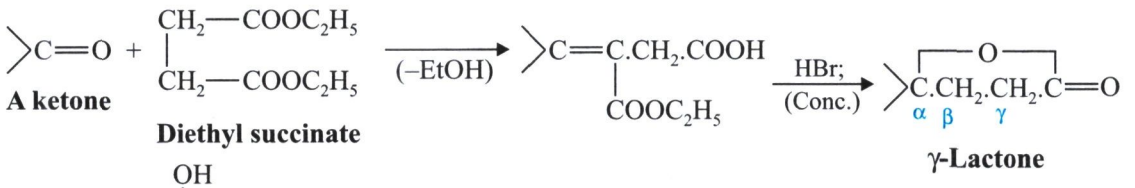
The reaction between **diphenyl ketone** and **α,β-ethane-diethyl carboxylate** in the presence of *trimethyl potassium butoxide* and ***tert*-butanol** yields an **intermediate (I),** which undergoes *cyclization* to form **2-*keto*-4-ethylcarboxylate-5-diphenyl furan (II).** The resulting **product (II)** on treatment with a *base* followed by *protonation* causes the cessation of the *furan ring system* to give the **ethylmonoester of α-arylidene succinic acid (III).**

In other words, the **Stobbe condensation** essentially refers to the reaction between:

- **a succinic ester**; and
- **a carbonyl (>C=O) chemical entity,**

in the critical presence of ***sodium ethoxide.*** Interestingly, Johnson and Daub (1951)* have indeed made a significant improvement in the overall yield of the **final product** by making use of **potassium *t*-butoxide [$KOC(CH_3)_3$]** in ***t*-butanol**, as the prevalent *condensing agent*; and they successfully employed the proposed method in the introduction of the ***'propionic acid residue'*** at the specific site of the **carbonyl (>C=O) moiety** in an **aromatic lactone.** Consequently, the **condensation product** thus formed is duly refluxed with *concentrated hydrobromic acid (HBr)* (in glacial acetic acid) to obtain the respective **γ-lactone**, which is subjected to *reduction*** *via* the corresponding **sodium salt.**

Thus, we may have the following expression:



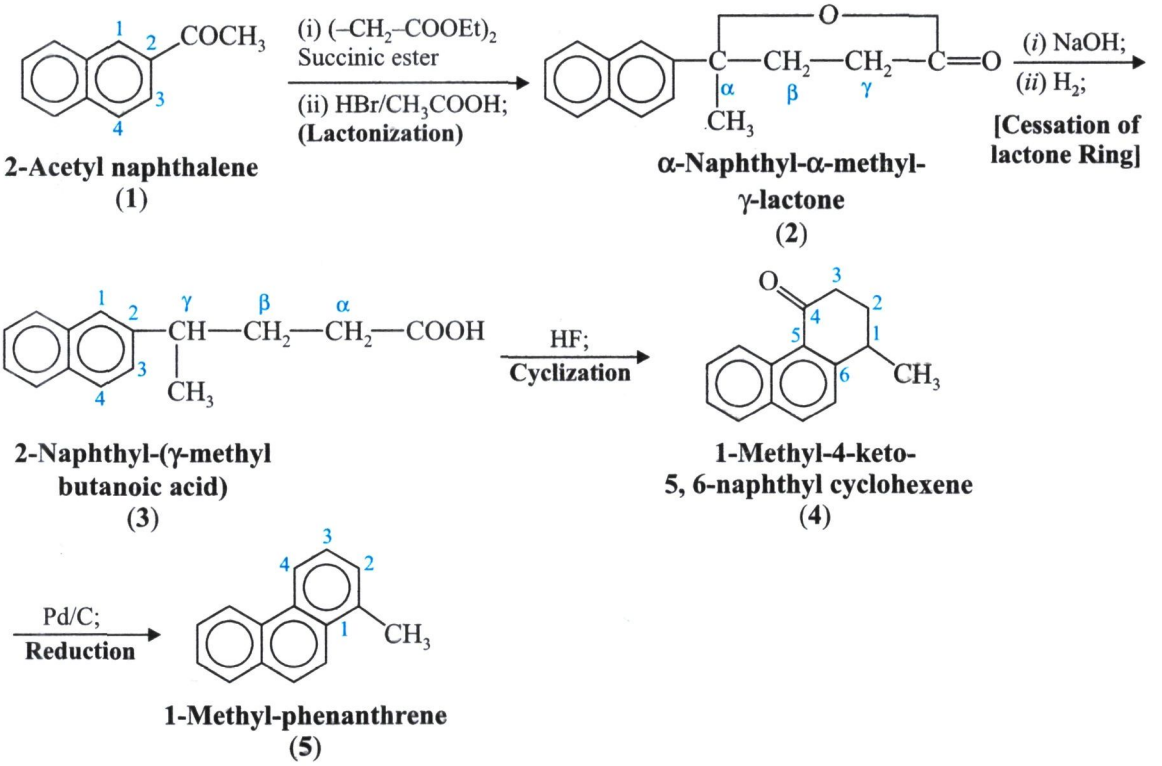
Besides, Johnson (1951) used this method to synthesize a host of **polynuclear chemical entities** (*compounds*), also termed as the **'polynuclear aromatic hydrocarbons'** (*e.g., naphthalene, anthracene, phenanthrene*).

---

* Johnson WS and Daub GH: *Org React.*, **6**: 1, 1951.

** That is, using **copper oxide** and **chromic oxide [CuO + CrO_3].**

Example: Preparation of 1-methylphenanthrene from 2-acetyl naphthalene as stated under:



2-Acetyl naphthalene (1)

α-Naphthyl-α-methyl-γ-lactone (2)

2-Naphthyl-(γ-methyl butanoic acid) (3)

1-Methyl-4-keto-5, 6-naphthyl cyclohexene (4)

1-Methyl-phenanthrene (5)

Explanation

The various steps involved in the above reactions may be explained as under:

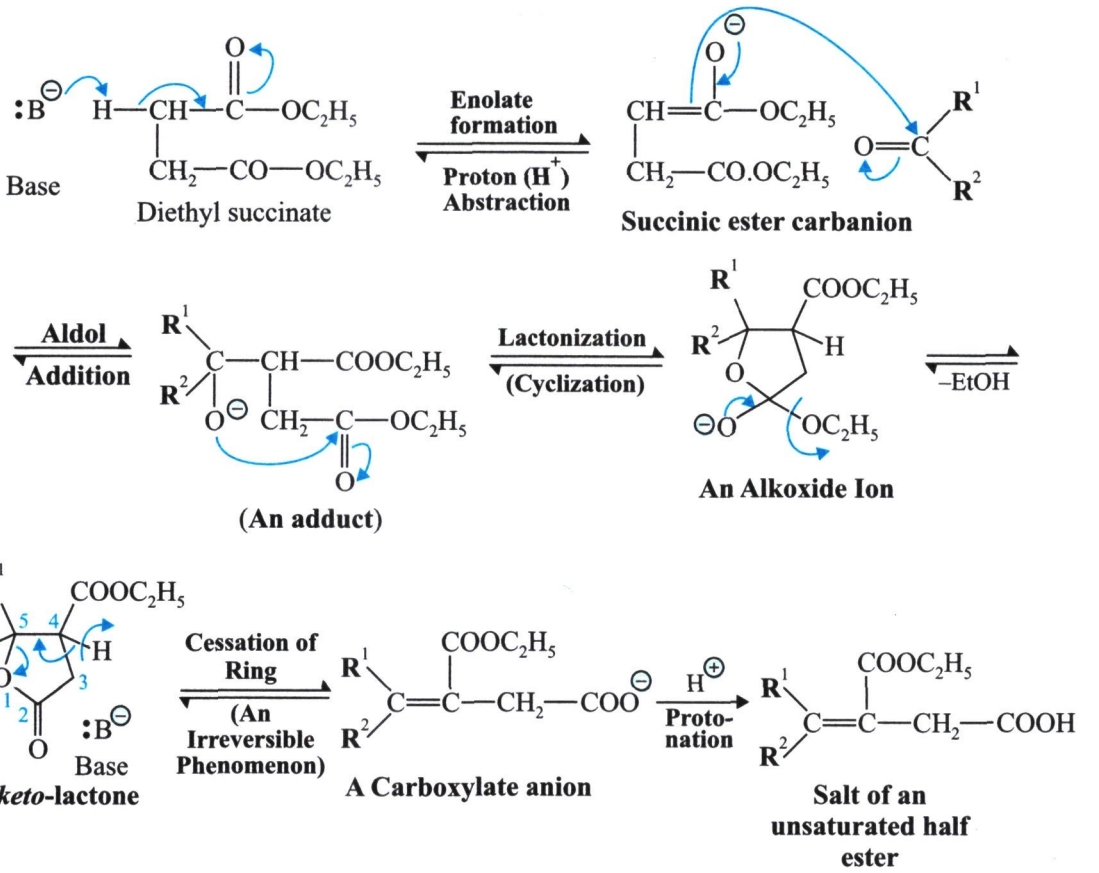
1. The starting material **2-acetyl naphthalene (1)** when reacted with a *succinic ester* followed by a mixture of HBr/AcOH results into the *lactomization* to yield **α-naphthyl-α-methyl-γ-lactone (2).**
2. The **product (2)** on subsequent treatment with an *alkali* (NaOH) and then *hydrogenation* affords the cessation of the lactone ring system to give **2-naphthyl-(γ-methyl butanoic acid) (3)** which on reaction with *hydrofluoric acid (HF)* undergoes *cyclization* to produce **1-methyl-4-*keto*-5, 6-naphthyl cyclohexane (4).**
3. The resulting **product (4)** on being subjected to *reduction* with **Pd–C** gives rise to the formation of **1-methyl-phenanthrene (5).**

NOTE: **The *Stobbe condensation* is found to be highly specific for the *succinic ester*; however, the carbonyl (>C=O) compounds *viz.*, aliphatic, α, β-unsaturated aldehydes; ketoesters; alicyclies; and cyanoketones may also be employed. Ketones are more often used than aldehydes.**

Mechanism of Stobbe Condensation

The **Stobbe condensation** is initiated broadly by the critical ***abstraction*** of a **proton (H^+)** preferentially right from one of the two prevailing **methylene (—CH_2—) moieties** duly present in the ***'succinate ester'*** by the respective base.

Let us consider the following sequence of reactions to expatiate logically the precise underlying mechanism of the **Stobbe condensation:**



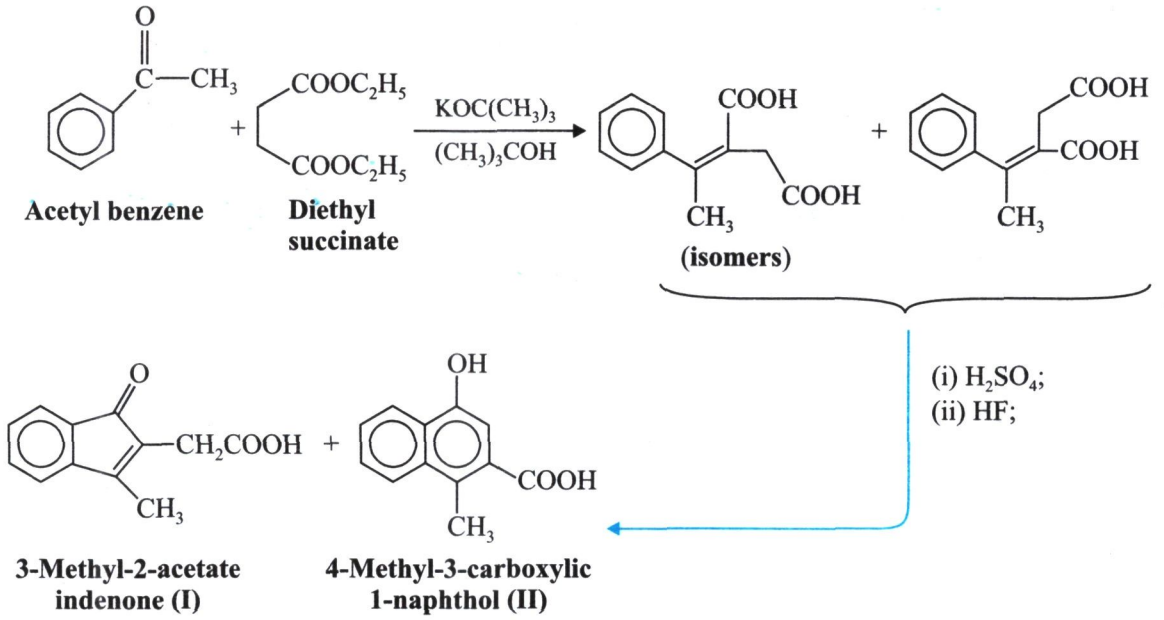
The resultant **succinate ester carbanion** (obtained by the reaction of a **base** and **diethyl succinate**) is now incorporated to the respective **carbonyl (>C=O) carbon atom** (*i.e., **aldol addition***) to give rise to the formation of an **'adduct'.** The resulting **'adduct'** undergoes the **lactonization phenomenon** [*i.e., **cyclization*** due to **ester-lactone interchange** to yield an ***'alkoxide ion'*** by utilizing the so-called *remote-ester moiety*]. Thus, **2-*keto* lactone** is obtained as the **cyclized product,** which upon cessation of ring (an irreversible reaction) gives a **carboxylate anion.** Finally, the resulting *anion* on protonation gives the desired **salt of an unsaturated half-ester.**

Saturated and Unsaturated Aliphatic/Aromatic Acids by Stobbe Condensation

A survey of literation would reveal that the **Stobbe condensation** may be intelligently extended for the preparation of unsaturated breed of **aromatic and aliphatic** carboxylic acids.

Example: (*a*) Formation of 4-methyl-3-carboxylic-1-naphthol (1) and 3-methyl-2-acetate indenone (II).

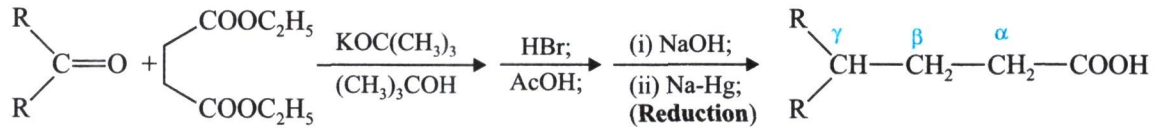
Let us look into the following sequence of reactions starting from **acetyl benzene** and **diethyl succinate** as stated below:



Comments: Thus, the **Stobbe condensation** with acetyl benzene and diethyl succinate yields *two* distinct products **(I)** and **(II)** as shown above.

(*b*) Formation of γ-dialkyl butanoic acid from a dialkyl ketone and diethyl succinate

Thus, we may have the following reactions:



The above reactions are self-explanatory.

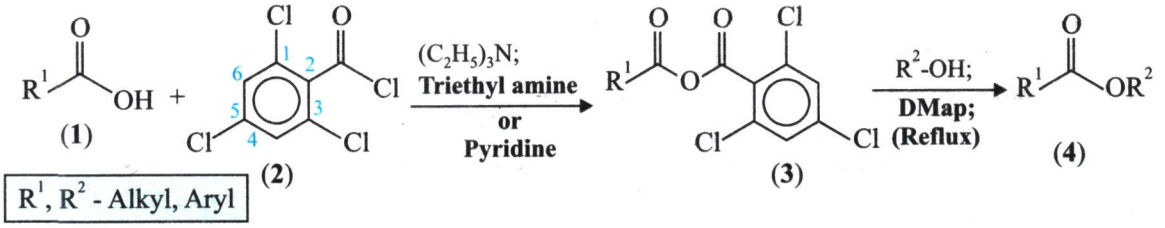
8.2.8 Yamaguchi Esterification* [Yamaguchi Macrolactonization]

The **Yamaguchi esterification** helps to synthesize the class of highly ***'functionalized esters'*** derived from:

- **carboxylic acids;** and
- **alcohols,**

preferentially *via* the application of **2, 4, 6-trichlorobenzyl chloride** and **4-(dimethylamino) pyridine [DMAP].** Nevertheless, in the respective **Yamaguchi macrolactonization** the procedure is critically applied to the particular ***intramolecular cyclization*** of the *hydroxy acids* to prepare the corresponding **'lactones'** conveniently.

* Inanaga J *et al.*: *Bull Chem Soc Jpn.*, **52**: 1989, 1979.

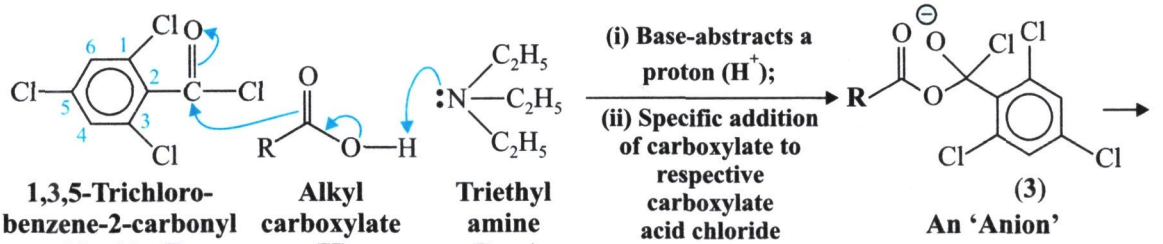


EXPLANATION

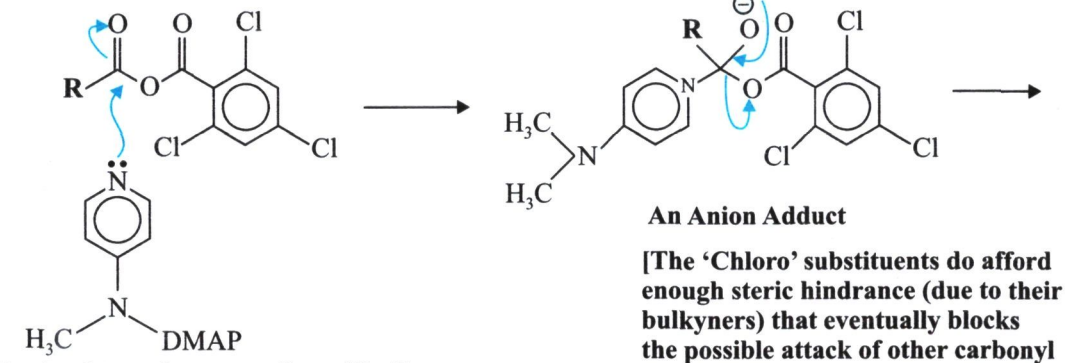
The interaction between an **alkyl carboxylate (1)** and **1,3,5-trichlorobenzene-2-carbonyl chloride (2)** in the presence of either *triethylamine (base)* or *pyridine (base)* yields the corresponding **1,3, 5-trichlorobenzene-5-alkyl-*keto*-ester (3).** The resulting **product (3)** on further treatment with *R^2–OH* in **DMAP** gives the highly **functionalized ester (4) [where, R^1, R^2 = Alkyl, Aryl moieties]**.

Mechanism of Yamaguchi Esterification

In order to understand the **underlying mechanism of Yamaguchi esterification** in a comprehensive manner we may have to study the various sequential reactions starting from **1,3,5-trichlorobenzene-2-carbonyl chloride** to obtain the desired **functionalized ester**, as stated under:



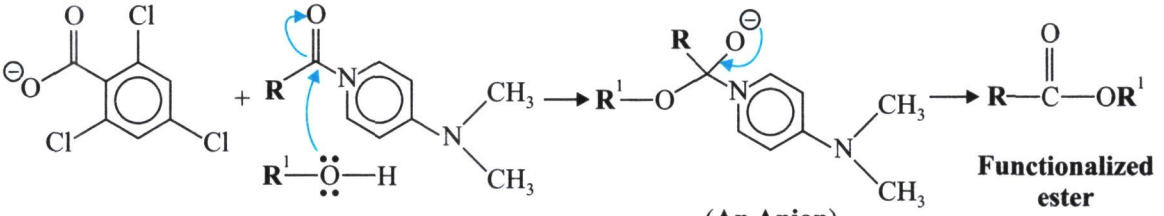
1,3,5-Trichloro-benzene-2-carbonyl chloride (I) | **Alkyl carboxylate (II)** | **Triethyl amine (Base)** | **An 'Anion'**



[An 'acyl transfer reagent' specifically reacts regioselectively at the relatively less hindered carbonyl (>C=O) site]

An Anion Adduct

[The 'Chloro' substituents do afford enough steric hindrance (due to their bulkyners) that eventually blocks the possible attack of other carbonyl (>C=O) moiety]



The reaction between **(I)** and **(II)** in the presence of a base gives an **'anion'**, which on treatment with an **acyl-transfer reagent** reacts *regioselectively* at the so-called relatively *less hindered* **carbonyl site.** The end product obtained above gives an **anion adduct** that eventually yields an anion plus 4-dimethyl amino-N-pyridyl ketoalkyl derivative which reacts with another alkyl alcohol to give an **anion (substituted).** Finally, the **anion** produces the desired **functionalized ester.**

Remarks: Santa Lucia *et al.* (2006)* put forward a logical and plausible assumption that:

"that *aliphatic carboxylates* do act as much better *nucleophiles vis-a-vis* the aromatic alcohols or carboxylates."

However, one may also take cognizance of the fact that the **'aliphatic anhydrides'** (*viz.*, succinic anhydride) is certainly a **more viable electrophilic entity** particularly towards **DMAP** in comparison to the corresponding:

"aromatic carbonyl of the mixed anhydride so generated."

Suggested Reading

Clayden J *et al.*: **Organic Chemistry,** Oxford University Press, Oxford (UK), 2001.

Gutsche CD: **The Organic Chemistry of Carbonyl Compounds,** Prentice-Hall, Englewood, Cliffs, N.J., 1967.

Heathcock CH: **Modern Synthetic Methods** (Ed., R Scheffold), VHCA, Basel (Switzerland), 1992.

Loudon GM: **Organic Chemistry,** 4th edn., Oxford University Press, Oxford (UK), 2002.

Peter J *et al.*: **Organic Synthesis. Coll. Vol. 6,** 1988.

Solomons TWG and Fryhle CB: **Organic Chemistry,** 9th ed., Wiley and Sons (Asia) Pvt. Ltd., New Delhi, 2008.

❑❑❑

*Dhimitruka I and Santa Lucia J., *Org Lett.*, **8**: 47–50, 2006.

Chapter 9

Reactions Giving Heterocyclic Compounds and its Derivatives

LESSONS AT A GLANCE

9.1 Introduction

9.2 Reactions Giving Heterocyclic Compounds and Its Derivatives

- 9.2.1 Bartoli Reaction [Bartoli-Indole Synthesis]
- 9.2.2 Bischler-Napieralski Reaction
- 9.2.3 Chichibabin Reaction [Amination of Nitrogen Heterocycles]
- 9.2.4 Fischer Indole Synthesis
- 9.2.5 Hegedus Indole Synthesis
- 9.2.6 Paterno-Büchi Reaction [Photoaddition of Alkenes to Carbonyl Compounds]

9.1 INTRODUCTION

The **heterocyclic compounds** relate to the class of ***'cyclic compounds'*** with the ring essentially comprising:

• **Carbon** and • **Other Elements (*viz.*, O, S and N)**.

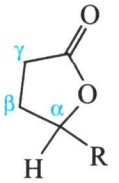
Nevertheless, a survey of literature would reveal vividly an array of such typical ***'heterocyclic rings'***—that do have an inherent tendency to *open* both easily and conveniently; and hence, are completely devoid of fundamental **basic characteristic features**, as given under:

Examples: A few such typical examples of organic chemical entities are:

- **Ethylene oxide**

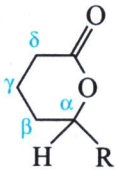


- **γ-Lactone**



[A cyclic ester 5-membered ring system]

- **δ-Lactone**



[A cyclic ester 6-membered ring system]

NOTE: **The aforesaid *three* examples are not considered to be the heterocyclic compounds.**

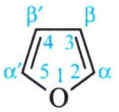
Importantly, the **'heterocycles'** are only those chemical entities (compounds) having essentially either:

'5- or 6-membered heterocyclic ring systems',

that do possess such properties predominantly as:

- **found to be fairly stable,**
- **contain conjugated double bonds (*viz.*, —CH=CH—CH=CH_2),** and
- **do exhibit typical aromatic character.**

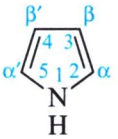
❑ **Five-Membered Heterocyclic Ring Systems:** Following are a few classical examples of **5-membered heterocyclic ring systems** *e.g.*,



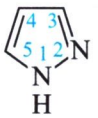
Furan [Furfuran]



Thiophene [Thiofuran;] Thio fur furan]



Pyrrole [1H-Pyrrole; imidole

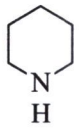


Azole; Pyrazole [1H-Pyrazole; 1, 2-Diazole]

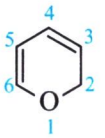
❑ **Six-Membered Heterocyclic Ring Systems:** A few typical **six-membered-heterocyclic ring systems** are as given below:



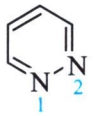
Pyridine



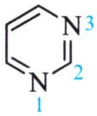
Pyridine [Azacyclohexane]



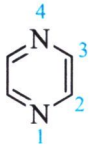
1, 2-Pyran [α-Pyran]



Pyridazine [1, 2-Diazine]



Pyrimidine [1, 3-Diazine]



Pyrazine [1, 4-Diazine]

9.2 REACTIONS GIVING HETEROCYCLIC COMPOUNDS AND ITS DERIVATIVES

Having understood the basics of the ***five*- and *six*-membered heterocyclic ring systems,** we may now undertake an elaborated study regarding the various reactions giving the plethora of important **heterocyclic compounds and its respective derivatives** (or *structural analogues*) as stated below:

(*i*) **Bartoli Reaction [Bartoli-Indole Synthesis],**

(*ii*) **Bischler Napieralski Reaction,**

(*iii*) **Chichibabi Reaction [Amination of Nitrogen Heterocycles],**

(*iv*) **Fischer Indole Synthesis,**

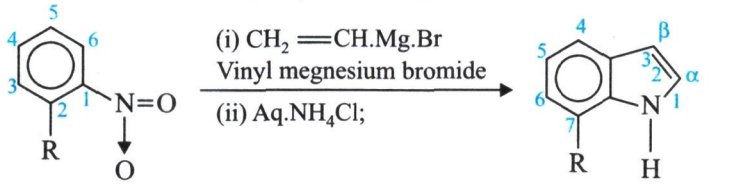
(*v*) **Hegedus-Indole Synthesis,** and

(*vi*) **Paterno-Buchi Reaction,**

which shall now be discussed individually in the sections that follows:

9.2.1 Bartoli Reaction [Bartoli-Indole Synthesis]

The **Bartoli reaction*** involves essentially the interaction between the ***ortho*-substituted nitroarenes** and the **Grignard reagent (RMgX)** [*i.e.,* precisely **vinyl magnesium bromide**] to give rise to the formation of the desired **substituted indoles**,–as shown below:

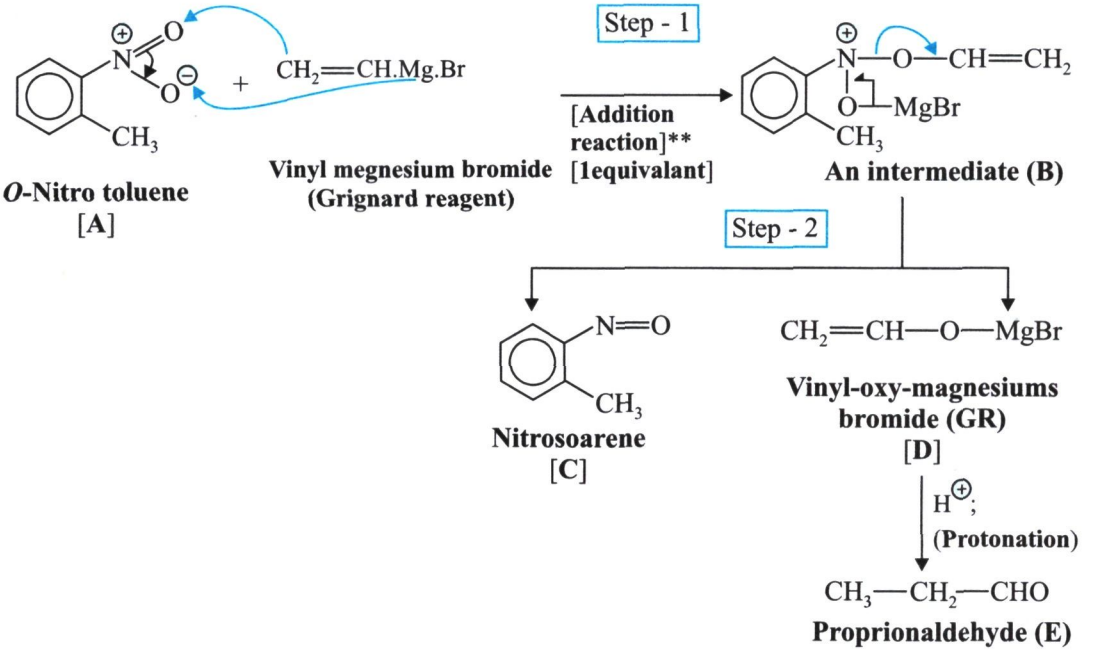


ortho-Substituted nitroarene **7-Substituted indole**

Remarks: Perhaps it serves as one of the most frequently used methods to prepare the so-called–**'substituted indoles'.**

Mechanism of Bartoli Reaction

Following are the various sequential reactions being taken up to understand explicitly the **mechanism of Bartoli reaction:**



***O*-Nitro toluene [A]**

Vinyl megnesium bromide (Grignard reagent)

An intermediate (B)

Nitrosoarene [C]

Vinyl-oxy-magnesiums bromide (GR) [D]

Proprionaldehyde (E)

* Bartoli G *et al.*: *J Chem Soc Perkin Trans.*, **1**: 892, 1978; Bartoli G *et al.*: *J Chem Soc Commun.*, 807, 1988; Bartoli G *et al. : Tetrahedron Lett,* **30**: 2129, 1989.

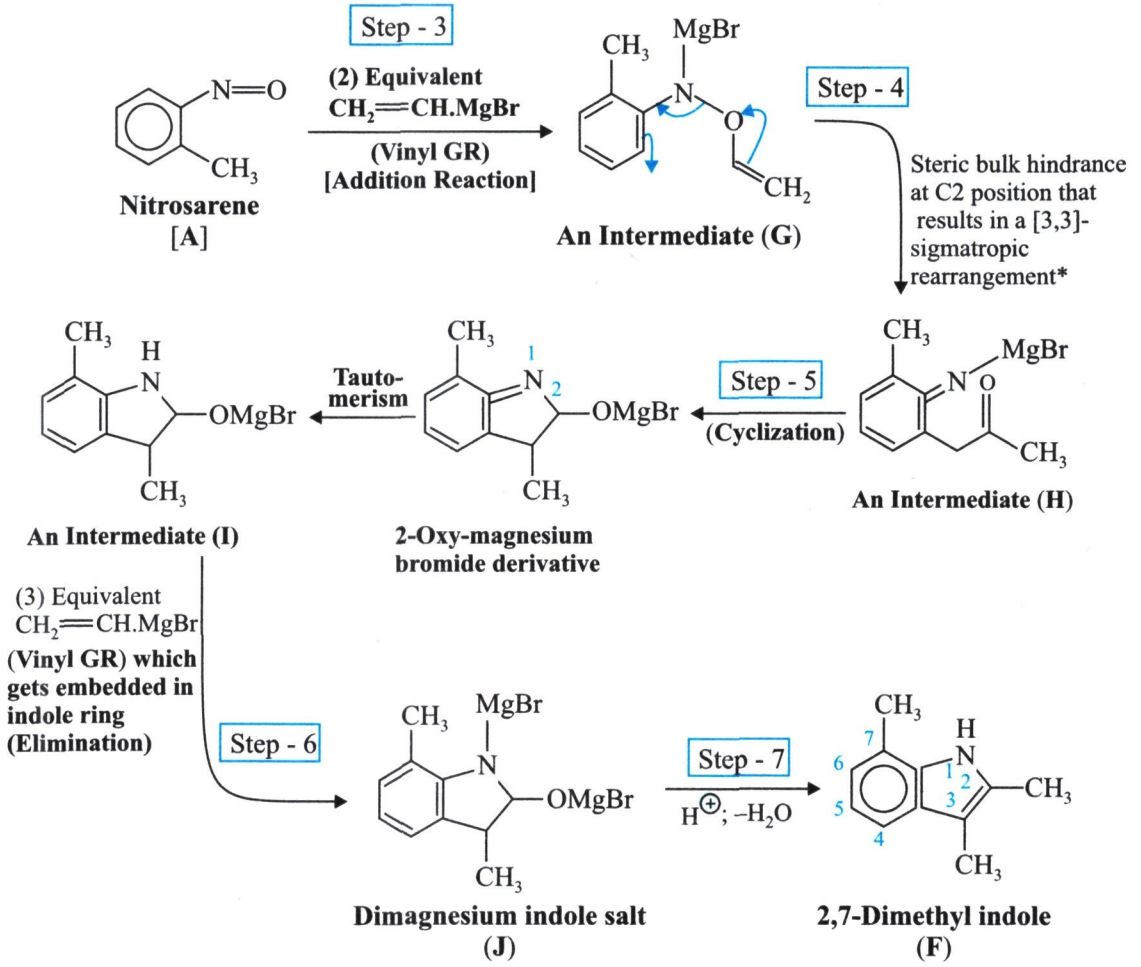
** That is, gets, converted to a respective carbonyl compound.

Comments: The interaction between ***O*–nitrotoluene (A)** and *vinyl magnesium bromide* **(Grignard reagent)** gets engaged into an *addition reaction* **[Step 1]** to yield an **intermediate (B).** The resulting **product (B)** through **[Step 2]** gives *two* reaction products, namely:

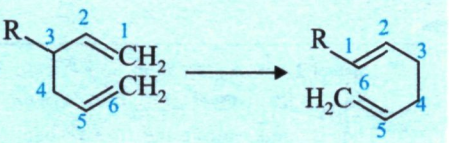
- **Nitrosoarene (C);** and
- **Propionaldehyde (E)**–*via* the formation of *vinyl-oxy-magnesium bromide* **(D)** followed by its protonation (H^+).

Conversion of Nitrosoarene (A) into Indole (F)

The various sequential steps involved in the conversion of **nitrosoarene (A)** into the respective **indole (F)** may be expressed as under:



*** Sigmatropic Rearrangement (Reaction):**
In the **sigmatropic rearrangement (reaction)** the **alkyl residue (R)** gets shifted duly from C–3 to the respective C–1 position.



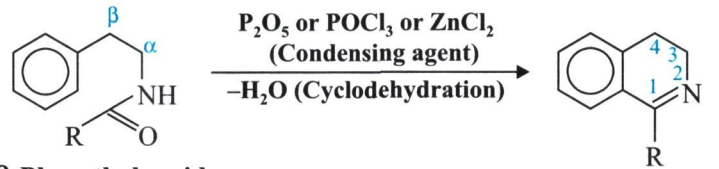
EXPLANATION

1. **Nitrosoarene (A)** in *step 3* undergoes an **addition reaction** with *(2) equivalents of vinyl GR* to yield an **intermediate (G)**, which in *step 4* encounters a steric-bulk hindrance at C–2 position thereby resulting in a **[3, 3] sigmatropic rearrangement** to produce an **intermediate (H).**
2. **Intermediate (H)** in *step 5* undergoes *cyclization* to give a 2-oxy magnesium bromide derivative, which undergoes **tautomerism** to yield the **intermediate (I).**
3. **Intermediate (I)** in *step 6* reacts with *(3) equivalents of vinyl GR* to give **dimagnesium indole salt (J)** due to the incorporation of the **indole ring.**
4. The resulting **product (J)** in *step 7* under *protonation* (H^+) followed by *dehydration* ($-H_2O$) gives the desired product **2, 7–dimethyl indole (F).**

9.2.2 Bischler-Napieralski Reaction*

The **Bischler-Napieralski Reaction** essentially involves the *cyclodehydration* of **β-phenethylamides (I)** to the respective **3,4-dihydroisoquinolines (II)** by the help of a *condensing agent viz.,*

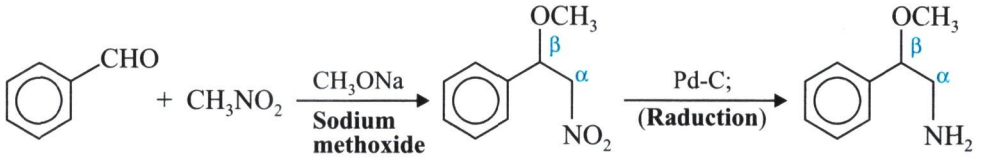
- **Phosphorus pentoxide (P_2O_5)**
- **Phosphorus oxychloride ($POCl_3$)** or
- **Zinc chloride ($ZnCl_2$).**



β-Phenethyl amide (I) → **3,4-Dihydro-isoquinolines (II)**

Alternative Method to Prepare 3, 4–Dihydroisoquinolines (II) [or 1-Alkyl Isoquinolines]

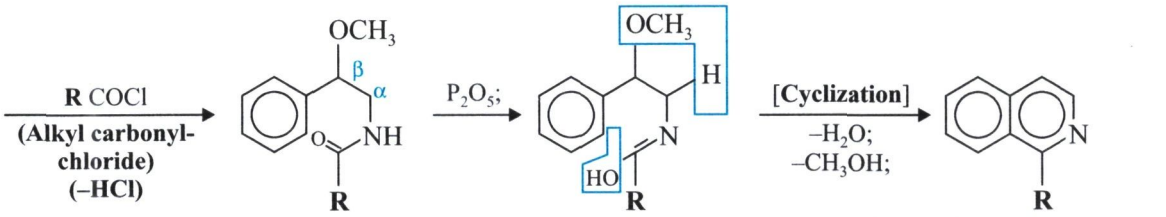
In an **alternative method** the **product (II)**, as obtained above can also be obtained by the interaction of *benzaldehyde* and *nitromethane* followed by various sequential steps given under:



Benzaldehyde + **Nitromethane** → **β-Methoxyphenyl nitro ethane (A)** → **β-Methoxyphenyl amino ethane (B)**

(Contd...)

* Bischler A and Napieralski B: *Ber.*, **26**: 1903, 1893.

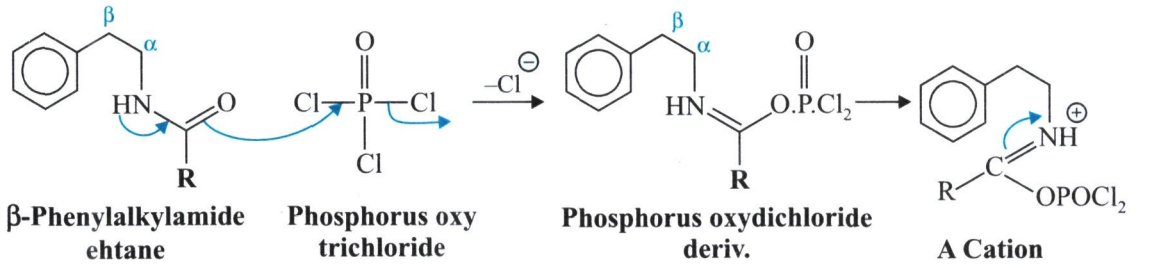


β-Methoxyphenyl-alkylamide ethane (C) | **A Hydroxyalkyl derivative (D)** | **1-Alkyl isoquinoline (E)**

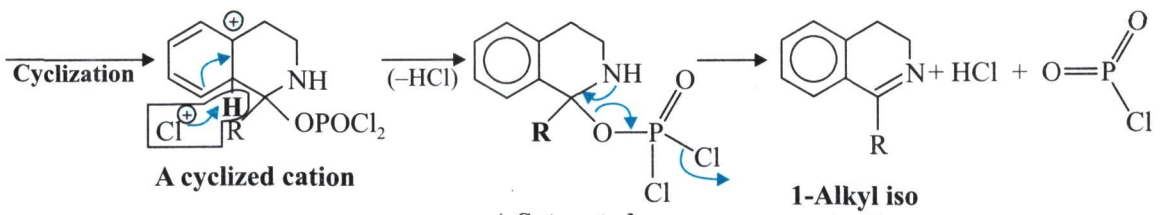
The various steps involved in the above reactions are self explanatory.

Mechanism of Bischler-Napieralski Reaction

The following sequential steps involved in the reactions explain the mechanism of the **Bischler-Napieralski reaction** explicitly:



β-Phenylalkylamide ehtane | **Phosphorus oxy trichloride** | **Phosphorus oxydichloride deriv.** | **A Cation**



A cyclized cation | **A Saturated isoquinoline derivative** | **1-Alkyl iso quinoline (E)**

The interaction between *β-phenylalkylamide ethane* and $POCl_3$ yields the **phosphorus oxychloride derivative** which forms a *cation*; and this upon *cyclization* gives a **cyclized cation.** The resulting product loses a mole of HCl to produce a **saturated isoquinoline derivative** which subsequently to give rise to the formation of the desired product **1-alkyl isoquinoline (E)** plus a mole each of HCl and **phosphorus dioxychloride.**

9.2.3 Chichibabin Reaction [Amination of Nitrogen Heterocycles]

It is also known as the **Chichibabin pyridine synthesis.*** **Chichibabin reaction** essentially involves either:

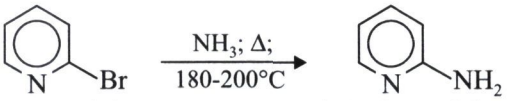
- **amination of pyridine,** or
- **amino-dehydrogenation of pyridine,** or

* Chichibabin AE: *J Russ Phys Chem Soc.*, **37**: 1229, 1906; *J Prakt Chem,* **107**: 122, 1924.

- **other heterocyclic compound with ammonia,** or
- **alkali-metal amides.***

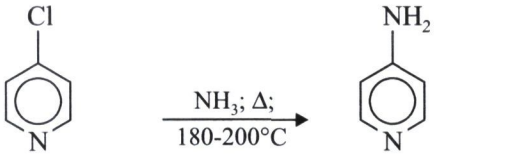
Thus, we may have the following expressions:

(*i*)



2-Bromopyridine **2-Aminopyridine**

(*ii*)



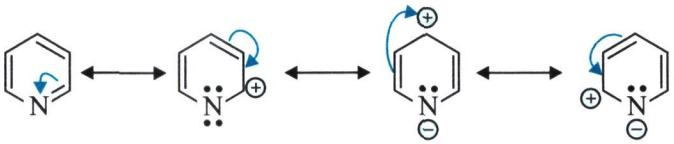
4-Chloropyridine **4-Aminopyridine**

Explanation

As could be seen in **'electrophilic substitution'** the pyridine ring *closely resembles to a benzene ring* which consists of strongly **electron withdrawing groups (EWGs).** However, the **nucleophilic substitution** occurs quite readily at the **C–2** and **C–4 positions** on the *pyridine ring* itself, which could be due to the underlying fact that:

"the critical presence of rather *'heavier nuclear charge'* resting on the respective N–atom embedded in the ring."

Besides, the *π-electrons* of the **pyridine ring** get duly polarized towards the *N-atom* thereby rendering the **C–2, C–4, and C–6** of the ring both **electron deficient** and **electronprone** towards the subsequent attack of the ***nucleophile***, as depicted under:



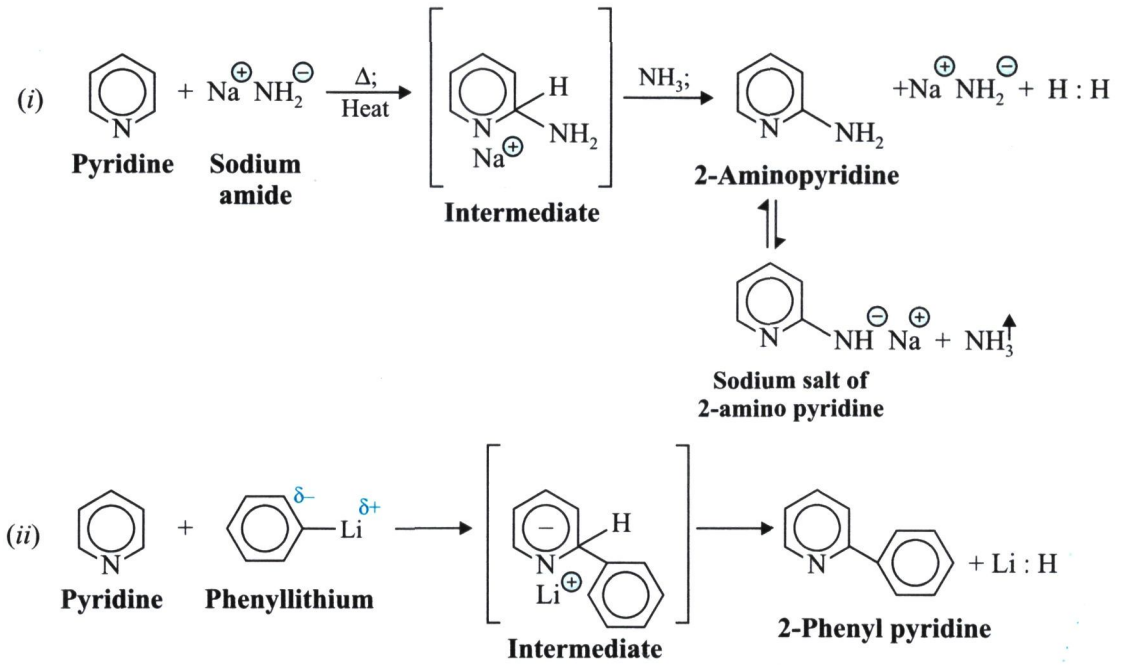
Mechanism of Chichibabin Reaction

Let us look into the following *two* sequence of reactions, namely:

- **Pyridine yields 2-aminopyridine and then sodium salt of 2-amino pyridine,** and
- **Pyridine gives 2-phenylpyridine.**

(*a*) **Reactions starting from pyridine to yield sodium salt of 2-amino pyridine *via* formation of 2-amino pyridine.**

* Vorbruggen, *Adv. Heterocycle Chem.*, **49**: 117–192, 1990.



In (*i*) above, the so-called **nucleophilic aromatic substitution** may usually occur by a mechanism which is quite analogous to the respective mechanism for the **electrophilic substitution.** First of all *pyridine* interacts with sodium amide in a slightly warm condition to yield a **–vely charged intermediate**, which on being subjected to treatment with ammonia gives rise to the formation of **2-amino-pyridine** plus a mole each of *sodium amide* and *hydrogen**. The resulting product **2-amino-pyridine** further undergoes a *reversible reaction* to produce the **sodium salt of 2-aminopyridine** and a *mole of ammonia.*

In (*ii*) above, pyridine reacts with *phenyllithium* to give an **intermediate** bearing a **–ve charge in the pyridine nucleus** and a **+ve charge of Li** which subsequently yields **2-phenyl pyridine** plus a mole of ***lithium hydride.***

Comments: The ability of the **pyridine ring** to accomodate generously the **–ve charge** virtually determines the following ***two* commendable aspects:**

- **stability profile of the intermediate**; and
- **stability of the transition state,**

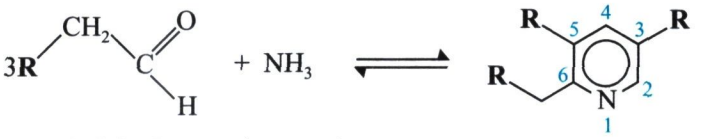
thereby leading to the end product; and hence, serves as the **rate-determining step of the reaction.**

NOTE: **It may be added that except the chichibabin reaction, a *nucleophilic substitution*, the pyridine ring virtually undergoes an *electrophilic substitution* at C–3 and C–5 position which may be regarded to be rather difficult perhaps due to the formation of the so-called *positively charged pyridinium ions,* duly obtained from the respective *'electron-poor pyridine'*. In general, the above stated fact appreciably lowers the probability of an ensuing *'electrophilic attack'*.**

* That is, the formation of **–vely charged intermediate** (*pyridine nucleus*) determines the **rate of the overall reaction** squarely.

The Chichibabin Pyridine Synthesis

The **Chichibabin pyridine synthesis** refers to the precise method that essentially relates to the condensation of **aldehydes (–CHO)** with **ammonia (NH_3)**, as given under:

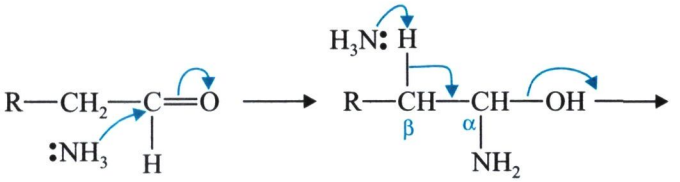


An Aldehyde **Ammonia** **3, 4, 5-Alkyl pyridine**

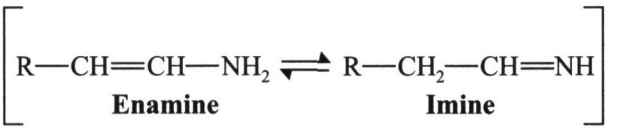
Mechanism of Chichibabin Pyridine Synthesis

The probable mechanism of **Chichibabin pyridine synthesis** may be explained in the following ***two*** **steps**:

Step–1:



α-Amino-β-alkyl ethanol

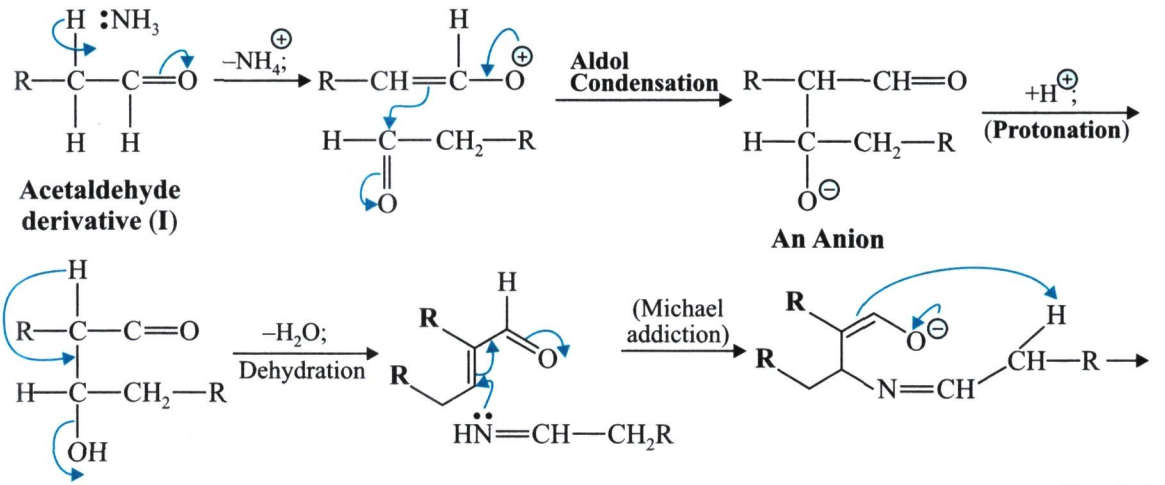


Enamine **Imine**

The interaction between an *aldehyde* and *ammonia* yields a condensed product, **α-amino-β-alkyl ethanol**, which on further *amination* with NH_3 gives:

- *first*–an '**enamine**'; and
- *secondly*–an **'imine'** through a *reversible reaction*.

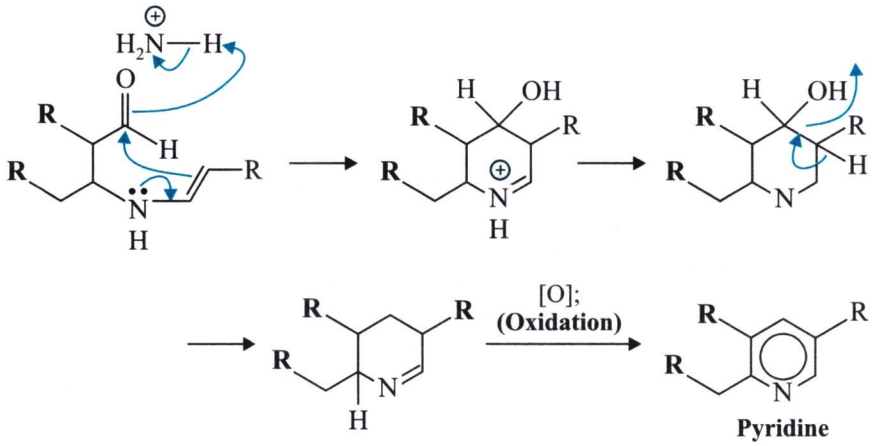
Step 2: It is a **multi-step synthesis** as shown under:



Acetaldehyde derivative (I)

An Anion

(Contd...)



The various steps in the above synthesis from an **acetaldehyde derivative** up to **pyridine** are self-explanatory.

Comments: These essentially include:

1. It may be emphasized that the **'N' present in the ring** (*i.e., pyridine*), in fact, critically serves as:

   "a comparable purpose exclusively in substitution phenomenon—as usually done by the *oxygen atom* present in the *nitro (-NO_2) moiety* in *nitrobenzene.*"

2. Obviously, one may not be able to lay hands on to a **'pyridine kind of an intermediate'** perhaps due to the fact that some typical **'heterocycles'** which cannot form an *aryne*—may not be **aminated successfully.**

3. It has been ascertained that the following ***three*** **types of synthesis** are virtually possible, such as:

- **Isoquinoline may be aminated at C–1 position,**
- **Quinoline may be aminated at C–2 position,** and
- **Sulphapyridine (a *sulpha drug*) may be prepared from 2-amino pyridine.**

9.2.4 Fischer Indole Synthesis*

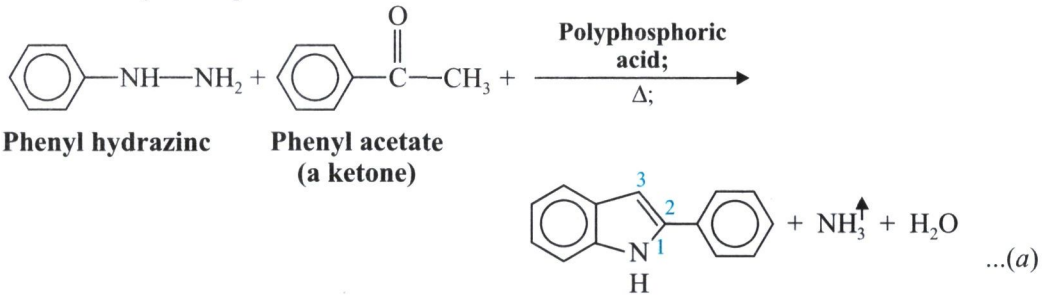
The **Fischer indole synthesis** is recognized to be the best ever known techniques for the specific synthesis of **'indoles'.**

NOTE: **Emil Fischer was a great German chemist, who first reported the synthesis of indole (*viz.*, 2-phenylindole).**

The said reaction essentially makes use of either an **'aldehyde'** or a **'ketone'** having atleast '***two* α-H-atoms'**, which is then subjected to treatment with **phenylhydrazine [C_6H_5–NH·NH_2]** or its suitable structural analogue in the critical presence of: **an acid catalyst and/or heat.**

* Fischer E and Jourdan F: *Ber.* **16**: 2341, 1883; Fischer E and HessO: *ibid.*, **17**: 559, 1884.

The reaction may be expressed as under:



Phenyl hydrazinc **Phenyl acetate (a ketone)**

2-Phenyl indole [Yield : 76%]

...(*a*)

Thus, *phenylhydrazine* when reacts with *phenyl acetate* (a *ketone*) in the presence of *polyphoric acid* and heated gently to yield **2-phenyl indole** plus a mole each of *ammonia* and *water*.

Remarks: It has been observed that a variety of either:

- **Lewis acid catalyst,** or
- **Bronsted acid catalyst,**

may be used both judiciously and effectively, such as:

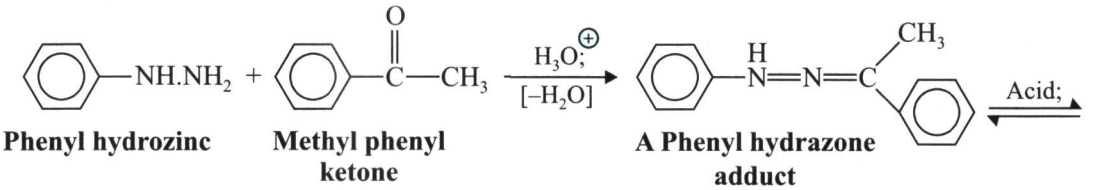
- **H_2SO_4** - **BF_3** - **$ZnCl_2$ and other etc.**

However, the acid employed in **Eqn. (*a*)** above *i.e.,* **polyphosphoric acid**–designates a *syrupy mixture* of **P_2O_5** and **H_3PO_4** (*Phosphoric acid*). Besides, *Eqn. (a)* may also be accomplished bny making use of a variety of ***divergent substituted*** **phenylhydrazines** along with a **carbonyl (>C=O) compound** (*viz., aldehydes* or *ketones*). Nevertheless, **acetaldehyde,** that would eventually in principle be used to give **indole** itself, but *fails to work in the reaction,* perhaps due to the fact that it gets *duly polymerized* under the ensuing **reaction parameters.**

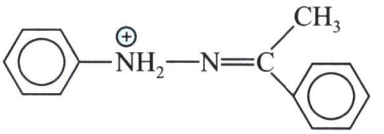
Mechanism of Fischer Indole Synthesis

It actually commences with a *common reaction i.e.,* conversion of the **carbonyl (>C=O) compound** into the corresponding **phenylhydrazone** (a kind of ***'imine'***).

Thus, we may have the following expression:

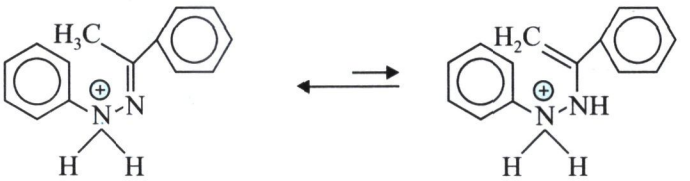


Phenyl hydrozinc **Methyl phenyl ketone** **A Phenyl hydrazone adduct**



A Protonated form of Phenylhydrazone adduct

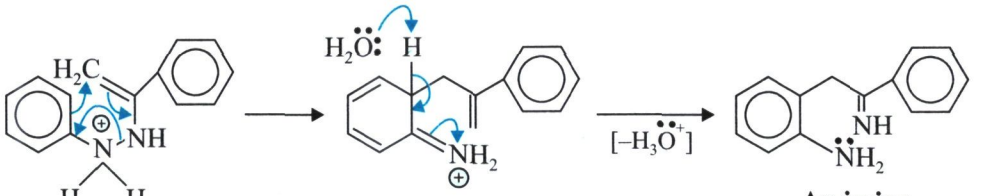
Importantly, one may also take cognizance of the underlying fact that eventually the so-called **protonated phenylhydrazine** (I) obtained above remains in *equilibrium* with a relatively smaller quantum of a **protonated *enamine* isomer (II)** as shown below:



Protonated Phenylhydrazine (I) **Protonated Enamine Isomer (II)**

Conversion of Protonated Enamine Isomer (II) into an Imine Intermediate (III)

Let us look into the following reactions from (II) to obtain (III)

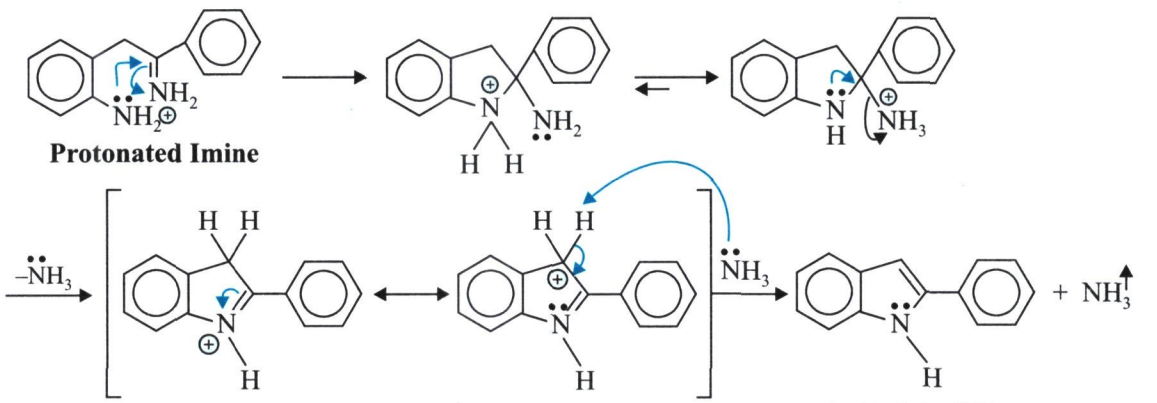


(II) **An Intermediate** **An imine Intermediate (III)**

Remarks: The **protonated enamine isomer (II)** undergoes a *pericyclic reaction* essentially involving ***3-electron pairs*** **(6-electrons)** to yield an altogether **new intermediate**, wherein the respective **N–N bond** of the inherent **phenylhydrazine**—has been cleaved apparently. Thus, the *new intermediate* formed duly in the above reaction is an **'imine' (III).**

Conversion of Imine Intermediate (III) to the Enamine-derivative *i.e.*, Indole (IV)

The resulting **'imine intermediate (III)'** gets first *protonated on its N–atom*; and subsequently, undergoes the **nucleophilic attack** by the inherent **amino (—NH_2) moiety** present in the **same molecule (III).** Thus, the ultimate product so obtained is an ***'enamine'*** **structural analogue** (derivative)—**indole (IV).**



Protonated Imine **[Intermediates]** **An Indole (IV)** [2-Phenyl indole]

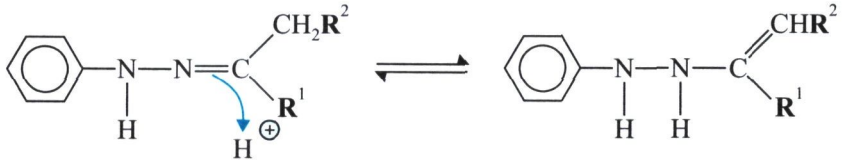
NOTE: **In majority of instances, the so-called substituted *phenyl-hydrazines* do work wonderfully in the *Fischer Indole synthesis*; however, quite a few are indeed both tedious and cumbersome to prepare. Therefore, in an overwhelming approach the *Fischer synthesis* is invariably used with *phenylhydrazine* itself *i.e.*, to synthesize particularly such *'indoles'* that are duly substituted at C–2 and C–3 positions (of the 5-membered pyrrole ring) *vis-a-vis* the phenyl ring.**

Another Mechanism of Fischer-Indole Synthesis [Robinson *et al.* (1918)*]

The proposed mechanism by Robinson *et al.* (1918) comprises of the following ***three*** **sequential steps** as detailed under:

Step 1 **The very *first* step consists of a *reversible rearrangement* of phenylhydrazine (A) to yield an *ene*-hydrazine (B)–a reactive entity.**

Thus, we may have the following expression:

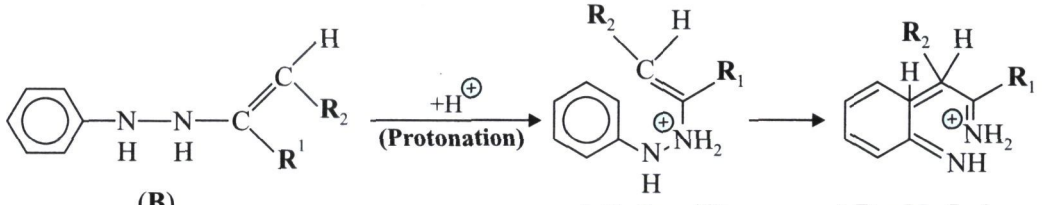


Phenylhydrazine (A) ⇌ **An *ene*-Hydrazine (B) (Reactive Specie)**

Comments: It may be noted that the so-called **Fischer Indole synthesis** bears a somewhat close similarity to the respective **Benzidine rearrangement** (or **Semidine rearrangement**).*

Step 2 **The *ene*-hydrazine (B)—a reactive specie undergoes critically the [3, 3]–sigmatropic rearrangement thereby giving rise to the formation of an altogether *new C–C bond* along with a cation (C) which being a *double imine* (D).**

The various steps involved are as stated under:



(B) → (Protonation) → **A Cation (C)** → **A Double Imine (D)**

Comments: It may be observed that the **electrophilic reaction** is indeed intimately related to the **Claisen rearrangement**** of the ***phenyl vinyl ether*** **[C_6H_5–O–CH_2·CH=CH_2)**.

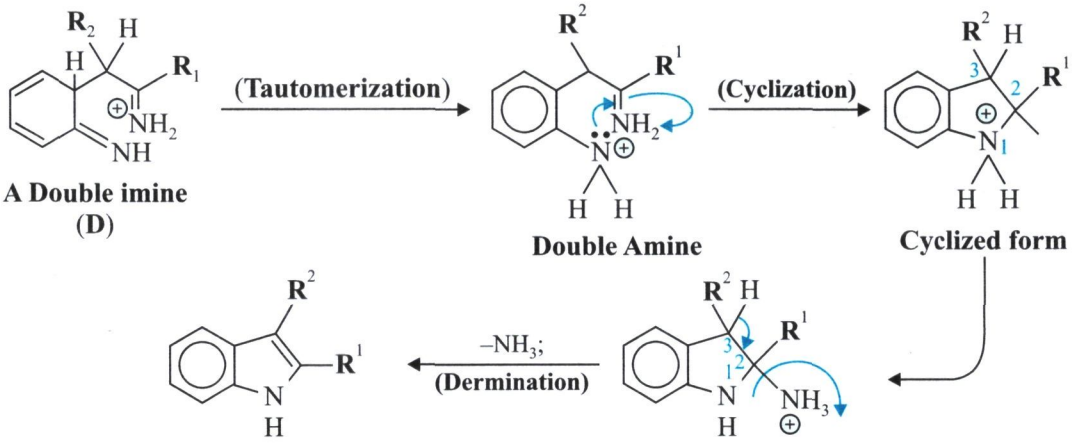
* Robinton GM *et al.*: *J Chem. Soc.*, **113**: 1639–643, 1918.

** Hofmann AW: *Proc R Soc.*, (London), **12**: 576, 1863; Jacobson P *et al.*: *Ber*, **26**: 688, 1893.

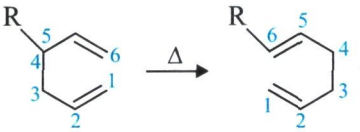
*** Claisen L: *Ber*, **45**: 3157, 1912; Claisen L and Tietze E, *ibid*, **58**: 275, 1925; **59**: 2344, 1926.

Step 3 **Double imine (D) on being subjected tautomerism, cyclization, and elimination of ammonia to give indole (E).**

The various sequential steps involved are as described under:



EXPLANATION

1. The key step of the aforesaid mechanism is the **[3, 3] sigmatropic rearrangement*** [*i.e.*,  the shifting of **'R'** from **C–4** to **C–6 position**].
2. The said mechanism is being duly supported by the *experimental findings* since the compound **'double amine'** has been:
   - **isolated****, and
   - **characterized (identified) by NMR–spectroscopy.*****
3. The metal halides *viz.*, $ZnCl_2$ may be employed as the **Lewis acid catalyst.**
4. Interestingly, the major function of the **Lewis acid catalyst ($ZnCl_2$)** is to augment the actual rate of formation of the **cation (C)** from the ***ene*-hydrazine (B)** in *Step 2.*
5. **^{15}N–labelling** (*radioisotope*) experiment vehemently supports the generous evidence that the **N–atom** gets eliminated as **ammonia (NH_3)** as depicted above.

NOTE: **Fischer indole synthesis may also be accomplished by making use aryl bromides.******

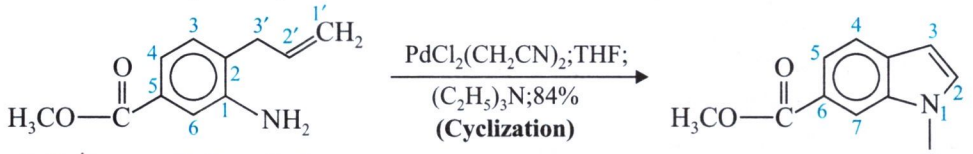
* Robinson GM *et al.*: *J Chem Soc.*, **113**: 639–643, 1918.
** Forest TP and Chen. FMF : *J Chem Soc.*, **1067** 1972.
*** Douglas AW: *J Am Chem Soc.*, **100**: 6463–6469, 1978.
**** Buchwald SL *et al.*: *J Am Chem Soc.*, **120**: 6621–22, 1998.
***** Hegedus LS *et al.*: *J Am* chem soc., **98**: 2674, 1976.

9.2.5 Hegedus Indole Synthesis

Hegedus *et al.* (1976)***** reported the synthesis of the **indoles** by means of the so-called:

"stoichiometric Pd (II)–mediated oxidative cyclization of the alkenyl anilines [*e.g.*, 2-(1-propenyl)-5-methyl carboxylate aniline]."*

The reaction may be expressed as under:



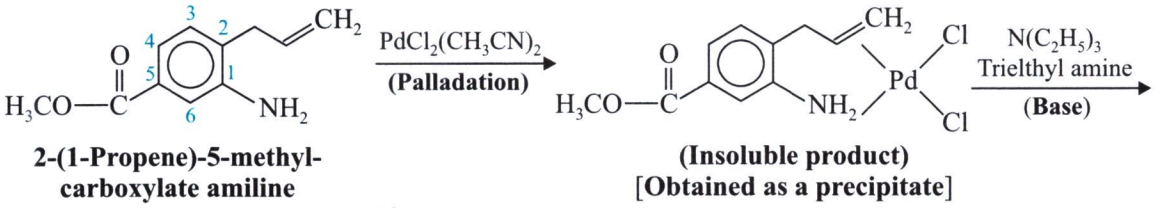
2-(1-Propenyl)-5-methyl-carboxylate amiline (A)

2-methyl-6-methyl carboxylate indole (B)

Thus, the reaction of **(A)** with *dichloro-dimethylnitrile palladium* in **tetrahydrofuron** and **triethylamine (base)** undergoes *cyclization* to yield **2-methyl-6-methyl carboxylate indole (B)** up to an yield of **84%.**

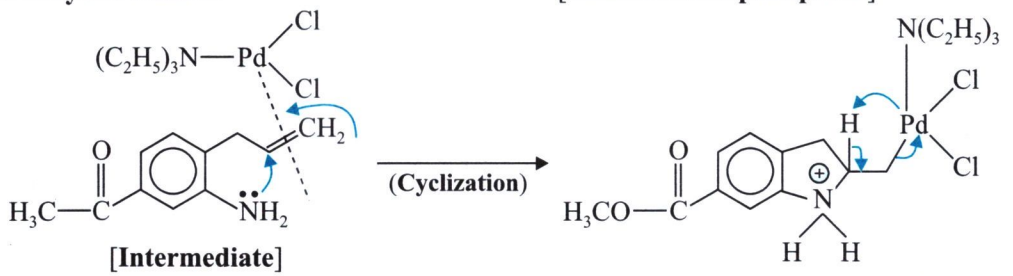
Mechanism of Hegedus Indole Synthesis

The mechanism of the **Hagedus indole synthesis** specifically involves the **palladium (Pd)–mediated oxidative cyclization** followed immediately by **β-elimination** according to the following sequential reactions:



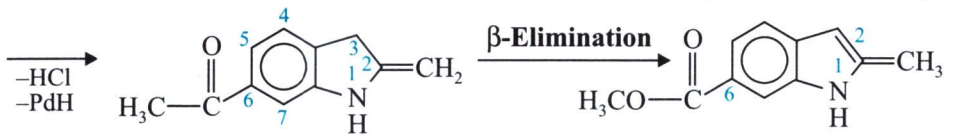
2-(1-Propene)-5-methyl-carboxylate amiline

(Insoluble product) [Obtained as a precipitate]



[Intermediate]

[Indole derivative]



2-Methylene-6-methyl carboxylate indole

2-Methyl-6-methyl carboxylate indole

* Kondo T *et al.*: *J Am Chem Soc.*, **124**: 186, 2002; Johnson JN: **Hegedus Indole Synthesis**, In: *Name Reactions in Heterocyclic Chemistry*, Li JJ *et al.* [Eds]: Wiley and Sons, Hoboken, NJ, pp. 135–139, 2006 (Review).

EXPLANATION

1. 2-(1-Propene)-5-methyl carboxylate aniline on being subjected to *palladation* yields an **insoluble product**, which upon treatment with a base (*triethyl amine*) gives an **intermediate.**
2. The resulting **intermediate** undergoes *cyclization* to produce an **indole derivative**, which subsequently loses a mole each of **HCl** and **PdH** to give **2-methylene–6-methyl carboxylate indole.**
3. The resulting **substituted indole** undergoes **β-elimination** critically to yield **2-methyl-6-methyl carboxylate indole.**

Other Important Methods for Indole Synthesis

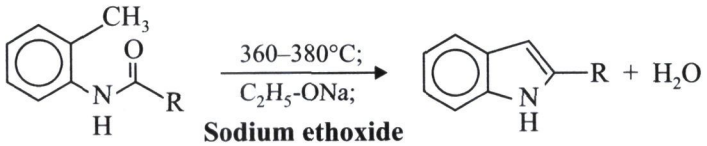
A survey of literature reveals that there are quite a few **other important methods for the synthesis of indole,** such as:

- **The Madelung Synthesis,**
- **The Reissert Synthesis**
- **The Gassman Synthesis**, and
- **The Nenitzeseu Synthesis,**

which shall now be discussed briefly in the sections that follows:

9.2.5.1 The Madelung Synthesis*

It relates to the **synthesis of indole derivatives** by means of the *intramolecular cyclization* of an **N–(2-alkylphenyl) alkanamide (I)** in a *strong base at high temperature,* as given under:

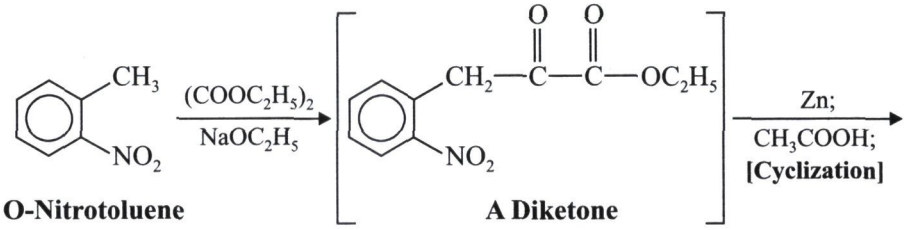


(I) **2-Alkyl indole (II)**

The actual yields are quite low; and for *decarboxylation* (removal of >C═O moiety) of the *starting material* also takes place.

9.2.5.2 The Reissert Synthesis**

It is also known as the **Reissert Indole synthesis.** It refers to the typical *condensation* of an ***O*-nitrotoluene** with *oxalic ester*,–thereby causing a *reduction* to the ***amine*** first and then *cyclization* to yield the **'indole'**, as given under:

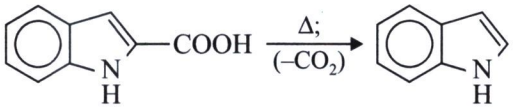


O-Nitrotoluene **A Diketone**

(Contd...)

* Madelung W: *Ber,* **45**: 1128, 1912.

** Reissert A: *Ber,* **30**: 1030, 1897.



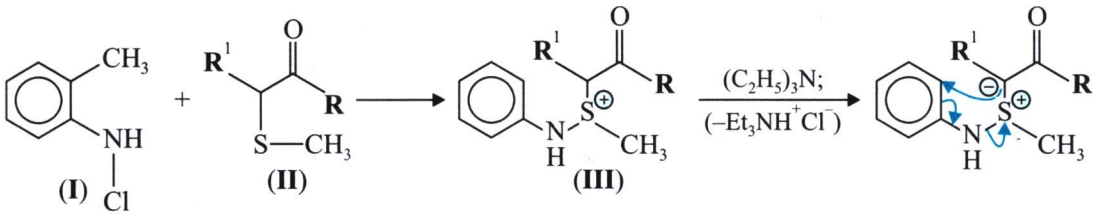
2-Carboxylate indole **Indole**

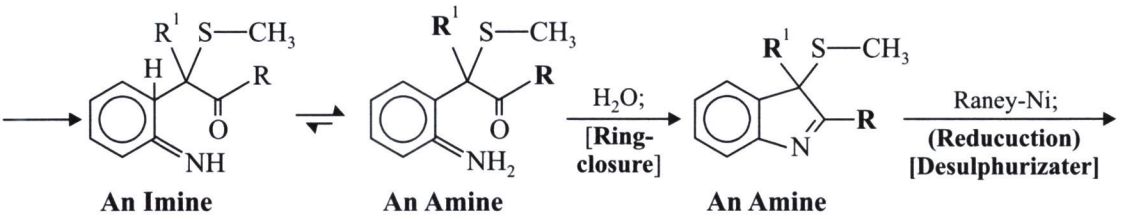
EXPLANATION

An ***O*-nitrotoluene** when reacted with *diethyl oxalate* in the presence of a **base** (*sodium ethoxide*) yields **α-ketoester**–(a **diketone**) as an intermediate. The resulting **product** on being subjected to reduction with Zn/CH_3COOH undergoes *cyclization* to give **2-carboxylate indole** which upon heating affords *decarboxylation* to produce the **indole.**

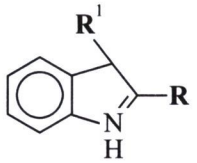
9.2.5.3 The Gassman Synthesis*

The interaction between an **N-chloro-aniline (I)** and a **β-keto-sulphide (II)** form a **sulphonium salt (III)**, which now undergoes a ***[3,3] sigmatropic rearrangement*** followed by *cyclization* (**ring closure**). Finally, *desulphurization* gives the **indole**, as given under:





An Imine **An Amine** **An Amine**



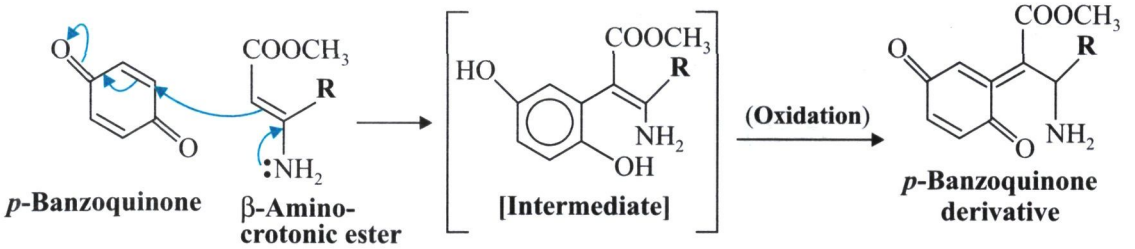
Indole
(2, 3-substituted)

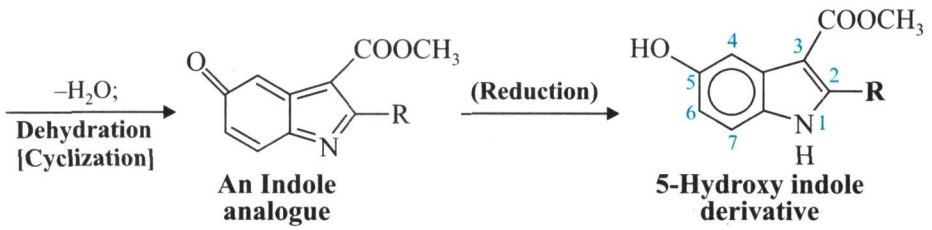
9.2.5.4 The Nenitzescu Synthesis**

In this particular synthesis, one may obtain **5-hydroxyindoles** from ***p*-benzoquinones** as the starting material. The first *intermediate* is duly oxidized by further reaction with *benzoquinone* to one such chemical entity that gets *cyclized.* Thus, the **quinol** so formed in this reaction reduces the *cyclized product* to the desired **indole**, as expressed below:

* Gassman PG: *Tetrahadrn*, **28**: 3833, 1972

** Nenitzeseu CD: *Bull Soc. Chim Romania*, **11**: 17, 1929.





9.2.6 Paterno-Büchi Reaction* [Photoaddition of Alkenes to Carbonyl Compounds]

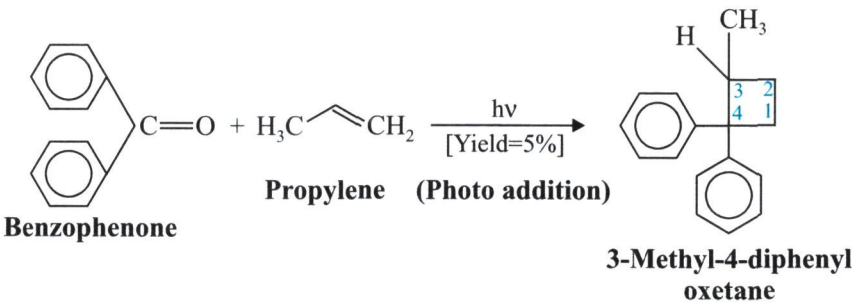
The **photoaddition** normally takes place by interaction of the *triplet state of the carbonyl* >C=O *compound* with the corresponding *ground state of the 'alkene'*. As could be seen in ***photoreduction***, it is indeed found to be more efficient when the said ***'triplet'*** happens to be of **(n, π^*)** rather than **(π, π^*)** type.

Let us now examine the following ***two* typical examples:**

- **addition of benzophenone to propylene**; and
- **addition of benzophenone to isobutylene,**

which explicitly display the ***distinct variation*** in the actual *yields* of the **end-products.**

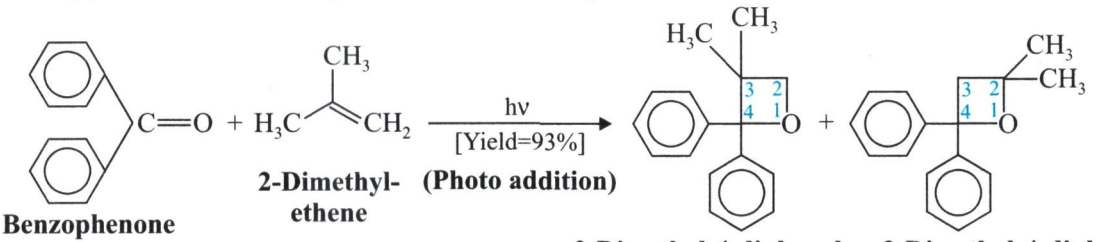
(*a*) Addition of benzophenone to propylene



A mole each of *benzophenone* and *propylene* undergoes **photoaddition** to yield **3-methyl-4-diphenyl oxetone** (*up to a yield of 5% only*).

* Paterno E and Chieffi G; *Gazz chim Ital*, **39**: 341, 1909.

(*b*) Addition of benzophenone to 2-dimethyl ethene



Benzophenone **2-Dimethyl-ethene** **3-Dimethyl-4-diphenyl oxetane [Yield = 9 parts]** **2-Dimethyl-4-diphenyl oxetane [Yield = 1part]**

The photoaddition between *benzophenone* and *2-dimethyl ethene* gives one mole of each of:

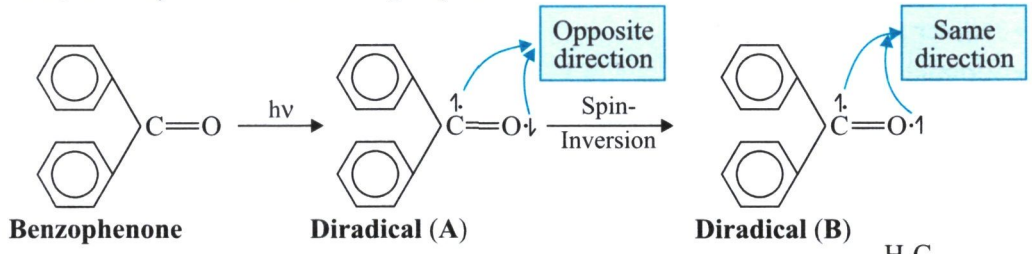
- **3-dimethyl-4-diphenyl oxetane (yield : 9 parts); and**
- **2-dimethyl-4-diphenyl oxetane (yield : 1 part).**

Mechanism of Reaction

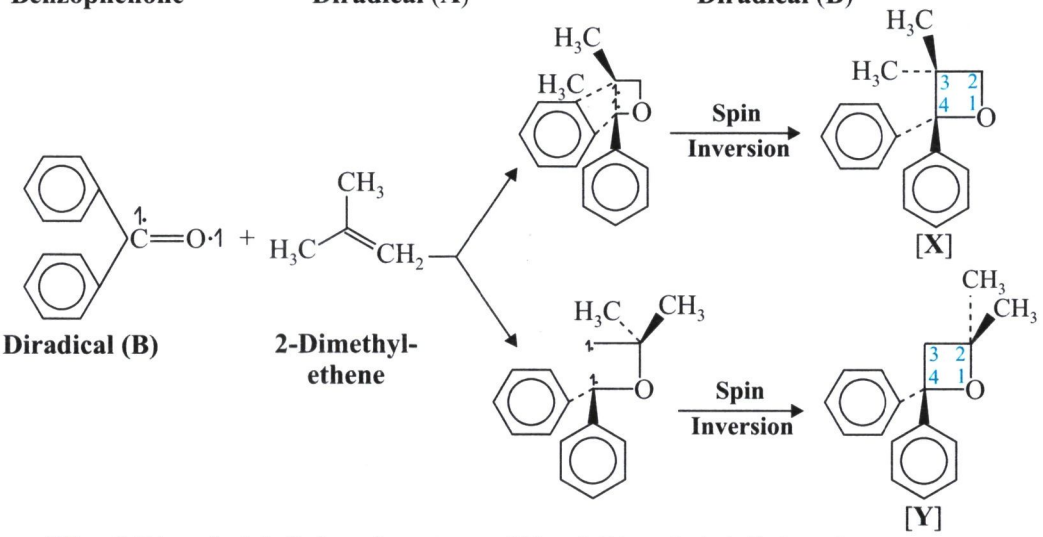
In true sense, the **ring formation** takes place in ***two* stages**, namely:

- ***First*–the excited carbonyl (>C=O) compound (*benzophenone*) (*triplet*) adds *via* its O-atom to the respective 'alkene' in order to yield mostly the more stable of the *two* possible diradicals**; and
- ***Secondly*–the so-called *'spin-inversion'* then comes into play; and thus, the *second bond is duly formed*.**

Thus, we may have the following expressions:



Benzophenone **Diradical (A)** **Diradical (B)**



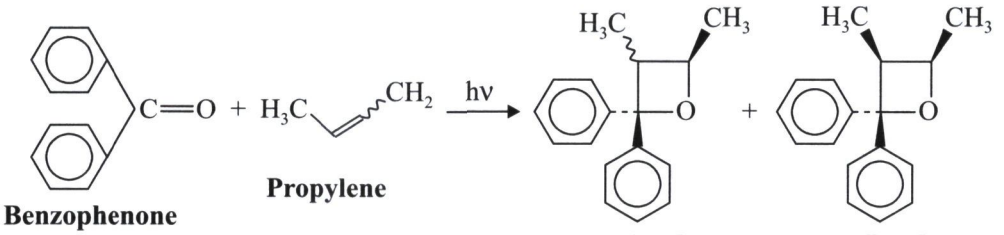
Diradical (B) **2-Dimethyl-ethene**

[X] = 3-Dimethyl-4-diphenyl oxetane; [Y] = 3-Dimethyl-4-diphenyl oxetane;

Remarks: It is, however, pertinent to state here that the **Paterno-Büchi reaction** is ***not stereospecific*** at all since the observed *time-lage* before the **final spin-inversion** is found to be definitely more than enough for enabling the rotation to take place about the ***single bonds.***

Example: The ***cis*- and *trans*-2-butene** do yield the same mixture of ***cis*- and *trans*-oxetanes with benzophenone:**

Thus, we may have the following expression:



Benzophenone **Propylene** **[6-Part] *trans*-Form** **[1-Part] *cis*-Form**

NOTE: **The percentage yield of the *trans*-oxetane is much more *vis-a-vis* the *cis*-oxetane.**

A General Observation

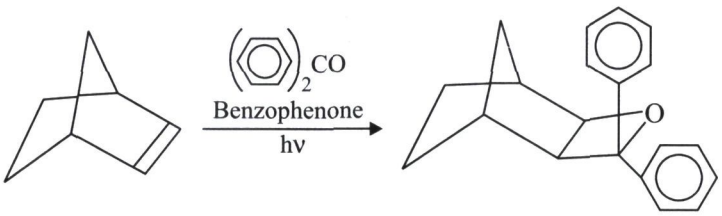
Importantly, one may come across a general observation in an instance wherein the energy difference occurring between the so-called:

- **triplet form,** and
- **ground state,**

with respect to the **carbonyl (>C=O) chemical entity** is definitely more than that prevailing between the respective forms of the ***'alkene'.***

Therefore, in such a case, the overall excited **carbonyl (>C=O) compound** may obviously help to transfer its inherent energy to the ***'alkene'***, —thereby enabling it to return to its ***ground state*** and yielding a ***'triplet-form alkene'***. This is, now further followed up for the so-called ***'alkene dimerization'*** eventually.

Example: The observed energy of the **'triplet-form benzophenone'** is found to be comparatively much *lower than that from norbornene*; and, therefore, the **photoaddition phenomenon** comes into play, as shown under:



Norbornene **A Photoaddition product**

Thus, the **photoaddition product** is accomplished between the *norbornene* and *benzophenone.*

Suggested Reading

Brückner R: **Advanced Organic Chemistry**, Harcourt (India) Pvt. (Ltd), New Delhi, 2003.

Finar IL: **Organic Chemistry, Vol. 1**, 5th ed., Longmans Green and Co., Ltd., London (UK), 1967.

Loudon GM: **Organic Chemistry**, 4th ed., Oxford University Press, Oxford (UK), 2004.

Morrison RT *et al.*: **Organic Chemistry**, 7th ed., Pearson Education Inc., (Published by Dorling Kinderslay (India) Pvt. (Ltd.), India, 2012.

Norman R and Coxon JM: **Principles of Organic Synthesis**, 3rd ed., Nelson Thornes, Cheltanham (UK), 2001.

O' Neil MJ (Ed): **The Merek Index**, 15th ed., The Royal Society of Chemistry, London (UK), 2013.



Chapter 10

Reactions Giving Halogen Derivatives

LESSONS AT A GLANCE

10.1 Introduction
- 10.1.1 Radical Halogenation of Hydrocarbons

10.2. Reactions Giving Halogen Derivatives
- 10.2.1 Haloform Reaction
- 10.2.2 Hell-Volhard-Zelinsky Reaction [HVZ-Reaction]
- 10.2.3 Hunsdiecker Reaction [or Borodine-Hunsdieker Reaction]
- 10.2.4 Hydroboration [or Hydroboronation] Reaction
- 10.2.5 Wohl-Ziegler Bromination

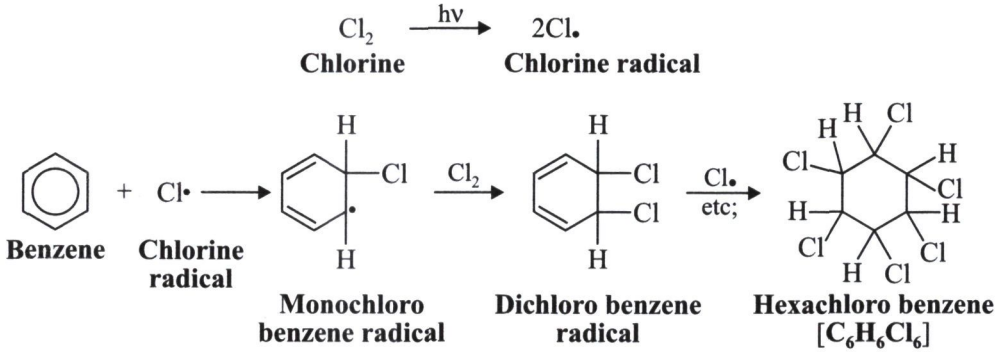
10.1 INTRODUCTION

In general, there are *three* variants of **'halogen chemical entities'** (*compounds*), such as:

- **Addition Compounds**
- **Nuclear Substitution Products** and
- **Side-chain Substitution Products.**

❑ ***Addition Compounds:*** Benzene when treated with either **chlorine** or **bromine** in the presence of *sunlight (UV-rays)*, the former gets converted to **benzene hexahalides ($C_6H_6Cl_6$)** and **($C_6H_6Br_6$)** respectively.

Thus, we may have the following expression:



❑ ***Nuclear Substitution Products*** **(Aryl Halides)**

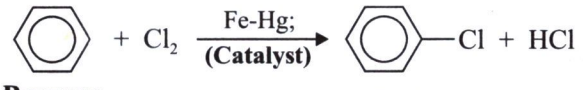
In true sense, these compound may be prepared easily and conveniently as under:

Direct Halogenation: It has been proven and established that *low temperature and the presence of a halogen-carrier* **do favour the nuclear substitution to a great extent.**

Therefore, both ***chlorination*** and ***bromination*** may be accomplished easily and conveniently even at ordinary *room temperature* **(RT) (20 ± 2°C)** in the critical presence of either:

• **Fe–Hg** or • **Al–Hg**

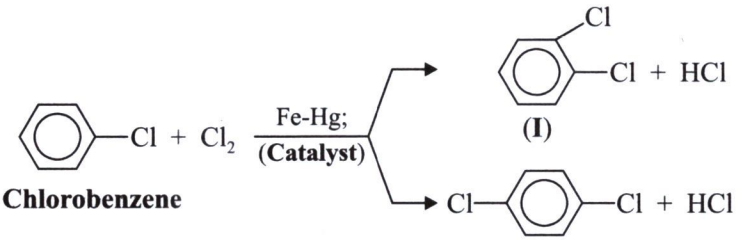
i.e., amalgams being employed as the potential **'catalyst'.** Besides, the ***degree of substitution*** depends exclusively upon the precise and exact quantum of **'halogen'** being used up in the reaction itself *i.e.,* formation of **'chlorobenzene'**–when benzene is being treated with ***chlorine*** **(1 mole)** in the presence of **Fe–Hg (as catalyst)**, as given under:



Benzene **Chlorobenzene [Yield : 90%]**

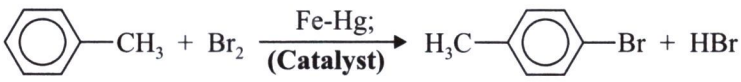
In a particular instance, when *two* **moles of chlorine** are being employed, one may lay hands onto an admixture of • ***o*–dichlorobenzene (I) and *p*-dichlorobenzene (II),**

as shown below:



Chlorobenzene

Likewise, when **toluene** (C_6H_5–CH_3) is duly *brominated* in the presence of **Fe–Hg** (*as catalyst*), using *one mole of bromine only*, we may also obtain an admixture of ***o– and p–bromotoluenes*** (*syn:* **Tolyl bromides**), as given below:



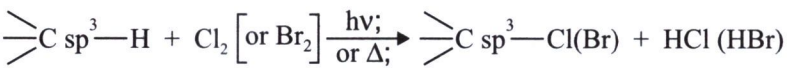
Toluene ***o*-and *p*-Bromotoluenes**

10.1.1 Radical Halogenation of Hydrocarbons

Evidence from the literature reveals explicitly that quite a few **'hydrocarbons'** may be *halogenated* articulately having essentially either:

• **Chlorine** **or** • **Bromine,**

on being subjected to either ***heat*** and/or ***irradiation*** together. Thus, we may have the following expression:



Comment: The overall net result may be ***'simple'*** or ***'multiple halogenation'***.

10.1.1.1 Simple and Multiple Chlorinations

Since we are fully aware with the underlying **mechanism for the thermal chlorination of methane (CH_4)**, so we may now have a *quick review* to the overall equation *i.e.,*

- **initiation step**; and
- **propagation step,**

pertaining to the so-called **'monochlorination of methane'**,–as depicted below in Fig. 10.1.

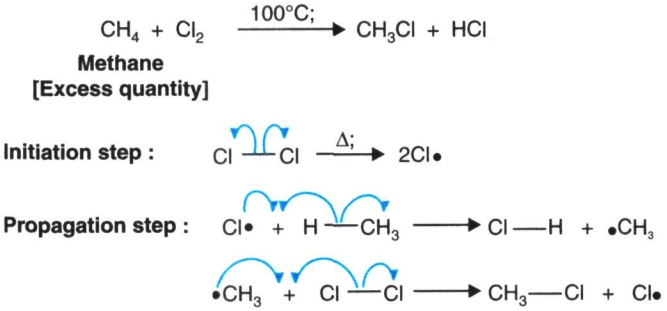


Fig. 10.1. Mechanism for the Monochlorination of Methane with Chlorine (Cl_2).

Figure 10.2 illustrates the *energy profile* of the **propagation steps** being involved specifically in the aforesaid reaction.

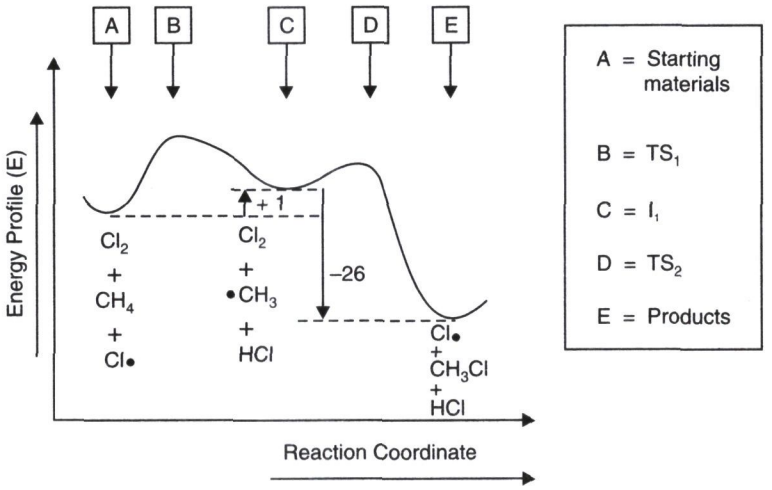


Fig. 10.2. The Energy Profile of the Various Propagation Steps of the Monochlorination of Methane (CH_4) with Chlorine (Cl_2) [Enthalpies in Kcal.mole^{-1}]

EXPLANATION

1. In the **energy profile** episode, each of the *two* separate **propagation steps** is duly designated as:

   "the *'transition state'* from one energy minimum over an energy maximum right into an altogether *new energy minimum state.*"

2. Nevertheless, the critically observed ***'energy minima'*** in an *energy profile* invariably characterize either:
   - **as the *long-lived species viz.*, starting material(s) and product(s)**; or
   - **as the *short-lived intermediates.***
3. Besides, the so-called ***'energy maxima'*** as observed in an *energy profile* (*i.e.*, **transition states**) do represent as:

"the snapshots of the geometry of a molecular system".*

10.1.1.2 Regioselectivity of Radical Chlorinations

It is, however, pertinent to state here that the perfect **monochlorinations** may be duly accomplished solely with the *hydrocarbons*,–which eventually **undergo reaction** *via* **the resonance stabilized radicals.**

Regioselectivity: It refers to a pre-determined **molecular transformation** that may be further expatiated with the help of the following *example:*

The reaction, **C—H ⟶ C—Cl**, is normally called as ***regioselective***—whenever it comes into play either *exclusively* or *preferentially* at:

"one particular place located on a substrate."

Importantly, the particular **resonance-stabilized radicals** are ***generated regioselectively*** as: **"a consequence of the so-called *product-development control* in the specific *radical-forming step.*"**

Commercial Synthesis of Benzyl Chloride $\left[\bigcirc\!\!-CH_2Cl\right]$

Figure 10.3 depicts clearly the commercial synthesis of **benzyl chloride** as stated under:

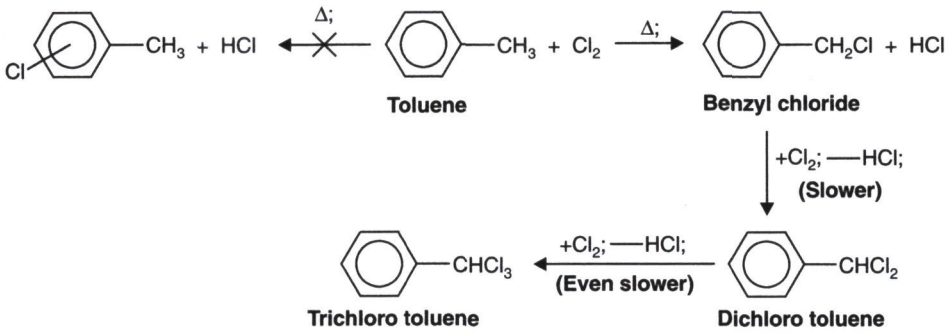


Fig. 10.3. The Commercial Synthesis of Benzyl chloride.

EXPLANATION

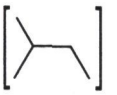
1. *Toluene* and *Chlorine* (gas) when heated together gives **benzyl chloride** and a mole of HCl; whereas, it never yields *toluene* and *HCl.*
2. The resulting **benzyl chloride** on being subjected to further reaction with *chlorine* (Cl_2) in a rather **slower mode** to give **dichlorotoluene** with the loss of a mole of HCl.
3. Finally, the resulting **product (dichlorotoluene)** even reacts in a **slower mode** with Cl_2 to give **trichlorotoluene** and a mole of HCl.

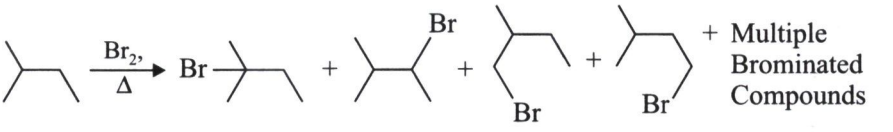
* That is, whose lifetime corresponds to the actual duration of a **'molecular vibration'** (ca.10^{-13}s).

10.1.1.3 Regioselectivity of Radical Brominations *vis-a-vis* to Chlorinations

It has been grossly observed in a sharp contrast to: **chlorine (Cl_2), bromine (Br_2)**, and **isopentane [$(CH_3)_2CH{\cdot}CH_2{\cdot}CH_3$]** with respect to the formation of ***monosubstitution*** products with marked and pronounced **regioselectivity**, as recorded in Table 10.1.

Table 10.1: Systematic Presentation of Regioselectivity in Radical Bromination of

Isopentane 



The relative yields of the above monobromination products are...	...92.2%	7.38%	0.28%	0.14%
In order to produce the above compounds in the individual case...	...1	2	6	3...
...H atoms were available for the substitution. Yields on a per-H-atoms basis were...	...92.2%	3.69%	0.047%	0.047%...
...for the monobromination product above. In other words: $k_{C-H \rightarrow C-Br,\ rel}$ in the position concerned is	...2000	79	$\equiv 1$	$\equiv 1$
..., that is, generally for...	...C_{tert}—H	C_{sec}—H	C_{prim}—H	

Comments: Obviously, the first predominant observed **monobromination product** is duly generated up to **92.2%** ***relative yield*** *via* the critical **substitution of C_{tert}–H**. However, the *second* most abundant **monobromination product** with a *relative yield* of **7.4%** being due to **substitution of C_{sec}–H.** Thus, the *two* **monobromination products** wherein a ***primary*** **H–atom** is duly replaced by a **Br–atom** eventually take place only in **negligible quantum.**

NOTE: **The analyses of these *regioselectivities* (as provided in Table 10.1) yields duly the relative rates of 2000, 79, and 1 for the *bromination* of:**

C_{tert}–H, C_{sec}–H, and C_{pri}–H respectively.

Hammond's Postulate*

It relates to the major factors essentially contributing to the instability of the *transition state* that eventually render the **carbocation unstable**; and thus, the **+ve and –ve charges** plus the development of an **'electron-deficient site'.** Obviously, recognizing the inherent and apparent strong resemblance of the *transition state* to the respective **carbocation**–let us make an *legitimate approximation:*

* Loudon GM: *Organic Chemistry*, 4th ed., Oxford University, Press, Oxford (UK), p.148, 2002.

"assuming that the structure of the transition state closely resembles to the structure of the carbocation intermediate."

Hence, the aforesaid approximation may be duly generalized in an important and vital statement invariably termed **Hammond's postulate.**

Importantly, in the present context **Hammond's postulate** may be applied intelligently to the aforesaid **selectivity-determining steps** of the so-called ***radical chlorination*** phenomenon as depicted in Fig. 10.4.

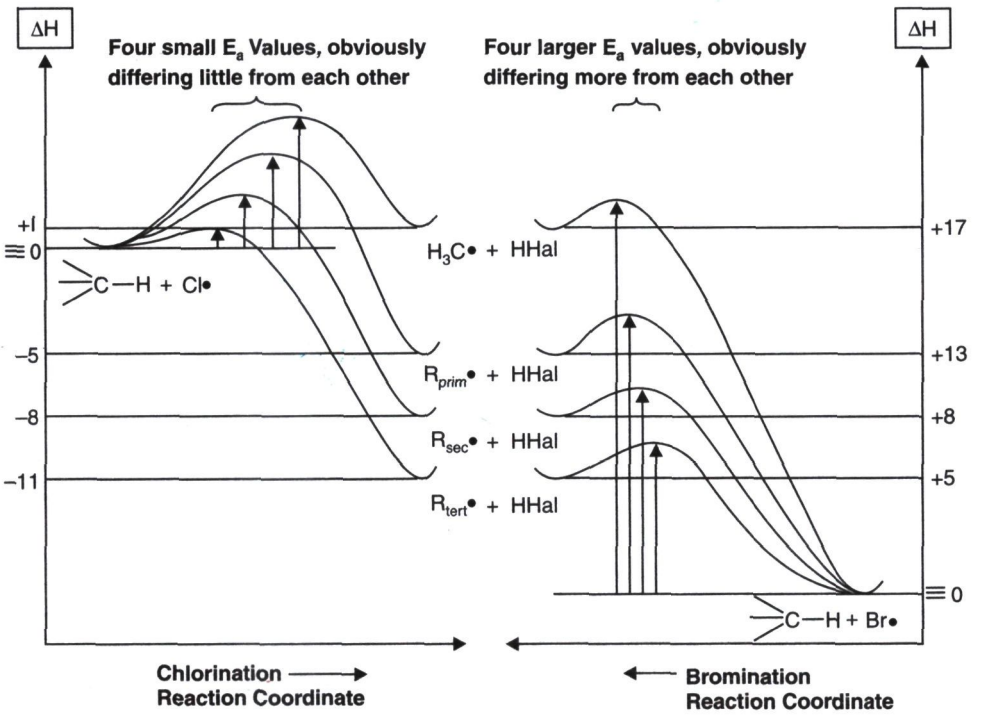


Fig. 10.4. Graphic Representation of Thermochemical Analysis of: Propagation Step of Radical Chlorination (left) and Bromination (right) of Alkanes that Determines Explicitly Regioselectivity of the Overall Reaction.

[The ΔHr (reaction enthalpy) values were determined experimentally; the ΔH (enthalpy) values are estimated duly].

[*Adapted from*: Brückner R: **Advanced Organic Chemistry**, Academic Press, (Harcourt (India) Pvt. Ltd., New Delhi), 2003].

Remarks: These essentially include:

1. Most steps do occur *via* early **transition states** *i.e.,* through the *transition states* which are very much akin to the *starting materials.*
2. Thus, *more stable the resulting radical, the more* close similarity to the starting materials would be the observed transition state.
3. Obviously, the observed overall *stability differences* occurring between these **radicals,** therefore, may be duly manifested only to a **negligible degree** since the *stability differences* between the **transition states** are also very small.

4. Amazingly, almost *all of the transition states* are found to be quite identical in *energy level*; and hence, are able to float across having quite similar **reaction rates**. Ultimately, it implies vehemently that:

   "the *regioselectivity* of the ensuing *'radical chlorination'* under the present consideration is so low."

10.1.1.4 Rate Law for Radical Halogenations: Reactivity–Selectivity Principle

A rather ***simplified*** **reaction scheme** showing the ***kinetic analysis*** of the so-called **'radical chain halogenations'** may be duly designated as under:

$$Hal_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2\,Hal\bullet \text{ with } K_{dis} = \frac{k_1}{k_2}$$

$$Hal\bullet + RH \xrightarrow{k_3} Hal\,H + R\bullet$$

$$R\bullet + Hal_2 \xrightarrow{k_4} R\,Hal + Hal\bullet$$

Now, let us make an assumption that only the above cited **reaction steps**—based solely in the said scheme do participate in the so-called:

'radical chain halogenations of the *hydrocarbons*'.

Thus, one may not be in a position to down play the fact that the *phenomenon of chain termination* may also come into play by virtue of the **radical-consuming reactions**, such as:

$$R\bullet + Hal\bullet \longrightarrow R\text{–}Hal \text{ and}$$

$$2R\bullet \longrightarrow R\text{—}R$$

Besides, the possibility of **disproportionation of alkyl radicals (R)** to yield the respective ***'alkane'*** that critically possesses **1 H-atom more**; and the ***'olefin'*** having **1 H-atom less.** Hence, as per this scheme one may eventually take cognizance of the fact that:

"the thermolysis of *halogen molecules* yields *halogen atoms* having the rate constant k_1."

Subsequently, they do recombine with the **rate constant k_2** to yield the **halogen molecule** *once again*. In this manner, the *halogen atoms* do participate actively as the so-called **initiating radical** in the ***first*** **propagation step**–that invariably comes into play with the **rate constant k_3.** The ***second*** **and the *last* propagation step** usually occurs with the **rate constant k_4.**

Reactivity-Selectivity Principle: It has been generalized that–**"a *highly reactive reagent* commonly reacts with the lower selectivity entity *vis-a-vis* a *less reactive reagent.*"**

10.2 REACTIONS GIVING HALOGEN DERIVATIVES

Based on the survey of literature reveals that there are certain specific reactions that give rise to the formation of halogen derivatives, namely:

- **Haloform Reaction,**
- **Hell-Volhard–Zelinsky Reaction,**
- **Hunsdiecker Reaction (or Borodin Hunsdiecker Reaction),**
- **Hydroboration (or Hydroboration Reaction), and**
- **Wohl-Zeigler Bromination,**

which shall now be discussed at length separately in the sections that follows:

10.2.1 Haloform Reaction

1. It has been observed that **all ketones (>C=O)** containing the *acetyl moiety* **(CH_3—CO–)** usually undergo the **haloform reaction** perceptively. However, this reaction is performed in a best way by dissolving the compound in *dioxan*, adding diluted NaOH solution, followed by a slight excess of **I_2 in KI solution** warming, and ultimately adding distilled water. In case, the compound comprises the **acetyl moiety, iodoform** gets duly precipitated.

Important Points:

In reality, the **haloform reaction** is found to be extremely beneficial in carrying out the so-called **organic degradation** phenomenon.

2. A distinct **positive test** is invariably given by majority of *chemical entities* containing the **acetyl moiety** duly attached either to: • **Carbon-atom** or • **H-atom.**

Besides, it is also given by such compounds that are duly *oxidized* under the laid down parameters of the test to such structural analogues containing the **acetyl moiety** *viz.,*

• **Ethanol [CH_3–CH_2–OH]** and • **Isopropanol [$(CH_3)_2$ CHOH].**

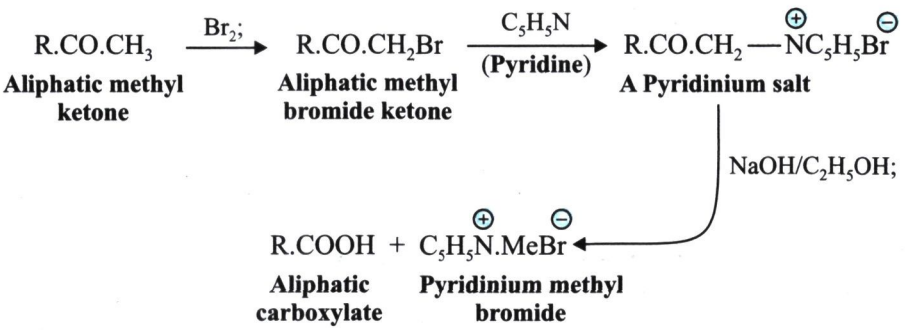
3. Booth and Sanders (1950) have demonstrated that a good number of other chemical entities (besides also those already cited earlier) also undergo the **haloform reaction** *viz.,*

• **Quinones** • **Quinols** and • ***m*-Dihydric phenols.**

Exception: Interestingly, the **acetoacetic ester** (or *ethylacetoacetate*) **[$CH_3COCH_2COOC_2H_5$],** fails to give the test even though it does contain an *acetyl moiety.* Perhaps such an anamoly may be expatiated logically due to the fact that it contains an **'active methylene (—CH_2—) moiety'**, which predominantly gets ***halogenated*** on priority and certainly **not** the *methyl (CH_3)* **of the acetyl moiety (CH_3Cl).**

Alternative Method: An **alternative method** to the so-called **haloform reaction** relates to the respective treatment of the respective **monobrominated methyl ketone** with ***pyridine.*** Subsequently, the *precipitated* **'pyridinium salt'** is being decomposed with ***diluted ethanolic sodium hydroxide*** [Krohuke (1933); and King (1944)].

Thus, we may have the following expression:



NOTE: **The greatest advantage of this method is that the entire reaction may be performed solely in a non-aqueous medium.**

PRODUCTION OF HALOFORM [HCX_3] (OR TRIHALOMETHANE)

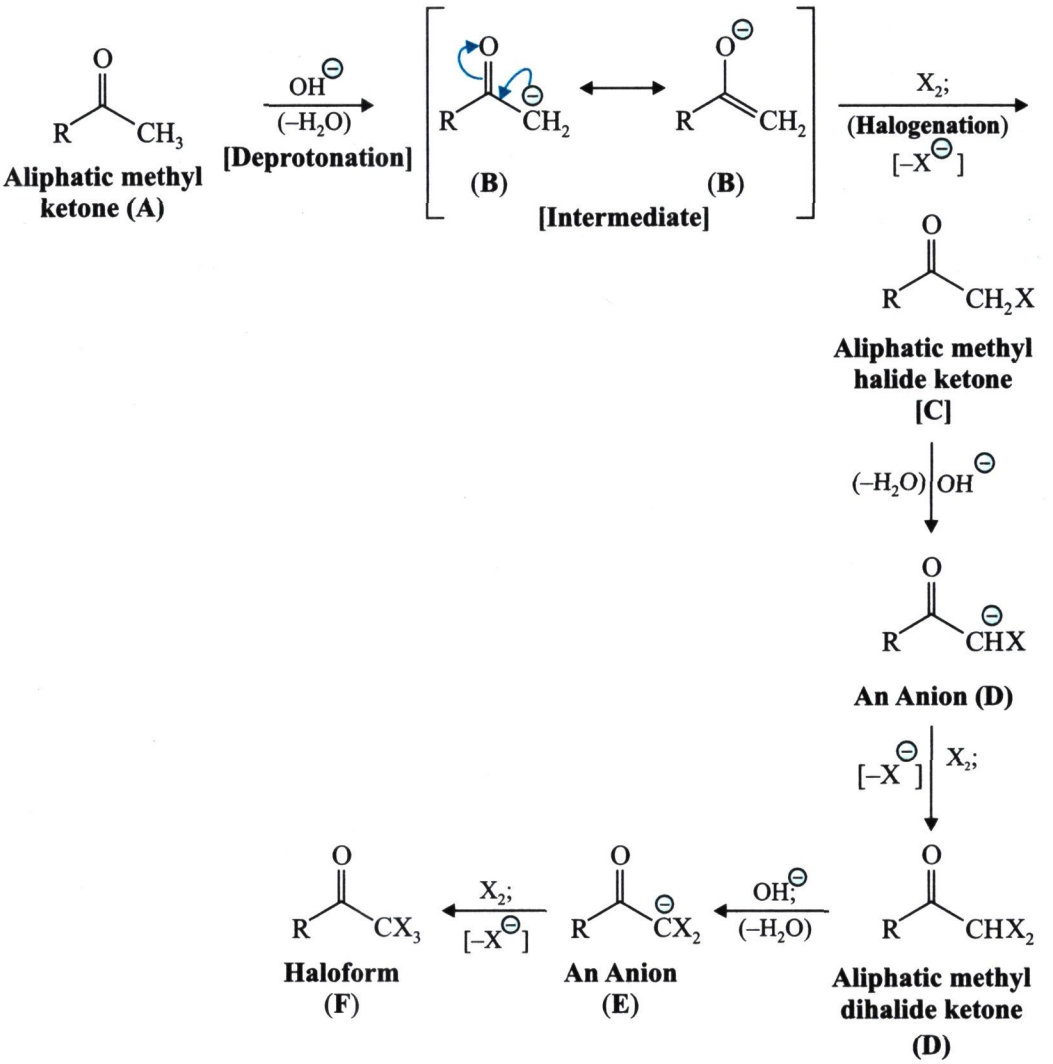
Another school of thought relates the **'haloform reaction'** to the critical involvement of the production of **'haloform (HCX_3)'** by:

"the specific *oxidative cleavage* of *methyl ketones* ($RCOCH_3$) by multiple halogenation phenomena."*

Thus, after carrying out the **trihalogenation** phenomenon, the corresponding *methyl (—CH_3) moiety* of an **alkyl methyl ketone** gets duly converted into:

'α, α, α–trihalomethyl moiety'.

The various sequential reactions involved are enumerated as under:



* Lieben A: *Justus Liebigs Am Chem Supp.*, **7**: 218–236, 1870; Guthrie *et al.*: *Can J Chem.*, **64**: 1250, 1986; Zacco *et al.*: *J Org Chem.*, **52**: 5356, 1987.

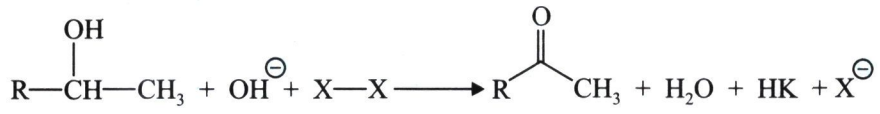
Explanation

The various steps involved may be explained as below:

1. Deprotonation of **aliphatic methyl ketone (A)** yields an **intermediate** in *two* **forms (B)**, which upon *halogenation* gives an **aliphatic methyl halide ketone (C)**.
2. The resulting **product (C)** in an alkaline environment undergoes *dehydration* to produce an **anion (D)**, which on *halogenation* gives rise to the formation of an **aliphatic methyl dihalide ketone (D).**
3. **Product (D)** in an alkaline medium loses a mole of water to give an **anion (E),** which again on *halogenation* yields the desired **haloform (F).**

Important Observation

One may critically note an **important observation** that the ***'haloform reaction'*** may also be performed with either ***primary*** **carbinols** or ***secondary*** **carbinols**, as given under:



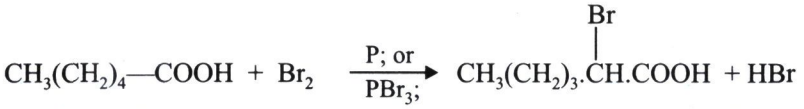
α-Alkyl ethanol (A *sec* - Carbinol) **Halogen** **Alkyl methyl ketone (A)**

NOTE: **In a situation, when the *ketone* possesses α′–H atoms, a *side-reaction* is generally come into effect thereby causing a *halogenation* at that particular position.***

10.2.2 Hell-Volhard–Zelinsky Reaction** [HVZ–Reaction]

The **carboxylic acids** may be specifically *brominated* at their **α–C atoms.** Thus, a **bromine** gets duly substituted for an **α-H-atom** as and when a **carboxylic acid** is being treated with *bromine* (Br_2) and a catalytic equivalent quantum of *red phosphorus (P)* or *phosphorus tribromide* (PBr_3).***

Thus, we may express the reaction as follows:



Hexanoic acid **Bromine** **2-Bromohexanoic acid [Yield : 83-89%]**

The aforesaid reaction is usually termed as the **Hell-Volhard-Zelinsky reaction**; and hence, is sometimes nick named the **HVZ-reaction.**

Mechanism of HVZ Reaction

Infact, the very *first* step in the mechanism of the **HVZ-reaction** is the critical conversion of the *carboxylic acid* into the respective small quantum of *acid bromide* under the influence of the ***catalyst*** **PBr_3**.

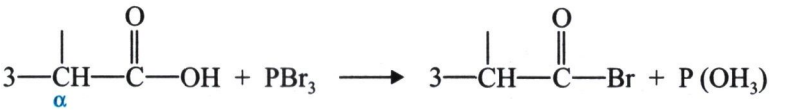
---

* Chakrabartty SK: **Oxidation in Organic Chemistry, (Part C)**, Academic Press, New York, pp. 343–370, 1978.

** Volhard J: *Annalender Chemie*, **242**: 141–46, 1887; Zelinsky N, *Berichte*, **20**: 2026, 1887.

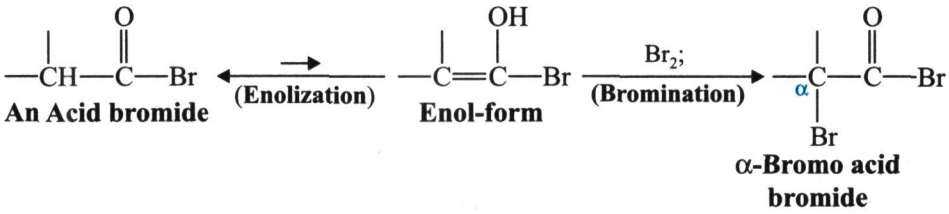
*** The actual **catalyst** is **PBr_3**; **phosphorus (P)** may also be used instead since it reacts with Br_2 to yield **PBr_3**.

We may have the following expression:

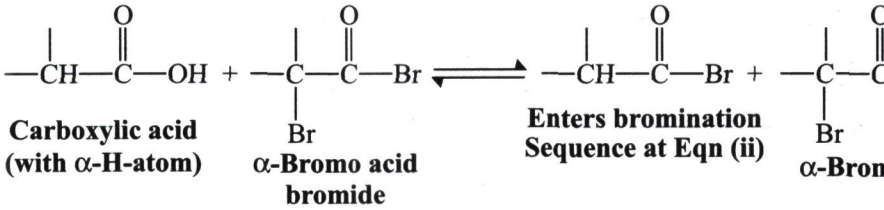


❑ **Formation of α-Bromo Acid Bromide:** Right from this ***particular*** **stage** the mechanism resembles quite intimately to the corresponding **acid-catalyzed bromination of ketones.** Thus, the resulting ***'enol'*** of the *acid bromide* designates profusely the species which **brominates** in actual practice.

The various steps involved may be expressed as under:



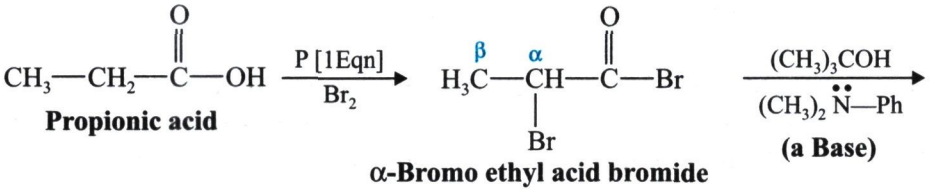
❑ **Formation of more Acid Bromide:** Amazingly, when a *small quantum* of the ***catalyst*** $\mathbf{PBr_3}$ is employed then the respective **α-bromo acid bromide** interacts specifically with the available *carboxylic acid* to form **more acid bromide,** which eventually gets brominated as depicted below:

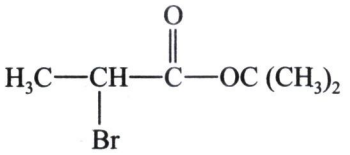


Comments: Therefore, one may conclude that when a *catalytic quantum* of $\mathbf{PBr_3}$, is employed, the final reaction product is invariably the **α-bromo acid** [see Eqn. (*iii*)].

❑ **Formation of *tert*-Butyl-2-Bromopropanoate:** Now, in a particular instance, when one **full equivalent of the catalyst** $\mathbf{PBr_3}$ is used, the respective **α-bromo acid bromide** is the usual *reaction product*; and hence, it may be used intelligently in several reactions of the *acid halides.*

Example: The said *reaction mixture* may be subjected to treatment with an *alcohol* to yield an **α-bromoester** *i.e.,* ***tert*-butyl-2-bromopropionate from propionic acid,** as given under:





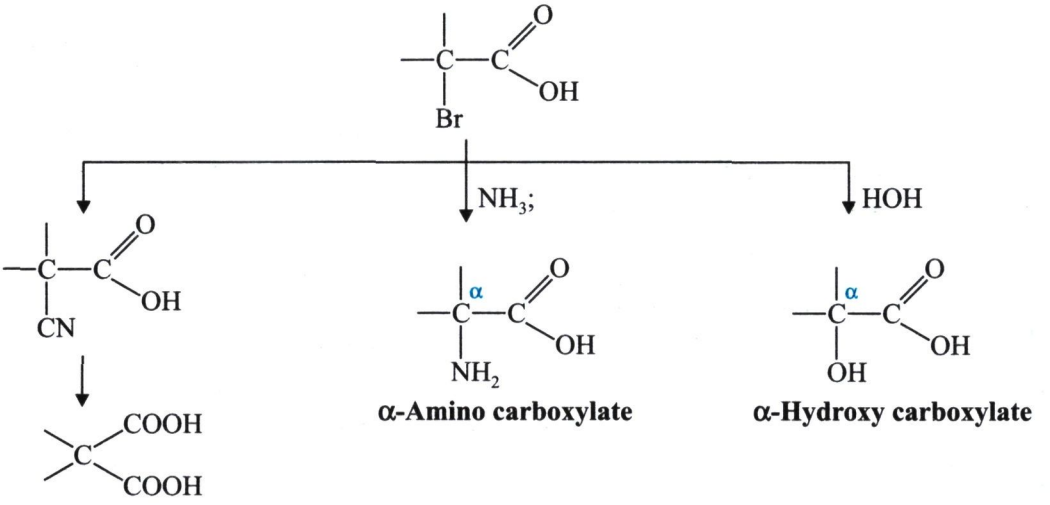
...(*iv*)

***tert*-Butyl-2-bromo propionate**

Thus, in Eqn. (*iv*), *propionic acid* with one equivalent of phosphorus as catalyst followed by *bromination* yields **α-bromoethyl acid bromide**, which on further treatment with *trimethyl butanol* in the presence of *dimethyl phenyl amine* (as a **base**) gives the desired product, ***tert*-butyl-2-bromopropionate.**

NOTE: **It has been duly observed that it is rather difficult to accomplish either the *mono-iodinate* or *mono-fluorinate* products since the *second* α-H-atom may also be replaced duly by the respective halogen.**

Points to Ponder: It may, however be added that either the so-called **α-bromo** or **α-chloro carboxylates** may be able to undergo reactions as given under:



α-Amino carboxylate

α-Hydroxy carboxylate

Dicarboxylate

Solvent Effect upon the Mechanism of the HVZ–Reaction

In an event when the **HVZ-reaction** is duly performed in a ***slight* nucleophilic solvent**, we may eventually obtain **α-bromo carboxylic acid** right from the interaction between:

- **α-bromoacetyl bromide, and**
- **a carboxylic acid,**

together with critical formation of the ***acyl bromide intermediate.***

Besides, when the said reaction is being carried out in a *neutral* to *slightly acidic aqueous solution*, one may actually obtain an explicit **nucleophilic acyl substitution** thereby producing an *α-bromo carboxylic acid* from the corresponding hydrolysis of **α-bromo acyl bromide.**

In this manner, the **α-H-atom** present duly in a *carboxylate* is critically replaced either by:

- **Bromine** or - **Chlorine,**

to yield an ***α-bromo-*** **or** ***α-chloro-*****carboxylate.***

10.2.3 Hunsdiecker Reaction* [or Borodine-Hunsdieker Reaction]**

Hunsdiecker reaction refers to the synthesis of the **organic halides** by means of the ***thermal decarboxylation*** of the respective **carboxylic acids** in the presence of *halogens*, as shown below:

$$\underset{\text{Alkyl silver carboxylate}}{R.\overset{\overset{O}{\|}}{C}.OAg} + X_2 \xrightarrow[\text{(Thermal decarboxylation)}]{\Delta;} \underset{\text{Organic halide}}{RX} + CO_2\uparrow + AgX\downarrow$$

Hunsdiecker *et al.* (1939) observed critically that the divergent salts of the *fatty acids* are duly decomposed by either **chlorine (Cl_2)** or **bromine (Br_2)** to yield the respective ***'alkyl halide'*** *viz.*,

$$\underset{\substack{\text{Alkyl silver carboxylate} \\ \text{[Silver salt]}}}{R.\overset{\overset{O}{\|}}{C}.OAg} + Br_2 \longrightarrow \underset{\text{Organic halide}}{RBr} + CO_2\uparrow + AgBr$$

Remarks: In true sense, the **'silver salt'** seems to provide the optimized yield of the corresponding **'organic halide'**; however, the yield also depends exclusively upon the specific solvent being employed in the reaction.

Stoll *et al.*, (1951) observed critically that '**trichloroethylene [$ClCH{=}CCl_2$]** definitely proves to be a '***much better*** **solvent**' in comparison to either:

- **Carbon tetrachloride (CCl_4)** or - **Carbon disulphide (CS_2).**

Interestingly, the yield of respective **'halide'** shows the following order:

Primary > Secondary > tertiary,

when **bromine (Br_2)** is employed. However, **chlorine (Cl_2)** gives a much lower overall yield of the **'alkyl chloride'.**

Mechanism of Hunsdiecker Reaction

The exact underlying mechanism of **Hunsdiecker reaction** is uncertain; nevertheless, a possibly favoured theory being that:

* Slack DE *et al.*: *Org Lett*, **4**: 4487, 2002; Sharma A *et al.*: *J Org Chem.*, **64**: 8059, 1999; Jhang LH: *Tetrahedron Lett.*, **30**: 9621, 1996.

** Hunsdiecker C *et al.*: US2176181 (1939); Hunsdiecker C *et al.*: *Ber.*, **75**: 291, 1942; Borodine A: *Ann.*, **119**: 121, 1861.

"the very first step is the formation of an '*acyl hypohalite*', that eventually gets decomposed into *free radicals*."

The elaborated details of the **later steps** are *quite less certain*:

$$R.\overset{\overset{O}{\|}}{C}.O.Ag + Br_2 \longrightarrow R.CO.OBr + AgBr$$

$$R.\overset{\overset{O}{\|}}{C}.OBr \longrightarrow Br^{\ominus} + R.\overset{\overset{O}{\|}}{C}.O: \longrightarrow R\cdot\cdot + \uparrow CO_2$$

$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot$$

$$R\cdot + R{:}CO.OBr \longrightarrow RBr + R.COO\cdot$$

Cristol *et al.* (1961) reported the much appreciable yields of the **alkyl bromide** by the careful incorporation of **bromine (Br_2)** into a refluxing *carbon tetrachloride (CCl_4) solution* of the respective *'acid'* in the critical presence of an excess quantum of **red mercuric oxide (HgO).**

NOTE: **Davis *et al.* (1965) soon after the observation of Cristol *et al.* (1961) suggested that a marked improvement in the yields of *alkyl bromide* may be achieved by making use of *tetrachloro ethane* [$CHCl_2{\cdot}CHCl_2$] instead of *carbon tetrachloride* [CCl_4] as the solvent. Besides, they also ascertained vehemently that the *yellow mercuric oxide* (HgO) was found to be as effective as the red form.**

10.2.4 Hydroboration (or Hydroboronation) Reaction*

The *diborane* **(B_2H_6)** reacts readily at room temperature (RT) [20 ± 2°C] with the *olefins* **($RCH{=}CH_2$)** thereby giving rise to the formation of **trialkylboranes [$R{\cdot}CH_2CH_2)_3B$]**. However, the so-called *terminal olefins* usually yield ***primary*** **alkylboranes**, that may be eventually *oxidized* by **alkaline hydrogen peroxide** *($H_2O_2/NaOH$)* to produce the ***pri*-alcohols (1°)**, as given below:

$$\underset{\textbf{An Olefin}}{R.CH{=}CH_2} \xrightarrow[\textbf{(Diborane)}]{B_2H_6} \underset{\substack{\textit{pri}\textbf{-Alkyl borane}\\ \textbf{[Trialkyl borane]}}}{(R.CH_2.CH_2)_3\ B} \xrightarrow[NaOH;]{H_2O_2;} \underset{\textbf{A }\textit{primary}\textbf{ Alcohol}}{3R.CH_2CH_2.OH}$$

Thus, the critical addition of **diborane** is usually termed as **hydroboration** (or **hydroboronation**). It is, however, pertinent to state here that:

"Borane (BH_3) is being added on to the *olefinic bond* following the Markovnikov's Rule."**

Furthermore, **Markovnikov's rule** explicitly states that the **'boron'** goes to that particular **olefinic bonded C–atom** that critically bears ***more number of* H–atoms** *i.e.,* irrespective of the fact whether the ***substituents*** located strategically upon the **olefinic bonded carbons** are either ***alkyl*** or ***aryl*** in nature. In reality, the aforesaid vivid observation is solely based upon the fact that **boron (B)** is found to more positive than H–atom.

Anti*-Markovnikov's Alcohol:** Interestingly, the final product obtained duly from **hydroboration** is invariably followed by *oxidation* of the ***newly formed **'borane'**, which is found to be **Markovnikov's alcohol.**

---

* Brown HC and Subba Rao: BC : *J Am Chem Soc.*, **78**: 5694, 1956; *J Org Chem.*, **22**: 1135–36, 1957.

** For discussions on **Markovnikov's Rule:** See Isenburg, Grdinic: *J Chem Edu.*, **46**: 601, 1969; Grdinic; Isenburg: *Intra Sci; Chem Rep.*; **4**: 145–162, 1970.

NOTE: **In view of the aforesaid vital and important observations, the *hydroboration-oxidation reaction* finds a plethora of useful applications for the typical regioselective and stereoselective synthesis of *'alcohols'*.**

IMPORTANT POINTS

These essentially include:

1. *Addition of Diborane (B_2H_6) to a Terminal Olefin Bond*: The crucial addition of *diborane to a terminal olefin bond* is observed to relatively much faster *vis-a-vis* a *non-terminal olefin bond.* Obviously, by making use of ***'insufficient diborane'***–it would be lot easier to accomplish:

"a selective addition to the terminal olefin bond".

Besides the subsequent conversion of ***olefin*** to the corresponding ***alcohol*** has been grossly shown to occur by an overall ***cis*-addition.**

Example (*i*): The **aluminium alkyls [R_3Al]** usually have a tendency to *add* onto the **1-olefins;** and hence, the resulting product may be duly **oxidized to alcohols** as shown under:

$$R_3Al + 3R^1.CH{=}CH_2 \xrightarrow[100°C]{\text{Benzene}} (R.CHR^1.CH_2)_3Al \xrightarrow[\text{(ii) Acid;}]{\text{(i) } O_2;} 3R.CHR^1.CH_2OH$$

Aluminium alkyl **1-Olefin** **Trialkyl aluminium** ***Pri*-alcohol**

***(ii)* Preparation of Alkane by Protolysis:** When the **trialkylborane** is subjected to treatment with *propionic acid,* the respective **alkane** is duly obtained by **protolysis,** as expressed under:

$$(R.CH_2CH_2)_3B \xrightarrow[(-BH_3)]{H^+;} 3R.CH_2.CH_3$$

Trialkylborane **An alkane**

Remarks: Thus, the *ultimate product* is duly formed by the reduction of an ***olefin by a non-catalytic procedure.***

***(iii)* Preparation of *cis*-Olefin from Acetylenes (—C≡C—) by mono-hydroboration and protolysis**

Thus, we may have the following expression:

$$\underset{\textbf{Acetylene}}{—C{\equiv}C—} \xrightarrow[\text{(Diborane)}]{B_2H_6;} (—CH{=}\underset{|}{C}—)_3B \xrightarrow[\substack{\text{Protolysis}\\(-BH_3)}]{H^+;} \underset{\textbf{\textit{cis}-Olefin}}{—CH{=}CH—}$$

2. Addition of Diborane (B_2H_6) to a Non-terminal Double Bond: It often occurs at the so-called **least-hindered C–atom,** and the prevalent nature of the resulting product solely depends upon the *quantum of hindering* taking place at the **double (olefine) bond.** Thus, we may have the following expression:

$(H_3C.CH{=}CH.CH_3$	$(CH_3)_2C{=}CH.CH_3$	$(CH_3)_2C{=}C(CH_3)_2$
↓	↓	↓
$(H_3C.CH_2.CH.CH_3)_3B$	$[(CH_3)_2.CH.CH.CH_3]_2BH$	$[(CH_3)_2.CH.C\,(CH_3)_2]BH_2$
(Tributyl borane)	**1-Methyl-2-dimethyl borane**	**1, 2-Dimethyl borane**

OBSERVATIONS

1. However, these **selective (S–) and terminal (t–) alkylboranes** do undergo ***isomerization*** finally to the respective ***pri*-alkylboranes** when heated gently.

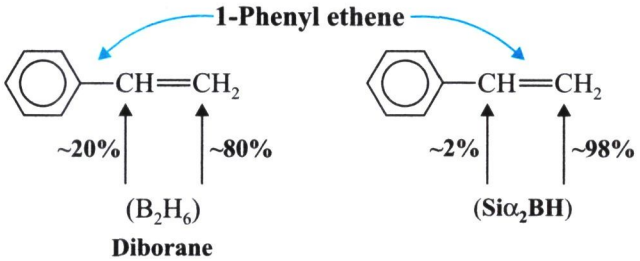
   Thus, we may have the following reaction:

$$(CH_3.CH_2.CH.CH_3)_3B \longrightarrow (CH_3.CH_2.CH_2.CH_2)_3B$$

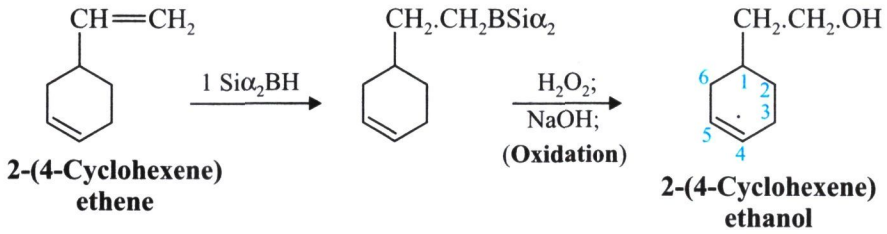
Tri(2-Methyl butyl) borane **Tributyl borane**

2. **Bis-3-methyl-2-butyl borane (or disiamylborane)** is proved to be specifically useful for accomplishing the so-called **'selective hydroboration'.**

   Thus, **borane** (BH_3) is invariably written as **$Si\alpha_2BH$.** We may have the following expressions:



- **Brown *et al.* (1961)** reported that a chemical entity (compound) comprising *more than one olefin bond* may be converted easily into **one specific alcohol**, as shown below:



- **Brown *et al.* (1960)** proposed a *conventional method* to prepare ***pri*-alkyl borane** (or **trialkyl borane**), as given below:

$$3R.CH{=}CH_2 + 3LiH + BF_3 \longrightarrow (R.CH_2.CH_2)_3\,B + 3LiF$$

An Olefin **Lithium hydride** **Trifluoro borane** ***Pri*-Alkyl borane [Trialkyl borane]** **Lithium fluoride**

NOTE: **We may also use either *sodium hydride (NaH)* or *lithium aluminium hydride ($LiAlH_4$)*.**

Mechanism of Hydroboration Reaction

The **mechanism of the hydroboration (or hydroboronation) reaction** essentially involves the following ***two* distinct steps**, such as:

- ***First* step**–critically consists of the incorporation of ***borane (BH_3)*** to the **olefin (double) bond** following the known **Markovnikov's rule**; and

❑ ***Second* step**–essentially involves the articulated *substitution* of the **boron moiety ($-BH_2$)** with the corresponding **hydroxyl (—OH) moiety** on being subjected to *oxidation* thereby obviously leading to the desired **'final product'** ***alcohol***.

Thus, **borane (BH_3)** undergoes typical ***dimerization**** phenomenon to give **diborane (B_2H_6)** (*i.e.*, a *highly toxic colourless gas*) wherein the ***two* H-atoms** gets meticulously bonded to the ***two* B-atoms** by the aid of ***'single-electron pairs'***, which is commonly known as:

"three centre-two-electron bonds."

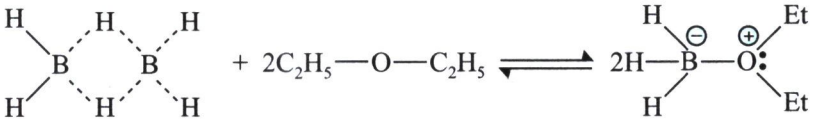
Therefore, by virtue of the aforesaid **'delocalization of electrons'** the ***'octet'*** of each boron is duly completed–which eventually helps to minimize the ***electrophilicity*** of each **boron.**

NOTE: **Thus, the diborane (B_2H_6) more or less behaves very much as the *'Lewis Acid'* with regard to its so-called *inherent vacant p-orbital.***

Preparation of Borane-Ether Complex

The preparation of **borane-ether complex** may be accomplished chemically by treating **diborane (B_2H_6)** with *diethyl ether* **[$(C_2H_5)_2O$]** or an *amine.*

Thus, we may have the following *reversible reaction.*

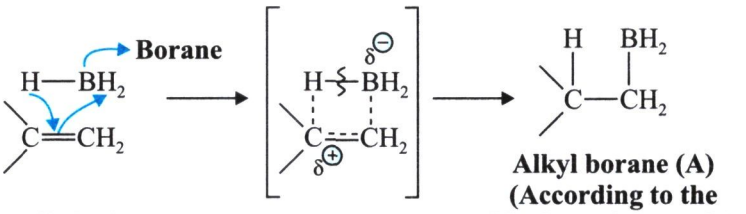


Diborane (B_2H_6) **Diethyl ether** **Borane-Ether complex**

Mechanism of Borane-Ether-Complex Formation

Following are the *two* important steps that are involved in the formation of the **borane-ether complex:**

Step–1:

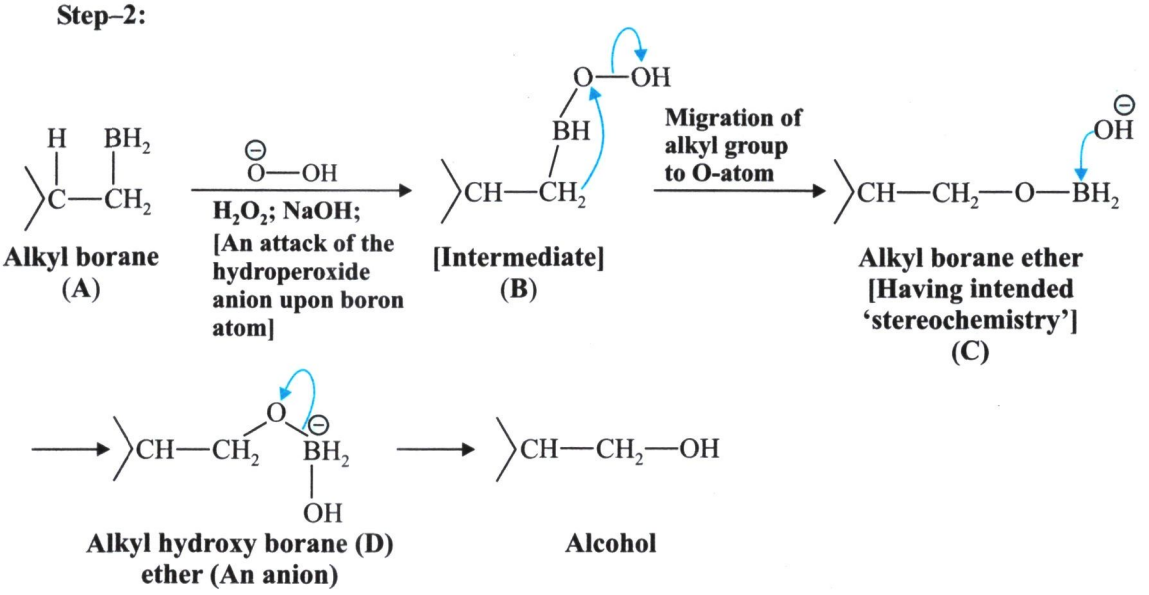


Alkyl ethene **Partial carbocation** **Alkyl borane (A) (According to the Markovnikov's rule)**

Comments: The above step implies a–**'stereospecificity-determining'** step predominantly.

* That is, formation of a mole each of **2,4,4–trimethyl-2-pentene** and **2,4,4-trimethyl-1-pentene** from *two* moles of **isobutylene.**

Step–2:



Comments: Alkyl borane (A) when treated with *hydroperoxide anion* $\left[\overset{\ominus}{O}\text{–OH}\right]$ affords an attack on the *boron atom* to give an **intermediate (B)**. The resulting **product (B)** undergoes migration of the *alkyl group* to the respective *O-atom* to give an **alkyl borane ether (C)** having an intended **stereochemistry.** The **product (C)** subsequently gives the **alkyl hydroxy borane ether (D)** an anion, which ultimately gives rise to the formation of an **'alcohol'.**

NOTE: **It is, however, pertinent to state here that the so-called *'alkyl migration'* yields the corresponding *alkyl borane* having the intended *stereochemistry* of the desired compound.**

Regioselectivity of Hydrorboration Reaction

Brown *et al.* (1966)* were pioneer in advocating the **regioselectivity of hydroboration reaction.** Perhaps the major logical intention behind the so-called regioselectivity of the said reaction may be its:

"inherent *steric factor* in addition to the *electronic factor.*"

Brown *et al.* carried out an exhaustive investigative study with respect to the critical effect of:

"the ring substituents upon the direction of attack, and also upon the *'kinetics of the on-going reaction'.*"

Infact, they concluded eventually that the actual attack by **boron** happens to be that of an **electrophilic character** perceptively.

* Brown HC *et al.: J Am Chem Soc.*, **88**: 5851, 1966.

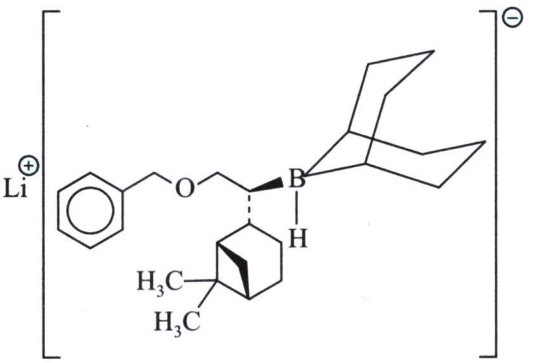
Important Observations

These essentially include:

1. The so-called *symmetrically substituted olefin bonded C–atoms* invariably yields an **equal quantum of each *isomer*.**
2. However, the aforesaid intended *addition* may be duly accomplished to be **'regioselective'** in character by thoughtful usage of relatively **'large attacking molecule'.**

Example: Following reagent has proved to be a versatile one in *synthetic organic chemistry* having reasonably **high regioselectivity.***

NB–Enantride [*Syn:* Lithium hydro (9-BBN-napol benzyl ether adduct)]



Special Remarks: These essentially comprise:

1. The ***stereoselectivity* of hydroboration reaction** is observed to be occurring in the –**'*Syn*-mode'** *i.e.,* it takes place upon the *same phase of* ***'alkene'***; and thus, the actual attack obviously takes place particularly from the so-called ***'hindered side'.*****
2. This is perhaps the actual reason why **1-methylcyclopentene** [-CH_3] undergoes interaction specifically with the **diborane (B_2H_6)** preferentially to the ***trans*-alkene.*****
3. The **'alkynes'** also shows a tendency to undergo **hydroboration reaction** specifically engaging the so-called ***syn*-mode of action.** Besides, it also yields an array of ***secondary*-reaction products**, such as:
   - **Aldehydes**–from the *terminal-alkynes*; and
   - **Ketones**–from the *internal-alkynes.*
4. **Hydroboration with *anti*-mode of action:** In an instance, when the *substrate* happens to be an **amine** or **alkylic alcohol**, the respective **hydroboration reaction** explicitly shown an ***anti*-mode reaction******, –that may ultimately cause a definite change in the ***regioselectivity*** profile.

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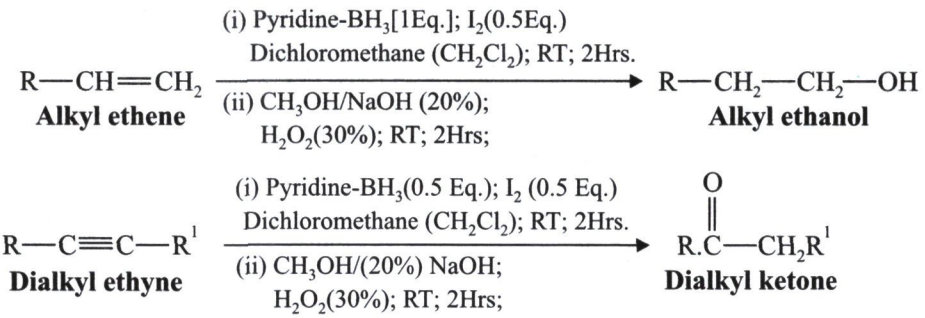
* Brown HC *et al.*: *J Org Chem.*, **52**: 5406, 1987.

** Brown HC *et al.*: *J Am Chem Soc.*, **83 (11)** : 2544–51, 1961.

*** Brown HC *et al.*: *J Am Chem. Soc.*, **94 (12)**: 4370–71, 1972.

**** Clay JM and Vedjes E: *J Am Chem Soc.*, **127**: 5766–67, 2005.

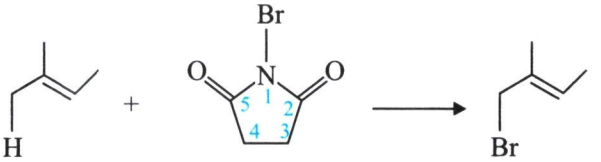
5. **Hydroboration Reaction with Pyridine Borane:** Clay *et al.*, (2005)* studied in an elaborated manner the **hydroboration reaction** with **pyridine borane**, as given under:



Remarks: Hirano *et al.* (2007)** reported the *1,4-addition* of **trialkylboranes** to yield the respective **α, β-unsaturated esters** in the presence of **Ni-as catalyst.** Thus, when *methanol* was duly added to the *reaction mixture* carefully an *appreciable enhancement* in the **'rate of reaction'** was duly observed.

10.2.5 Wohl-Ziegler Bromination***

It relates to the *allylic bromination* of the **olefins** with ***N-bromosuccinimide* (NBS);** and in the presence of *UV-light* or *peroxides* (H_2O_2, Na_2O_2), as stated under:



An Olefin + **1-Bromo 2, 5-diketo-2, 4-dihydro pyrrole** → **A Bromo olefin**

In a broader perspective, the **Wohl-Ziegler bromination reaction** with *N-bromosuccinimide (NBS)* gives rise to a ***selective substitution*** specifically with an **allylic H-atom of olefin or alkene** by the so-called *bromine (Br) atom* to yield the corresponding **allylic bromide** (Dauben and McCoy, 1959).****

Walling *et al.* (1963)***** proposed the ***mechanism of*** the **Wohl-Ziegler reaction** in particular compliance to the well-known **'Free Radical Chain Mechanism'** critically involving the following *two* distinct types of *chemical reactions* known as:

- ***Radical Initiation* Reaction**; and
- ***Propagation* of a Free–Radical Chain Reaction**

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* Clay JM and Vedjes E: *J Am Chem Soc.*, **127**: 5766–67, 2005.

** Hirano K *et al.*: *Org Lett*, **9**: 1541–44, 2007.

*** Wohl A., *Ber*, **52**: 51, 1919 : Ziegler K *et al.*, *Ann.*, **551**: 30, 1942.

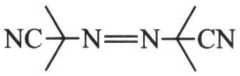
**** Doaben HJ (Jr.) and McCoy LL, *J Am Chem Soc.*, **81**: 4863–73, 1959.

***** Walling C *et. al.*: *J Am Chem Soc.*, **85**: 3129-3134, 1963

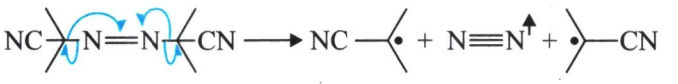
which shall now be treated individually in the sections that follows:

❑ ***Radical Initiation Reaction:*** In general, the **radical initiators** do designate the **thermolabile chemical entities** that rapidly decomposes into the respective ***radicals*** upon moderate heating. However, these ***radicals*** actually initiate the so-called formation of **radical chain** *via* the generation of the **'initiating radical'.**

Example: Following are the *two* most abundantly used **radical initiators,** namely:

➢ **Azobisisobutyronitrile (AIBN):** 

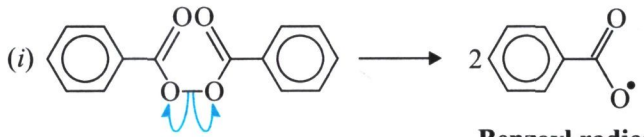
Thus, we may have the following expression:



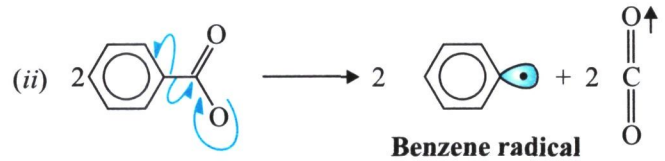
AIBN **Isopropyl nitrile radical** **Isopropyl nitrile radical**

➢ **Dibenzoyl Peroxide:** $C_6H_5{\cdot}CO{\cdot}O{-}O{\cdot}CO{\cdot}C_6H_5$

Thus, we may have the following expression:



Dibenzoyl peroxide **Benzoyl radical (2 moles)**



Benzoyl radical **Benzene radical**

Remarks: The **radical initiators** and their ensuing mode of action *i.e.,* in the ***'arrow formalism'*** for displaying the prevalent *reaction mechanisms* invariably employed in **Organic Chemistry, arrows** with ***half-arrow heads*** where the *single-electrons* are shifted meticulously; whereas, the arrows with ***full-arrow-heads*** usually display explicitly where the ***'electron pairs'*** are being shifted finally.

❑ **Propagation of a Free-Radical Chain Reaction**

In the **propagation** steps of free-radical chain reaction, the starting materials are duly consumed, products are generated; and hence, one may not obviously observe either:

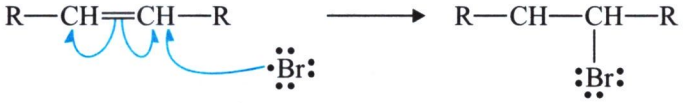
- **no net consumption;** or
- **destruction of free-radical,**

eventually takes place.

Besides, the *free-radical* **by product** obtained through *one propagation step* critically caters as the **starting material** for another sequential step predominantly.

Example:

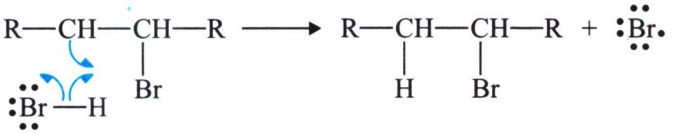
***First* Propagation Step:** Let us consider the **free-radical** addition of *hydrobromic acid (HBr)* to an **'alkene'**, as given below:



...(*a*)

NOTE: **Thus, one may take cognization of the underlying fact that the–*'reaction of a free-radical with a C—C π-bond'* is regarded to be another common phenomenon usually encountered in the so-called *'free-radical chemistry'* overwhelmingly.**

Second* Propagation Step:** It represents another kind of an *atom abstraction reaction i.e.,* the particular removal of a **H-atom from HBr** by the ***free-radical **product** of Eqn. (*a*) to yield the respective **'addition product'** plus a **new bromine atom**, as shown under:



...(*b*)

Remarks: Obviously, one may observe that the *bromine atom,* in turn, may also react perceptively with another mole of **alkene [Eqn. (*a*)]**; and thus may be followed by the critical formation of another mole of *product* together with ***another*** **bromine atom [Eqn. (*b*)].**

Therefore, one may understand squarely the fundamental basis of the terminology ***'chain reaction'*** without the least ambiguity. In short, it may be added that the aforesaid ***two*** **propagation steps** eventually proceed continuously in a **'Chain-like modality'** until such period the entire *reactants* are **totally consumed.** In other words, the *product free radical* of one propagation step actually becomes the *starting free radical* for the **next propagation step.** Thus, for each **'link in the chain'** or the *'cycle* of ***two*** **propagation steps,** *one mole of the* **product** is duly generated and **one mole of alkene starting material** is consumed.

Suggested Reading

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Grimmett MR: **Halogenation of Heterocycles,** *Adv. Heterocycle Chem.,* **58**: 271–345, 1993.

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Trost BM and Fleming I (Eds): **Comprehensive Organic Synthesis. Vol: 4,** Pergamon Press, London (UK), 1991.

Zollinger H: **Diazo Chemistry 1. Aromatic and Heteroaromatic Compounds,** VCH Verlagsgesellschaft, Weinheim (Germany), 1994.

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Chapter 11

Miscellaneous Organic Reactions

LESSONS AT A GLANCE

11.1 Introduction

11.2 Miscellaneous Organic Reactions

- 11.2.1 Bucherer Reaction
- 11.2.2 Chapman Rearrangement
- 11.2.3 Claisen Ester Condensation (The Claisen Condensation, The Synthesis of β-Keto Esters)
- 11.2.4 Diazo Coupling Reactions (Coupling Reactions of Arene-diazonium Salts)
- 11.2.5 The Diels-Alder Reaction
- 11.2.6 Fischer Oxazole Synthesis
- 11.2.7 Gabriel Synthesis (or Gabriel's Phthalimide Synthesis)
- 11.2.8 Overmann Rearrangement
- 11.2.9 Sharpless Epoxidation
- 11.2.10 Smiles Rearrangement (Truce-Smiles Rearrangement)
- 11.2.11 The Ulmann Reaction (De-Halogen Coupling)
- 11.2.12 Wolff Rearrangement

11.1 INTRODUCTION

The present discourse on the **miscellaneous organic reactions** provides an ample *exposure, opportunity* and *means* to the students of pure science **'organic chemistry'** who intend to opt and plan their futuristic careers either in the ***allied health disciplines*** or ***biological sciences,*** namely:

• **Medicine** or • **Pharmacy**

Of course, there is not even an ***iota* of doubt** that the domain of ***Organic Chemistry*** is certainly going to be an immensely vital and important as:

"the fundamental foundation of such ever-expanding fields of knowledge",

not only in the 21st, century but also beyond that. Hence, glancing through the so-called modern textbooks or scientific journals of science/biology/pharmacy/biochemistry/biotechnology to appreciate

elegantly the kingdom of **'sophisticated organic chemistry'**,—which being articulately central to these disciplines in one way or the other. Besides, the availability of a host of *computer-based websites or softwares* one may even keep into the *3D/2D-structures* of **organic compounds** to choose and select only the useful synthesis of such compounds—thereby rendering the entire course of journey from *ab imtio* to the *final stage*:

• **cost-effective** • **conserving on man-hours** • **hitting the Bull's-Eye and** • **by passing hit and miss methods.**

In a broader perspective, bearing-in-mind the so-called *live-in-relationship* with a *technologically advanced blissful companion*—it might be a lot easier task to utilize intelligently and extensively by gainful applications of ***Organic Chemistry*** in an array of **divergent industries,** such as:

- **food products/beverages,**
- **pharmaceutical,**
- **textile,**
- **plastics/polymers/acrylics,**
- **clothings,**
- **transportation, and**
- **communications**

11.2 MISCELLANEOUS ORGANIC REACTIONS

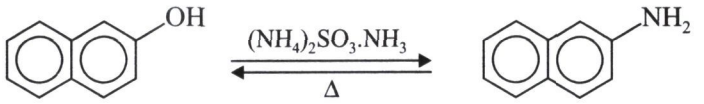
Following are some of the **miscellaneous organic reactions,** which will be treated separately along with their *mechanism of action* (wherever applicable):

(*i*) **Bucherer Reaction,**
(*ii*) **Chapmann Rearrangement,**
(*iii*) **Claisen Ester Condensation,**
(*iv*) **Diazo Coupling Reaction (Diazo Compounds),**
(*v*) **The Diels-Alder Reaction,**
(*vi*) **Fischer-Oxazole Synthesis,**
(*vii*) **Gabriel Synthesis (or Gabriel's Phthalimide Synthesis),**
(*viii*) **Overmann Rearrangement,**
(*ix*) **Sharpless Epoxidation (Epoxy Alcohol)**
(*x*) **Smiles Rearrangement,**
(*xi*) **The Ullmann Reaction (De-Halogen Coupling), and**
(*xii*) **Wolff Rearrangement**

11.2.1 Bucherer Reaction*

It relates to the *reversible formation* of **β-naphthylamine** (or *2-naphthylamine*) by the interaction of **β-naphthol** and aqueous either *ammonium sulphite* $[(NH_4)_2SO_3]$ or *ammonium bisulphite* (NH_4HSO_3) or *hydrogen sulphite* (H_2SO_3) *via* the formation of **tetralonesulphonic acid** and **tetralone iminosulphonic acids,** as given under:

* Bucherer HT: *J Prakt Chem.* [2], **69**: 40, 1904.

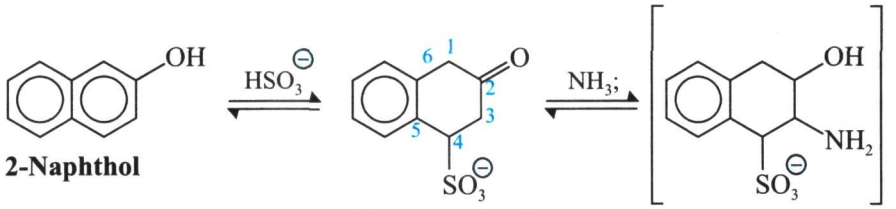


β-Naphthol
[or 2-Naphthol]

β-Naphthylamine
[2-Naphthylamine]

Mechanism of Bucherer Reaction

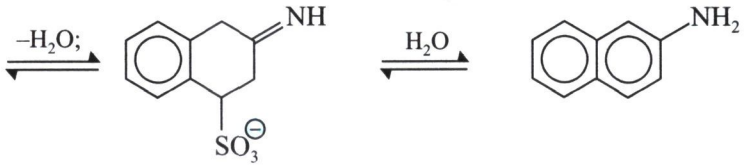
Rieche *et al.* (1960) first and foremost proposed the mechanism of the critical formation of **2-napthylamine** from **2-naphthol,** *sodium hydrogen sulphite* **($NaHSO_3$)** and ***ammonia*** **(NH_3),** as depicted below:



2-Naphthol

2-keto-4-sulphite cyclohexane-5, 6-benzene (I)

Intermediate anion (II)



2-Imino-4-sulphite cyclohexane-5, 6-benzene (III)

2-Naphthylamine (IV)

Explanations

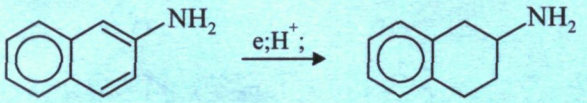
Various steps involved in the above mechanism may be explained as under:

1. The reversible reaction between **2-naphthol** and **bisulphite** yields **compound (I),** which on treatment with *ammonia* gives an **intermediate anion (II).**
2. The resulting **anion (II)** undergoes *dehydration* to give **compound (III),** upon hydration (H_2O) undergoes a reversible reaction to produce **2-naphthylamine (IV)** *i.e.,* the intended product.

Remarks: These essentially comprise:

1. Importantly, the ***keto*-form of the naphthol (I)** and the ***imino*-form (III)** so produced are duly stabilized by the critical addition of the **hydrogen sulphite ion** (HSO_3^-)—to result into the formation of the respective **sulphonic acid derivative (III).**
2. The **2-naphthylamine (IV)** is prepared commercially by heating **2-naphthol** (or *β-naphthol*) with aqueous *ammonium hydrogen sulphite* (NH_4HSO_3) at 150°C under reduced pressure **(Yield = 94-96%).** Besides, the **2-naphthylamine (IV)** may also be prepared from **2-naphthoic acid.**

3. **2-Naphthylamine**—is a colourless solid, mp 112°C, insoluble in water but soluble in *ethanol* and *ether*. It is also odourless, reduces specifically the *ammoniacal silver nitrate* (to give *Ag-mirror*)—but fails to give any colouration with **ferric chloride ($FeCl_3$)**.
4. It gets duly *oxidized* by $KMnO_4$ to *phthalic acid* and *reduced* by an admixture of **Na/isopropanol** to the corresponding **octahydro-2-naphthylamine** (or **1, 2, 3, 4-tetrahydro-2-naphthylamine)**.
5. However, the ***prefix*** *'ac'*—is the abbreviation of *'alicyclic'* and vividly indicates that the ***four*** **inherent H-atoms** are present in the ring comprising duly the **amino ($-NH_2$) moiety** (see above):

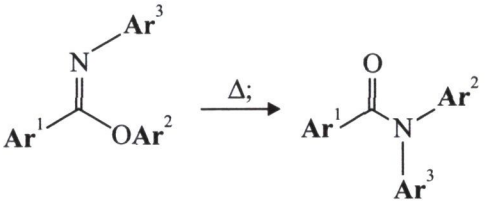


2-Naphthylamine **1, 2, 3, 4 - Tetrahydro -2-amino naphthyl-;**

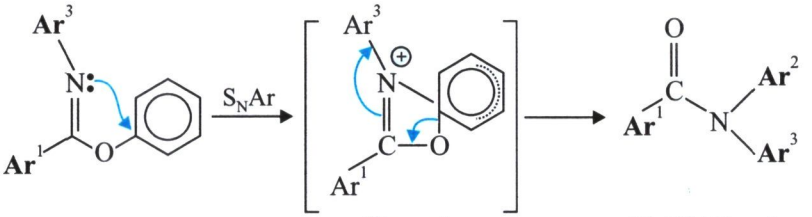
NOTE: ***2-Naphthylamine*** **specifically couples with the** ***diazonium salts*** **exclusively at the 1-position, and if this is already coupled,** ***–no coupling*** **takes place.**

11.2.2 Chapman Rearrangement*

The **Chapman rearrangement** refers to the ***thermal aryl*** rearrangement of ***ortho*-arylamino ethers** (or *aryl imidates*) to the respective **N, N'-diaryl amides,** as shown below:



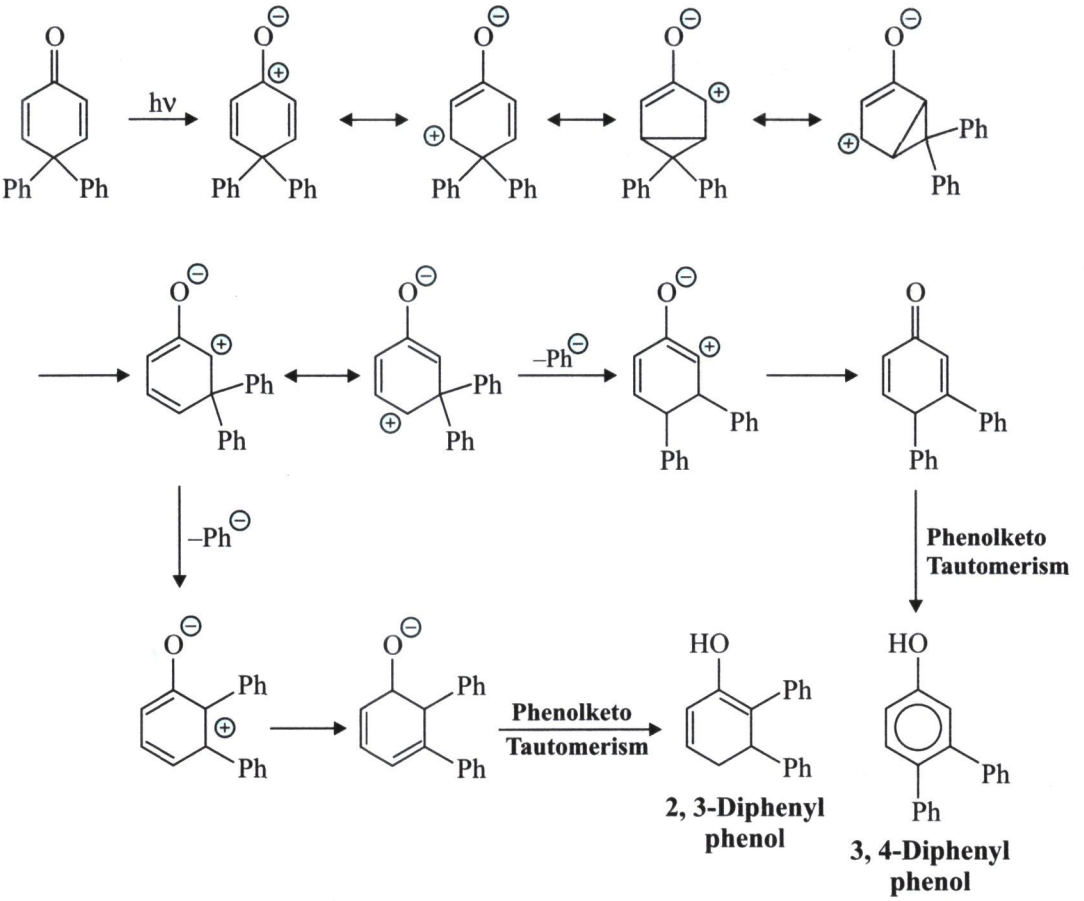
Mechanism of Chapman Rearrangement: In true sense, the underlying mechanism of the rearrangement essentially involves the so-called **aromatic nucleophilic substitution reaction** *via* an ***intermediate*** termed as **'oxazete'**, as given under:



Oxazete [An Intermediate] **N, N'-Diaryl amide**

* Chapman AW 1 *J Chem Soc.*, **127**: 1992, **(1925)**; **1927**, 174; **1929**, 569.

Another Representation of Chapman's Mechanism—Likewise, **4,4′-biphenyl cyclohexadienone** may usually undergo a ***photo-induced rearrangement*** critically involving the *polar intermediates* to yield an **admixture of phenols,** as shown under:



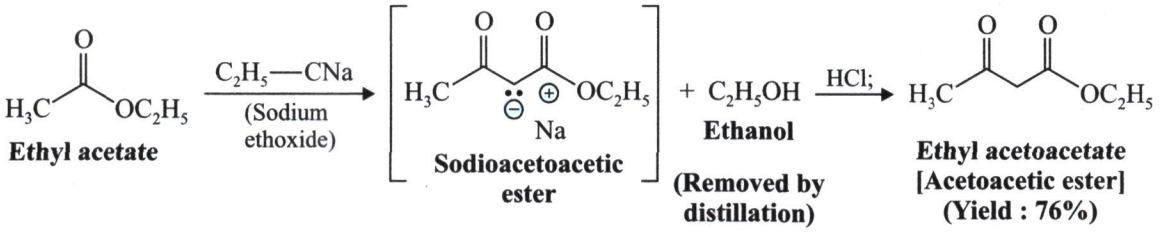
NOTE: (*i*) **The various steps involved in the above sequential steps are self-explanatory.**

(*ii*) **The aforesaid-*polar-intermediate-ivolving-mechanism* is invariably termed as *'Chapman's Mechanism'*.**

11.2.3 Claisen Ester Condensation (The Claisen Condensation, The Synthesis of β-*Keto* Esters)

The **Claisen-ester condensations** (or **Claisen condensation**) reaction involves the formation of **β-*keto* esters** from the respective **carboxylic esters**. In other words, when an *'alkyl acetate'* reacts with *sodium ethoxide* $[C_2H_5\text{-}ONa]$, it readily undergoes a so-called **condensation reaction.** After due *acidification*—the resulting product is a **β-keto ester,** known as **'ethyl acetoacetate'** (also called as the *'acetoacetate ester'*). The various sequential steps involved are as stated under:

* Bhatacharjee SK *et al.*: **Organic Chemistry,** 7th ed., Pearson Education Inc., New Delhi, 2012.



Thus, *two* moles of **ethyl acetate** (or even *one ester* and *another carbonyl compound**) undergoes a *condensation* reaction involving critically the formation of **C-C linkage** in the presence of a **reasonably strong base** *e.g.,* freshly prepared *sodium ethoxide* **(C_2H_5-ONa)**, to produce a **β-*keto* ester** or a **β-diketone****.

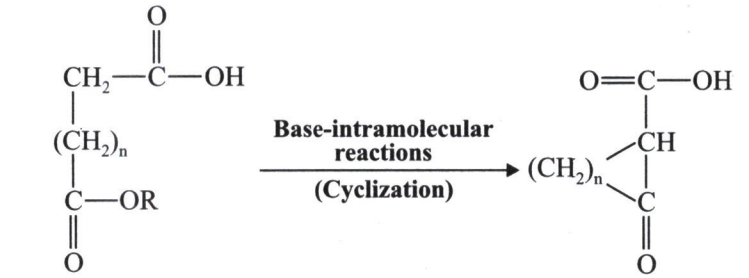
Two Important Points: A survey of literature reveals that the **Claisen ester condensation** may also be referred to as:

- **Acetoacetic Ester Condensation, and**
- **Retro-Claisen Condensation, and**
- **Crossed Claisen Condensation**

which will be expatiated individually as under:

(*a*) **Acetoacetic Ester Condensation:** The corresponding ***intra-molecular reaction*** is usually termed as the **Dieckmann Condensation**.***

Thus, we may have the following expression:



Remarks: It is, however, pertinent to state here that the *most common base* employed duly in the aforesaid reaction is **sodium ethoxide [C_2H_5ONa];** whereas, a few other equally strong bases that may be used effectively are:

- **Sodium amide ($NaNH_2$)** and
- **Sodium hydride (NaH)******

* That is, either *mixed* or *crossed* **claisen condensation** also comes into play between *two different esters* or *one ester plus one ketone.*

** Claisen L *et. al.*: *Ber Dtsch Chem.*, **20**: 651-57, 1887; Hanser CR *et al.*: *Org React,* **1**: 266-302, 1942.

*** Dieckmann W: *Ber Dtsch Chem. Gen,* **33**: 2670-2684, 1900; Schaefen JP *et al.*: *Org React*, **15**: 1-203, 1967.

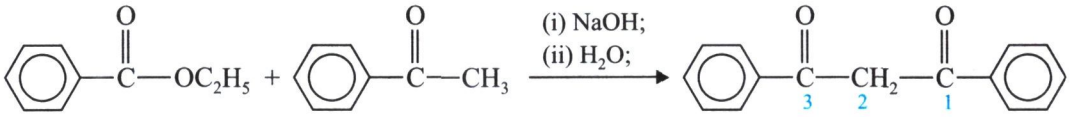
**** Crowley JI and Rapport H: *J Org Chem*:, **45**: 3215-3227, 1980.

(*b*) **Retro-Claisen Condensation:** It has been duly proven and established that the **α, α-disubstituted β-keto-esters** is being subjected to treatment with an *alkoxide* **($C_2H_5O^-$)** *i.e.*, **ethoxide** the former eventually undergoes cleavage into the so-called ***simple* ordinary esters** *i.e.*, a ***reverse-condensation reaction*** comes into play, and is invariably termed as: the **Retro-Claisen condensation**.

(*c*) **Crossed-Claisen Condensation:** When the *condensation* reaction is carried out by making use of ***'mixed reactants'*** usually comprised of:

- **an *enolizable ester*,** or
- **a *non-enolizable ester*,** and
- **a *ketone*,**

we may eventually lay hands on to **'mixed products of reaction'** as shown below:



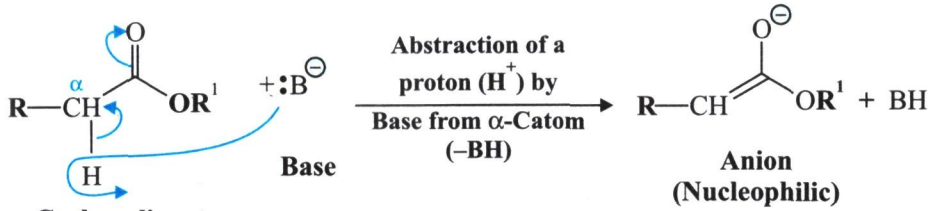
Ethyl benzoate (an '*enolizable ester*') + **Acetophenone (a '*ketone*')** → **1, 3-Diphenyl propane-1, 3- diene** + C_2H_5—OH

NOTE: **It may be added that if only one of the *initiating esters* does consists of an *α-H-atom*, one may certainly anticipate a reasonably *good yield* of the '*mixed products of reactions*' by means of the '*crossed Claisen condensation*'.**

There are ***three* cardinal steps** that eventually reveal the:

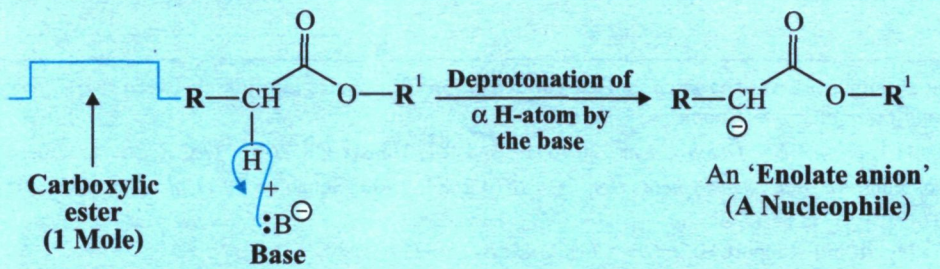
Mechanism of Reaction:

***Step-1*: Deprotonation:** The interaction between a *carboxylic ester* and a *base* causes an **abstraction of a proton by the base** from the **α-C-atom** to yield an **anion** *(nucleophilile)*, as shown below:



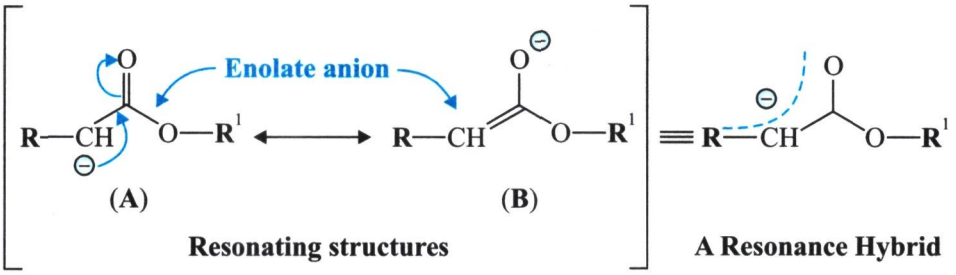
Carboxylic ester + **Base** → **Anion (Nucleophilic)** + BH

Comments: Hence, the **deprotonation** (or *abstraction of a proton*) right from the **α-C atom** by the base thereby resulting into the formation of an **'anion'**, which being a ***strong nucleophile,*** as shown under:

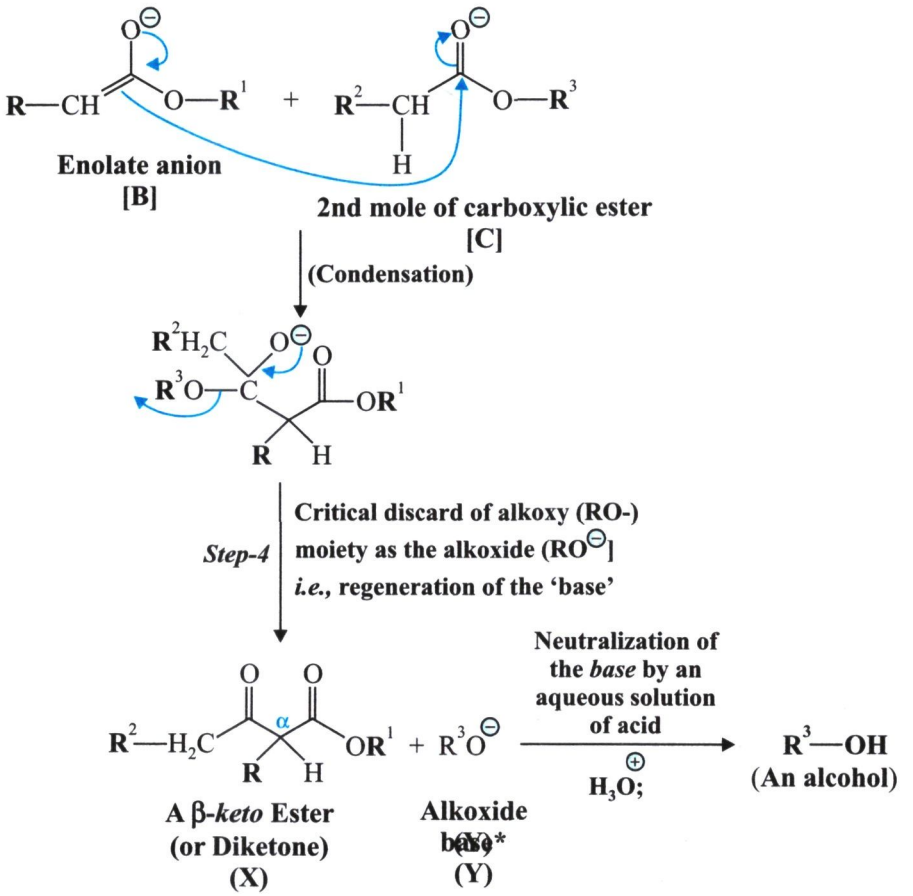


Carboxylic ester (1 Mole) + **Base** → **An 'Enolate anion' (A Nucleophile)**

Step-2: Stabilization of '*Enolate Anion*' by Resonance: Thus, the ***'enolate anion'*** obtained in **Step-1** duly yields *two* distinct **resonating structures (A)** and **(B)**, which ultimately attains an ***equilibrium status*** to produce the **'Resonance Hybrid'**, as given below:]



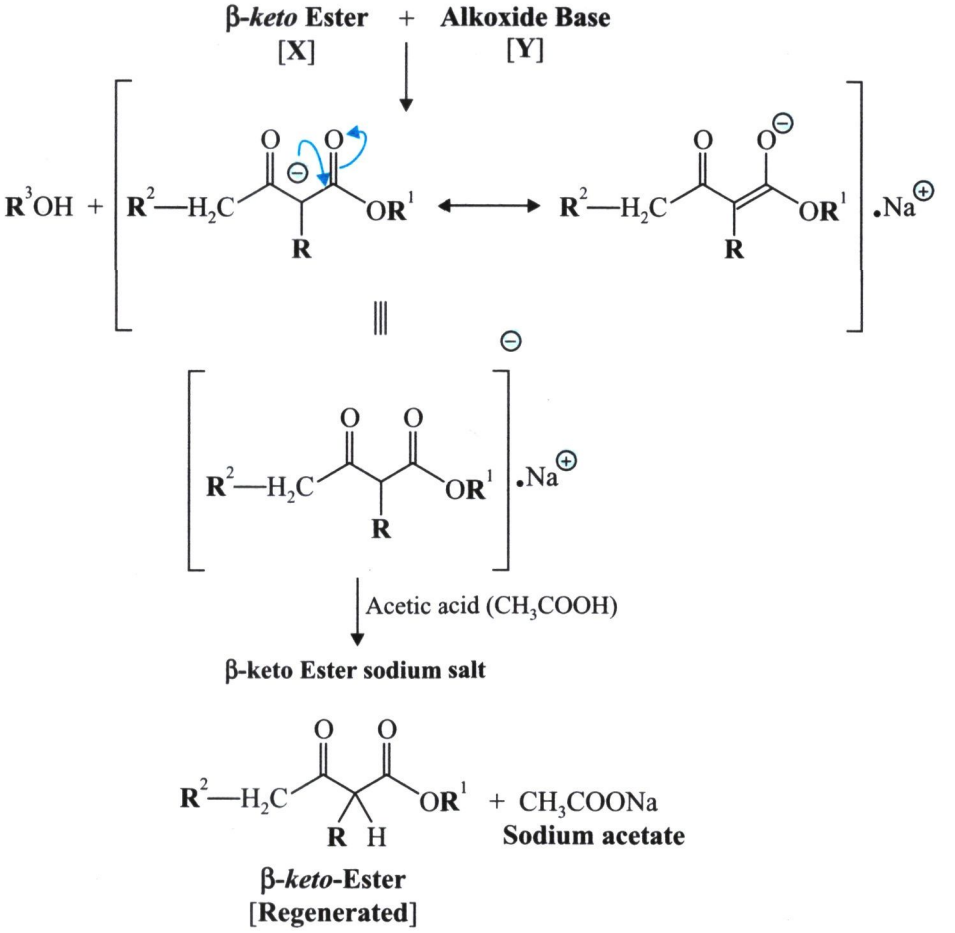
Step-3: Condensation of 2nd Mole of Carboxylic Ester (C) with Enolate Anion (B): In this particular case the critical *condensation* of a 2nd mole of the **carboxylic ester (C)** with an **enolate anion (B)** thereby indulging in the typical ***nucleophilic attack*** upon the *C-atom* of the **ester (C)** (*second mole*) by the **α-C-atom of the enolate**. The various sequential steps involved are as given below:



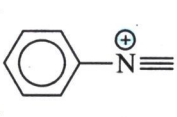
* The **'Base'** is duly generated at the end of the reaction.

Isolation of β-*keto* Ester (or Diketone)

Thus, at the *end of the reaction i.e.,* complete formation of the **'alcohol'**, the generated **β-*keto* ester (X)** possessing an ***active α-H-atom*** specifically reacts with freshly prepared *sodium ethoxide* (C_2H_5ONa) to produce the respective **sodium enolate** (salt), which on subsequent careful *acidification* with *acetic acid* (CH_3COOH)—amazingly regenerates the intended **β-keto ester**. The various steps involved in the above *regeneration of* ***β-keto*** **ester** may be expressed as under:

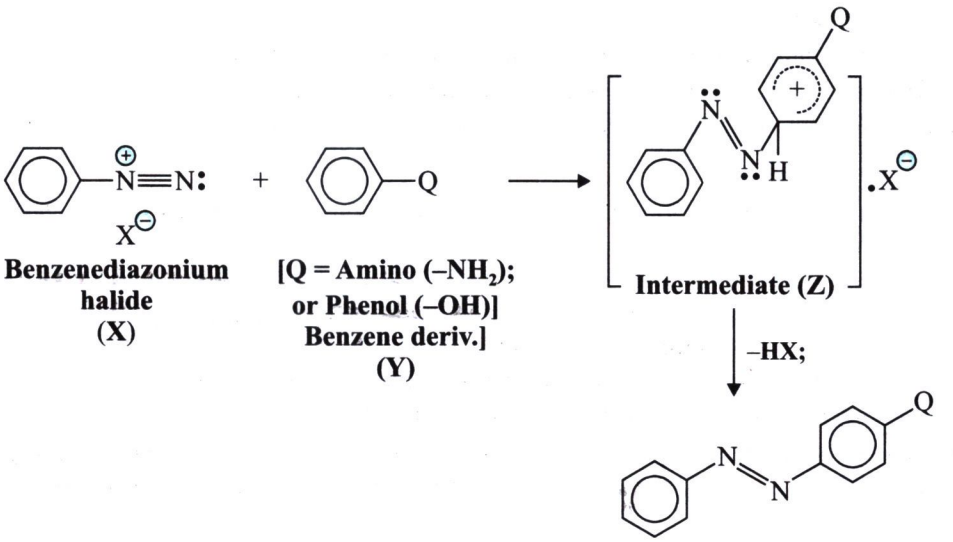


11.2.4 Diazo Coupling Reactions (Coupling Reactions of Arene-diazonium Salts)

The **arenediazonium ions** [*viz., benzenediazonium ion* ] are characterized to be **weak electrophiles;** and hence, they usually interact with so-called ***highly reactive aromatic chemical entities*** **(compounds)**, such as: **phenols** or ***tert*-aryl-amines**—to give ***'azo'*-compounds**. The aforesaid '*electrophilic aromatic substitution*' is invariably termed as a **'diazo-coupling reaction** (or **coupling reaction of arenediazonium salts**).

Let us now examine a few '*general*' **and** '*specific*' **reactions** under the present context:

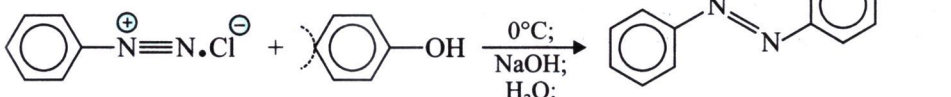
❑ **General Reaction**



Comments: An ***azo*-compound** is duly obtained by the interaction of **benzenediazonium halide (X)** and a **benzene derivative (Y)** *via* the formation of an **intermediate (Z),** which loses a mole of **HX** to produce the desired ***azo*-compound.**

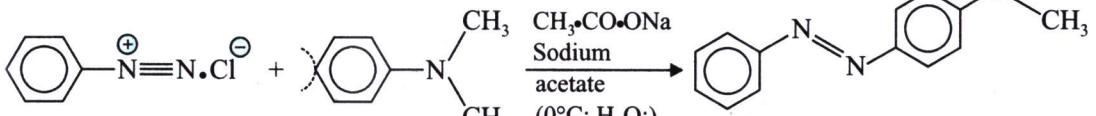
❑ **Specific Reactions**

(*i*)



Benzene diazonium chloride + **Phenol** → ***p*-(Phenylazo)-phenol (A)** [*Orange solid*]

(*ii*)

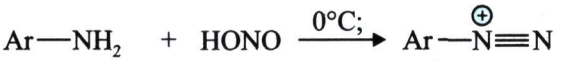


Benzene diazonium chloride + **N, N-Dimethyl aniline** → **N, N-Dimethyl-*p*-(phenylazo) aniline (B)** [**Yellow solid**]

Comments: *First* reaction entails *benzene diazonium chloride* and *phenol* in an alkaline aqueous medium at **0°C** to yield a mole of ***p*-(phenylazo)-phenol (A)** an *orange solid* product with the loss of a mole of **HCl**.

Second reaction relates to the interaction of *benzene diazonium chloride* and *N,N-dimethylaniline* in the presence of aqueous sodium acetate at **0°C** to give **N,N-dimethyl-*p*-(phenylazo)-aniline (B)** with the elimination of a mole of **HCl**.

NOTE: **Formation of Diazonium salts from *pri*-aromatic amines usually occurs as below:**



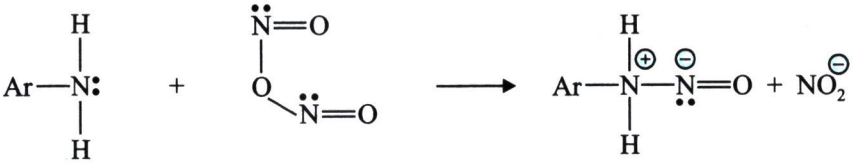
***pri*-Aromatic amine** **Nitrous acid** **Diazonium Ion**

Thus, the nitrosation of *primary aromatic amines* with *nitrous acid* followed by *dehydration* ultimately lead to the formation of *diazonium ions*.*

Mechanism of Diazo Coupling Reactions: The **mechanism of the diazo coupling reaction** may be illustrated explicitly by the following schematic reactions involving ***three*** **different steps,** namely:

Step-1: Critical Transferance of Nitrosyl Cation

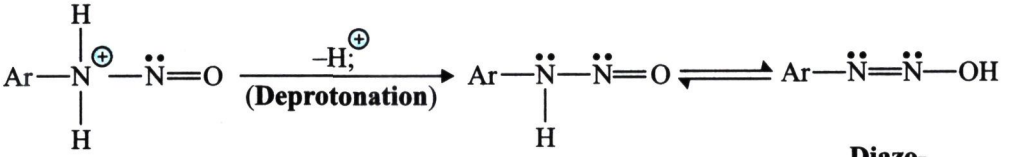
We may have the following expression:



An Aryl amine (I) [Free Amine] **Reactive specie (II) [Critical transferance of nitrosyl cation]** **A Cation (III)**

Comments: Thus, during the on-going **diazotization phenomenon** in an *acidic environment*—the ***free*** **amino (-NH_2)** moiety crucially reacts with the **nitrosating agent (II).****

Step-2: Deprotonation of cation with Formation of Nitrosoamine



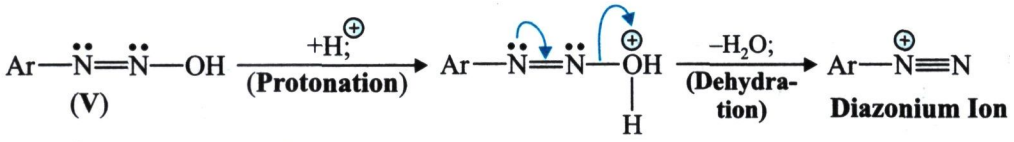
Cation (III) **Nitroso amine (IV)** **Diazo-hydroxide (V)**

* Challis BC and Butler AR: In: **Chemistry of the Amino Group,** Wiley, New York, 1968, Schank K: In: **Chemistry of the Diazonium and Diazo Groups, Vol. 2,** Wiley, New York, 1978, Rid JH: *Rev Chem Soc.* **15**: 418-441, 1961.

** Wolf L. *Justus Liebigs Ann Chem.*, **394**: 25, 2012.

Remarks: Cation (III) obtained from ***Step-1*** undergoes *deprotonation* to yield **nitrosoamine (IV)**, which gets engaged to a *reversible reaction* to give **diazo-hydroxide (V)**.

Step-3: Protonation of Hydroxyl (—OH) Moiety in Diazohydroxide (V) followed by Dehydration

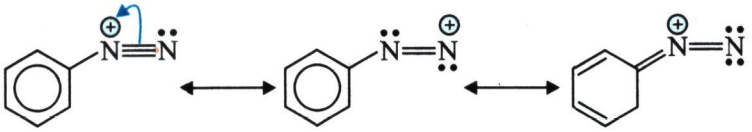


Thus, **a diazonium ion** is obtained ultimately.

Special Observation: In addition to the so-called aromatic amines—the **aliphatic amines** do also interact with **nitrous acid (HNO_2)** in a relatively *weaker acidic medium* thereby, giving rise to the formation of: **'unstable aliphatic diazonium ions'**, that eventually get duly decomposed into:

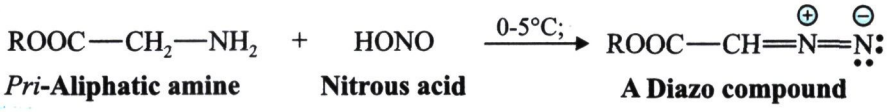
• **nitrogen** and • **carbenium ions.**

Hence, the aforesaid observation is very much unlike the contemporary **aromatic diazonium ions,** which are ***resonance stabilized*** at 0-5°C in a way as depicted under:



Diazotization with pri-Aliphatic Amines: Thus, when the *diazotization* takes place using a **primary aliphatic amine** bearing an ***electron withdrawing*** **functional moiety at the α-C-atom,** one may lay hands onto a:

'*diazo compound* instead of *diazonium salt*', as expressed under:*



NOTE: **The most vital and important application of the *diazo coupling reaction* is the critical formation of the well-known synthetic '*azo*'-dyes.****

11.2.5 The Diels-Alder Reaction***

The **Diels-Alder reaction** relates to the **1, 4-addition** of the *olefin bond* (double bond) of a **dienophile** to a **conjugated diene** so as to give rise to the formation of a ***6-membered ring system;*** and thus, the miraculous creation of ***four*** **altogether newer stereocentres** almost simultaneously. However, the ***(4 + 2) cycloaddition*** invariably comes into play with:

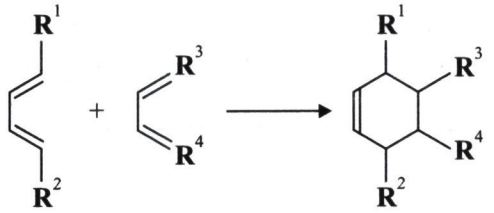
- **high regio-specificity,** and
- **high stereoselectivity**

The reaction may be expressed as under:

* Regitz M: In: **Chemistry of Diazonium and Diazo Compounds, Vol 2,** Wiley, New York, 1978.

** Moumne R *et al. J Org Chem.*, **71**: 3332-34, 2006.

*** Diels O and Alder K, *Ann*, **460**: 98, 1928, **470** : 62, 1929, *Ber*, **62**: 2081–87, 1929.



NOTE: **The *Diels-Alder reactions* bear the names of *two* famous *organic chemists*: *Otto Diels* and *Kurt Alder*, who performed the first-ever type of reaction.**

The ***substrate*** that eventually reacts with the *diene* in there ***'cycloadditions'*** is usually called the ***"dienophile"***.

Figure 11.1 illustrates the *simplest version* of **Diels-Alder reactions** *i.e.,* the ones occurring between **ethene** ($CH_2{=}CH_2$) and **butadiene** $\left[H_2C{=}{-}{=}CH_2\right]$; and also between **acetylene** **(HC ≡ CH)** and **butadiene** respectively (which only takes place under *drastic experimental parameters*).

In reality, the **acceptor-substituted alkenes** serving as the ***dienophiles***, do yield the desired products [*viz.,* **(2 + 4) cyclo-additions**] *via* well-designed **Diels-Alder reactions**.

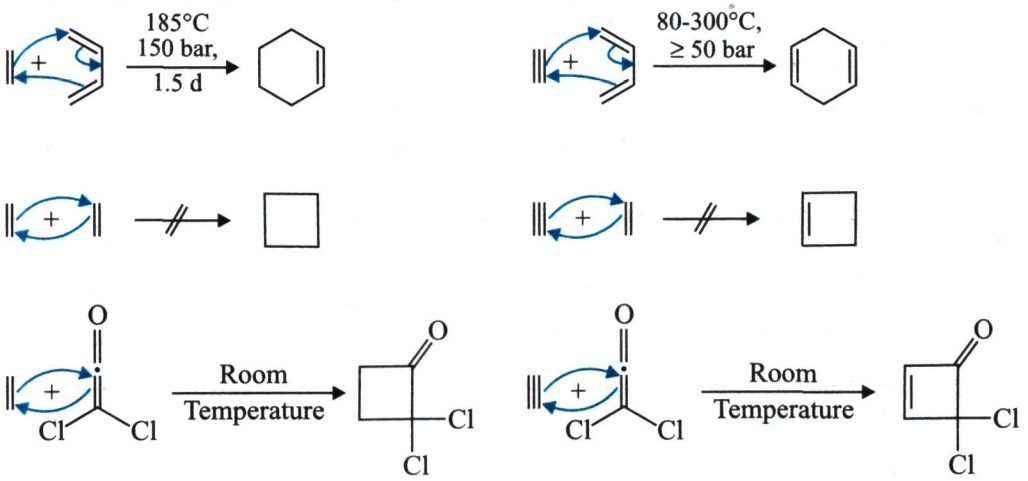


Fig. 11.1: One Step [2 + 4] and [2 + 2] Cycloadditions and Their Feasibility in the Absence of Light

(*i*) The [2 + 4] cycloaddition between ethene or acetylene and 1, 3-butadiene (top) needs drastic experimental parameters.

(*ii*) The one-step [2 + 2] cycloaddition between two alkenes (ethene or acetylene) or between an alkene and an acetylene (centre) cannot be obtained at all.

(*iii*) The only [2 + 2] cycloadditions which may proceed at room temperate (RT) are those that occur between ethene or an alkyne and dichloroketone perceptively.

The **Diels-Alder reactions** in *organic chemistry* do occupy a highly deserving and well-recognized status; and hence, need to be studied and explored rather more exhaustively in the present context with particular reference to the following *three* aspects:

- **Stereoselectivity of Diels-Alder Reaction,**

- **Substituent Effects upon Reaction Rates of Diels-Alder Reactions,** and
- **Orientation Selectivity of Diels-Alder Reactions,**

which shall now be discussed individually in the sections that follows:

11.2.5.1. Stereoselectivity of Diels-Alder Reactions

It may be made abundantly clear at the very outset that almost all **Diels-Alder reactions** are indeed a ***one-step phenomenon*** perceptively. Under these circumstances, if the reactions are *stereogenic* in character, they invariably take place with a **predictable stereochemistry**.

Example: Obviously, the ***cis, trans*-1, 4-disubstituted-1, 3-butadienes** do afford the so-called **cyclohexanes** having:

'a *trans*-arrangement of the substituents at C-3 and C-6',

[as could be seen in Fig. 11.2 **(top segment)**].

In contrast, ***trans, trans*-1, 4-disubstituted-1, 3-butadienes** do produce the **cyclohexenes** wherein:

'the substituents at C-3 and C-6 are *cis*-with respect to each other'

[as could be seen in Fig. 11.2 **(bottom segment)**].

Remarks: Thus, according to **Diels-Alder reactions** do normally exhibit **'stereospecificity'** with respect to the ***'diene'***.

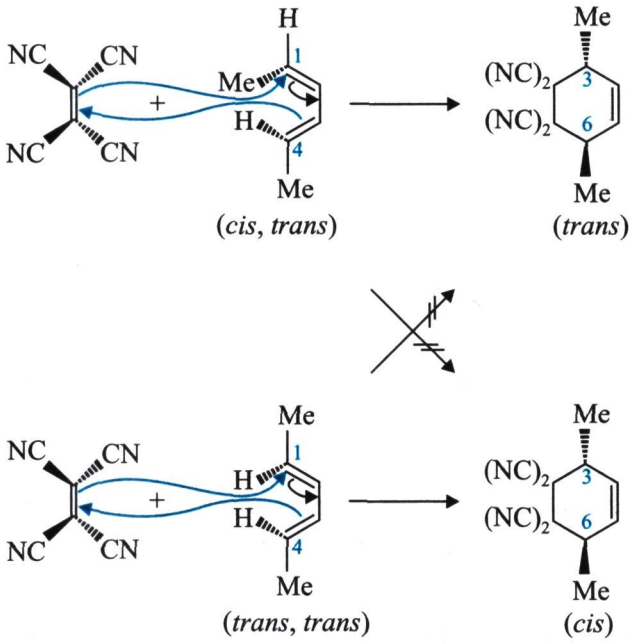


Fig. 11.2: Explicit Evidence for Stereoselectivity and stereospecificity with respect to the Butadiene Moiety in a Pair of Diels-Alder Reactions. The *cis-trans*-1, 4-disubstituted-1, 3-butadiene forms Cyclohexene having a *trans*-Arrangement of the methyl (—CH_3) moieties. The *trans-trans*-1, 4-disubstituted-1, 3-butadiene forms Cyclohexene having *cis*-Methyl Moieties

Interestingly, the respective ***cis-cis*-1, 4-disubstituted-1, 3-butadiene** do undergo the **Diels-Alder reactions** exclusively when they form an integral part of a ***'cyclic diene'***.

Example: Let us look into the classical, example of **cyclopenta-diene,**—which eventually designates as one of the ***most reactive dienes*** in general. However, in stark contrast, one may observe the various *transition states* of the **Diels-Alder reaction** of:

'the acyclic *cis-cis*-1, 4-disubstituted-1, 3-butadienes

that invariably suffer from a *huge repulsion almost prehibitively between the substituents at the C-1 and C-4 positions,* that particularly comes into being as and when these substrates, *as any 1, 3-diene should,* vehemently assume the ***cis*-conformation** very much about the C-2 and C-3 bond.

Points to Ponder: **Stereoselectivity** is being observed overwhelmingly in the **Diels-Alder reactions** of '***dienophiles***, that essentially comprise a ***stereogenic* C=C olefin bond**, as shown in Fig. 11.3

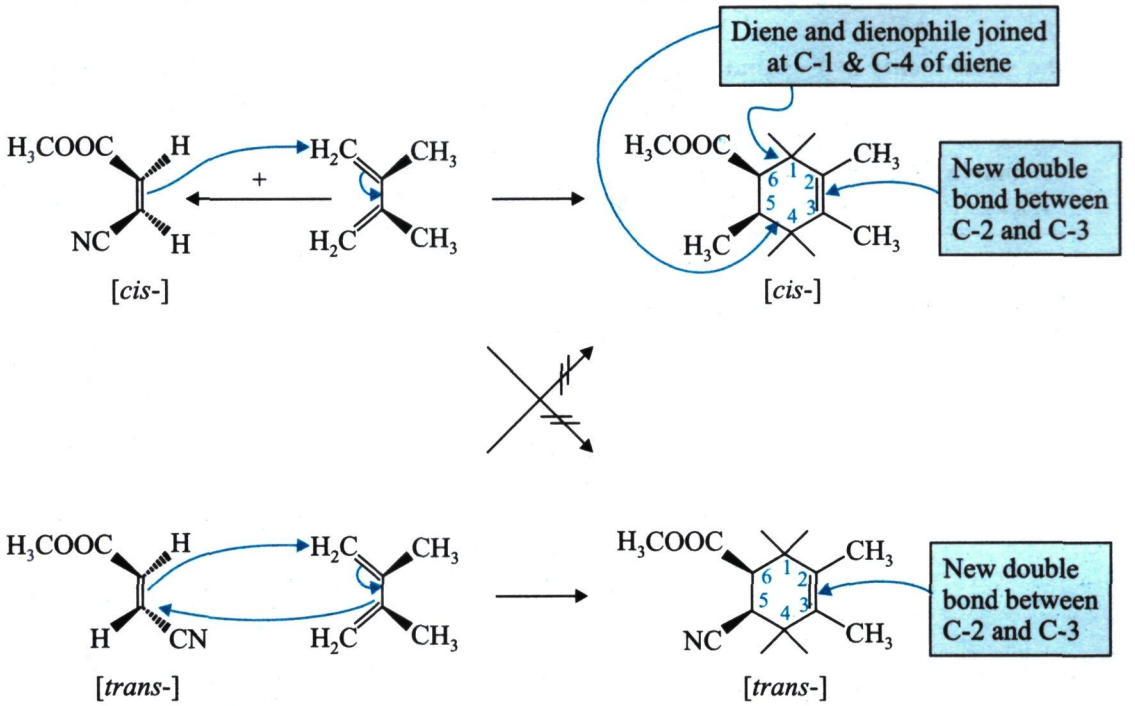


Fig. 11.3: Explicit Evidence for Stereoselectivity and Stereospecificity with respect to the Dienophile in a pair of Diels-Alder Reactions. The *cis*-Conformational Dienophile Affords a 5,6-*cis* Substituted Cyclohexene; whereas, the *trans*-Isomer gives a 5, 6-*trans* Substituted Cyclohexene

Explanations

A ***cis-trans* pair** of these types of **dienophiles** react *stereospecifically* with **1,3-dienes.*** Therefore, the so-called ***cis*-conformational dienophile** affords a **5, 6-*cis*-disubstituted cyclohexene** (see Fig. 11.3 *top segment*), whereas, the corresponding ***trans*-isomer** yields the **5,6—*trans*-disubstituted product** (see Fig. 11.3 ***bottom segment***).

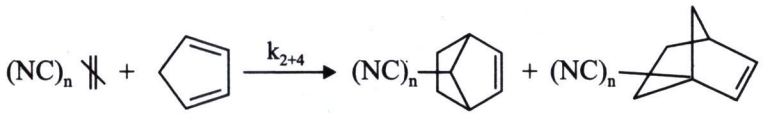
* As long as the latter do not contain any **stereogenic olefin bonds.**

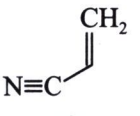
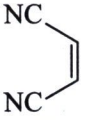
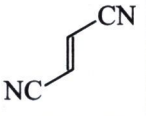
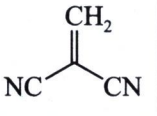
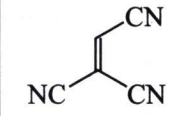
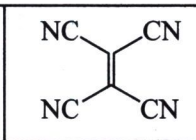
11.2.5.2 Substituent Effects Upon Reaction Rates of Diels-Alder

Reaction: Evidence from literature reveals that the chemical entity **'cyclopentadiene'** turns out to be an ***extremely reactive* 1, 3-diene;** and hence, it preferentially undergoes the **Diels-Alder reactions** practically with most of the **cyanosubstituted ethenes**. Importantly, the *rate constants* of there **cycloaddition products**, as recorded in Table 11.1, depicts that each ***cyano-substituent*** helps to augment the so-called **reaction rate** appreciably, and hence, one may vehemently take-cognizance of the fact that:

"geminal-cyano moieties* do accelerate much more *vis-a-vis* the respective *vicinal-cyanomoieties".

Table 11.1: Relative Rate Constants $k_{2+4,rel}$ of Analogous Diels-Alder Reactions of Polycynaoethenes



						
$k_{2+4,rel}$	≡ 1	81	91	45500	480000	43000000

Important Observations: These essentially include:

1. The **Diels-Alder reactions** belonging to the specific type as depicted in Table: 11.1 clearly expatiates that such reactions occurring between:
   - ➢ **electron-deficient *dienophiles*;** and
   - ➢ **electron-rich *dienes*,**

   are invariably termed as:

   "Diels-Alder reactions with normal electron demand".
2. Thus, the appreciable majority of the already known **Diels-Alder reactions** do invariably exhibit such a ***'normal electron demand'***.
3. The most prevalent examples of the classical **dienophiles** essentially comprise:
   - **Aerolein (or Acrylic aldehyde)**
   - **Acrylic acid esters**
   - ***trans*-butenedioic acid esters and**
   - **Methyl vinyl ketone**
   - **Maleic anhydride**
   - **Tetracyanoethene**
   - **Acrylonitrile**
   - **Formic acid esters**

   [All of these compounds are: *acceptor-substituted alkenes*]
4. Besides, the so-called typical **dienes** are, namely:
   - **cyclopentadiene,** and
   - **acyclic-1, 3-butadienes*,**

   incidentally all of which are ***'dienes'*** having a critical **donor substituent**.

* Such as; having *alkyl-*, *aryl-*, *alkoxy-*, and/or *trimethylallyloxy substituents*.

5. Importantly, the prevailing **reaction rates** pertaining to the **cycloaddition** of quite a good number of the aforesaid ***dienophiles*** to the respective **'electron-rich dienes'** are enhanced appreciably upon the addition of a catalytic quantum of **Lewis acid** [*viz.*, **$AlCl_3$, $FeCl_3$, Tl $(OAC)_3$ etc**].
6. Amazingly, the so-called **Lewis acid ($AlCl_3$)-complex** of methyl acrylate critically reacts almost 10^5 folds faster with **butadiene** in comparison to **methyl acrylate,** as given in Fig. 11.4.

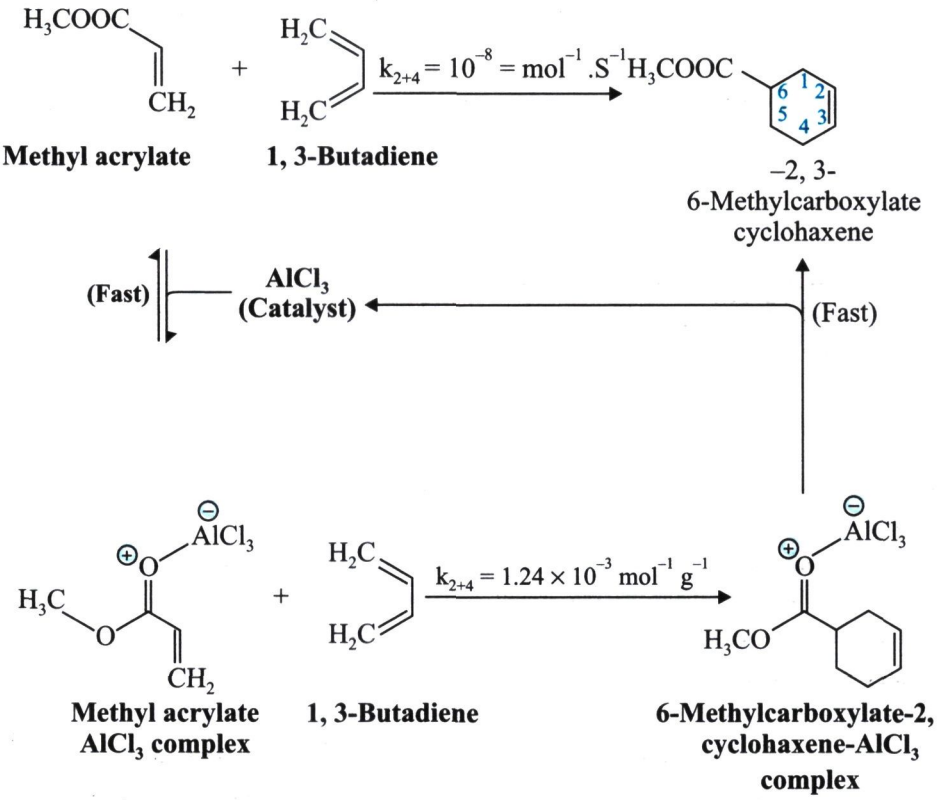


Fig. 11.4: The Diels-Alder Reaction with Normal Electron Demand Enhancement of the Overall Reactivity upon Addition of a Lewis Acid ($AlCl_3$). The resulting $AlCl_3$-Complex of the Acrylate Reacts 10^5 Folds Faster with Butadiene (1, 3-) *vis-a-vis* the Uncompleted **Acrylate**

Explanations

Obviously, the C=C olefin bond (or double bond) present in the ***Lewis acid-complex*** (see above) of an **acceptor-substituted dienophile** is duly connected to a rather ***stronger acceptor substituent*** *vis-a-vis* the respective **Lewis acid-free structural analogue**.

Neverthless, a **'better acceptor'** definitely enhances the so-called:

"dienophilicity of the *dienophile*",

very much akin to the ensuing effect of an array of ***'acceptors'***, as could be seen in the series of Table: 11.1

11.2.5.3 Orientation Selectivity of Diels-Alder Reactions

The formation of **'cycloadducts'** by the aid of Diels-Alder reactions may be accomplished elegantly either:

- **with symmetrically substituted *dienophiles*, and/or**
- **with symmetrically substituted *dienes*,**

that eventually afford the generation of **'cycloadducts'** *i.e.,* a congregation of ***constitutionally homogeneous products***.

Importantly, quite contrary to the **Diels-Alder reactions** between the following ***two*** **chemical entities,** namely:

- **an asymmetrically substituted dienophile,** and
- **an asymmetrically substituted diene,**

may ultimately give rise to the formation of ***two*** **constitutionally isomeric cycloadducts**.

At this point in time it is pertinent to state here that:

"if only one of these '*isomers*' gets generated actually, the *Diels-Alder reaction*, may be duly acclaimed to be '*orientation selective*' positively".

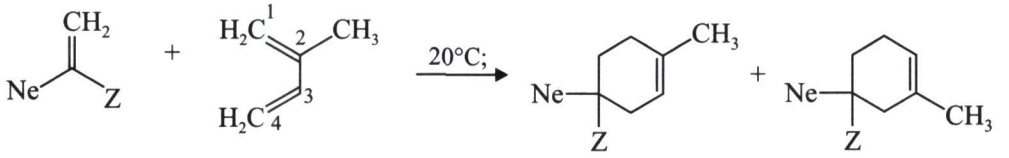
Example: Interestingly, the **1,3-butadienes** having the strategically located substituents at the *C-2 position* generously favour the formation of the so-called ***para*-products** exclusively, as depicted in Fig. 11.5, (where Z=H, with respect to their ensuing reactions having the **acceptor-substituted dienophiles**. In this way, one may lay hands onto the ***meta*-product** in comparatively smaller quantum perceptively.

Nevertheless, this **orientation selectivity** enhances positively in a situation when the **'dienophile'** critically holds ***two*** **geminal acceptors** (as shown in Fig. 11.5 where Z=N).

Remarks: Therefore, the chemical entity **2-phenyl-1, 3-butadiene** explicitly exhibits a **higher degree of 'para' selectivity profile** in its various reactions having each and every ***asymmetric dienophile*** in comparison to any of the so-called **2-alkyl-1, 3-butadiene** does.

Obviously, the above scientific revelations are certainly even more *genuine, true,* and *convincing* for:

"2-methoxy-1, 3-butadiene; and 2-(trimethyl silyloxy)-1, 3-butadiene".



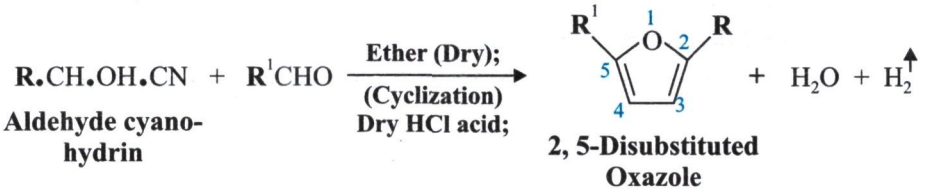
Cyano ethylene [Z = H] | **2-Methyl-1,3-butadiene** | **A *para*-product** | **A *meta*-product**

Z = H	70 : 30
Z = CN	70 : 9

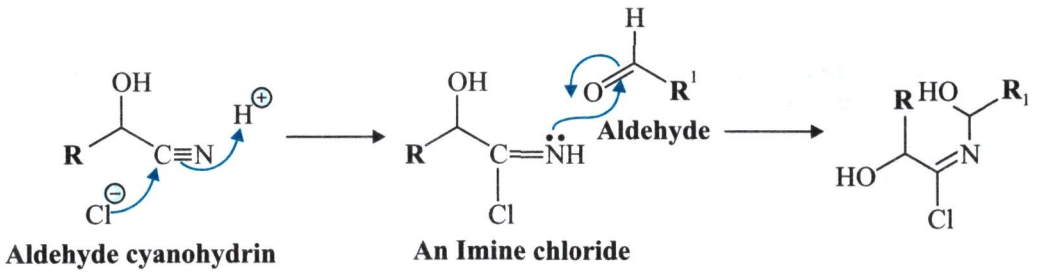
Fig. 11.5: The Orientation-Selective Diels-Alder Reactions having a 2-Substituted-1,3-diene. A Comparison of the Effects duly Exerted by one or two Dienophile Substituents.

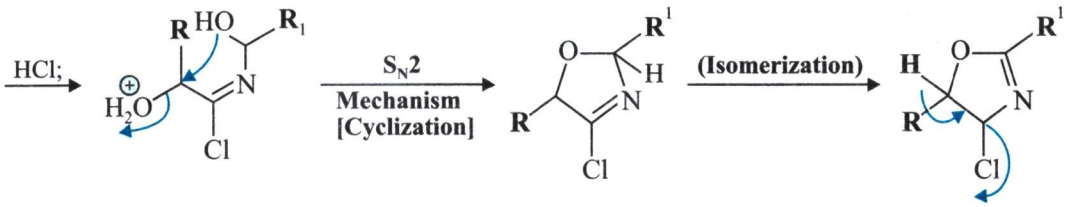
11.2.6 Fischer Oxazole Synthesis*

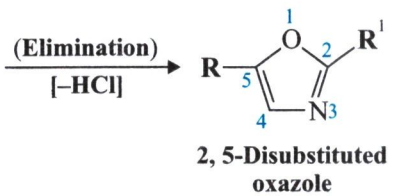
It refers to the *condensation* of **equimolar amounts** of the *aldehyde cyanohydrins* and *aromatic aldehydes* in absolute diethyl ether (dry) in the presence of dry HCl**,-as given under:



Mechanism of Fischer Oxazole Synthesis: The mechanism of **Fischer oxazole synthesis** involves *bimolecular nucleophilic substitution reaction, isomerization,* and *elimination* in a sequential manner as given under:







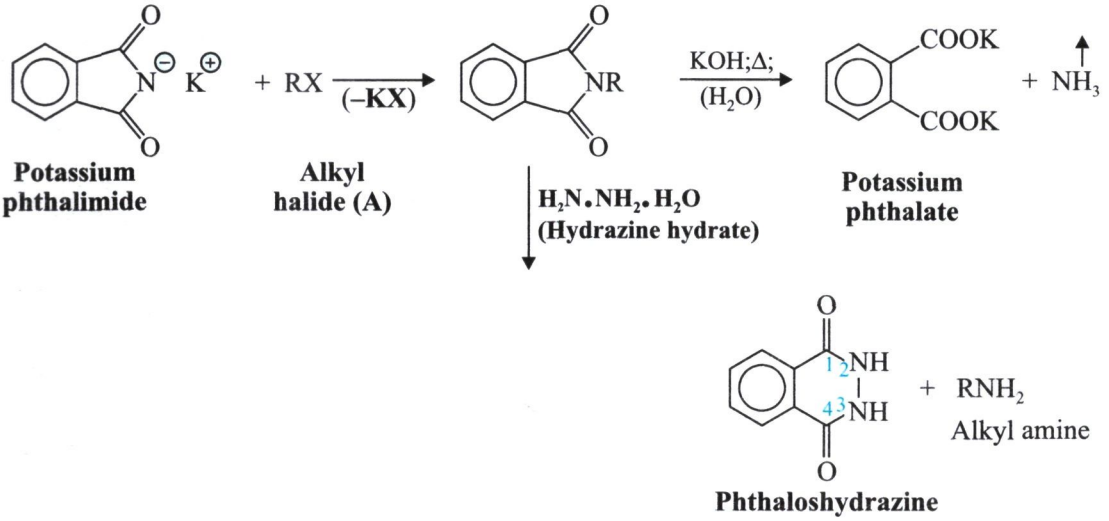
All the sequential steps involved in the above scheme of reactions are self-explanatory.

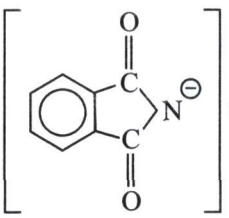
* Fischer E: *Ber,* **29**: 205, 1896.

** Wiley RH: *Chem Rev.,* **37**: 401, 1945; Brooks DA: **Fischer Oxazole Synthesis in Name Reactions in Heterocyclic Chemistry. Wiley and Sons, Hoboken NJ, 2005 (Review).**

11.2.7 Gabriel Synthesis* [or Gabriel's Phthalimide Synthesis]

The **Gabriel synthesis** relates to the ***'Alkylation of Phthalimide'*** thereby leading to the conversion of *alkyl halides* to the respective *primary amines***. Obviously, once the *phthalimide gets duly alkylated* it no longer remains *nucleophilic* in character, and hence, fails to react oxymore. Thus, the resulting product undergoes cleavage by the aid of **hydrazine (base)** that ultimately leads to a ***stable* cyclic product,** as shown under:



Interestingly, the **alkyl halide (A)** (see above) critically undergoes a ***nucleophilic displacement*** by the so-called **phthalamide anion**  to result into the formation of **N-substituted phthalimide**—that on subsequent **hydrolysis** either:

- **in an acidic environment,** or
- **in an alkaline medium,**

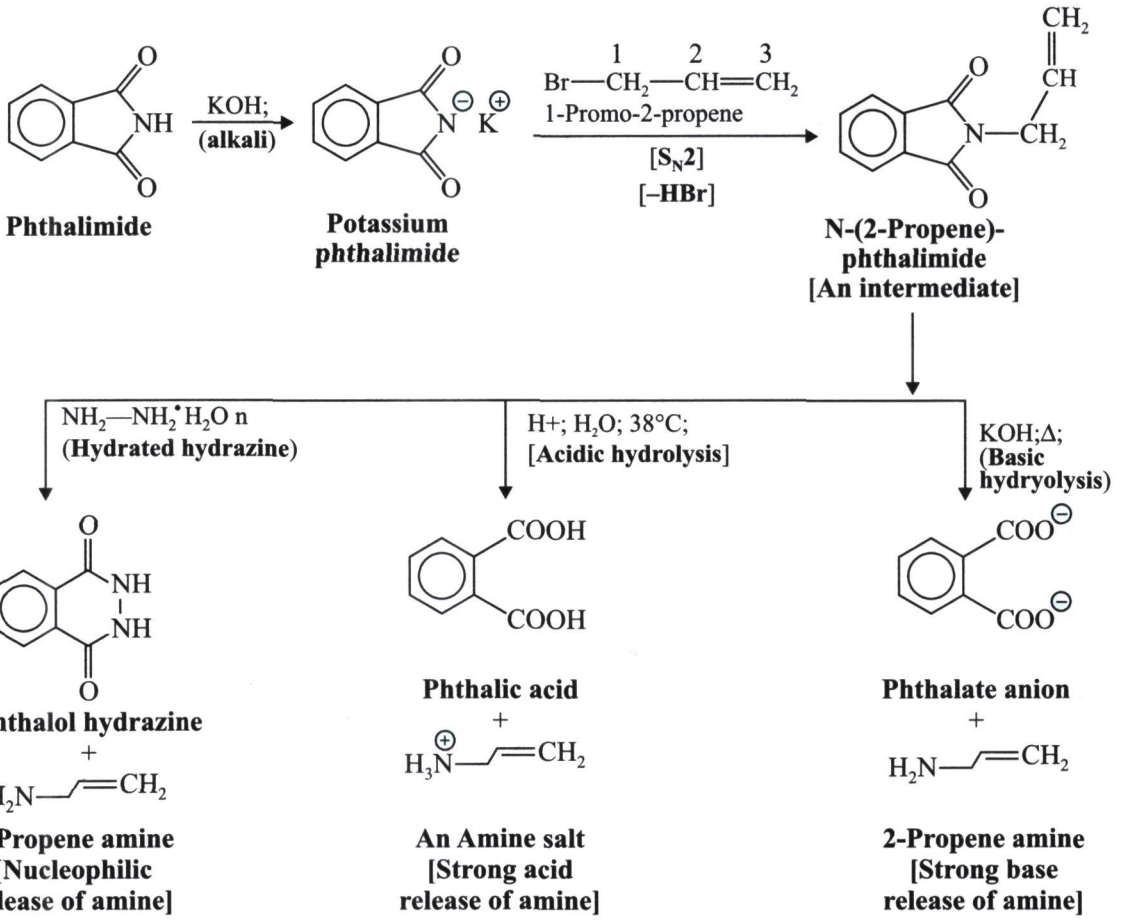
to yield the desired product eventually. However, it has been duly observed that occasionally **N-substituted phthalimide** gets *hydrolyzed* with great difficulty and efforts. Therefore, in such critical instances, we may make use of the **hydrated hydrazine** ($H_2N.NH_2.H_2O$) to obtain the ***'free* primary amine'***** as illustrated in the following sequential reaction mode:

---

* Gabriel S: *Ber*, **20**: 224, 1887.

** Sheeham JC and Bolhofer VA, *J Am Chem Soc.*, **72**: 2786, 1950; Mitsunobu O, *Comp Org Syn.*, **6**: 79-85, 1991 (Rev.), Gibson MS *et al.*: *Angew Chem Int Ed.*, **7**: 1919, 1968.

*** That is, almost free from either *sec-* or *tert-*amine.



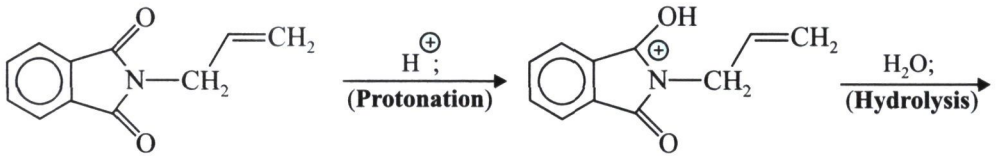
The various steps involved in the above sequential reactions are self-explanatory.

Mechanism of Gabriel Phthalimide Synthesis: Interestingly, based upon the ensuing *hydrolysis* of **N-alkyl phthalimide** duly accomplished by the interaction of *phthalimide* and *alkyl halide* (as detailed earlier), one may arrive at the ***crossroad*** to determine precisely whether the said reaction is:

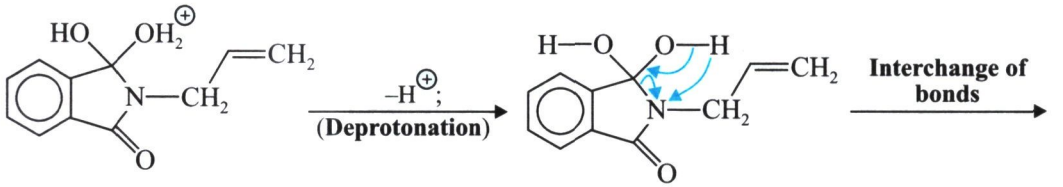
- **base-catalyzed**, or
- **acid-catalyzed,**

which may be ascertained squarely right from the following proposed mechanism of **Gabriel phthalimide synthesis:**

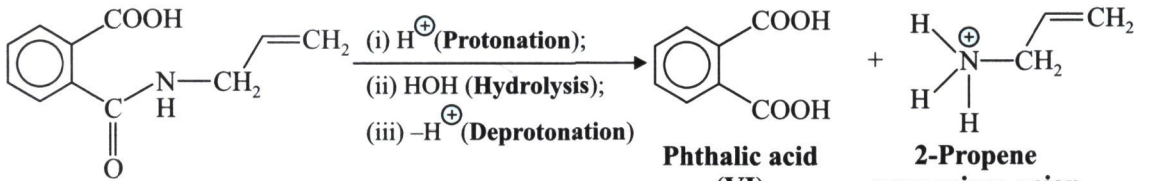
(*a*) **Acid Catalyzed Hydrolysis:** The various steps involved duly in the **acid catalyzed hydrolysis** are as stated below:



N-(2-Propene) phthalimide (I) → **Protonated deriv. (II)**



Hydronium ion deriv. (III) → **An '*Unstable*' specie (IV)**



***O*-(2-Propene amino) benzoic acid (V)** → **Phthalic acid (VI)** + **2-Propene ammonium anion**

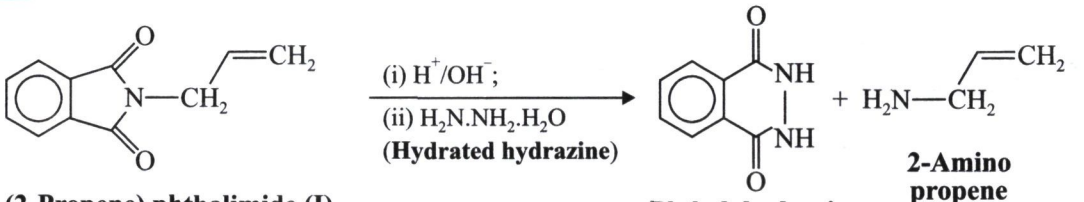
Explanations

N-(2-propene) phthalimide (I) on being subjected to *protonation* **(H+)** yields a **protonated derivative (II)**, which on being subjected to hydrolysis gives the respective **hydronium ion derivative (III)**. The resulting **product (III),** upon *deprotonation*, gives rise to the formation of an **'unstable' specie (IV)**, which on **interchange of bonds** gives ***O*-(2-propene amido) benzoic acid (V)**. Finally, the end-**product (V)** upon *protonation-hydrolysis-deprotonation* gives a mole each of **phthalic acid (VI)** and **2-propene ammonium anion** respectively.

Special Remarks: The **N-alkyl substituted phthalimide (I)** [*i.e.,* N-(2-propene) phthalimide] invariably poses a rather difficult task to undergo *hydrolysis;* and hence, we may make use of the so-called **'hydrated hydrazine ($H_2N.NH_2.H_2O$)'** for effectively pursuing the said reaction* (*as given under*).

* That is, to produce the ***pri*-amine** efficaciously.

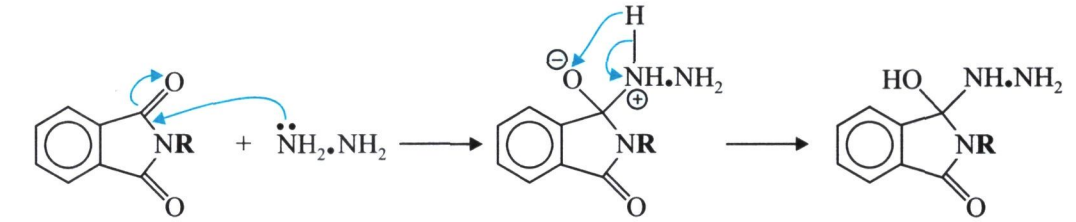
NOTE: **In reality, the reaction of the following type is usually termed as '*hydrazinolysis*'.***



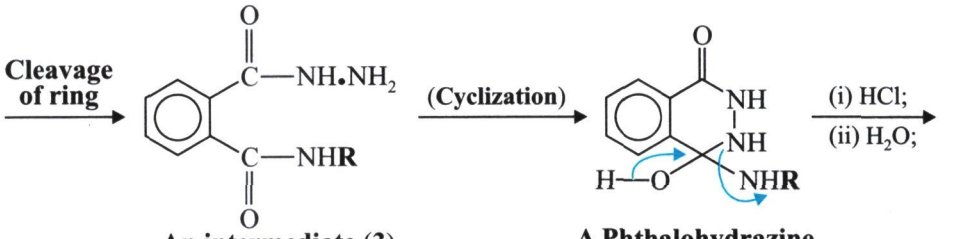
N-(2-Propene) phthalimide (I)
[An N-alkyl substituted phthalimide]

Phthalohydrazine

Mechanism Proposed for '*Above Reaction*': The various sequential steps involved are as follows:

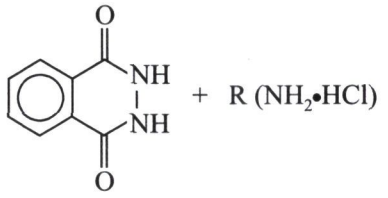


Alkyl phthalimide **Hydrazine** **Phthalimido-hydrazine salt (1)** **Hydroxy hydrazine derivative (2)**



An intermediate (3)

A Phthalohydrazine derivative (4)



Phthalohydrazine derivative (5) **Alkyl ammonium chloride**

* Han Y and Hu H: *Synthesis,* 122, 1990.

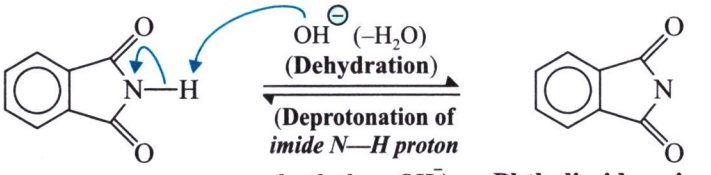
EXPLANATIONS

1. Interaction of *alkyl phthalimide* and *hydrazine* yields the **phthalimido hydrazine salt (1)**, which on intramolecular rearrangement gives the respective **hydroxy hydrazine derivative (2)**.
2. The resulting **product (2)** undergoes *cleavage of ring* to produce an **intermediate (3)**, which upon *cyclization* gives a **phthalohydrazine derivative (4)**.
3. Finally, the **product (4)** on treatment with HCl followed by H_2O gives rise to the formation of a mole each of **phthalohydrazine (5)** and **alkyl ammonium chloride**.

(*b*) **Base Catalyzed Hydrolysis:** The corresponding **base-catalyzed hydrolysis** of the ***Gabriel phthalimide synthesis*** is usually expatiated duly in the following ***three*** **individual steps**:

Step-1: Deprotonation of Imide N—H Proton by Base OH^-

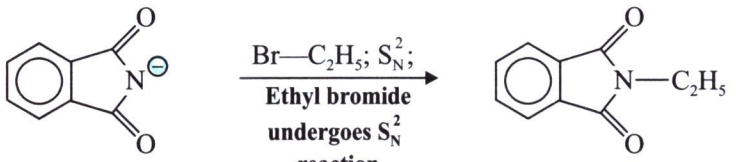
The reaction involved may be expressed as under:



Thus, the *deprotonation* of the **imide N-H proton** by the base OH^- causes *dehydration* ($—H_2O$) to produce the respective **phthalimide amion (A)** which represents a rather **strong nucleophile**.

Step-2: Bimolecular Nucleophilic Substitution Reaction

In this case the **phthalimide anion (A)** (*i.e.,* the *strong nucleophile* obtained in *Step-1*) undergoes the S_N^2 **reaction*** with *ethyl bromide* whereby the ***N-nucleophile*** clearly attacks the ***electrophile 'C'*** of the *alkyl halide* (*i.e.,* **ethyl bromide**) thereby displacing the **bromide (Br^-)**; and hence, generating the newly formed **C—N bond**. Thus, we may eventually obtain the **N-ethyl phthalimide (B),**—as depicted below:

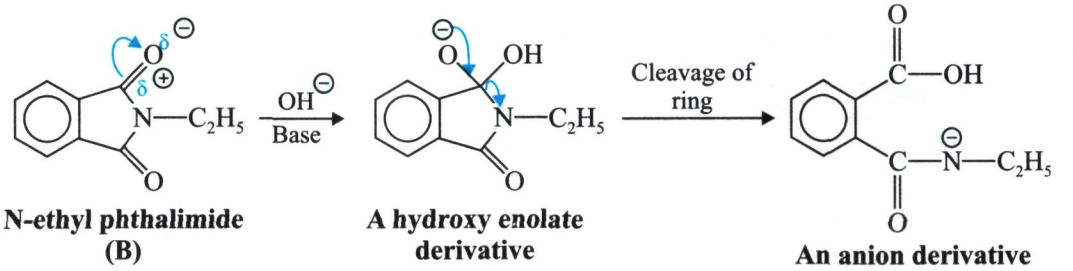


Step-3: The Critical Base Attack

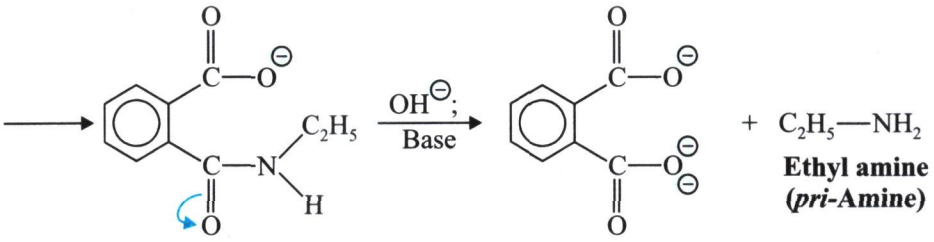
The resulting product **N-ethyl phthalimide (B)** (obtained from *step-2*) is treated with a *base (OH⁻)* to yield a *hydroxy enolate derivative*, which undergoes cleavage of the *heterocyclic ring* to give an **anion derivative**. The **end-product** undergoes an *intramolecular rearrangement* to produce a **carboxylate anion derivative**, which on being subjected to the **critical base attack (OH^-)** gives an *intermediate*. Finally, the *intermediate* gives a **phthalate anion** plus a mole of ethyl amine (*i.e.,* a **primary amine**).

* **S_N^2 Reaction:** It refers to the **substitution neucleophilic bimolecular reactions** only.

Thus, we may express the various reactions as under:



N-ethyl phthalimide (B) — **A hydroxy enolate derivative** — **An anion derivative**



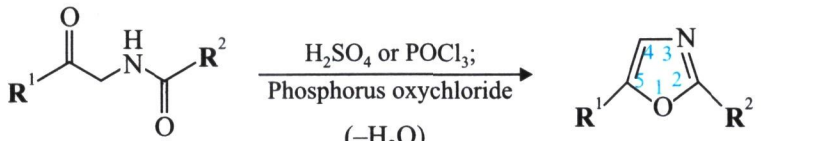
[An intermediate] — **Phthalate anion** — **Ethyl amine (*pri*-Amine)**

Extensions of the Gabriel Synthesis: Based on the literature survey we may rightfully indulge in the **extensions of the Gabriel Synthesis** with regard to the following *two* glaring aspects:

- **Robinson-Gabriel Synthesis,** and
- **Gabriel Colman-Type Rearrangement,**

which shall now be discussed individually in the sections that follows:

❑ ***Robinson-Gabriel Synthesis:*** The reaction essentially involves the formation of **'oxazoles'** due to the *dehydration* of **2-acylaminoketones***, as given below:



2-Acrylamino ketone — **Substituted oxazoles [2, 5-Disubstituted oxazole]**

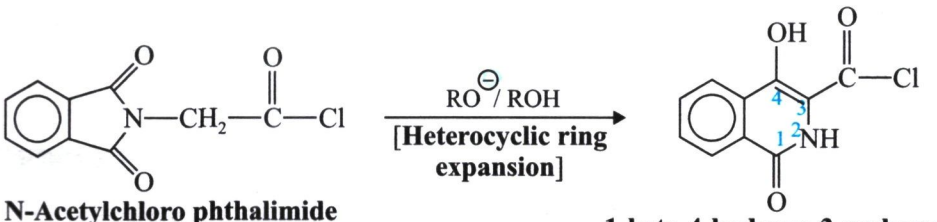
Thus, *cyclization* takes place to result into the formation of a **2, 5-disubstituted oxazole**.

❑ ***Robinson Colman-Type Rearrangement:*** Gabriel and Colman (1902)** suggested that the rearrangement of **N-substituted phthalimides,** is specifically induced by the aid of ***hot* alkoxides,** which is recognized to be a well known procedure to accomplish **3-substituted-4-hydroxy isoquinolines (X),** as per the following reaction scheme:

---

* Robinson RJ: *Chem Soc.*, **95**: 2167, 1909; Gabriel S: *Ber,* **43**: 134, 1910.

** Gabriel S and Colman J: *Ber.*, **33**: 2630, 1900, *ibid,* **35**: 2421, 1902.



N-Acetylchloro phthalimide

1-keto-4-hydroxy-3-carbonyl chloride-isoquinoline

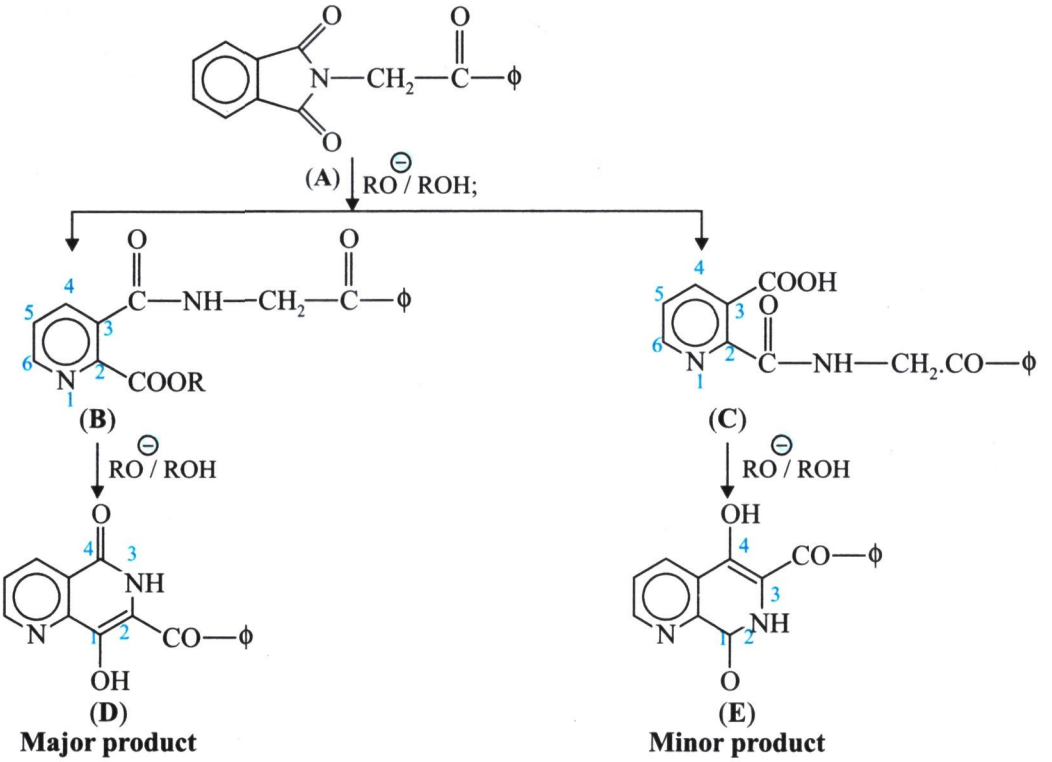
Remarks: The above cited method is a **general one** which is solely meant for the so-called—**"pentagonal cyclic aromatic imides"**, for instance:

- **the *'Quinolinimides'**, and**
- **the *'Ciinchomeron imides***,**

via, which we may eventually obtain the duly substituted **hydroxylnaphthyridinones.**

Therefore, the ***ring expansion*** essentially requires that the *functional moiety attached to N-atom* possesses an **enolizable H-atom.**

Mechanism of Reaction: The mechanism of **Robinson-Colman type rearrangement** may be expatiated by the help of following sequential reactions:



(D)
Major product

(E)
Minor product

* Blanco MM *et. al.*: *Heterocyclic Chem.*, **33**: 361, 1996, Blanco MM *et. al.*: *Heterocyclic Chem.* **42**: 493, 2005.

** Gabriel S and Colman J., *Ber*, **35**: 1358, 1902.

(A): N-Acetyl substituted phthalimide

(B): 2-Alkyl carboxylate-3-acetyl substituted amido pyridine

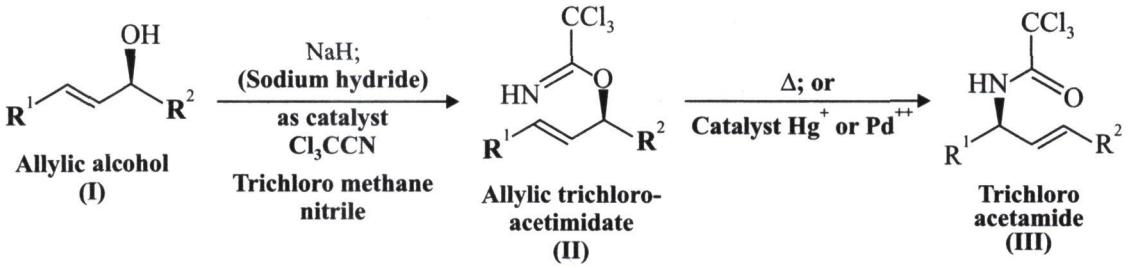
(C): 2-Acetyl substituted amido-3-carboxylate pyridine

(D): 1-Hydroxy-2-carbonylester-4-keto-3-isoquinoline

(E): 1-keto-4-hydroxy-3-carbonyl ester isoquinoline

11.2.8 Overmann Rearrangement*

The Overmann-rearrangement refers to the **[3,3]-sigmatropic rearrangement** of the *trichloro acetimidate* **(II)** of the respective **allylic alcohols (I)** to the corresponding **allylic trichloroacetamides (III),** thereby transposing the ***hydroxyl*** **(*—OH*) and *amino* (*—NH_2*) functions** having a reasonably good **'chirality transfer'**, as depicted under:

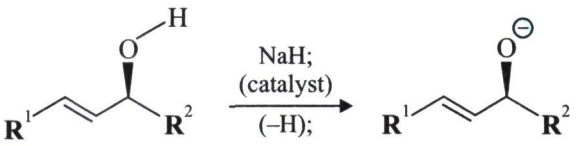


Allylic alcohol (I) — **Allylic trichloro-acetimidate (II)** — **Trichloro acetamide (III)**

Mechanism of Overmann Rearrangement:** The proposed precise and probable mechanism of the reaction essentially involves the following sequential ***four*** **distinct steps**:

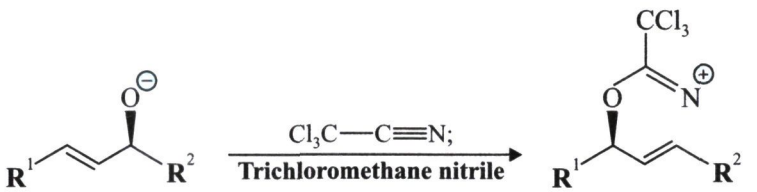
Step-1: Deprotonation of Allylic Alcohol

The **allylic alcohol** undergoes *dehydrogenation* **(-H)** in the presence of *sodium hydride (NaH)* as a catalyst, as given under:



Allylic alcohol — **Allylic alkoxide (A deprotonated alcohol)**

Step-2: Addition of Deprotonated Alcohol to Trichloroacetonitrile to yield Intermediate (Z)



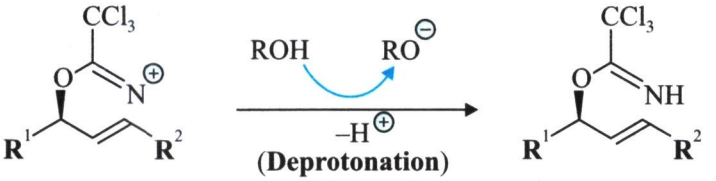
Allylic alkoxide — **Addition reaction** — **Intermediate (Z)**

* Overmann LE, *J Am Chem Soc.*, **96**: 597, 1974,; *ibid:* **98**: 2901, 1976.

** Overmann LE, *Acc Chem Res.*, **4**: 49, 1971 (Review).

Thus, the end-product from *Step-1* with *trichloromethane nitrile* gives an **intermediate (Z)** as the *addition product*.

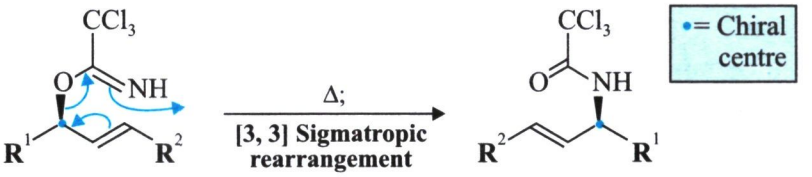
Step-3: Deprotonation of Allylic Alcohol (starting meterial) by the Intermediate (Z)



Intermediate (Z) **An Imine derivative**

Thus, the *deprotonation* of **(Z)** gives rise to the formation of an **'imine' derivative**.

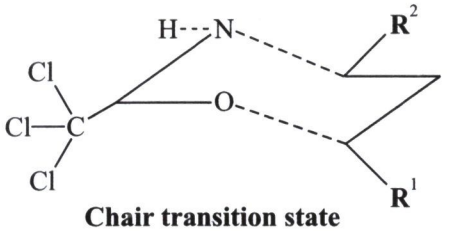
Step-4: The [3,3] Sigmatropic Rearrangement of *Imine* Derivative



Imine deriv. **Imine derivative [Chirality transfer]**

Obviously, the **'imine' derivative** obtained from *Step-3* on heating undergoes **[3,3] sigmatropic rearrangement** (discussed earlier) to give *another version* of the **'imine' derivative** showing vividly the ***chirality transfer*** (see structures in *Step-4*).

Points to Ponder: The reaction involved in ***Step-4*** predominantly bears the **'chair-transition state'** as shown below:



Chair transition state [Imine derivative)

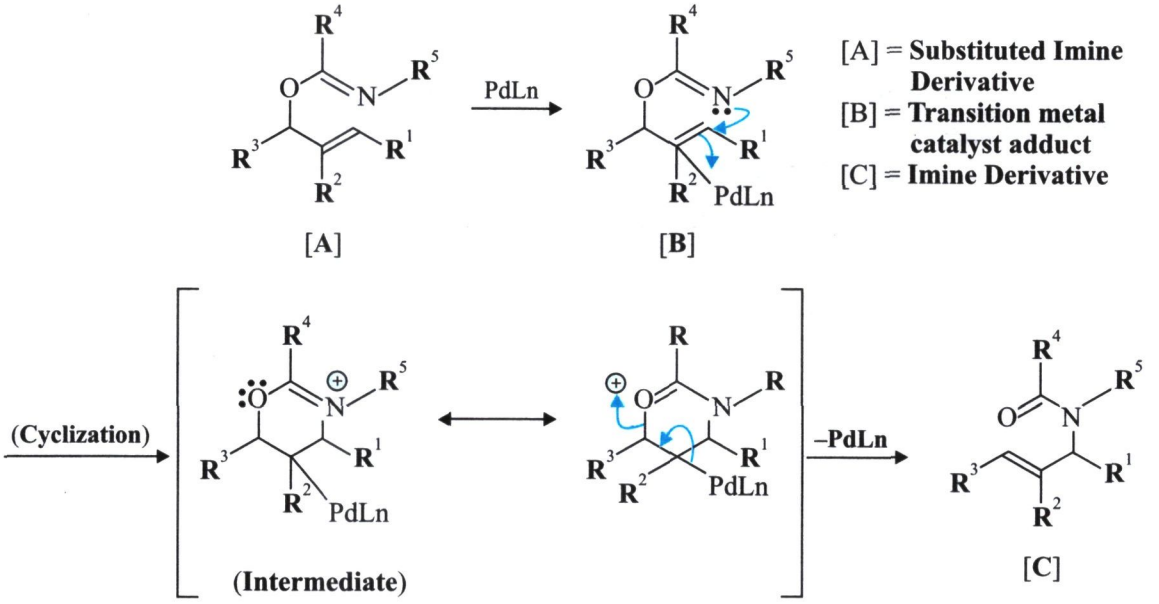
NOTE: **It is, however, important to state here that the ensuing thermal [3,3] sigmatropic rearrangement to form '*allylic imine*', is very much comparable to the *Claisen rearrangement**—since both of them do prefer to proceed *via* chair transition state.**

Inducement of Rearrangement by a Transition-Metal Catalyst [Pd (II) or Hg (II)]:** Let us look into the following steps:

---

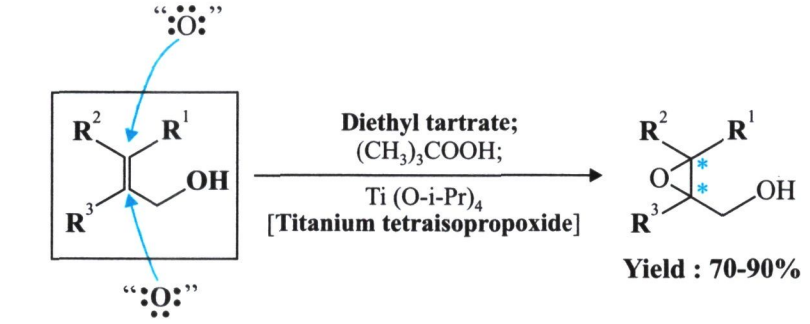
* Claisen L: *Ber.*, **45**: 3157, 1912; Claisen L and Tietze E, *ibid*, **58**: 275, 1925, **59**: 2344, 1926.

** Marion N *et al.*: *Org Lett*, **9**: 2653-56, 2007; Ramachandran PV *et al. Tetrahedron Lett.* **46**: 2121, 2008.



11.2.9 Sharpless Epoxidation*

The **Sharpless epoxidation** refers to the *titanium-catalyzed asymmetric epoxidation* of the **allylic alcohols** by making use of **titanium alkoxide [Ti (O-i-Pr)$_4$]**, an ***optically active*** **tartrate ester*****, and an **alkyl hydroperoxide,** as given below:



NOTE: **The asterik (*) at a *'chiral centre'* designates a preponderance of either the *'R'* or *'S'*-configuration.**

Williams *et al.* (1984)**** proposed that by the aforesaid **epoxidation reaction**, the ensuing ***achiral*** **starting material** (*i.e., allylic alcohol*) may be readily converted into:

---

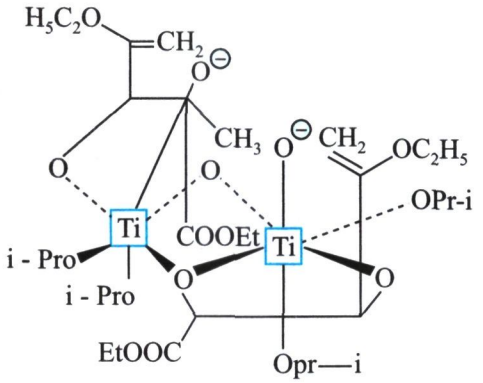
* Katsuki T and Sharpless R: *J Am Chem Soc.*, **102**: 5974, 1980.

** Also known as **titanium tetraisopropoxide**.

*** That is, **pure diethyl tartrate**.

**** Williams ID *et. al.*: *J Am Chem Soc.*, **106**: 6430, 1984.

"a chiral non-racemic product ultimately".



Ti = Titanium Centres

The above structure shows a **'dimer'** with **2-Titanium centres** that are critically joined by ***two chiral tartrate bridges***.

Quality of Enantioselective Reactions: Interestingly, the prevailing **quality of enantioselective reactions** is expressed numerically as the so-called **enantiomeric excess** (abbreviated as ***'ee'***). In fact, it is equal to the overall *yield of the* **major enantiomer** ***minus*** the yield of the **minor enantiomer** in the resulting product **(whose 'normal yield' is usually normalized to 100%)**.

Example: Obviously, in the **Sharpless epoxidation** phenomenon of ***'allyl alcohol'***, as depicted in Fig. 11.6, we may eventually lay hands onto the respective ***R*-and *S*-glycidol** duly generated in a **ratio of 1:19**. Therefore, for a total **glycidol yield standardized to 100%**, the actual ***R*-glycidol fraction** (***5% yield***) is duly exceeded by ***90%*** for the respective ***S*-glycidol fraction** (*i.e.*, ***95% yield***). Consequently, the latter (*i.e.*, ***S*-glycidol**) is produced generously with an **enantiomeric excess** (**ee**) of **90%**.

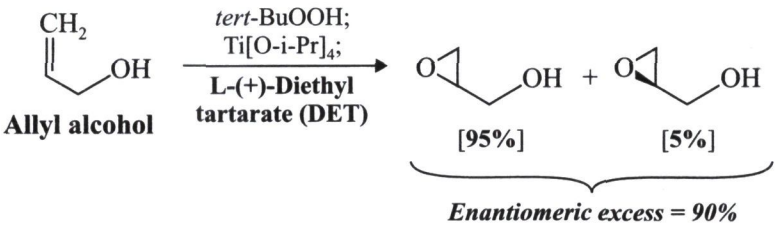


Fig. 11.6: The Definition of the Enantiomeric Excess or Making use of the Sharpless Epoxidation of Allyl Alcohol as an Example. The Chiral Auxilliary is Tartaric Acid Diethyl Ester [*i.e.*, Diethyl Tartrate (DET)]

NOTE:

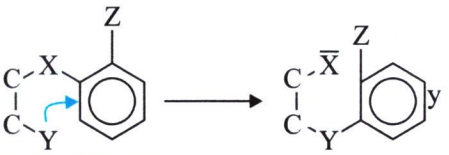
1. **Importantly, the underlying concept of *stereospecificity* has been duly incorporated so as to characterize particularly the so-called stereochemical course of pairs of the extremely *diastereoselective reactions*. Also another *terminology, stereo convergence* is found to be quite useful in this connection.**
2. **The *Sharpless epoxidation reaction* has been found to be limited to *'allylic alcohol'* exclusively since other *alkene variants* fail to get bound to the *Titanium (Ti)* efficaciously.**

11.2.10 Smiles Rearrangement* (Truce-Smiles Rearrangement)

The **Smiles rearrangement** critically represents an:

"intramolecular nucleophilic aromatic rearrangement or substitution".

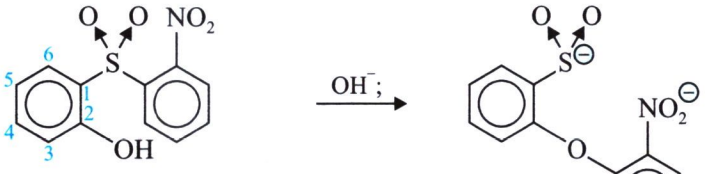
It actually comprises a group of rearrangements which eventually follow the pattern depicted under:



X = S, SO, SO_2, O, CO_2
Y = OH, NHR, SH, CH_2R, CONHR

In a broader perspective, the **Smiles rearrangement** essentially comprises a ***'congregation of rearrangements'*** which usually follow the *pattern* provided above.**

Let us now consider a *specific example* as given under:



1-(6-Sulphoxide-nitro benzene) 2-phenol (A)

Smiles rearrangement product (B) [with *two* anionic functions]

Explanations

In the aforesaid example, the *aryl sulphoxide* (SO_2Ar) happens to be the *leaving moiety* and the *nucleophile* **(ArO^-)** and the **nitro moiety (NO_2^-)** serves to **activate its *ortho*-position** specifically. Besides, the *ring* at which the *substitution* occurs is nearly always **activated**, invariably by ***ortho*- or *para*-nitro moieties**. Thus, **X** is usually S, SO, SO_2, O or CO_2; whereas, **Y** is invariably the conjugate base: OH, NH_2, NHR, or SH.

NOTE: **The reaction has even been performed successfully with Y = CH_2^- (*phenyllithium* was the base used).*****

Enhancement of Rate of Reaction****:** In fact, the *rate of reaction* gets virtually increased significantly due to:

"the *substitution* in the 6th position of the *'attacking ring'*, perhaps by virtue of the steric factors involved".

---

* Evans WJ and Smiles S: *J Chem Soc.*, 181, 1935; *ibid*, 329, 1936; Levy. AA *et al.*, *J Chem Soc.*, 3264, 1931.

** Truce, Kreider, Brand, *Org React.*, **18**: 99-215, 1971 (Review).

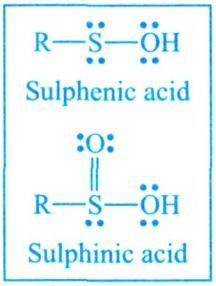
*** Truce, Ray: *J Chem. Soc.*, **81**: 481, 1959, Drozd, Nikonova: *J Org Chem.*, **5**: 313, 1969.

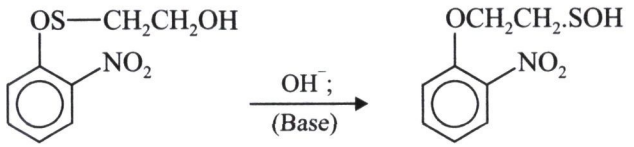
**** Bunnett, Okamoto, *J Am Chem Soc.*, **78**: 5363, 1956.

Example: The very presence of a **methyl** (*-CH_3*), chloro (*-Cl*) or bromo (*Br*) moiety at the **6th position** of **compound (A)** actually helped to raise the ***reaction rate*** to nearly **10^5 folds faster** *vis-a-vis* when the same functional groups were attached to the **4th position**, even though the inherent *electrical effects* must be at par in the **respective 4th and 6th positions**.

Importantly, the so-called *increased rate of reaction* is being observed crucially since the ***most preferred conformation*** which the molecule may adopt to suit appropriately the **'bulk of the 6-substituent'** ultimately becomes the conformation *essentially needed for the rearrangement*. Thus, a reasonably **lower entropy of activation is required**.

Kent and Smiles (1934)* advocated evidently the **Smiles rearrangement** may not only be confined to compounds comprising ***two*** **rings** but could be feasible even with compounds having ***one*** **ring** only, as shown below:



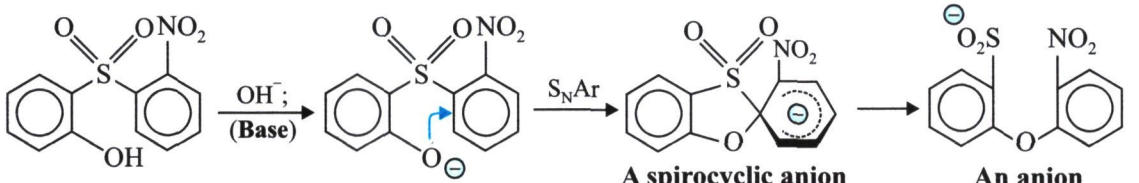


Sulphinic acid **Sulphenic acid (unstable)**

Comments: Therefore, in the above specific instance, the **sulphenic acid** is found to be ***unstable*** in nature; and hence, the actual products isolated were the respective **sulphinic acid (RSO_2H)** and **disulphide (R_2S_2)**.

NOTE: **According to *Truce-Smiles modification* (Truce and Smiles, 1935) the so-called *incoming meleophile* is sufficiently strong enough so that the *'arene'* fails to require any sort of an *additional activation* when the said nucleophile happens to be an *'organolithium'* entity.**

Another school of thought suggests the following alternative illustration for the **Smiles rearrangement**, as given under:



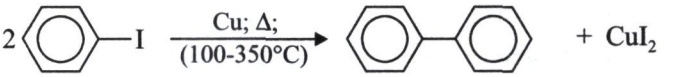
1-(6-Sulphoxide-nitrobenzene)-2-phenol (A) **An anion [Oxide]** **A spirocyclic anion [Intermediate] [The Meisenheimer complex]** **An anion [Sulphoxide]**

* Kent, Smiles, *J Chem Soc.*, 422, 1934.

** Nakamura: *J Am Chem Soc.*, **105**: 7172, 1983.

11.2.11 The Ulmann Reaction* (De-Halogen Coupling)

It refers to coupling of *aryl halides* in the presence of *copper (Cu)* and mild heat to result into the formation of **'biaryls'**, as given under:



Phenyl iodide **Biphenyl** **Cupric iodide**

Walter and Weirich (1990)** suggested that **Ulmann reaction** vehemently possesses a broad scope; and, therefore, has been duly utilized to prepare scores of:

- **Symmetrical biaryls** and
- **Unsymmetrical biaryls.**

Interestingly, the **Ulmann reaction** has proven to be successful with **aryl iodides**. Nevertheless, the corresponding variants: **aryl bromides (C_6H_5—Br)** and **aryl chlorides (C_6H_5—Cl)** do also react adequately as and when the so-called:

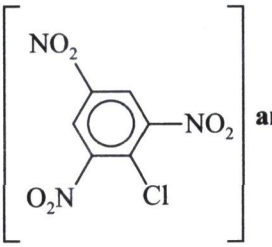
"halogen activating electronegative substituents are duly present".

It has also been demonstrated and ascertained that the *overall transformation(s)* of **ArI** is certainly an **'oxidative addition phenomenon'**.

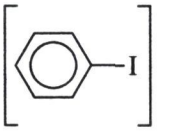
Remarks: Obviously, when an admixture of ***two*** **different aryl halides (C_6H_5—X)** is being employed, there could be ***three*** **possible products,** but amazingly **only one is obtained.**

Example: Two classical examples are of:

⊙ **Picryl chloride**



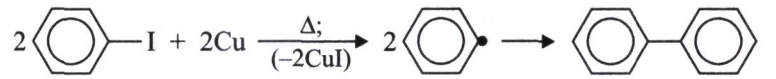
and ⊙ **Iodobenzene**



that eventually yielded exclusively 2,4,**6-trinitrobiphenyl*****.

Comments: The best leaving functional moiety is *iodo,* and the reaction is quite often done with *aryliodides*, but *bromide, chlorides*, and even the *thiocyanates* have also been used.

Mechanism of Ulmann Reaction: The precise **mechanism of reaction** of **Ulmann reaction,** appears to be uncertain as on data; however, a ***'radical mechanism'*** may be proposed as stated under:



Iodobenzene **Phenyl radical** **Biaryl [4, 4-Diphenyl]**

* Ulmann F, *Ann*, **332**: 38, 1904; Ulmann F and Sponagel P: *Ber,* **38**: 3211, 1905.

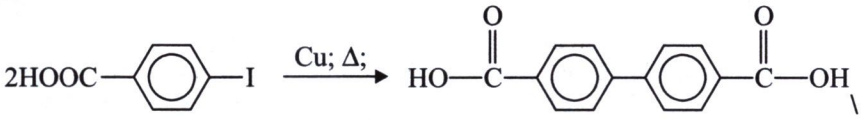
** Walter and Weirich: *Angew Chem Int. Ed. (Engl.),* **29**: 977-991, 1990.

*** Rule and Smith: *J Chem. Soc.*, 1096, 1937.

Thus, the **Ulmann reaction** predominantly bears an ***immense synthetic utility and importance*** *i.e.,* one may virtually synthesize an array of: **Biaryls** and **Polyaryls.**

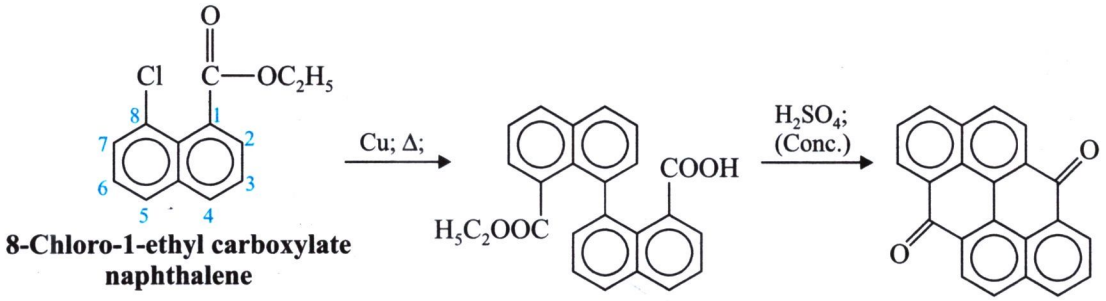
Let us consider the following typical examples:

(*i*) Conversion of *p*-Iodobenzoic Acid to 4, 4′-Diphenic Acid



***p*-Iodobenzoic acid** **4, 4′-Diphenic acid**

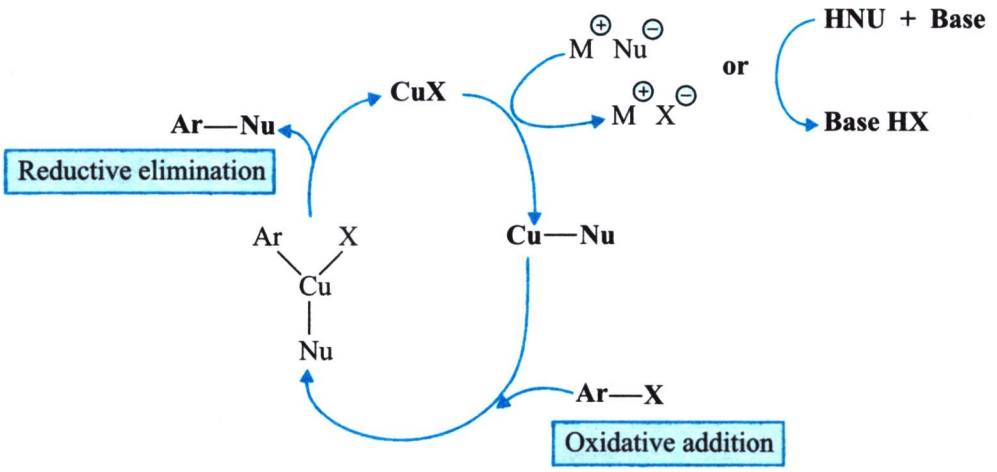
(*ii*) Formation of Anthanthrone from 8-Chloro-1-ethylcarboxylate naphthalene



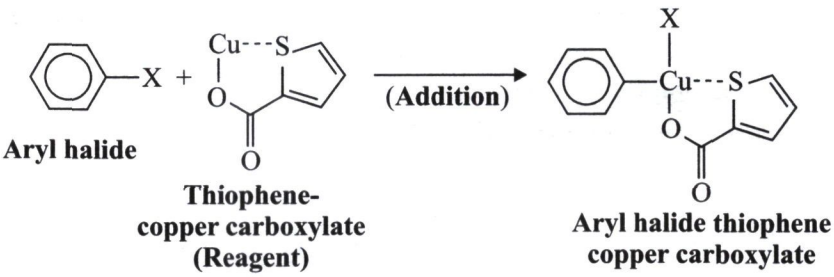
8-Chloro-1-ethyl carboxylate naphthalene **[An intermediate]** **Anthanthrone**

Specific Important Ulmann Reactions: Let us consider a few *typical, specific,* and *important* **Ulmann reactions,** namely:

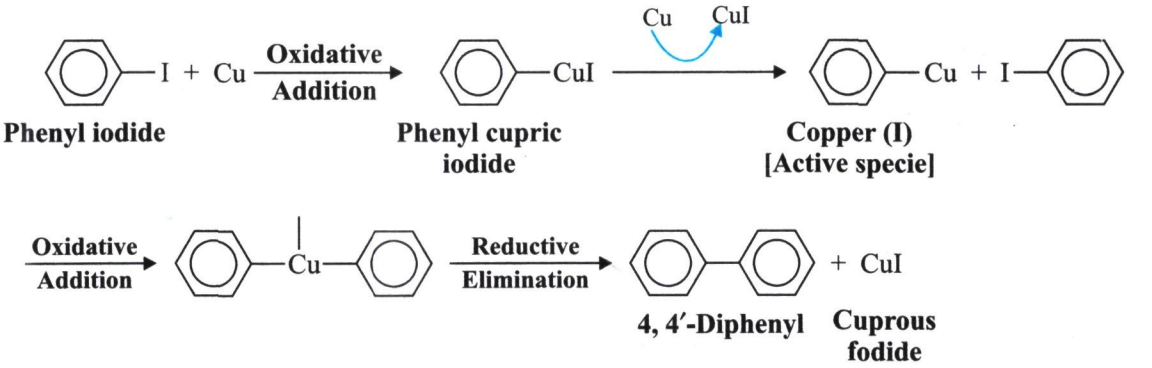
(*a*) **Reactions Involving a *Catalytic Cycle*:** In this particular instance, the underlying mechanism of **Ulmann reaction** critically involves the ***oxidation*** **of Cu (I) to Cu (II),** as depicted below:



(*b*) **Formation of the Organocopper Intermediate from Thiophenecarboxylate Reagent:** The interaction of an *aryl halide* with *thiophene copper carboxylate* undergo an *addition reaction* to yield the **aryl halide thiophene copper carboxylate** *via* the **Ulmann reaction,** as expressed under:



(*c*) **Formation of 4, 4′-Diphenyl by the Coupling of an Excess of Cu with Aryl Halide at 200°C:** The aryl halide gets duly coupled with an excess of Cu at an elevated temperature **(~ 200°C)** *via* various sequential steps, as depicted below:



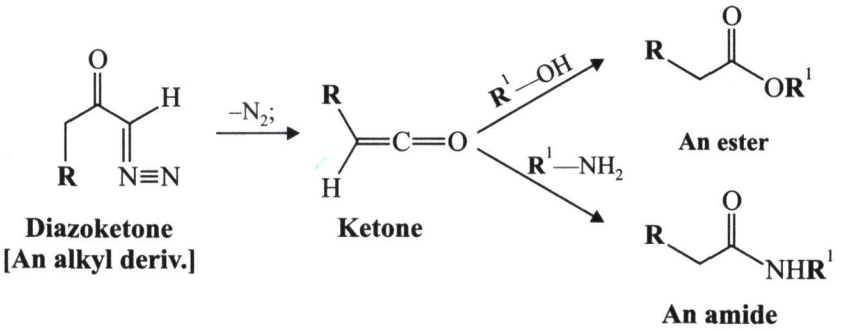
Thus, the ***active*** **specie Copper (I)** compound undergoes *oxidative addition* **(2nd time)** with the ***second*** **equivalent** of the *halide*. Now, the resulting product specifically undergoes ***reductive elimination*** with the generation of **aryl-aryl carbon linkage,** thereby yielding **4, 4′-diphenyl.***

11.2.12 Wolff Rearrangement**

It relates to the rearrangement of *diazoketones* to **'ketones'** by any of these ***three*** **known modalities**:

- **Thermally**
- **Photochemically or**
- **Catalytically.**

The reaction may be expressed as under:



* Fang Y and Li C: *J Am Chem Soc.*, **129**: 8092-93, 2007; Pan Y *et al.*: *Synthesis*, 1242-46, 2007: Lu H and Li C: *Org Lett*, **8**: 5365-67, 2006.

** Wolff I: *Ann.*, **394**: 25, 1912.

NOTE: **The *Wolff rearrangement* is the '*key step*' in the Ardt-Eistert synthesis.***

Another school of thought advocates that the **Wolff rearrangements** do designate the so-called rearrangements of:

"α-diazoketones leading to carboxylic acid structural analogues via the ketene intermediates".

Thus, we may virtually accomplish the **Wolff rearrangements** by making use of either:

➢ **metal catalysts,** or ➢ **photochemically.**

Figure 11.7 depicts the **α-diazoketone (IV)** initially lose a *N-molecule* and there by forms a **ketene (VII).**

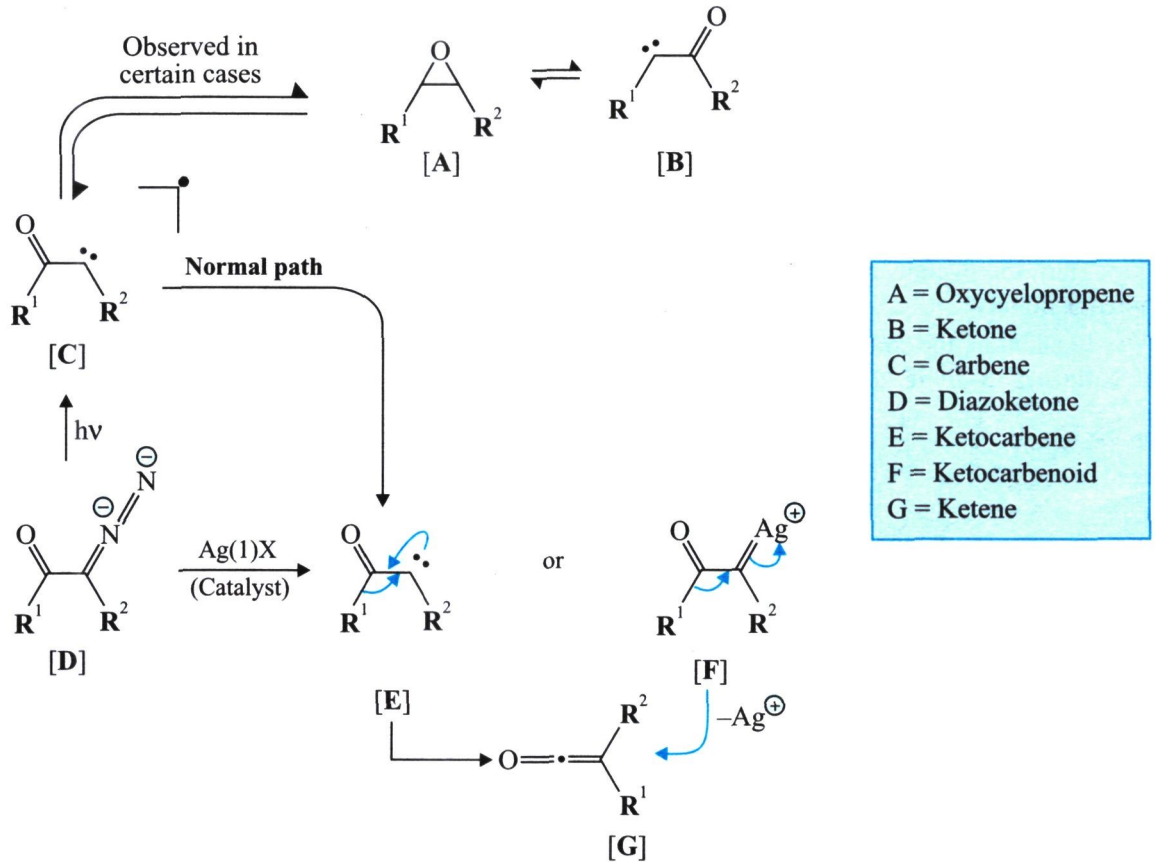


Fig. 11.7: The Mechanisms of the Photochemically initiated and Ag (I) catalyzed Wolff rearrangements with formation of **Ketocarbene (E)** and/or the **Ketocarbenoid (F)** by dediazotization of the **Diazoketone (D)** in the critical presence of catalytic quantum of **Ag (I) E and F** are duly converted into **G** *via* a [1,2]–shift of the alkylmoiety R^1. Besides, N_2 and an excited **Carbene [C]** are also formed in the photochemically initiated reaction. The excited carbene usually relaxes to the normal **Ketocarbene (E)**; and this **Carbene (E)** continues to react to yield **(G)**. The **Ketocarbene (C)** may sometimes isomerize to **(B)** *via* an **Oxycyclopropene (A)**. The [1,2]–shift of **(B)** also leads to the **Ketene (G)**

* Wolff L: *Justus Liebigs Ann Chem.*, **394**: 25, 1912; Bechmann WE *et al.*: *Org React.* **1**: 38-62, 1942; Mattalabi S and Müller P: *Chimia*, **48**: 119-122, 1992.

Thus, we may eventually obtain a ***ketene* (G)** starting from ***oxycyclopropene (A)*** by the help of **Wolff rearrangement** (as expatiated in the description of *Fig.11.7*).

Reaction Conditionalities: The **Wolff rearrangement** is usually guided by the following **two reaction conditionalities,** namely:

- **Effect of Reaction conditions,** and
- **Effect of Catalyst.**

❑ **Effect of Reaction Conditions:** Importantly, the following **two reaction conditions**, such as:

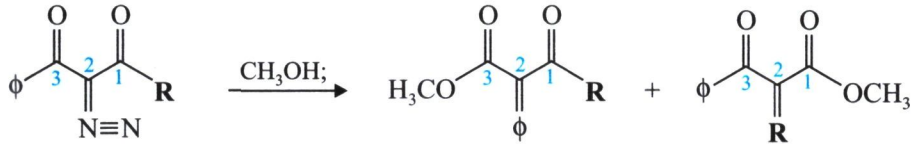
- **pathway preferences, and**
- **migratory group preferences,**

are observed to be grossly affected by any one of these aspects: ***photochemical condition*** or ***thermal condition*** or ***metal-ion catalysis***. Obviously, the so-called ensuing **migratory aptitude of the functional moiety** (that eventually undergoes rearrangement) may be determined precisely by the *analysis of the product ultimately*. It has also been observed critically that:*

"under photochemical parameter, methyl (—CH_3) moiety migrates perceptively; whereas, under thermal parameter phenyl (—C_6H_5) moiety migrates preferentially".

Thus, the overall **'migratory aptitude of H-atom'** is found to be certainly more *vis-a-vis* the **'phenyl moiety'**.

In addition, the so-called **migratory aptitude** may be determined conveniently by the reaction of **2-diazo-1, 3-dione**, as given below:



2-Diazo-1,3-dione **[Migratory aptitude of ϕ and R may be observed explicitly between C-1 & C-2 respectively]**

where, **R** = H, CH_3, OR^1

R = Alkyl or Aryl

NOTE: **The *Wolff rearrangement* is fairly versatile, and may useful for *alkyl* or *aryl* groups.**

Suggested Reading

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* Muller A *et. al.*: *Syn Lett.*, 837-841, 2006; Bogdanova A *et al.*: *J Am Chem Soc.*, **125**: 1436, 2003.

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SECTION 3

Rearrangements: Classification and Mechanism

Chapter 12. Rearrangements Induced by Cationic or Electron Deficient Sites (Carbon)

Chapter 13. Rearrangements Related to Electropn Deficient Heteroatoms

Chapter 14. Rearrangements Related to Acyl Carbenes

Chapter 15. Sigmatropic Rearrangements

Chapter 16. Rearrangements Influenced by Stong Bases [and/or] Electron Rich Sites

Chapter 17. Rearrangements due to Addition-Elimination Mechanism

Chapter 18. Rearrangements in Pericyclic Reactions

Chapter 19. The Aromatic Rearrangements

Chapter 12

Rearrangements Induced by Cationic or Electron Deficient Sites (Carbon)

LESSONS AT A GLANCE

12.1 Introduction

12.2 Name Reactions Based on Rearrangements Induced by Cationic or Electron Deficient Sites

- 12.2.1 Pinacol Rearrangement
- 12.2.2 Tiffeneau-Demjanov Rearrangement
- 12.2.3 Wagner-Meerwein Rearrangement
- 12.2.4 Allylic Rearrangements

12.1 INTRODUCTION

Scientific evidences and logical explanations do reveal explicitly that the so-called ***electron-deficient C-containing*** specie, ***'Carbonium Ion'*** is indeed of immense, theoretical as well as practical interest to the **organic chemists** in the detailed and elaborative studies related to:

- **Organic Reactions,** and
- **Their Intricate Mechanisms**

Olah GA strongly advocated that the terminology **'Carbonium Ion'** is certainly for more convenient *vis-a-vis* the terms:

- **Carbonium Ion,** and
- **Carbocation.**

However, the very existence of the **'Carbonium Ion'** was precisely ascertained and evidenced *via* the authentic **experimental data** (Bayer and Villiger, 1902) while performing critical experiments upon the **triarylmethyl** $[(C_6H_5)_3CH]$, but these *end-products (species)* were actually accepted and recognized almost after a spell of ***three*** **decades** (~ **1930**). Obviously, prior to the above epoch making discovery (*i.e.,* **before 1930**) the majority of scientific community vehemently based their arguments/logistics on the ***'carbocation concept'*** in order to expatiate certain **'rearrangement mechanisms'** explicitly.

Importantly, as-on-date a series of documented and widely recognized **'rearrangements'** are based exclusively;

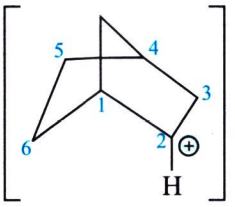
"On the Carbonium Intermediate Concept".

***Characterization of Carbocation Species*:** Following are a few commonly utilized *sophisticated analytical techniques* that are helpful for the accurate evidences of the so-called **rearrangement mechanisms,** as stated under:

- **Infrared Spectrophotometric (IR) Spectra of [$(CH_3)_3C^+$]:** *i.e.,* **trimethyl carbocation;** and it was found to be very much akin to the respective **isoelectronic chemical entity [$(CH_3)_3Bu$].**
- **Raman Spectra of [$(CH_3)_3C^+$]:** and comparing the spectra obtained with those of **[$(CH_3)_3$. Bu]** representing the similar kind of an **isoelectric compound.**
- **Electronic Spectroscopy of Chemical Analysis [ESCA]:** *i.e.,* the **ESCA-spectrum** of the ***tertiary*-butyl cation [$(CH_3)_3Bu^+$]** does provide a concrete and solid evidence for the critical presence of the **carbocation species.**

Besides, the following ***two*** **cations,** namely:

- **Butyl cation [$C_4H_9^+$],** and
- **2-Bornyl cation**



that eventually have had a pretty long *controversial ion* issue got ultimately resolved almost unanimously by the help of the **Isotopic Tracer Techniques, Solvolytic Investigative Studies,** and **Cross Polarization Magic Angle Spinning (CPMAS)–^{13}C NMR Spectroscopic Techniques** (*i.e.,* the most powerful resource now available in the ***Modern Analytical Armamentarium***).

Important Functional Characteristics of Carbonium Ions: There are *four* cardinal *important functional characteristics of the* **carbonium ions**

- **Nucleophilic substitution reactions,**
- **S_N1 Reactions,** (or *Substitution Nucleophilic Monomolecular Reaction*),
- **Elimination reaction (E_1),** and
- **Addition reactions to *Olefinic Bond*.**

Non-classical Carbocation Concept: It has been amply proven and demonstrated that according to the **non-classical carbocation concept**, one may critically observe that the so-called **carbocation** more or less sources as an *intermediate* in quite a few **Organic Reactions**. Thus, we may invariably come across a host of divergent **'carbocations'**, for instance.

- **Primary**
- **Secondary**
- **Tertiary**
- **Allylic** and
- **Benzylic.**

Fate of *Allylic* and *Benzylic Carbocations*: In true sense, these are duly stabilized by the most critical **delocalization phenomenon of the π-electrons** *i.e.,* due to ***resonance***. The ***tertiary*** **carbocation** *viz., tert*-**butyl carbocation [$(CH_3)_3Bu^+$]** gets duly *stabilized* by **hyperconjugation phenomenon,** whereas, a few of these are *stabilized* by means of:

"bridging to the adjoining nucleophiles *via* either the so-called neighbouring moiety participation or anchi-metric assistance (from the *Greek* word: *anchi* meaning "*near*")

Remarks: In a broader perspective, the **carbocations** are found to be electron deficient in character. They have only ***six* electrons in their valence shell and because of this characteristic feature, the 'carbocations' behave more or less as Lewis acids.** Therefore, they invariably come into being very much like **BF_3** and **$AlCl_3$**. Besides, a good number of **carbocations** are found to be **transient** (*short-lived*) and also *very reactive*. They also occur as the **'intermediates'** in certain **organic reactions.**

Reactivity of Carbocations: It may be added that the **carbocations** usually react rapidly with the **Lewis bases, molecules or ions** which may eventually donate the ***'electron pair'*** which they require to accomplish a **fairly stable *octet* of electrons** (*i.e.*, the *electronic configuration* resembling a **'noble gas'**):

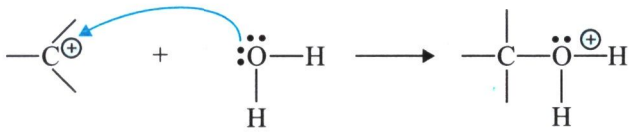
Thus, we may have the following expressions:

(a)



Carbocation (A Lewis Acid) **Anion (A Lewis Base)**

(b)



Carbocation (A Lewis Acid) **Water (A Lewis Base)**

EXPLANATIONS

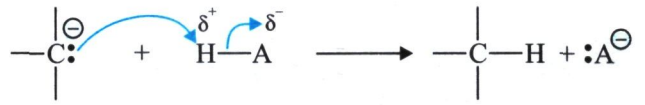
1. Since the **Carbocations** do designate the *electron-seeking reagents*—they are commonly known as the *electrophiles* amongst the *Organic Chemists*.
2. In fact, the **'electrophiles'** represent:

   "the reagents which in their reactions normally seek the *extra electrons* that will eventually provide them with *stable valence shell of electrons*".
3. All **Lewis acids,** including the *protons*, are considered to be *electrophiles*; and hence, by *accepting an* ***electron pair***, a **'proton'** accomplishes readily the **valence shell configuration of helium (He)**. Besides, the carbocations also retain the **valence shell configuration of Neon (Ne)**.

Carbocations as the Lewis Bases: Interestingly, in their respective reactions the **carbocations** usually seek a **proton** or certain other **positive charge borne centre** to which they may eventually *donate* their inherent ***electron pair***; and thereby ***neutralize* their negative charge** perceptively. Thus, such **reagents** *viz.*, **carbanions**—'that seek a proton or certain other **positive charge bearing centre** are termed as ***'nucleophiles'*** (**since the *nucleus designates* the +ve portion of an atom**).

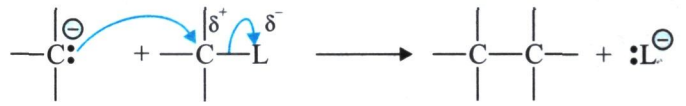
We may have the following reactions:

(a)



Carbanion **Lewis acid**

(b)



Carbanion **Lewis acid**

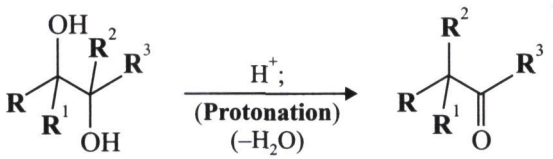
12.2 NAME REACTIONS BASED ON REARRANGEMENTS INDUCED BY CATIONIC OR ELECTRON DEFICIENT SITES

In the present context, we shall deal with the detailed discussion and reaction mechanism of the following ***four* vital and important rearrangements,** namely:

- **Pinacol Rearrangement,**
- **Tiffeneau-Demjanov Rearrangement,**
- **Wagner-Meerwin Rearrangement,** and
- **Allylic Rearrangement**

12.2.1 Pinacol Rearrangement*

Pinacol rearrangement refers to the *acid catalyzed rearrangement* of **vicinal diols** to the respective ***aldehydes* or *ketones*** [*i.e.*, the carbonyl (>C=O) compounds], as shown under:



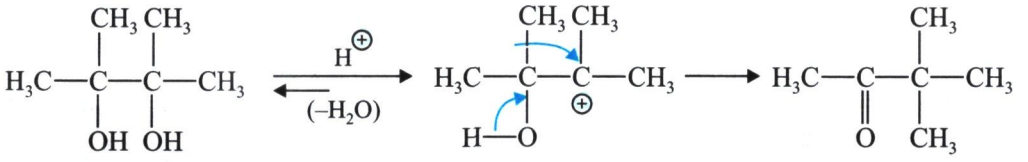
Vicinal diol **A ketone**

Thus, **acetone** on being subjected to Mg^{2+} *reduction* yields **pinacol** *via* the **ketyl intermediate**. Importantly, the *vicinal diol* is observed to be *symmetrical in nature;* and, therefore, both *protonation* and *elimination of a mole of water* (H_2O) moiety occurs having the **same probability profile at either** hydroxy (—OH) moity.

Important Point: In fact, the **trivial name** of the *simplest glycol* of this nature is known as **pinacol,** and hence, this kind of reaction is invariably called as **pinacol rearrangement** [however, in this specific instance,—the ensuing reaction is usually known as the—***'pincol-pinacolone rearrangement'.***]

* Fittig R: *Ann*, **114**: 54, 1960.

We may have the following expression:



Remarks: It is obviously pre-empted that the so-called *driving force* of the **pinacol-pinacolone rearrangement** being the carbonyl (>C=O) formation. Thus, the most prevalent *electron rich* **alkyl moiety** (*i.e.*, the more abundantly substituted C-atom) gets migrated *first viz.*,

3° Alkyl > Cyclohexyl > 2° Alkyl > Benzyl > Phenyl > 1° Alkyl > Methyl > H.

NOTE: **Therefore, such reactions may be promoted by the typical *electrophilic reagents viz.*, Lewis acids.**

Mechanism of Pinacol-Pinacolone Rearrangement: The arrangement essentially involves *four* distinct steps, namely:

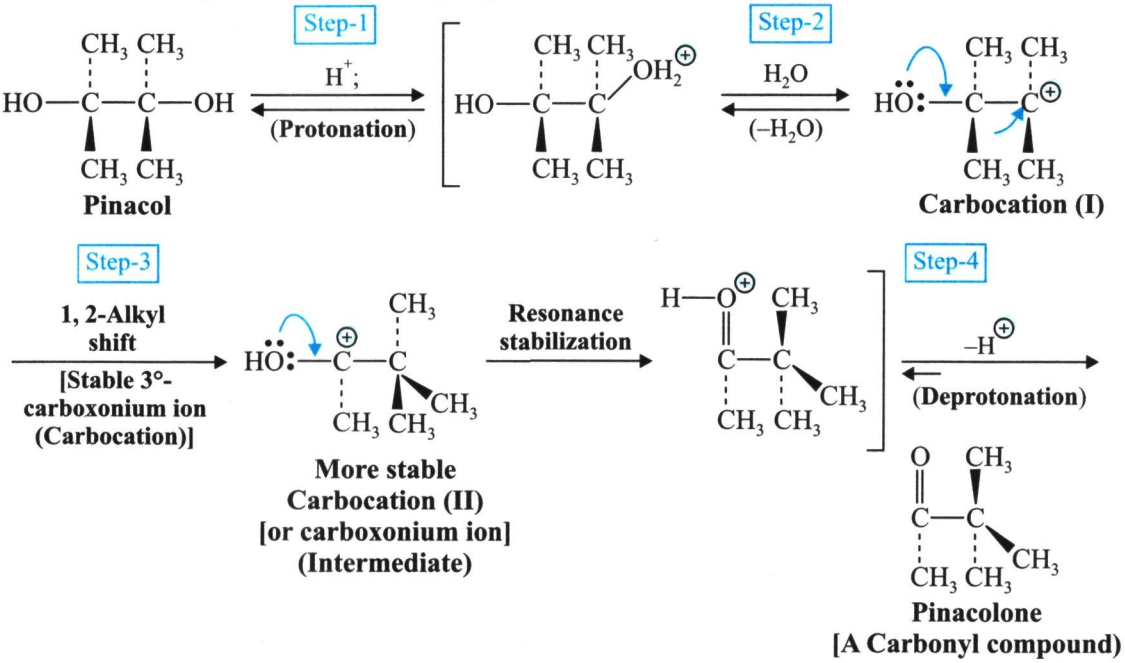
Step-1: Protonation of one of the hydroxyl (—OH) moieties.

Step-2: Elimination of a mole of water (H_2O) thereby resulting into the formation of a **carbanium ion**.

Step-3: Rearrangement of the **carbanium ion** into a rather more *stable* **carboxonium ion** (or *carbocation*) *via* a **[1, 2]-rearrangement**.

Step-4: *Deprotonation* of **carboxonium ion (or carbocation)** and the desired product **Pinacolone** (a *ketone*) is duly obtained.

Thus, we may have the following expression:



All the above *four* sequential steps are self-explanatory.

Five Cardinal Factors Guiding Mechanism of Rearrangement: Following are the *five* cardinal factors that essentially guide the underlying mechanism of **Pinacol rearrangement**:

- Obviously the ***more stable*** **carboxonium ion (or carbocation)** invariably undergoes the **rearrangement phenomenon**.
- Inherent **migrating aptitude** of various *substituent moieties*.
- Prevalent influence of *steric hindrance* plus other **strain factors** exerting their effect upon the **rearrangement phenomenon**.
- Critical generation of the ***'epoxides'*** as the ensuing **intermediates** in the **rearrangement phenomenon**.
- Overall stability of the **product formed** and **reaction parameters**.

Comments: At this material time it is worthwhile to undertake a brief discussion with respect to the following *six* important aspects pertaining to the mechanism of **Pinacol-Pinacolone Rearrangement,** namely:

(*i*) **Stability Profile of Carbocation,**
(*ii*) **The Influence of Migratory Aptitude,**
(*iii*) **The Steric Hindrance,**
(*iv*) **Epoxide Formation,**
(*v*) **Product Stability Profile,** and
(*vi*) **The Influence of Reaction Parameters.**

which shall now be treated individually in the sections that follows:

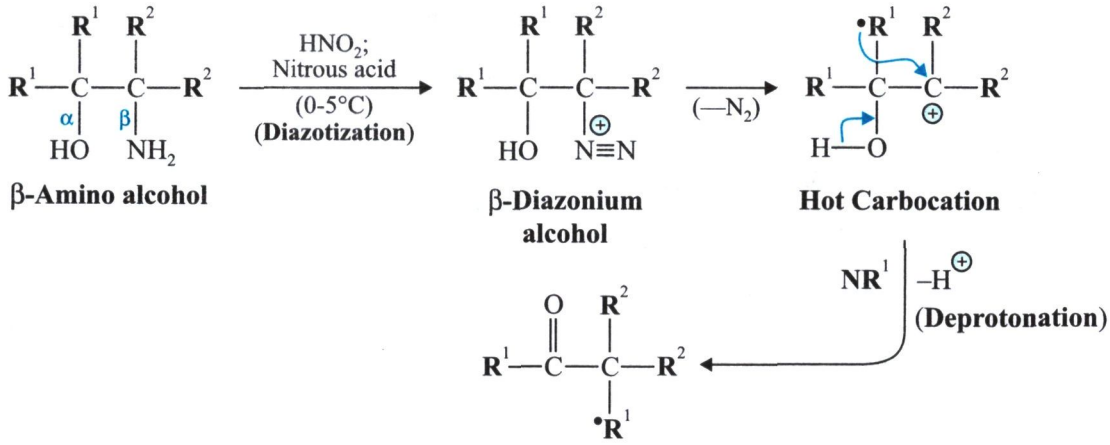
(*a*) ***Stability Profile of Carbocation:*** Importantly, the main plausible reason of the reaction solely rests upon the so-called **carbocation** (or ***carboxonium ion***) **intermediate**. Therefore, in the **pinacol-pinacolone rearrangement** it may be observed that the resulting **carbocation (I)** through ***1, 2-alkyl shift*** **(Step-3)** gives the more stable **carbocation (II) (intermediate)** due to the *tertiary (3°C) stability.*

Hot Carbocation*:* The very existence of any **carbocation** bearing a **+ve charge** on the C-atom located adjacent to the **Carbon bearing hydroxyl (OH) moiety** is invariably termed as the **'hot carbocation'**. Incidentally it also undergoes an **identical rearrangement** usually known as the **semi-pinacol rearrangement**.

The **mechanism of pinacol rearrangement** is overwhelmingly supported and influenced by this concept,**—as depicted under:

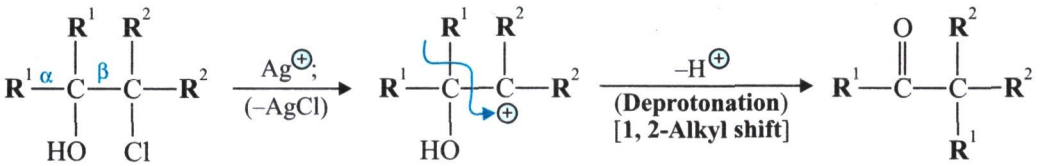
* Kirmse IW and Gruber W: *Chem Ber*, **106:** 1365, 1973.

** Zollinger H: **Azo and Diazo Chemistry: Aliphatic and Aromatic Compounds**, Inter-Science Publishers Inc., New York, 1961.



Curtin and Crew (1954)* critically observed a glaring difference in the ***semipinacol*** and ***pinacol*** **rearrangement** and pointed the same due to the so-called **'migratory aptitudes'** of the **aryl moieties**.

Thus, the *dehalogenation (removal of halogen group) reactions* do mostly exhibit an apparent ***lower*** **reactivity profile,**—as may be seen from the following sequence of reactions:



Remarks: In conclusion, it may be added that the ***pinacol-pinacolone rearrangement*** vividly designates a kind of **intramolecular rearrangement** since the *'migrating moiety'* retain its *original configuration*. Besides, one may hardly lay hands on to any kind of ***cross-over products*** whenever ***two*** **identical 1, 2-diols** are being duly subjected to treatment with an *acid*. Thus, in the prevailing **transition state** one may explicitly observe that the ***'migrating moiety'*** invariably remain firmly attached to the respectively ***first*** **(*i.e.*, α–) and** ***second*** **(*i.e.*, β–) C-atoms at a time.**

(*b*) ***The Influence of Migratory Aptitude*****:** In certain reactions especially the **pinacol rearrangements**, the molecule itself may comprise ***many*** **functional moieties** which, ***geometrically*** at least, do possess nearly ***equal chances of migrating;*** and hence, these reactions have often been employed for the direct study of ***relative*** **migratory aptitudes**. Interestingly, in the particular **pinacol rearrangement** one may face with the additional question of which **hydroxyl (OH)** leaves and which does not, because a specific moiety may actually migrate only if the **hydroxyl (OH) moiety** located on the other **C-atom is lost**.

* Curtin Dy and Crew MC, *J Am Chem Soc.*, **76:** 3719, 1954.

** Koptying and Shubin, *J Org Chem.*, USSR, **16**: 1685-1714, 1980.

In general, the overall **migratory aptitude** is guided by the following observed dictum:

$$\boxed{\text{H} > \text{Aryl} > \text{Alkyl}}$$

Comments: It may be observed that virtually each and every step in the **pinacol rearrangement** is ***reversible potentially***.

Points to Ponder: These essentially include:

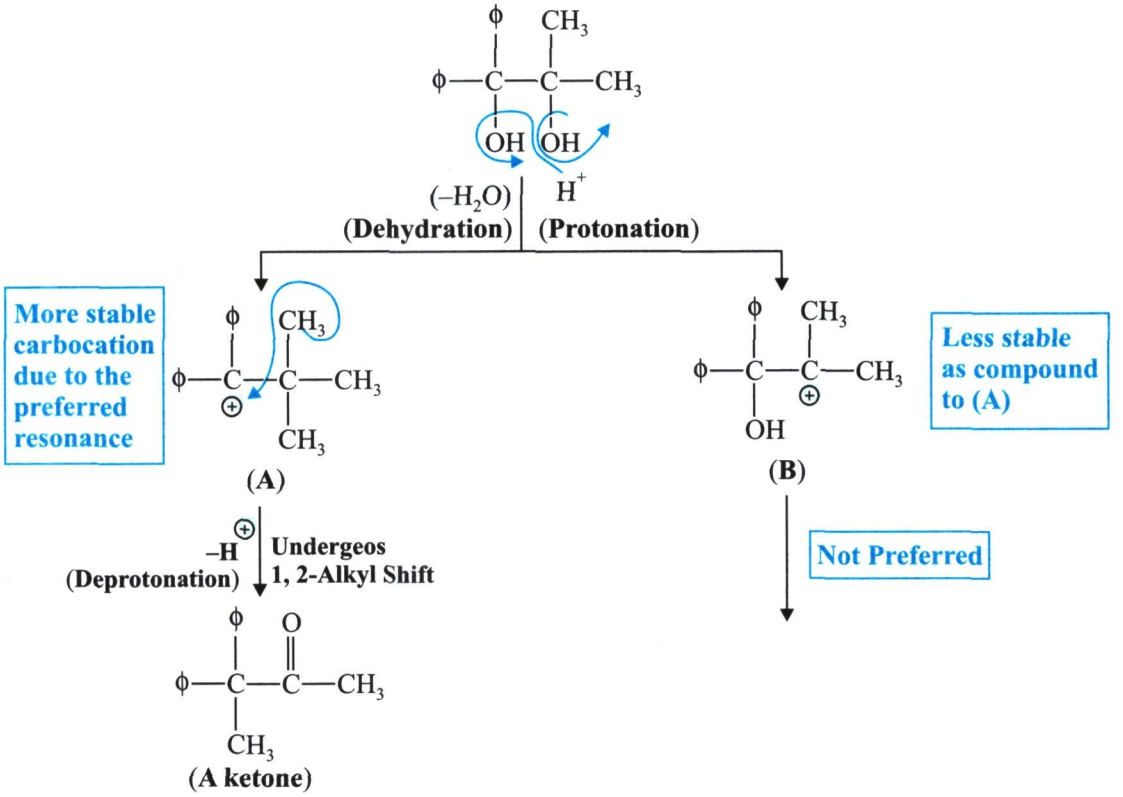
1. Importantly, the **migrating moiety** migrates with an *electron pair*; and hence, the ***more* nucleophilic moiety** invariably migrates, whereas, the **electron-withdrawing group (EWG)** would slow down the reaction significantly.
2. The *inherent* **migratory aptitude against**:
   - **Aryl Moieties:** is as given under–

$$\boxed{p\text{-Anisyl} > p\text{-Tolyl} > p\text{-Phenyl} > p\text{-Chlorophemyl}}$$

   - **Alkyl Moieties:** is as stated below–

$$\boxed{(CH_3)_3C- > (CH_3)_2CH- > CH_3-CH_2-}$$

Nevertheless, it may also be observed that the ensuing stability of the ***first*** **generated 'carbocation'** might also compensate articulately the—**'migratory aptitude order'**. Amazingly, the aforesaid statements of facts may be duly evidenced by the following **classical illustration**:

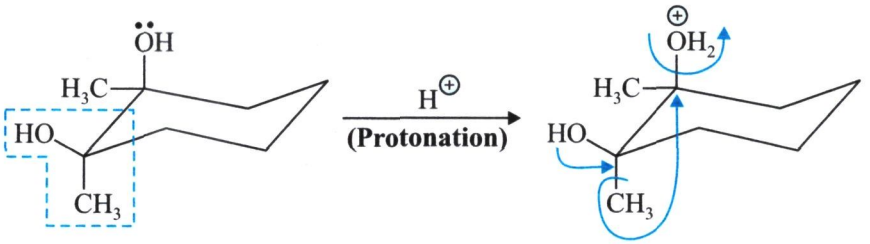


OBSERVATION

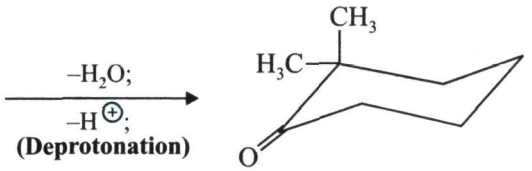
The critical migration of **methyl (CH_3) moiety** instead of the **phenyl ($-C_6H_5$) moiety** is observed to be a ***clear contradiction*** to the **above cited order**.

(*c*) ***The Steric Hindrance:*** It relates to **'the spatial arrangement of the atoms or groups at or in the vicinity of the *reacting site* of a molecule either *retards* or *hinders* a normal reaction'.**

Based on the above idea and concept the rate of **1, 2-alkyl shift** is duly affected by the aid of ***steric hindrance***. Perhaps by virtue of the underlying logistic reasonings we may predominantly take cognizance of the fact that the ***cyclic structures*** invariably do indulge in the **preferred back side attack** of the ensuing ***migratory moiety*** to the so-called **'leaving group'**, as illustrated below:

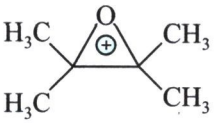


A Cyclic diol



A Cyclic ketone

(*d*) ***Epoxide Formation*:** In this particular instance, the **pinacol rearrangement** (or *reaction*) involves specifically the crucial generation of an ***'epoxide intermediate'*** thereby suggesting vehemently the so-called **'intramolecular nature'** of the said rearrangement.



An 'Epoxide'

(*e*) ***Product Stability Profile*:** In a broader perspective, the prevailing **product stability profile** virtually modulates the overall outcome of the various ***competing rearrangements***. Importantly, the following *sequel of reactions* do exhibit:

- **the effect of *thermodynamics*,** and
- **the effect of *kinetics*,**

most preferentially upon the ultimate **product formation**. Thus, we may have the following expression:

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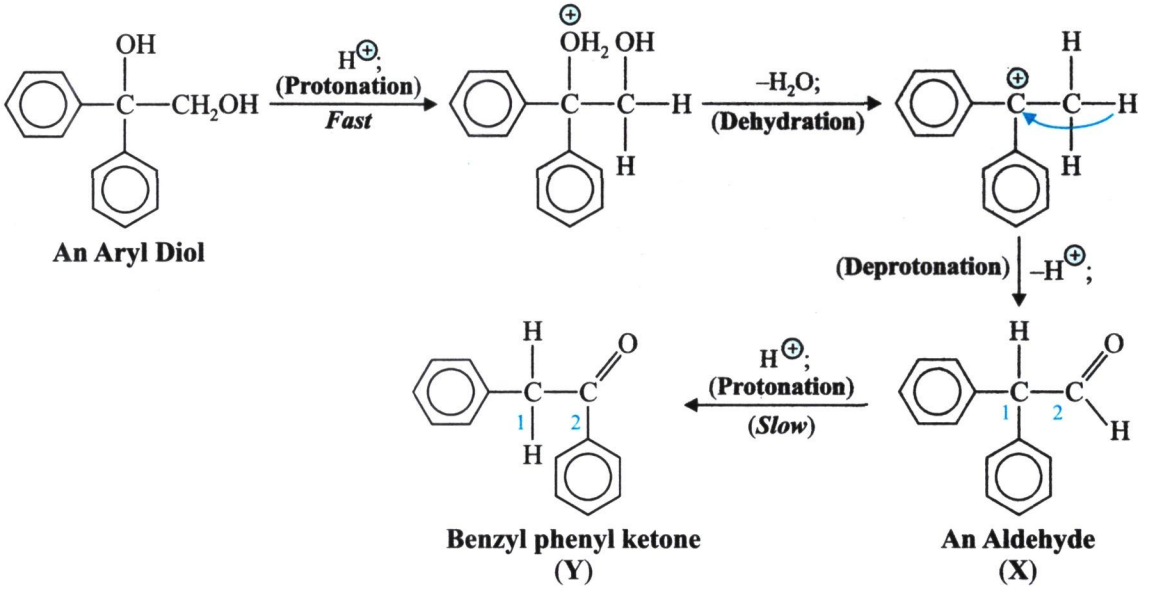
* The **methyl (CH_3) and hydroxyl (OH) moieties** are having a ***trans*-configuration** in the **cyclic diol [C]**.



Comments: Starting from an **aryl diol** *via* a sequel of reactions: *protonation-dehydration—deprotonation-protonation,* the last but one **end-product (X)** (an *aldehyde*) affords a typical migration of **one phenyl moiety** from from the **α-C-atom** to the respective **β-C-atom** to yield product **(Y)** which is a **ketone.**

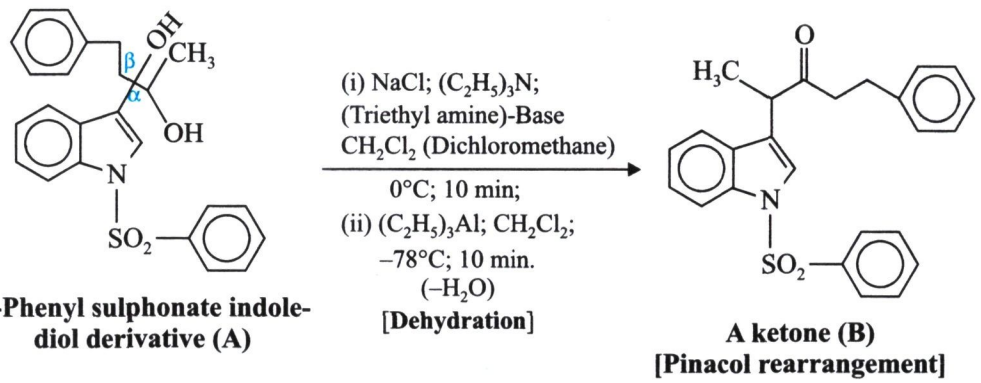
(f) **The Influence of Reaction Parameters:** It has been duly proven and ascertained that under a **mild acidic-environment** the ensuing **'diol'** gets itself meticulously rearranged to give rise to the formation of an ***aldehyde*** **(—CHO)** due to the so-called **1, 2-hydrogen shift** in the initially generated **diphenyl *tert*-carbocation**. However, a definite *more vigorous* **acidic environment** applied specifically to either:

- **Diol,** or • **Aldehyde,**

does result into the formation of relatively:

"more stable *phenyl ketone* due to the enhanced conjugation phenomenon of *carbonyl* ($>C=O$) and *phenyl* ($—C_6H_5$) *moieties*".

Example:



Thus, the starting material **(A)** undergoes meticulous rearrangement to form a **ketone (B)** due to the **1,2-Hydrogen shift,** thereby losing a mole of water.

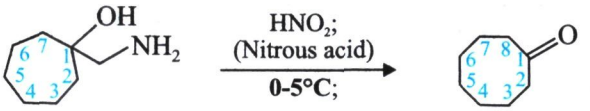
Comments: In the aforesaid *organic reaction* one may obviously understand the glaring influence of the **reaction parameters** that are not only highly specific but also extremely critical (*viz.*, *– 78°C* and use of *triethyl aluminium [$(C_2H_5)_3Al$] in dichloromethane (CH_2Cl_2).*

12.2.2 Tiffeneau-Demjanov Rearrangement*

It relates to the rearrangement of **β-amino alcohols** on being subjected to *diazotization* with nitrous acid (HNO_2) to yield the corresponding **carbonyl (>C=O) chemical entities** (*compounds*). Importantly, the so-called **cyclic alcohols** usually undergo predominantly either:

- **ring expansion,** or
- **contracted products.**

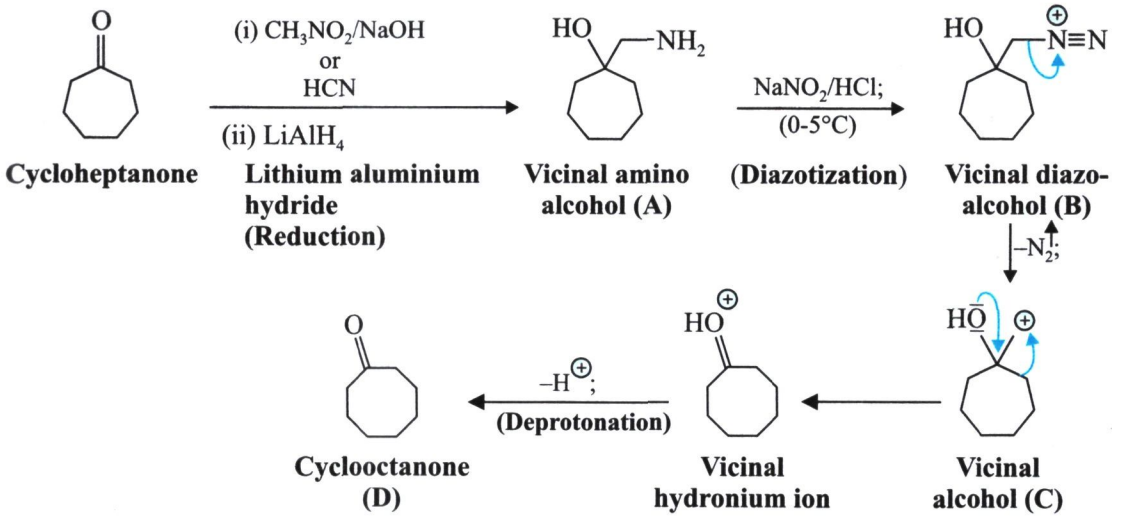
Thus, we may have the following expression:



Vicinal amino alcohol [7-membered-amino cyclic alcohol — **Cyclo octanone [8-membered-cyclic ketone**

Thus, a *ring expansion* from **7-to 8-member cyclic** structure has come into being due to the **TD-rearrangement.**

Mechanism of Tiffeneau-Demjanov Rearrangement: The exact mechanism of **TD-rearrangement** by means of the following *five* sequential step reactions starting from **'cycloheptanone'**:



Cycloheptanone — **Lithium aluminium hydride (Reduction)** — **Vicinal amino alcohol (A)** — **(Diazotization)** — **Vicinal diazo-alcohol (B)** — **Vicinal alcohol (C)** — **Vicinal hydronium ion** — **Cyclooctanone (D)**

* Tiffeneau M *et. al. Compt Rend.*, **205**: 54, 1937.

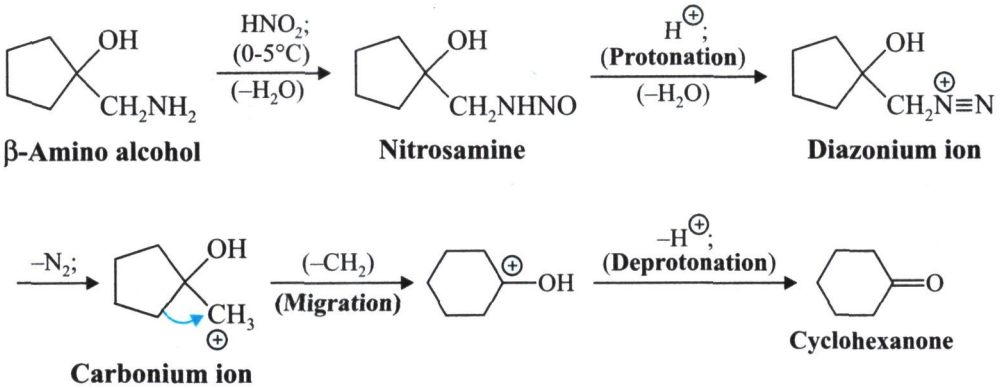
Explanations

The various steps involved in the above **TD-rearrangement** may be explained as under:

1. A nitrogen-containing C-1 nucleophile is added to the *substrate ketone i.e.*, **cycloheptanone**. The **nucleophile** is either **HCN** or **nitromethane(CH_3NO_2);** and hence, the addition usually gives a **cyanohydrin** or a **β-nitroalcohol** respectively.
2. Both these aforesaid compounds may be subsequently reduced with *lithium aluminium hydride* **($LiAlH_4$)** to the respective **vicinal amino alcohol (A)**.
3. The **Tiffeanau-Danjanov rearrangement** of the **amino alcohol (A)** is now initiated by *diazotization** (at 0-5°C) of the ***free*** **amino moiety** to obtain **vicinal diazonium alcohol (B)**.
4. **Product (B)** loses a *mole of nitrogen (N_2^+)* to yield **vicinal alcohol (C)**, which ultimately gives the desired **cyclooctanone (D)** *via* the formation of *vicinal hydronium ion* and its **deprotonation**.

Tiffeneau-Demjanov Rearrangement in Expansion of Ring System

Importantly, the **TD-rearrangement** may also be exploited intelligently in the expansion of a **5-membered cyclic ring** to a **6-membered cyclic ring,** as detailed under:



Explanations

1. **β-Amino alcohol** on treatment with nitrous acid (at 0-5°C) loses a mole of water to yield **nitrosamine,** which on *protonation* eliminates a mole of water again to give the **diazonium ion**.
2. The resulting product loses a mole of **nitrogen (N_2)** to produce a **carbonium ion,** which on *migration of a methylene residue* gives a **protonated cyclohexanol**.
3. Finally, the deprotonation of the above product yields a ***six-membered*** **cyclohexanons**.**

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* The **diazotization** is duly accomplished either with *$NaNO_2$ in aq. acid* or with **isoamyl nitrite** in the *absence of acid* and *water*.

** Hesse M: **Ring Enlargement in Organic Chemistry,** VCH, Weinheim, 1991.

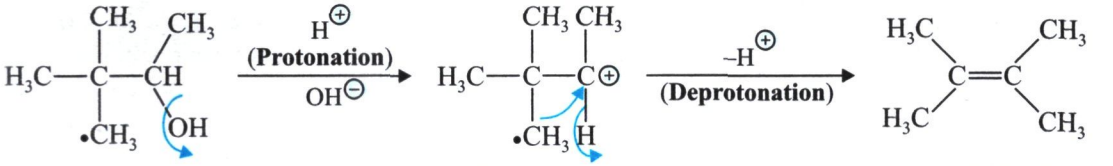
12.2.3 Wagner-Meerwein Rearrangement*

Importantly, when the **alcohols** (or **carbinols**) are duly made to react with **acids** either:

- **simple substitution,** or
- **elimination,**

invariably accounts for *most or all the products* perceptively. Nevertheless, in several instances, specifically where either ***two* or *three* alkyl or aryl moleities** are located strategically on the ***β-C-atom,*** a few or all of the products gets **rearranged** squarely. Thus, these ensuing rearrangements are usually termed as **Wagner-Meerwein rearrangements**.

Let us look into the following sequential reactions:

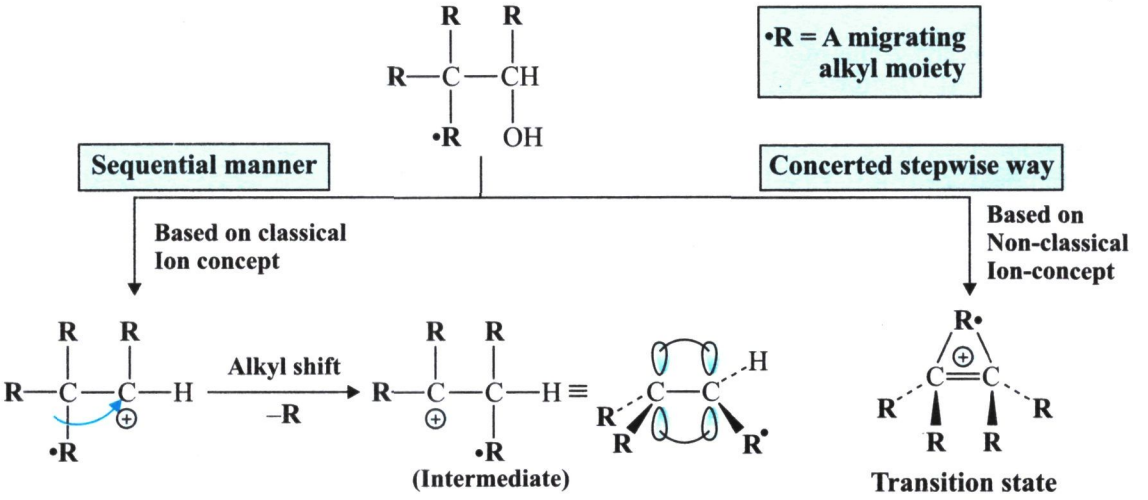


Methyl *tert*-butyl carbinol **Carbonium ion** **Tetra-methyl ethylene**

Thus, the **methyl-*tert*-butyl carbinol** on being subjected to *protonation* yields a **carbonium ion** specie, which undergoes the so-called **skeletal rearrangements** to the corresponding ***nucleophilic-1, 2-migrations of the alkyl groups***** from an **α-C-atom** to the respective **carbonium ion site** either:

- **in a sequential manner,** or
- **in a concerted stepwise way,**

as stated under***:



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* Wagner G: *J Russ Phys Chem Soc.*, **31**: 690, 1899, Meerwein H: *Ann.*, **405**: 129, 1914.

** Meerwein H and Unkel W: *Justus Liebigs Ann Chem*, **376**: 152-165, 1910, Hogeveen H *et. al.*: *Top Curr. Chem.*, **80**: 89-124, 1979.

*** Bartlett PD: **Non-Classical Ions.**, Benjamin, Menlo Park, (California), 1966.

Remarks: Based on the above **nucleophilic-1,2-migrations of the alkyl groups** in a sequential manner (*i.e., due to the classical ion concept*) we may ultimately take cognizance of the fact that the **Wagner-Meerwein rearrangement** is nothing but the reverse of **pinacol rearrangement** (see section: 2.1), and therefore, the **WM-rearrangement** is also known as the—***'Retrograde Pinacol Rearrangement.***

Important Observations

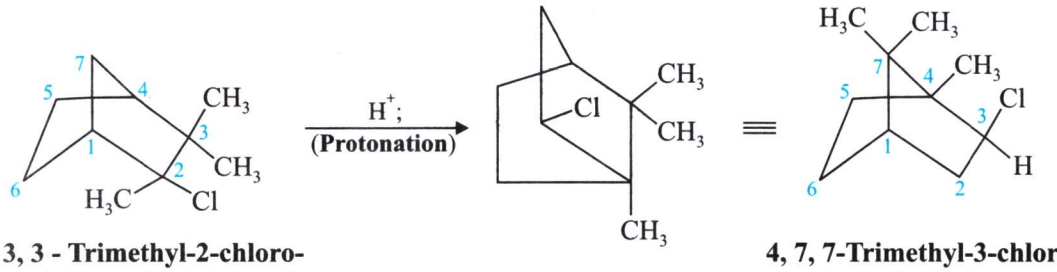
These essentially comprise:

1. The *stereochemical aspect* pertaining to the respective **1,2-alkyl shift** is dependent solely upon the **relative departure time** of the ***actual leaving moiety***. In other words, if **R$^{\bullet}$** gets duly migrated well before the departure of the respective **alkyl groups**, an ***inversion in configuration*** takes place precisely at the **'C' = terminus** is observed explicitly.
2. Nevertheless, the **leaving alkyl group** if gets departed *first*, the critical formation of the *carbonium ion* comes into being whereby the respective migration of the ***alkyl moiety*** right from C-1 to C-2 occurs, which eventually results into the phenomenon of ***racemization***.*

❑ **Wagner-Meerwein Rearrangement: Limited Synthetic Advantages**

Let us consider the following classical examples:

(*a*) **Conversion of [A] into [B] *via* Protonation** (***see below***)

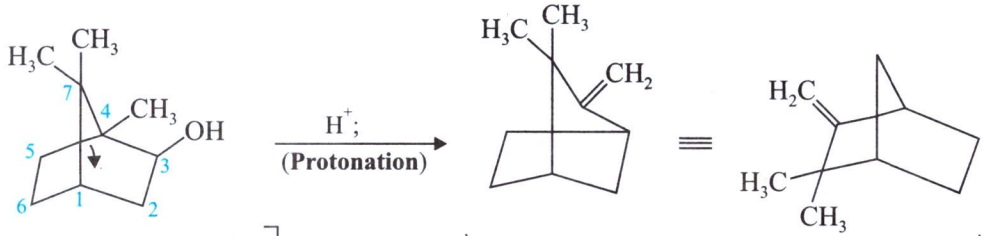


2, 3, 3 - Trimethyl-2-chloro-*bis* cyclo [2, 2, 1] - hepton (A)

4, 7, 7-Trimethyl-3-chloro *bis* cyclo [2, 2, 1] - hepton (B)

Comments: In fact, the *original example* is taken to be the *acid-catalyzed rearrangement of* **camphene hydrochloride to isobornyl chloride.**

(*b*) **Conversion of Isoborneol to Camphene**



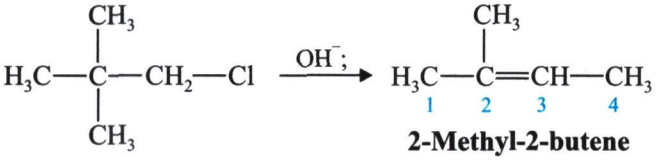
Isoborneol
4, 7, 7-Trimethyl *bis* cyclo-[2, 2, 1] heptan-3-ol

Camphene

* **Racemization:** It essentially involves the generation of an admixture of *two* distinct products: *One* having the **inverted configuration;** whereas, the other is with the **retended configuration.**

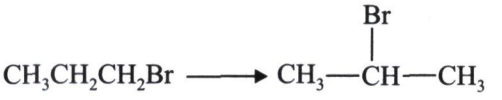
Examples of Simpler Systems: are depicted as under:

(*i*) **Conversion of *tert*-Butyl methane chloride to 2-Methyl-2-Butene**



***tert*-Butyl methyl chloride** **2-Methyl-2-butene**

(*ii*) **Conversion of Propyl bromide to 2-Promo propane**



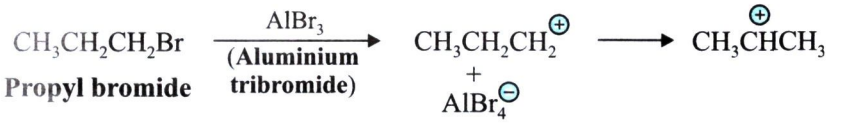
Propyl bromide **2-Bromo propane**

EXPLANATIONS

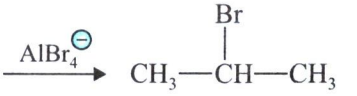
The above glaring examples illustrate explicitly the following points:

1. From the **example (*ii*)** it may be observed particularly that the **hydride ion ($H^{\ominus}$) can migrate** *i.e.,* in reality it was the **hydride ion ($H^{\ominus}$) which gotten shifted eventually and not the bromine:**

   Thus, we may have the following expression:



Propyl bromide **Aluminium bromide anion** **Carbonium ion**



2-Bromo propane

2. Besides, the *leaving moiety* need not be water (H_2O) mole, but could be any **leaving species** whose loss generates a **carbocation** (or *carbonium ion*) *i.e.,* including $\mathbf{N_2^{\oplus}}$ derived from **aliphatic diazonium ions***.
3. **Example (*ii*)** vividly illustrates that the ***last step*** may be actually *substitution* instead of *elimination* phenomenon.
4. **Example (*i*)** depicts explicitly that the new olefinic bond **(double bond)** is formed duly with the **Zaitsev's Rule****.

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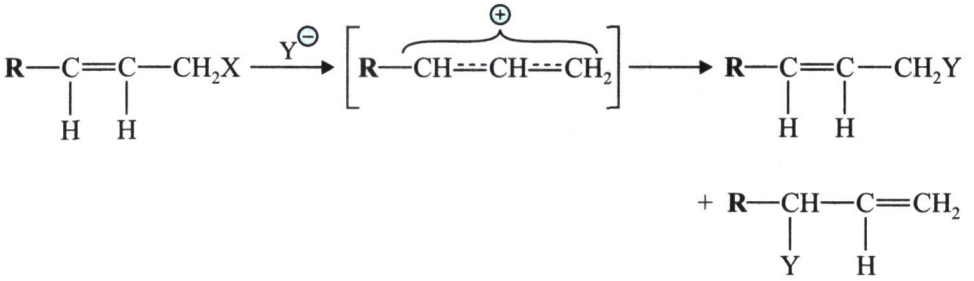
* **Patai: The Chemistry of the Amino Group,** Wiley, New York, 1968.

** **Zaitsev's Rule:** According to this rule the **double bond goes mainly towards the most highly substituted C-atom.**

12.2.4 Allylic Rearrangements*

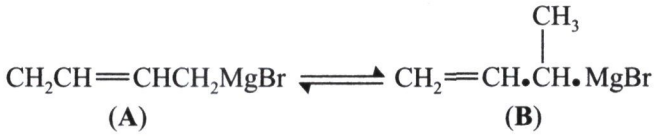
The **allylic rearrangement** deals with the *migration of a C-C double bond* critically in a **3-Carbon (allylic) system** on being subjected to the treatment with **nucleophiles** under the **S_N1 conditionalities** (or even under **S_N^2 parameters** whenever the ***nucleophilic attack*** comes into play at the **γ-C atom**).

Thus, we may have the following sequential reaction:



In other words, due to the **prevailing resonance, the allylic system is quite prone to rearrangement.** Interestingly, the so-called **allylic rearrangement** is established to be quite common in the ***allyl-based*** **Grignard reagents.****

Example: **Conversion of 2-Butenyl magnesium bromide (A) into 1-Methyl-propenyl magnesium bromide (B),**—as given under:



Remarks: Importantly, in the **allylic rearrangement** it may be noted clearly that the **olefin bond** (*double bond*) present in the **allyl chemical entity** invariably gets shifted to the *next* **C-atom** predominantly. However, it may also be observed that in the ***nucleophilic substitution*** the ensuing arrnagement would proceed either:

- ***via*** **the S_N1 mechanism;** or
- ***via*** **the S_N2 mechanism.**

S_N1-Mechanism: It normally comes into play critically *via* the **carbocation (an intermediate)** that may be eventually stabilized by **resonance** exclusively. In addition, the **S_N1 mechanism** occurring in the **allylic chemical entities** (*compounds*) usually gives rise to the formation of ***two*** **distinct products,** namely:

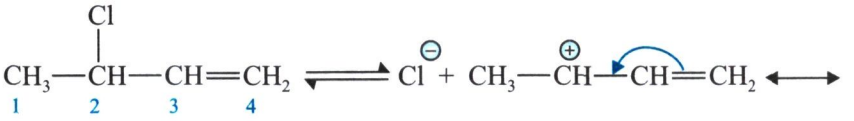
- ***first*—the normal product;** and
- ***second*—the rearranged product.**

Hence, such a **S_N1-mechanism** is normally designated as **S_N1'**.

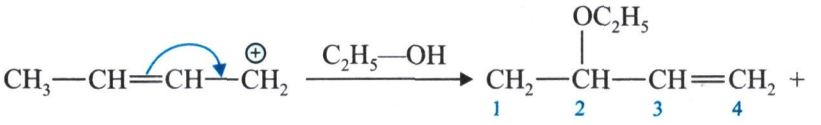
* Claisen L: *Ber.*, **45**: 3157, 1912.

** Utsugi *et. al.*: *Org. Lett.*, **8** (14): 3973-3976, 2006.

Thus, we may have the following expressions:



2-Chloro-3-butene



Carbonium ion **2-Ethoxy-3-butene [Normal product]**



4-Ethoxy-2-butene [Rearranged product]

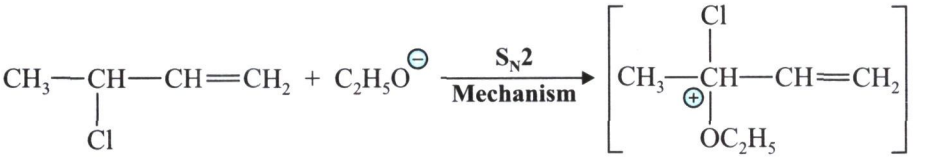
Comments: Starting from **2-chloro-3-butene** *via two* reversible steps obtained a **carbonium ion,** which on treatment with **ethanol** yielded *two* distinct products *viz.,* one mole each of **'Normal'** and **'Rearranged'** products.

S_N2-Mechanism: It essentially involves the so-called **direct attack** of the ensuing *nucleophile* at the **allylic position** prominently.

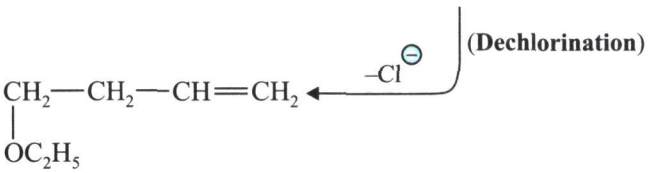
EXAMPLE: Following are the *two* typical examples:

❑ **Reaction of 2-chloro-3-butene in the presence of sodium ethoxide (EtO^-) and ethanol (EtOH) gives only one product (*i.e.,* 1-ethoxy-3-butene):**

Thus, we may look at the following reaction:



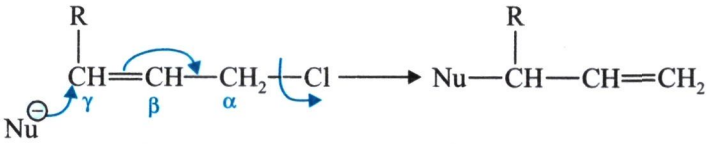
2-Chloro-3-butene **[Intermediate] T.S.**



1-Ethoxy-3-Butene

❑ **S_N2-reaction usually undergoes an *allylic rearrangement* generating thereby a *rearranged product* by the attack of a nucleophile upon the unsaturated *γ-C atom* rather than the *γ-C atom*.**

Let us look at the following expression:



Suggested Reading

Hesse M: **Ring Enlargement in Organic Chemistry,** VCH, Washington, 1991.

Zollinger H: **AZO and Diazo Chemistry: Aliphatic and Aromatic Compounds,** (*English Translation*), Interscience Publishers, Inc., New York 1961.

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Bruckner R: **Advanced Organic Chemistry,** Harcourt Academic Press, New York, 2002.

March J: **Advanced Organic Chemistry,** 4th ed., John Wiley & Sons, New York 2001.

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Chapter 13

Rearrangements Related to Electron Deficient Heteroatoms

LESSONS AT A GLANCE

13.1 Introduction

13.2 Rearrangements Related to Electron Deficient Heteroatom

13.2.1 Rearrangement Related to Electron Deficient Cationic Oxygen

13.2.2 Rearrangement Related to Electron Deficient Cationic Nitrogen

13.1 INTRODUCTION

Rearrangement: The term is being used to describe *two* altogether divergent types of **organic chemical reactions**, namely:

- **Molecular Rearrangement:** Which may critically involve the ***one-step*** **migration of an H-atom** or of a relatively **bigger molecular fragment** located strategically very much within a definitely short-lived intermediate.
- **Molecular Rearrangement:** That may be intimately engaged in a ***multistep reaction*** which crucially involves the actual **migration of an H-atom** or of a ***bigger molecular fragment*** as one of the major steps.

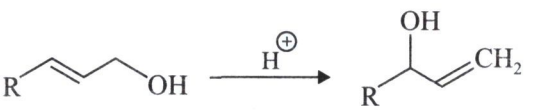
Rearrangements: Another school of thought relates these reactions with the prevailing typical:

'bond connectivity occurring within the molecule changes to yield an altogether divergent chemical entity (compound) having the same molecular formula'.

In actual practice, this kind of a change in the ***'bond connectivity'*** invariably comes into play by virtue of the migration of an *atom* or a *group* from one **specific location** to a **new location** very much within the same molecule. Thus, explicitly such a *migration of an atom or group* usually occur within the same molecule in so-called **intramolecular processes** or may involve altogether *two different molecules* belonging to the same species is termed as **intermolecular processes**.

Example: Following are *two* classical examples to expatiate the above *two* **phenomena**:

(*a*) **Allylic Rearrangement**



(*b*) **Wagner-Meerwein Rearrangement**



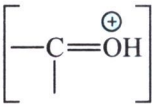
13.2 REARRANGEMENTS RELATED TO ELECTRON DEFICIENT HETEROATOM

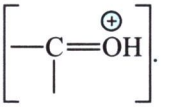
A survey of literature would reveal that the **rearrangements related to electron deficient heteroatoms** may be categorized into the following *two* heads, namely:

- **Rearrangements Related to Electron Deficient Cationic Oxygen,** and
- **Rearrangement Related to Electron Deficient Cationic Nitrogen,**

which shall now be discussed separately at length in the sections that follows:

13.2.1 Rearrangement Related to Electron Deficient Cationic Oxygen

Preamble: The interaction taking place with *the alcohols* or *ethers* and the **strong acid** (mineral acids), their **divalent oxygen atom** get duly protonated to give rise to the formation of the respective—'***tricoordinate oxonium ion***  that may not be quite appropriate as a *rearrangement terminus* since it fails to serve as the desired or perspective **'electron deficient site'** perhaps due to the ***complete valence shell octet***.

Therefore, in order to justify fully the aforesaid rearrangement profile the so-called **tricoordinate oxygen** has got to be converted into an **'oxacation'** (*i.e.*, an **uncoordinate form**)—which may ultimately get duly converted into a rather **more stable *carbonium ion***  .

In the present context, we may look into the following ***two*** **name reactions** in an elaborated manner, namely:

- **Baeyer–Villiger Oxidation,** and
- **Dakin Rearrangement**

13.2.1.1 Baeyer-Villiger Oxidation [Baeyer-Villiger Rearrangements]

The **Baeyer-Villiger rearrangement** is often called the **Baeyer-Villiger oxidation**. In the **Baeyer-Villiger rearrangement** a **carboxyl (>C=O) compound** (***ketones*** being always employed) and an ***aromatic*** **peracid** (*viz.*, **monoperoxophthalate**) to yield the respective ***esters*** *via* the insertion of the **'peroxo-O atom'** located adjacent to the carbonyl (>C=O) bond of the **carbonyl compound.**

Example: **The Baeyer-Villiger rearrangement of the *cyclic* ketones** results in the formation of **lactones,** as depicted in Fig. 13.1.

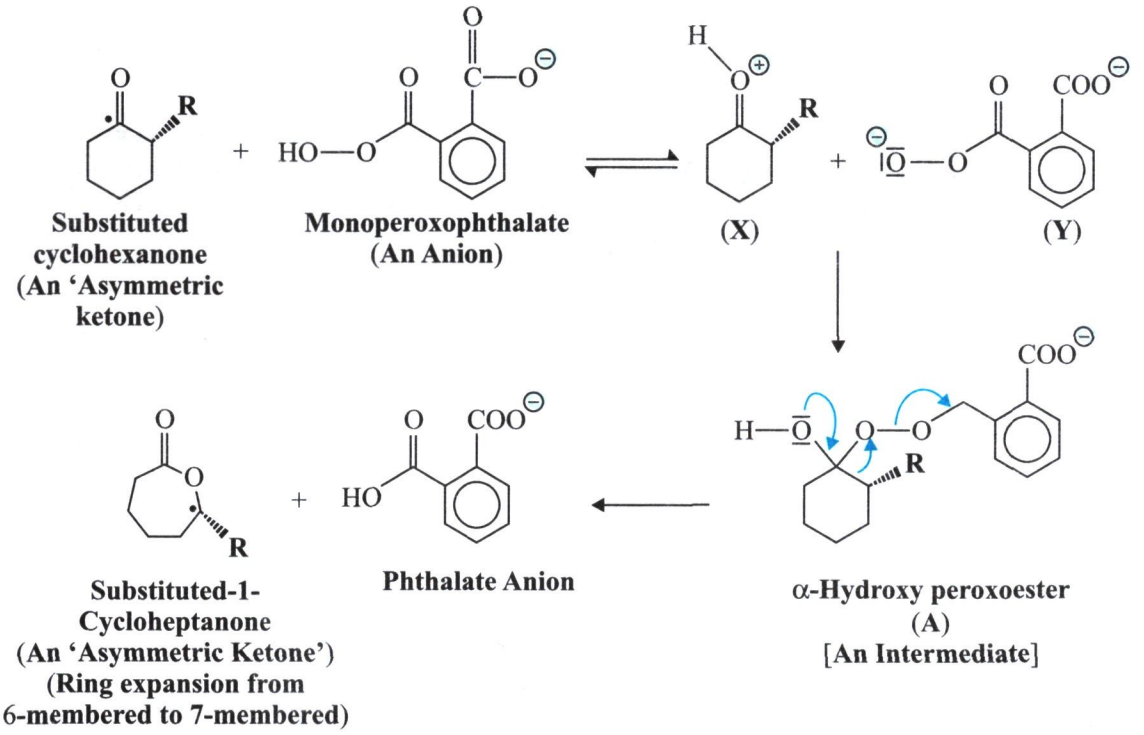


Fig. 13.1: The Regioselective and Stereoselective Baeyer-Villiger Rearrangement of an Asymmetric Ketone with Magnesium Monoperoxophthalate Hexahydrate.

EXPLANATIONS

1. The **BV-rearrangement** of an **asymmetric ketone** with **magnesium (Mg) monoperoxophthalate hexahydrate*** entails a reversible reaction to yield *two* products *e.g.*, a protonated-substituted cyclohexanone **(X)** and a monoperoxophthalate dianion **(Y)**.

2. The resulting product *via* the **regioselective and stereoselective BV-rearrangement** gives rise to the formation of **α-hydroxyperoxaester (A)**.

Mechanism: The O—O bond of **(A)** is found to be labile in nature; and hence, undergoes eleavage even without *prior protonation* of the **leaving moiety**. Obviously, it is definitely different from the fate of the **O—O bond** of a *hydroperoxide* that fails to undergo **cleavage unless it is protonated**.

However, the observed different behavioural pattern is perhaps based on the fact that the **BV-rearrangement** critically releases the ***Mg-phthalate,*** and, that this **anion** is found to be **fairly stable**.

Comments: It may be added that the so-called cleavage of a **'hydroperoxide'** in the absolute absence of an *acid* would ultimately result in the much more basic; and hence, much less stable **hydroxide ion (OH^-)**.

* In the above *drawing* Mg^{2+} is omitted knowingly to maintain **clarity**.

3. The O—O bond eleavage of the **α-hydroxyperoxoester (A)** intermediate of a **BV-rearrangement** is usually accompanied by a **[1,2]-rearrangement**. Thus, one of the ***two*** **substituents** of *the former* **carbonyl (>C=O) moieties migrates**.

4. In Fig. 13.1 either a ***pri*-or a *sec*-alkyl moiety** in principle could undergo migration. As in the particular instance of the **Wagner-Meerwein rearrangement,** the so-called inherent **intrinsic propensity towards migration** in the **BV-rearrangements** follows the following order:

$$R_{tert} > R_{sec} > R_{pri}$$

5. Therefore the ***sec*-alkyl moiety** migrates solely in the **intermediate (A)**. It certainly migrates with **complete retention of the configuration**.

NOTE: **Interestingly, in the substrate of the BV-rearrangement of [Fig. 13.1] is indeed an *enantiometrically pure ketone*.**

Special Remarks: Following are the ***three*** **special remarks** pertaining to the **Baeyer-Villiger reaction,** namely:

1. It is regarded to be an **acid-catalyzed reaction;** and, therefore, solely depends upon the in-built strength of the so-called:

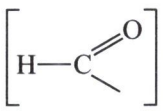
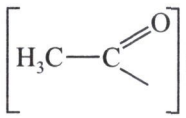
- ***electron-releasing (ER) moieties:*** present in **'ketone'**; and
- ***electron-withdrawing (EW) moieties:*** present in **'peracids'**.

2. In **compound (X)** [Fig. 13.1] and in the subsequent steps, [Ar—CO—$O^{\ominus}$] **compound (Y)**—the ensuing ***dihedral angle*** must be of 180° which eventually lowers the interaction taking place between the following *two* segments, such as:

- **Ar—C σ (sigma) bond;** and
- **antibonding O—O σ (antibonding sigma) bond**

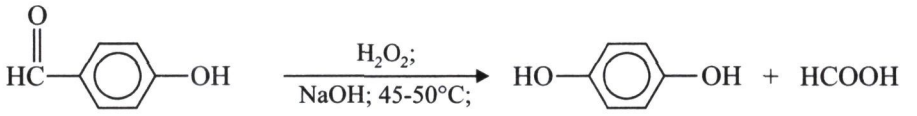
3. Importantly, the **BV-Oxidation reactions** are found to be ***stereospecific* in nature** and is duly substantiated by the presence of a **'*chiral* C-atom'** located in the aryl moiety thereby resulting in the-**'absolute retention of stereochemistry of the reaction'***.

13.2.1.2 Dakin Rearrangement** [or Dakin Reaction]

The **Dakin rearrangement** (or **Dakin Reaction**) relates to the replacement of either the formyl  or **acetyl**  moieties in **phenolic aldehydes** or **ketones** by a *hydroxyl (—OH) group* by means of *hydrogen peroxide* (H_2O_2), as depicted under:

* Crudden CM *et. al.*: *Agnew Chem Int. Ed.,* **30** (16): 2851-2866, 2000.

** Dakin HD: *Am Chem. J.,* **42**: 477, 1909.



***p*-Hydroxy benzaldehyde** **1, 4-Dihydroxy benzene** **[Formic acid]**

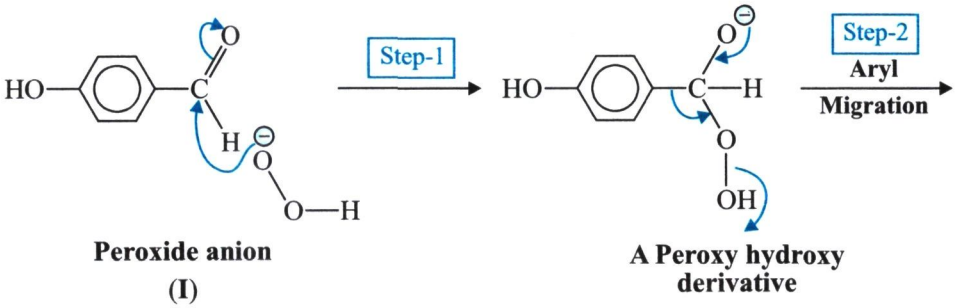
Leaffler (1949)* reported that the underlying condition for the **Dakin reaction** is the critical presence of either:

➢ **a hydroxy (—OH) group,** or ➢ **an amino ($—NH_2$) group,**

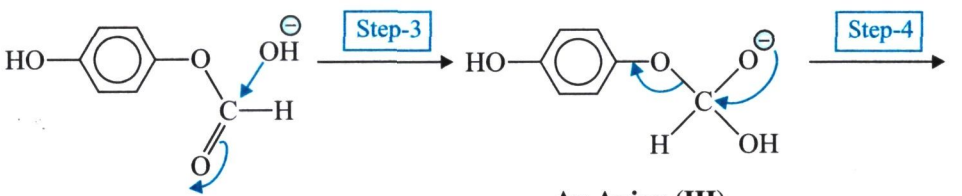
positioned strategically at ***ortho*-or *para*-position**.

Mechanism of Dakin Rearrangement

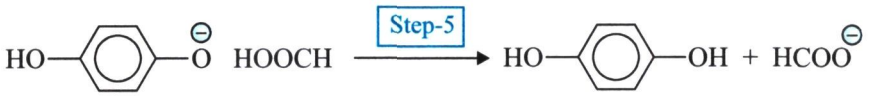
The probable mechanism of **Dakin rearrangement** may be depicted by the following ***five* sequential steps**, starting from ***para*-hydroxy-benzaldehyde (I)**, as given below:



Peroxide anion (I) **A Peroxy hydroxy derivative**



***p*-Hydroxy-peroxy benzaldehyde (II)** **An Anion (III)**



***p*-Hydroxy-phenolate anion (IV)** **Formic acid** **1, 4-Dihydroxy benzene (V)** **Formyl ion**

* Leaffler JE: *Chem Rev.*, **45**: 385, 1949.

EXPLANATIONS

1. **Step-1** shows the interaction between ***p*-hydroxy benzaldehyde (I)** and the **peroxide anion** to yield the **peroxy hydroxy derivative,** which in **step-2** affords an *aryl migration* to give ***p*-hydroxy peroxy benzaldehyde (II)**.
2. The resulting **product (II)** in **step 3** gives an **anion (III),** which in **step-4** yields the ***p*-hydroxy phenolate anion (IV)** plus a mole of *formic acid.*
3. In **step-5**, we obtain from **product (IV)** the desired product **1, 4-dihydroxy benzene (V)** plus the **formyl ion**.

NOTE: **Interestingly, we may observe a close similarity between the mechanism of *Dakin rearrangement* with the *Baeyer-Villiger rearrangement* (see section 2.2.1).**

13.2.2. Rearrangement Related to Electron Deficient Cationic Nitrogen

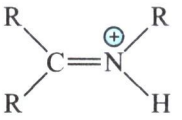
Preamble: In certain typical instances, it may be observed explicitly that in *some rearrangements* the so-called ***'migrating moiety'*** invariably:

- ➢ **migrates from an atom,** and
- ➢ **shifts along with its *bond pair of electrons* to the respective migration terminus,**

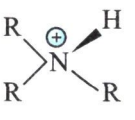
that is to the **'electron deficient nitrogen atom'**. Importantly, the **ammonium [$NH_4^{\oplus}$] cation** and the **iminium [$=\overset{\oplus}{N}H_4$] cation** do have a ***N-valence shell electron oetet;*** and, therefore, fails to serve as the **'migration terminus'**.

Nevertheless, the actual **rearrangement initiation** process essentially requires the *unfilled valence shell* present in the **nitrogen cation** *viz.*, **ammonium [$NH_4^{\oplus}$]** and **iminium [$=\overset{\oplus}{N}H_4$]**. Besides, the aforesaid rearrangement may also be accomplished with the help of a *neutral specie* having an **electron deficient N-atom** *viz.*, **nitrene** $\left[R—\ddot{N}:\right]$—a neutral entity.

Thus, we may have the following *three* common structures:



Iminium Ion



Ammonium Ion



Nitrene (Neutral)

Points to Ponder:

1. It is, however, pertinent to mention at this material time that the **molecular rearrangements** pertaining to the **electron deficient nitrogen** essentially involves a change *in the basic skeleton of the ensuing molecule* taking part in the **chemical reaction**.
2. In a broader perspective, the said **rearrangements** could be either within the *same chemical entity* **(molecules)**—usually known as the **Intramolecular Rearrangement,** or between ***two* molecules** *undergoing chemical reaction*—normally termed as the **Intermolecular Rearrangement**.

Intramolecular Rearrangements Involved in an Electron Deficient System: Electron Deficient N-Atom

Importantly, one may observe in the *same molecule*, the **migrating moiety** critically migrates along with its ***bonding electron-pair*** right from:

"the migration origin to the corresponding electron deficient *migration terminus*".

Obviously, such a phenomenon could be observed vividly in the following ***two*** **classical instances,** namely:

- **Beckmann Rearrangement,** and
- **Hoffmann Rearrangement,**

wherein these rearrangements usually come into play in the **'electron deficient system'** exclusively.

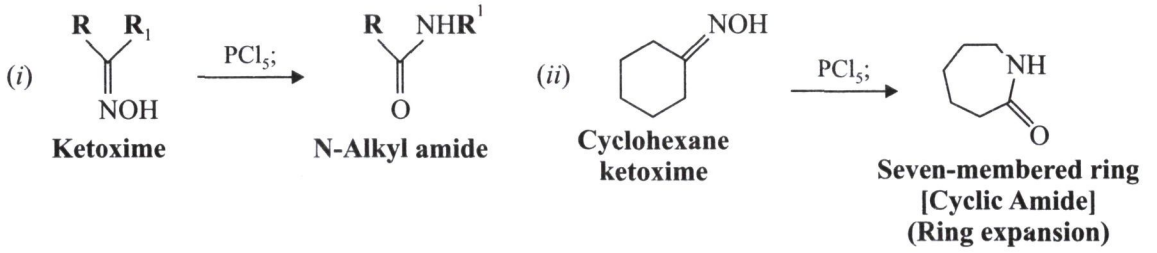
We would now discuss the following *five* **rearrangements** individually together with its mechanism wherever possible:

(*i*) **Beckmann Rearrangement,**
(*ii*) **Hoffmann Rearrangement,**
(*iii*) **Curtius Rearrangement,**
(*iv*) **Lossen Rearrangement,** and
(*v*) **Schmidt Rearrangement.**

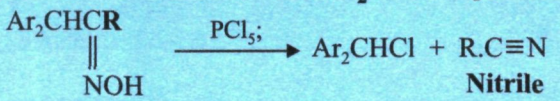
13.2.2.1 Beckmann Rearrangement

It is also known as the **Beckmann Fragmentation**. In reality, the **Beckmann rearrangement** relates, to the acid-mediated racemization of the **oximes to amides**. Thus, the ***oximes*** **of cyclic ketones** give rise to the formation of **ring enlargements** *viz.*, conversion of a **6-membered benzene ring** to a **seven-membered ring system**.

Thus, we may have the following expressions:



Special Remarks: There are certain **oximes,** specifically those possessing a **quaternary C-atom** *anti* to the *hydroxyl*, are most likely to undergo the **Beckmann fragmentation** to yield the **nitriles (—CN)** instead of the **amides (—$CONH_2$),**—as expressed under:



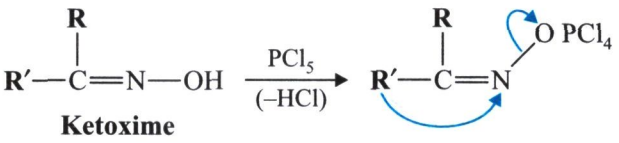
Further more, the **Beckmann rearrangement** can also be expatiated with the help of **ketoxime** wherein the **R′** and **R** represent the ***alkyl* or *aryl* moiety**. The widely used catalysts are as given below:

- **Sulphuric acid:** H_2SO_4;
- **Phosphorus pentoxide:** P_2O_5;
- **Phosphorus pentachloride:** PCl_5; and
- **Thionyl chloride:** $SOCl_2$.

What is the function of the 'Acidic Reagents'? The main function of the aforesaid **acidic reagents** (*viz.*, H_2SO_4, P_2O_5, PCl_5, or $SOCl_2$) is to affect the conversion of the **hydroxyl (OH) moiety** to a relatively better **leaving moiety,** for instance:

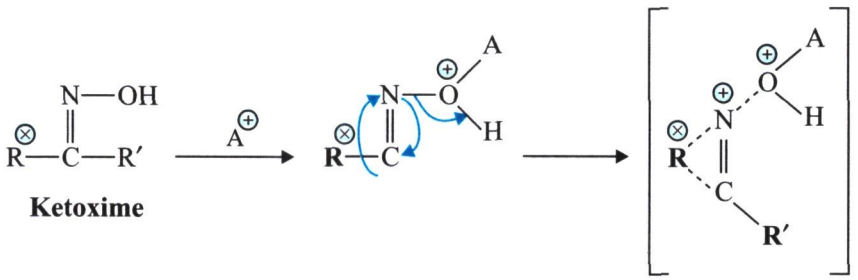
- **By using sulphuric acid (H_2SO_4)**—the *hydroxyl (OH) group* gets duly converted to H_2O; and
- **By using phosphorus pentachloride (PCl_5)**—the *phosphate (PO_4) group* is the leaving moiety.

Thus, we may have the following expression:

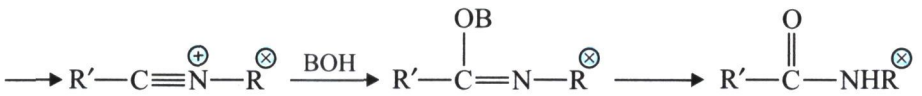


Ketoxime

General Observation of Beckmann Rearrangement: Chandin (1986)* observed that the **functional moiety located just opposite to that of the leaving moiety** shall migrate preferentially to the ***N-atom* in a perfect concerted manner,**—as given under:



Ketoxime **Intermediate**



Comments: From the above sequence of reactions it may be observed critically that **$R^{\otimes}$ attached duly to the C-atom in the 'ketoxime'** gets migrated to the respective **N-atom of the amide function**.

* Chandin JP: **Polymers in the Chemical Industry,** Eaton CE (Ed), B Packie and Son Ltd., London (UK) 1986.

Interconversion Between Stereoisomeric Forms '*syn*'–and '*anti*'—of Ketoxime Showing C-N Rotation.

Preamble: According to the ***Bronsted-Lowry Theory*:**

➢ **Acid—is a substance which can donate (or lose) a proton;** and

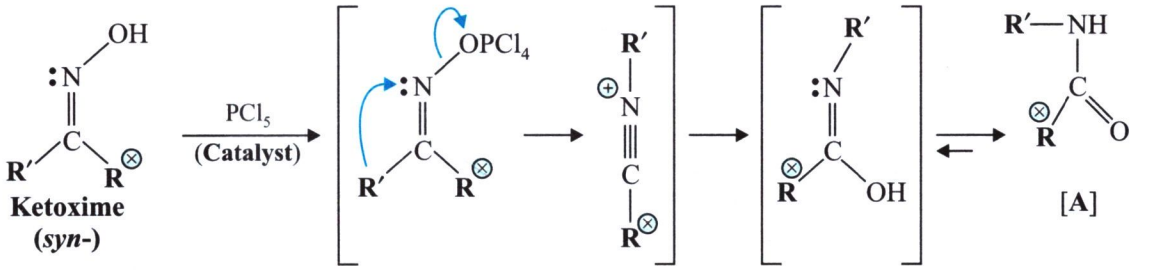
➢ **Base—is a substance that can accept (or remove) a proton.**

Therefore, using the Bronsted-Lowry acids, one may eventually obtain both:

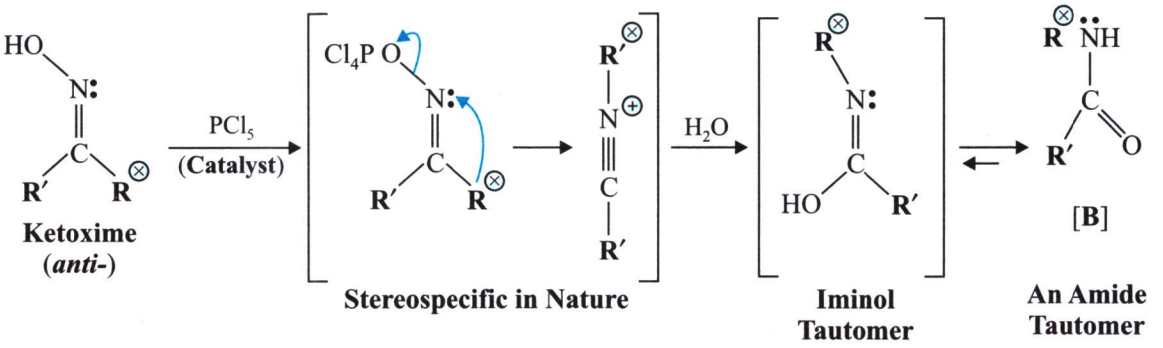
- **$R^{\otimes}$ CO—NHR′ (A),** and
- **R′ CO—NH$R^{\otimes}$ (B)**

The aforesaid ***analogy*** and ***conviction*** may be adequately substantiated by the critical observation pertaining to the interconversion between the so-called stereoisomeric forms **'*syn*'–and '*anti*'–of ketoxime** thereby *showing explicitly* the **C-N rotation** perceptively.

(*a*) **'*syn*'-Ketoxime**



(*b*) **'*anti*'-Ketoxime**



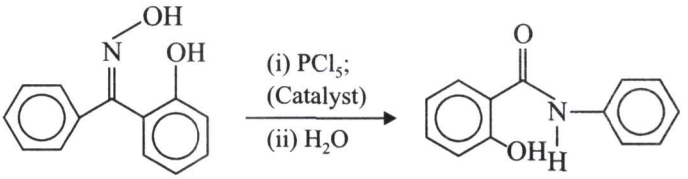
NOTE: **The stereospecificitycity nature for the migration of *R′ and* $R^{\otimes}$ explicitly shows the exclusive dependence of the *1,2-shift with the N—O cleavage* precisely.**

Stereospecificity of Beckmann Rearrangement: The exact and precise **stereospecificity of Beckmann rearrangement** may be expatiated by means of the following ***two*** **reactions** involving:

➢ ***syn-ortho*-Phenyl Oxime Phenol,** and

➢ ***anti-ortho*-Phenyl Oxime Phenol,**

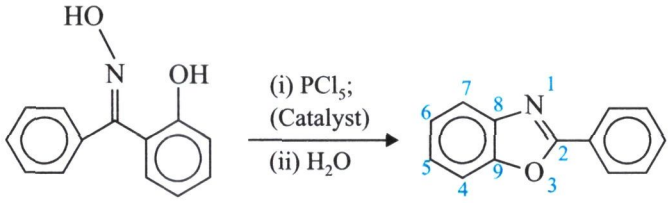
(*a*) ***syn-ortho*-Phenyl Oxime Phenol (A)**



[A]
syn-

***ortho-keto*-aniline phenol**

(*b*) ***anti-ortho*-Phenyl Oxime Phenol (B)**



[B]
anti-

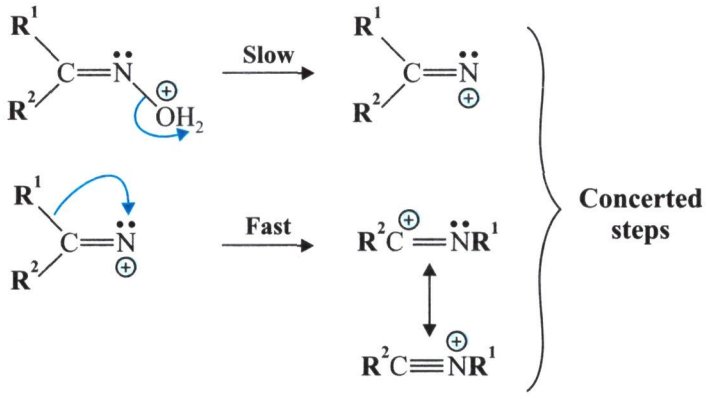
2-Phenyl benzoxazole

Remarks: It may be observed critically that the **1, 2-shift** of the ***ortho*-phenol substituents** is found to be definitely much faster *vis-a-vis* the **unsubstituted phenyl moiety**. Besides, the **hydroxyl (OH) functional moiety** is found to be located strategically to get bound to the respective **electrophilic C-atom** of the *intermediate*. However, the so-called ***anti*-isomer** specifically gives rise to the formation of the **benzoxazole heterocycle** *i.e.*, **2-Phenyl benzoxazole.**

Beckmann Rearrangement an Example of 1, 2-Shift Arrangement: Shargie and Hosseini (2002)* reported that the following *two* activities almost proceed simultaneously:

- **migration of the substituent,** and
- **loss of water molecule.**

Thus, we may have the following expressions:



* Shargie H and Hosseini M: *Synthesis,* 1057-1060, 2002.

Importantly, the **Beckmann rearrangement** serves as a critical example of the **1,2-shift arrangement**. It could be seen in the above set of reactions in the **'slow'** and **'fast'** mode in which the so-called:

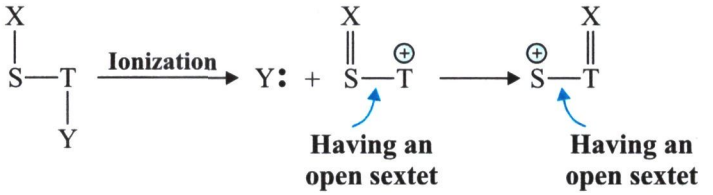
- **migration origin:** is the C-atom, and
- **migration terminus:** being the adjacent N-atom.

Let us now examine the following *three* critical aspects in details, namely:

- **Status of Migrating Moiety,**
- **S_N1 Migration,** and
- **S_N2 Migration,**

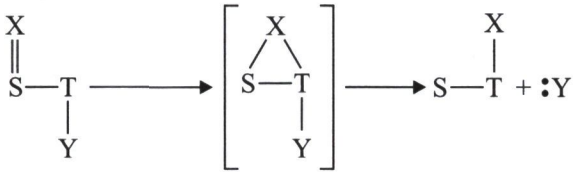
which shall now be treated briefly as under:

❑ **Status of Migrating Moiety*:** It has been ascertained that the migrating moiety happens to be a ***nucleophile*** (or **electron rich**); and, therefore, has a tendency to migrate with the so-called ***'bonding electron pair'***. In other words, it also supports the **intramolecular nucleophilic rearrangement'**, as given under:



❑ **S_N1 Migration*:** In fact, the S_N1 like migration more or less behaves as the ***migrating moiety*** eagerly waits for the departure of the ***leaving moiety***

Thus, we may have the following expression:



Intermediate

❑ **S_N2 Migration:** In reality, the **S_N2 like migration** acts as the viable **neighbouring (adjacent) moiety** trying to push out the so-called *leaving moiety* in **one single-step**. Hence, it is also known as the ***anchimeric assistance*** [*Greek* word: *anchi* + *meros* means: the **adjacent portions**].

Important Uses of Beckmann Rearrangement: Following are the *two* important uses of the **Beckmann rearrangement**.

[A] Ring Enlargement: The **5-membered ring** gets enlarged to the **6-membered ring** and the **6-membered ring** to the corresponding **7-membered ring**.

Thus, we may have the following expressions:

---

* **S** = Migration Origin
T = Migration Terminus
} Adjacent at 1 – 2 position
X = Migrating Moiety
Y = Leaving Moiety

Example (1): The cyclic oximes (both **5-and 6-membered**) undergo the **Beckmann rearrangement** to yield the corresponding ***expanded*** **cyclic amides** *i.e.*, involving the respective **ring enlargement**.

(*a*) **Conversion of a 5-membered dibenzo oxime to 6-membered dibenzo amide**



A 5-membered-dibenzo oxime **A 6-membered-dibenzo amide**

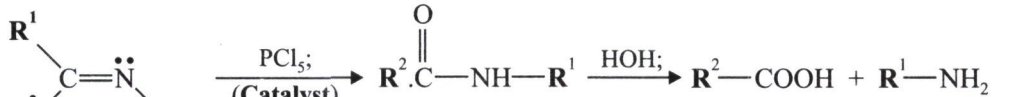
(*b*) **Conversion of a 6-membered dibenzo dioxime (I) l to 8-membered dibenzo amide (II)**



(I) **(II)**

Example (2): Precise determination of the 'configuration of ketoximes': In this particular instance, the ***two*** **isomers,** namely: ***'syn'***—and ***'anti'***—**isomers of ketoxime** invariably give rise to the formation of altogether ***different*** **amides upon hydrolysis,**—as given under:

(*i*)

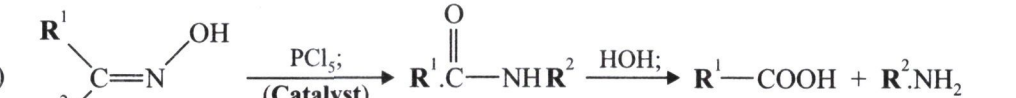


'*syn*'-Ketoxime **Amide** **Carboxylate** **Amine**

It may be stated that $\mathbf{R^1 \neq R^2}$.

Thus, the ***syn*-ketoxime** under the influence of catalyst (PCl_5) yields an **amide**, which on treatment with a mole of water (H_2O) gives each mole of a **carboxylate** and an **amide**, thereby showing the critical migration of both $\mathbf{R^1}$ and $\mathbf{R^2}$ groups.

(*ii*)



'*anti*'-Ketoxime **Amide** **Carboxylate** **Amine**

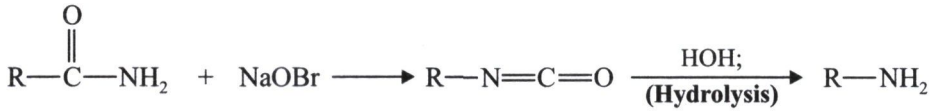
Comments: It may, however, be observed from the above sequential reactions starting from **'*anti*'-ketoxime** to obtain ultimately a mole each of **carboxylate** and **amine**, but the ***configurations*** **do have opposite groups** attached to them *i.e.*, here the carboxylate possesses the $\mathbf{R^1}$ **moiety** and **amide** the $\mathbf{R^2}$ **moiety (assuming that** $\mathbf{R^1 \neq R^2}$**)**. In other words, the location of $\mathbf{R^1}$ and $\mathbf{R^2}$ are absolutely different in the resulting products (*viz.*, **carboxylate and amine**) in the **'*syn*'–and '*anti*'–ketoximes**.

13.2.2.2 Hoffmann Rearrangement*

It relates to the typical **'Bishydrogen (2/→1/N-alkyl)-micro-detachment'**,

i.e., the critical formation of an ***'isocyanate'***.

Let us look into the following expression:



Amide (Unsubstituted) | **Sodium-hypobromite** | **Isocyanate** | **An Amine [Having one C-atom less than the starting amide]**

Thus, in the **Hoffmann rearrangement** an ***unsubstituted*** **amide** is subjected to the treatment with *sodium-hypobromite* (NaOBr), or an admixture of NaOH and Br_2 to yield a **primary amine**—that essentially possess **one C-atom less than the starting unsubstituted amide***.

However, the major poduct of interest being the **'isocyanate'**, but amazingly this chemical entity (compound) is rarely isolated**.

If desired, one may isolate the **isocyanate** so formed by means of the proposed **phase-transfer parameters**. Besides, the **isocyanate** gets invariably *hydrolyzed* under the prevailing reaction conditions. In the aforesaid reaction, **R** may be either ***alkyl*** or ***aryl***, but in case it is an **alkyl moiety** having more than **6 or 7 C-atoms** one may obtain relatively *lower yields*, unless and until one makes use of an admixture of **Br_2 and NaOMe** instead of **Br_2 and NaOH*****.

Side Reactions: Thus, when NaOH is the base it gives rise to the formation of the following products:

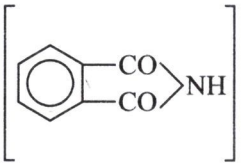
- **ureas:** RNH·CO·NHR; and
- **acylureas:** R·CO·NH·CONHR,

by the *addition*, respectively, of **RNH_2** and **$R{\cdot}CO{\cdot}NH_2$** to **RNCO**. Importantly, when intends to obtain solely the **'acylurea'**,—they may be prepared (*as the major products*) by employing merely **50%** of the requisite quantities of **Br_2** and **NaOH**.

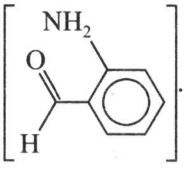
Side Products: The **side product** only forms the *primary R*—which is the ***nitrile*** duly obtained from the oxidation of **RNH_2**.

Examples:

(*i*) **Imides (—CO—NH—):** They react to give the **amino acids** *viz.*, **phthalimide**



yields **α-aminobenzoic acid**



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* Hoffmann AW: *Ber Deut Chem Ges*, **15**: 762, 1882; Wallis and Lane, *Org. React*, **B**: 267-306, 1946 **(For a Review)**.

** Sy and Raksis, *Tetrahedron Lett*, **21**: 2223, 1980.

*** Radlick and Brown, *Synthesis*, 290, 1974.

(*ii*) **α-Hydroxy** and **α-Halo amides** give ***aldehydes*** and ***ketones*** *via* the formation of the ***unstable* α-hydroxy-or α-haloamines.**

(*iii*) A side-product having an **α-halo amide** is a ***gem*-dihalide**.

(*iv*) The ureas yield analogously the **'hydrazines' [$H_2N—NH_2$]**.

Mechanism of Hoffmann Rearrangement: There are ***two*** **pathways** that predominantly depict the **mechanism of Hoffmann rearrangement** in the widely-accepted manner, namely:

- **Pathway–1:** It is broadly evidenced by the critical recovery of **N-bromoamide** plus **isocyanate**; and
- **Pathway–2:** It illustrates explicitly the mechanism involving the so-called *electron deficient* **'Nitrene (R—$\overline{N}$)'** as an ***'intermediate'*** may also be taken into consideration legitimately.

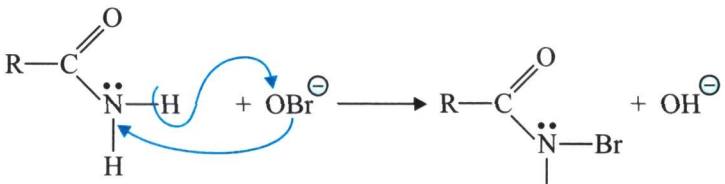
In a broader perspective, the **Hoffmann rearrangement mechanism** essentially involves the so-called:

"base-promoted bromination of an amide (—$CONH_2$)".

The **base (OH^-)** precisely abstracts a *proton* **(H^+)** from the **nitrogen** to yield a **Bromoamide**. However, it may be adequately accounted for the reasonable behaviour of the **hydroxide (OH^-) ion,** whereas, the critical presence of the **electron-withdrawing bromine atom** enhances prominently the inherent **'acidity'** of the **'amide'** thereby rendering the **'desired cleavage'** of the ***N—H bond***—a lot easier and convenient.

Step-I and **Step-II** are found to be **quite common** for the aforesaid ***two*** **Pathways–I and II,** as detailed below:

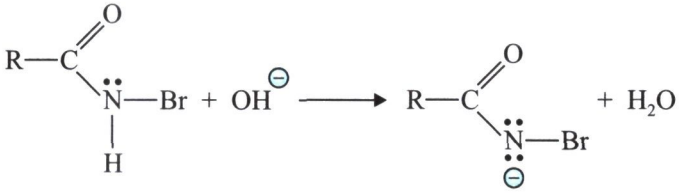
Step-I: Base Promoted Bromination of an Amide



An Amide **N-Bromoamide**

Thus, the interaction of **an amide** and **hypobromiteanion ($OBr^{\ominus}$)** gives rise to the formation of the **N-bromoamide** and the respective **hydroxide (OH^-) ion**.

Step–II: Abstraction of a Proton (H^+) by the Base



N-Bromoamide **Bromoamide anion**

The interaction of **N-bromoamide** and the **hydroxide ion** yields **bromoamide anion** plus a mole of water.

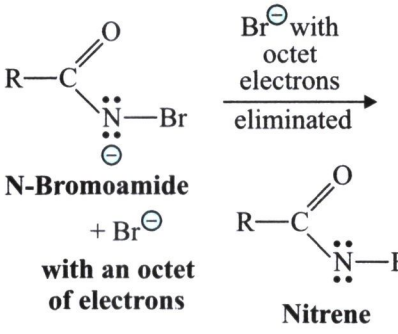
Remarks: The **Pathway-1** includes the following cardinal aspects for critical understanding and consideration, namely:

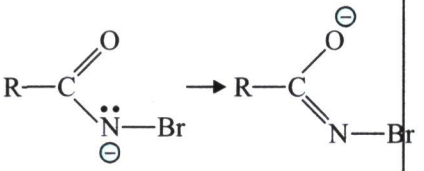
- The **bromoamide anion** undergoes split off to give *bromide* along with its ***'complete octet'*** thereby leaving the **N-atom** with its ***'sextet'*** **of electrons in 'Nitrene (R—$\bar{N}$)** *i.e.,* the so-called ***electron deficient intermediate species***.
- Thus, the subsequent formation of **'Nitrene'** is duly followed by the actual migration of the alkyl moiety with the **bonding pair of electrons** from the corresponding:

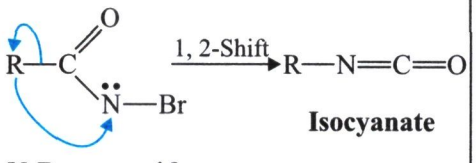
  'migration origin—carbonyl (>C=O) carbon—electron deficient N-atom',

  i.e., leading finally to the so-called **'migration terminus'**.
- Both formation of **'Nitrene'** and migration of **'alkyl moiety'** do come into play **simultaneously** *i.e., via* the **'concerted steps'**.
- Ultimately, the **'isocyanate'** so formed undergoes the phenomenon of ***hydrolysis*** to produce an **'amine'**.

The categorically ***three*** **steps** (*viz.,* 3, 4 and 5) for the **Pathway-1** and ***two*** **STEPS** (*viz,* 3 and 4 only) for the **Pathway-2** are presented explicitly as under:

<table>
<tr><th colspan="2">Pathway-1</th><th colspan="2">Pathway-2</th></tr>
<tr><td>Step-III</td><td>Formation of Electron Deficient Nitrene
 

N-Bromoamide
+ Br⊖
with an octet of electrons
Nitrene
[An electron deficient specie]</td><td>Step-III</td><td>Conversion of N-Bromoamide to carbonyl anion derivative
 

N-Bromo amide Carbonyl anion derivative</td></tr>
<tr><td>Step-IV</td><td>Rearrangement of Electron Deficient System plus 1,2-Shift
 

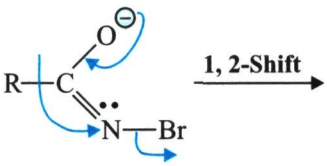
Isocyanate
N-Bromoamide</td><td>Step-IV</td><td>Conversion of Carbonyl anion derivative to Primary Amine plus carbon dioxide via Isocyanate (Intermediate)</td></tr>
</table>

Remarks: The above cited *two* **steps: 3 and 4** *i.e., abstraction* of the **bromide ion ($Br^{\ominus}$)** and *migration* of an alkyl moiety from the ***C-atom*** to the ***N-atom*** do occur almost simultaneously.

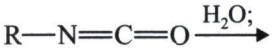
Besides, the **Hoffmann rearrangement** critically involves a **1, 2-shift** as the group migrates from **'C'** to the adjacent **'N'**.

Thus, in the above reaction, **N-atom** is regarded to be **electron deficient** even though it loses electrons to the respective **bromide ion ($Br^{\ominus}$)**; whereas, the **migration takes place** more efficiently than before.

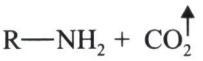
Note: Obviously, the strongest element of support to the *mechanism* is based on the fact that several proposed intermediates have been duly isolated, and subsequently these intermediates proved to yield the Hoffmann degradation products. Besides, the actual rearrangement step fits squarely into the stated pattern of the 1, 2-shift to the electron-deficient N-atom [Nitrene].



Carbonyl anion derivative



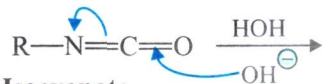
Isocyanate (Intermediate)



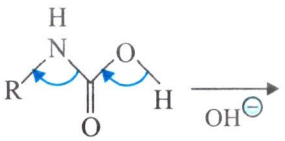
***Primary* amine** **Carbon dioxide**

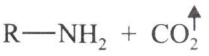
Note: It is, however, pertinent to state here that **Pathway-2** does not include the so-called *'Nitrene'* formation.

Step-V **Conversion of Isocyanate (Intermediate) to *Primary* Amine**



Isocyanate Intermediate





***Primary* amine** Carbon dioxide

Thus, one mole of **isocyanate** yields a mole each of ***pri*-amine** plus carbon dioxide.

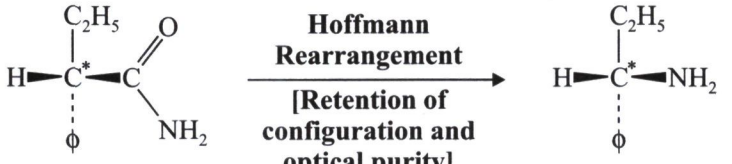
Stereochemical Aspects of Hoffmann Rearrangement

The survey of literature reveals that the *stereochemical aspects of* **Hoffmann rearrangement** invariably comes into play with the:

"absolute retention in configuration around the *chiral centre* of the ensuing 'migration group'.

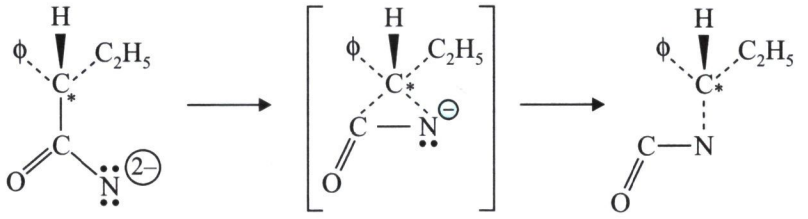
Example: Let us consider the classical example of an **optically active compound *α-phenyl butanamide*** (Wallis and Moyer, 1933)* which critically undergoes the **Hoffmann rearrangement,** thereby producing an **α-phenyl propylamine** having practically the ***same configuration*** and also with the ***same optical purity*** (as that of the starting material),—as illustrated under:

(*i*)



α-Phenyl butanamide [Optically active] — α-Phenyl propylamine

(*ii*)



α-Phenyl butane amide anion — **Migrating moiety migrates from atom to atom** — **Retained Configurations**

Remarks: Based upon the prevailing **stereochemical aspect** of the **Hoffmann rearrangement,** illustrated in (*i*) and (*ii*) above, one may infer explicitly that:

"Nitrogen atom essentially occupies the same relative position on the *chiral C-atom* (marked*) which was earlier retained by the C-atom of the amide (—$CONH_2$) group. Besides, the *chiral C-atom* (*) fails to undergo any sort of a cleavage right from the carbonyl ($\rangle C{=}O$) C-atom unless and until it has already commenced to attach itself to the N-atom. Thus, in (*ii*) *above*, the *migrating moiety* fails to *become free*, however, it certainly remains attached strategically with the *'substrate'*, thereby ascertaining the so-called *intramolecular nature* of the Hoffmann rearrangement [(*ii*)—above]".

Hoffmann Rearrangement: forms an Electron Deficient Atom

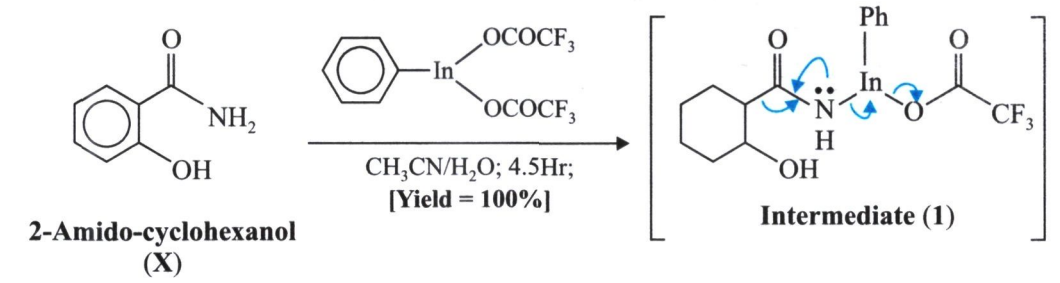
It has been adequately proven and established that as and when an **electron deficient atom** is duly formed due to the strategic departure of the so-called **'leaving moiety'** that eventually grabs the available ***'bonding pair of electrons'*** along with it. Therefore, the ensuing **migrating moiety** designates a ***'nucleophile'*** that eventually migrates together with the ***'bonding electrons'*** perceptively; and hence, the **rearrangement** represents the **intramolecular nucleophilic rearrangement.**

* Wallis ES and Moyer WW: *J Amer Chem 80C*, **55**: 2598, 1933.

Jew and Kang (1994)* reported the following *two* important observations, namely:

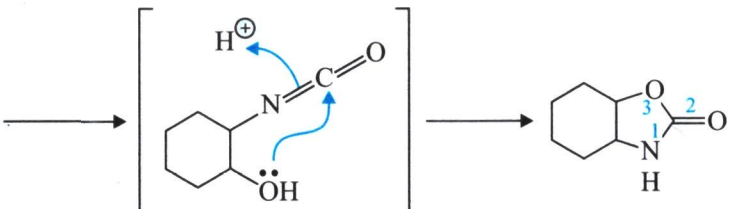
- **Steps-III and IV—*upheld the S_N1 mechanism,*** and
- **Concerted Steps-III and IV—*upheld the S_N2-mechanism.***

Example: Formation of **2-keto-3-oxo-cyclohexane pyrole (Y)** from **2-amido cyclohexanol (X)** *via* ***two*** **intermediates (1) and (2)** respectively, as given under:



2-Amido-cyclohexanol (X)

Intermediate (1)

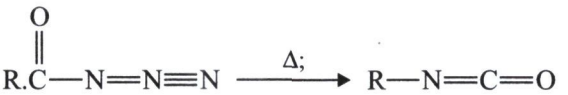


Intermediate (2) **(Y)**

Comments: The **stereochemical observation** ascertains that if the **C-atom** is **chiral (asymmetric) in nature**, the resulting configuration of the product critically remains retained as such.

13.2.2.3 Curtius Rearrangement* [or Curtius Reaction]

The formation of **isocyanates** by means of the *thermal decomposition* of **acyl azides**, as given below:

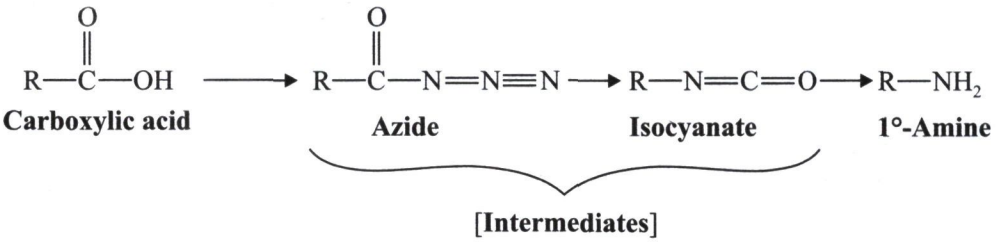


Acyl azide **Isocyanate**

However, the **Curtis reaction** relates to the stepwise conversion of a **carboxylic acid** to a respective ***1°-amine*** essentially having **one fewer C-unit** (or **C-atom**) *via* the **'azide'** and **'isocyanate' intermediates,**—as stated under:

* Jew S and King M: *Arch Pharmacol Res.*, **17**: 490, 1994.

** Curtius T, *Ber.* **23**, 2023, 1890, *idem J Prakt Chem.*, [2] **50**: 275, 1894.



Besides, the **Curtius degradation** of **'acyl azides'**, as depicted in Fig. 13.1, essentially consists of the *thermolysis* of the so-called ***'inner'*** **double bond**.

Mechanism of Curtius Degradation: The incurred thermolysis phenomenon helps to expel particularly the **molecular nitrogen (N_2)** and at the same leads to the ensuing:

'[1, 2]–rearrangement of the substituent',

which is duly attached to the **carboxyl (—COOH) C-atom precisely**.

Thus, the simultaneous existence of **these *two* critical events** eventually prevents the formation of an:

"energetically unacceptably disfavoured acylnitrene intermediate",

and the end-product **'isocyanate'** is obtained due to the ***rearranged product*** ultimately.

Thus, we may have the following expression:

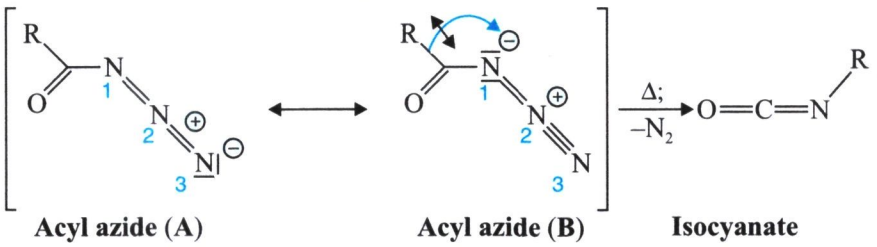


Fig. 13.1: The Underlying Mechanism of Curtius Degradation

Comment: The acyl azide (A) bears **–ve charge on N-3** and **+ve charge on N-2**, whereas, **acyl azide (B)** the **–ve charge resides on N-1** and **+ve charge on N-2.**

EXPLANATIONS

1. The end-product **'isocyanate'** may be isolated carefully if the **Curtius degradation** is performed in an **'inert solvent'**.
2. However, the **isocyanate** may also be reacted with a ***heteroatom*** (*viz.*, **N, S, O, S, P etc.**)—***nucleophile*** either:
   - **already *in situ*,** or
   - **subsequently.**
3. The respective *heteroatom* nucleophile adds on to the incumbment **C=N double bond** of the ***isocyanate molecule*** due to the *uncatalyzed mechanism*.
4. Perhaps due to the so-called consecutive reaction, the **Curtius rearrangement** vehemently presents an extremely valuable **amine synthesis**.

Remarks: The **resulting amines** thus generated invariably comprise **one C-atom lower** *vis-a-vis* the **acyl azide substrates.**

NOTE: **Based on the aforesaid feature we prevalently, rely upon this reaction as the *'Curtius Degradation'*, and certainly not as the *'Curtius Rearrangement'*.**

The One-Spot Diastereoselective Degradation of a Carboxylic Acid to *tert*-Butoxycarbonyl (or BOC)-Protected Amine *via* the Curtius Rearrangement

The illustrated sequence of reactions depicting the way a *carboxylic acid* (**—COOH**) duly prepared by the **Saponification** of the ***methyl ester*** may be specifically subjected to a **Curtius degradation** carried out:

"in a one-pot reaction"

Merits: The ***'one-pot'*** **procedure** is found to be quite easy and convenient since there is absolutely no need to isolate the so-called ***dangerously*** **'explosive acylazides'**.

Figure 13.2 vividly shows the underlying **conversion of the carboxylic acid** into the ***acyl* azides** that usually takes place in the ***earlier phase of the one-pot reaction*** by making use of a **phosphorus (V) reagent***.

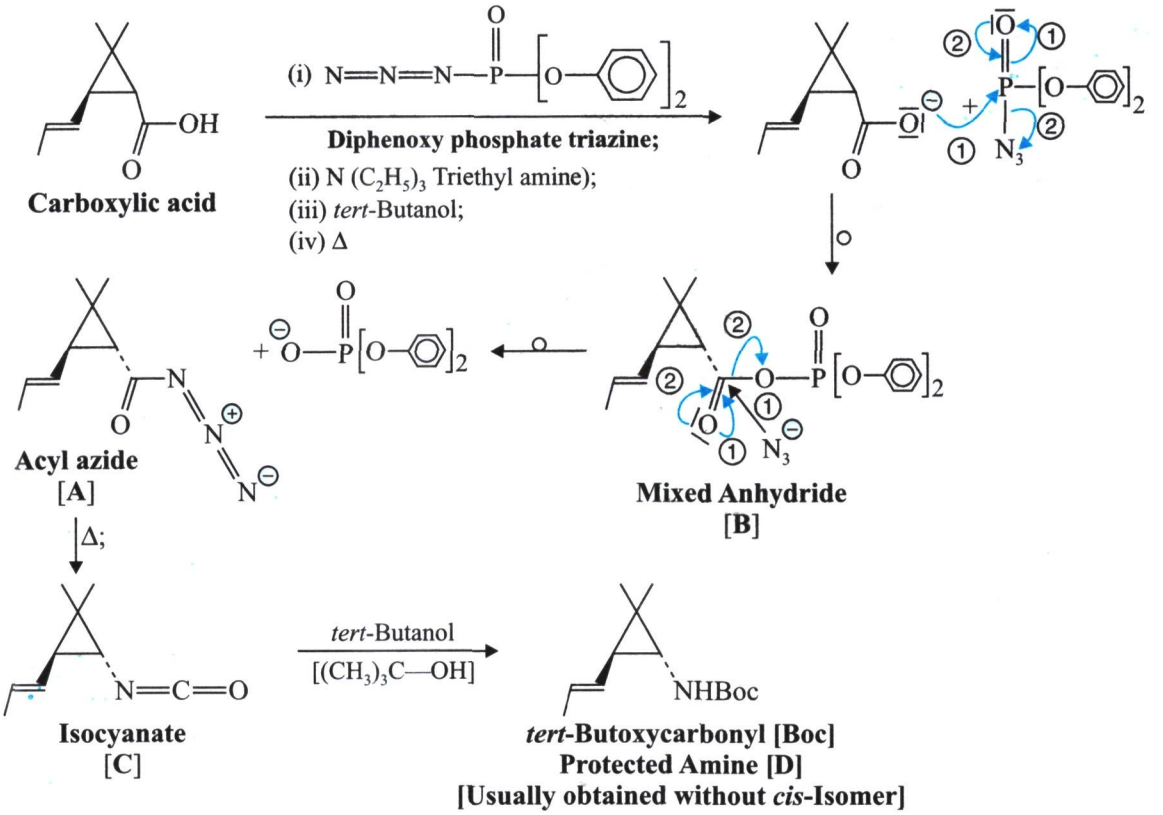


Fig. 13.2: A Schematic Representation of a One-Pot Diastereoselective Degradation of a Carboxylic Acid to a Respective BOC**—Protected Amine *via* a Curtius Rearrangement.

* **Phosphorus (V) Reagent:** This reagent reacts in a manner similar to the role of $POCl_3$ in the conversion of **carboxylic acids,** into the corresponding **acid chlorides** [or similar to $SOCl_2$ or $(COCl)_2$].

** **BOC:** It refers to ***tert*-butoxycarbonyl**.

EXPLANATIONS

The various steps involved may be explained as under:

1. The **carboxylic acid (A)** designates the so-called **immediate substrate** of the **Curtius degradation.**
2. The **compound (A)** essentially comprises a ***trans*-configured cyclopropyl substituents.**
3. Importantly, the ***trans*-configuration of the substituent remains critically unchanged during the [1, 2] rearrangement** thereby leading to the corresponding **isocyanate [C].** Hence, it *migrates* predominantly having:

   "the absolute retention of the ensuing configuration at the migrating C-atom".
4. Because it is perhaps a lot *easier, convenient,* and *possible* to synthesize the so-called:

   'α-chiral (a symmetric) carboxylic acids having well-defined absolute configurations'.

Remarks: In a nut shell, it may be stated that the **Curtius degradation** predominantly designates an ***interesting method*** for their respective ***one-step conversion*** into **enantiometrically pure amines** of the following given structure:

R^1R^2 CH—NH_2 *i.e.,* a *primary* amine

5. Finally, Fig: 13.2, also ascertains how the said **Curtius degradation** of an ***acyl azide*** may be intelligently combined with the critical incorporation of ***tert*-butanol** to the **originally obtained isocyanate.** However, in the present case a ***tert*–butoxycarbonyl (BOC)—protected amine (D)** is produced.

Based on the foregoing discussions we may further extend the scope of the **Curtius Rearrangement** under the following ***two* cardinal sub heads,** namely:

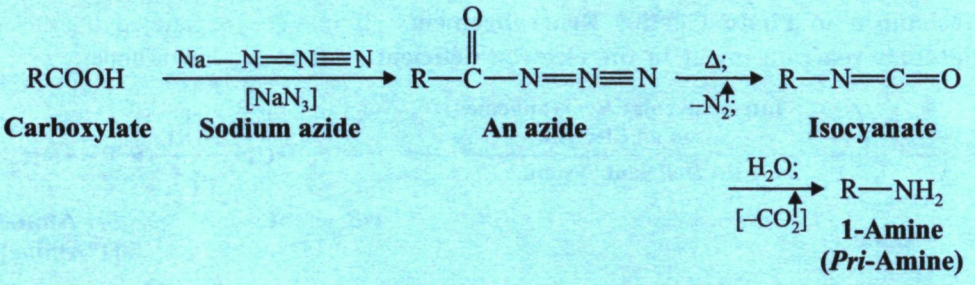
- **Thermal Rearrangement,** and
- **Photochemical Rearrangement (Photo Curtius Rearrangement)**

which shall now be discussed individually along with their *mechanism* in the sections that follows:

13.2.2.1 Thermal Rearrangement

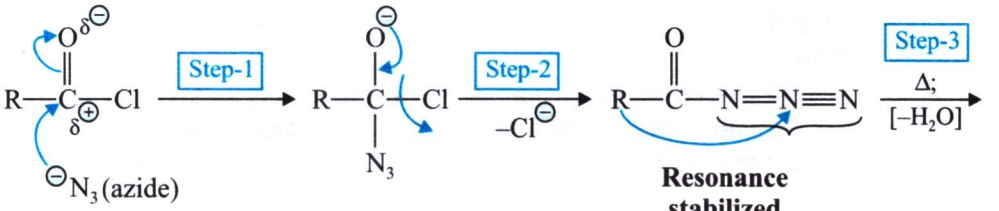
At this point in time, it may be observed that the **Curtius rearrangement** allows splendidly the formation of a ***pri*-amine** (1°-*amine*) *via* the so-called **'isocyanate intermediate'.**

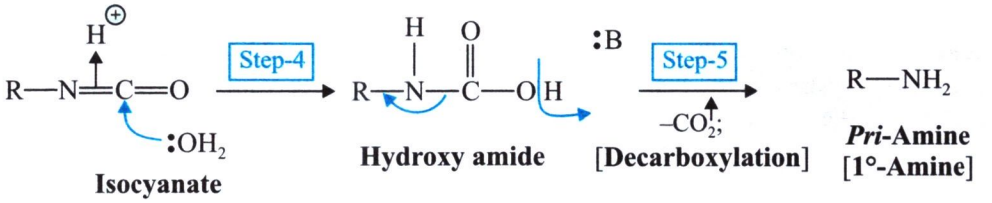
Comments: Thus, it resembles the **Lossen and Hoffmann rearrangement*** we may have the following expression:



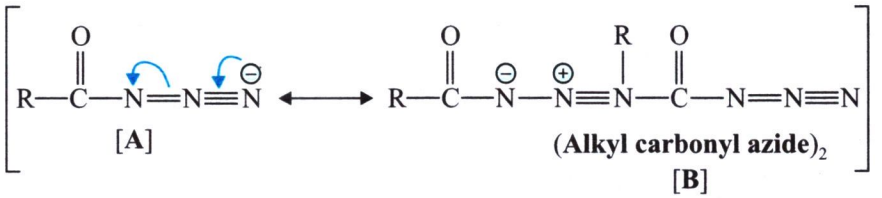
* Sp. W: *Ann.*, **161**: 347, 1872; **ibid, 175**: 271, 313, 1874.

Mechanism of Thermal Rearrangement: The underlying **mechanism of thermal rearrangement** may be expatiated by means of the following ***five*** **sequential steps**:



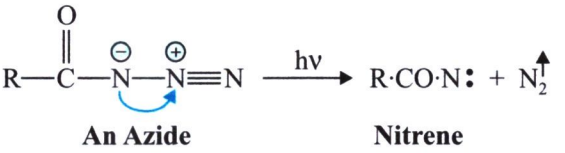


Resonance Stabilization: The phenomenon of **resonance stabilization** may be explained with the aid of the following **reversible reaction** starting from a **alkyl carbonyl azide [A]:**

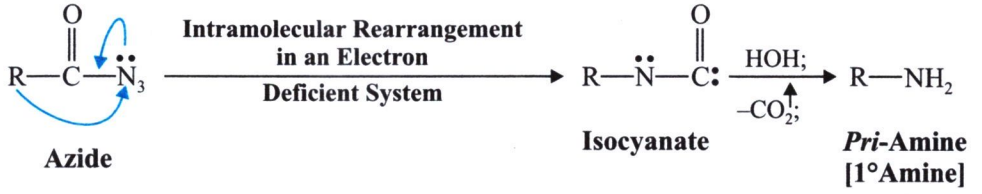


13.2.2.2 Photochemical Rearrangement [Photo Curtius Rearrangement]

The **photochemical rearrangement** (or **photo Curtius rearrangement**) by the photochemical reaction of an **azide** to yield a mole each of **nitrene [R—$\bar{N}$ or RCON:]** and **nitrogen ($N_2\uparrow$),** as given below:



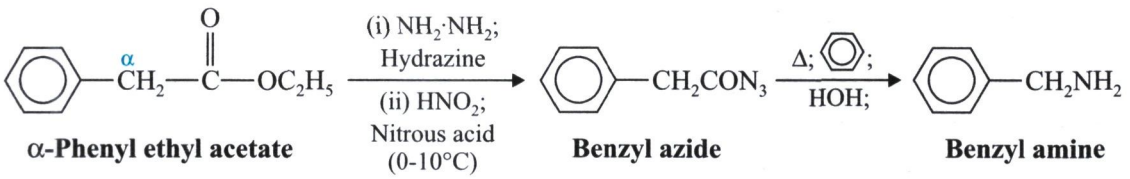
Mechanism of Photo Curtius Rearrangements: It may be expatiated by the so-called **intramolecular rearrangement in the electron deficient system,** as shown under:



Importance of Curtius Rearrangement: These essentially comprise the following ***two* vital and important** modalities for the preparation of:

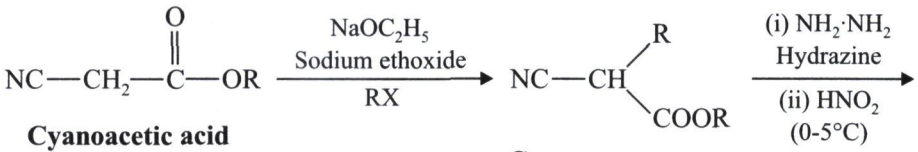
- **Primary—Amines,** and
- **α-Amino acids.**

❑ **Primary-amines:** Conversion of **α-phenyl ethyl acetate to benzyl amine-**(*i.e.,* a **primary aromatic amine**) *via* the formation of **benzyl azide,**—as given under:

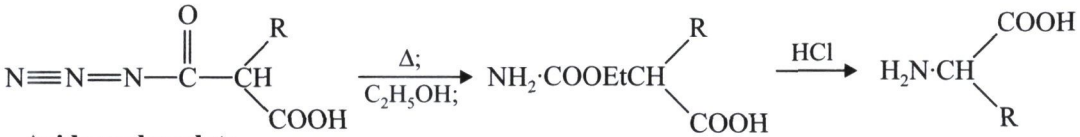


α-Phenyl ethyl acetate **Benzyl azide** **Benzyl amine**

❑ **α-Amino acids:** Conversion of α-**cyanoacetic acid** into an **α-amino acid,** as given under:



Cyanoacetic acid **Cyano acetate ester**



Azide carboxylate **(Intermediate)** **α-Amino acid**

13.2.2.3 Schmidt Rearrangement [Schmidt Reaction]*

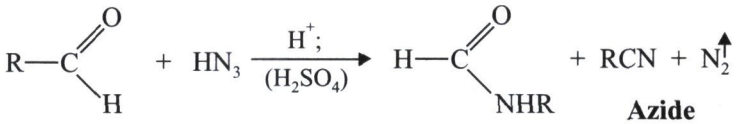
The **Schmidt rearrangement** (or *Schmidt reaction*) refers to the **'acid-catalyzed reactions'** of ***three* classes of organic chemical entities,** such as:

- **Aldehydes (—CHO)** • **Carboxylic Acids (—COOH) and** • **Ketones (>C=O),**

with the **hydrogen azide [H—H=N≡N; HN_3]** in the critical presence of a **strong acid** indulging in a *rearrangement phenomenon* rather than a **dehydration process** precisely.

Let us now look into the **hydrogen azide (HN_3)** reactions involving each of the aforesaid class of organic compounds individually:

❑ **Aldehydes**

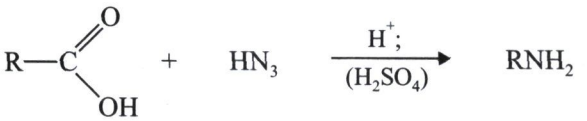


Aldehyde **Hydrogen azide** **Amide** **Azide**

* Schmidt RF: *Ber.*, **57**: 704, 1924.

Thus, the reaction critically involves the migration of ***an alkyl moiety (R)*** over the **C** to **N** chemical bond in an ***azide*** **(R—C≡N)** with the explusion of a mole of **nitrogen** (N_2)*.

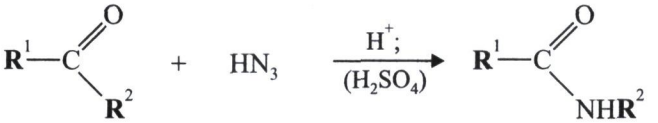
❑ **Carboxylic acids**



Carboxylate **Hydrogen azide** **Amine**

Here, the **carboxylate** gets converted to an amine having a **concomitant chain degradation process** by a ***single C-atom only***.

❑ **Ketones**



Ketone **Hydrogen azide [or Hydrazoic Acid]** **Amide**

Therefore, the **ketone** on deing subjected to reaction with **hydrogen azide** leads to the generation of an **'amide'** instead of the usual **chain degradation phenomenon****.

NOTE: **In all the aforesaid *three* typical examples (*viz.*, aldehydes, carboxylic acids, and ketones) the sulphuric acid (H_2SO_4) is found to be the *most provalent catalyst* used frequently in the reactions. However, one may also make use of the *Lewis acids* for the same purpose.**

Remarks: The interaction between a *ketone* and *hydrogen azide* (or **hydrazoic acid**) critically introduces the **imino (—NH—) moiety** in between the **carbonyl (>C=O) group** and **one R group** *i.e.*, the ***incumbment*** **keto (>C=O) moiety** gets duly converted into the respective **amide $(—CONH_2)$ group*****.

Importantly, the reaction between the **hydrazoic acid** and **ketone** fails to afford the ***'chain degradation'***; however, it does help to form an **amide $(—CONH_2)$** due to the **formal induction** of an **imino (—NH—) moiety** (as shown above).

At this point in time, let us *explore candidly* the underlying **mechanisms** encountered in *different chemical entities* **(compounds)**, namely:

- **Carboxylic Acids;** and
- **Ketone,**

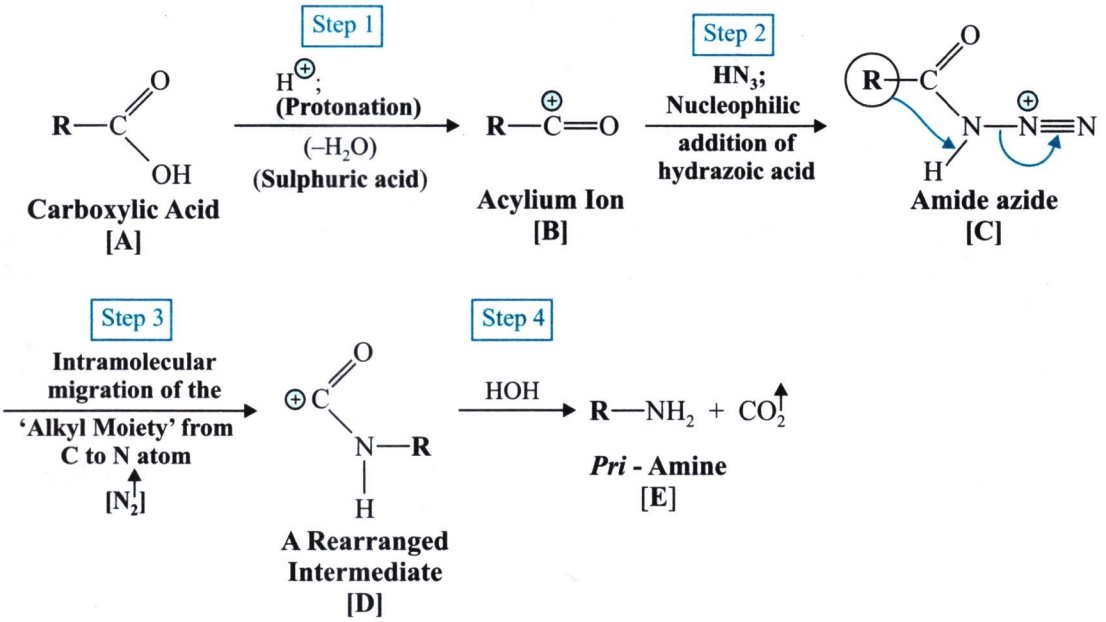
which will now be discussed individually in the sections that follows:

* Lane T and Plagens A: **Organic Reactions,** John Wiley and Sons, New York, p.320, 2006.

** Koldobaskii *et. al.*: *Russ Chem Rev.*, 1084-1094, 1978.

*** Koldobaskii *et. al.*: *Russ Chem Rev.*, **40**: 835-846, 1971; Backwith: In-**The Chemistry of Amides**, Wiley, New York, pp, 137-145, 1970.

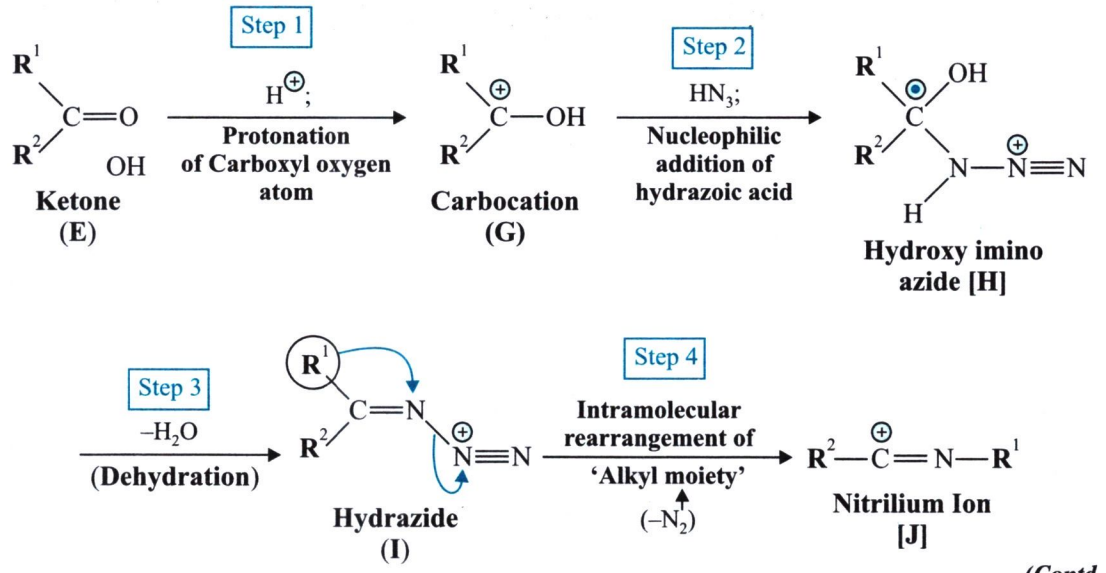
(*a*) **Mechanism with a Carboxylic Acid:** It essentially involves four sequential steps, as given below:



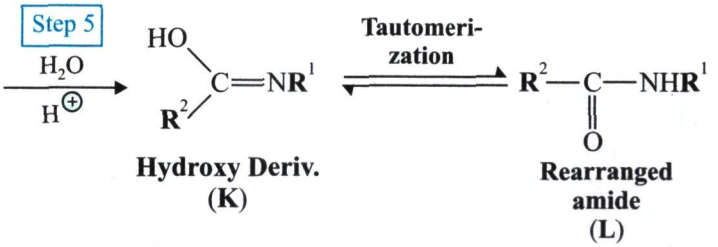
EXPLANATIONS

The **Carboxylic acid (A)** on *protonation* yields an **acylium ion (B),** which on treatment with *hydrazoic acid* (HN_3) gives an **amide azide [C].** The **product (C)** undergoes **intramolecular migration** to produce a **rearranged intermediate (D),** which on further treatment with water gives rise to the formation of a ***pri*-amine (E)** and the elimination of a mole of CO_2.

(*b*) **Mechanism with a Ketone:** It critically involves *five* sequential steps as stated under:



(Contd...)



EXPLANATIONS

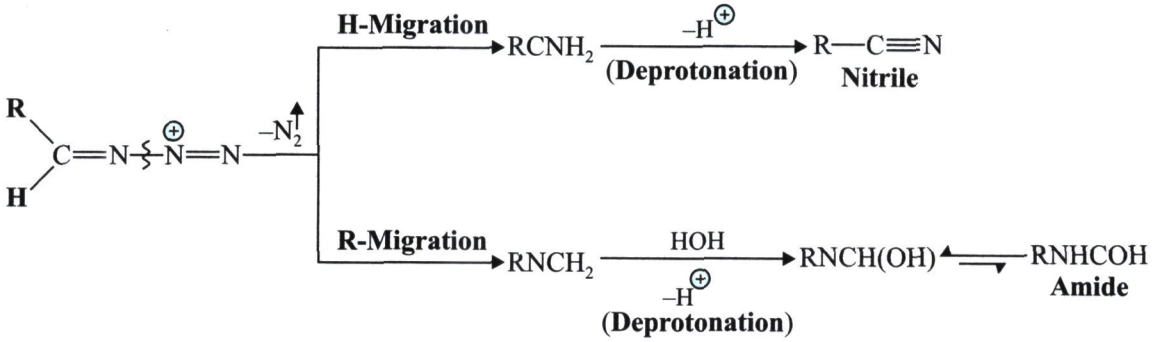
The **ketone (F)** on protonation of the *carbonyl ( )CO) O-atom* yields the **carbocation (G)**, which on reaction with *hydrogen azide* undergoes the *nucleophilic addition* to give **hydroxy imino azide (H)**. The **product (H)** on *dehydration* produces a **hydrazide (I),** which undergoes *intramolecular rearrangement* of the alkyl moiety to yield the **nitrilium ion (J)**. The resulting **product (J)** on *hydrolysis* followed by *protonation* gives a **hydroxy derivative (K),** which ultimately yields the **rearranged amide (L)** due to *tautomerization.*

Remarks: The critical formation of the **Nitrilium Ion (J)** *Step-4* under the **'mechanism of ketone'** reveals explicitly its intimate resemblance to **Schmidt rearrangement** with the **Beckmann Rearrangement;** whereas, the further reaction with *water (H_2O)* followed by *tautomerism* gives rise to the formation of the so-called ***rearranged*** **amide (L).**

Demerit: The aforesaid reaction has the following **demerits:**

1. The side-reaction leads to the formation of the **nitrite/cyanide** together with the ***reduced yield*** **of the 'amide'.**
2. The **'nitrile'** formation essentially involves the most predominant **'migration of H-atom'**; whereas, the typical **'migration of alkyl moiety'.**

Thus, we may have the following expression:



Let us now look into the details of the following *two* cardinal aspects:

[A] Stereochemical Feature: Dehydration of Hydroxy imino azide [H]: The above specific reaction [*see section (b): mechanism with a ketone*] vividly shows the phenomenon of dehydration of the **hydroxyimino azide (H)** that results in the critical formation of:

"an isomer having the *bulky* 'alkyl moiety R^1 attached, strategically in the *trans*-configuration to the diazonium moiety."

However, the said $\mathbf{R^1}$ as the ***trans*-substituent** happens to be an **alkyl moiety,** which migrates subsequently in preference to an **aryl moiety** ($\mathbf{R^2}$), and hence, the so-called **migrating moiety** ($\mathbf{R^1}$)* retains it **chirality** perceptively.

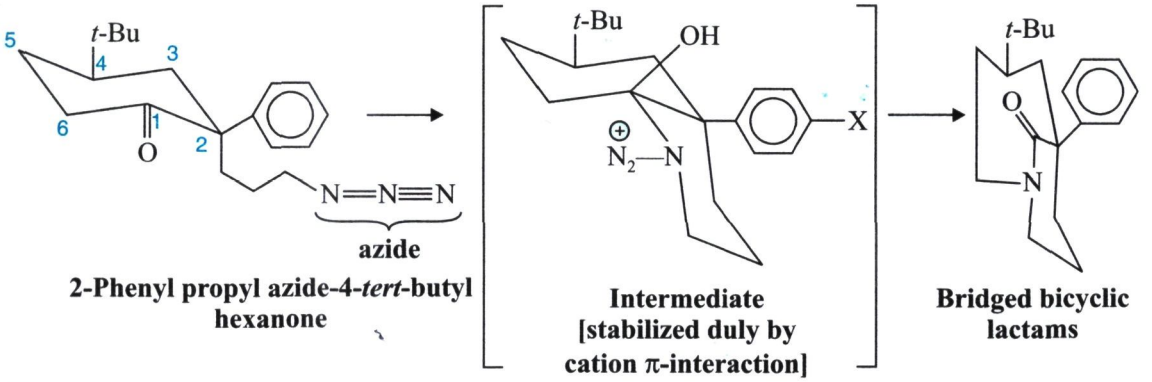
[B] Regiochemistry of Intermolecular Schmidt Reaction: The reaction of **2-phenyl-propyl azide-4-tertbutyl hexanone (a-substituted ketone)** has vehemently proved to be quite susceptible to effect a legitimate control by the so-called *strategical placement* of an **aromatic moiety** at an *adjacent position,* to the inherent ***keto* ( )C=O) group,** that eventually allowing the ***selective formation*** of a typical series of:

"bridged bicyclic lactams from these ensuing substrates".

Importantly, the prevailing vital phenomenon is ascribed almost exclusively due to the crucial presence of:

"the inherent stabilizing process *via* the spatial interactions between the positively charged leaving moiety azide [—$\overset{\oplus}{N}$=N, or—$\overset{\oplus}{N}_2$] present in the intermediate".**

The reaction may be expressed as under:



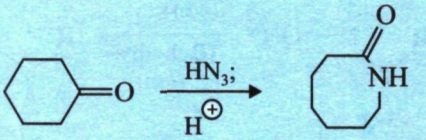
2-Phenyl propyl azide-4-*tert*-butyl hexanone

Intermediate [stabilized duly by cation π-interaction]

Bridged bicyclic lactams

Remarks: These essentially include:

1. The very first step is very much akin to the **Beckmann's rearrangement** perhaps based on the fact that it also gives rise to the formation of the **nitrilium ion**.
2. The **cyclic ketones** (*viz.*; hexanone) yield **'lactams'** in **Schmidt reaction***. Thus, we may have the expression:



Cyclohexanone **Cyclooctanone amide**

* Bach BB and Worker GJ: *J Org Chem.* **47**: 239-245, 1982.

** Lei *et. al.*: *J Am. Chem Soc.*, **129** (10): 2766-67, 2007.

*** Krow: *Tetrahedron*, **31**: 1283-1307, 1981.

13.2.2.4 Lossen Rearrangement**

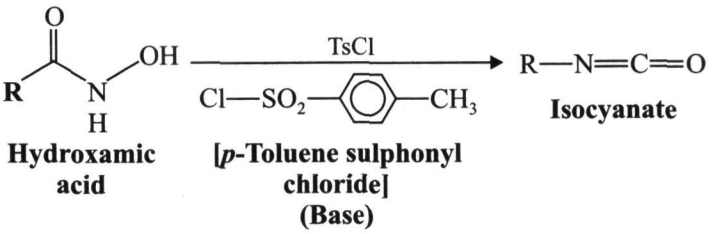
The **Lossen rearrangement** relates to the conversion of a **hydroxamic acid** into an ***isocyanate*** *via* the so-called *intermediacy* of either:

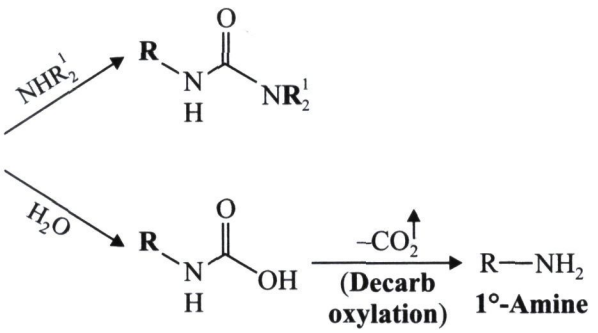
- **its *O*-acyl sulphonyl;** or
- **its phosphoryl derivative.**

Thus, we may lay hands onto the following ***two* different class** of compounds, namely:

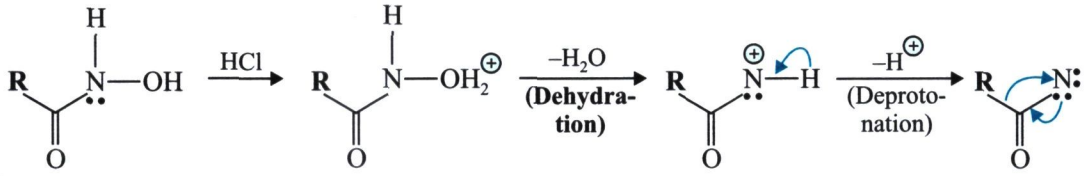
- **ureas**—in the presence of ***'amines'*** and
- **amines** (*having one C-atom less than starting material*)—in the presence of ***'water'***,

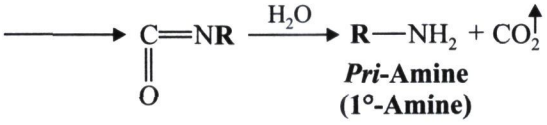
we may have the following expressions:



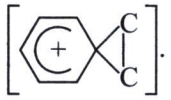


Mechanism of Lossen Rearrangement: The underlying mechanism of the **Lossen rearrangement** is found to be intimately related to that of the ***Hoffmann amine preparation;*** and hence, may be formulated as under:



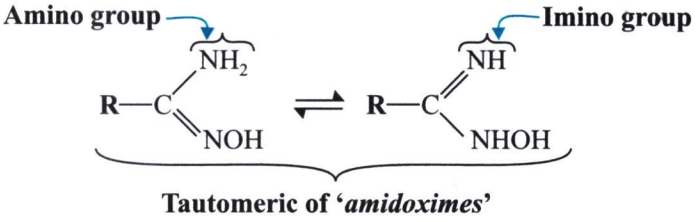


* Lossen W: *Ann.*, **161**: 347, 1873, **175**: 271-313, 1874.

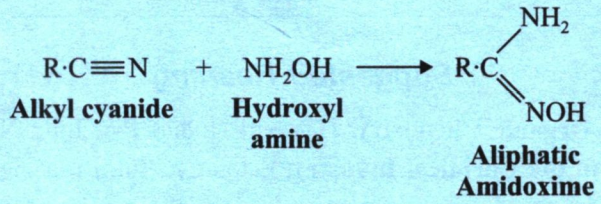
The *aforesaid rearrangement* **(1, 2-shift)** has been ascertained to be **'intramolecular'**; and thus, the *electron releasing moieties* present in a **migrating aryl moiety** certainly accelerate the reaction, thereby supporting the formation of a **phenonium ion**  .

Besides, the **amides** of the **hydroxamic acids** [R·CO·NH(OH)] are invariably termed as the **'amidoximes'** and these are mostly encountered as the ***definite* tautomeric substances.**

Thus, we may have the following expression:



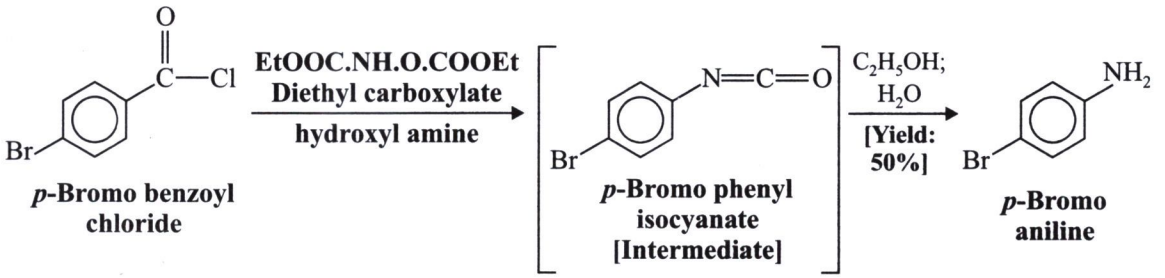
Remarks: Nevertheless, one may obtain the **'aliphatic amidoximes'** by the interaction of the *hydroxylamine* an *alkyl cyanide*, as given under:



Applications of Lossen Rearrangement

Following are the *two* glaring examples pertaining to the **applications of Lossen rearrangement,** namely:

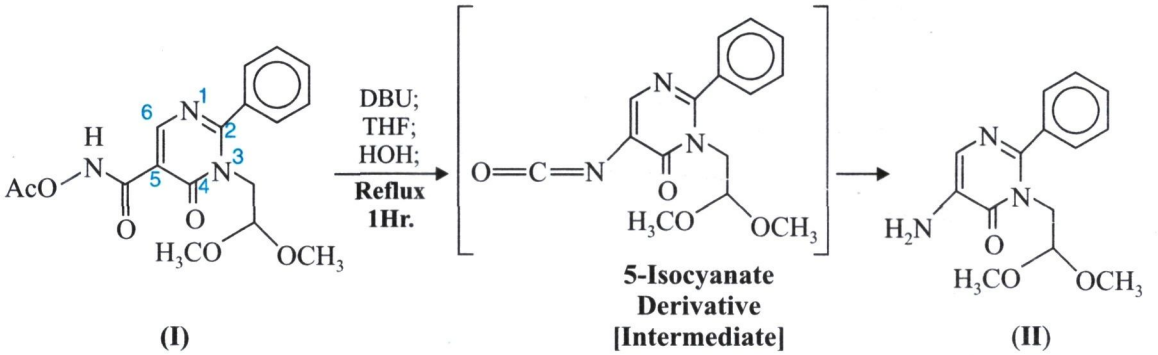
(*a*) **Preparation *p*-Bromoaniline from *p*-Bromo benzoyl chloride:** Kumar *et. al.* (2000)* proposed the method of preparation of ***p*-bromoaniline** from ***p*-bromobenzoyl chloride** *via* the formation of an **isocyanate**—as an ***intermediate***—as stated under:



The various steps in the above reactions are self-explanatory.

* Kumar AR *et al.*: *Tetrahedron Lett,* **41**: 5291, 2000.

(*b*) **Formation of 2-Phenyl-4-*keto*-3-dimethoxyl ethyl-5-amino pyrimidine (II) from 2-phenyl-4-*keto*-3-dimethoxy-ethyl-5-acetyl ketoxime (I)*:** Let us look into the following sequential reactions starting from **(I)** to obtain **(II)**:



(I) **(II)**

Comments: At the end it may be added that the **Lossen rearrangement** may be further exploited judiciously not only in the synthesis of *simple organic chemical entities* like: ***p*-bromoaniline,** but also in the synthesis of rather *complex organic entities* like: **2-phenyl-4-*keto*-3-dimethoxy ethyl-5-acetyl ketoxime**.

Suggested Reading

Bruckner R: **Advanced Organic Chemistry,** Harcourt (India) Pvt. Ltd., New Delhi, 2002.

Chandin J P: **Polymers in the Chemical Industry,** Eaton CE (Ed.), Blackie and Sons Ltd., London (UK), 1986.

Kar A: **Medicinal Chemistry,** 6th ed., New Age International Pvt. Ltd., Publishers, New Delhi, 2015.

March J: **Advanced Organic Chemistry,** 4th ed., John Wiley & Sons., New York, 1992.

Royals EE: **Advanced Organic Chemistry,** 2nd ed., Prentice Hall Inc., Englewood Cliffs. NJ., 1954.

Zabicky L: **The Chemistry of Amides,** Wiley, New York, pp: 137-145, 1970.

❑❑❑

* Ohmoto K *et al.*: *Synlett*, 299, 2001.

Chapter 14

Rearrangements Related to Acyl Carbenes

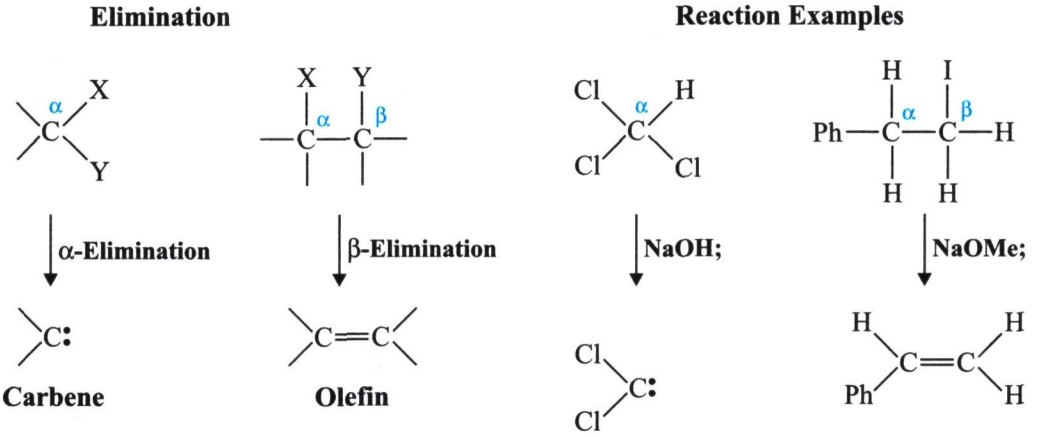
LESSONS AT A GLANCE

14.1 Introduction
14.2 The Criegee Rearrangement

14.1 INTRODUCTION

First of all, let us look into the formation of **'carbenes'**; and hence, the underlying concepts of the so-calld ***elimination reactions***.

The Concepts of α,β-Elimination*:** In this particular instance, all such reactions wherein ***two **atoms or atom moieties** *viz.*, **X** and **Y** are being removed intelligently from a *chemical entity (compound)* are invariably referred to as the **eliminations**, as depicted in the following typical reactions:



Modus Operandi*:** In true sense, such **eliminations** do come into play in ***two **different modalities,** for instance:

- ***First*** **Method:** In several **eliminations** both **X** and **Y** are being removed subjectively in such a manner that:

  'they foil to become the integral constituents of one and the same molecule'.

❑ ***Second* Method:** In this type of **eliminations** they (**X** and **Y**) eventually get hooked on to one another in such a fashion that they usually leave as a **molecule** of the type:

- **X—Y** or **X=Y** or as **N≡N**.

Comments: Obviously, the **atoms** or **moieties X** and **Y** may finally get bound to the **C-atoms** and/or to the **heteroatoms (N, S, O)** duly present in the **substrate itself.** However, these ensuing **atoms** could be either **sp^3** or **sp^2 hybridized** squarely.

α-Eliminations: In general, the term **'elimination'** refers to a **chemical reaction** leading to the loss of a **radical** or **moiety (group)** from a *respective molecule.*

In the present context, the **α-eliminations** are described solely pertaining to their applications:

➢ **α-elimination of HCl from $CHCl_3$ + Base** *(as depicted in Fig. 14.1),*

➢ **α-elimination of XZnI from *carbenoids* X—CH_2—ZnI** *(as shown in Fig. 14.2),* and

➢ **α-elimination of LiBr from *carbenoids* Br—C R^1R^2—Li in thermal rearrangements** *(as illustrated in Fig. 14.3 and Fig. 14.4).*

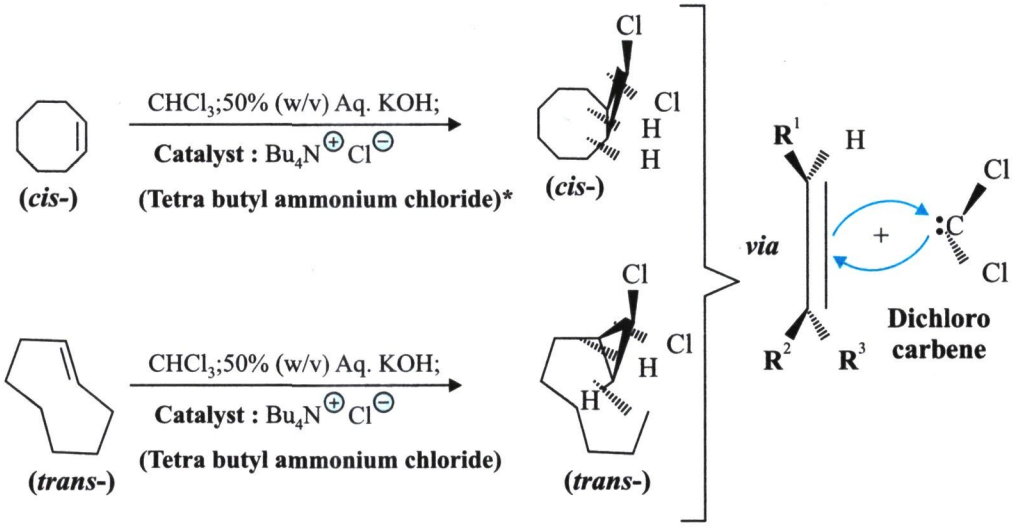


Fig. 14.1: Two Reactions Showing *cis*-Cyclooctene and *trans*-Cyclopropene that Explicitly Demonstrate the Stereospecificity of the *cis*-Addition of Dichlorocarbene to the Olefins.

NOTE: **Two *'dichlorocarbene'* generated in this manner in the *chloroform* medium adds not only *stereoselectively* but also stereospecifically to the *olefins*.**

Remarks: Thus, one may effectively get rid of **chlorine** *e.g.,* using the **Bu_3SnH**; and hence, be able to prepare **'dichloro carbene'** as easily and conveniently as stated above thereby rendering the **2-step process** more congeneal in producing the so-called **chlorine-free cyclopropanes** generously.

* That is, a phase transfer catalyst.

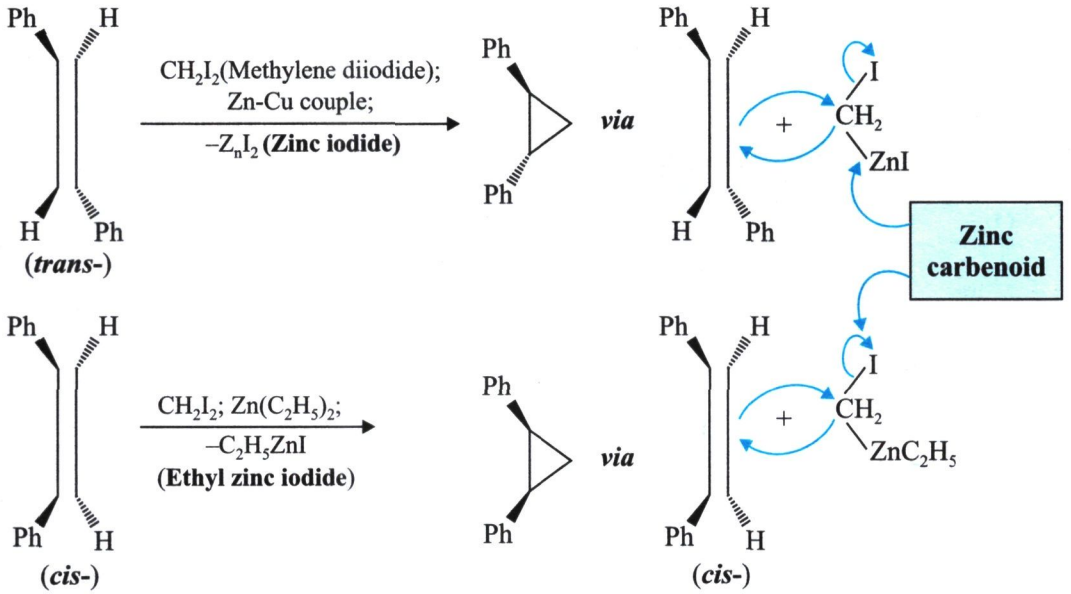


Fig. 14.2: Two Reactions that clearly Demonstrate the Stereospecificity of *cis*-cyclopropanations with the Simmons-Smith Reaction*. In the *First* Reaction: the Zinc Carbenoid is duly Produced as per the Original Method; and in the *Second* Reaction is duly Generated by the known Furukawa Variant.

EXPLANATIONS

1. Amazingly, the addition of the **Simmons-Smith reagent** to the **olefins** ultimately leads to a **single-step** in the corresponding **chlorine-free cyclopropanes** (see *Fig. 14.2*).
2. Besides, the addition also comes into play **stereoselectively** and **stereospecifically**.
3. Importantly, we may also produce the **Simmons-Smith reagent** from ***diiodomethane and Zn-Cu couple*** (which eventually gets generated from the ***Zn-dust*** plus the ***catalytic quantum of $CuSO_4$, $CuCl_2$, or $Cu(OAc)_2$***.
4. The structural formula of **Simmons-Smith reagent** has been duly assigned as: **I—CH_2—ZnI.**
5. The above assigned (proposed) structure of the **species** is invariably subject to an **'equilibrium status'** very much akin to the one which is termed as the so-called **Sehlenk equilibrium** particularly for the ***Grignard reagents*** **(compounds).**

   Thus, we may have the following expression:

   $$2\ I—CH_2—ZnI \rightleftharpoons I—CH_2—Zn—CH_2—I + ZnI_2$$

6. Therefore, based on the aforesaid scientific thoughts amalgamated with sound reasonings, in *Fig. 14.3,* the formulations as per the **Simmons Smith reaction,** has been substantially expatiated thereby confirming as well as ascertaining the underlying fact that:

   "the attacking species is definitely *I—CH_2—ZnI* instead of *I—CH_2—Zn—CH_2—I,* that predominantly remains in equilibrium with it in small quantum only".

---

* Simmons HE and Smith RD: *J Chem. Soc.,* **80:** 5323, 1958.
It relates to the **stereospecific synthesis of cyclopropanes** by treatment of *olefins* with methylene iodide and Zn-Cu couple.

7. Therefore, a reagent which essentially bears the characteristic features very much identical to those of the actual **Simmons-Smith reagent*** surely results right from a **'halogen/metal exchange'** between: **diiodomethane (CH_2I_2)** and **diethylzinc ($ZnEt_2$).** It may be written as: **I—CH_2—ZnEt.**

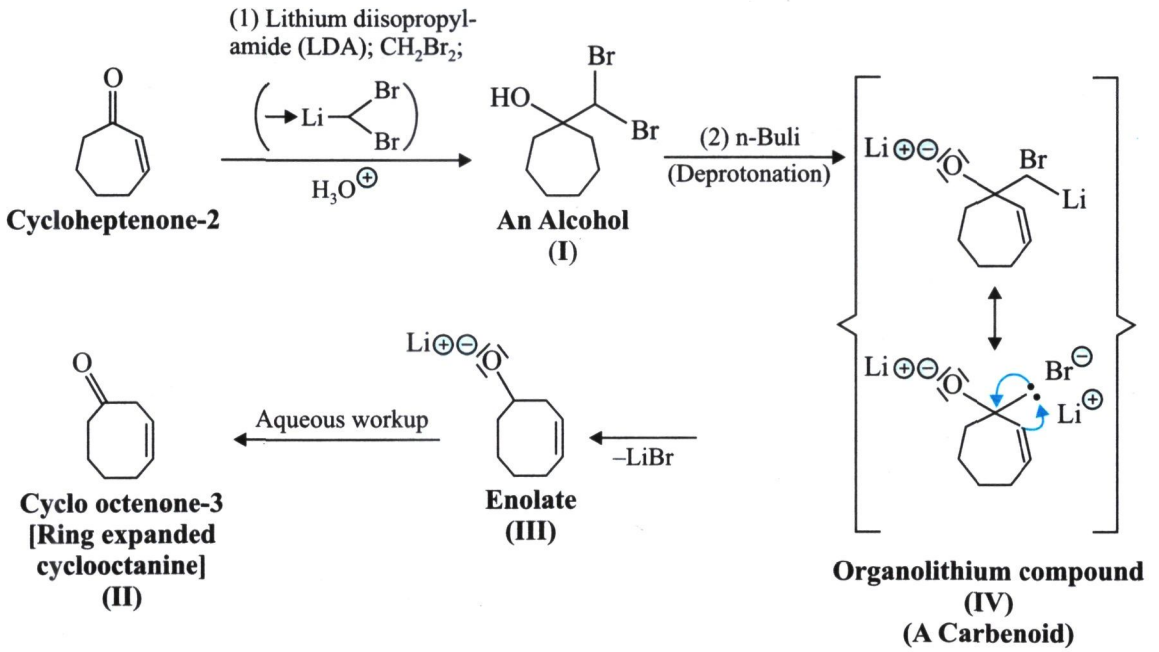


Fig. 14.3: The Ring Expansion of Cycloheptenone *via* a Carbenoid Intermediate. The subsequent Elimination of LiBr from the Carbenoid takes place with or is Followed Critically by a [1,2]-Alkenyl Shift. The Enolate (III) is thus Formed and Upon Aqueous Workup it gets Converted to the Ring Expanded Cyclooctanone (II).

Explanations

1. The very *first step* of the reaction, **dibromomethane (CH_2Br_2)** is duly *deprotinated* by **LDA**; and thus, the **organolithium compound (Li—CH—Br_2)** is obtained.
2. The **resulting product [Li-$CHBr_2$]** meticulously adds on to the **carbonyl (>C=O) double bond** of the ***ketone substrate,*** and forms an **alkoxide**. Subsequently, the usual **acidic workup** gives the respective **alcohol (I).**
3. Thus, the *alcohol moiety* of **alcohol (I)** gets duly *deprotonated* with one equivalent of **n-BuLi** in the *second step of the reaction.*
4. It gives rise to a **Bromine/Lithium exchange event** (see *mechanism in Fig. 14.3, top row)* is being duly accomplished in the resulting **alkoxide** with ***another equivalent of n-BuLi.***
5. Hence, the newly formed **organolithium compound (IV),** which is a **carbenoid**;** and therefore, one may vehemently consider the **carbenoid (IV)** to be a ***resonance hybrid*** between:

* Simmons HE and Smith RD: *J Chem Soc.*, **80:** 5323, 1958.

** **Carbenoid:** It relates to a species whose activity closely resonables that of a **'Carbene'** even though there is **no free-carbene involved** at all.

- **an organolithium compound;** and
- **a *'carbene'* associated with LiBr.**

6. Now, the critical *elimination* of **LiBr** from this **carbenoid (IV)** is *accompanied perceptively* or *followed by a respective [1, 2]-rearrangement.*
7. The **alkenyl moity** most probably gets migrated *much faster than the corresponding alkyl moiety.*
8. In fact, the primary product, thus produced, most presumably is the **enolate (III),** and hence, it is being duly converted into the ***ring-expanded*** **cyclooctanone (II)** upon an *aqueous work up.*
9. The **C=C double bond** in (II) is found to be ***not conjugated with the carbonyl (>C=O) double bond.*** However, it may be largely attributed to:

"a kinetically controlled and modulated termination of the reaction".

NOTE: **In case, the *thermodynamic control* had taken place almost 1/5th of the *unconjugated ketone* would have undergone *isomerization to the respective conjugated ketone.***

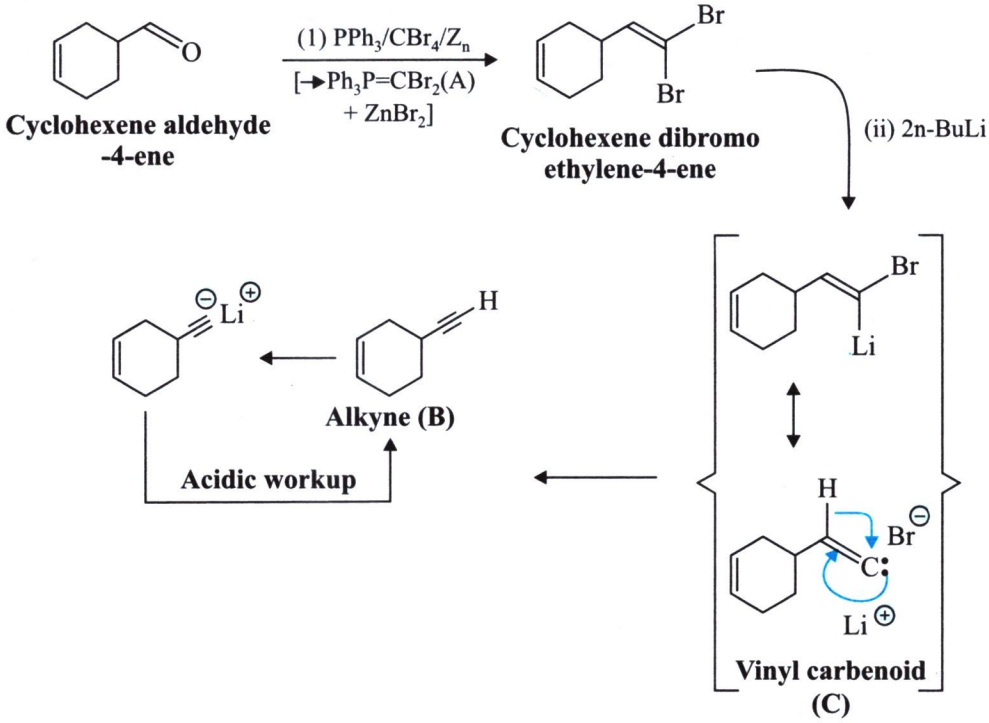


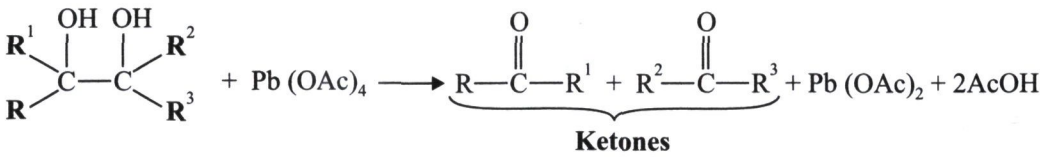
Fig. 14.4: Aldehyde [Cyclohexene aldehyde-4-ene] → Alkyne [Cyclohexene dibromoethylene-4-ene] Chain Elongation *via* [1, 2]—Rearrangement of a Vinyl Carbenoid [Corey-Fuchs procedure]. The Aldehyde and Phosphorium Ylide **(A)** [$Ph_2P{=}CBr_2$] reduced *in situ* do Undergo a Witting Reaction and Form the 1,1-Dibromoalkene (*i.e.,* Cyclohexene dibromoethylene-4-ene). In the 2nd Stage: the Dibromoalkene is Reacted with Two Equivative of n-BuLi and the Respective Vinyl Carbenoid **(C)** is Formed. The Carbenoid Undergoes H-Migration to Form the Alkyne (B). Finally the Alkyne (B) Reacts Immediately with the Second Equivalent of n-BuLi to Yield the Lithium Acetylide [HC≡CLi].

The above course of reactions is self-explanatory.

Having understood the intricacies and logistics associated with the array of **α-elimination profiles,** as discussed in Figs. 14.1 through 14.4, dealing with the **carbene, halo-carbene,** and **carbenoids,** we may now focus our attention to the detailed discussion on the **Criegee Rearrangement.**

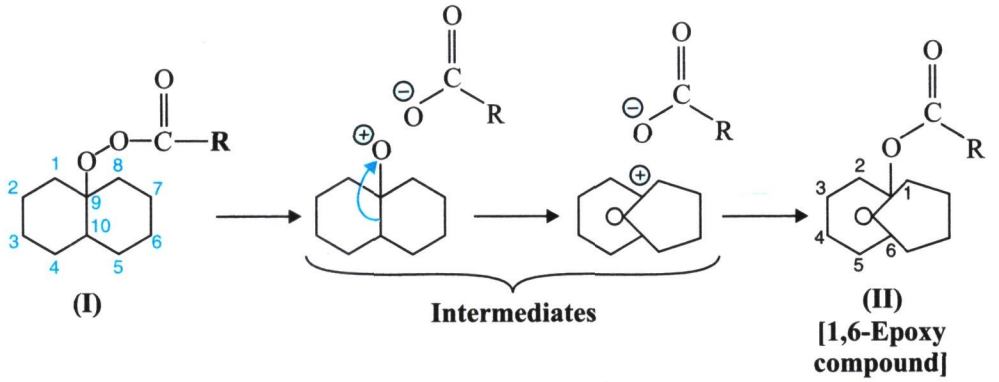
14.2 THE CRIEGEE REARRANGEMENT

The **Criegee rearrangement* (or Criegee reaction)** refers to the ***oxidative cleavage of*** **vicinal glycols** by means of the **lead tetraacetate [Pb (OAc)$_4$],**—as stated under:



Criegee (1994)* observed critically that the ***trans*-9-decalyl peroxyesters (I)** eventually rearranged to the respective **1,6-epoxy-cyclohexyl esters (II)** on being kept undisturbed for a certain stretch of time.

Thus, we may have the following sequence of reactions:



Important Points: These essentially include:

1. In the aforesaid sequential reactions, **Criegee** did provide adequate glaring evidence specifically in support of an ***'ion-pair'*** (as shown in the above **'intermediates'**), which is solely based upon his research upon the **rearrangement in polarity medium exclusively**** that ultimately justified the **inference** ascertaining the **rearrangement** to be for sure an **'ionic one'.**

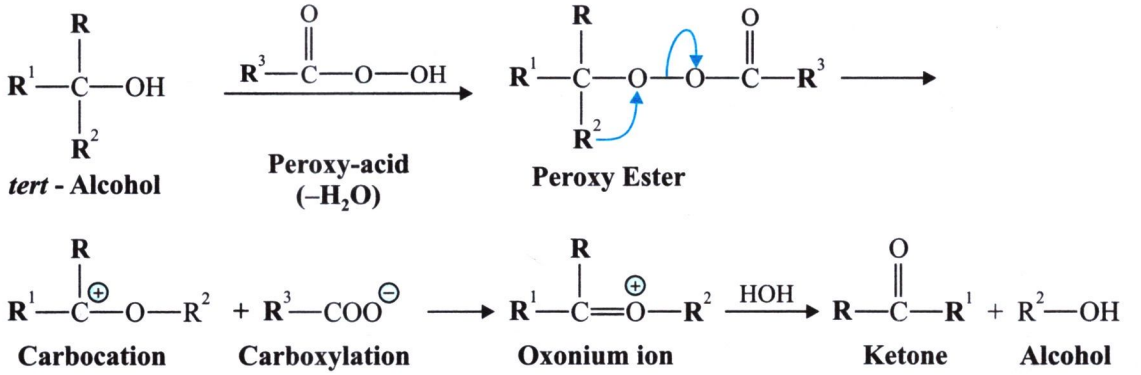
* Criegee R: *Ber,* **64,** 260, 1931; Criegee R: *Ber Deut Chem Gas.,* **77** 722, 1944, Criegee R: In: **Newer methods of Preparative Organic Chemistry, Vol. 1,** Wiberg JK (Ed.): Academic Press, New York, pp: 367-407, 1965.

** Criegee R and Kaspor R: *Justus Liebigs Ann Chem.,* **56:** 127, 1948.

2. The so-called clear cut deviation of the **'leaving moiety'** in the above *rearrangement phenomenon* is perhaps by virtue of an **'anchimeric assistance',*** as reported by Winstein *et al.* (1967)**.
3. **Cleavage of Tertiary Alcohol:** Under the influence of the **Criegee rearrangement**—a ***tertiary*** **alcohol [R_3COH]** undergoes a systematic cleavage by means of an ***oxidation*** **reaction** in the presence of a **peroxyacid [R-COOOH]** to result into the formation of a **'ketone'.**

NOTE: **Most prevalent *peroxyacid* being used for this purpose happens to be the *p*-nitroperoxy bonzoic acid: [O_2N-C_6H_4-COOOH].**

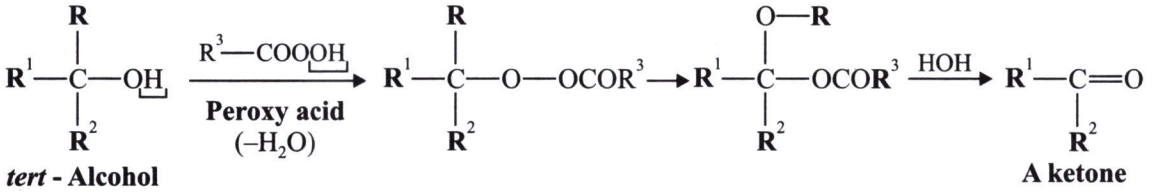
The above reactions may be summarized under the following scheme in an elaborated manner:



Remarks: Thus, the **Criegee rearrangement** essentially involves the so-called **'ionic rearrangements'** of a ***peroxy ester*** *via* an *oxonium ion* to produce a **ketone** and may be performed in a solution from **alcohol***** or even **esters******** as the **intermediate peroxy ester** duly produced in the **reaction media itself.**

Mechanism of Criegee Rearrangement: The precise and exact mechanism of the **Criegee rearrangement** in associated intimately with that of **Baeyer-Villiger rearrangement** *via* the **peroxy esters,** as illustrated under:

(*a*) ***Criegee Rearrangement***



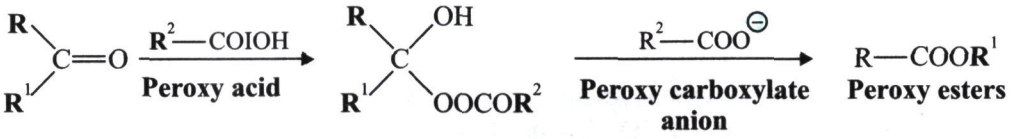
* **Anchimeric Assistance:** It refers to the participation of the adjacent moiety in the departure of leaving moiety.

** Winstein S and Hedaya AE: *J Am Chem Soc.*, **89:** 1661, 1967.

*** Deno NCB *et al.*: *J Org Chem.*, **35:** 3080, 1970.

**** Krasutaky PA *et al.*: *J Org Chem.*, **65:** 3926, 2000.

(*b*) ***Bayer-Villiger Rearrangement***



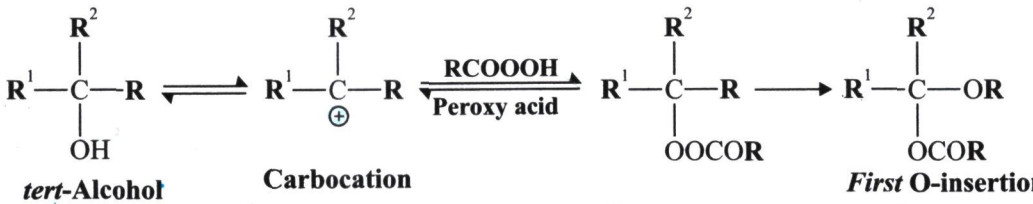
NOTE: **Importantly, the both *synthetic* and *mechanistic* aspect have been further explored, expatiated, and explained by a good number of *organic chemists.*****

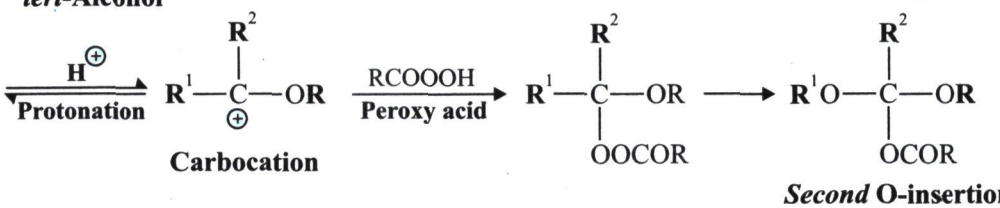
***Points to Ponder*:** It is, however, pertinent to state here that the **Bakyer-Viltiger rearrangement** is very much restricted to the underlying fact that:

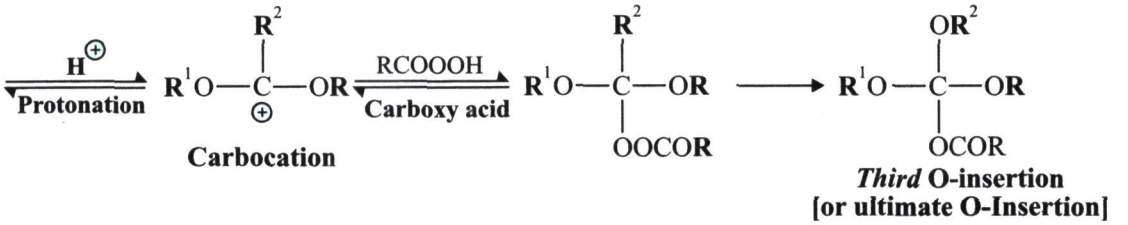
'the actual insertion of a *single O-atom,* but the same was *not observed* in the Criegee rearrangement (wherein the *insertion of 3 O-atoms* were noticed predominantly)'.

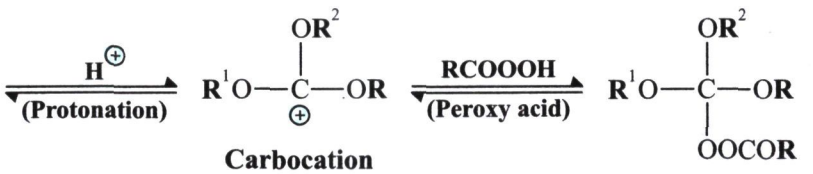
In addition, the respective ***carboxonium ion*** or the ***ester*** often do get duly **stabilized** either in an ***acidic medium*** or an ***anhydrous medium*** that eventually reacts further to the ***second*** **peracid** to give a **peroxy ester;** and thus, to the ***third*** **peracid** thereby enabling the so-called **triple oxygen insertion** squarely (*i.e.,* usually termed as the ***'ultimate oxygen insertion'***).

We may have the following sequential expressions:









All the aforesaid sequential reaction steps are self-explanatory.

* Sewaki Y: In: **Organic Peroxides,** Ando W (Ed.). Wiley and Sons, New York, pp 425-477, 1992; Pavel A et al.: (NJ-1517 J): Open Access Publication, pp: 151-171, 2005.

Suggested Reading

Briickner R: **Advanced Organic Chemistry,** Academic Press, An Imprint of Elsevier, San Diego CA., 2002.

Pavel A *et al.*: **NZ-1517 J:** Open Access Publishers; pp: 151-171, 2005

Sewaki Y: In: **Organic Peroxides,** Anda W (Ed.), Wiley and Sons, New York, pp: 425-477, 1992.



Chapter 15

Sigmatropic Rearrangements

LESSONS AT A GLANCE

15.1 Introduction
15.2 General Survey of Sigmatropic Rearrangement
15.3 [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts of Hydrogen And Alkyl Moieties
  15.3.1 The Computational Characterization of Transition Structures for [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts
  15.3.2 Typical Examples of Sigmatropic Shifts of Hydrogen and Alkyl Moieties
15.4 Overview of [3,3]-Sigmatropic Rearrangement
  15.4.1 Claisen Rearrangment
  15.4.2 Cope Rearrangements
  15.4.3 [3,3]-Sigmatropic Rearrangement in Triene Systems Containing Oxygens
  15.4.4 [3,3]-Sigmatropic Rearrangement of Trienes Containing Nitrogen
  15.4.5 [2,3]-Sigmatropic Rearrangements

15.1 INTRODUCTION

The **sigmatropic rearrangements** (or ***sigmatropic reactions***) actually relates to a *pericyclic reaction* which essentially involves:

"concerted uncatalyzed intramolecular migration of a σ-*bonded atom* or moiety from one end of a π-*system* to other", which being very much akin to the typical observed **migration of a σ-bond.***

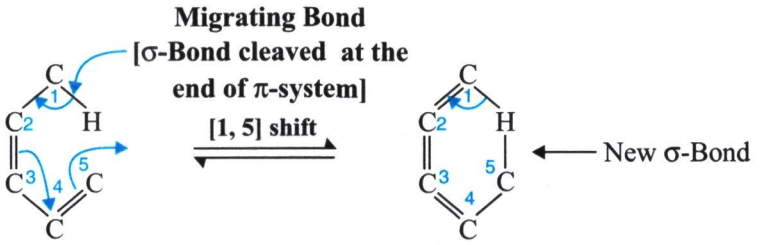
Figure 15.1 illustrates clearly the **sigmatropic rearrangement** in *two* altogether different situations, namely:

(*a*) **An example of [1, j] shift;** and

(*b*) **An example of [i, j] shift.**

*Carey FA and Sandberg RJ: **Advanced Organic Chemistry-Part A,** Springer, 2007

(*a*) **Example of [1, j] shift**



(*b*) **Example of [i, j] shift**



Fig. 15.1: Representation of the Sigmatropic Rearrangement.

EXPLANATIONS

1. The **σ-bond** broken (cleaved) in the aforesaid reaction is required to be identified *first*; and only then **'1'** is duly assigned to both the atoms critically involved in this bond.
2. Subsequently, the atoms in each direction from the bond to be cleaved,–including atoms that eventually form the **new σ-bond** in the product, are now numbered as 2, 3 and so on so forth.
3. Thus, the atoms between which the **new σ-bond is duly formed,** are assigned numbers, separated by commas and put in the ***square brackets*** to identify their respective **'reaction order'** (see Fig. 15.1).

Important Characteristic Features of Sigmatropic Rearrangements: These essentially include:

1. The σ-bond that undergoes cleavage gets duly bonded to an **'allylic C-atom'**.
2. The ultimate number of **π-bonds** almost remain the same both in the **'reactants'** and the **'products of reaction'**.
3. The **σ-bond** so formed is duly cleaved either:
   - **at the end of π-system,** or
   - **at the middle of π-system.**
4. Finally, an attempt is duly made to identify the precise and exact–**'Sigmatropic Sift'**.

After the preliminary exposure to the **sigmatropic rearrangement**, we may look into the following important and intricate aspects of the *said rearrangement* so as to understand the theoretical aspects in a better way, such as:

- **General Survey of Sigmatropic Rearrangements;**
- **[1,3]-, [1,5]-, and [1, 7]-Sigmatropic shifts of Hydrogen and Alkyl Moieties;**
- **Overview of [3,3]-Sigmatropic Rearrangments; and**
- **[2,3]-Sigmatropic Rearrangements,**

which shall now be discussed at length in the sections that follows:

15.2 GENERAL SURVEY OF SIGMATROPIC REARRANGEMENT

Woodward and Hoffmann (1965)* proposed vehemently that the **'sigmatropic rearrangements'** do invariably constitute another equally important class of the so-called ***concerted pericyclic reactions*** governed critically by the **orbital symmetry**. In reality, they prominently enter into a reorganization phenomenon of **electrons** in the course of which a group gets attached by:

'a σ-bond migrates promptly to the other terminus of a conjugated π-electron system',

having an *almost simultaneous shift of the π-electrons.*

Alternatively, the **sigmatropic rearrangements** are usually described by stating the relationship prevailing between:

- **reacting centres in the migrating fragment,** and
- **π-system.**

Thus, there exists *two* different **'orders'**, namely:

➢ **Order [i]**–which specifies the exact number of atoms prevailing in the ***migrating fragment***; and

➢ **Order [j]**–that implies the precise quantum of atoms existing in the ***π-system***.

Points to Ponder: Therefore, very much akin to **other concerted reactions,** one may obviously take cognizance of the fact that:

"the *topology* of the interacting orbitals helps to determine the facility as well as the stereochemistry of each and every stigmatropic rearrangement".

Variants in Topologically Distinct Processes: There are *two* different and distinct **topological processes** which eventually enables the causation of a ***sigmatropic migration***.

First* Process:** It relates to the situation when the ***migrating moiety remains intimately associated with the *same face* of the **conjugated π system** throughout the reaction; and hence, the migration is termed as—***'superficial'***.

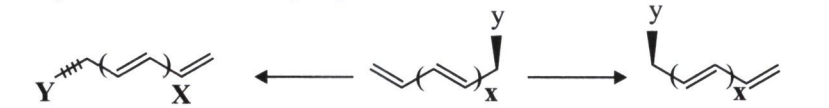
Second* Process:** It refers to a particular mode usually known as–'antarafacial'***, in which the ensuing ***migrating moiety*** moves to the ***opposite face of the* π-system** during the **migration process**.

Another Vital Element of Stereochemistry for Migration of Alkyl Moieties: In this specific instance, the ***migrating moiety*** do essentially possess the ability to retain its so-called **'original configuration' (retention)** or even undergo ***'inversion'*** perceptively. In true sense, however, one may be able to ascertain the underlying fact that either:

- **stereochemical features,** or
- **number of electrons involved,**

virtually determine whether a reaction is ***allowed* or *forbidden*** at the end of the episode.

Thus, we may have the following expressions:



Antarafacial Rearrangement

[Y Located above the plane]

Suprafacial Rearrangement

[Y Located below the plane]

*Woodward RB and Hoffmann R: *J Am. Chem. Soc.*, **87:** 2511, 1965.

Generalized Orbital Symmetry Selection Rules*: The following Table 15.1 records the generalized **orbital symmetry selection rules.**

Table 15.1: The Observed Generalized Orbital Symmetry Rules for Sigmatropic Processes

Orders	Supra/Retentions	Supra/Inversion	Antara/Retention	Antara/Inversion
Order [1, j] 1 + j				
4 n	Forbidden	Allowed	Allowed Forbidden	Forbidden Allowed
4 n + 2	Allowed supra/ supra	Forbidden supra/ Antara	Antara/Antara	—
Order [i, j] i + j				
4 n	Forbidden	Allowed	Forbidden	—
4 n + 2	Allowed	Forbidden	Allowed	—
	—	—	—	—

NOTE: **The fundamental bases of the aforesaid rules are duly discussed for each of the major classes of the *'Sigmatropic Rearrangements'*.**

15.3 [1,3]-, [1,5]-, AND [1,7]-SIGMATROPIC SHIFTS OF HYDROGEN AND ALKYL MOIETIES

Preamble: The broader perspective of the *orbital symmetry requirements* of the so-called **sigmatropic reactions** may be analyzed judiciously by taking into consideration the underlying inherent interactions between the following ***two*** **entities,** namely:

- **frontier orbitals of π-system;** and
- **migrating fragment.**

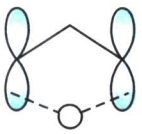
Fig.: 15.2 depicts the *simplest instance* wherein:

"1,3-sigmatropic shift of a H-atom is being illustrated clearly in the so-called very *first entry* itself".

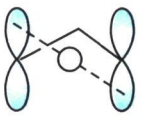
Importantly, an **FMO-analysis** of the present phenomenon critically treats the system as a *H-atom* reacting with an **allyl radical** perceptively. Thus, the **frontier orbitals** are:

- **hydrogen 1s,** and
- **allyl ψ_2 orbitals.**

Besides, the aforesaid ***interactions*** are illustrated below for both the **'suprafacial'** and the **'antarafacial modes'**:



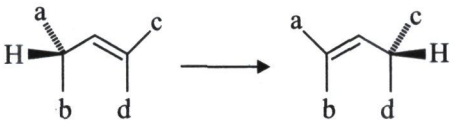
Suprafacial mode



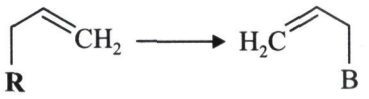
Antarafacial mode

*Woodward RB and Hoffmann R: *J Am Chem. Soc.*, **87:** 2511, 1965.

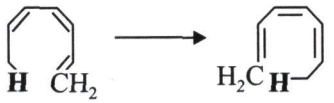
(a) [1, 3]- Suprafacial shift of H-atom



(b) [1, 3]- Sigmatropic alkyl shift



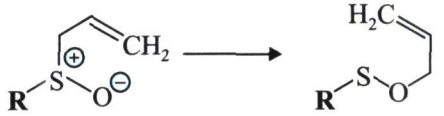
(c) [1, 7]- Sigmatropic Hydrogen shift



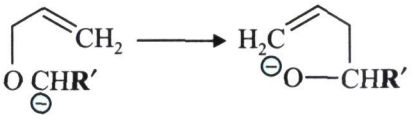
(d) [3, 3] - Sigmatropic Rearrangement of 1,5 - Hexadiene (Cope Rearrangement)



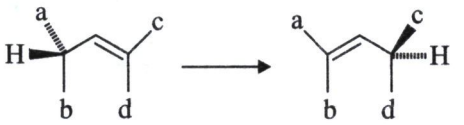
(e) [2, 3] - Sigmatropic Rearrangement of Allyl Sulphoxide



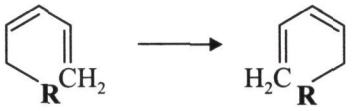
(f) [2, 3] - Sigmatropic Rearrangement of Allyloxy Carbanion Wittig Rearrangement)



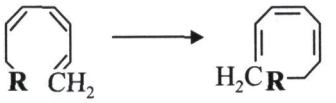
[1, 3]- Antarafacial shift of H-atom



[1, 5]- Sigmatropic Alkyl Shift



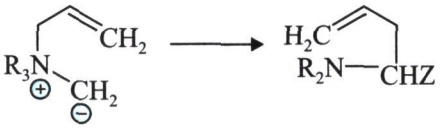
[1, 7]- Sigmatropic Alkyl Shift



[3, 3] - Sigmatropic Rearrangement of Allyl Vinyl Ether (Claisen Rearrangement)



[2, 3] - Sigmatropic Rearrangement of N-Allyl Ammonium ylide



[2, 3] - Sigmatropic Shift of N-Allyl Amine Oxide

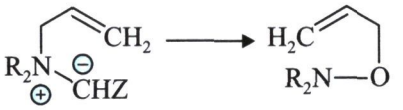


Fig. 15.2: Certain Classical Examples of Sigmatropic Rearrangements [Including: Cope Rearrangement; Claisen Rearrangement; and Wittig Rearrangement.

Salient Features: The **salient features** of **[1,3]-, [1,5]-, and [1,7]-sigmatropic shifts** of the respective **hydrogen and alkyl moieties** are as enumerated under:

1. The intensive and extensive **'Computational Studies'** do reveal explicitly that:

"the 1,3-shift of hydrogen must be *'antarafacial'*, but at the same time should be in complete agreement with the specific expectations based solely upon the so-called *Molecular Geometry*".

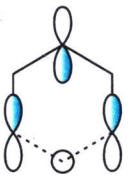
Hence, the **transition state (TS)** is invariably found to be so energetic in nature that it is almost very close to the ensuing **stepwise-bond dissociation phenomenon.***

2. **The Orbital Symmetry Analysis (OSA):** The **OSA** of the **[1,5]-sigmatropic shift of hydrogen** virtually results into the just ***'opposite conclusion'***. Obviously, the so-called relevant and critical **frontier orbitals** in this particular instance are:

- **the hydrogen 1*s* orbital;** and
- **the ψ_3 of pentadienyl radical.**

Thus, the prevailing ***'suprafacial mode'*** is permitted generously; whereas, the corresponding ***'antarafacial mode'*** is forbidden absolutely. Interestingly, the **suprafacial shift** does correspond to the respective:

'geometrically favourable 6-membered ring'



Allowed [1,5]-suprafacial shift in 1,3-pentadiene

3. **Alternative Means of Analysis of Sigmatropic Reactions:** It essentially involves in conceptualizing the fundamentals related to:

- **set atomic orbitals,** and
- **classifying the resulting system,**

either as **Mobius** or **Hiickel** in its inherent character. Hence, in a particular instance when the proper ***classification*** has been duly carried out, the ***electrons*** that are intimately engaged in the entire phenonmenon–or now metialowly:

"counted so as to determine whither the *'transition state (TS)'* is either aromatic or anti-aromatic in nature".

NOTE: **At this point in time, one may observe that the *conclusions* so reached are mor or less exactly the same as for the ones accomplished by the *frontier orbital approach (FOA).***

EXPLANATIONS

1. The observed **suprafacial 1,3-shift of hydrogen** is duly ***forbidden***; whereas, the respective **suprafacial 1,5-shift** is ***allowed***.
2. The **1,7-shift of hydrogen** on being subjected to analysis clearly reveals that the respective **antarafacial shift** is ***allowed***. The following Fig.: 15.3 explicitly depicts the aforesaid *analysis profile*:

*Hess BA *et al*: *J Am Chem. Soc.*, **107:** 149, 1985; Bernardi F *et. al.*: *J Am Chem. Soc.*, **106:** 1198, 1984.

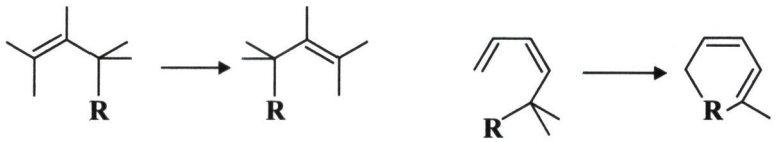


Suprafacial 1,3-Hiickel; [4e Antiaromatic Forbidden] | **Suprafacial 1,5-Hiickel; [6e Aromatic Allowed]** | **Suprafacial 1,7-Mobius, [6e Aromatic Allowed]**

Fig. 15.3: The Excellent Classification of Sigmatropic Hydrogen Shifts with respect to Basis Set Orbitals (BSOs).

Remarks: Importantly, the above conclusions that are solely based upon the so-called **Orbital Symmetry Considerations (OSCs)** are adequately supported by **HF/6-31 G calculations,** that eventually infer that the corresponding **1,5-shifts must be *suprafacial*;** whereas, the **1,7-shifts should be *antarafacial**.**

4. Migration of an Alkyl Moiety Ensures an Additional Stereochemical Feature for Consideration: It is, however, pertinent to state here that the so-called **sigmatropic migration** critically engaging an *alkyl moiety* causes the occurrence of its respective ***shifts***,—as expressed under:



1,3-Alkyl shift **1,5-Alkyl shift**

15.3.1 The Computatinal Characterization of Transition Structures for [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts

In a broader perspective, an array of exhaustive **computational studies** relate to the *transition structures* and especially aimed at providing substantial information with respect to the **transition states (TSs)** of the **sigmatropic rearrangements**.

Camorro *et al.* (2002)* critically characterized the **transition state (TS)** for:

'prototypical [1,3]–sigmatropic shifts of hydrogen and methyl'.

Thus, one may distinctly observe that the **1,3-hydrogen shift** designates an **antarafacial phenomenon;** whereas, the corresponding ***methyl* migration** represents a **suprafacial phenomenon** which essentially takes place with the observed inversion at the specific **alkyl moiety**.

Figure 15.4 illustrates the so-called respective 'nuclear positions'.

*Hess BA JT, Schaad IJ, and Pauelr I, *J Am Chem. Soc.*, **107**: 149, 1985.

Camorro E *et al.*: *J Phys Chem. A.*, **106: 1153, 2002.

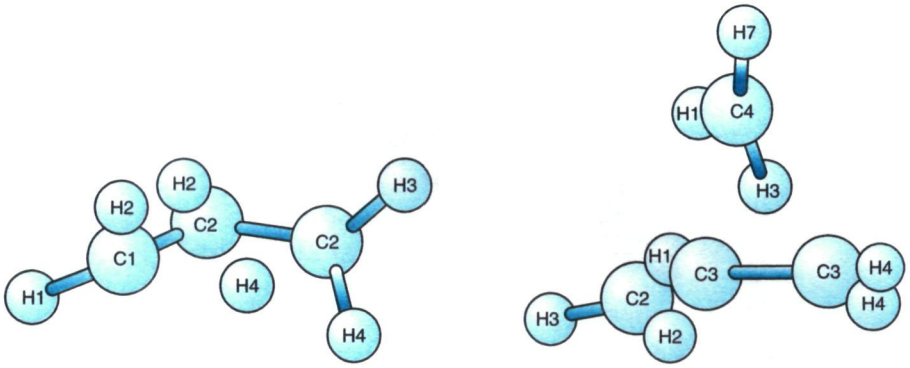


Fig. 15.4: The Nuclear Positions and for Antarafacial [1,3]-Sigmatropic Migration of Hydrogen and for Suprafacial [1,3]-Sigmatropic Migration of Methyl with [B 3LYP/6-311 ++ G (d,p). [*Adapted from: J Phys Chem A*, **106**: 11533, 2002]

15.3.2 Typical Examples of Sigmatropic Shifts of Hydrogen and Alkyl Moieties

Based on the broadly conceptualized and **generalized selection rules** as a duly designated ***unifying theoretical framework*** (see *section 3*),—one may legitimately consider certain particular examples of the **sigmatropic rearrangements**.

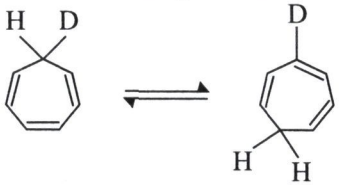
Based on the newer emerging *concepts, ideas,* and *principles*; and also very much in accordance with the so-called **orbital-symmetry general ideas,** there are quite a few typical examples of:

"sigmatropic [1,5]–hydrogen migrations in organic molecules which categorically include a *'pentadienyl'* component".

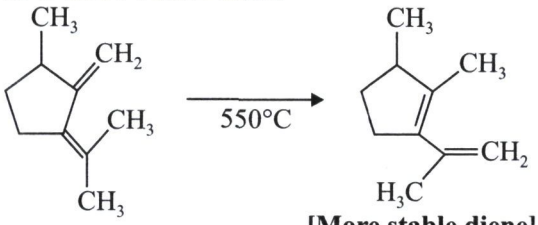
Nevertheless, the overall **activation energies** for such ***organic reactions*** are almost very close to **35 kcal.mol^{-1},** and perhaps this could be the valid reason why such reactions do essentially need ***moderately elevated temperatures****.

Examples: There are *two* classical examples:

(*a*) **Detection of rearrangement due to migration of Isotopic Label****



(*b*) **Transformation to a more stable diene*****



[More stable diene]

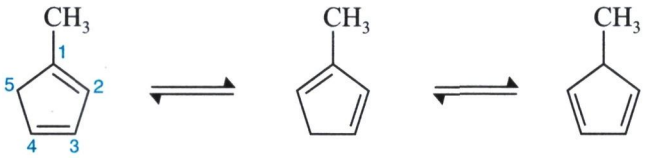
*Roth W R and Koenig J: *Liebigs Ann. Chem.*, **699**: 124, 1966.

**Ter Borg AP *et al.*: *Proe Chem. Soc.*, 359, 1962.

***Weliveben J. *et al. J Am. Chem.* Soc., **86**: 232, 1964.

Sigmatropic Shifts of Hydrogens in Cyclic Systems: It has been *explored*, *examined*, and *evaluated* in an extremely systematic manner by various **organic chemists**:

- Mironov *et. al.* (1963)* first demonstrated the explicit **equilibration** phenomenon occurring amongst the **methylcyclopentadienes**,—as stated under:



[1-Methyl-2,3-cyclopentadiene] **[1-Methyl-2,5-cyclopentadiene]** **[1-Methyl-2,4-cyclopentadiene]**

- Mironov *et. al.* (1969)** proven and ascertained the **equilibration** phenomenon taking place amongst the **methylcyclo-heptadienes,**—as given below:



[1-Methyl-1,6-cycloheptadiene] **[1-Methyl-5,6-cycloheptadiene]** **[1-Methyl-4,6-cycloheptadiene]** **[1-Methyl-3,5-cycloheptadiene]**

Important Computational Investigative Studies: In the recent past the ***computational investigative studies***, using the **B3LYP/6-31G system,** were duly performed on the following ***four*** **chemical entities,** namely:

- **Cyclopentadiene** [E_a = 27 kcal.mol^{-1}]***
- **1,3-Cyclohexadiene** [E_a = 41.9 kcal.mol^{-1}];****
- **1,3-Cycloheptatriene** [E_a = 32.7 – 35.3 kcal.mol^{-1}];***** and
- **1,3-Cyclooctadiene** [E_a = 32.2 kcal.mol^{-1}]****

Importantly, one may take cognizance of the fact that there prevails a **reasonable agreement with the ensuing experimental data.** However, the *actual overall energy essential parameter* solely depends upon the ***emnated structure of the*** **transition state (TS)**—that gets enormously influenced and modulated by the so-called **'ring-geometry'** perceptively.

Example: **Methyl-substituted 1,3-Cyclopentadienes**

In this particular instance, there exists predominantly the following ***two*** **proven criteria,** namely:

- **presence of seven minima;** and
- **presence of *seven TS* for the [1,5]-sigmatropic shifts.**

*Mironov VA *et al.*: *Tetrahedron*, **19**: 1939, 1963.
**Mironov VA *et al.*: *Tetrahedron Lett.*, 499, 1969.
***Alkorta I and Elasion *J. J. Chem. Soc.*, Perkin Trans. **2**, 2497. 1990.
****Hess BA Jr. and Baldwin JE: *J Org Chem.*, **67**: 6025, 2003.
*****Hess Ba Jr.: *J Quantum Chem.*, **90**: 1064, 2002.

NOTE:

1. **The *energy requirement* (Ea) varies between 29.6 (4 → TS34 to 35.3 (2 → TS34) kcal. mol^{-1}.**
2. **These cited *'energy relationships'* are beautifully illustrated in Fig. 15.5.**

Fig. 15.5 depicts the various *chemical structures* and the ensuing *relative energies* of **isomeric methyl-1,3-cyclohaptatrienes;** and the **transition state (TS)** for **[1,5]-sigmatropic hydrogen** shift observed between them.

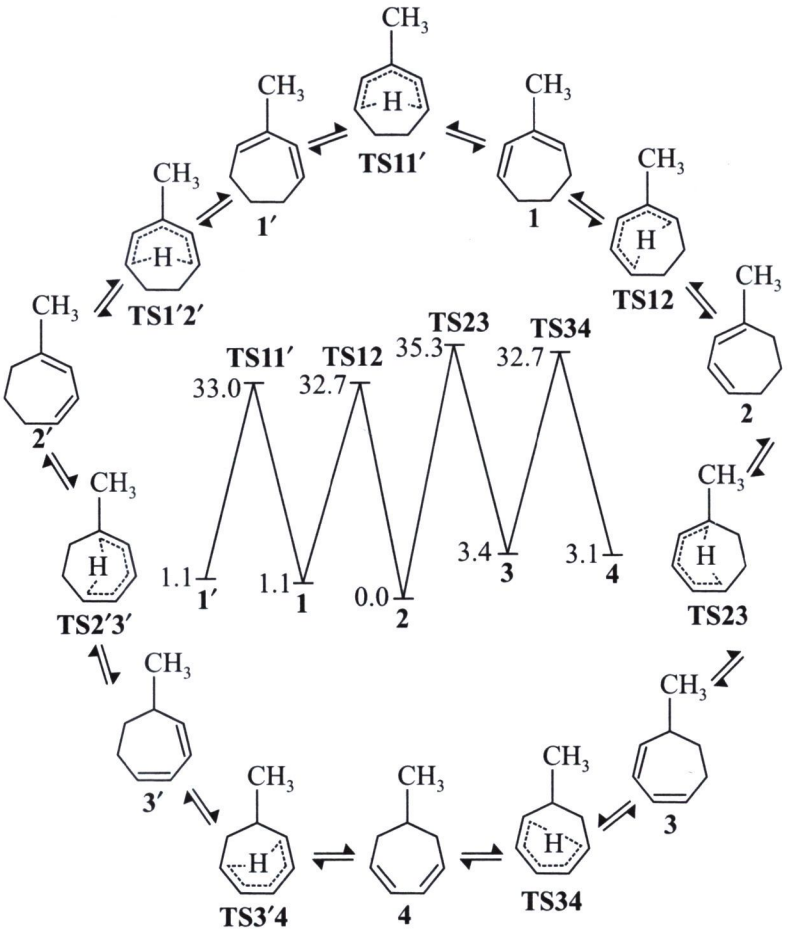
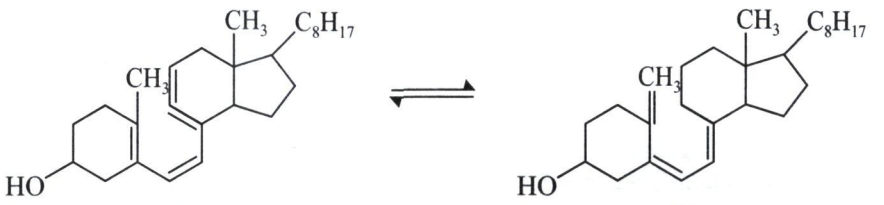


Fig. 15.5: Various Structures and Relative Energies of the Isomeric Methyl-1, 3-Cycloheptatrienes and the Transition State (TS) for [1,5]-Sigmatropic Hydrogen Shift Prevailing between them.

[Data Used From: *Int. J Quantum Chem.*, **90**: 1064, 2002].

❑ **Thermal Equilibrium between Precalciferol [Previtamin D_3 (X)] and Calciferol [Vitamin D_3 (Y)]: Showing [1, 7]-Hydrogen Shift**—Let us examine an extremely vital and important example of the **[1,7] hydrogen shift** which relates to the thermal equilibrium prevailing between **precalciferol [previtamin D_3 (X)]** and **calciferol [vitamin D_3 (X)]**—as expressed under:



(X)
Precalciferol
[Previtamin D_3]

(Y)
Calciferol
[Vitamin D_3]

NOTE: **The above reaction possesses an *energy requirement* (E_a) of 19.2 kcal.mol^{-1}.**

Fig. 15.6 vividly summarizes the precise comparative *energy requirement* (E_a) for the respective **[1,3]-, [1,5]-, and [1,7]-hydrogen shifts:**

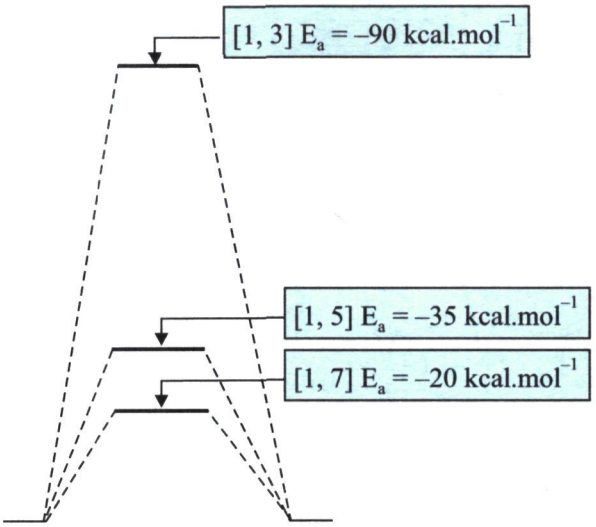


Fig. 15.6: The Schematic Comparison of Energy Requirement (E_a) for [1,3]-, [1,5]-, and [1,7]-Sigmatropic Hydrogen Shifts.

15.4 OVERVIEW OF [3,3]-SIGMATROPIC REARRANGEMENT

A survey of literature and scientific evidences reveal vchemently that the **[3,3]-Sigmatropic rearrangements** are indeed an extremely *vital*, *useful*, and *important* reaction.

Nevertheless, the most important **[3,3]-Sigmatropic rearrangement** right from the ***organic synthesis*** point of view are those that critically influence the formation of:

'newer carbon-carbon bonds'.

Certain Classical Examples of [3,3]-Sigmatropic Rearrangements

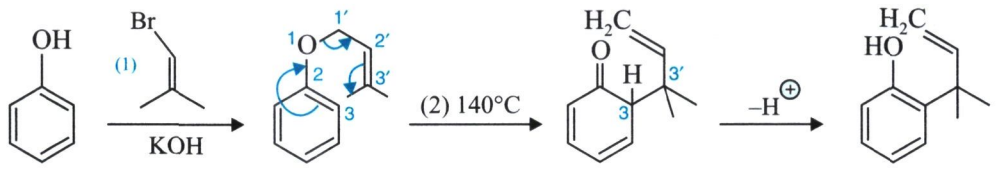
Following are a few classical examples involving the **[3,3]-sigmatropic rearrangements,** namely:

15.4.1 Claisen Rearrangement

The classical **Claisen rearrangement** is represented by the ***first* and *slow* step** of the *isomerization phenomenon* of:

"allyl aryl ethers to *ortho*-allylated phenols".

Figure 15.7 shows the preparation of an allyl aryl ether and the subsequent **Claisen rearrangement***.



Phenol **(A)** **Cyclohexadienone** **(B)** **More stable Phenol**

EXPLANATIONS

1. A **cyclohexadienone (A)** is first generated in the actual **rearrangement step,** that is a **[3,3]-sigmatropic rearrangement.**
2. Thus, **3-valence electron pairs** are being shifted almost at the same time in the said step.
3. **Cyclohexadienone (A)** being a nonaromatic chemical entity may not be isolated; and hence, undergoes *tautomerization* to the corresponding *aromatic compound*; and ultimately a **more stable phenol (B)** is obtained.

Participation of an Alkenyl Moiety in the Claisen Rearrangement of Allyl Ethers

Interestingly, the so-called **allyl-enol ethers** are being utilized as the ***substrates*** in this particular instance:

Figure 15.6 illustrates how such an—**'allyl alkenyl ether', (IV),** may be prepared right from an **allyl alcohol** just in a **single operation modality**. Thus, the **allyl alcohol** gets simply treated with a ***large excess of* ethyl vtnyl ether [C_6H_5. $\overline{O}$—CH=CH_2]** in the presence of ***catalytic quantum* of mercuric acetate [$Hg(OAc)_2$]**. We may have the following sequential reactions:

*The rearrangement is duly named after the German Organic Chemist: **Ludwig Claisen.**

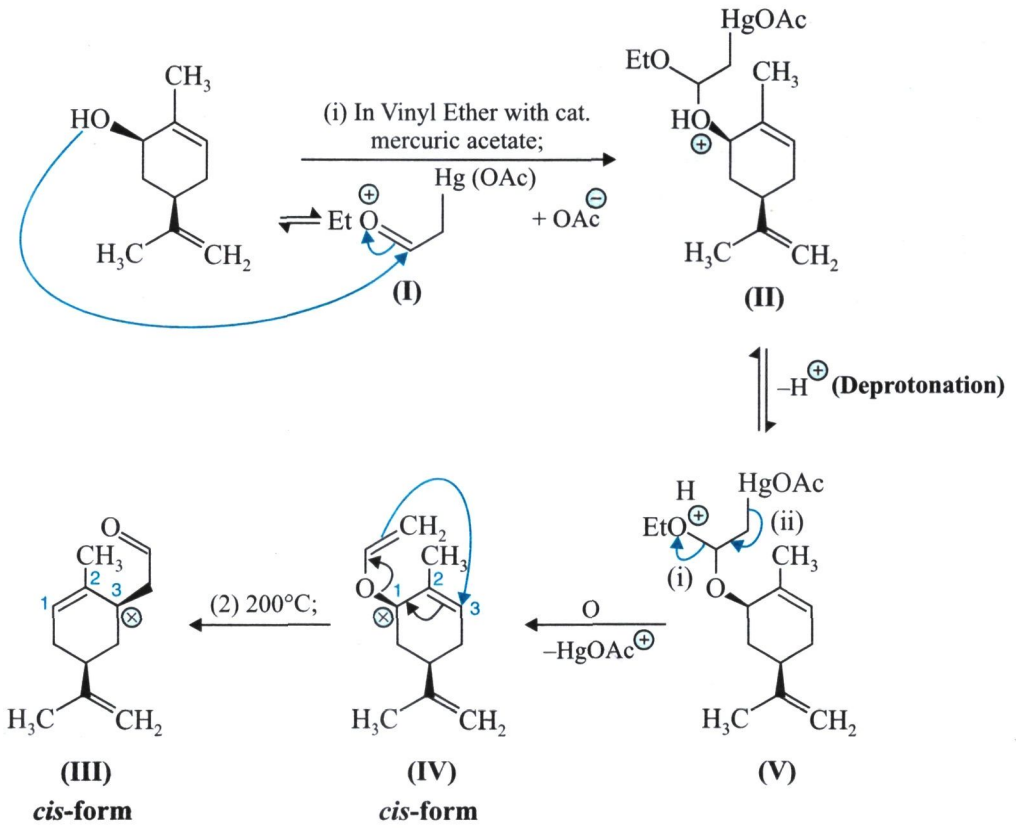


Fig. 15.6: Sequential Reaction Steps Leading to the Preparation of an Allyl Enol Ether (IV) from an Allyl Alcohol and a Large Excess of Ethyl Vinyl Ether. Subsequent Claisen Rearrangement [(IV) to (III) Results into a Chirality Transfer (*i.e.*, chirality ⊗ being transferred from C-1 (in IV) to C-3 (in III).

Explanations

The preparation of an **alkenyl moiety** in the **Claisen rearrangement** of ***allyl ethers*** involves various sequential steps that may be explained as under:

1. The aforesaid preparation essentially involves an **oxymercuration phenomenon** of the **C=C olefinic bond** of the so-called **ethyl vinyl ether [Et. $\overline{O}$ —CH=CH_2).**
2. The **mercuric acetate cation [Hg $(OAc)^+$]** serves as the **attacking electrophile,** as expected probably; however; it critically gives rise to the formation of:

   "an *open-chain cation (I)* as the intermediate instead of a cyclic mercurinium ion", (see Fig. 15.6).

Comments: Importantly, the so-called open-chain cation (I) is definitely proven to be ***much more stable*** in comparison to the respective **mercurinium ion** since it may be adequately **stabilized** by means of the **carboxonium resonance.**

3. Thus, the **cation (I)** subsequently takes up the **allyl alcohol;** and thereby forms a **protonated mixed acetal (II)**. Amazingly, the resulting **compound (II)** undergoes an **E_1-elimination process** that critically eliminates:
   - **Ethanol (EtOH);** and
   - **Mercuric acetals ion [Hg (OAc)$^{\oplus}$],**

   thereby gives rise to the desired **enol ether (IV).**
4. The resulting **compound (IV)** is found to be in *complete equilibrium* with the **substrate alcohol** and the **ethyl vinyl ether (Step-1)**. The observed **equilibrium constant** is found to be ~ **1**.

Remarks: Importantly, the intelligent use of a large excess of the **ethyl vinyl ether** helps predominantly to ***shift the equilibrium*** towards the direction of **enol ether (IV)** so that the latter may be isolated in an appreciable **good yield.**

5. **Enol ether (IV)** on being subjected to *heating* gets subsequently converted to the corresponding **aldehyde (III)** *via* a ***Claisen rearrangement*** as shown in Fig. 15.6. Thus, the **compound (III)** and its ***precursor*** **(IV),** both are found to be ***cis*-substituted cyclohexanes.**

Mechanism: The **σ-bond** which has since migrated helps to maintain the connectivity with **2 C-atoms** duly present in the product; whereas, it meticulously connected to a **C-atom** and an **O-atom** present in the ***substrate***.

Besides, the **σ-bond** does remain on the same side of the **cyclohexane ring system;** and, therefore, the **Claisen rearrangement** takes place:

"having almost *complete* transfer of the inherent *stereochemical information* right from the *original oxygenated stereocentre* to the newly generated stereocentre".

Chirality Transfer*:** Interestingly, such a ***stereocontrolled transformation of an ***old*** **stereocentre** into a ***new*** **stereocentre** is variably termed as the **'chirality transfer'**. Thus, the **Claisen rearrangement,** leading to **conversion of Compound (IV) to Compound (III),** (as shown in *Fig. 15.6*), explicitly designates the *highly specialized case of*:

"a 1,3–chirality transfer",

since the **newly assigned stereocentre** is located at **C-3** with respect to the **old stereocentre,** that is considered to be at **C-1 position.**

15.4.2 Cope Rearrangements

The **[3,3]-sigmatropic rearrangement** of **1,5-hexadienes** is usually known as the **Cope rearrangement,**—as shown under:



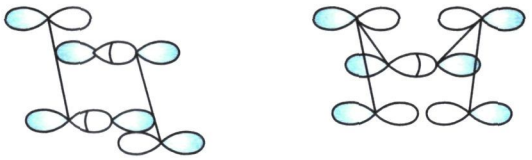
1,5-Hexadiene **2,4-Hexadiene**

Thus, the **transition state (TS)** for the **[3,3]–sigmatropic rearrangements** may be actually regarded to be:

'two distinct interacting allyl fragments'.

Therefore, in a particular instance when the entire ensuing process is found to be ***suprafacial* in both the functional moieties,** it results into an array of **'aromatic orbitals'**; and hence, the prevailing process is allowed thermally.

Shea *et al.* (1992)* vehemently proposed a **'chairlike'—transition state conformation;** however, a **'boatlike' conformation** may also be possible largely,—as depicted below:



'Chairlike'- transition conformation **'Boatlike'- transition conformation**

Basis set orbitals for **Chair** and **Boat** transition structures for [3,3]-sigmatropic shifts, 6π-electrons; Niickel aromatic.

The **Cope rearrangements** refers to the so-called **thermal [3,3]-sigmatropic rearrangement** of ***1,5-dienes,*** and are found to be ***reversible reactions***. Since there exists obsolutely little change either:

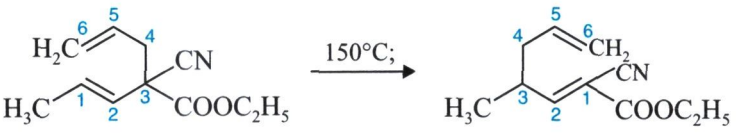
- **in the total number;** or
- **in the types of bonds,**

and hence, to a ***first* approximation** the total ***bond energy* remains almost unchanged.**

Importantly, the **Cope rearrangement** reaction is found to be intimately governed by the **'thermodynamic control'**; and thus, prominently establishes a perfect equilibrium status between the ***two* aforesaid 1,5-dienes.**

Comments: The precise and exact expected place of the ***'final equilibrium'*** is, in fact, solely monitored and governed by the: **'inherent *relative stability* of both starting material and product'.**

Example: Conversion of 1-methyl-3-cyano-3-ethyl carboxylate-1,5-ene hexane **(X)** to 3-methyl-1-cyano-1-ethyl carbonylate-1,5-ene hexane **(Y)**,–serves as a befitting example:



(X) **(Y)**

Points to Ponder:

1. In this typical case the **'equilibrium'** is duly being controlled and monitored by the ensuing *conjugation phenomenon* with the **carbonyl (>C=O)** and the **cyano (CN)** moieties present in the product **(X)** and **(Y)**.

*Shea KJ *et al.*: *J Am. Chem. Soc.*, **114:** 2635, 1992.

2. The 1, 5-ene position in both **(X)** and **(Y)** are the same.
3. The **cyano (CN)** and **ethyl carboxylate ($COOC_2H_5$)** functional moieties have been duly interachanged between **C-3 in (X) to C-1 in (Y)**.

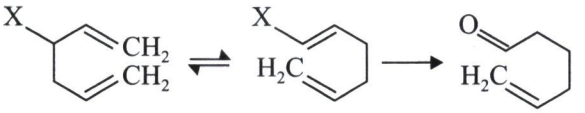
The following Fig. 15.7 clearly shows the typical and classical examples of the **[3,3]–Sigmatropic Rearrangements**

(*a*) Cope Rearrangement[1]



1. Rhoads SJ and Raulins NR, *Org React*, **22** : 1, 1975

(*b*) Oxy-Cope and Anionic Oxy-Cope Rearrangement[2]



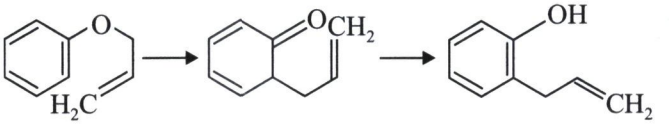
2. Evans DA and GolobAM, *Jam Chem Soc*, **97**:4765, 1975

(*c*) Claisen Rearrangement of Vinyl Ethers[3]



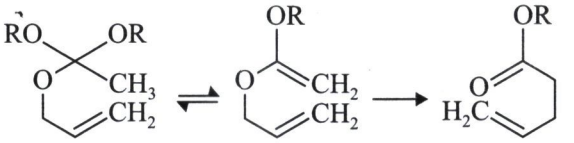
3. Castro Amm, *Chem.Rev.*, **104**:2939, 2004.

(*d*) Claisen Rearrangement of Aryl Ethers[4]



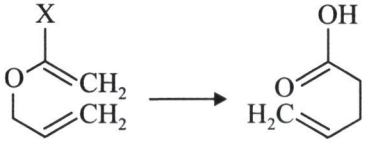
4. Tarbel DS, *Org React*, **2:1**, 1944.

(*e*) Orthoester Claisen Rearrangement[5]



5. Johnson WS et al; *J Am Chem Soc*, **92**; 741, 1970

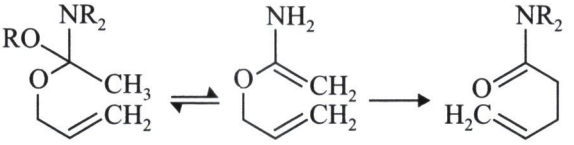
(*f*) Ester Enolate and Ireland-Claisen Rearrangement[6]



6. Ireland RE *et al.*, *J Am Chem Soc*, **98**:2868, 1976

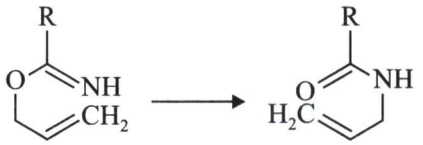
$X{=}O^{\ominus}$ or $OSiR_3$

(*g*) N, N-Dialkyl Ketene Aminal Rearrangement[7]



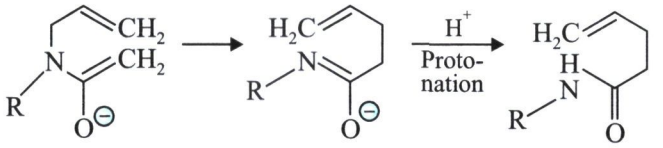
7. Felix D *et al.* : *Helv Chim Acta*, **52**: 1030, 1969.

(*h*) *O*-Allyl Imidate Rearrangement[8]



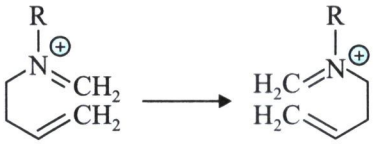
8. Overman LE, *Acc. Chem Res.*; **13**:218, 1980

(*i*) N-Allyl Amide Enolate Rearrangement[9]



9. Nubbemeyer U, *Synthesis*, 961, 2003

(*j*) Azonia-Cope Rearrangement[10]



10. Overman LE, *Acc. Chem Res.*; **13**:218, 1980

Fig. 15.7: Typical and Classical Example of [3,3]-Sigmatropic Rearrangement.

15.4.3 [3,3]-Sigmatropic Rearrangement in Triene Systems Containing Oxygens

Based on the foregoing theoretical conceptualizations, discussions, interpretations, and inferences drawn so far, one may arrive at another vulnerable and the most interesting episode where in the **[3,3]–sigmatropic rearrangement reaction profile** is found to be absolutely general for:

"a host of other system that essentially include one or more *'heteroatoms'* in place of the C-atom in the so-called 1, 5-hexadiene unit".

Hurd and schmerling (1937)* duly established the so-called **intramolecular nature** of the **[3,3]–sigmatropic rearrangement** by the help of a *crossover experiment performed* wherein the compound **A** and **B** on being subjected to heating simultaneously produced:

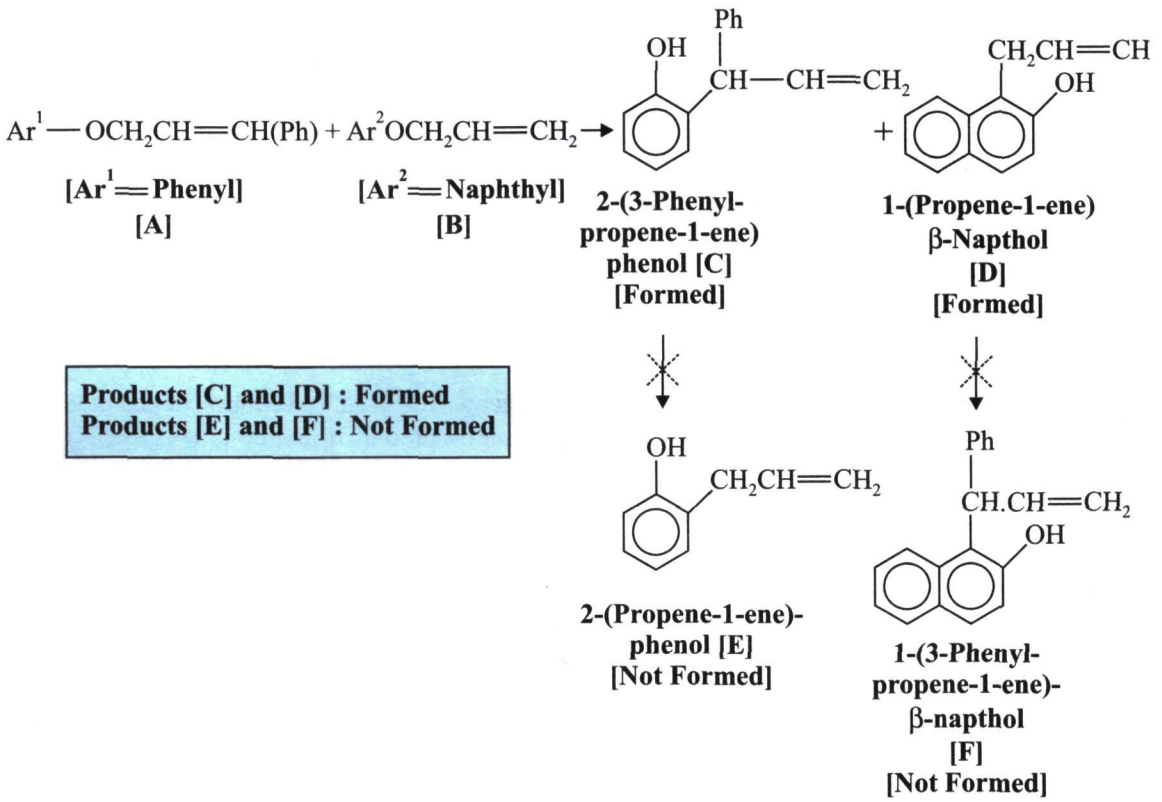
'the *identical products* as when they were *heated individually*'.

Obviously, there was almost little concrete evidence available to prove and ascertain the actual formation of the **crossover products E** and **F**,—thereby suggesting strongly that the:

'ensuing [3,3]-Sigmatropic, rearrangement should be intramolecular in nature'.

Thus, we may have the following expressions:

*Hurd CD and Schmerling L, *J Am Chem. Soc.*, **59**: 107, 1937.



Some Classical Examples: Following are a few important classical examples pertaining to the present context, namely:

(*a*) **Stereochemistry of Silyl Ketene Acetal:** It may be duly controlled and monitored by the *actual prevailing parameters of preparation.*

Importantly, **lithium diisopropylamide (LDA)** serves as the base which is used preferentially for the **enolate formation**.

Example: Enolate Prepared in Pure Tetrahydrofuran (THF): The **E-enolate** so formed invariably maintains its ***stereochemistry*** also in the respective ***silyl derivative***.

EXPLANATIONS

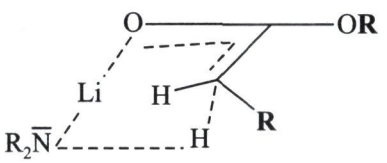
Interestingly, the *preferential generation* of the **E-enolate** may be explained judiciously in terms of a **cyclic transition state (TS)** wherein the *proton* (H^+) is being abstracted from the corresponding:

"stereoelectronically preferred orientation almost perpendicular to the carbonyl plane perceptively".

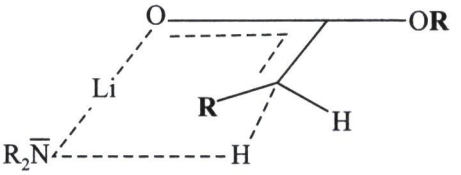
Nevertheless, the prevailing interaction between:

- **Base** and - **α-substituent,**

virtually disfavours the **transition state (TS)** for the **Z-enolate**—as shown under:



Transition State (TS) for E-enolate Favoured



Transition State (TS) for Z-enolate Disfavoured

NOTE: **If *hexamethyl phosphoric acid (HMPA)* is being incorporated in the solvent, the so-called *Z-enolate* predominated exclusively*.**

(*b*) **Stereoselectivity of Ireland-Claisen Rearrangement:** It is indeed controlled and modulated by the actual prevailing configuration of the **double bonds** present in both:

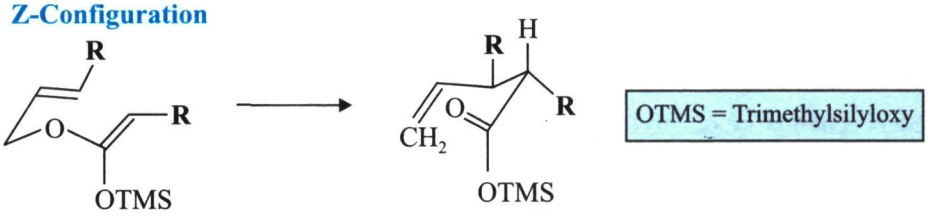
- **allylic alcohol;** and
- **silyl ketene acetal.**

Example: It has been duly proven and demonstrated that the ***'chair form'*** of the respective **transition state (TS) model** does predict precisely and accurately that the **inherent configuration** at the *newly generated C-C bond* shall be determined either:

- **by the Z-configuration of *slilyl ketene acetal*,** or
- **by the E-configuration of *silyl ketene acetal*.**

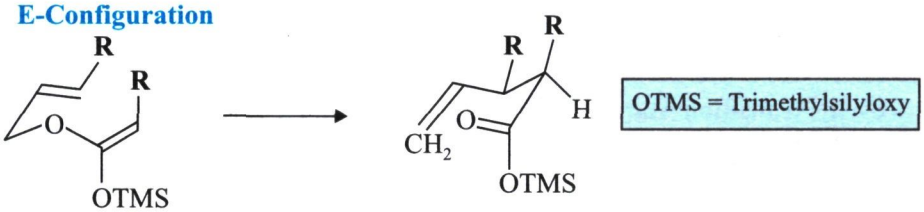
Thus, we have the following expressions:

Z-Configuration



Z-Silyl ketene acetal ***syn*-Isomer**

E-Configuration



E-Silyl ketene acetal ***anti*-Isomer**

*Ireland RE *et al.*: *J Am Chem. Soc.*, **98**: 2868, 1972, Ireland RE and Will and AK, *Tetrahedron Lett.*, 3975, 1975. Ireland Re *et.al. J Org. Chem.* **56**. 650, 1991.

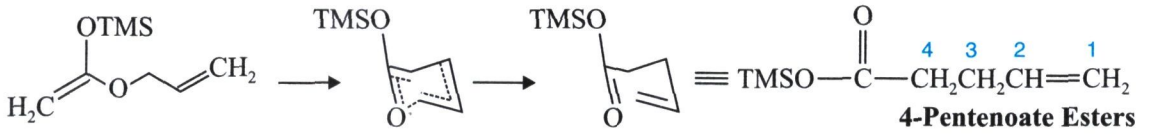
(*c*) **Other Donar Substituents [*viz.*, Trimethylsilyloxy (OTMS):** In this particular instance, the **donar substitutents (OTMS)** located strategically at **C-2** are found to be **strongly accelerating*** in nature. Besides, the aforesaid effect forms the fundamental basis of the so-called:

'synthetic importance of the *ester-enolate Claisen-rearrangements*'

wherein either the **enolates** or the **allyl ketone acetals of allylic esters**—are meticulously rearranged into the respective **4-pentenoate esters****.

NOTE: **The above reaction is called as the '*Ireland-Claisen Rearrangement*'.**

Thus, we may have the following expressions:



Silyl ketene acetals of allylic esters

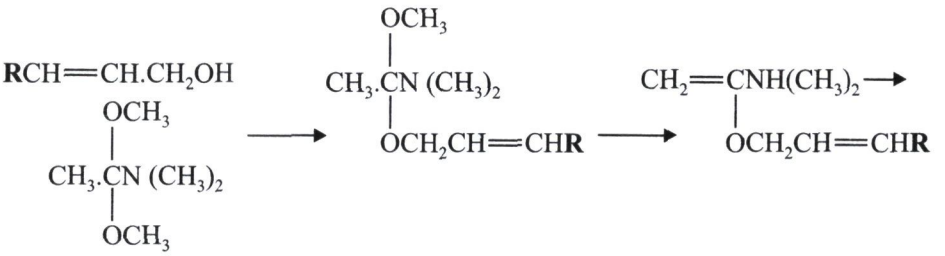
15.4.4 [3,3]-Sigmatropic Rearrangement of Trienes Containing Nitrogen

It relates to a reaction which is associated intimately to the ***orthoester*** **Claisen-rearrangement;** and hence, makes use of an **'amide acetal'** *viz.*, **dimethylacetamide dimethyl acetal** critically being involved in the ***exchange reaction*** having the **allylic alcohols**—which ultimately yields

'amides of γ, δ-unsaturated carboxylic acid's.***

Sueraw *et al.* (1975) proposed that the inherent **stereochemistry of the reaction** is found to be quite analogous to the other respective variants of the **[3,3]-sigmatropic rearrangement.**

We may have the following expressions:



Mechanism: The ***O*-allyl imidate esters** do have a tendency to undergo the so-called **[3,3]-sigmatropic rearrangements** to give **N-allyl amides.**

Perhaps it could be the possible reasons for it being sometimes referred to as:

"an aza-Claisen Rearrangement".

Thus, the observed resonance stabilization of the ensuing *amide* ***linkage*** which is duly created definitely provides a **theromodynamic driving force.**

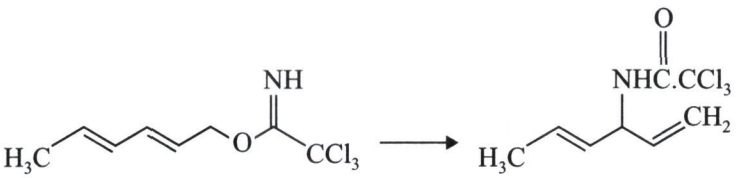
*Gajewaski JJ and Emrani J: *J Am. Chem. Soc.* **106**: 5733, 1984.

Periera S and Srebrik M: *Aldriohimiea Acta.*, **21: 17, 1993.

***Wiek AE *et al.*, *Helv Chem Acta*, **47**: 2425, 1964: Felix D *et al. Helv Chem Acts* **52**: 1030, 1969.

- The **trichloromethyl imidates** may be prepared convenently from the **allylic alcohols** by interaction with **trichloroacetonitrile** (CCl_3CN).
- The subsequent rearrangement gives rise to the formation of **trichloroacetamides of N-allylamines***.
- Amazingly, the overall yields in the reaction are invariably improved upon by the judicious inclusion of **potassium carbonate (K_2CO_3)** in the ***initial reaction mixture itself***.

Thus, we may have the following expression:



15.4.5 [2,3]-Sigmatropic Rearrangements

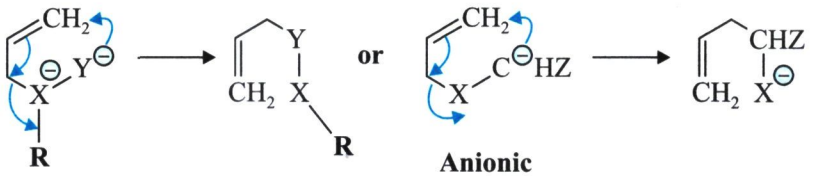
Mechanism of [2,3]-Sigmatropic Rearrangements: Based on the scientific evidences and logical explanations we may invariably come across an array of so-called: concerted rearrangements,—which essentially exhibit:

'an explicit [2,3]-sigmatropic reactivity profile'.

Importantly, the **[2, 3]-sigmatropic type of rearrangements** has been duly designated by the following ***two*** **recognized** ***'generic charge variants'***, such as:

- ➢ **involving oxides (or ylides);** and
- ➢ **involving anions.**

We may express the aforesaid rearrangements as given below:



Neutral (oxide or ylide) **Anionic**

- **Neutral (oxide or ylide) Variation:** The one major requirement for a facile **[2,3]–sigmatropic phenomenon** being that the **atom 'X'** present strategically at the ***allylic position*** should be able to act the **'leaving moiety'** since the **atom 'Y'** located in its vicinity commences the **bonding process** to the *allyl systems,* where the atoms **X** and **Y** do possess the formal charges (as in the case of **oxides and ylides**).

  Following are a few glaring and most well-developed reactions involving the rearrangements, namely:

  - **Allyl Sulphoxides:** [Evans DA and Andrews GC: *Acc Chem. Res.,* **7**: 147, 1974];
  - **Selenorides:** [Sharpless KB and Lauer RF: *J Am Chem Soc.*, **95**: 2697, 1973; Nishibayashi Y and Uemura S: *Top Curr Chem.*, **208:** 201, 2000];

*Overman LE: *J Am Chem. Soc.,* **98**: 2901, 1976, *ibid, Acc Chem. Res.*, **13:** 218, 199

Nishkawa T *et al.*: *J Org Chem.*, **63: 188, 1998.

- **Ammonium Ylides:** [Vedejs E *et al.*: *J Org Chem.*, **43**: 1185, 1978]; and
- **Sulphonium Ylides:** [Trost BM and Melvin LS Jr.,: **Sulfur Ylides**, Academic Press, New York, 1975].

❑ **Anionic Variation:** In this case, the **group Z** should be all means be able to facilitate the formation of the **carbonion**.

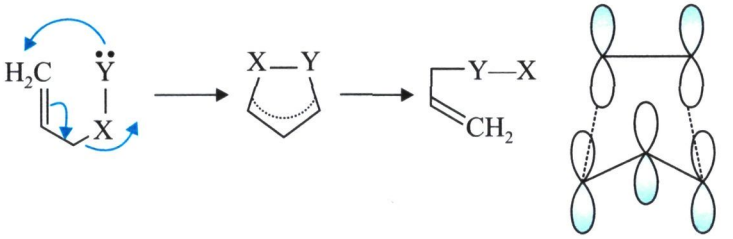
Example: The most vital and important examples of the **anionic type** are the rearrangements of the ***carbonions*** **of ethyl ethers**.

Transition state (TS) for [2,3]-Sigmatropic Shifts: It is usually viewed as engaging an **allylic system** and a **migrating component**. However, one may take cognizance of the fact that:

"there exist in all *six* participating electrons in a Hiickel type array"

and, therefore, the **transition state (TS)** is found to be **aromatic in character**.

Thus, we may have the following expressions:



Computational Investigative Studies: In the recent part, there have been quite a few **computational investigative studies** partaining to the:

[2,3]–sigmatropic rearrangement. Importantly, the so-called **MP 3/3-216$^{\otimes}$**–level calculations of:

"allyl sulphoxide rearrangement reproducing vividly the *stereoselectivity* and the *activation energies*".*

It is, however, pertinent to state at this point in time that not only this but also many such related rearrangements do extribit predominantly the ***transition state (TS) arromaticity*** in terms of the **magnetic criteria,** such as:

- **NICS,** and
- **magnetic susceptibility.****

Suggested Reading

Doyle MP *et al.*: **Reactions and Synthesis with α-Diazocarbonyl Compounds,** Wiley, New York, 1997.

Harwood M (Ed.): **Polar Rearrangements,** Oxford University Press, New York, 1992.

Hudlieky T (Ed.): **Organic Synthesis: Theory and Applications,** JAI, Greenwich (CT), 1996.

*Jones Hertzog DK and Jorgensen WL: *J Am Chem. Soc.*, **117**: 9077, 1995, *Ibid*: *J Org Chem.* **60**: 6682, 1995; Jursic BS: *Theochem.*, **338**: 131, 1995.

Fonkin AA *et al.*: *J Org Chem.* **65: 2984, 2000.

Hoffmann R W *et al.* (Eds.): **Methods in Organic Chemistry,** Verlag, Stuttgart (Germany), pp: 3810, 1996.

Katritzky AR *et al.* (Eds.): **Comprehensive Organic Functional Group Transformations, Vol. 1,** Elsevier Science, Oxford (UK), 1993.

Mayo P dc (Ed.): **Molecular Rearrangements, Vol. 1,** Interscience, New York, pp: 655-684, 1963.

Mayo P de (Ed.): **Rearrangements in Ground and Excited States, Vol. 1,** Academic Press, New York, 1980.

Morrison JD (Ed.): **Asymmetric Synthesis Stereodifferentiating Reactions, Part-A, Vol 3,** Academic Press, New York, 1984.

Trost BM and Melvin LS Jr.: **Sulfur Ylides,** Academic Press, New York, 1979.

Trost BM and Fleming I (Eds.): **Comprehensive Organic Synthesis, Vol. 5,** Pergamon Press, Oxford (UK), 1991.



Chapter 16

Rearrangements Influenced By Strong Bases [and/or] Electron Rich Sites

LESSONS AT A GLANCE

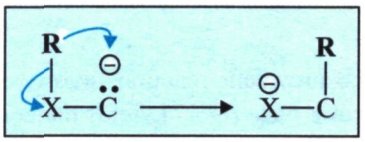
16.1 Introduction
16.2 Various Rearrangements Based on Carbonyl Moieties
- 16.2.1 Benzylic Acid Rearrangement
- 16.2.2 Favorskii Rearrangement
- 16.2.3 Neber Rearrangement
- 16.2.4 Stevens Rearrangement
- 16.2.5 Wittig Rearrangement

16.1 INTRODUCTION

In a broader perspective, the rearrangment that are found to be particularly influenced by **strong bases** and/or the so-called **electron-rich sites** *(usually C-atoms)* invariably are being critically initiated by:

'an anion formation both meticulously and preferentially',

thereby affording the specific removal of a **proton** (H^+) by means of a ***strong base*** **(KOH)**. Thus, the ensuing ***alkyl moiety*** gets duly migrated without its inherent ***'bond-pair of electrons'***,—which seems to be *quite unlike the rearrangements usually occurring* ***in an*** *electron-deficient system,*—as given under:



where, X = An **'heteroatom'** (*viz.*, N, O, S).

Alternatively, all the aforesaid rearrangements may be categorized into the following head:

"REARRANGEMENT ON CARBONYL (>C=O) MOIETY"

16.2 VARIOUS REARRANGEMENTS BASED ON CARBONYL MOIETY

Following are the *five* vital and important typical and divergent rearrangements that are exclusively based upon the **carbonyl (>C=O) moiety,** namely:

(*i*) **Benzylic Acid Rearrangment,**

(*ii*) **Favorskii Rearrangement,**

(*iii*) **Neber Rearrangement,**

(*iv*) **Steven Rearrangement,** and

(*v*) **Wittig Rearrangement**

which, shall now be discussed individually in the sections that following:

16.2.1 Benzylic Acid Rearrangement*

It is also known as the **Benzil-Benzillic Acid Rearrangement.** It refers to the *base-induced* rearrangement of **benzil** to **benzylic acid** *via* **the migration of phenyl moiety.** Importantly, it is regarded to be a relatively *more abandantly perceived rearrangment* that essentially include:

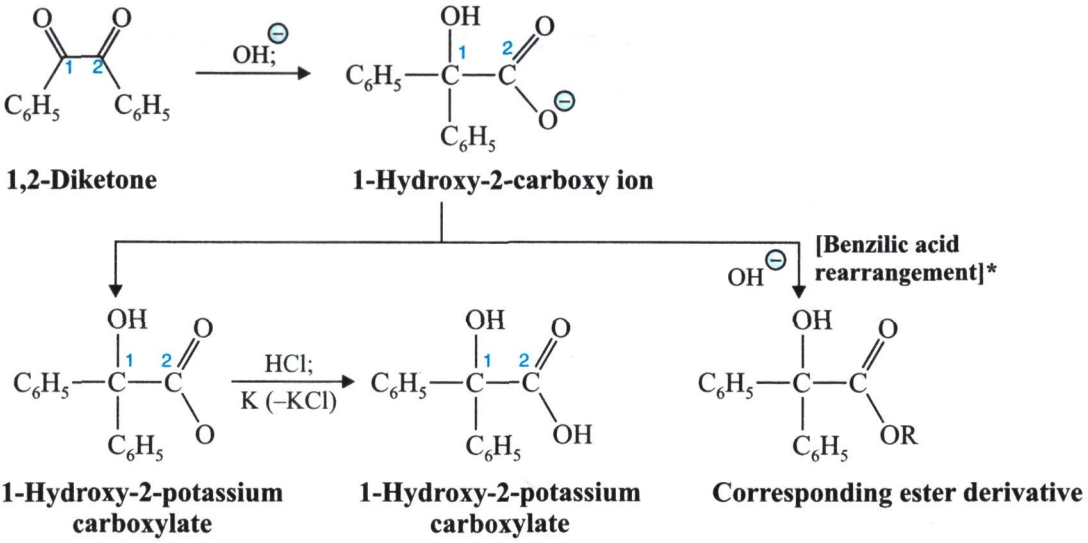
"the critical migration of other moieties in *α-dicarbonyl chemical* entities (compounds)".

It may be expressed as under:



- *First*: Conversion to a Respective *'ester'* due to the ensuing *benzilic acid rearrangement** in the presence of *alkoxide ion* ($OR^{\ominus}$); and
- *Second*: Conversion to a *1-hydroxy and 2-carboxy derivative via* the formatin of *1-hydroxy and 2-potassium carboxylate* by treatment with KOH followed by HCl:

Thus, we may have the following expressions:



Remarks: Obviously, the aforesaid reaction relates to a typical **1,2-rearrangement** essentially involving a ***migrating carbanion*** **instead of a** ***migrating carbocation.***

Interstingly, Lee and Uff (1967)** proposed vehemently that one of the most crucial features of the so-called **Benzylic Acid Rearrangement** being:

"obviously the *better migration ability profile* of the *phenyl moiety* substituted prominently with the respective-*weaker electron-donating moieties* (*viz.*, *m*-chloro) *vis-a-vis* with much stronger electron-donating moieties (*viz.*, *p*-methoxy)".

NOTE: **In reality, in-coming *substitutents* must not possess the *α-H-atoms* at all so as to avoid the so-called *'aldol reaction'* perceptively.**

Mechanism of Benzylic Acid Rearrangement: The precise mechanism of **Benzylic acid rearrangement** has been *explored, studies* and *reported extensively****.

Nevertheless, earlier Ingold (1928)**** duly substantiated the possible mechanism based solely on the various experimental evidences of the **Benzylic acid rearrangment.**

Importantly, we may now discuss the underlying **mechanism of the Benzylic acid rearrangement** sequentially by the following cardwel steps, namely:

*Lee JB and Uff BC: *Quart Rov* (London, UK), **21:** 429, 1967.

Collins CJ and Eastham JF: In: **The Chemistry of Carbonyl Group [Patais (Ed.)], Willey Y mk. pp. 783-787, 1966.

***Sehnen S and Eastham JF: *Q Rov Chem Soc.*, **14:** 221-235, 1960.

****Ingold CK: *Ann Rept Prog Chem* (London UK), **25:** 124, 1928.

(*a*) **Initiation Step: From Benzil to 1-hydroxy-2-carboxylate:**

[Lee JB and Uff BC: *Quart Rev.* London (UK), **21**: 429, 1967]

(*b*) **Benzilic Acid Rearrangement of the Cyclic Diketones Leading to Ultimate Ring Contraction:**

[Schattegger A and Bigler P: *Helv Chim Acta,* **69**: 1666-70, 1986]

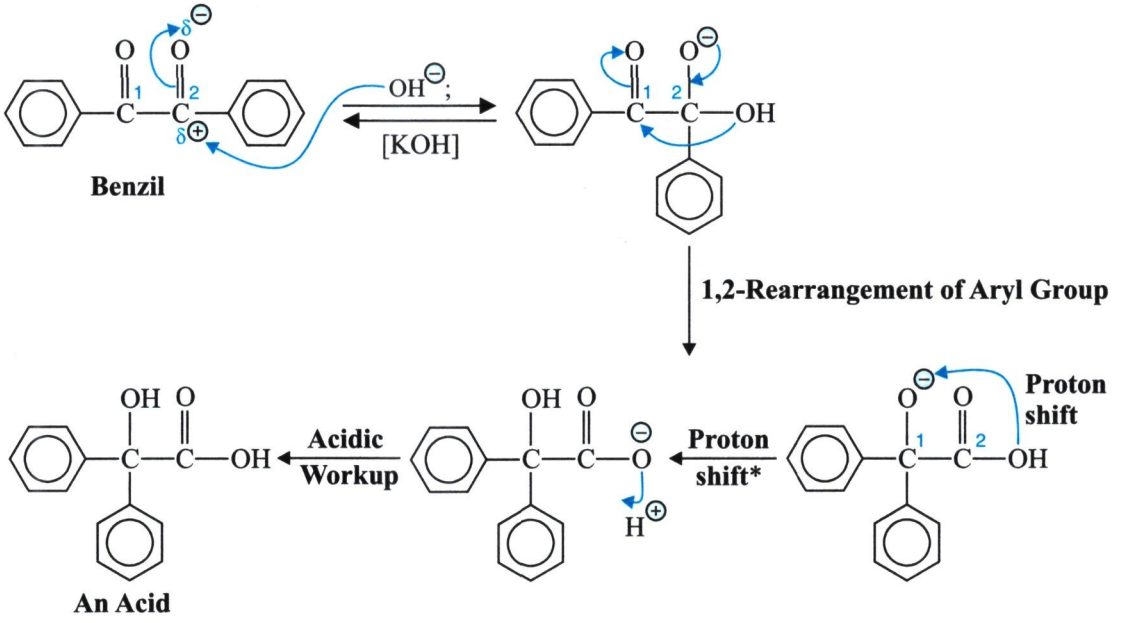
(*c*) **Established and Recognized Mechanism duly Updated Using a *Silico Data*:**

[Yamabe S *etal.*: *J Org. Chem.,* **71** (5): 1777-83, 2006]

(*d*) **Suggested *'Orbital Diagram'***

[Sehinichi Y *etal.*: *J Org Chem.*, **71** (6): 1880-83, 2006]

[*a*] **Initiation Step: From Benzil to 1-Hydroxy-2-Carboxylate**



EXPLANATIONS

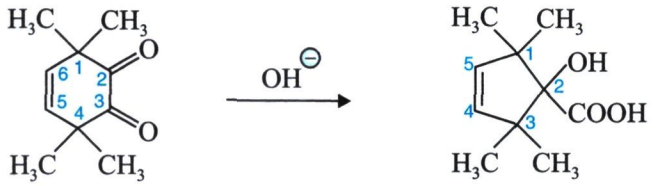
The various steps involved may be explained as under:

1. *First* **initiation step** of the sequence of reaction is indeed a **nucleophilic addition** of the **hydroxide ion ($OH^{\ominus}$)** to the carbonyl group located strategically at **C-2** position.
2. *Secondly*, the corresponding **aryl (C_6H_5) moiety** subsequently migrates along with an **inherent bend pair of electrons (:) from C-2 to the C-1 position** (*i.e.*, the so-called **1,2-rearrangment**).
3. It is now followed by the critical shifting of the **π-electrons** right from the ensuing ***migrating* terminal C-atom** (*i.e.*, C-2) to the respective **O-atom** present in the **carbonyl moiety (at C-1).**

*The reaction is moved in the forward direction by **'Protonation'** ultimately.

4. Thus, it results into the *formation of a specie* that eventually undergoes a typical ***Proton shift,*** immediately followed by an **acidic workup** to give rise to the formation of an **acid** (*i.e.,* **1-hydroxy-2 carboxylate**).

[*b*] **Benzilic Acid Rearrangement of the Cyclic Diketones Leading to Ultimate Ring Contraction**

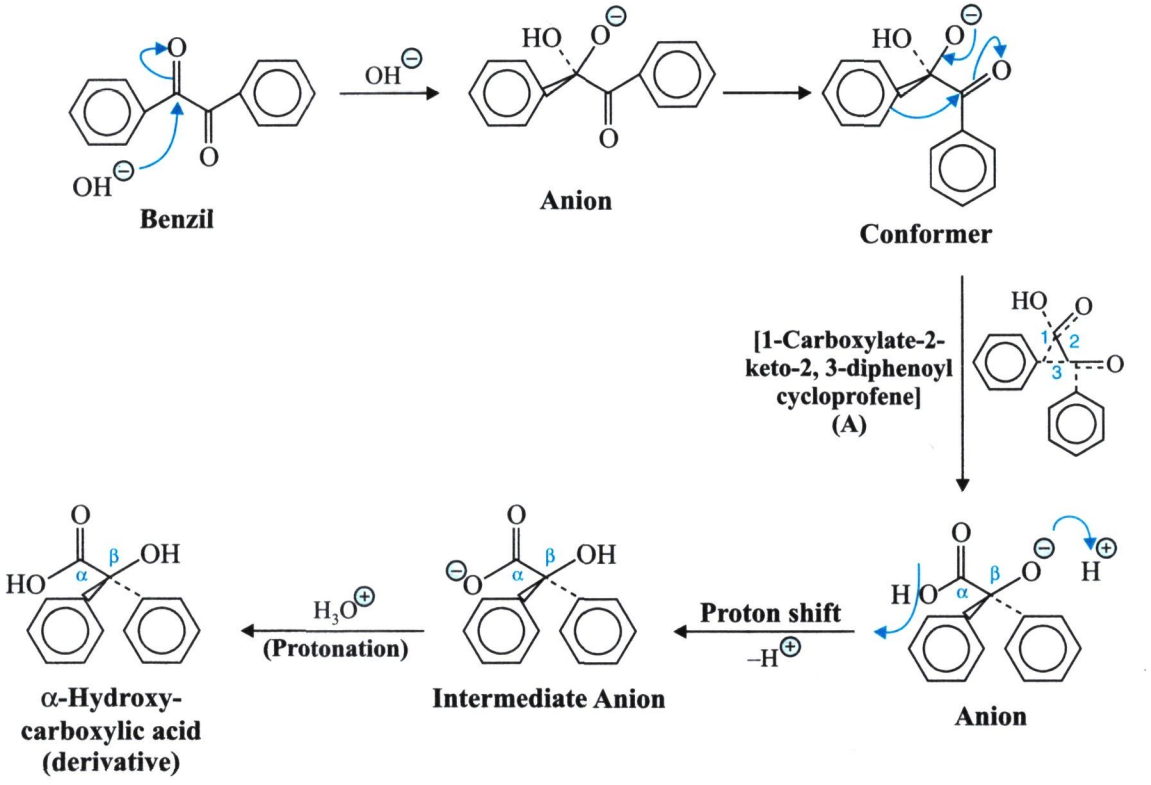


Ring contraction from 6-membered to 5-membered cyclic ring system

Cyclohexene-5-ene, 2, 3-diketone-1,4-tetra methyl **Cyclopentene-4-ene, 2-hydroxy 2-carboxylate-1, 3-tetra methyl**

[*c*] **Established and Recognized Mechanism duly Updated Using a *Silico Data***

Starting from **benzil** there are ***five*** **sequential steps** *via* the formation of: **an anion–a conformer–an anion–an intermediate anion** and–**an α-hydroxy carboxylic acid,** that are illustrated as given below:



EXPLANATIONS

1. **Benzil** yields an **anion** in an *alkaline medium*, which undergoes a **1,2-rearrangement** to give a **conformer**.
2. The resulting **conformer** on being subjected to treatment with the interactive reagent **(A)** to produce another **anion**, that eventually undergoes:
   - **Deprotonation at α C-atom; and**
   - **Protonation at β C-atom,**

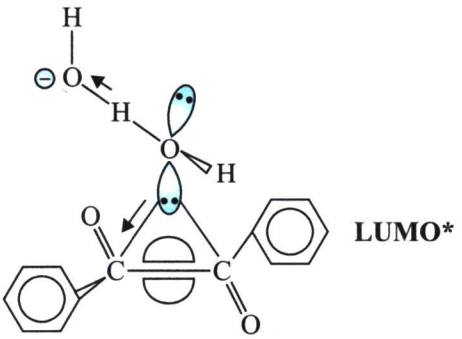
   to give rise to the formation of an **'intermediate anion'**.
3. The **intermediate anion** so obtained on further *protonation* produces the desired **α-hydroxy carboxylic acid (derivative)**.

[*d*] **Suggested Orbital Diagram**

Shinichi *et al.* (2006) suggested intelligently the following ***two* probable structures**, such as:

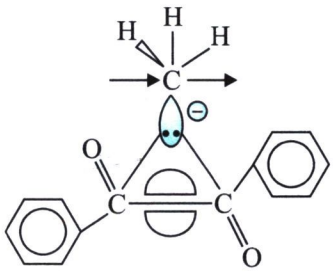
- **Transition State (TS) showing the *'Addition of hydroxyl (OH^-) ion'*, and**
- **Transition State (TS) depicting the *'Migration of Phenyl Moety'*.**

Following are the above *two* proposed ***'Orbital Diagrams'*:**



LUMO*

Transition state (TS) depicting addition of hydroxyl Ion (OH^-)



LUMO*

Transition state (TS) showing migration of phenyl moiety

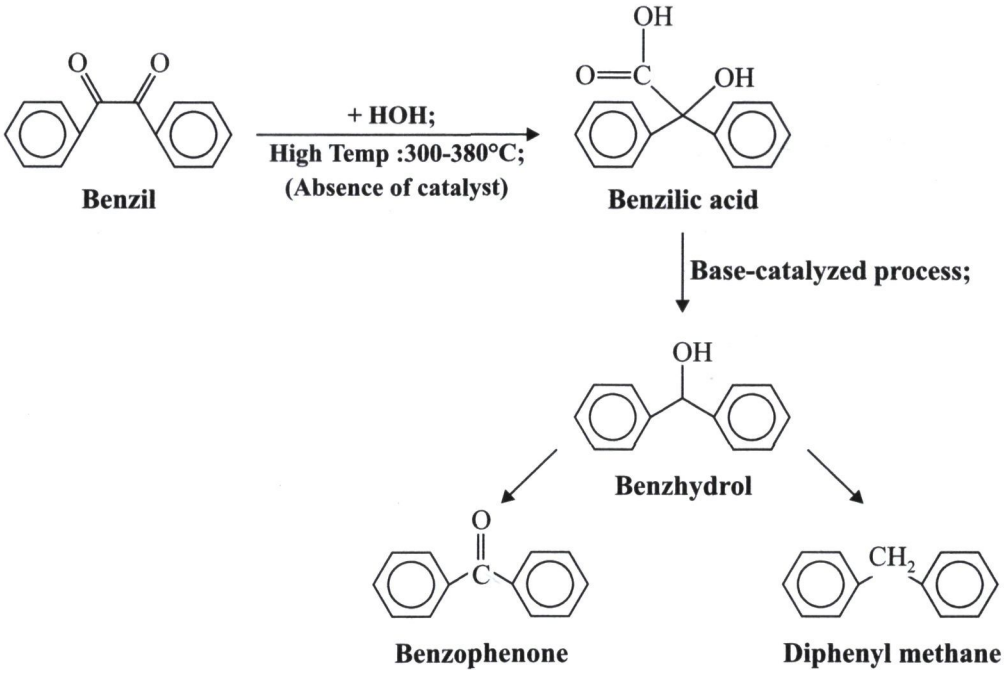
***LUMO: Lowest Uncoupled Molecular Orbitals**

❑ **Benzylic Acid Rearrangement: A Base-Catalyzei Phenomenon**

Craig and Philip (2005)* critically observed that the **organic reaction** specifically conducted at *high temperature* ranging between **300-380°C** invariably comes into play as the **base-catalyzed phenomenon exclusively**. Therefore, the so-called **benzylic acid rearrangement** experimentally is **also a base-catalyzed episode** very much under the *conventional parameters* (*viz.*, **in an admixture of water/dioxane at ~ 100°C**).

*Craig MC and Philip ES: **ARKIVOC, 7:** 800-806, 2005.

Thus, we may have the following expressions:



Comments: The base-catalyzed process of **benzilic acid** ultimately gives rise to the formation a mole each of **benzophenone** and **diphenyl methane** *via* the **formtion of benzhydrol** by the proposed method of **Craig and Phillip (2005)**.

NOTE: **Craig *et al.* (2005) concluded vehemently that the *Benzil-Benzylic acid rearrangement* is obviously catalyzed by:**

- **Acid**
- **Base and**
- **Water at High Temperature (300-380°C).**

16.2.2 Favorskii Rearrangement*

Preamble: It is also called as the **Wallach Degradation****. In a broader perspective, the **Favorskii rearrangement** relates to the ***base-catalyzed*** **rearrangement** of:

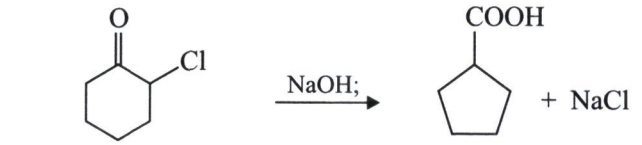
'α-haloketones to the respective *acids* or esters'.

Wallach Degradation: It refers to the rearrangement of **α, α′-dibromocyclohexanones** to the corresponding **1-hydroxycyclopentane-carboxylic acids,** duly followed by *oxidation to the ketones.*

*Favorskii AE: *J Prokt Chem.*, **88** (2): 658, 1913.

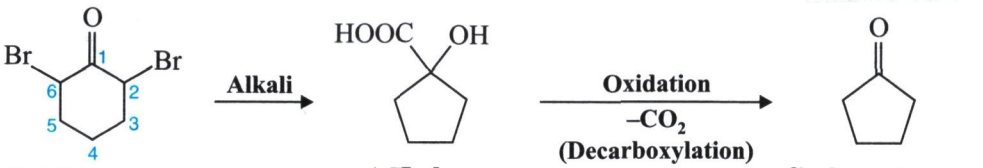
Wallach O: *Ann.*, **414: 296, 1918.

Thus, we may have the following expressions:



2-Chloro-cyclohexane **Cyclopentane-1-carboxylate**

Conversion of 6-membered ring to 5-membered ring system

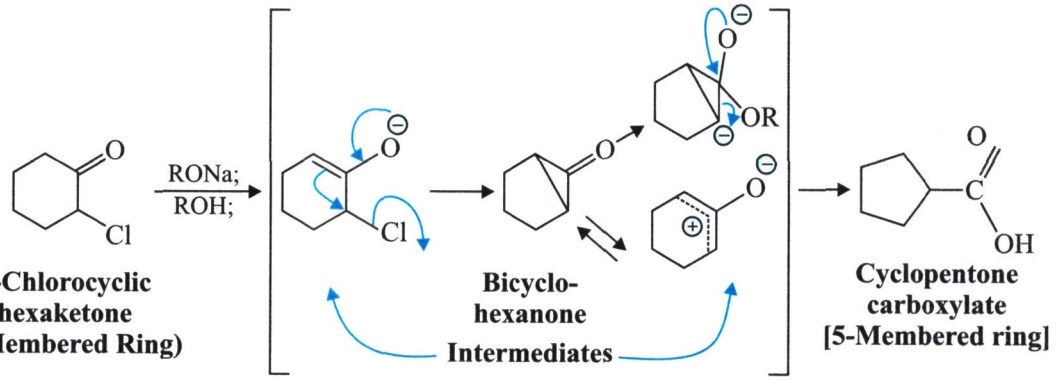


2,6-Dibromo-cyclohexanone **1-Hydroxy 1-carboxy cyclo-pentane** **Cyclopentanone**

In other words, the **Favorskii rearrangement** entails a **skeletal 1,2-rearrangement** essentially induldging the specific treatment of the so-called **α-haloketones** (with the so-called **α-H-atoms**) and also the ***'nucleophilic bases'***.

Ring Contraction of 2-Chloro-cyclohexanone

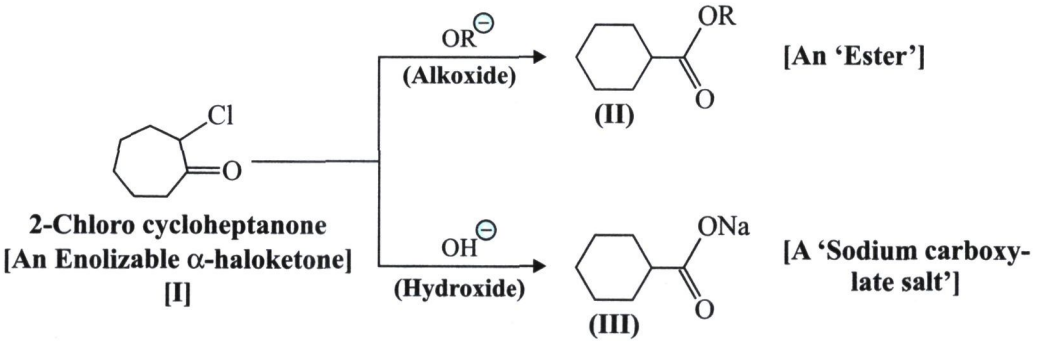
Favorski and Boshowski (1914)* observed critically that when **2-chlorocyclohexanone** (or **2-chlorocyclic hexaketone**) is being subjected to treatment with an *alcoholic alkali (NaOH/EtOH)*—it causes a definite **Ring contraction,**—as shown under:



2-Chlorocyclic hexaketone [6-Membered Ring) **Bicyclo-hexanone** **Cyclopentone carboxylate [5-Membered ring]**

Mechanism: The above rearrangement critically involves the ***intramolecular transformation*** of the so-called **enolizable α-haloketones (I)** to the corresponding ***esters***, ***carboxylic acids***, or ***amides*** through the spectacular: **alkoxide**–(OR^-), **hydroxide–(OH^-)**, or even the **amine-catalyzed rearrangements,**—that are illustrated as under:

*Favorskii A and Boshowski V: *J Russ Phys. Chem Soc.*, **46**: 1098, 1914.

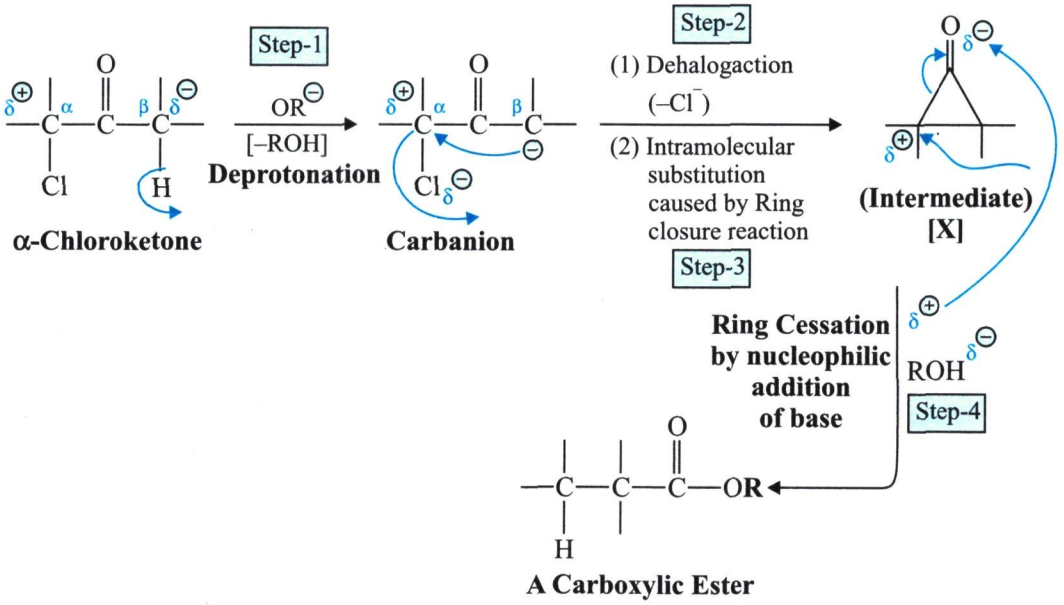


Remarks: It is, however, pertinent to state here that the underlying **mechanism** predominantly involved in the conversion of the **α-haloketone (I)** into the corresponding **esters (II)** (*with* $OR^{\ominus}$) or **sodium carboxylate salt (III)** (*with* $OH^{\ominus}$).

Importantly, the above cited ***proposed*** **'mechanisms'** may be summarized most **explicitly**, **logically**, and **intelligently** in the following ***two*** **individual schemes,** such as:

- **Open-chain α-haloketone;** and
- **Cyclic α-haloketone.**

(*a*) **Open-chain α-haloketone Scheme:** Let us look into the following scheme dealing exclusively with the **open-chain α-haloketone**.



EXPLANATIONS

1. In **step-1**: the **α-chloroketone** undergoes *deprotonation* to lose a mole of ROH to yield a **'carbanion'**, which on **dehalogenation (—$Cl^{\ominus}$) (step-2)** affords a **ring closure** reaction due to the *intramolecular substitution* **(step-3)** to give a cyclic (cyclopentane) **intermediate (X)**.

2. The resulting **intermediate (X)** undergoes *ring cessation* (opening) by the **nucleophilic addition of base (step-4)** in the presence of ROH, to give rise to the formation of a **carboxylic ester**.

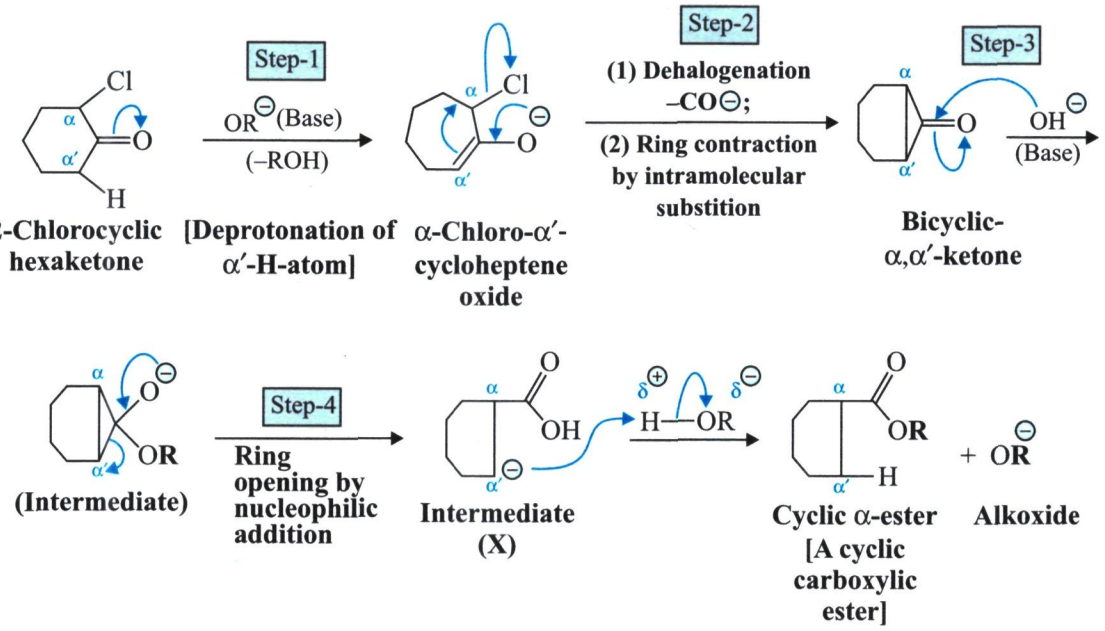
(*b*) **Cyclic α-Haloketone Scheme:** In thus particular instance, the formation of a **cyclic α-haloketone** takes place starting from **2-chloro cyclohexanous** through ***four* sequential steps (*i* to *iv*),** namely:

(*i*) Deprotonation of α′-H-atom (*i.e.,* an abstraction of a proton (H+) by the base);

(*ii*) Departure of the 'Leaving Functional Moiety';

(*iii*) Ring closure by *'intramolecular substition'* thereby affording the formation of an **intermediate**; and

(*iv*) Ring cessation due to the **nucleophilic addition** of the *base* to **intermediate (X).**



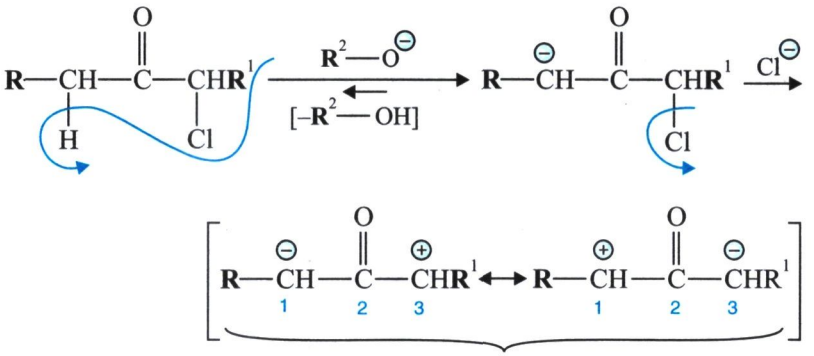
EXPLANATIONS

1. Deprotonation at *α′-H-atom* of **2-chlorocyclic hexaketone (Step-1)** causes a *ring expansion* (from **6-member ring to 7-member ring system**) to yield **α-chloro-α′-cycloheptene oxide,** which undergoes **dehalogenation** (—$Cl^{\ominus}$) followed by **ring contraction by intramolecular substitution (Step-2)** to give a **bicyclic α,α′-ketone**.
2. The resulting **bicyclic α,α′-ketone** when treated with a base gives an **intermediate (Step-3)**, which specifically affords a **ring opening by nucleophilic addition (step-4)** to produce an **intermediate (X)**.
3. Finally, the **intermediate (X)** when treated with **HOR** yields *two* products, namely:
   - **a cyclic ester** (*i.e.,* **a cyclic carboxylic ester**); and
   - **an alkoxide ($OR^{\ominus}$)**

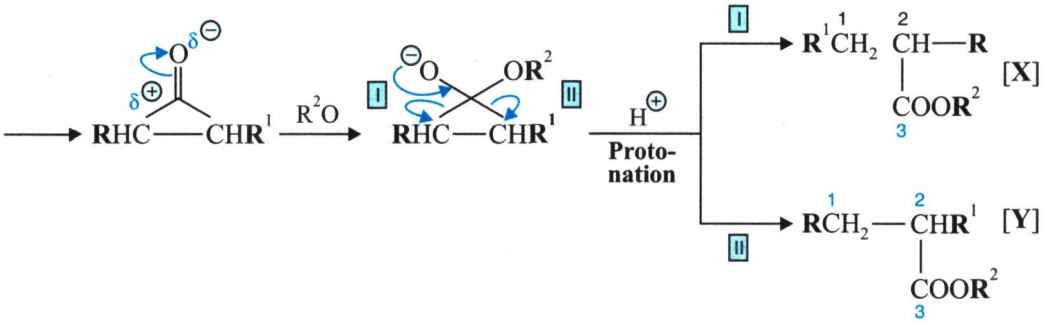
Another Approach to Illustrate the Favorskii Rearrangement (or Wallach Degradation):

Conversion of 2,6-Dibromocyclo-hexanone to cyclopentanone.*

Importantly, we may also expatiate the underlying **mechanism**** of the aforesaid reaction,— as given under:



1, 3-Dipolar structure



- The *two* reversible 1,3-dipolar structure the charges located on **C-1** is ***negative*** and on **C-3** is ***positive*** in the *first* while in the *second*, ***vice-versa.***
- The **end product (X),** an 'ester', has C-1 attached to $\mathbf{R^1}$, C-2 attached to **R**, and C-3 attached to $\mathbf{R^2}$; whereas, the **other end product (Y),** also as '*ester*', has C-1 attached to **R**, C-2 attached to $\mathbf{R^1}$, and C-3 attached to $\mathbf{R^2}$ respectively.

NOTE: **The $\mathbf{R^2}$ attached to C-3 in both the functional ester moieties in X and Y are the same.**

Ring Contraction: Always Proceeds with Favorskii Rearrangement

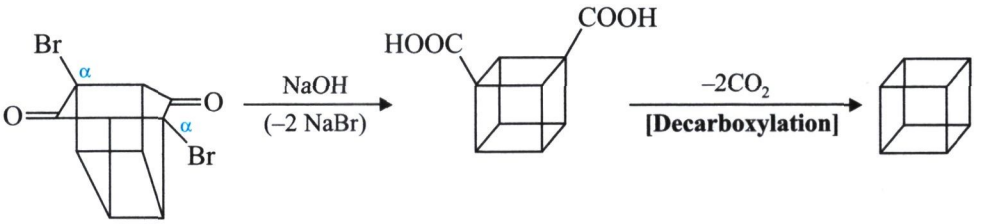
Eaton and Cole (1964)*, and Barborak *et. al.* (1966)** critically and vehemently pointed out that the **Favorskii rearrangement** invariably comes into play with the usual **ring contraction** *i.e.,* from 7-membered ring to 6-membered ring, and from 6-membered ring to 5-membered ring system.

*Wallach O: *J Chem. Soc; Abstr,* **1:** 487, 1916

Bordwell FG *et al., J. Am. Chem.* **91. 2087, 1969.

Therefore, the **Favorskii rearrangment** is of utmost usage as well as importance in the desired synthesis of an array of **organic chemical entities (compounds),** such as:

- **the '*steroids*'; and**
- **the '*cubane*' [*i.e.*, Pentacyclo (4, 2, 0, $0^{2.5}$, $0^{3.8}$, $0^{4.7}$) octane]**



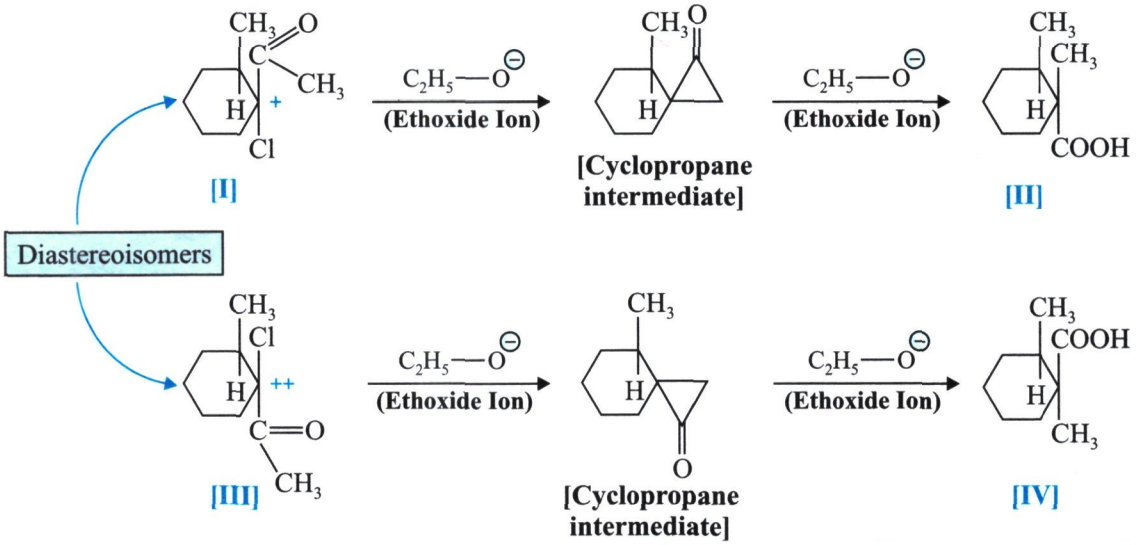
Abad *et al.* (1981)*** reported that when the **Favorskii rearrangement** is carried out with either:

- **α, α-dihaloketones,** or
- **α,α′-dihaloketones** (*i.e.*, **with one α′-H-atom**),

the so-called **'resultant rearranged product'** is found to be an α,β-unsaturated ester.

Stereospecificity of Favorskii Rearrangement [or Wallach Degradation]

The observed **stereospecificity of the aforesaid reaction** may be explored and subsequently revealed based upon the following sequential step wise reactions:



† The **Favorskii reaction** must not be confused with **Mayer-Schiister Rearrangement.**
†† In the **Meyer-Schiister Rearrangement 'acid'** is being used instead of a **'base'.**

Explanations

These essentially comprise:

1. The **diastereoisomers (I) and (III)** ultimately yielded the **corresponding products [II] and [IV].**

*Eaton PE and Cole TW Jr.,: *J Am Chem. Soc.*, **86**: 96, 1964.
Barborak JC *et al.*: *J Am Chem. Soc.*, **88: 1328, 1966.
***Abad A *et al.*: *Tetrahedron Lett.*, 1733-36, 1981.

2. The observed **configurations of (II) and (IV)** are found to be just **opposite to each other perceptively** *i.e.*, **+ C-atom attached with chloro (—Cl)** are **acetyl ($—COCH_3$) moieties** critically undergoes:

   "an inversion in configuration, which being definitely a stereochemical characteristic feature of the S_N2, reaction mechanism".

   Hence, it strongly indicates the **stereospecificity of the Favorskii rerrangement (reaction)**.

3. Importantly, the rearrangement is being usually performed with the **'halo-ketone'** essentially comprising:

   "an *α-H-atom* positioned strategically on the other side of the carbonyl (>C=O) moiety; and hence, the ensuing *mechanism* proceeds predominantly with the distinct formation of *cyclopropanone intermediate*".

Quasi Favorskii Rearrangement

It has been observed most importantly that such ***'ketones'*** that are **totally devoid of any α-H-atom** do also get rearranged squarely to yield almost the ***similar kind of end-product***; however, the exact and precise course of the **ensuing rearrangment** fails to proceed *via* the so-called **'cyclopropanone mechanism'** (*as discussed earlier*). It is, therefore, termed as the—**'Quasi Favorskii Rearrangement'** (Harmata and Wacharasindhu, 2005)*.

Retro-Favorskii Reaction

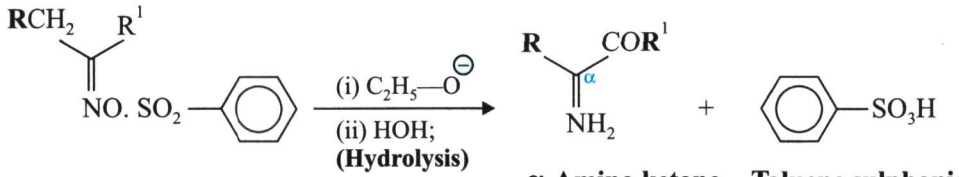
In reality, the **Favorskii reaction** is invariably employed as a means to **protect the 'alkymes'**. Thus, in an instance when the ***'alkyme'*** **is subjected to treatment with acetone**, it may yield the respective **2-hydroxy prep-2-yl-alkyne**. Besides, the **alkyne** having **3-methyl-1-butyne-3-ol** may also be converted into ***'protected alkyne'***. Interestingly, the ***'protective moiety'***** may be eliminated easily and conveniently by:

'simple and careful heating of the chemical entity with KOH solution in isopropanol',

and this is commonly known as the **Retro-Favorskii reaction**.

16.2.3 Neber Rearrangement****

It relates to the formation of the **α-amino ketones** by treatment of **sulphonic esters of ketoximes** with *potassium ethoxide* **(C_2H_5—OK)** and subsequently subjecting it to **hydrolysis**,—as given below:



Toluene sulphonic ester of Ketoxime **α-Amino ketone** **Toluene sulphonic acid**

*Harmata M and Wacharasindhu S: *Org Lett.*, **7**: 2563, 2005.

Greene T and Wuts P: **Protective Groups in Organic Synthesis, Wiley Interscience, New York, 1998.

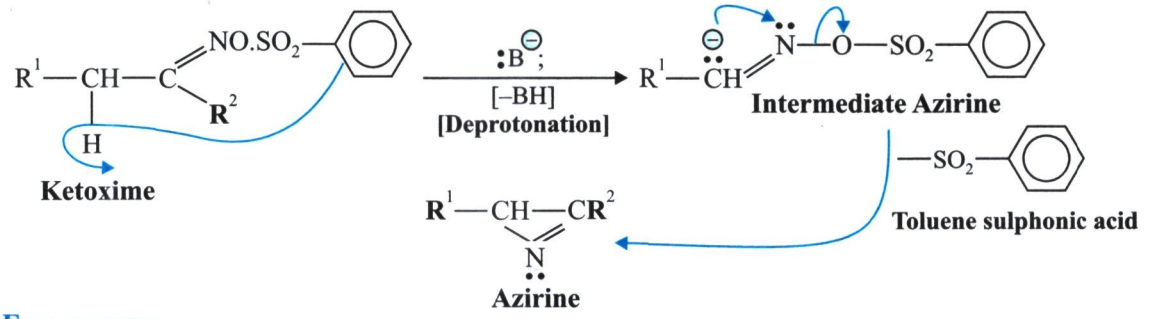
***__Protective Moiety:__ It is introduced into a **chemical entity (molecule)** with a missa to its immense importance in a multistep synthesis by the careful chemical potentiation of a **'functional moiety'**. It also critically endorses the **chanoelectivity in a chemical reaction**.

****Neber PW and Friedoloheim AV: *Ann*, **449**: 109, 1926; Neber PW and Huh G *ibid*, **515**: 283, 1935.

where, **R** = Alkyl/Aryl/Hydrogen;
R^1 = Alkyl/Aryl (No Hydrogen);
$C_6H_5—SO_2—O$ = Toluene sulphonic ester;

Mechanism of Neber Reaction

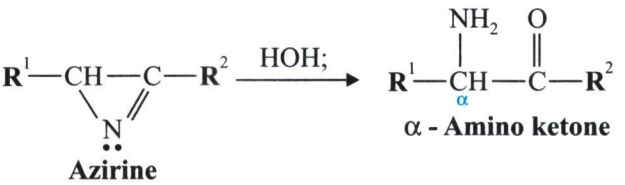
Neber and Burgard (1963)* first and foremost reported the most probable mechanism of **Neber Reaction,**—as shown under:



Explanations

These essentially comprise:

1. *First* step specifically involves the *deprotonation* of ketoxime to eliminate a mole of **BH** (base) thereby giving rise to the formation of an **'intermediate azirine'** (bearing a **carbonion**).
2. The **resulting product** *i.e.,* **intermediate azirine** now loses a mole of **toluene sulphonic acid [—SO_2·C_6H_5]**; however, its respective *isolation* and *characterization* provides a concrete and logical evidence in full support of the aforesaid mechanism.
3. The actual formation of the end-product **'azirine'** may be duly accomplished in a **2-step reaction,** namely:
   - ***First* step–Crucially involves the generation of an *electron-deficient specie*: nitrene**–duly obtained by the removal of toluene sulphonic acid;** and
   - ***Second* step–entails the particular establishment of the *bond* between:**
     - **electron-rich C-atom,** and
     - **electron-deficient N-atom.**
4. The ***first* and *second* step** [*in (3) above*] may be clubbed together. Importantly, the next ***third* step** essentially involves the **hydrolysis** of the ***intermediate azirine*** to give rise to the ultimate formation of an **α-amino ketone**,—as shown below:



*Neber PW and Burand A.: *Leistrias Ann. Chem.* **493:** 281-286. 1932.

****Nitrenes:** Molecular fragments with **6-electrons on the N-atom**. These are the **N-analogs of 'carbenes'**.

Remarks: Based on the scientific evidences and logical explanations one may rightly infer that the **Neber rearrangement** has not yet given any ***concrete*** **and** ***specific*** **stereochemistry** so as to suggest vehemently that:

- **initial *'oxime'* derivative comprises *two* altogether *divergent α-methylene moieties*;** and
- ***reaction mechanism*** **is absolutely independent of the rensuing configuration of the so-called *'oxime structural analogue'* (*i.e., either E-or Z-oxime* would yield the identical product)*.**

16.2.4 Stevens Rearrangement**

The **Stevens rearrangement** relates to the typical migration of either:

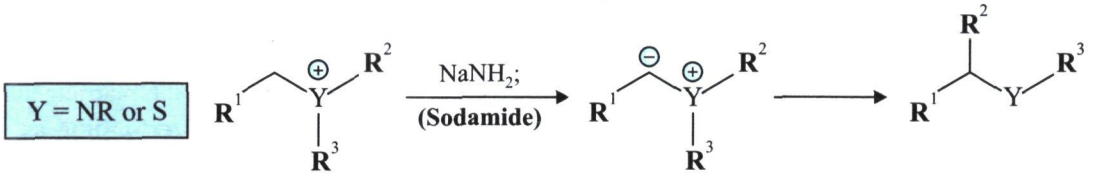
- **from a *sulphonium salt*,** or
- **from a *quaternary ammonium salt*,**

an adjacent **'Carbonionic Centre'** upon treatement with a ***strong base***.

However, the *ultimate product* is essentially:

"a rearrange a tertiary amine or sulphide".

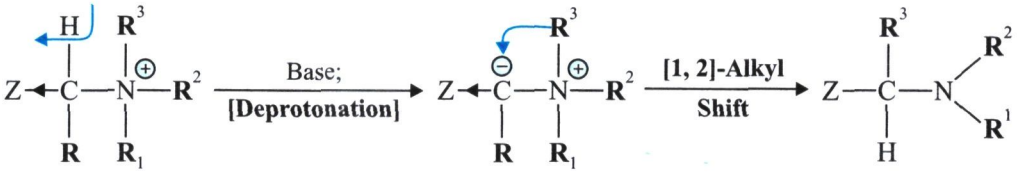
We may express the reactions as under:



Another school of thought, brings about the **Stevens rearrangement** in terms of its critical involvement partaining to:

"the [1,2]-shift of an alkyl moiety from N to C atom in the course of its conversion of the corresponding: *quaternary ammonium* and *sulphonium salts* into the respective amines or sulphides in the presence of a definite strong base"*.**

Thus, we may have the following expressions:



where, Z = An *electron withdrawing group (EWG)* located strategically at *α-C-atom i.e.,* C-adjacent to the N-atom present in the **Quaternary Ammonium Salts (QASs)** or **Sulphonium Salts (SSs)**.

*House and Berkowitz: *J Org Chem.*, **28:** 2271, 1963.

Stevens TS *et al.*: *J Chem Soc.*, 3193, **1928; 2107, 2119, **1932**; 55, 1926, **1932**.

***Pine SH: *Org React*, **18:** 403-464, 1970.

Mechanism of Stevens Rearrangement

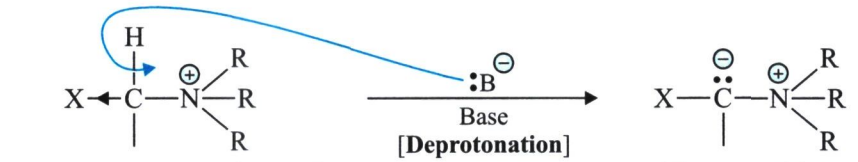
Pine (1971)* was pioneer in describing the underlying mechanism of **Stevens rearrangment** in ***two* different modalities,** namely:

- **Mechanism of Stevens Reaction Involving Radical-Pair Intermediates,** and
- **Mechanism of Stevens Reaction Involving Ion-Pair Intermediates,**

which shall now be discussed separately in the sections that following:

(*a*) **Mechanism of Stevens Reaction Involving Radical-Pair Intermediates:** It essentially involves ***two* individual steps**—as described under:

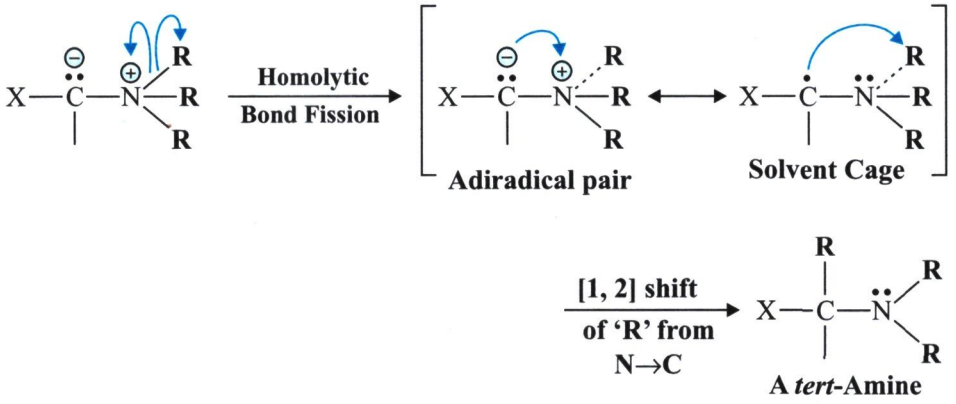
Step-1*:** The first and foremost step critically deals with the formation of ***'Nitrogen Ylide'** by carrying out the so-called **deprotonation phenomenon** right from the **α-C-atom** of the respective *quaternary-ammonium salt (QAS)* in the crucial presence of a **strong base,*****—as given below:



Quatonary Ammonium salt [QAS] **Nitrogen Ylide**

Step-2*:** It predominantly relates to the **'homolytic bond eleavage'** pertaining to the **N–R bond** present in the **Nitrogen Ylide**; and hence, carrying on further with the rearrangement of ***'diradical pair'—thereby leading the ultimate generation of a ***tert*-amine** as the desired product.******

Thus, we may have the following expression:



A *tert*-Amine

*Pine SH: *J Chem Edu.*, **48:** 99, 102, 1971.

Smith MB and March J: **March's Advanced Organic Chemistry, John Wiley and Sons, New York, 2007.

***That is, the removal of an **α-proton** is duly promoted by the presence of an **electron withdrawing group (FWG) 'X'** at the **α-C-atom** *i.e.*, **Ester,** Keto, **Nitro. Carboxylic** Acid **Group.**

****Schollkop f U *et al.*: *Tetrahedron Lett.*, 3415-18. 1969.

Comments: It is, however, pertinent ot state here that the 'Diradical Pair' is held together prominently by means of the **'solvent cage'**—that eventually prevents the so-called:

"drifting of radicals but certain instances one may even isolate the *intermolecular coupling product* as well"*.

(*b*) **Mechanism of Stevens Reaction Involving Ion-Pair Intermediates:** An intensive and extensive investigative studies with respect to the prevailing ***stereochemistry*** of the **Stevens rearrangement** which predominantly reveals the **presence of any kind of retention in the observed configuration of the product**. Therefore, to justify the same, the ensuing concept of:

'an *Ion-Pair Intermediate* or *Cation-Anion Pair Intermediate'*

was duly provided with an adequate thoughtful attention and inputs.

Example: In the so-called **Quaterary Ammonium Salts (QASs)**–the ***tert*-butyl [$(CH_3)_3C$–]** was invariably considered as a ***probable*** **substituent located strategically at the α-C-atom**; and hence, the ultimate experimental results so obtained were in perfect agreement with the prevailing—**'Cation-anion pair mechanism'****.

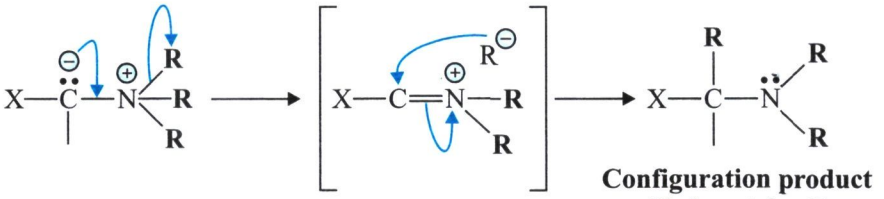
Woodword and Hoffmann (1970)*** revealed that the **stereochemistry of the rearrangment**** and the **orbital symmetry principle** fails to allow the so-called **[1,2]–shift concept of the rearrangement** both perseptively and squarely.

Obviously, the very **initial step**, critically comprising the generation of **Nitrogen Ylide**—is found to be precisely the same as that of:

'the 'di-radical-pair mechanism',

which actually differs largely in the 2nd step that involved prominently the so-called—***'heterocyclic bond fission'***.

We may have the following expression:



Bi-Ion Intermediate **Configuration product [Duly retained]**

Remarks: Since the usual **Stevens rearrangement** does possess a very ***restricted* and *limited* overall synthetic application**, and hence, we may make use of the ***Double* Stevens rearrangement** particularly for the so-called:

"macrocyclic ring expansion"***.

*Hennion GF and Shoemaker MJ: *J Am Chem Soc.*, **92**: 1769-70, 1970.

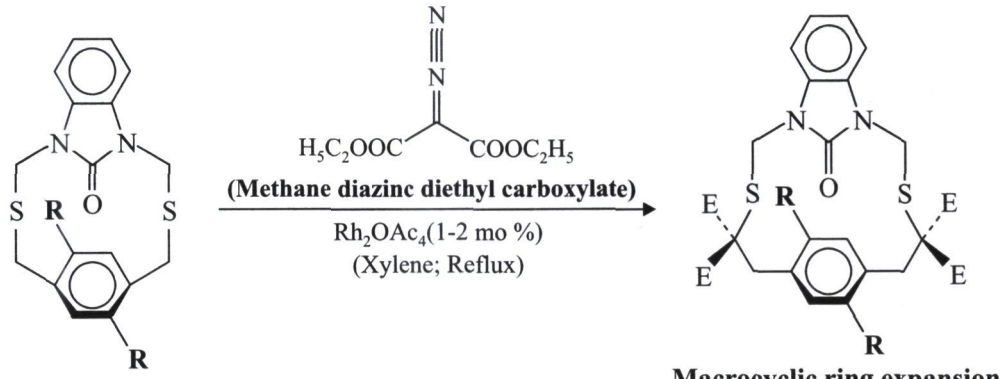
Pine SH *et. at.*: *J Org. Chem.*, **35: 3663, 1970.

***Woodward and Hoffmann: **The Conservation of Orbital Symmatry,** Academic Press, New York. 1970.

****That is, inversion in configuration prevalently.

*****Keisha K *et al.*: *Org. Lett,* **8** (12): 2511-14, 2006.

Thus, we have the following expression:



Macrocyclic ring expansion

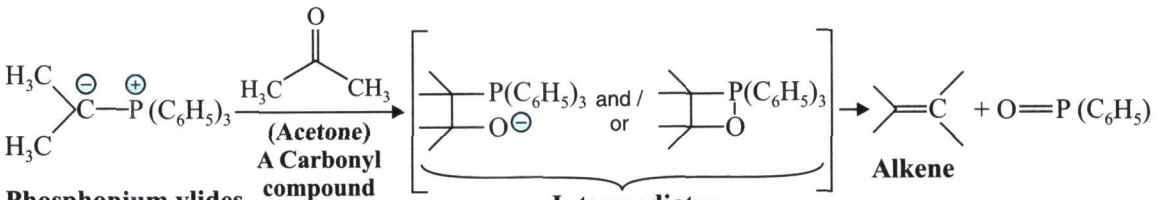
16.2.5 Wittig Rearrangement [or Wittig Reaction]*

The **Wittig rearrangement** (or **Wittig reaction**) refers to the **alkene formation** starting from:

- **Carbonyl (>C=O) chemical entities (compounds); and**
- **phosphonium ylides [$(CH_3)_2C^{\ominus} - P^{\oplus}(C_6H_5)_3$],**

preceeding primarily *via* the proposed **betaine** and/or **Oxophosphetane intermediates**. Nevertheless, the ensuing **stereochemistry** may be *controlled* and *modulated* by the precise and exact choice of **ylide**, **carbonyl compound**, and **reaction parameters**.

It may be expressed as under:



Phosphonium ylides

Intermediates [Oxophosphetanes]

Alkene

NOTE:

1. **The *ylide* on being replaced with a *phosphine oxide carbanion*, the reaction is referred to as the *Horner Reaction*:**

   Horner I *et. al.*: *Ber*, 91: 61, 1958, *idem et al.*; *ibid*, 92, 2499, 1959.

2. **The *ylide* on being replaced with a *phosphine oxide carbanion*, the reaction is invariably referred to as the *Horner-Emmous-Wadsworth reaction*:**

   Wadsworth WS and Emmous WD: *J Am Chem Soc.*, 83: 1733, 1961.

In a broader perepective, the **Wittig reaction** relates to a **C,C-forming olefin synthesis** commencing from both phosphonium **ylides** and **carbonyl chemical entities**. Amazingly, in more than **99% of all Wittig reactions** we usually come across:

*Wittig G and Sohöllkopf U: **87**: 1318, 1954, Wittig G and Haag W: *ibid*, **88**: 1654, 1955.

- ***ylides* having the structure $Ph_3\ P^{\oplus}—CH^{\ominus}—X$ (*i.e.*, the triphenylphosphonium ylides);** and
- **'*X*' invariably stands for: H, alkyl, aryl, or CO_2–alkyl and rather rarely for other *relevant substituents*.**

In the present context, the **Wittig rearrangement** (or **Wittig reaction**) will be discussed with particular reference to the following **important aspects**, for instance:

(*i*) **Nomenclature and Preparation of Phosphonium Ylides [P Ylides],**

(*ii*) **Mechanism of the Wittig Reactions,**

(*iii*) **[1,2]–Wittig Rearrangment, and**

(*iv*) **[2,3]–Wittig Rearrangment.**

16.2.5.1 Nomenclature and Preparation of Phosphonium Ylides [P Ylides]

It has been observed that a majority of the **phosphonium ylides** (***P Ylides***) solely employed in the **Wittig reactions** are usually prepared ***in situ*** (*i.e.*, **never isolated separately**). In actual practice, these are always prepared ***in situ*** whenever the **ylide $Ph_3P^{\oplus}—CH^{\ominus}—X$** critically consists a **substituent X** that is quite incapable of:

"stabilizing the negative formal charge of the *carbonionic centre*"

***Nonstabilized Ylide*:** The above typical type of **P Ylide** is termed as the **nonstablized ylide**.

Semi-Stabilized Ylides*:** The **$Ph_3P^{\oplus}—CH^{\ominus}—X$** on the other hand, essentially comprise a **substitutent X** that eventually gets only stablized to the bare minimum extent at the **Carbonionic centre.

Stabilized Ylides: They designate the 3rd and last variants in **P Ylide**. Beside, they usually carry a relatively **strong electron-withdrawing substituent** located strategically upon the:

'Carbanionic carbon atom',

and hence, represent the so-called ***exclusive* triphenylphosphonium ylides** that are found to be both:

- **self-stable** and
- **stored adequately.**

NOTE: **Perhaps this could be the possible reason that these are being added as the—*'neat compound in Wittig reaction'*.**

Preparation: Almost all **P Ylides** specifically needed for the **Witting rearrangement** are accomplished by carrying out:

'the careful deprotonation of the phosphonium salts'.

Table: 16.1 records the various **triphenylphosphonium ylides** along with their respective *nomenclatures*, *preparation*, and *stereoselectivity vis-a-vis* their corresponding **Wittig reactions**:

*In fact, this kind of **ylide** may also be prepared ***in situ***.

Table: 16.1: The Various Triphenylphosphonium Ylides: Nomenclature, Preparation, and Stereochemistry of Their Respective Wittig Reactions.

P-Ylide	$Ph_3\overset{\oplus}{P}—\overset{\ominus}{C}H$ Alkyl	$ph_3\overset{\oplus}{i}—\overset{\ominus}{C}H$ Aryl	$Ph_3\overset{\oplus}{P}—\overset{\ominus}{C}H—COOR$
Ylide Type	**Non stabilized Ylide**	**Stabilized Ylide**	**Stabilized Ylide**
Ylide is prepared...	***in situ***	***in situ***	**in prior reactions**
...from $Ph_3P^{\oplus}—CHR\ Hal^{\ominus}$ and	**n–BuLi or $Na^{\oplus\ominus}CH_2S(=O)CH_3$ [1] or $Na^{\oplus}NH_2^{\ominus}$ [1] or $K^{\oplus\ominus}O$ *tert*-Bu [2]**	**$NaOC_2H_5$ or Aqueous NaOH**	**Aqueous NaOH**
1,2-Disubstituted Olefins typically result [3]	**...with > 90% *cis*-selectivity**	**...as *cis*-, *trans*-mixture**	**...with > 90% *trans*-selectivity**

Remarks: 1. Based on the informations given in Table: 16.1, certain **'bases'** are particularly suitable to propabone:

Nonstabilized • **Semi-stablized** or • **Stabilized Ylide.**

2. Besides, in the ***stereogenic Wittig reactions*** with **aldehydes**, **P ylides** do invariably orhibit a **highly characteristic stereosleectivity profile**.

16.2.5.2 Mechanism of the Wittig Reactions

The **mechanism of the Witting reaction** has been broadly divided into ***these*** **important categories**, namely:

- ***cis*-Selective Wittig Reactions;**
- ***trans*-Selective Wittig Reactions,** and
- **Wittig Reactions without Stereoselectivity,**

which shall now be dealt with individually in the sections that follows:

16.2.5.2.1 *cis*-Selective Wittig Reactions

A comprehensive underlying conception pertaining to the ***cis*-selective Wittig reaction (s)** is provided in Fig. 16.1.

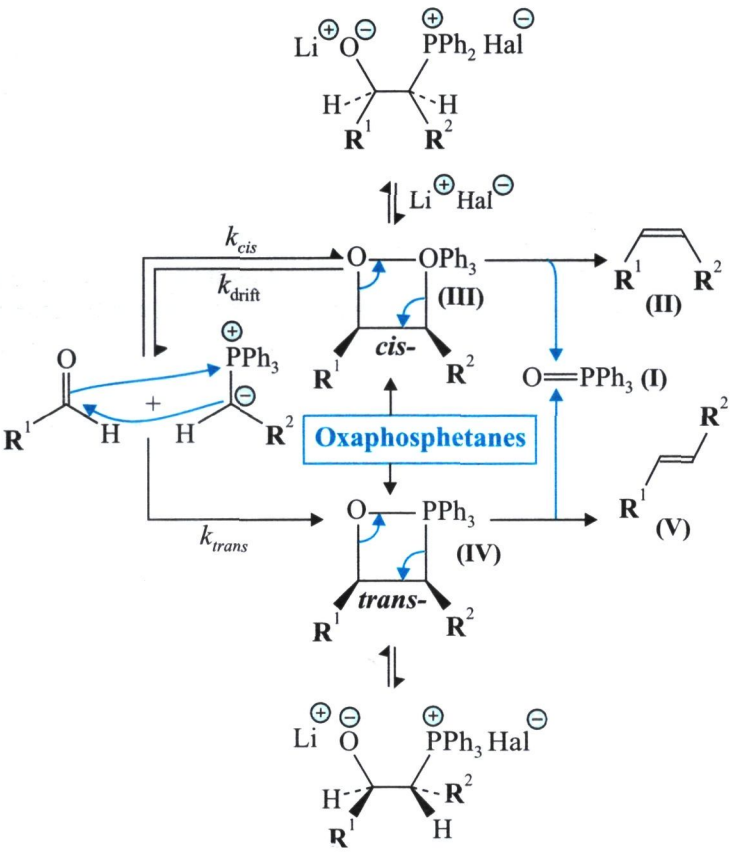


Fig. 16.1: Showing the Mechanism of the Wittig reaction. k_{cis} is the rate constant for the formation of cis-oxaphosphetane, k_{trans} is the rate constant for the formation of *trans* oxaphosphetane, and k_{shift} is the rate constrant for the isomerization of *cis* to *trans* configuration oxaphosphetane—which is known as the **'Stereochemical Drift'**.

Explanations

These reactions may be explained as under:

1. The very ***first*** **step** commences with a ***one-step*** **[2+2]–cycloaddition of the ylide** to the respective *aldehyde*, which subsequently loaded to the formation of a typical ***heterocyclic*** **chemical entity** termed as **'oxaphosphotane'** (see the **'box'**).
2. Eventually, **oxaphosphetane** gets duly *decomposed* in the ***second*** **step** itself, that explicity indicates:

   'a *one-step* [2+2]–cycloreversion',

   so as to give rise to the formation of a mole each of:

   - **Triphenylphosphine (I)** and - **Olefin (II).**

Comments: Interestingly, the above *decomposition* invariably comes into play almost ***stereoselectively***'.

3. Thus, a ***cis*-disubstituted oxaphosphetane (III)** interacts almost exclusively to yield a corresponding ***cis*-olefin (II);** whereas, a ***trans*-disubstituted oxaphosphetane (IV)** gives solely a ***trans*-olefin (V)**.

NOTE: **Therefore, the so-called phenomenon of *stereospecificity* takes place critically in a *pair of decomposition reactions*—as illustrated above.**

Remarks: Importantly, the ensuing **[2+2]–cycloaddition** occurring between **P ylides** and **carbonyl (>C=O) compounds** to yield the **oxaphosphetanes** may be ***stereogenic in nature***. Obviously, the **stereogenic features** duly exhibited when the **carbonionic C-atom** of the respective **ylide** essentially possesses:

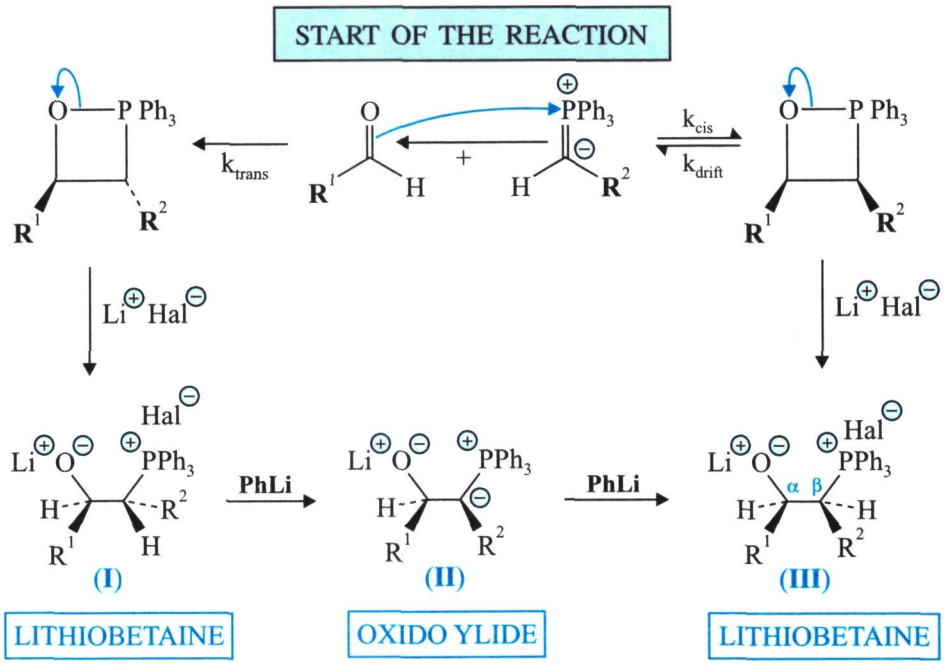
- **two different substitutents in addition to the 'P-atom'** and
- **when the above also holds good for carbonyl (>C=O) moiety.**

Nevertheless, the extremely important and prevalent *stereogenic* **oxaphosphotane** generation of such a configuration invariably, takes off from the so-called **'monosubstituted ylides [$Ph_3P^{\oplus}$—$CH^{\ominus}$—X]'** and from the ensuing **'substituted aldehydes [R—CH=O]'** instead of *formaldehyde* **[HCHO]** (see *Fig: 16.1*).

16.2.5.2.2 TRANS-SELECTIVE WITTIG REACTIONS

In this specific instances an altogether divergent reaction mode of the ***'lithiobetaines'*** is being employed in the so-called **Schlosser variant** of the respective **Wittig reaction**.

Fig: 16.2 shows the underlying mechanism of the **Schlosser variant** of the **Wittig reaction** of **'nonstabilized ylides'**:



(Contd...)

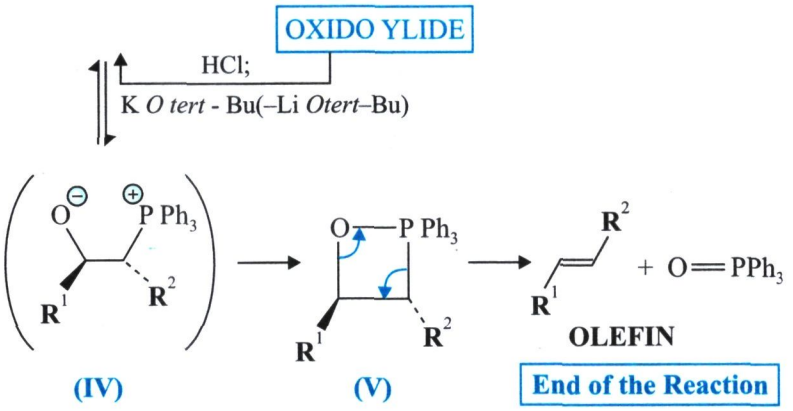


Fig. 16.2: The Comprehensive Mechanism of the Schlosser Variant of the Wittig Reaction of Nonstabilized Ylides.

[**Adapted From:** Figs: 16.(1) and (2): Briickner R: **Advanced Organic chemistry**, Academic Press—(An Imprint of Elsevier), New Delhi, 2003].

EXPLANATIONS

The steps involved in the sequential reactions may be explained as under:

1. **Lithiobetaines (I) and (III)** do represent the **phosphonium salts**. Obviously, they do essentially comprise an ***acidic H-atom*** located strategically at the ***position* α to the P atom**.
2. The judicious incorporation of the so-called ***second*-equivalent** of the earlier mentioned **PhLi/LiBr reagent** into the said **reaction mixture**—enables the prompt ***removal of this H-atom* as a proton (H^+)**.
3. Thus, at this critical point in time, we may lay our hands on to a ***single* so-called oxido ylide (II)** duly produced from each of the corresponding **'*diastereomorphic* lithiobetaines (I) and (III)'**.
4. Amazingly, precise and exact **1.0 equivalent of HCl is now added carefully**, which (HCl) helps predominantly to ***protonation* of the ensuing oxide ylide (II)**.
5. In this manner, it again generates another mole of **lithiobetaine** perceptively; however, it is now retained in its **purest version** *via* **diastereometrically as compound (I)**.
6. The resulting ***pure* lithiobetaine (I)**, obtained in the previous *step (5)*, reacts to yield the respective **'olefin'** on being subjected to treatment with ***KOtert*-Bu** [or $K^{\oplus\ominus}$ *Otert*-Bu]*.

Comments: Importantly, the aforesaid treatment ultimately helps to establish a classical **'equilibrium reaction'** wherein the ensuing **Li^+ion** duly gets migrated from:

"the Lithiobetaine (I) to the corresponding *tert*-Bu $\overset{\ominus}{O}$ ion".

7. Thus, it produces a **betaine (IV)**,—that is completely devoid of the so-called **'stabilizing Li^+ion'**. Since the **Li–free betains** are found to be extremely ***unstable* and *fragile***; and, therefore, as a result the **betaine (IV) collapses exergonically**** to the **oxaphosphetamine (V)**.

* Potassium *teritary* butoxide (Base).

** That is a reaction that loses energy during the process of the reaction. The activation energy catalyzes the reaction to occur in a spontaneous manner.

Remarks: The particular **stereocentres** present in **(V)** do possess the *same configuration* as the **stereocentres in its precursor molecule (IV)** plus an **identical configuration** as could be seen in the **extremely distereoselectively** accomplished **lithiobetaine (I)**. Hence, the **oxaphosphotane (V)** is uniformly trans-confirmed.

16.2.5.2.3 Wittig Reactions without Stereoselectivity

Let us now consider a specific instance when the so-called:

'nonstabilized P ylides do react with the *carbonyl compounds* in the presence of the Li-salts',

thereby an array of *crucial alterantions* do occur *vis-a-vis* the ***cis*-selective Wittig reactions** [see *Fig.: 16.1 under section 2.5.2.1*].

Cardinal Li-Effects: In the present context there are ***three* cardinal and recognized *Li-effects***, namely:

- ***First* Li-Effect:** The ***cis*-oxaphosphotanes** are invariably generated having a definite ***lower selectivity profile***; which seems to be very much in contract to the particular **sold-free instance** thereby ascertaining the fact that:

  "the rate constant k_{cis} is never too higher than k_{trans}".

- **Second Li-Effect:** In this case, a few of the earlier generated ***cis*-oxaphosphotane** possesses an unique opportunity to undergo typical **isomerization phenomenon** to yield the ***trans*-oxaphosphates**. In other words, the said *geometrical transformations* actually experience the so-called ***stereochemical drift***—prior to the formation of an **'olifin'**; nevertheless, the aforesaid ***cis* → *trans* isomerization** never attains completion at all.

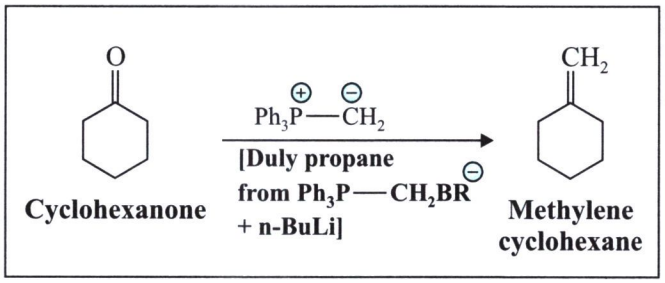
Comments: Perhaps it may be a *solid-valid reaction* that the **'olefin'** thus accomplished ultimately proves to be:

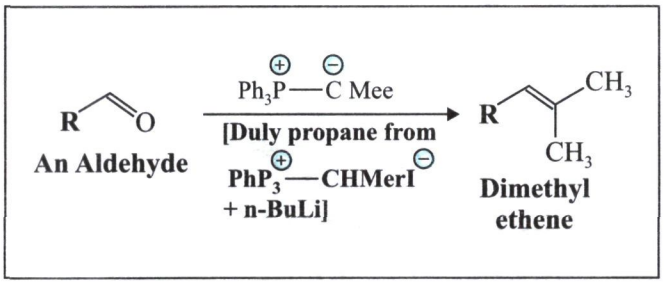
'a *cis/trans*–admixture of the oxaphosphotanes'.

Since, such accomplished **'admixture' of products** turns out to be invariably **useless**; and hence, the ***'aldehydes'*** and normally ***not* treated with nonstabilized P ylides** very much in the **non-salt-free parameters** mostly.

Amazingly, the ***non-salt-free Wittig reaction*** belonging to the **nonstabilized ylides** may be employed rather ***advantageously*** whenever there occurs a total absence of the **stereogenic olefin bond**.

Thus, we may have the following expressions:





❑ ***Third* Li-Efect:** This effect becomes persistence under the so-called **non-salt-free condition**. Amazingly, at the very outse,t it seems to be merely relevant **mechanistically**. It is pertenent to mention here that the **Li-salts** are capable of inducing the **'heterolysis'** of the ***O-P linkage*** duly present in the **oxaphosphotanes**. In this manner, they effectively cause the conversion of the **oxaphosphotanes** right into the respective **lithiobetaines (I) and (III)**,—as depicted in Fig. 16.1.

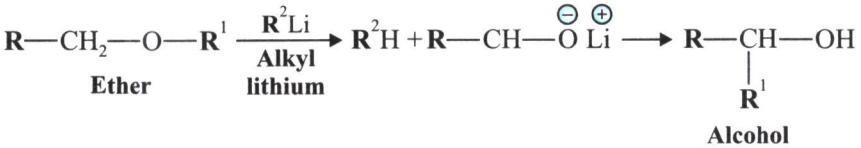
Importantly, the following ***two* inportant aspects**, namely

- **absolute disappearance of *'ring strain'*;** and
- **consequent *gain in* Li^+O^- *bond energy*,**

really go a long way to compensate for the actual energy needed to cleave the **P-O bond**; and also to produce **a gainful cationic and a anionic charge** respectively.

16.2.5.3 [1,2]–Wittig Rearrangement*

It relates to the rearrangement of **ethers** with the help of ***alkyl* lithiums** so as to give the **alcohols** *via* a **[1,2]-shift**, as shown under:



NOTE: **The couversion of an ether to an alcohol, in the presence of an *alkyl lithium*, takes place *via* the [1,2]–shift.**

EXPLANATIONS

1. It essentially represents the so-called **'base-promoted reaction'** that leads to the formation of either:
   - **secondary alcohols,** or
   - **tertiary alcohols,**

   but at the same time the **[1,2]–Wittig rearrangment** does provide specifically
   - ➢ **a limited substrate scope,** and
   - ➢ **a definite moderate yield.**
2. The **[1,2]-Wittig rearrangement** has been subjected to both intensive and extensive investigative studies**.

*Wittig G and Löhmann L: *Ann*, **550**: 260, 1942, Wittig G: *Experientia*, **14:** 389, 1958.

Gartner P *et al.*: *Tetrahedron: Asymmetry*, **10: 4811, 1999.

3. Ultimtely, it was inferred vehemently that:

   'the said Wittig rearrangement does proceed by a proven and established–*radical dissociation-recombination mechanism*'*.

4. Later on, Nakai *et al.* (1996)** pronounced that the so-called **[1,2]-Wittig rearrangement** actually designates:

   'a carbanion rearrangement proceeding *via* a-*radical dissociation recombination mechanism*',

   that is solely based on the fact the typical formation of the ensuing **radical intermediates** have also been identified and confirmed perceptively.

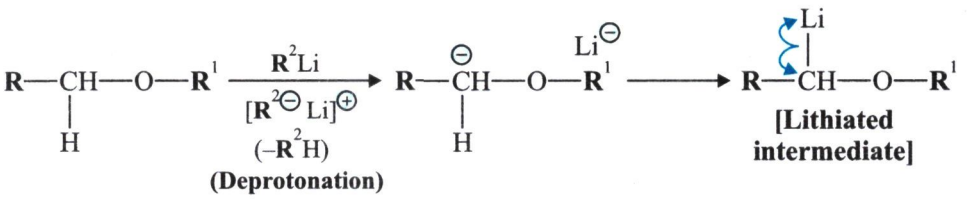
5. Besides, one may take cognizance of the fact that there prevails the so-called actual formation of:

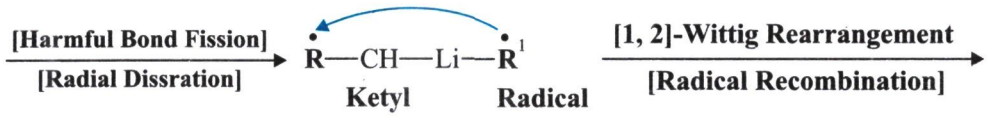
   'the free-radical pair with Li that subsequently gets duly rearrangemed from C to O,—thereby ensuing dissociated free-radical then gets combined to *ketyl* to form finally the specific—*'radical-ketyl pair'* having a very short life span'.***

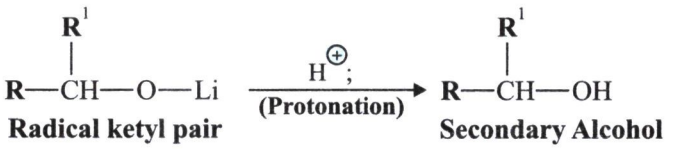
Based on the foregoing scientific delebrations and logical explanations one may straight way put the overal stereochemistry of the **[1,2],–Wittig rearrangement mechanism** that reveals predominently the so-called *retention in the configurations* caused exclusively by virtue of the **isomerization phenomenon** obtained as an excellent revelation from:

"the solvent cage effect".

MECHANISM OF [1,2]-WITTIG REARRANGEMENT







*Maleczka RF Jr. and Geng P: *J Am Chem Soc.*, **120:** 8551, 1998

Nakai *et al.*: *J Am. Chem. Soc.*, **118: 3317-18. 1996.

***Strunk T and Schlosser M: *Eur J Org Chem.* **19:** 4393-97, 2006.

Remarks: Interestingly, the underlying ***stereochemical aspect of the rearrangement*** virtually lies in the fact that despicted its ***inherent*** **radical characteristics**, the fundamental ***integrity*** **of the *two* radical stereocentres** located strategically at:

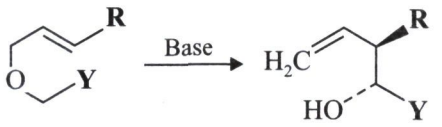
- **the migrating C-atom;** and
- **the Li-containing terminal,**

is being retained to a certain degree since it has been observed meticulously that:

'the so-called *migrating C-segement* critically undergoes *retention* as well as *configuration* specifically; whereas, the respective *Li-bearing atom* affords an *inversion in its configuration* sequarely'.*

16.2.5.4. [2,3]-Wittig Rearrangement**

It refers to the **[2,3]-sigmatropic rearrangement** of the *conjugate bases* of the *allylic ethers* having having appreciable **high regioselectivity**. However, the prevailing selectivity is found to be *highly dependent* upon the ensuing **nature of the substrate**. We may have the followng expression:



Base : LDA, $NaNH_2$, n-BuLi
Y : Alkynyl, Alkinyl, Ph, CN, CoR

Important Revalations: It has been amply proven and established that the so-called **[2,3]-Wittig rearrangment** is more or less a kind if **[2,3]-sigmatropic reaction** (see *Chapter 15*), wherein a ***thermal-isomerization*** **phenomenon** comes into play *via* a **6-electrons** and **5-membered cyclic transition state,**—as given below:

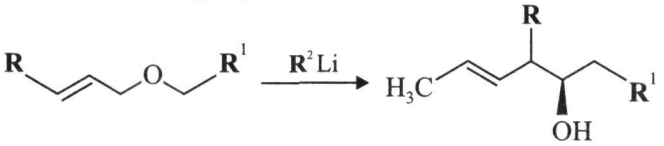


where, Y = Anion Ylides;
X and Y = Atom-pair involved.

Thus, it rightly designates the so-called *[2,3]-sigmatropic version* of **[1,2]–Wittig rearrangement** essentially engaging the prevailing conversion of the:

***'deprotonated* allyl ethers into the corresponding *homoallylic alcohols'*.**

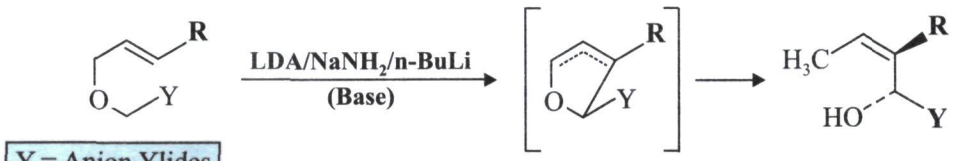
Thus, we may have the followng expressions:



(Contd.)

*Maleczka RF Jr. and Geng F: *J Am Chem Soc.*, **120**: 8551, 1998.

Cast J et. al.: *J Chem Soc.*, 3521, 1960: Schöllkop f U and Fellenberger K: *Ber.*, **698: 80, 1968; Markisumi Y and Notzumoto S: *Tetrahedron Letters*, 6393, 1966.



(A Disubstituted Furan)
[Intermediate]

Mechanism of [2,3]–Wittig Rearrangement: It has been proven and demonstrated that the **[2,3]–Witting rearrangement** may afford the **'ring expansion'**,—which is caused due to the **C-C bond formation** explicity,—as depicted below:



A 7 - Membered Ring **A 11 - Membered Ring**

The so-called **[2,3]–sigmatropic rearrangment** may be divided into ***two*** **distinct categories,** namely:

- **Neutral Rearrangements** *viz.*, rearrangments pertaining to
  - **Allylic Sulphoxides** • **Selenoxides** • **Oxides** and **Amines.**
- **Anionic Rearrangements** *viz.*, rearrangements related to:
  - **Allylic Ethers.**

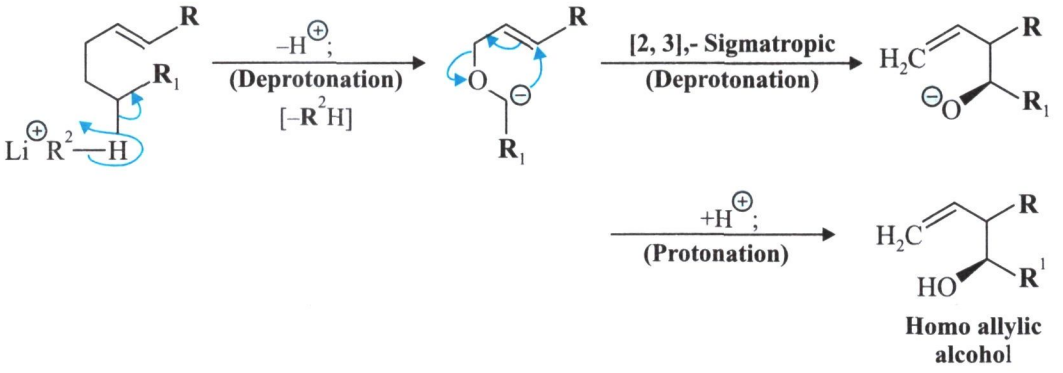
Importantly, the underlying **mechanism of the [2,3]–Witting rearrangement** involves predominantly the following *two* aspects

- **Deprotonation process,** and
- **[2,2]–Sigmatropic rearrangement,**

that ultimately lead to the generation of an **'alcohol'**. In a rather explicit manner, the said rearrangement critically involves the followingv ***three*** **most import sequential steps:**

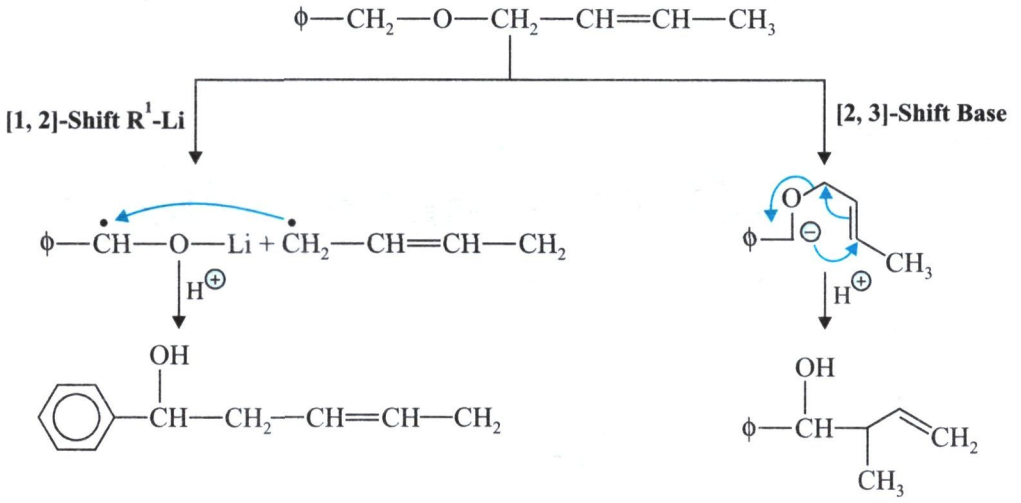
- **Formation of C-C bond with '*allylic transposition*' of O-atom;**
- **Creation of '*particular olefinic geometries*'**; and
- **Transfer of '*chirality*' (*i.e.*, asymmetric C-atom).**

Thus, we may have the following expressions:



Homo allylic alcohol

A survey of literature reveals that in many instances, the prevalent ***concerted* [2,3]–shift** invariably compacts with the respective **[1,2]–shift**.



Suggested Reading

Bertmann HJ and Zimmerman R: **Synthesis of Phosphonium Ylides,** In: *Comprehensives Organic Synthesis* [Trost BM and Fleming I (Eds.)], *Vol. 6*, Pergamon Press, London (UK), 1991.

Cadegan JIG (Ed.): **Organophosphorus Reagents in Organic Synthesis** Academic Press, New York, 1979.

Hartly ER (Ed.): **The Chemistry of Organophosphorus Compounds: Phosphine Oxides, Sulfides, Selenides, and Tellurides. The Chemistry of Functional Groups, Wiley,** Chictester (UK), 1992.

Johnson AW: **Ylide Chemistry,** Academic Press, New York, 1966.

Johnson AW: **Ylides and Imines of Phosphorus,** Wiley, New York, 1993.

Katritzky AR *et al.*: **ARKIVOC** (vii), pp: 146-150, 2002.

Patai S (Ed.): **Chemistry of Carbonyl Group**, Wiley, New York, 1966.



Chapter 17

Rearrangements Due to Addition-Elimination Mechanism

LESSONS AT A GLANCE

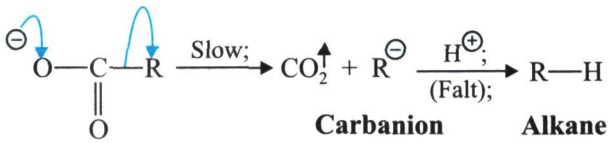
17.1 Introduction
17.2 Grob Rearrangement (or Grob Fragmentation)
17.3 Payne Rearrangement
17.4 Sommelet–Hauser Rearrangement

17.1 INTRODUCTION

Addition Reactions: The precise and exact number of *addition reactions* that are invariably involved in the typical formation of the **carbanions [$R^{\ominus}$]**, such as:

- **Aldol Condensation** • **Claisen Condensation** and • **Schmidt Reaction.**

Elimination Reaction: Quite a few **elimination reactions** *viz.*, *decarboxylation*, *deprotonation*, *deamination*, *dehydration* and the like does involve more of less the **carbanion [$R^{\ominus}$]**—that eventually serves as an intermediate—as exemplified under:



In the present context, we will *explore*, *examine*, and *explain* certain classical rearrangement that are solely caused due to the so-called **addition elimination mechanism** perceptively, namely:

(*a*) **Grob Rearrangement (or Grob Fragmentation),**

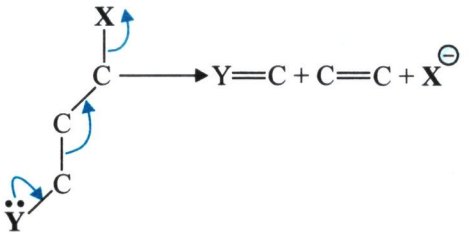
(*b*) **Payne Rearrangement,** and

(*c*) **Sommelet-Hauser Rearrangement,**

which shall now be discussed individually in the sections that follows.

17.2 GROB REARRANGEMENT (or GROB FRAGMENTATION)*

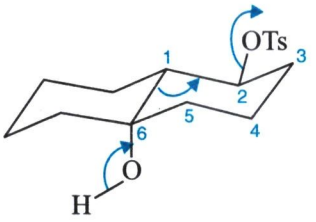
The **Grob rearrangement** entails the critical **C-C bond cleavage** primarily *via* a typical *concerted systematic process* involving a ***five*-atom system**, as depicted under:



$X = CH_2^+$, Cl, Br, I, OTs, NR_2 and $Y = 0^{\ominus}$

It would be worthwhile to state here that the ***'intramolecular version'*** is indeed absolutely advantageous for the specific preparation of the so-called **'medium-sized ring systems'**.

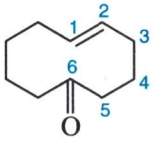
Thus, we may have the following expression:



1, 6-Bicyclohexane-2-toxylate-6-hydroxy (A)

NaH;

Sodium Hydride (–TsOH) [p-Toluene sulphonic acid]



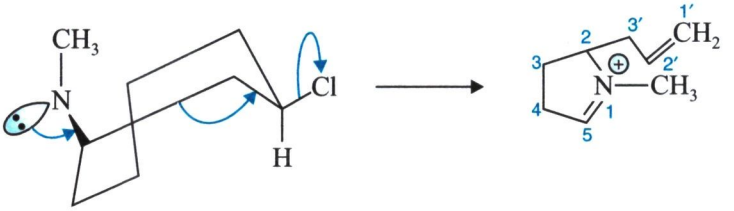
1, 6-Bicyclohexane-1-ene-6-*keto* (B)

Comments: The **compound (A)** in the presence of *sodium hydride (NaH)* loses a mole of ***p*-toluene sulphonic acid [TsOH]** to yield **compound** (B) via the **intramolecular version.**

Likewise, the **Grob fragmentation** invariably serves as a useful means of accomplishing the most sought after attempt in the ***'skeletal transformation process'*** thereby engaging particular **C-C bond cleavage** efficaciously due to the inherent:

'conversion of the *σ-bonds* to the respective *π-bonds*'.

The above reaction involving the **skeletal transformation** phenomenon may be expatiated as under:



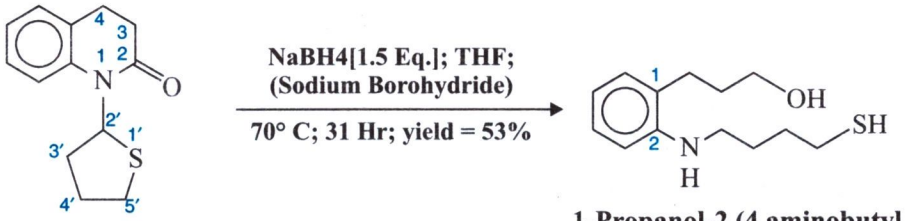
N-Methyl cyclobutyl, chloro-cyclopentane (C)

N-Methyl-1-ene-pyrrohidyl-2(1′-propene) (D)

* Grob CA and Baumann W: *Helv Chim Acta*, **38**: 594, 1955

Comments: From the aforesaid example one may observer vividly how the **Grob fragmentation** enables the **skeletal transformation** of a **bicyclic substituted chemical entity (C)** gets duly converted into a **substituted 5-membered heterocyclic ring system** (*i.e.*, the **pyrrolidine ring**).

Hu *et al.* (2002)* reported meticulously the well-known **Aza-Grob fragmentation** reaction which may elaborated as under:



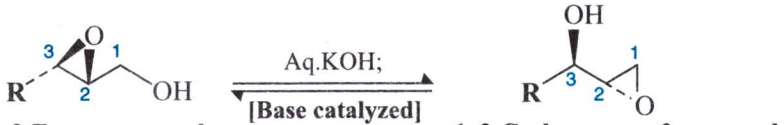
1, 2, 3, 4 - Tetrahydro-2-keto-N-(2-thienyl quinoline)

1-Propanol-2 (4 aminobutyl ethiol) benzene

Comments: Amazingly, starting from a **substituted quinoline-N-(2-thenyl)** derivative one may lay hands onto a simple **benzene derivative** by means of the **Aza-Grob fragmentation reaction.**

17.3 PAYNE REARRANGEMENT**

The **Pyne rearrangement** relates to the ***base-promoted*** **isomerization** process involving the **2, 3-epoxyalcohols**, as illustrated under:



2, 3-Epoxy propanol [3-substituted]

1, 2-Cyclopropoxy-3-propanol [3-substituted] [An Isomerized Product]

Comments: Thus, the aforesaid reaction gives rise to an **inversion in the configuration at C-2;** and, therefore, the ***end-product*** may be converted right into the ***reactant*** by the **same route.**

Nevertheless, in the critical presence of either:

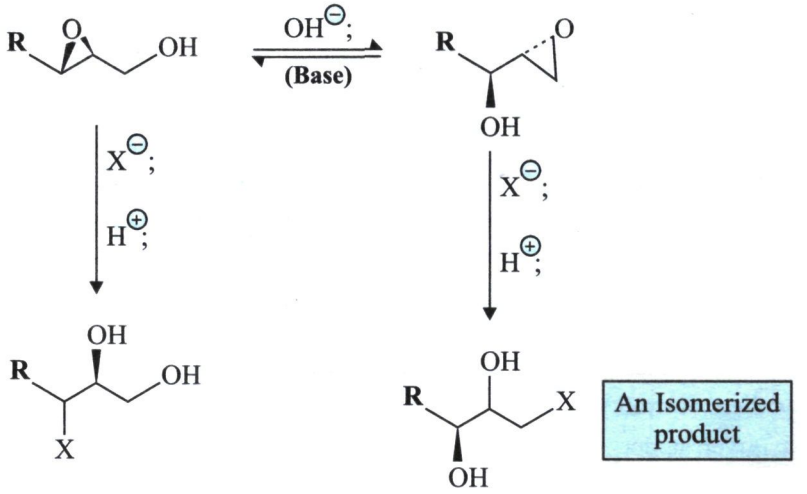
- **a hydroxide (OH-),** or
- **other nucleophiles,**

one may obviously visualize the **'opening of the epoxide vividly'**.

* Hu WP *et. al.*: *J Org Chem.*, **65:** 4208, 2002.

** Parma GB: *J Org Chem.*, **27:** 3819, 1962.

Thus, we may have the following expressions:

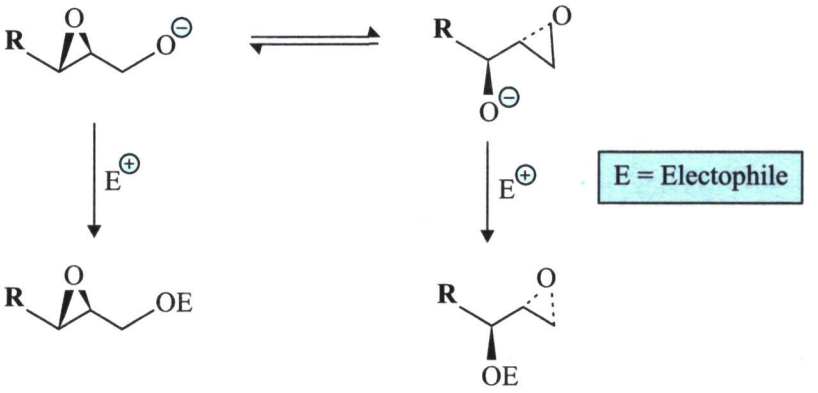


NOTE: **The so-called reversible intramolecular '*epoxide migration*' phenomenon is of immense *synthetic significance*.**

Electrophilic Trapping Process: Bulmanpage *et al.* (1990)* reported that the particular **electrophilic trapping process** may be either:

- **an intermolecular process,** or
- **an intramolecular process,**

which is exclusively based upon the **C-2 or C-3 selectivity**. The above reactions may be expressed as under:



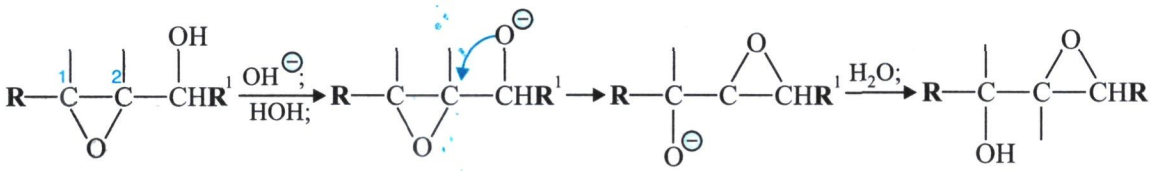
Mechanism of Payne Rearrangment: The underlying **mechanism of Payne rearrangement** critically entails the **'epoxide migrations'** which are being performed in the particular presence of a **strong base (NaOH/KOH)** in an aqueous environment. Besides, it predominantly engages the so-called ***deprotonation of the expoxy alcohol*** to give rise to the formation of an ***'alkoxide'***—being followed immediately by:

'a direct *intramolecular displacement* of the expoxide centre'.

* Bulmanpage PC *et. al.*: *J Chem Soc.*, (Perkin Trans.), **1**: 1375-82, 1990.

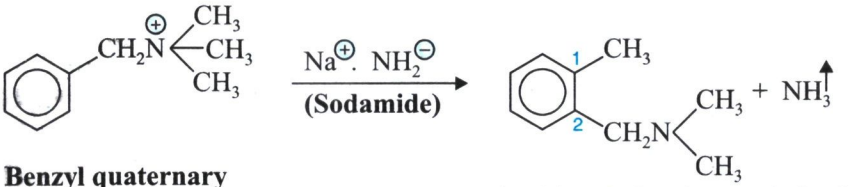
Consequently, one may ultimately lay hands onto an ***isomeric alkoxide*** having an interesting **inverted stereochemistry**.

Thus, we may have the following expressions:



17.4 SOMMELET-HAUSER REARRANGEMENT*

It essentially involves the rearrangement of **benzyl quaternary ammonium salts** to the respective ***ortho*-substituted benzyl-dialkylamines** on being subjected to treatment with alkali metal amides (*viz.*, **$NaNH_2$**), as given under:



Benzyl quaternary ammonium cation

***ortho*-Dimethylamino methyl toluene**

According to Hu *et al.* (2002)** the so-called **Sommelet-Hauser rearrangement** virtually represents the **[2, 3]–Wittig rearrangement** pertaining to the aforesaid **benzylic quaternary ammonium salts** on reaction with **sodamide ($NaNH_2$)** leads to the formation of ***ortho*-dimethyl aminomethyl toluene** (or ***ortho*-methyl dimethylamino benzyl**).

***Special Remarks*:** A survey of literature reveals that the **Sommelet-Hauser rearrangement** quite often competes intimately with the **stevens rearrangement;** and hence, included intelligently under the classification of **[2,3]– sigmatropic shift** (see *Chapter: 15*). Moreover it designates obviously an **addition-elimination phenomenon** as revealed by the ensuing **mechanism**.

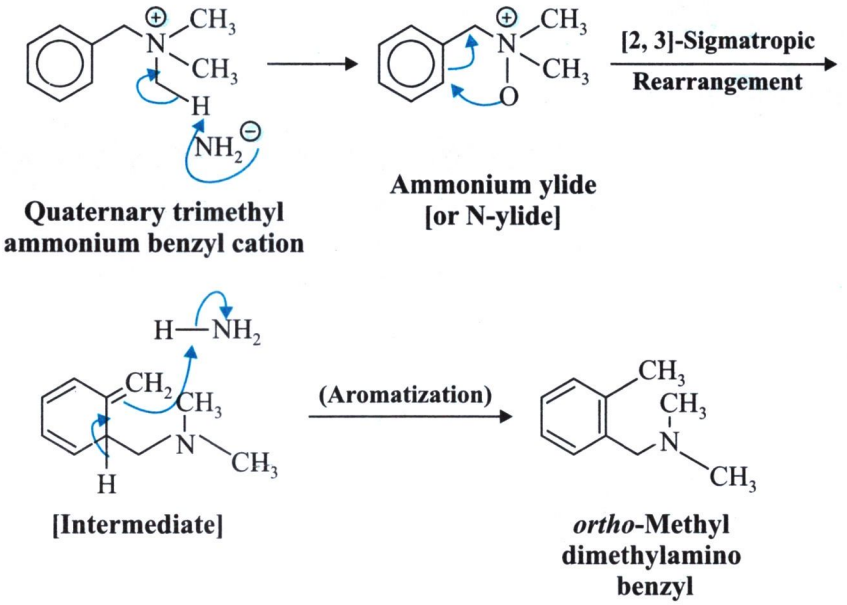
Mechanism of Sommelet-Hauser Rearrangement: It is, however, pertinent to state at this point in time that the **quaternary ammonium salt [$—\overset{\oplus}{N}(CH_3)_3$]** on being treated with a *strong base* duly produces a **nitrogen ylide**,—that ultimately yields the desired ***ortho*-methyldimethylamino benzyl** upon:

"[2,3]–Sigmatropic rearrangement followed by aromatization".

* Sommelet M: **Compt Rend., 205**: 56, 1937.

** Hu WP et al. *J Org Chem.*, **65**: 4208, 2002.

We may have the following sequential reactions:



Quaternary trimethyl ammonium benzyl cation

Ammonium ylide [or N-ylide]

[Intermediate]

***ortho*-Methyl dimethylamino benzyl**

The above *sequential steps* are self-explanatory.

Suggested Reading

Briickner R: **Advanced Organic Chemistry**, Academic Press, An Imprint of Elsevier, San Diego (USA), 2002.

Green T and Wuts P: **Protective Groups in Organic Synthesis,** Wiley Interscience, New York, 1998.

Kar A: **Medicinal Chemistry**, 6th ed., New Age International, New Delhi, 2015.

Li JJ and Corey EJ [Eds.]: **Heterocyclic Chemistry,** Wiley and Sons, Hoboken, NJ., 2005.



Chapter 18

Rearrangements in Pericyclic Reactions

LESSONS AT A GLANCE

18.1 Introduction
18.2 Concerted Pericyclic Reactions
  18.2.1 Cycloaddition Reactions
  18.2.2 The Diels-Alder Reaction
18.3 Claisen Rearrangement
  18.3.1 Preparation of Allyl Enol Ethers
  18.3.2 Applicability of Allyl Vinyl Ethers/Allyl Ethers of Enols
  18.3.3 Represents a Concerted Process
  18.3.4 Oxa-Version of the Cope Rearrangement
18.4 Cope Rearrangement* [or Oxy-Cope Rearrangement]

18.1 INTRODUCTION

In a broader perspective, the **Pericyclic Reactions** are preferentially called as:

- **Sigmatropic Shift,** or
- **Sigmatropic Rearrangement,**

instead of being naming them as the so-called **'rearrangements'**. Importantly, one may also take cognizance of the fact that the aforesaid reactions are grossly involved in the critical transference of either:

- **H-atom,** or
- **alkyl moiety,**

having an exceptional predominance to a strategically located **π-bond** very much within the molecule either:

- **thermally** **or** - **photochemically.**

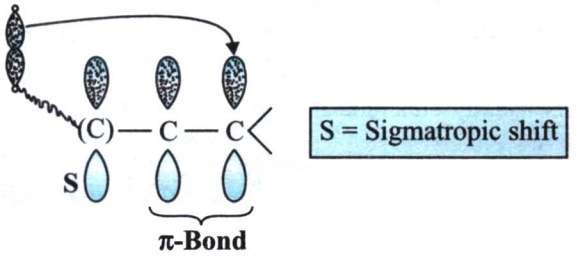
According to Woodward and Hoffmann (1965, 1970)* a **sigmatropic shift** is normally shown by **n, m**:

*Woodward RB and Hoffmann R: *J Am. Chem. Soc.*, **87: 395**, 1965, Woodward RB and Hoffmann R: **The Conservation of Orbital Symmetry**, Academic Press, New York, 1970.

where, **n** = Migration origin, and

m = Migration terminus,

of attachment of the respective ***moving bond ends,***—as shown below:



In the present context, a comprehensive deliberations on the following ***three*** **important aspects** shall be dealt with in a systematic manner, namely:

(*a*) **Concerted, Pericyclic Reactions,**

(*b*) **Claisen Rearrangement,** and

(*c*) **Cope Rearrangement [or Oxy-Cope Rearrangement]**

18.2 CONCERTED PERICYCLIC REACTIONS

In true sense, the **concerted reactions** invariably come into play—***'without an intermediate'***. However, the emerging **transition structure (TS)** essentially involves the following *two* gallantry events occurring predominantly:

• **bond breaking;** and • **bond formation,**

that noticeably never accompliches to the **same extent perceptively**.

Woodward and Hoffmann (1970) were pioneer in recognizing a specifically important group comprising the so-called **concerted pericyclic reactions**—that are solely characterized by an almost continuous ***reorganization of the electrons*** *via*:

"the cyclic transition structures (TS)".

Based on the scientific revelations and concrete evidences, the respective **'cyclic TS'** should by all means strictly consistent' to an arrangement of the ***participating orbitals*** that:

"may maintain and sustain a viable bonding interaction profile between the incumbment reacting atoms through the entire course of the on-going reaction".

Thus, one may interestingly observe that such vital and important requirements indeed render the **Pericyclic Reactions** absolutely predictable in terms of:

- **relative reactivity,**
- **regioselectivity,** and
- **stereoselectivity**

Salient Features: These essentially comprise:

1. The crucial requirement for the **conservation of orbital symmetry**.

2. The basic idea and concept that the symmetry of each and every **participating orbital** should be broadly conserved during the ensuing reaction phenomenon which substantially transformed the explicit understanding of:

"the *concerted pericyclic reactions* and stimulated enough experimental workup to *test*, *implicate*, and *extend* their theoretical aspects overwhelmingly"*.

3. The Woodward and Hoffmann *general idea* actually paved the way towards other **related interpretations of orbital characteristic features**, which are found to be of immense help in:

"predicting and interpretting successfully the laid down path of the *concerted pericyclic reactions*".**

4. Various approaches usually conclude that the ensuing **transition structures (TSs)** having certain ***orbital alignments*** are either:

- **energetically favourable (*i.e.*, allowed);** and
- **others leading to high-energy status (*i.e.*, forbidden).**

Comments:

1. It has been ascertained that the **stabilized transition structures (TSs)** do share some definite ***electronic features*** having the **aromatic systems;** whereas, the so-called **high energy TSs** are more akin to the **antiaromatic systems.**
2. In fact, it finally leads to the rules almost identical to the **Hückel and Mobius relationships** for determining the **'aromaticity'**; and hence, permit the **legitimate prediction** of the overall outcome of the various reactions based upon the *characteristics of the orbitals* pertaining to the reactants.***

5. Wiest *et at.* (1997)**** made an appreciable effort to model the relevant **transition structures** of the **'concerted pericyclic reactions'**. Besides, a host of *major theoretical approaches*, such as:

- **semi-empirical molecular orbital (MO),**
- ***ab initio* molecular orbital (MO),** and
- **DFT,**

have been duly applied to the problem and certain interesting comparisons have been accomplished gainfully.

Having understood the *vast*, *intricate*, and *important* gainful, plus points of a plethora of **concerted pericyclic reactions**, the following *two* aspects, namely:

- ❑ **Cycloaddition Reactions,** and
- ❑ **The Diels-Alder Reaction,**

will be discussed briefly and separately in the sections that follows:

18.2.1 Cycloaddition Reactions

The **cycloaddition reactions** do essentially involve the typical combination of ***two* molecules** to result into the formation of an altogether **New Ring System**. In other words, the ensuing **concerted pericyclic cycloadditions** virtually affect:

*Marchand AP and Lehr RE (Eds.): **Pericyclic Reactions, Vols I and II**, Academic Press, New York 1977.

Houk KN *et at.*: *Angew Chem Int Ed. Engl.*, **31: 682, 1992.

***Carpenter JE and Sosa CP; *Theochem.*, **311**: 325, 1994; Jursic B: *Theochem.*, **423**: 189, 1998.

****Wiest O *et al.*: *J Phys Chem.*, A. **101**, 8378, 1997.

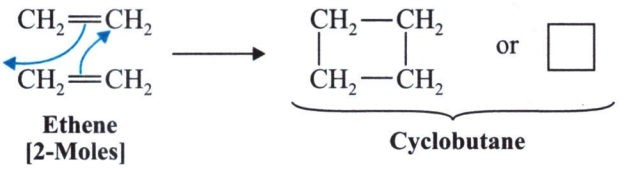
'the reorganization of the entire *π-electron systems* of the reactants to generate *two* newer σ-bonds'.

Example: A few classical examples usually comprise:

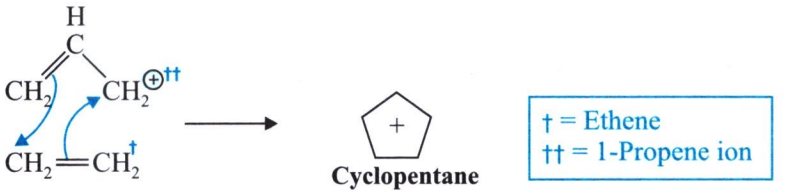
- **cyclodimerization of alkenes,**
- **cycloaddition of allyl cation to an alkene,** and
- **addition reaction between *alkenes* and *dienes* (Diels-Alder reaction).**

Thus, we may look into the following typical examples:

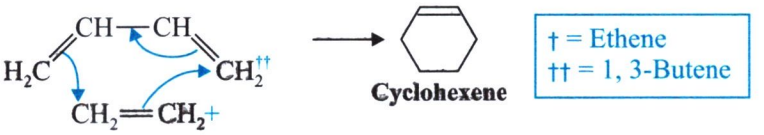
(*a*)



(*b*)



(*c*)



Points to Ponder:

1. The **cycloadditions** may be characterized precisely by mentioning the number of **π-electrons** being actively involved for each particular species, such as:

➢ ***First:*** **Conversion of Ethene to Cyclobutane**—the number of **π-electrons** involved is **[2 + 2]**;

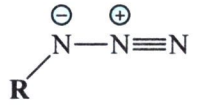
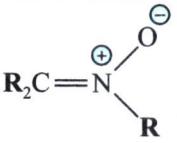
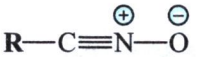
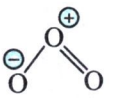
➢ ***Second:*** **Conversion of one mole each of Ethene and 1-propene ion**—the number of **π-electrons** involved is again **[2 + 2]**; and

➢ ***Third:*** **Conversion of one mole each of Ethene and 1, 3–Butene**—the number of **π-electrons** involved is **[2 + 4]**.

2. Importantly, amongst the *three* aforesaid **cycloaddition reactions** only the ***third* species** *i.e.*, ***alkene–diene* cycloaddition** takes place **most rapidly**.

NOTE: **Thus, the *overall pattern of reactivity* may be adequately understood *via* the intelligent and appropriate application of the underlying—'*principle of conservation of orbital symmetry*'.**

3. We may usually come across an array of **combinations of atoms** that are fairly ***conceivable*** in nature, such as;

• Azides	• Nitrones	• Nitrile Oxides	• Ozone
			

4. However, in certain instances **[2 + 2] cycloadditions** are quite possible and feasible *viz.*, specifically with the ***'ketenes'***, as exemplified under:



Ethene (2-moles) **Cyclobutanone**

Ketene [or Ethenone] or Carbonethene]
[CH_2=C=O]

5. The preliminary discussion of the **concerted cycloaddition reactions** may be initiated by exploring how the ensuing **orbital symmetry requirements** enable an explicit distinction between the reactions which are found to be either:

- **Favourable** or
- **Unfavourable**

6. The **cycloaddition reactions** which normally take place *via* a ***pericyclic covarted mechanism*** may be generally written as a:

'continuous rearrangement of electrons'.

7. In true sense, the so-called **orbital symmetry considerations** do afford a ***fundamental insight*** right into the ***inherent*** **electronic** feature of the **cycloaddition reactions;** and hence, permit us to observe that a few of the **TS structures** are *absolutely favourable* from an **electronic profile squarely**.

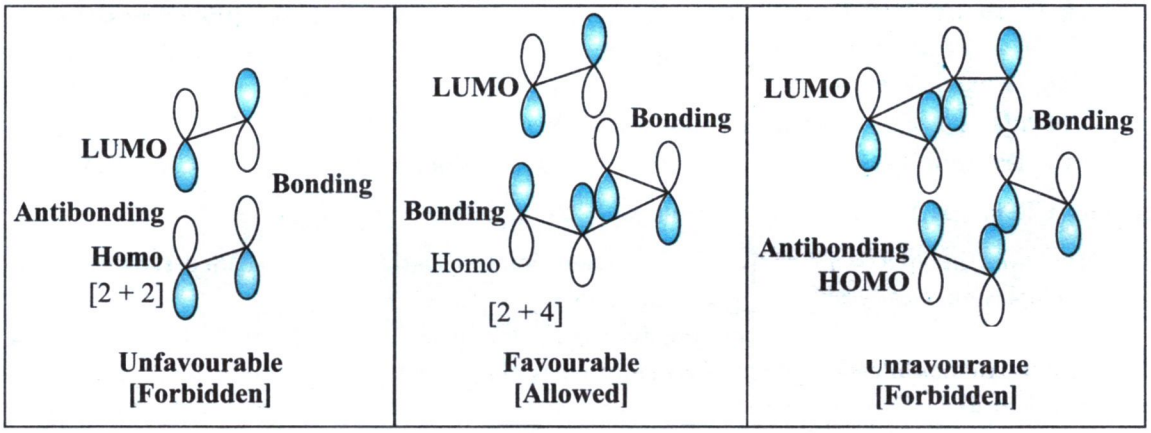
8. Thus, an **energetically conducive and accessible TS** needs a perfect overlap of the ***frontier orbitals*** to allow:

'smooth creation of the newer σ-bonds generously'.

9. In a situation, if it is pretended that the ensuing **reactants** do have a chance to approach one another face-to-face, as would be expected for those reactions engaging the **π-orbitals**.

Thus, the actual need for the *bonding interactions* occurring between the **highest occupied molecular orbitals (HUMO)** and the **lowest unoccupied molecular orbitals (LUMO)** are invariably accomplished for **[2 + 4],** but not for the respective **[2 + 2] or [4 + 4] cycloadditions**.

NOTE: **The systems involving predominantly *4n + 2π electrone* are *favourable (allowed);* whereas, the systems having *4nπ electrons* are not at all.**



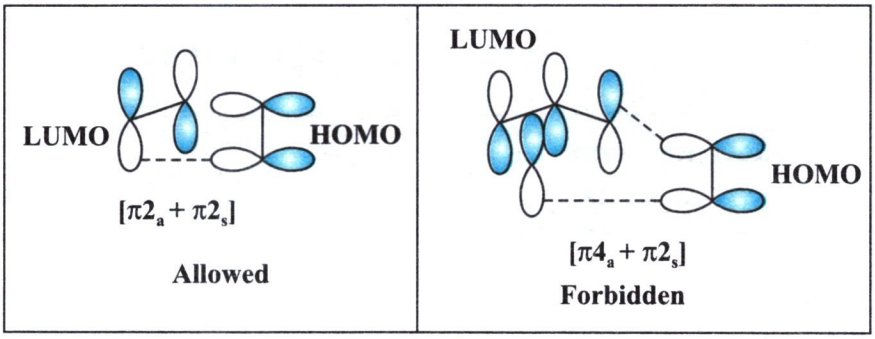
10. **The Antrafacial and Suprafacial Mode of Addition:** The **Mobius systems** may also be accomplished by meticulous, addition to the corresponding—**'opposite faces of the π-system—** invariably termed as the ***antrafacial addition;*** whereas, the—**'face-to-face addition of the π-system'—** is usually known as the ***suprafacial addition***.

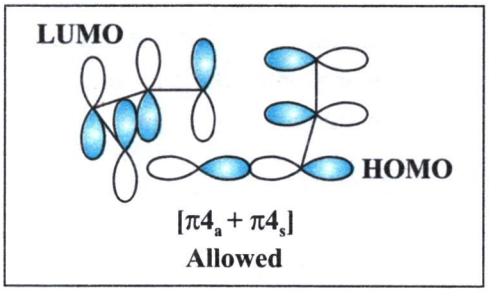
Therefore, in order to specify clearly the so-called **'topology of cycloaddition reactions'**, one may add the ***subscripts 's' and 'a'*** to the respective ***numerical classification*** elegantly.

According to Zimmerman (1971)*, for the systems of **Mobius Topology:** as for ***'aromaticity'***, one may have:

- **4n combinations—as 'Favoured' [or allowed];** and
- **4n + 2 combinations—as 'Unfavoured' [or forbidden].**

Thus, we may have the following diagramatic expressions:





*Zimmerman HE: *Acc Chem Res.*, **4**: 272, 1971.

11. **Orbital Correlation Diagram:** Longuet-Higgius and Abrahamson (1965)* proposed the *orbital symmetry principles* that may also be applied by constructing intelligently and meticulously a—**Orbital Correlation Diagram**.

Example: Let us now construct first of all construct:

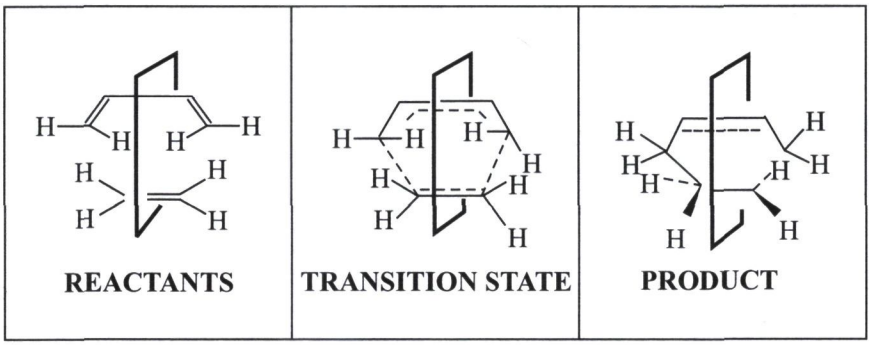
"a correlation diagram for the addition of 1, 3-butadiene [CH_2=CH—CH=CH_2] and ethene [CH_2=CH_2] to yield cyclohexene  ".

Therefore, in order to afford the **concerted addition** to materialize **the so-called 1, 3-butadiene** should adopt strategically an ***$-cis*** **conformation**.

Since the electrons which do get involved intimately happen to be the **π-electrons** in both: • **diene and** • **dienophile–**,—the ***actual reaction*** takes place *via* **a face-to-face instead of an edge-to-edge orientation**. Thus, in a particular instance when the orientation between the **reacting complex** and **transition state (TS)** is being duly adopted,—it may be observed keenly that:

"a plane of symmetry perpendicular to the planes of the various reacting molecules is maintained squarely in the entire course of the cycloaddition phenomenon".

The aforesaid conceptualized transformations occurring across the: **reactants—transition state—product** is illustrated in an elaborated fashion as under:



18.2.2 The Diels-Alder Reaction

In a broader perspective, the **[2 + 4]—cycloadditions** are invariably known as—**'the Diels-Alder reactions'**,—in a great honour to: **Otto Diels** and **Kurt Alder**, the famous organic chemists, who were pioneer in carrying out such reactions. **Dienophile**: The substrate which react specifically with the ***diene*** (*viz.*, **1, 3-butadiene**) in there *cycloaddition reactions* is usually termed as the **'dienophile'**.

It is indeed a well-known fact that the so-called simplest **Diels-Alder reactions**, for instance:

• **Between Ethene and Butadiene and** • **Between Acetylene and Butadiene,**

actually take place under **extreme experimental parameters**.

As on date, based on excellent break throughs and well designed **Diels-Alder reactions** has indeed made it a lot easier and convenient to tackle efficiently the vast majority of such cases that deal with:

'the acceptor-substituted alkenes being employed as *dienophiles*'.

*Longuet-Higgins HC and Abrahamson EV: *J Am Chem Soc.*, **87**: 2045, 1965.

Bearing in mind the copious volumes of research data published and documented in various *scientific journals, reviews,* and *text books* on the present topic of discussion—it would be worth while to focus our ensuing discussions confined to the following *two* topics, namely:

- **Stereochemistry of the Diels-Alder Reactions, and**
- **Substituent Effects Related to Reactivity, Regioselectivity, and Stereochemistry,**

which shall now be discussed individually in the sections that follows:

18.2.2.1 Stereochemistry of the Diels-Alder Reaction

Formation of Substituted Cyclohexenes*—The survey of literature reveals that the [π4s + π2s] cycloaddition of alkenes and dienes** has proven to be an extremely useful method for the **formation of substituted cyclohexenes**. In fact, this particular reaction is invariably termed as the **Diels-Alder reaction.

However, the ensuing **transition structure (TS)** required for a **concerted D-A reaction** necessiates that the ***diene*** must critically adopt the ***cis*-conformation**. Besides, the ***diene*** and ***dienophile*** (*i.e.,* the **substituted alkene**) do have tendency to approach each other in almost close proximity to the prevailing **parallel planes**.

NOTE:

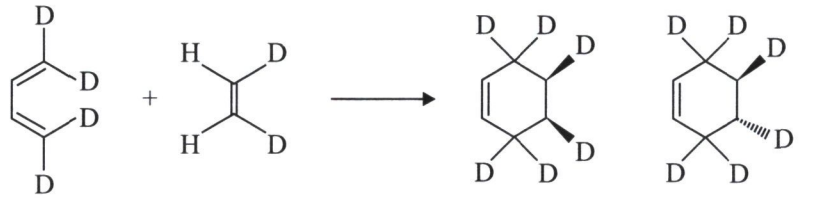
1. **Obviously, the aforesaid reaction has been predominantly extended to a well-deserved *mechanistic*, *computational*, and *synthetic* investigative studies across the globe in the recent past.**
2. **Nevertheless, for majority of existing systems such vital aspects as: *reactivity profile*, *regioselectivity*, and *stereoselectivity* are observed to be perfectly consistent with a concerted process.**

In a specific point of view, the reaction is ascertained to be:

'a stereospecific *syn* (Suprafacial) addition one',

with regard to either of the *two* species **'alkene'** and **'diene'**. Houk *et al.* (1986)** proven and demonstrated the **stereoselectivity** profile by using a host of ***substituted*** **dienes and alkenes**. In addition, the said analogy and theorization aspects also hold good for the *simplest possible example of the reaction*,—as shown by:

"ethene with butadiene duly demonstrated by isotope labelling".



1,3-Diene [Substituted] **Alkene [Substituted]** **Formed** **Not Observed**

*Fringuelli F and Taticohi A: **The Diels-Alder Reaction: Selected Practical Methods,** Wiley, Chichester (4k), 2002.

Houk KN *et al.*: *J Am Chem Soc.*, **108: 554, 1986.

Concertedness of the Diels-Alder Reaction: It has been *studied*, *deliberated*, and *debated* both intensively and extensively. Dewar *et al.* (1986)* put forward a logical explanation based on a plausible argument that there might be an ***'intermediate'*** that:

"remains predominantly *'diradical'* in character".

Remarks: It is, however, important to mention here that the **D-A reactions** most prevalently remains **stereospecific in nature** thereby supporting the fact that, in case, an ***intermediate*** does exist at all, it may not inherit a **sustainable *'lifetime'*** good enough to allow either **rotation** or **inversion** perceptively.

However, the broadly accepted opinion and belief entrusts vehemently that the large segment of the **D-A reactions** are nothing but the ***concerted pericyclic reactions;*** and therefore, the resulting **theoretical analyses mostly agree upon this View****.

The Asynchronus Phemomenon: It has been duly established and recognized that in all such typical interactions occurring between:

- **unsymmetrical alkenes,** and - **dienes,**

the resulting process of ***'bond formation'*** could be observed in a much more **advanced stage** existing between ***one pair of termini in comparison to the other pair***. Hence, such a typical process is normally termed as **the asynchronus phenomenon**.

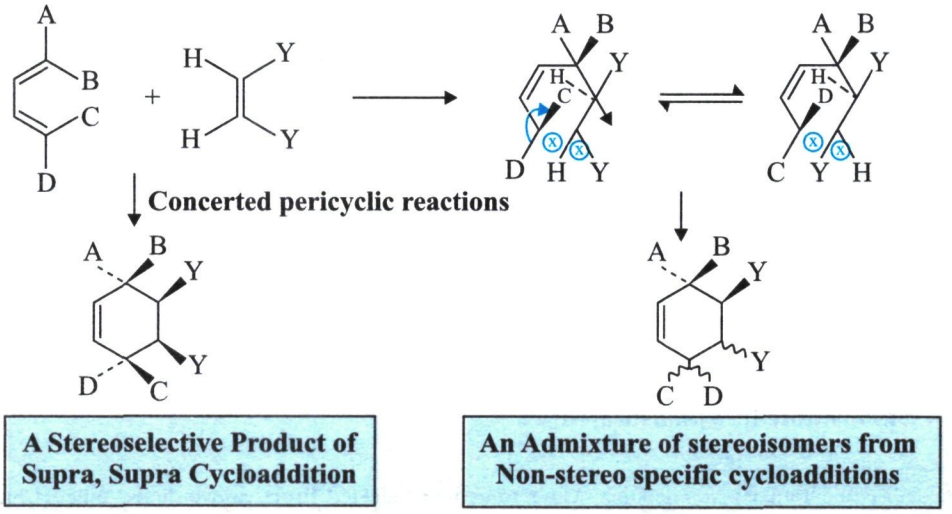
Loss of Stereospecificity: Thus, *two* distinct and typical situations normally arise evidently as state under:

❑ ***First*: When the loss of stereospecificity is duly expected:** In this episode, if there exists an *intermediate* wherein—

- **one bond is duly formed,** and - **other bond fails to do so,**

thereby critically allowing either the *inversion* or the *rotation* taking place at the **terminal position**.

Thus, we may have the following structural expressions:



*Dewar MJS *et al.*: *J Am Chem Soc.*, **108**: 5771, 1986.

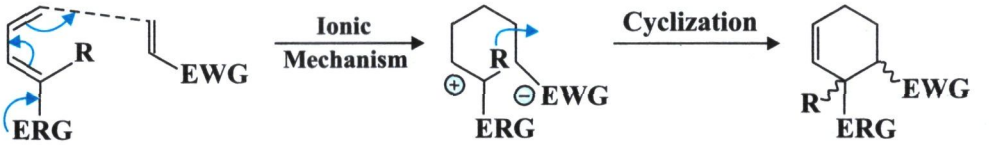
Branchadell Y: *Int J Quantum Chem.*, **61: 381, 1997.

❑ ***Second*: When the loss of stereospecificity involves the Ionic Intermediates:** Importantly, such an event usually takes place as and when the ensuing **reactants** do possess altogether extremely divergent ***electronic* characteristic features,** for instance:

- **one of the 'reactants' happen to be strongly electrophilic in character;** and
- **the other being rather strongly nucleophilic in nature.**

Example: One may, however, observe prevalently that more than one substituent belonging to each category is required invariably for the ***ionic mechanism*** to occur,—as given under:

ERG = Electron Releasing Group
EWG = Electron Withdrawing Group



endo-Sterioisomer [or endo-Mode of Addition]: It may be observed generally that for serveral ***substituted*** **butadiene structural analocynes**, the ***two*** **transition structures (TSs)** ultimately lead to ***two*** **different stereoisomeric products.** Amazingly, the ***endo*-mode of addition is preferred invariably** *viz.*,

- presence of an *electron-withdrawing substituent (EWG) e.g., a carbonyl (>C=O) moiety,* located strategically upon the **dienophile**; and hence, this preference is usually known as the—***'Alder Rule'***,
- rate of occurrence of a mixture having both the **stereoisomers** is accomplished; and in certain occasions the very presence of the ***exo*-product** predominates exclusively. Nevertheless, the ***'Alder Rule'*** certainly holds good and serves as a gainful ***initial guide* to prediction of**: **'the stereochemistry of Diels-Alder Reaction'.**

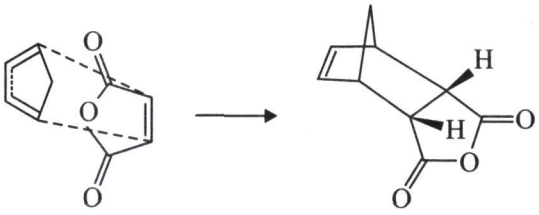
Besides, the ***endo*-product** is quite aften appear to be **more congested sterically**.

Example: The typical ***addition of dienophiles to cyclopentadiene*** invariably favours overwhelmingly the so-called—***'endo*-stereoisomer'** even though it falls into the class of:

'sterically more congested product'.

Thus, we may have the following expression:

Cyclopentadiene Dienophile *endo*-Addition

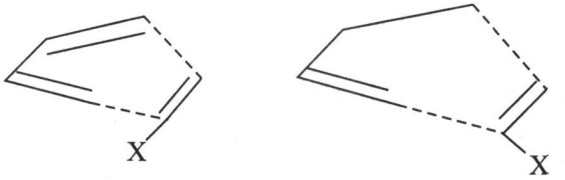


Sterically more congested product

***endo*-Addition** ***endo*-Stereoisomer**

Exo and *Endo* Transition Structures for the Diels-Alder Reaction

In reality, the preference for the ***endo*** **mode of addition** is never found to be confined to the **cyclic dienes** *viz.*, **cyclopentadiene**,—as depicted below:



endo-TS *exo*-TS

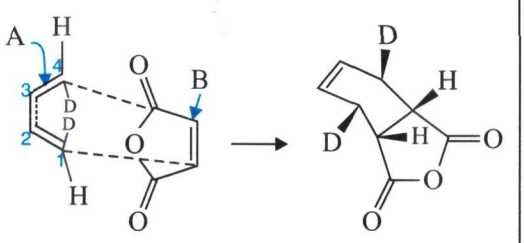
***Exo*-and *Endo* Transition structure for the D-A Reaction**

Preference for *endo*-Mode of Addition Over the *exo*-Addition: Stephenson *et al.* (1982)* critically observed the preference for the ***endo*-mode of addition over the corresponding *end*-addition;** and further ascertained that the *former* is not at all confined to the ***cyclic dienes*** *viz.*, **cyclopentadiene**.

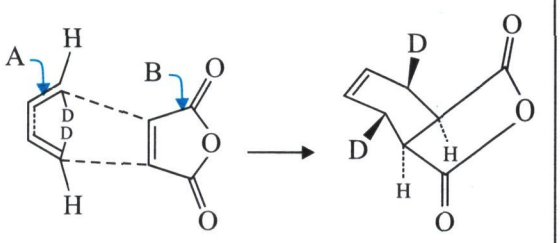
They have also proved and demonstrated that by making use of the so-called sophisticated **deuterium (D_2) labels** technique it could be shown predominantly that:

"in the particular addition of *1, 3-butadiene* (A) and *maleic anhydride* (B),—almost 85% of the entire end-product does arise from the *endo*-addition".

Thus, we may express the ***endo*-and *exo*-additions** as under:



***endo*-Mode of Addition**



***exo*-Mode of Addition**

A = 1, 3-Butadiene; and **B** = Maleic anhydride.

18.2.2.2 Substituent Effects Related to Reactivity, Regioselectivity and Stereochemistry

Based on the scientific revelations and experimental results one may observe critically that there prevails:

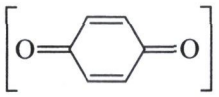
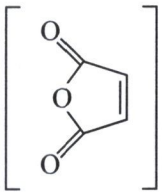
"an appreciably strong electronic substituent effect upon the Diels-Alder cycloaddition".

Since a pretty long duration one is fully aware that the aforesaid reaction is specifically rapid as well as efficacious whenever the ***dienophile*** comprises either:

- **one or more than one *electron-withdrawing group (EWG)*, and**
- **favoured adequately even to a greater extent if the inherent 'diene' essentially contains an *electron-releasing group (ERG).***

Following are a few recognized most *effective* and *reactive* ***'dienophiles'***, namely:

*Stephenson LM *et al.*: *J Org Chem.*, **47**: 4170, 1982.

- **Quinones** 
- **Maleic Anhydride** 
- **Nitroalkenes,**
- **α, β-Unsaturated Esters,**
- **Ketones,** and
- **Nitriles.**

Importantly, the **Diels-Alder reaction** taking place between:

- **unfunctionalized alkenes,** and
- **dienes,**

is found to be quite slow and sluggish in nature.

Example: Meinwald and Hudak (1963)* reported that the **D-A reaction** occurring between **cyclopentadiene** and **ethene** usually comes into play at **~ 200°C.**

Table 18.1 records the relative reactivity towards the cyclopentadiene in the D-A reaction in an elaborated manner:

Table 18.1: Observed Relative Reactivity toward cyclopentadiene in the Diels-Alder Reaction.

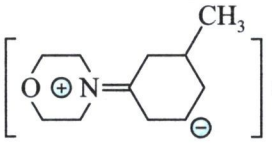
S.No.	Dienophile	Relative Rate†
1	Tetracyanoethene	43,000,000
2	1, 1-Dicyano ethene	4,50,000
3	Maleic anhydride	50,000
4	para-Benzoquinone	9,000
5	Z-1, 2-Dicyano ethene	91
6	E-1, 2-Dicyano ethene	81
7	Dimethyl fumarate	74
8	Dimethyl makate	0.6
9	Methyl acrylate	1.2
10	Cyano ethene	1.0

†From the ***2nd*** **order rate constants** in dioxane at 20°C.

[Sauer J *et al.: Chem Ber,* **97**: 3183, 1964]

Inverse Electron Demand Diels-Alder Reactions: In a situation when an ***electron-poor diene*** is employed, it is pertinent to state here that:

*Meinwald J and Hudak NJ: *Org Synth,* **IV**, 738, 1963.

"the preference gets significantly reversed; and hence, the ensuing electron-rich alkenes *viz.*, vinyl ethers [CH_2=CHOCH=CH_2] and examines  **are found to be the best dienophiles".**

Hence, such reactions are usually termed as **inverse electron demand Diels-Alder reactions**. Interestingly, the overall **reactivity relationships** are invariably decephered promptly with respect to the so-called—**Frontier Orbital Theory**.

In short, it may be added the **electron-rich dienes** do possess **high-energy HOMOs** which eventually interact quite strongly with the respective **LUMOs of the electron-poor dienophiles**. Obviously, when the prevailing:

- **substituent profile is just reversed, and**
- **incumbment diene is electron poor,**

one would grossly observe the ***strongest interaction*** taking place between the ***two*** **entities**, namely:

- **dienophile-Homo** and - **diene-LUMO.**

Important Remark: The **Frontier Molecular Orbital (FMO)** approach correctly and explicitly predicts the following ***two*** **cardinal aspects** of the so-called **Diels-Alder-reaction** squarely strectched over to a broad-spectrum of the **diene-dienophile combinations**:

- **relative reactivity,** and
- **regioselectivity.**

Table 18.2 Shows the typical relative reactivity profile of certain **substituted butadienes** in the D-A reactions.

Table 18.2: The Relative Reactivity of certain substituted Butadienes in The Diels-Alder Reaction*.

S. No.	Diene Substituents	Dienophile	
		Tetracyano ethene	Maleic Anhydride
1	None	1	1
2	1-Methyl	103	3.3
3	2-Methyl	45	2.3
4	1, 4-Dimethyl	1,660	—
5	1-Phenyl	385	1.65
6	2-Phenyl	191	8.8
7	1-Methoxy	50,900	12.4
8	2-Methoxy	1,750	—
9	1,4-Dimethoxy	49,800	—
10	Cyclopentadiene	2,100,000	1,350

*Rücker C *et al.*: *Chem. Ber.*, **113**: 1663, 1980.

Some important examples representing the **Electrophilic Dienophiles,** namely:

(*a*) **Substituted Alkenes,**

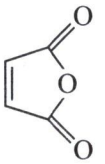
(*b*) **Substituted Alkynes,** and

(*c*) **Heteroatomic Dienophiles,**

are exemplified with their chemical *structures*, *nomenclatures*, and *references*:

(A) Substituted Alkenes

1. **Maleic anhydride**[1]



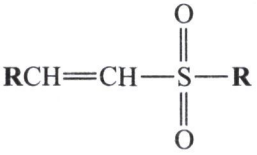
[1]Kloctzel MC: *Org React*, **4**: 1, 1948.

2. **Benzoquinone**[2]



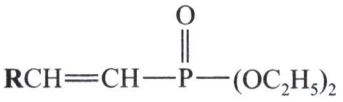
[2]Butz LW and Rytina AW: Org React, 5: 136, 1949

3. **α, β-Unsaturated Sulfones**[3]



[3]Philips IC and Oku M: *J Org Chem*, **37**: 4479, 1972

4. **α, β-Unsaturated Phosphonates**[4]



[4]Danieawski WM and Griffin CE: *J Org. Chem.*, **31**: 3236, 1966.

(B) Substituted Alkynes

5. **Esters of Acetylene dicarboxylic acid**[5]



[5]Sauer J *et al. Chem. Ber.*, **97**: 3183, 1964.

6. **Dibenzoyl acetylene**[6]



[6]White JD *et al.*: *J Org. Chem*: **36**: 1048, 1971

(C) Heterocyclic Dienophiles

7. **Esters of Azodicarboxylic acids**[7]

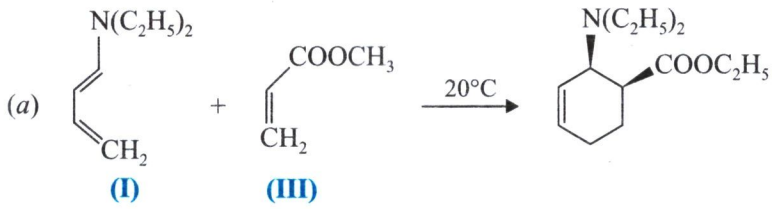


[7]Gillis BT and Beck PE: *J Org Chem.*, **28**: 3177, 1963.

8. **Iminocarbonates**[8]

[8]Krow G *et al.*: *J Am Chem Soc.*, **95**: 5273, 1973

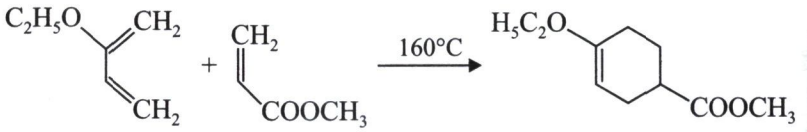
Interaction of Acetyloxyethene (III) wth N-Diethyl-1, 3-butadiene (I) and 2-Ethoxy-1, 3-butadiene (II)



REMARKS

'*ortho*'- Only Product [Yield = 94%]

(*b*)



'*para*'- Only Product [Yield = 50%]

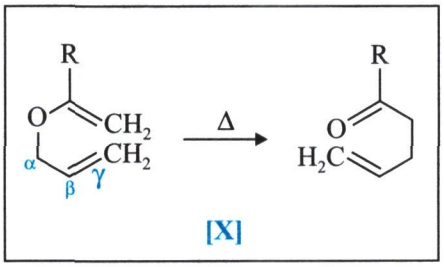
(III)

18.3 CLAISEN REARRANGEMENT

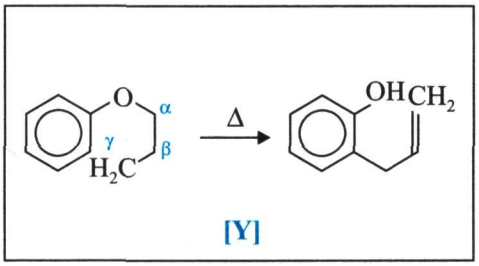
The **Claisen rearrangement*** designates a **highly stereoselective [3, 3]—sigmatropic rearrangement of** either:

- **Allyl vinyl (X)** or • **Allyl aryl ethers (Y),** to give rise to the formation of either:
  - ➢ **γ, δ-unsaturated carbonyl compounds,** or
  - ➢ ***ortho*-allyl substituted phenols,**

and expressed explicity as under:

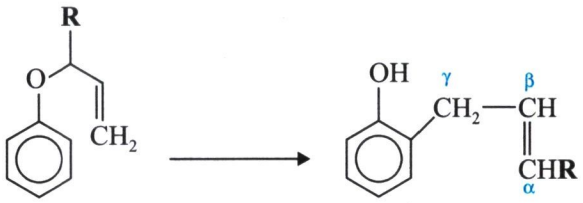


[X]



[Y]

Alternatively, the so-called **allyl aryl ethers (Y)** may also be re-arranged to the corresponding ***O*-allyl phenols****,—as shown below:



(Y) ***O*-Allyl phenol**

Important Features of the Claisen Rearrangement

A few important features of the **Claisen rearrangement** are as stated below:

- ➢ **Preparation of Allyl Enol Ethers,**
- ➢ **Applicability to Allyl Vinyl Ethers/Allyl Ethers of Enols,**
- ➢ **Represents a concerted Process,** and
- ➢ **Oxa-Version of the cope Rearrangement,**

which shall now be treated individually in the sections that follows:

*Claisen L: *Ber.*, **45**: 3157, 1912; Claisen L and Tietze E: *ibid*, **58**: 275, 1925; **59**: 2344, 1926.

That is, the *group* migrates to the ***ortho*-position, and the corresponding ***meta*-product** is never formed.

18.3.1 Preparation of Allyl Enol Ethers

The **Claisen arrangement** is not ony confined to the ***aromatic system*** exclusively but also applicable to **allyl enol ethers** (which do act as the *substrates* in this particular instance).

Fig. 18.1 depicts explicitly how such an **allyl alkenyl ether** (IV) may be prepared actually from an **allyl alcohol** in a ***single operation*** predominantly. The **allyl alcohol** is first and formost treated with a large excess of **ethyl vinyl ether** in the specific presence of *mercuric acetate [$Hg(OAc)_2$] in catalytic quantum only,*—as given under:

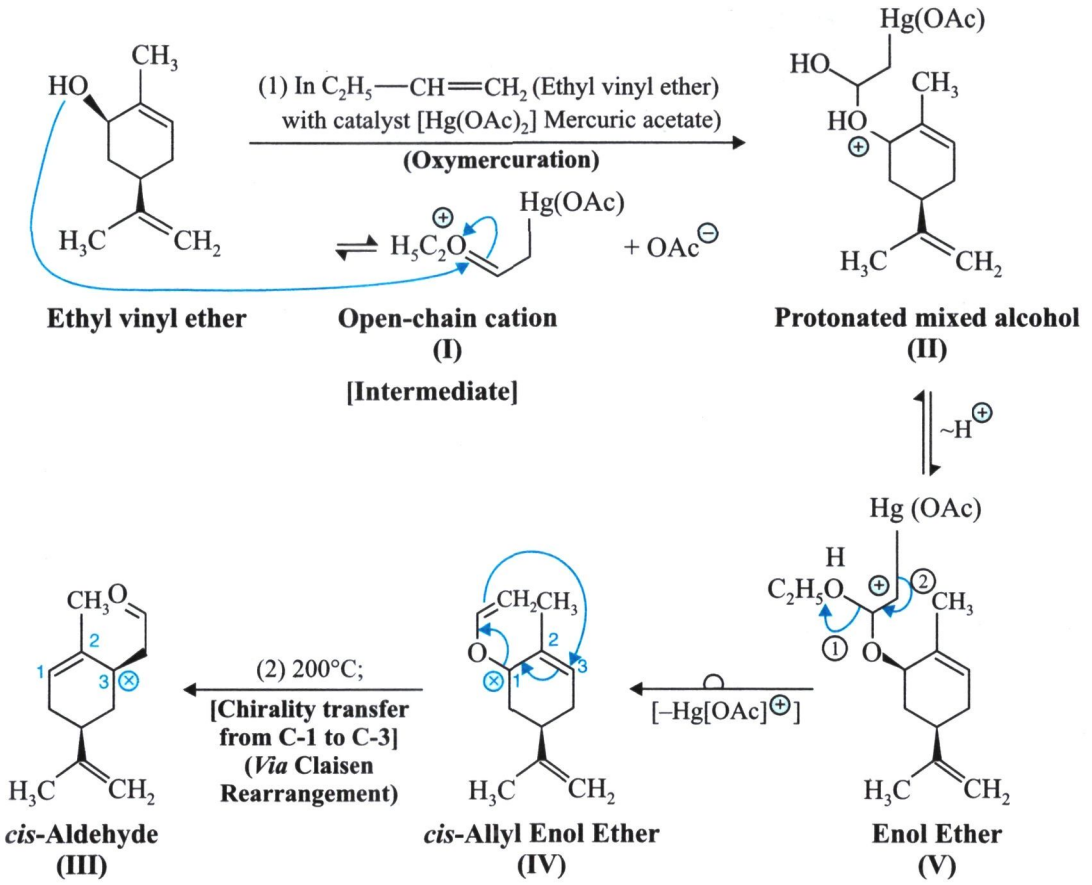


Fig. 18.1: The Preparation of an Allyl Enol Ether **(IV)** from Allyl Alcohol **(V)**, and a Large Excess of Ethyl Vinyl Ether. The Subsequent Claisen Rearrangement from **(IV)** to **(III)** Proceeds with Chirality Transfer from C-1 to C-3. **[⊗ = Chiral C-atom].**

Explanations

The various steps involved may be explained as under:

1. **Oxymercucation** of the C═C double bond present in the **ethyl vinyl ether** is the very first step.
2. The mercurioas acetate ion [Hg $(OAc)^{\oplus}$] serves as the **attacking nucleophile;** however, it does form an **open-chain cation (I)** as an ***intermediate*** perceptively instead of a **cyclic**

mercurinium ion. Besides, the said **open-chain cation (I)** is found to be rather more stable in comparison to the respective **mercurinium ion** since it may be duly stablized due to the **carboxonium resonance** grossly.

3. Thus, the **open-chain cation (I)** takes up the **allyl alcohol** thereby yielding a **protonated mixed alcohol (II)**.
4. The resulting **product (II)** undergoes the ***elimination*** **(E 1-process)** to lose a mole each of **ethanol (EtOH)** and **Hg(OAc) + – mercurous acetate ion** thereby resulting in the formation of desired **enol ether (V)**.
5. The **enol ether (V)** is found to be in equilibrium with the **substrate alcohol (II)** and the **ethyl vinyl ether** (*starting material*).

Remarks: The observed equilibrium constant is nearly **'1'**. Importantly the critical usage of a large excess of the **ethyl vinyl ether** (*i.e., starting material*) does help to **shift the equilibrium** toward the ***cis*-allyl enol ether (IV)** in order that the latter may be isolated in a definite **high yield**.

6. The resulting product ***cis*-allyl enol ether (IV)** gets duly converted to the respective ***cis*-aldehyde (III)** *via* a **Claisen rearrangement** as depicted in Fig. 18.1.

Obviouly, the **product (III)** and its **precursor (IV)** both happen to be the so-called ***cis*-substituted cyclohexanes**.

Comments: The **σ-bond** which has thus migrated virtually connects the ***two*** **C-atoms** in the **product (III);** whereas, it explicitly connected a *C-atom* and an *O-atom* in the **substrate alcohol (II)**. Obviously, the **σ-bond** remains clearly on the *same side* of the **cyclohexane ring;** and, therefore, the ensuing **Claisen rearrangement** takes place:

"with absolute (complete) transfer of the entire stereochemical information right from the original oxygenated stereocentre to the newly constracted stereocentre".

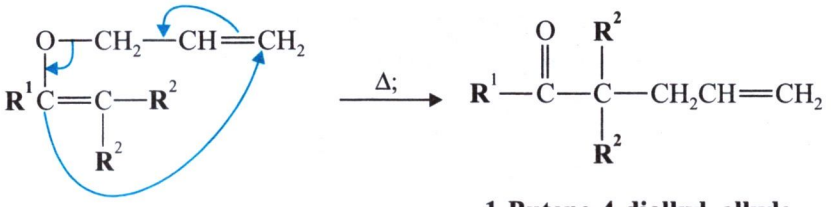
Cirality Transfer: It, therefore, relates to such a **stereocontrolled transformation** of a relatively *older version of a stereocentre* into an altogether ***newer one***. Importantly, the observed **Claisen rearrangement** of the product ***cis*-allyl enol ether (IV)** into the product ***cis*-aldehyde (III)** (in *Fig. 18.1*) represents predominantly the highly specialized instance of:

"a *1, 3-chirality transfer* because the *newly formed stereocentre* is located strategically at *position 3* with regard to the *old stereocentre* located at position 1".

18.3.2 Applicability of Allyl Vinyl Ethers/Allyl Ethers of Enols

It has been keenly observed that the **Claisen rearrangement** is not only restricted to the so-called **aromatic system solely** (as seen in *section 3.1*), but also fairly applicable to the **allyl vinyl ethers/ allyl ethers of enols**.

Thus, it may be expressed as under:



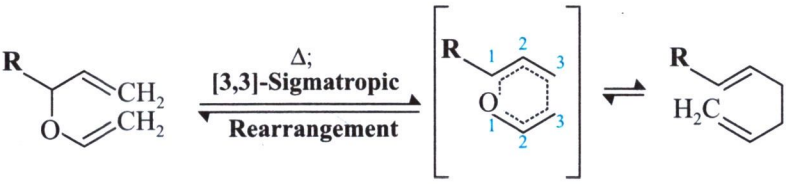
1-Propene-1,2-substituted ethene ether

1-Butene-4-dialkyl, alkyle ketone

NOTE: **It should be noted carefully that the overall *stability profile* of 'ketones' usually prevent their *enolization* phenomenon squarely.**

18.3.3 Represents a Concerted Process

The **Claisen rearrangement** is more or less a ***concerted process*** that may be expressed as given below:



Intermediate

EXPLANATIONS

It essentially includes:

1. The ***conceted process*** involving the **[3,3]-sigmatropic rearrangements,** in fact, have been used, almost to the full extent, specifically for the crucial *synthesis* of an array of:

'structurally complex organic molecules',

by virtue of the case with which the bonds are duly-formed in a:

"perfect regio-and stereo-chemically controlled and planned way".

2. Perhaps due to the availability of **fewer [3, 3]–sigmatropic rearrangement** required ardently for the so-called ***selective formation of C-N bonds***,—even through it does possess an enormous potential and ability for the critical preparation of such reactions as—the ***stereodefined*** **'allylic amines'**.

The Allylic Phosphorimidates: The [3, 3]—sigmatropic rearrangement mechanism duly involved in the so-called:

"allylic phosphorimidates",

that invariably renders a gainful access to the most preferred—**'stereo-defined allylic amines with a diverse chemical structure'**.

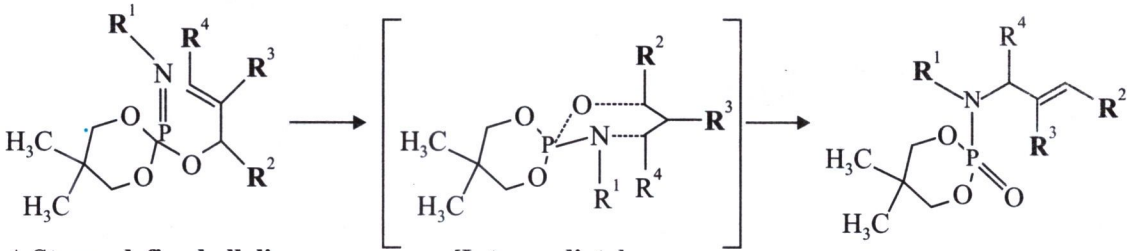
Therefore, the so-called **reactive intermediate** duly generated in the said reaction yields the **allylic phosphorimidate *in situ via*** the meticulous and intelligent combination (s) of the readily available *starting chemical entities* **(compounds)** *viz.,*

- **Allylic alcohols** • **Chlorophosphites** and • **Organic azides,**

thereby enabling the ensuing reaction:

'an efficient 3-component phenomenon'*.

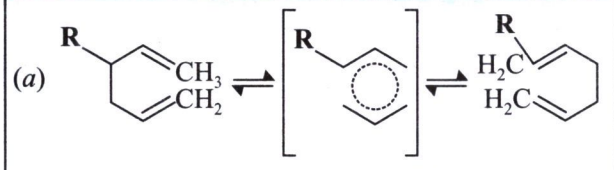
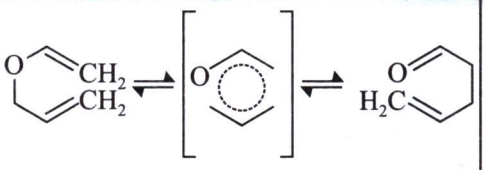
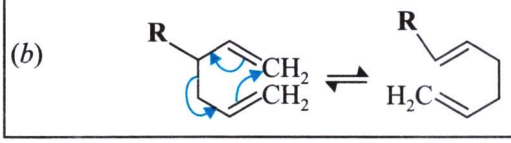
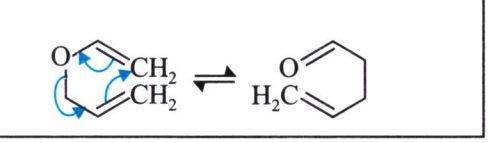
We may have the following expressions showing the formation of an allylic **phosphorimidate**:



A Stereo-defined allylic amine **[Intermediate]** **[Allylic phosphorimidate]**

18.3.4 Oxa-Version of the Cope Rearrangement

Interestingly, the **Claisen rearrangement** may be favourably compared as the **oxa-version of the cope rearrangement**. Therefore, we may look at the explicit and commendable comparison of the underlying mechanism of the **cope and Claisen rearrangement,**—as illustrated below:

Cope Rearrangement*	Claisen Rearrangement**
	
[Intermediate]	**[Intermediate]**
	

NOTE: **Both (*a*) and (*b*) under the *Cope* and *Claisen rearrangements* do compliment each other duly.**

Some Important Versions of Claisen Rearrangement

Following are *some of the important versions of the* **claisen rearrangement** which shall now be discussed briefly:

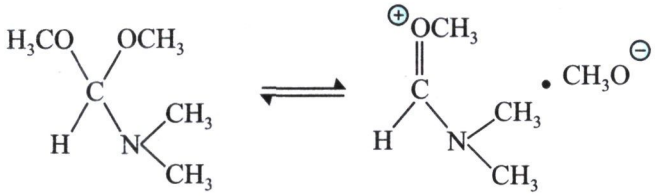
(*a*) **Eschenmoser-Claisen Rearrangement***:** It is also known as the **Eschenmoser-Claisen amide-acetal rearrangement**. It refers to the **[3, 3]-sigmatropic rearrangement** of the specific **N, O-ketone acetals** to give rise to the formation of **γ, δ-unsaturated amides****,—as given under:

*Cope AC and Hardy JM: *J Am. Chem. Soc.*, **62**: 441-444, 1940.

** Claisen L: *Ber Dtsch Chem Caes*, **45**: 3157-3166, 1912.

*** Coates *et. al.*: *Tetrahedron Letts*, 32: 4199, 1991

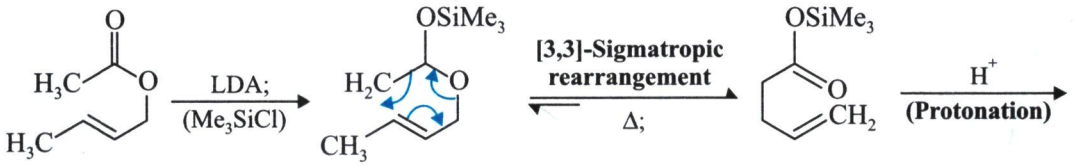
**** Khaledy MM et al.: *J Org Chem.*, **68**: 572, 2003; Gilbert MW *et. al.*: *J Synlett*, 2558, 2004.



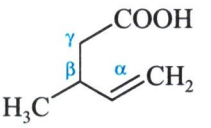
Dimethylamino-dimethoxy methane **An Amide-Acetal**

(*b*) **Ireland-Claisen Rearrangement*:** It is also called as the **Silyl-Ketene-Acetal rearrangement**. The **Ireland-Claisen rearrangement** relates to the chemical reaction of an **allylic ester** with a *strong base* to given an **γ-unsaturated carboxylic acid****. However, the mechanism of the reaction is reported to be a **concerted [3, 3]–sigmatropic rearrangement** exhibiting vividly the so-called: **suprafacial reaction pathway.*****

Thus, we may have the following expressions:



Allylic ester



γ-Unsaturated carboxylic acid

NOTE: **The Ireland-Claisen-rearrangement is extremely useful with regard to the E/Z-geometry control.**

Formation of *p*-Substituted Phenol: The articulated **formation of the p-substituted phenol** may be duly expatiated by the **Claisen rearrangement** particularly in the *early steps involved,*— extended to an ***o*-allyl intermediate**, that fails to undergo the *phenomenon of* ***tautomerism*** (*i.e.*, ***cis-trans* geometrical isomers**). Thus, it results into the formation of the following sequential steps:

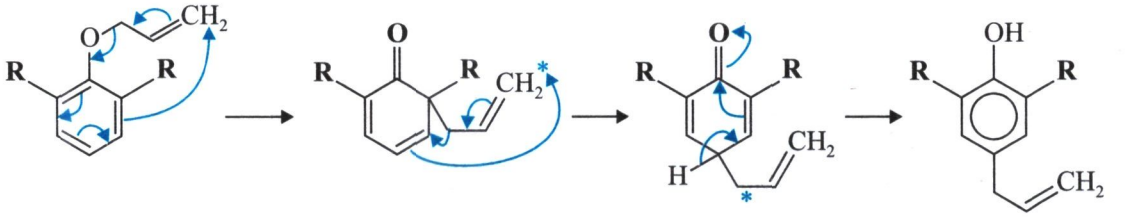
- **aromatic *ortho*-allyl phenol,**
- **Cope rearrangement to yield *para*-allyl intermediate,** and
- **ultimately upon *tautomerization* to give *para*-allyl phenol.**

* Ireland RE and Müeller RH: *J Am. Chem. Soc.*, **94**: 5897, 1972; Ireland RE *et al.*: *J Org Chem.*, **56**; 650, 1991.

** Müller SP and Morken JP: *Org Lett.*, **60**: 2743-45, 2004.

*** Chai Y *et al.*: *Tetrahedron*, **58**: 2905-28, 2002.

These sequential steps involved may be expressed as under:



(A) **(B)** **(C)** **p-Allyl phenol (D)**

***(Asterisk) = Implies presence of a labelled C-atom [13C-atom].**

Remarks:

1. In case, the *two* respective ***O*-positions** do essentially bear the substitutents other than the **H-atom,**—the resulting allyl moiety rapidly migrates to the corresponding ***p*-positions;** and hence, usually termed as the ***para*-Claisen rearrangement**.
2. However, the **Claisen rearrangement** fails to occur whenever both the ***ortho*—and *para*-positions** are duly occupied by ***substituents* other than the H-atom**.
3. **Structure (B)** is devoid of the *H-atom* specifically at the ***ortho*-position** thereby critically preventing either the ***enolization*** or the ***aromatization*** phenomenon perceptively. Perhaps this could be the most plausible and feasible reason why the incumbent **allyl moiety** undergoes another ***'migration'*** to form **(C)** that ultimately undergoes **aromatization** to give ***p*-allyl phenol (D)**.

Mechanism of *para*-Migration: Importantly, the **mechanism of *para*-migration** predominantly involves either:

- **double migration of allyl moiety,** or
- **double inversion of allyl group.**

Therefore, in a situation when both the ***ortho*-positions** are duly *substituted*, the **'migration'** even then comes into play at the **same *ortho*-position** prevalently thereby giving rise to the generation of:

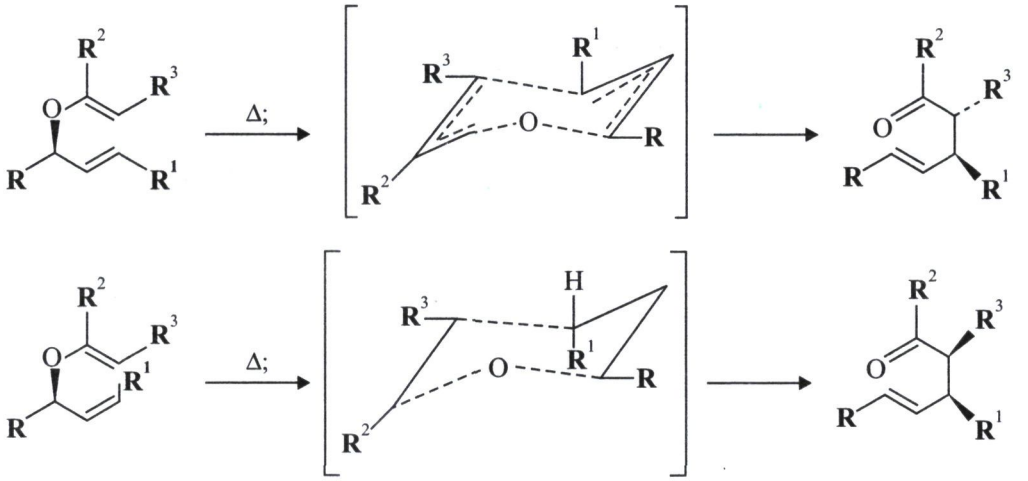
"a dienone intermediate duly substituted at the *ortho*-position".

Thus, the labelling of **C-atom** does provide a *concrete evidence* in revealing adequately the so-called **inversion of the allyl moiety mechanism** in an elaborated manner.

Nevertheless, the underlying **stereochemistry of the *p*-migration** is precisely and accurately determined by the prevailing **geometry** of the ensuing **transition state (TS)**. Various *organic chemists** vehemently supported and advocated the ***chair-like* conformation** as the most preferred **Claisen rearrangement**,—that predominantly adopts the so-called ***intramolecular pathway***.

*Ganem B: *Agnew Chem.*, **108**, 1014-1023, 1996; Gojewski JJ: *Acc Chem Res.*, **30**: 219-225, 1997; Ziegler FE: *Chem. Rev.*, **88**: 1423-52, 1988.

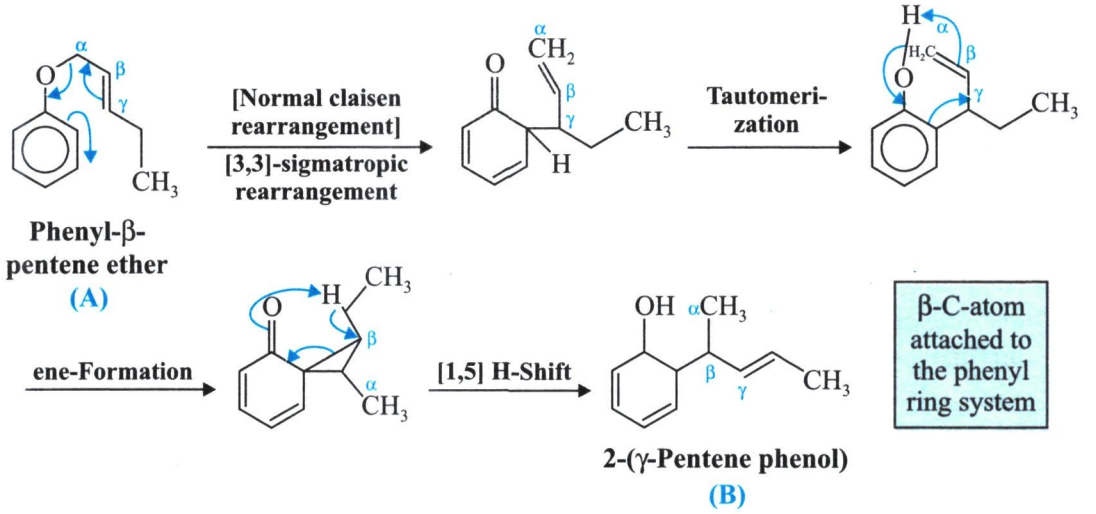
Thus, we may have the following expressions:



Comments: It would be worthwhile to state here that the above feature is found to be extremely advantageous in making of the **Claisen rearrangement** for carrying out the **stereoselective synthesis** since it is a lot easier to predict both:

- **stereochemical pathway,** and
- **configurations of stereogenic centres*.**

Unusual Claisen Rearrangement: Schobert *et al.* (2001)** and Puranik et al. (2002)*** reported the so-called **Unsual Claisen rearrangement** as the further extension of the **Normal Claisen rearrangement** and product having the classical attachment to the *aromatic ring* with the **β-C-atom** in an elegant manner,—as illustrated below:



*Burke SD and Pakofsky GJ: *Tetrahedron Lett.*, **27**: 445-448, 1986.

**Schobert R *et al.*: *Tetrahedron Lett.* 42: 4566, 2001.

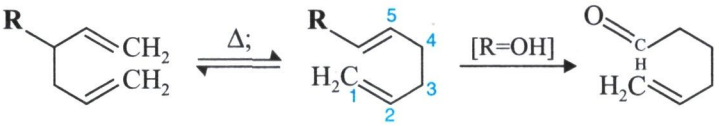
***Puranik R *et al.*: *Ind J Chem. Sect.*, B, 41B, 86B, 2002.

The above sequential steps are self-explanatory *i.e.*, showing the shifting of the **C-C double bond** from ***β-position in (A)*** to the respective ***γ-position in (B)***.

18.4 COPE REARRANGEMENT* [or OXY-COPE REARRANGEMENT]

The **Cope rearrangement** refers to the **lighly stereoselective [3, 3]-sigmatropic rearrangement of *'1, 5-dienes'*; *i.e.*, "all carbon"** equivalent of the **Claisen rearrangement** *q.v.*, **(as much as you wish)**.

We may have the following expression:

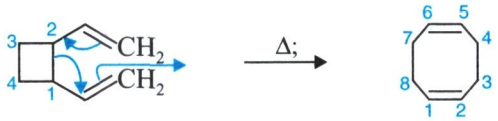


1,5-Diene

When **R=OH**, the transformation is usually referred to as the **oxy-cope rearrangement****.

Importantly, the **Cope rearrangement** is being employed abundantly in the domain of ***Organic Synthesis***.

Example: The classical example is the expansion of the ***4-membered*** **cyclobutane** to the respective ***8-membered*** **cyclooctadiene,**—as shwon under:



1,2-Ethene cyclobutane **1,5-Cyclobutadiene**

Mechanism of Cope Rearrangement

It has been duly proven and demonstrated that the **Cope rearrangement** invariably comes into play either *via*:

- **concerted mechanism,** or
- **biradical mechanism.**

❑ Amazingly, the said arrangement proceeds by means of a **concerted pericyclic reaction mechanism** (see *section 2*); and

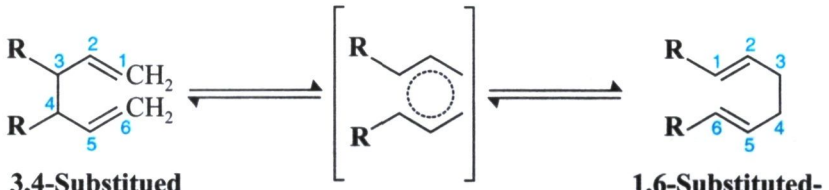
❑ Alternatively, using the **[3, 3]-sigmatropic arrangement** involving critically the cleavage of ***one single C-C bond*** and resulting the formation of an altogether **new bond** (—a **biradied mechanism**).

Therefore, it may be ascertained that the **cope rearrangement** designates a–***reversible and intramolecular*** **episode** whereby the ultimate product thus formed is definitely found to be **more stable and equally versatile,**—as illustrated under:

---

* Cope AC *et al.*: *J. Am. Chem. Soc.*, **62**: 441, 1940.

** Berson J and Jones M: *J Am. Chem Soc.*, **86**: 5019, 1964.



3,4-Substitued 1,5-hexadiene [X] | **Transition state [Intermediate]** | **1,6-Substituted-1,5-hexadiene [Y] [A thermodynamically more stable product]**

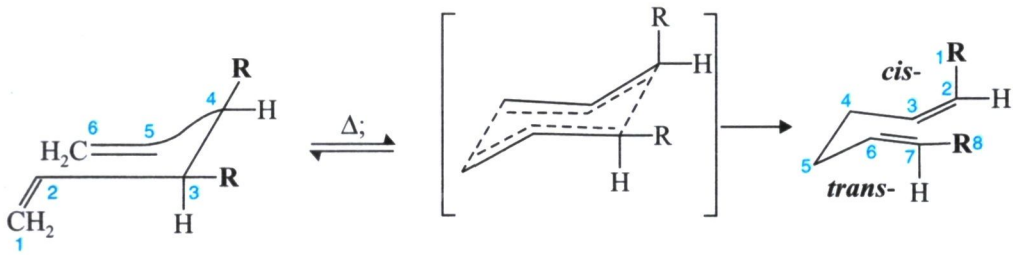
Comments: The above sequential reactions do exhibit a **reversible and intramolecular episode** wherein the *2-substitutions* are positioned at C-3 and C-4 in **(X)** and at C-1 and C-6 in **(Y)**; and the latter **(Y)** is found to be **more stable**.

NOTE: **The observed isomerization in (*X*) and (*Y*) proceeds meticulously *via* a *6-membered transition state*.**

Stereochemistry of Cope Rearrangement: The fundamental ideas and concepts pertaining to the **stereochemistry of cope rearrangement** broadly reveals and expatiates that the ensuing arrangement virtually proceeds *via* the following ***three*** **cardinal theoretical principles,** namely:

- **a chair-like conformation geometry;**
- **six-membered cyclic transition state;** and
- **implicating the stereospecific nature of rearrangement.**

Let us look into the following sequential reactions thoroughly:



***Meso*-1,5-Hexadiene [Substituted]** | **[Intermediate] (Transition state) (TS)** | ***cis-trans*-2,6-Octadiene**

EXPLANATIONS

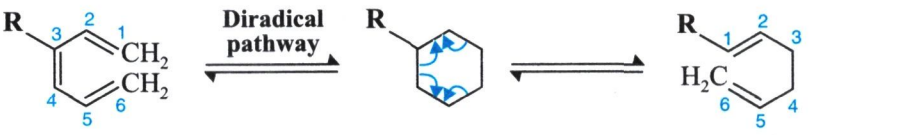
1. The starting chemical entity is ***meso*-1, 5-hexadiene (substituted)** which on being subjected to *thermal transformation* **(Δ)** yields an **intermediate** in the ***transition state*** **(TS)** (*i.e.,* **a 6-membered cyclic TS**).
2. The resulting **intermediate (in TS)** further undergoes a **stereospecific nature of rearrangement** to yield the desired ***cis-trans*-2, 6-octadiene** as the final product.

Remarks: The resultant product ***cis-trans*-2, 6-Octadiene** (*i.e.*, an **alkene**) obtained duly from the reaction from the ***meso*-reactant [*meso*-1, 5-hexadiene]** is obviously a ***cis-trans* compound**. Thus, it certainly provides a significant evidence in absolute favour and support of the so-called **'chair-life conformation'** of the **TS** *i.e.*, right from the **boat-like conformation** of the **TS**, one would only obtain either ***cis-cis* (Z, Z)** or ***trans-trans* (E, E)** end product would have been formed ultimately*.

The Diradical Pathway: In addition to the usual **converted pericyclic pathway** one may also come across the so-called **diradical pathway** based upon the experiemental investigative studies to explore further useful evidences for the ***mechanism* of the cope rearrangement** appropriately; and perhaps this logically provides the possible reason that actually leads us to the ***steric restrain*** to a great extent.

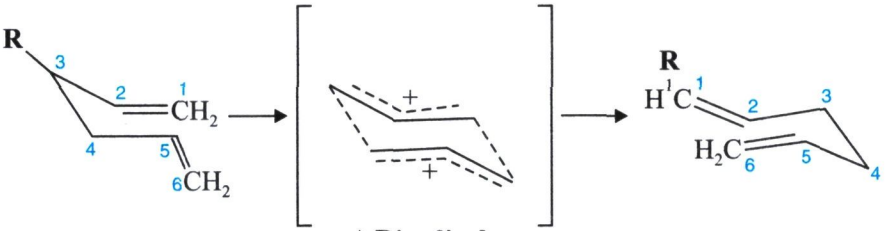
Dollinger *et al.* (1982)** were primarily responsible to pave the way for the **diradical pathway** which critically takes off with the legitimate formation of **C-C single bond** that leads to the ***diradical specie*** thereby yields the respective ***'diene'*** due to the **bond cleavage** ultimately,—as depicted under:

(a) **Usual Chemical Structure**



3-Substituted Hexa-1,5-diene — **A Diradical specie** — **1-Substituted Hexa-1,5-diene**

(b) **Chair Conformation**



A Diradical Transition state (TS) [Intermediate]

Degenerate Cope Rearrangement: It has been duly observed that **hexa-1, 5-diene** undergoes the **normal cope-rearrangement** to yield a product very much akin to the reactant itself; and hence, this is invariably termed as the **degenerate cope rearrangement** *viz.*, ***automerization* of the bicyclo [5, 1, 0] octa-2, 5-diene,**—as given below:



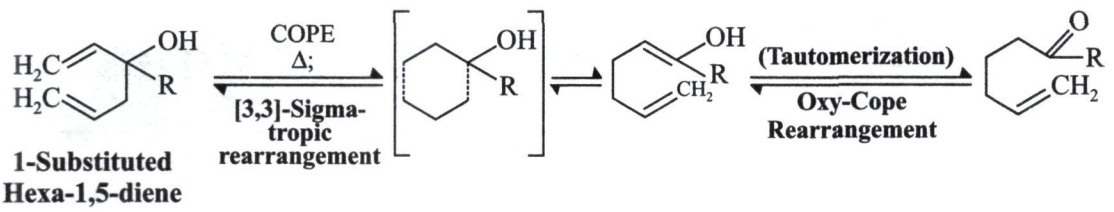
[5,1,0]-Octa-2,5-diene — **Hexa-1,5-diene**

[A Bicylo Diene]

*Deering WVE and Ruth WR: *Tetrahedron*, **18**: 67-74, 1962.

Dollinger M *et al*: *Chem Ber.*, **115: 2309-2325, 1982.

Oxy-Cope Rearrangement**:* In a situation when the ultimate **cope resulting product** undergoes the phenomenon of **tautomerization** into the corresponding **aldehyde (—CHO) or ketone (>C=O)** and is subsequently removed from the ***prevailing **equuilibrium status**, it is usually called as the **oxy-cope rearrangement**. Thus, it may be expressed as under:



The above sequential steps are self-explanatory.

Suggested Reading

Dewar MJS: **The Molecular Orbital Theory of Organic Chemistry**, McGraw Hill, New York, 1969.

Fringuelli F and Taticchi A: **The Diels-Alder Reaction: Selected Practical Methods,** Wiley, Chichester, 2002.

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Patai S (Ed.): **Chemistry of Alkenes**, Wiley Interscience, New York, 1964.

Watson WH (Ed.): **Stereochemistry and Reactivity of Systems Containing π-Electrons,** Verlag Chemie, Dcerfield Beach, FL., 1983.

Wasserman A: **Diels-Alder Reactions,** Elsevier, New York, 1965.

Woodward RB and Hoffmann R: **The Conservation of Orbital Symmetry,** Academic Press, New York, 1970.

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*Schmeider C: *Synlett*: 1079-1091 (Review), 2001; Dimartino G *et al.*: *Org Biomol Chem.*, **1**: 4423, 2003.

Chapter 19

The Aromatic Rearrangements

LESSONS AT A GLANCE

19.1 Introduction
19.2 Benzidine Rearrangment
19.3 Fries Rearrangement
19.4 Reimer-Tiemann Reaction

19.1 INTRODUCTION

The underlying analogy and concept of the **aromatic rearrangement** essentially deal with a broad spectrum of the ***Organic Reactions*** that mostly represent the so-called:

- **acid-catalyzed rearrangement,** or - **base-catalyzed rearrangements.**

The typical conversion of **hydrazobenzene** to **benzidine** in the presence of a *proton* (H^+) derived from diluted mineral acids *viz.*, HCl, H_2SO_4 etc., serves as a befitting example. Interestingly, such a reaction normally endorses the crucial involvement of **[5,5]–sigmatropic rearrangement** that affords the rearrangement of the **phenyl moietier**.

Likewise, the **aromatic rearrangements** do relate to the Lewis acid ($AlCl_3$)—catalyzed interaction of the **phenolic esters** to the corresponding ***o*-and/or *p*-phenolic ketones**.

In the same vein, the formation of the ***ortho*-formyl phenol** from pure **phenol,** in an alkaline environment also designates a kind of **aromatic rearrangement**.

Therefore within the purview of this chapter it would be worthwhile to have our discussions focussed upon the following ***three* important aspects,** namely:

- **Benzidine Rearrangement,**
- **Fries Rearrangement,** and
- **Reimer-Tiemann Reaction,**

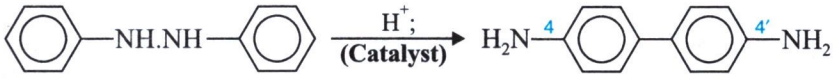
which shall now be treated separately in the sections that follows:

19.2 BENZIDINE REARRANGEMENT*

It is also known as the **Semidine Rearrangement**, which refers to the **acid-catalyzed rearrangement** of the ***hydrazobenzenes*** to **4,4'-diaminobiphenyls**. In a specific instance if the so-called **hydrazobenzene** comprises a ***para*-substituent**, the end-product so obtained happens to be a ***para*-aminodiphenylamine (Semidine rearrangement)**.

*Hofmann AW: *Proc. Roy Soc., London*, **12**: 576, 1863; Jacobson P *et al.*: *Ber*, **26**: 688, 1893.

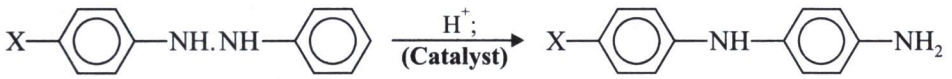
We may express the reactions as stated under:



Hydrazobenzene **4,4′- Diaminobiphenyl**

It has been reported that the **benzidine rearrangement** usually occurs in the presence of a ***strong mineral acid*** *viz.*, H_2SO_4, HCl etc., preferably in an aqueous environment.*

Substituted Diphenyl Hydrazine—also undergoes the **benzidine rearrangement** with equal efficiency,—as given under:



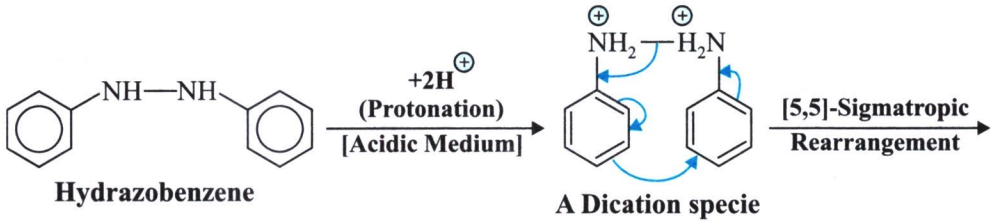
***p*-Halohydrazobenzene** ***p*-Haloanilino-N-*p*-aniline**

Mechanism of Benzidine Rearrangement**—The mechanism of the benzidine rearrangement may be expatiated with the help of the **[5,5]–sigmatropic rearrangement** that critically involves the phenomenon of **protonation** (H^+) with the rearrangement of **phenyl** ($-C_6H_5$) moieties.

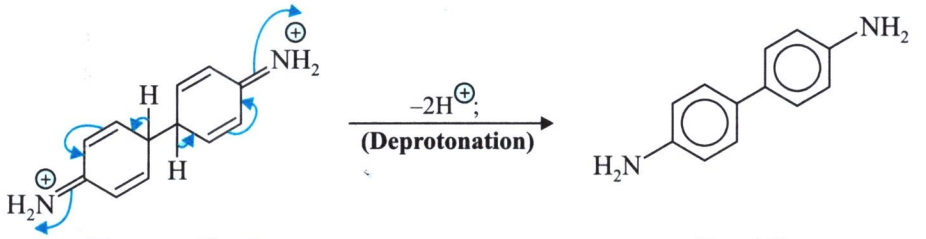
It is, however, pertinent to state at this point in time that the overall **benzidine rearrangement** is certainly *not*:

'a dissociation or recombination phenomenon'.

The *three* sequential steps involved in the said mechanism of reaction may be expressed as under:



Hydrazobenzene **A Dication specie**



[Intermediate] [Rearranged Structure of Dication sp.] **Benzidine {*p*-Diaminodi phenyl ; [1,1′-Biphenyl]-4,4′-diamine}**

*Moller F: *Mettroden Org Chem.*, (*Houben-Weyl*), Vol. 11/1, pp: 839-848, 1957.

Patis S' (Ed.): **Chemistry of Alkenes, Wiley Interscience, New York, 1964.

EXPLANATIONS

The various steps involved may be explained as under:

1. *Protonation* of **hydrazobenzene** in an acidic environment yields a typical ***dication* specie,** which on being subjected to **[5, 5]–sigmatropic rearrangement** gives an ***'intermediate'***—having an altogether *rearranged structure of the dication specie.*
2. *Deprotonation* of the resulting ***'intermediate'*** gives rise to the formation of **benzidine** *i.e.*, the desired product, which is also known as:
   - ***para*-Diamino diphenyl;** or
   - **[1, 1'–Biphenyl]–4, 4'–diamine.**

Comments: It may be understood quite explicitly that the aforesaid rearrangement is not regarded to be either:

- **a recombination phenomenon,** or
- **a dissociation process.**

Remarks: The **'dication specie'** obtained above is found to be a fairly **stable chemical entity** duly formed in a ***super-acidic solution* at – 78°C.** Therefore, the **basic kinetics** of the aforesaid reaction reveals predominantly that the so-called **benzidine rearrangement** essentially involves the ***most critical* specific acid catalysis process.** Nevertheless, one may reasonably draw a definite inference that the **benzidine rearrangement** may eventually be regarded as either:

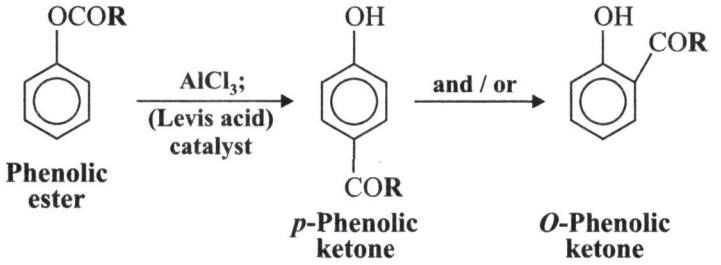
- ***First order kinetic*—in a *weakly acidic* medium,** or
- ***Second order kinetic*—in a *strongly acidic* medium.**

19.3 FRIES REARRANGEMENT*

The **Fries rearrangement** particularly refers to the typical rearrangement of the **phenolic esters** to the respective ***o*-and/or *p*-phenolic ketones** on being subjected to gentle heating either:

- **aluminium chloride ($AlCl_3$),** or
- **other *Lewis acid* catalysts.**

Thus, we may have the following expressions:



* Fries K and Fink G: *Ber.*, **41**: 4271, 1908; Fries K and Pfaffendorf W: *ibid*, **43**: 212, 1910.

A survey of literature reveals that the **Fries rearrangement** is also known as the **Fries-Finck rearrangement***. In addition, it ascertains the fact that the **phenols** do react with *esters* but fail to interact with the **acylhalogens** to give the corresponding **hydroxyaryl ketones** (or ***o*-and *p*-phenolic ketones** shown above) under the so-called ***Friedel-Crafts reaction*** (discussed elsewhere). **Medicinal Compounds (or Drugs)**—The aforesaid **'hydroxyaryl ketones'** by **Fries rearrangement** is of immense utility and importance in the production of **medicinal compounds (drugs)** *e.g.*, **Paracetamol** (used to lower high body temperature).

Importantly, such **'esters'** having *reasonably stable acyl component* may undergo the **Fries rearrangement** exclusively. However, in an event when either the **acyl portion (—$COCH_2$)** or the **aromatic segment (—C_6H_5)** are loaded with:

'bulky organic substituents',

may obviously afford an appreciable hindrance (obstruction) thereby hindering the reaction to occur effectively.

Mechanism of Fries Rearrangement: Based on the scientific investigative studies supported by logical explanations,—the precise and exact mechanism for **Fries rearrangement** has not yet been determined. Dewar and Hart (1970)** put forward an array of suggestive typical cross-over experiments were duly performed to establish the most probable and prevalent nature of the **Fries rearrangement**. Interestingly, Martin *et al.* (1986)*** provided a convincing and reasonable supportive evidence very much in favour of the so-called **intramolecular nature**. However, the usual smooth progress of the *actual reaction* is found to be perfectly independent of both:

- **Solvent** and
- **Substrate.**

Accepted Mechanism of Fries Rearrangement: It essentially involves a **carbonium ion intermediate;** and hence, can adopt either:

- ***ortho*-Substitution, or**
- ***para*-Substitution,**

which will be dealt with individually in the sections that follows:

[A] *ortho*-Substitution

EXPLANATIONS

Various steps involved may be expatiated as under:

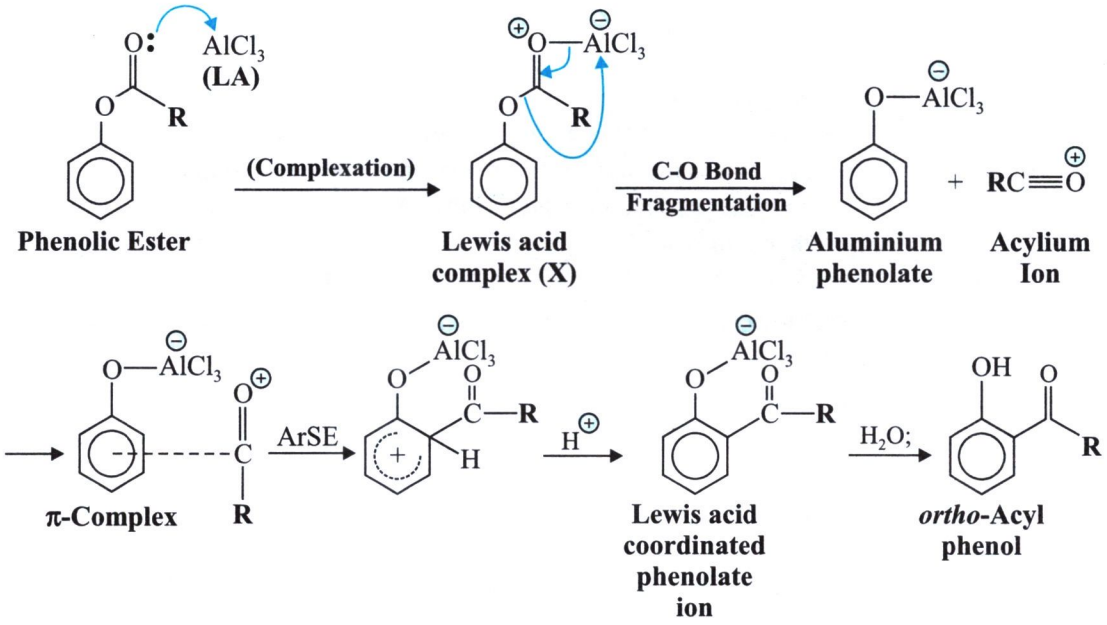
1. The *Lewis acid (LA)* may coordinate to the *substrate* **(Phenolate Ester)** at either:

- **one of the '*o*'-centres,** or
- **both of the '*o*'-centres (when LA is in excess).**

*March J: **Advanced Organic Chemistry**, 6th ed., John Wiley and Sons, New York, 2007; Blat AH: *Org. React,* **1**: 342-365, 1942; Martin R: *Org Prep Proced Int,* **24**: 369-435, 1992.

Dewar MJS and Hart LS: *Tetrahedron,* **26: 973-1000, 1970.

***Martin R *et al.*: *Bull Soc. Chem France*, 659, 1986.



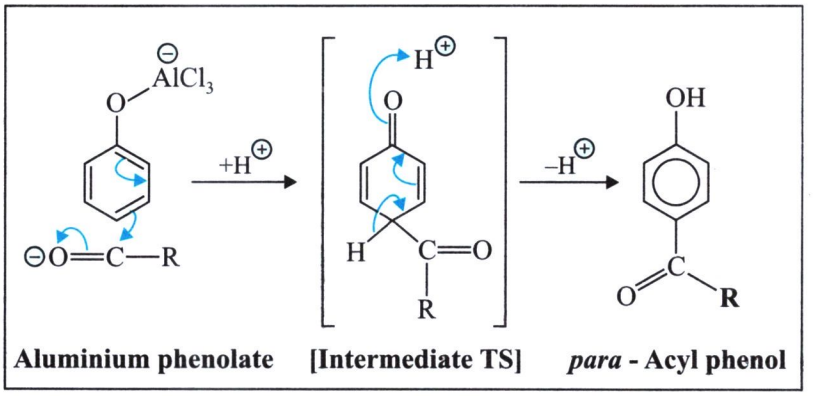
2. Preferentially, the *LA coordinates* to the **carbonyl (>C=O) 'o'-atom** present in the **acyl (—COR) moiety** by virtue of its **more richness in electrons** *vis-a-vis* the **phenolic (OH) 'O'–atom.**

3. The said **LA-coordination** strongly polarizes the bond existing between the **phenolic oxygen** and the **acyl moiety** perceptively.

4. Besides, the actual **complexation** occurring between the **Lewis acid ($AlCl_3$)** and the **phenyl ester** gives rise to the formation of the **Lewis-acid complex (X).**

5. Consequently, the **LA-complex (X)** splits into an **'Ion-Pair'** *viz.,* **Aluminium phenolate** and **Acylium ion**, due to the prevalent **C-O bond fragmentation,** which is duly *held together by the solvent cage securedly.*

[B] *para*-Substitution



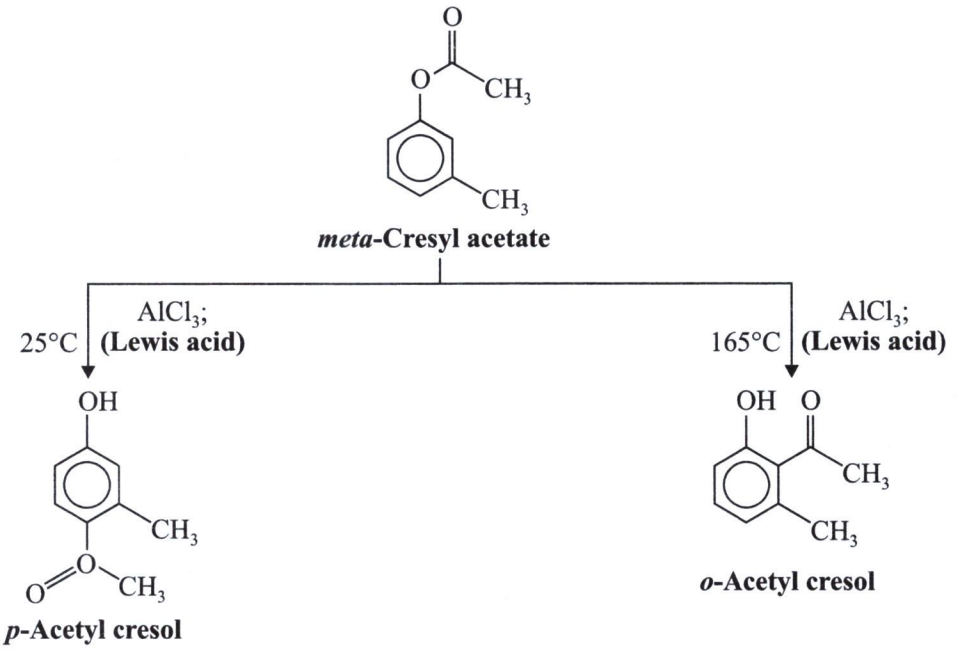
EXPLANATIONS

1. The **aluminium phenolate (anion),** obtained above in the ***ortho*-substitution** episode on being subjected to **protonation ($H^{\oplus}$)** gives an **intermediate *transition state (TS).***

2. The **intermediate (TS)** undergoes *deprotonation* phenomenon to give rise to the formation of ***para*-acetylphenol** as the ***end-product***.

DOES THE FRIES REARRANGEMENT BE DESIGNATED AS AN EQUILIBRIUM REACTION? In order to establish the above cited factual statement whether the **Fries rearrangement** be duly proclaimed and designated as an **equilibrium reaction,**—we may have to consider intelligently and thoughtfully the so-called:

"regioselectivity of the Fries rearrangement as shown clearly by the rearrangement of *meta*-cresyl acetate,—which is exclusively dependent upon the ensuing '*reaction temperature*'—thereby yielding the *ortho*-product at high temperature (185°C); whereas, the corresponding *para*-product at low temperature (25°C)",—as illustrated under:



Martin and Dermerseman (1989)* reported the successful use of an array of other **catalysts** in the **Fries rearrangement,** such as:

• **Zinc chloride ($ZnCl_2$)** • **Titanium Chloride ($TiCl_2$)** • **Boron Trifluoride (BF_3)** and • **Trifluoromethane sulphonic acid.**

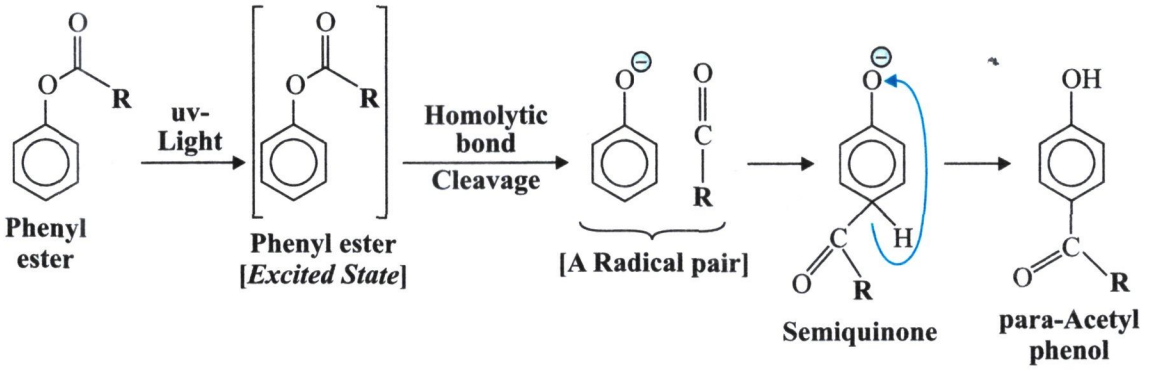
Photo-Fries Rearrangement:** Interestingly, the **photo-Fries rearrangement** may be splendidly performed in the absolute absence of any kind of a **'catalyst'** stated above; however, it does require the **UV-light** instead. Obviously, the underlying mechanism of the so-called **photo-Fries rearrangement** critically involves the—***'free-radical* intermediate'**. Nevertheless, the above reaction may also be carried out effectively provided:

*Martin R and Demerseman P: *Synthesis*, pp: 25-28, 1989.

Bellus D and Hardlovic P: *Chem Rev.*, **67: 599-609, 1967.

"the specific *deactivating substituents* are duly present strategically upon the aromatic moiety".

These reactions may be expressed as under:



EXPLANATIONS

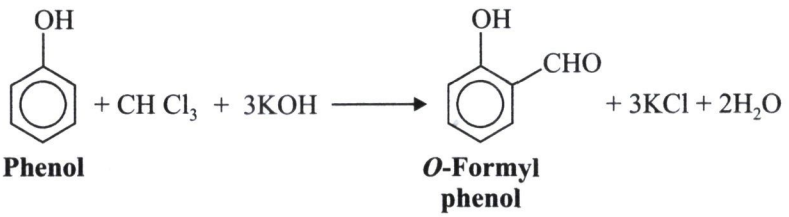
1. The **phenyl ester** on being irradiated **(with UV-light)** gets duly transformed into an **'excited state'** *i.e.*, from the initial *ground state* to the latter *excited state*.

2. The '*excited state*' of the **phenyl ester** undergoes the ***homolytic bond cleavage*** to give the **'radical pair'**, which after a series of reactions yield the **semiquinone anion**.

3. The **semiquinone anion** affords an **intramolecular** shifting of a **proton** (H^+) from C-4 to C-1 thereby producing the ***p*-acetyl phenol**.

19.4 REIMER-TIEMANN REACTION*

The **Reimer-Tiemann reaction** relates to the formation of the **phenolic aldehydes** from ***phenols*, *chloroform*, and *alkali*,**—as given below:



In other words, the **RT-reaction** explicitly entails the so-called:

'formylation of phenol with chloroform in an alkaline medium'.**

In actual practice, the aforesaid method is found to be *largely applicable* and *extremely useful* not only to the **'phenols'** but also to certain specific **'heterocyclic chemical entities (compounds)'**.

Remarks: Thus, out of the *two* products formed duly *viz.*, ***ortho*-and *para*-products**, the former one *i.e.*, ***ortho*-product is found to** be always predominant than the latter.

*Reimer K and Tiemann E: *Ber*, **9**: 824, 1268, 1285 (1876).

Reimer K: *Ber. Dtsch. Chem Ges.*, **9: 423-424, 1876; Simchen G: *Methoden Org Chem.*, Vol. E3, 16-19, 1983.

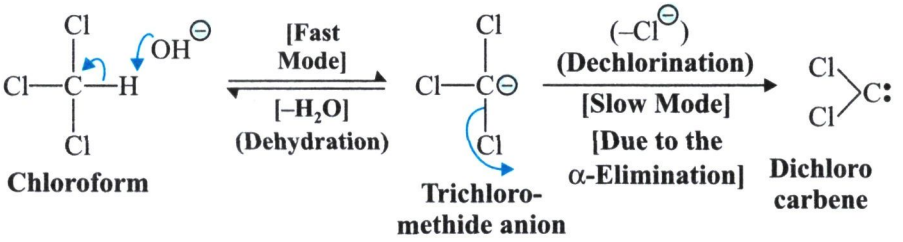
NOTE: **It may be observed that in other '*formylation reactions*' *viz.*, the Gattermann-Aldehyde Synthesis***—the *para*-product invariably predominates.**

Mechanism of Reimer-Tiemann Reaction: The underlying mechanism of the **RT-reaction** predominantly implicates the crucial generation of:

- ***First:*** **dichloro-carbene [:CCl_2]**—as the *reactive specie* or *attacking agent*; and
- ***Second:*** addition of **dichlorocarbene** to the *phenol*-followed by careful hydrolysis to obtain the desired ***ortho*-product**.

Therefore, these *two* individual **steps-1 and 2** shall now be explored and discussed separately as under:

***Step-1*: Carbene Formation**

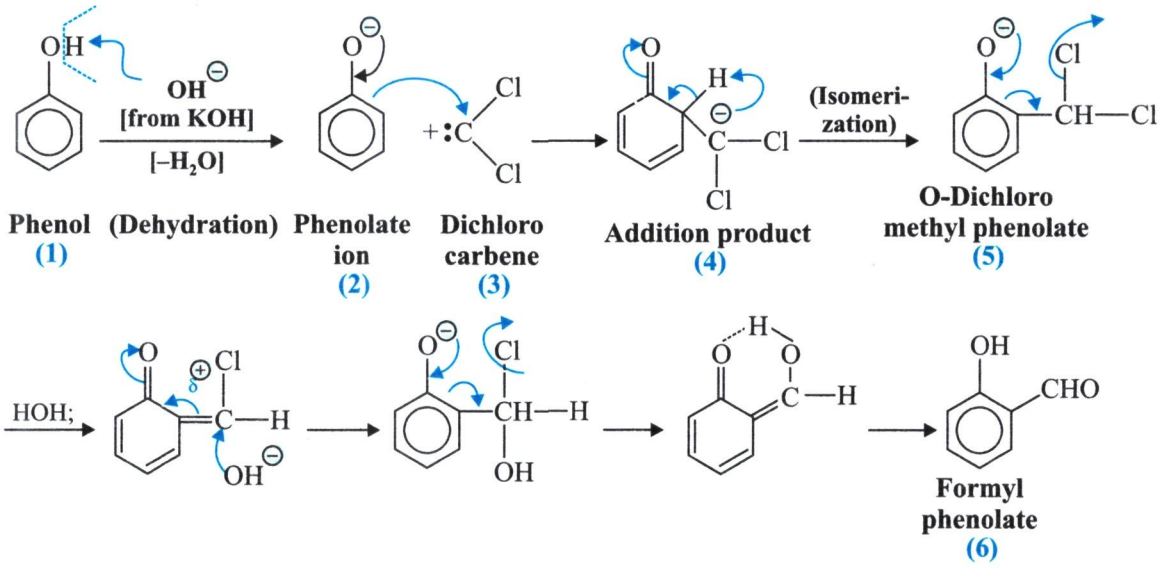


EXPLANATIONS

1. Chloroform gets duly *deprotonated* (**—$H^{\oplus}$**) is a fairly **strong basic environment** to give rise to the formation of **trichloromethide anion** in a definite **'fast mode'**.

2. The resulting product, **trichloromethide anion,** loses a **chlorides ion** (*dechlorination*) in a rather ***'slow mode'***, due to the so-called α-elimination—thereby producing the desired product **dichloro carbene**.

Step-2*: Generation of α-Formyl Phenolate from Phenol



*Gattermann L: *Ber,* **31**: 1149, 1898, *Ann.*, **313**: 1907.

**Robinson EA: *J Chem. Soc.*, 1663-1671, 1961.

EXPLANATIONS

1. **Phenol (1)** gets *deprotonated* in a basic medium to the corresponding **phenolate ion (2)** with the loss of a mole of water.

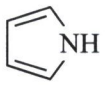
2. The **phenolate ion (2)** on being subjected to the treatment of **dichlorocarbene (3)** yields an addition product with **dichloro carbene at the *o*-position (4)**.

3. The resultant **product (4)** gets duly isomerized to the *aromatic product*: ***O*-dichloromethyl phenolate (5)**.

4. The **product (5)** upon successive hydrolysis intramolecular rearrangement sequences ultimately yields the desired product **formyl phenolate (6)**.

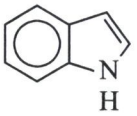
Points to Ponder: These essentially include:

1. The meritorious applications of **Reimer-Tiemann reaction** seems to be more or less confined to the specific phenomenon related to the so-called **formylation of phenols,** in addition to certain ***heterocyclic* chemical entities,** namely:



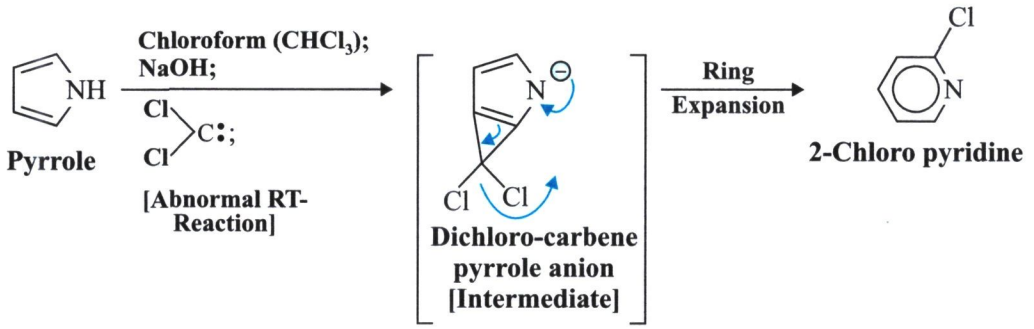
Pyrrole

and



Indole

2. Nevertheless, one may also come across an **abnormal Reimer-Tiemann reaction** which predominantly involves a spectacular ***'ring expansion'*** especially as an application to the **6-membered pyridine derivative preparation starting from pyrrole** (*5-membered hetero-cyclic ring*),—as illustrated under:



The **dichloro-carbene** helps in a big way in the **abnormal RT-reaction** to enable the formation of the **intermediate** *via* which the actual **ring expansion** gets materialized to produce finally the ***pyridine ring*** from a ***pyrrole ring*** system.

Suggested Reading

Bellus D: **Advances in Photochemistry, Vol. 8,** John Wiley and Sons, Chichester (UK), 1971.

Brandsma L: **Methoden Organic Chemistry (Houben-Weyl),** 4th ed., 1952.

March J: **Advanced Organic Chemistry,** 6th ed., Wiley and Sons, New York, 2007.

Taylor RJK: **Electrophilic Aromatic Substitution,** Wiley and Sons, Chichester (UK), 1990.

Trost BM and Fleming I (Eds.): **Comprehensive Organic Synthesis, Vol. 3.,** Pergamon Press, Oxford (UK), 1991.

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SECTION 4

Organic Reactions and Mechanisms

Chapter 20. Substitution Reactions

Chapter 21. Elimination Reactions

Chapter 22. Electrocyclic Reactions

Chapter 23. Thermodynamics of Organic Reactions

Chapter 24. Addition Reactions

Chapter 20

Substitution Reactions

LESSONS AT A GLANCE

20.1 Introduction
20.2 Substitution Reaction Variants
- 20.2.1 Nucleophilic Aliphatic Substitution
- 20.2.2 Nucleophilic Aromatic Substitution
- 20.2.3 Electrophilic Aliphatic Substitution
- 20.2.4 Electrophilic Aromatic Substitution
- 20.2.5 Free Radical Substitution Reaction
- 20.2.6 Neighbouring Group Participation

20.1 INTRODUCTION

Functional Groups: They usually refer to an atom or a group of atoms which splendidly relates to the specific structure of a particular ***family of*** **organic compound**, and also at the same time determines their **inherent characteristic features**. It is termed as the **functional group**.

In a broader perspective, a relatively large portion of the **organic chemistry** essentially comprises:

"the chemistry of different functional groups (or moities)".

Importantly, whenever one happens to come across a rather ***complicated organic chemical entity*** (*compound or molecule*), that eventually contains an array of altogether divergent functional moieties (groups), one would certainly expect the characterstic properties of this molecule suitably being transformed into:

"roughly a composite of the properties of divergent functional groups".

Example: The above expression of facts may be further expatiated by considering a compound that contains both **(-X) and (-OH)** behaves both as an ***alkyl halide*** **(RX)** and an ***alcohol*** **(ROH)**,— which solely rests upon the *prevailing experimental conditionalities* it may follow the ensuing reactions leading to the characteristic features of either kind of compound.

Comments: Thus, it may be observed critically that the underlying properties pertaining to ***one functional group*** may be duly modified due to the obvious presence of ***another functional group***. In addition, it is absolutely necessary for one to take cognizance of the fact **regarding all these modifications** *vis-a-vis* the ***basic chemistry of all the individual*** **functional groups.**

20.2 SUBSTITUTION REACTION VARIANTS

Following are the **cardinal, substitution reaction** variants, namely:

(*a*) **Nucleophilic Aliphatic Substitution,**

(*b*) **Nucleophilic Aromatic Substitution,**

(*c*) **Electrophilic Aliphatic Substitution,**

(*d*) **Electrophilic Aromatic Substitution,**

(*e*) **Free-Radical Substitution Reaction,** and

(*f*) **Neighbouring Group Participation,**

which shall now be discussed individually in the sections that follows:

20.2.1 Nucleophilic Aliphatic Substitution

The treatment of **methyl bromide** with *sodium hydroxide* in a solvent which dissolves both the reagents, ultimately gives rise to the formation of: **methanol** and **sodium bromide**. Thus, it relates to a **substitution reaction,** *i.e.,* the **hydroxyl (-OH) group** is duly substituted for **bromide (—Br)** group in the ***original compound***.

Thus, we may have the following expression:

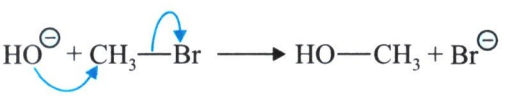
$$\underset{\text{Methyl bromide}}{CH_3{:}Br} + {:}OH^{\ominus} \longrightarrow \underset{\text{Methanol}}{CH_3{:}OH} + {:}Br^{\ominus}$$

The functional moiety already present on the so-called **substrate C-atom** the leaving moiety, leaves the **alkyl moiety** with the ***electron pair***.

***Mechanism*: An appropriate nucleophile attacks an alkyl halide, helps to displace the halogen, the halide anion gets duly released and the resulting nucleophile forms an altogether new bond with the C-atom.**

In other words, it is vividly a **heterolytic reaction;** and thus, the ***departing halide ion*** ($:Br^{\ominus}$) takes with it an **electron pair** it has been sharing with the C-atom; whereas, the **hydroxide ion** [$:OH^{\ominus}$] carries along with it an **electron pair** to bind it to the **C-atom**. In short, the **C-atom** losses one pair of electron on one hand and gains another pair on the other hand. Obviously, it is just one typical instance representing duly the *class of reactions* known as the—**Nucleophilic Aliphatic Substitution.**

Comments: In a situation, showing the formulas where a ***bond*** is duly represented by a ***line*** instead of a **pair-of-electrons** (shown as **'dots'**), we may logically make use of the ***curved arrows*** (↻) to depict the so-called actual *movement of the electrons*,—as shown below:



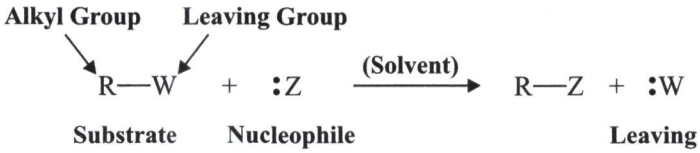
NOTE: **Importantly, the *nucleophilic substitution* elegantly shows the characteristic features of—*'Alkyl Halides'*.**

20.2.1.1 Nucleophilic Aliphatic Substitution: Nucleophiles and Leaving Moieties in S_N Reactions

Following are the ***three*** ~~**vital componenets**~~ normally required for the **nucleophilic substitution** are as given under:

- **Substrate** • **Nucleophile and** • **Solvent**

❑ ***Substrate:*** It essentially comprises ***two*** **components**: ***alkyl group***, and ***leaving group***,—as given under:



- Let us examine the ***two*** components *viz.,* **nucleophiles** and **leaving moieties**.
- Besides, the basicity does play a vital and important role in having an indepth knowledge of the **nucleophiles** and **leaving groups**.

❑ ***Nucleophiles:*** These are prevalently characterized due to their inherent **basic nature**, whereas, the **leaving groups**—are duly characterized by virtue of being the ***weak bases***.

❑ ***Solvent:*** There exists an approximate correlation between:

- **extent of basicity profile,** and
- **nucleophilic power (or leaving ability).**

Thus, one may observe that the **stronger of the *two* bases** proves to be invariably **more powerful nucleophile**; whereas, the **weaker of the *two* bases** is quite often the **better leaving moiety (*group*)**.

Remarks: However, the above stated analogy holds good only if the intimately related **sets of nucleophiles** or **sets of leaving groups**—that involve almost the **similar central element** *viz.,* **O** or **N**.

NOTE: **Hence, there could be several exceptions to the aforesaid *correlation*; and, therefore, obviously the basicity is considered to be one of the *cardinal factors involved* perceptively.**

Examples of Certain Nucleophiles: At this juncture, let us examine critically a few of the ***nucleophiles*** that may be employed in our studies. Obviously, we may come across several newer breed of products that are eventually formed; and thus, we must observe minutely how the structure of a **specific chemical entity** (*product*) obtained as the ultimate:

'so-called natural outcome of the structure of a specific nucleophile'.

Example: Following are a few **typical examples**:

1. **Hydroxide ion [:OH^-]:** It is a **nucleophile** serving as an ***anion***. Which on being treated with an **alkyl halide (R—X)** *i.e.,* a substrate we may observe the following reaction:



2. **Cyanide ion [:$CN^{\ominus}$]:** It is indeed the ***strongly*** **basic anion of the very weak acid, hydrocyanic acid (HCN);** and hence, the reaction may be expressed as:

$$\underset{\text{Alkyl halide}}{R{-}X} + \underset{\substack{\text{Cyanide ion}\\ \text{(A Nucleophile)}}}{:CN^{\ominus}} \longrightarrow \underset{\substack{\text{A nitrile}\\ \text{[Alkyl cyanide]}}}{R{-}OH} + \underset{\text{Halide anion}}{:X^{\ominus}}$$

3. **Iodide ion [:$I^{\ominus}$]:** It is only a **weak basic anion** and we may express the reaction as follows:

$$\underset{\text{Alkyl halide}}{R{-}X} + \underset{\text{Iodide ion}}{:I^{\ominus}} \longrightarrow \underset{\text{Alkyl iodide}}{R{-}I} + \underset{\text{Halide ion}}{:X^{\ominus}}$$

4. **Neutral Nucleophiles:** Amazingly, they may possess **unshared electron pair** *viz.,* **water [:OH_2],** behaves as *basic entity*, and hence, act as the **nucleophiles** perceptively.

Example: **Water [:OH_2]** provalently attacks the **alkyl halide [CH_3—X]** to give rise to the formation of an **alcohol** ultimately.

Thus, we may have the following reaction:

$$\underset{\text{Alkyl halide}}{R{-}X} + \underset{\substack{\text{Water (Neutral}\\ \text{nucleophile)}}}{:OH_2} \longrightarrow \underset{\text{Protonated alcohol}}{R{-}OH_2^{\oplus}} + \underset{\text{Halide ion}}{:X^{\ominus}}$$

Remarks: Obviously, the *O-atom of water* already possesses **2H–atoms** and when it gets duly attached to the **C-atom** then one would observe the following reactions in a sequential manner:

(*i*) **Alcohol**—not formed initially, instead it produces the **protonated alcohol** (see above) (which is a ***conjugate acid***).

(*ii*) The resulting **protonated alcohol** undergoes an easy transformation into the corresponding **alcohol** due to the *loss of a proton* (H^+)—as given under:

$$\underset{\substack{\text{Protonated}\\ \text{alcohol}}}{R{-}OH_2^{\oplus}} \rightleftharpoons \underset{\text{Alcohol}}{R{-}OH} + \underset{\text{Proton}}{H^{\oplus}}$$

(*iii*) However, for the *sake of convenience* we would quite often show the loss or gain of a **proton ($H^{\oplus}$)**. But it must be understood, explicitly that one never encounters with a so-called ***'naked proton'*** instead the ***crucial transfer*** **of a proton ($H^{\oplus}$) from the base to another,** as stated under:

$$\underset{\text{Alkyl halide}}{R{-}X} + \underset{\substack{\text{Water (Neutral}\\ \text{nucleophile)}}}{:OH_2} \longrightarrow \underset{\substack{\text{Protonated}\\ \text{alcohol}}}{R{-}OH_2^{\oplus}} + \underset{\text{Halide ion}}{:X^{\ominus}}$$

NOTE: **In the aforesaid instance, the *protonated alcohol* gets duly converted right into an *alcohol* by actual transfer of a proton (H^+) to water (H_2O)—which seems to be almost as basic as the alcohol itself; and also available in abundance.**

20.2.1.2 Kinetics of S_N Reactions

It is indeed a proven and established fact that the ensuing ***rate of a chemical reaction*** may be expressed elegantly as a product of ***three*** **cardinal factors**:

Rate = Collision Frequency × Energy Factor × Probability Factor

Salient Features: These essentially comprise:

1. The above relationship has been used in comparing the rates of various reactions to reveal the intricacise of:
   - **orientation profile,**
   - **relative reactivity,** and
   - **commencement of a specific reaction.**
2. Strict control and monitoring of *temperature* and *concentration* may eventually help the so-called closely related reactions to proceed at **different rates** mainly since they do possess altogether **different energy factors** *i.e.,* **different Eact values**. Hence, to account for **different Eact values** an attempt is made to determine the respective ***relative stabilities of the prevailing transtion states***.
3. Besides, it is also beneficial to ***study an individual reaction*** to asertain how precisely we may observe the rate being affected by the so-called **intended changes in the experimental parameters**.

Example: It is quite possible to determine **Eact values** provided one would **measure the rate at different temperatures**. However, the actual observed ***effect of changes in concentration on its rate*** has got to be studied meticulously.

How does a definite alteration in the concentration of the reactants could affect the rate of a reaction at a constant temperature? It may be observed that an **increase in concentration of the reactants** fails to change the **'fraction of collisions'** that essentially possess either:

- **sufficient inherent energy profile,** or
- **fractions of collisions,**

which ***possess the appropriate orientation*** so that it would in a state to eater exclusively to **enhance the total number of collisions**. Thus, if we have a large number of molecules duly packed into the same space, they would certainly collide more often and frequently thereby moving the reaction on a **faster mode**.

NOTE:

1. **In short, one may safely infer that the '*collision frequency*'; and hence, the *rate of a reaction* solely depends in a very exact manner upon the prevailing *concentration of the reactants* perceptively.**
2. **The underlying *field of chemistry* which deals with the specific *rates of reaction*; and in particular with absolute *dependence of rates upon the concentration* is invariably termed as the '*kinetics*'.**

20.2.1.3 Kinetics of Nucleophilic Aliphatic Substitution: Second Order and First Order Reactions

The reaction between **methyl bromide** and **sodium hydroxide** to produce ***methanol*** is as shown under:

$$\underset{\text{Methyl bromide}}{CH_3Br} + \underset{\text{Hydroxide ion}}{OH^{\ominus}} \xrightarrow{\text{Aq. EtOH}} \underset{\text{Methanol}}{CH_3OH} + \underset{\text{Bromide ion}}{Br^{\ominus}}$$

Importantly, the said reaction occurs in an *queous eqthanol*, wherein both the **reactants are soluble**.

Considering Three Different Conditions: Let us look into these ***three*** **conditions** separately:

Condition-1: When the reaction results due to the collision between a **hydroxide ion (OH^-)** and a **methyl bromide (CH_3Br) molecule**,—one would certainly expect the ***rate of reaction*** to depend solely upon the **actual concentration of both these reactants**.

Condition-2: When either the **hydroxide ion (OH^-) concentration** or **CH_3Br concentration** is increased to **double**,—the expected **collision frequency**; and hence, the **reaction rate** is ***doubled*** perceptively.

Condition-3: When the prevailing concentration is halved,—the ensuing **collision frequency** as well as the **reaction rate** must also be halved ultimately.

NOTE: **All *these* above mentioned conditionalities are found to be absolutely true and feasible.**

Consequently, based upon the above statement of facts and observations one may infer that the **rate of reaction** solely depends upon the *two* said reactants: **$[OH^{\ominus}]$ and $[CH_3Br]$,** which may be shown by the following expression:

$$\textbf{Rate} = k\,[CH_3Br]\,[OH^{\ominus}]$$

Comments: When the **concentration** is duly expressed in **moles, L^{-1}**, then **k** designates the precise number that, *multiplied by these concentration* indicates explicitly the **exact number of *'methanol'* are generated in each Riter during per second.**

In addition, at a *given temperature* and also for a *given solvent* **'k'** invariably has the **same value** and specifically shows the inherent characteristic features of the *aforesaid reaction*; and hence, **'k'** is usually known as the **Rate Constant**.

Comments: The ensuing reaction between **methyl bromide (CH_3Br)** and **hydroxide ion (OH^-)** present duly in an admixture of ***80% ethanol* and *20% water* at 55°C,**—the observed value of **'k'** is found to be:

'0.0214 $L.mol^{-1}.sec^{-1}$.'

20.2.1.4 Nucleophilic Aliphatic Substitution: Duality of Mechanism

The survey of literature reveals that the 1930s have witnessed a sea change with regard to the studies of **nucleophilic substitution** having an avalanche of **substrates,** such as:

- ***Methyl Primary Substrates:*** They usually react by the ***second*** **order kinetics.**
- ***tert-Butyl and other tert-Substrates:*** They are found to react by the ***first*** **order kinetics.**
- ***Secondary substrates:*** They eventually exhibit critically the **borderline behaviour** *i.e.,* a few sometimes show the ***first*** **order kinetics.** However, the ***secondary*** **substrates** do display the **border line behaviour** *viz.,*
  - **sometimes *second-order* kinetics,**
  - **sometimes *first-order* kinetics,**

  i.e., a **mixture of the two aforesaid kinetics.**

Interestingly, in addition to the prevailing **kinetic order,** the studies related to the **rate of reaction** showed something altogether different *pertaining to the substitution profile viz.,*

'the relative reactivities of various divergent substrates'.

Example: At a given concentration of a nucleophile (OH^-) the reactivity was observed to vary as depicted under:

$$\mathbf{CH_3X > 1^\circ > 2^\circ > 3^\circ}$$

EXPLANATIONS

Obviously, as we proceed along the series $\mathbf{CH_3 > 1^\circ > 2^\circ > 3^\circ}$, the reactivity profile observed duly at the very ***first*** **instance** gets reduced, and subsequently, passes *via,* a minimum level **(~ at 2°)** and ultimately seales up, as shown in Fig. 20.1. However, most prevalently the ***minimum usually occurs*** at almost precisely the point in the **series** $\mathbf{(CH_3 > 1^\circ > 2^\circ > 3^\circ)}$ where the **kinetics alters** from:

'the *second* order to the *first*-order kinetics'.

Hughes ED and Christopher Ingold (1935)* took into consideration these ***two*** **sets of striking evidences** *viz., **kinetic order*** and ***relative reactivity***; and thus, based on them put forward a broad well known theory called—**'Nucleophilic Aliphatic Substitution'**. However, the fundamental aspect of their theory was that:

"Nucleophilic Aliphatic Substitution can proceed by two distinctly different mechanism"

which are invariably termed as: $\mathbf{S_N2}$ **and** $\mathbf{S_N1}$. Amazingly, the so-called ensuing ***substrates*** do react by altogether divergent **kinetic orders** since they are undergoing the said reaction by means of ***different mechanism***, such as:

- $\mathbf{S_N2}$ **mechanism: methyl;** and
- $\mathbf{S_N1}$ **mechanism: tertiary butyl.**

Reactivity of the $\mathbf{S_N2}$ and $\mathbf{S_N1}$ Mechanism: It has been duly observed that the ***reactivity*** **profile** passes *via* a minimum with the so-called ***secondary*** **substrates** perceptively since the underlying mechanism critically alters at this point *i.e.,* from $\mathbf{S_N2}$ **to** $\mathbf{S_N1}$. Importantly, the observed occurrence of either:

- **a minimum** or • **a maximum,**

---

* **Hughes Edward David** (b. 1906), Caernar vonstire, North Wales, Ph. D, Wales (Watson); D. Se, London (Ingold), University Coll, London (UK);

Christopher Kelk Ingold (b.1893), Ilford, England, D.Sc., London (Thorpe), Univ. Coll., London (UK).

in a characteristic feature related to: ***reactivity***, ***activity***, **and** ***anti-microbial activity*** profile—as one moves forward along a so-called logical and intelligently selected series explicitly suggests the:

'actual working pattern of the various opposing factors'.

Interestingly, at this critical point **Hughes and Ingold** vehemently proposed the various underlying factors that eventually serve as:

"opposing reactivity sequences critically meant for the *two* divergent mechanisms (*viz.*, S_N2 and S_N1)".

While proceeding along the **series of reactivity profile** by the **S_N2 mechanism** gets lowered from **CH_3 to primary (1°);** and at **secondary (2°)** is found to be so low that the ensuing **S_N1 reaction** starts to make viable contribution appreciably; and hence, this really helps the ensuing **ractivity** duly caused by **S_N1 reaction** happens to **elevate charply**,—as shown in Fig. 20.1.

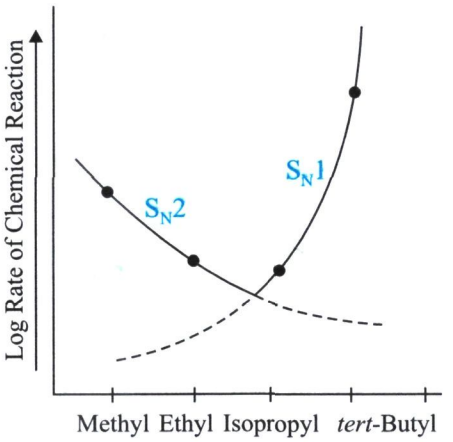


Fig. 20.1: *The Typical Effect of Nucleophilic Aliphatic Substitution upon the Rate of chemical* Reaction Caused Duly by Variations in the Structure of Substrate RX. The Minimum in Rate is duly Contributed to the Intersection of *two* Opposing Curves (S_N1 and S_N2) *i.e.,* an Observed Change in Mechanism from S_N2 to S_N1 perceptively.

[*Adapted From*: Ingold CK: **Structure and Mechanism of Organic Chemistry**, 2nd.ed., Cornell University Press, Cornell, 1969.]

Thus, we may eventually show the following expression:

S_N2		S_N2 Increases
		←
vs	RX =	CH_3X 1° 2° 3°
		→
S_N1		S_N1 Increase

20.2.1.5 Mechanism of S_N2 Reaction

The observed chemical reaction between the ***two*** **chemical entities**: **methyl bromide (CH_3Br)** and **hydroxide ion (OH^-)** to produce *methanol (CH_3OH)* usually follows a ***second order*** **kinetics**, which means explicitly that the ***rate of chemical reaction*** solely depends upon the ensuing ***concentration*** **of both the reactants**.

Thus, we may have the following expression:

$$CH_3Br + OH^{\ominus} \longrightarrow CH_3OH + Br^{\ominus}$$

Rate = k [CH_3Br] [OH^-]

Nevertheless, perhaps the easiest way to expatiate the **kinetics** is to have an assumption that the so-called **S_N2 reaction** essentially needs a collision occurring between each of the following entities:

- **hydroxide (OH^-) ion,** and
- **methyl bromide (CH_3Br) molecule.**

Based on the scientific and logical evidences, it has been duly proven and established that the ensuing **hydroxide ion (OH^-)** attacks the **methyl bromide (CH_3Br) molecule** from the ***rear***.

Fig. 20.2 shows that the reaction is believed to occur when the respective **hydroxide (OH^-) ion** collides with the **methyl bromide (CH_3Br) molecule** predominantly at the ***'face most remote from the bromine'***. Thus, when such a collision possesses enough energy, it gives rise to the formation of: **a C—OH bond**; whereas, the **C—Br bond** undergoes cleavage thereby liberating the **bromide ion (Br^-)**,—as depicted under:

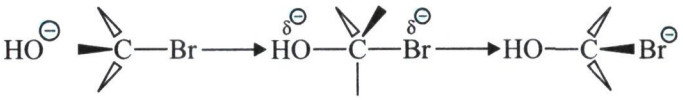


Fig. 20.2: The S_N2 Reaction Showing Complete Inversion of Configuration. The Nucleophilic Reagent Attacks from the Rear.

EXPLANATIONS

The various steps involved may be explained as under:

1. **Transition State (TS)** may be depicted as a structure wherein the **C-atom** gets partially bonded to both **-OH and -Br**. Besides, it also implies that the ensuing **C—OH bond** is ***not formed completely***, and the **C—Br bond** is ***not yet cleaved completely***.
2. The respective **hydroxide (OH^-) ion** critically possesses a much *reduced negative charge* since:

   'it has already begun to share mutually the electrons with the C-atom'.
3. Thus, **bromine** has developed a **partial –ve charge** due to the fact it has partly removed a ***pair of electrons from the C-atom***. Besides, the **-OH and -Br** are located strategically *as far apart as possible*; and hence, the **3H-atoms** plus **1C-atom virtually lie in a single plane** (*all bond angles are of 120°*).
4. The ensuing **C-H bonds** are found to be arranged, just like the *spokes* ***of a cycle wheel,*** having the respective **C—OH** and **C-Br bonds** located very much **along the axis**.

Remarks: The aforesaid ***mechanism*** is broadly termed as the:

"S_N2 substitution nucleophilic bimolecular".

The significance of the term **'bimolecular'** usually refers to the so-called ***rate-determining step*** that involves the **collision of *two* particles perceptively**.

NOTE: **In a broader sense, the S_N2 reaction normally follows a *second-order kinetics*.**

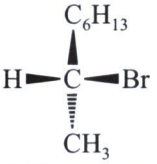
20.2.1.6 The Stereochemistry of S_N2 Reactions: Walden Inversion

As we know that both **(–)-2-Bromooctane** and **(–)-2-Octnanol** are ***'chiral'* organic compounds** (*i.e.,* bearing an **asymmetric C-atom**). Alternatively, the ensuing moleculas are found to be:

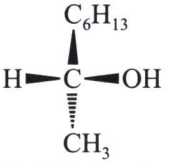
'not superimposable upon their corresponding Mirror Images'.

As a result, this compounds may usually exist as the ***'enantiomers'*** and, therefore, may exhibit **optical activity**. Hence, the **optically active 2-octanol** has been duly accomplished by carrying out the **resolution of the racemic modification**; and thus, from it the ***optically active* 2-Bromo-octane** has been duly prepared.

We may assign the following configurations for the said ***two* organic compounds**:



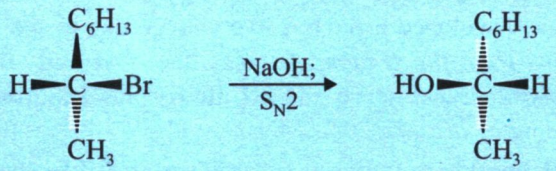
(–)-2-Bromooctane
[α] = –39.6°



(–)-2-Octanol
[α] = –10.3°

Remarks: These essentially include:

1. We may critically observe that the ***two* entities**, namely; **(–) bromide** and **(–) alcohol** do essentially possess almost **identical configurations** *i.e.,* the *hydroxyl (—OH) group* occupies the exact similar position in the **(–) alcohol bromine (—Br)** does in the **(–)-bromide**.
2. Since the compounds with **similar configuration** do not perceptively rotate the light in the **same direction,**—they just show up in the present instance.
3. Thus, in a situation when **(–)-2-bromoetane** is indended to react with *sodium hydroxide (NaOH)*, under such experimental parameters most suitable for the ***second order* kinetics,**—there is obtained **(4)-2-Octanol**, as given under:



(–)-2-Bromooctane
[α] = –39.6°
[Optical purity 100%]

(+)-2-Octanol
[α] = +10.3°
[Optical purity 100%]

Remarks: Based on the above reaction, it may be observed vividly that the **hydroxyl (—OH) group** has not taken the position occupied earlier by **bromide (—Br)**; and hence, the resulting *configuration of alcohol* is just the *opposite to that of the bromide*. Thus, a reaction:

"that yields a product whose configuration happens to be just the opposite to that of the reactant is invariably is said to proceed with the *inversion of configuration and termed as Walden Inversion*".

20.2.1.7 The S_N2 Reaction Structure of the Substrate and Reactivity

At this point in time, it would be worthwhile to study thoroughly the *reactivity profile* occurring in the so-called **nucleophilic aliphatic substitution**.

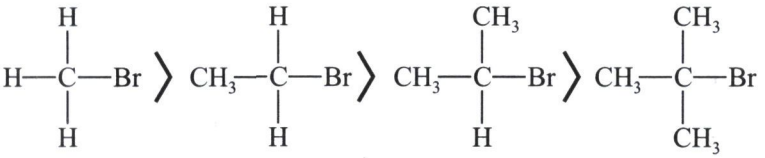
Importantly, as per the **dual mechanism theory** the most abundantly observed **order of reactivity** with a minimum at **2°**, is nothing but simply the **composite of two ensuing opposing reactivity** *i.e.,*:

- **one for S_N2 reaction,** and
- **other for S_N1 reaction.**

Direct Measurement of S_N2 Rates—For a series of substrates that eventually provides, as depicted under, using particularly **DMF** (**dimethyl formamide**) as a solvent which critically favours the **S_N2 reaction** perceptively:

S_N2 Substitution Relative Reactivity

$$R{-}Br + Cl^{\ominus} \xrightarrow{DMF} R{-}Cl + Br^{\ominus}$$



Relative Rate S_N2	**Methyl**	**Ethyl**	**Isopropyl**	***tert* - Butyl**
	37	1.0	0.02	0.0008

Based on the postulated analogy the *reactivity of substrates* in the so-called **S_N2 reaction** is:

$$CH_3W > 1° > 2° > 3°$$

***Inherent Structure Influencing the Rate of S_N2 Reaction*:** Let us compare critically the **transition state (TS)** and **reactants** with regard to the ***precise* shape**, commencing with the **methyl bromide (CH_3Br) reaction** specifically.

Thus, we may observe that the so-called **C-atom** present duly in the **reactant** as well as the **product** is found to be **tetrahedral** in nature; whereas, the **C-atom** duly present in the **transition state** is bonded to ***five* atoms**. As already stated earlier that:

"the C—H bonds are meticulously arranged just akin to the spokes of a wheel having the *C—OH bonds* and *C—Br bonds* lying along the axis",—as elegantly shown in Fig. 20.3.

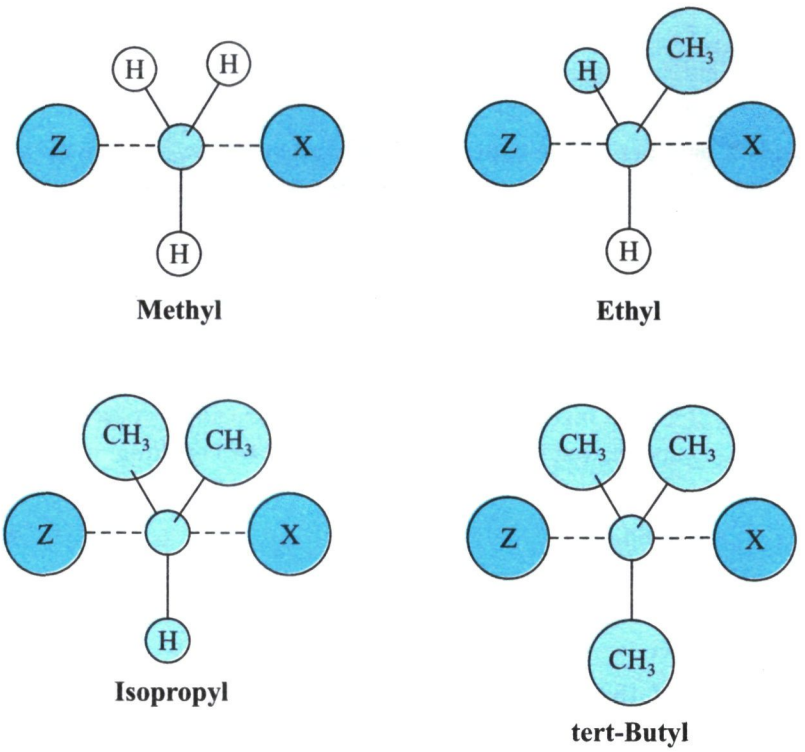


Fig. 20.3: The Explicit Molecular Structure and Reactivity. Showing the steric Factor in the S_N2 Reaction; and the Crowding Enhances the Energy Level of the Transition State (TS) thereby Retarding the Reaction Rate Finally.

Overall Effect Accomplished Duly by Replacing H-atoms Successively by Methyl (-CH_3) Moieties: In other words, how one would vividly observe the so-called **transition state (TS)** exhibiting a noticeable difference as one moves on from **Methyl Bromide (CH_3Br)** ***via***:

- **Ethyl Bromide**
- **Isopropyl Bromide** and
- ***tert*-Butyl Bromide.**

Points to Ponder

1. The crucial replacement of **H-atoms** by the relatively **bigger methyl moieties**,—one would certainly observe an *enhanced crowding* very much around the **C-atom**.
2. Fig. 20.4 clearly illustrates from the diagrammetic presentation of the ***'scale models'***—the **rear side** of the molecule, ***where the attack should occur predominantly***, thus turns out to be an obvious **inaccessible zone vehemently**.
3. Importantly, the ensuing observed **'crowding'** appears to be perceptively so severe in magnitude specifically in the so-called **transition state (TS)**,—wherein the ***methyl groups*** are thrown in the vicinity of both **hydroxyl (-OH)** and **bromide (-Br)** groups [see *Fig. 20.3*].
4. However, the **non-bonded interaction** taking place eventually enhances the ***prevalent energy*** of the ***crowded*** **transition state (TS)** much more than the ***spacious*** **reactant**; and hence, **Eact** is found to be of **greater value** and the overall reaction profile is rather **sluggish in nature**.

***Steric Factor*:** As on date, it has already been accepted universally that the so-called:

"observed differences in rate between *two* S_N2 reactions are due chiefly to the prevalent Steric Factors",

—and certainly not caused due to the ***polar Factors***. In other words, the differences observed critically in the rate are solely related to:

- **bulk of the substituents grossly,** and
- **certainly not to their effect upon the *electron* distribution.**

Remarks: It has been proven and ascertained that as an attempt is made to *increase the number of substituents duly attached to the C-atom bearing the respective halogen (X),* **the overall reactivity toward the S_N2 substitution gets decreased perceptively*.**

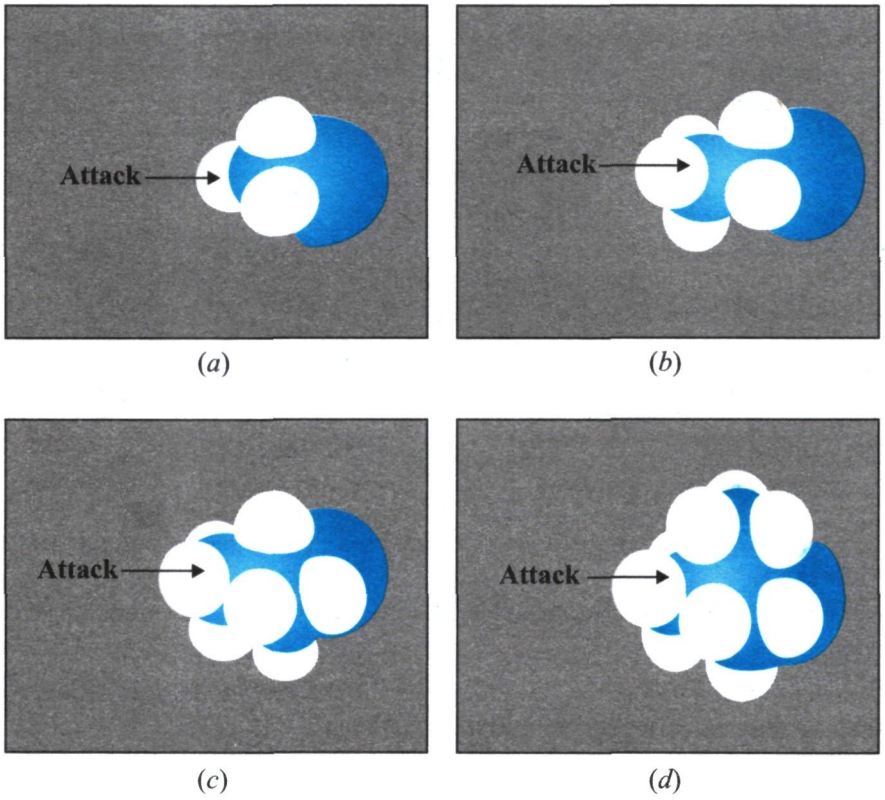


Fig. 20.4: Diagrammatic Representation of Molecular Structure and Reactivity: The observed Steric Factor in the S_N2 Reaction. Different Display of Models of Alkyl Bromides: (*a*) Methyl; (*b*) Ethyl; (*c*) Iso-propyl; (*d*) *tert*-Butyl.

[As the number of Substituents on the C-atom Bearing—Br increases Crowding at the specific point of Nucleophilic Attack Increase accordingly].

* That is, confirmed by the measurements shown for the series: **Methyl 1°, 2°, 3°.**

Another Series of Substrates: Confirming the Relative Rates

Importantly, in this specific case practically **all the substrates** are virtually ***primary*** in character; and, therefore, do possess essentially the *same number of substituents,*—whereby ***'one'*** gets duly attached to the **C-atom** bearing the **halogen (X) atom**. In this manner, the ensuing ***size of the substituent*** gets increased steadily:

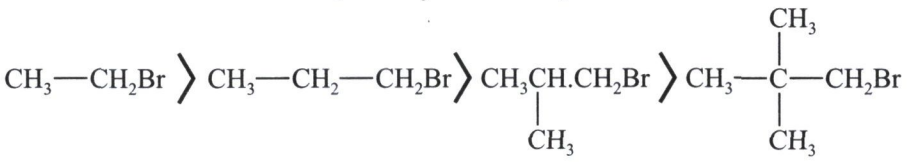
- **Methyl bromide (CH_3Br):** the incumbment substituent is **methyl (CH_3)**;
- **n-Propyl bromide ($CH_3CH_2CH_2Br$):** the substituent is **ethyl (C_2H_5)**,
- ***iso*-Butyl bromide [$(CH_3)_2$—CH_2—CH_2Br]:** the incumbment is ***iso*-propyl [$(CH_3)_2$–CH_2]**
- ***neo*-Pentyl bromide [$(CH_3)_3C$—CH_2—Br]:** the incumbment substituent is ***tert*-butyl [$(CH_3)_3C$]**

Remarks: Obviously, as the **inherent size** of the so-called (***single***) **substituent gets increased,** one may critically observe that:

"the corresponding steric hindrance (to attack) also increases accordingly,—thereby the relative rate of the ensuing reaction gets decreased proportionately".

Following is the expression showing the *S_N2 Substitution Relative Reactivity*:

$$R{-}Br + Cl^{\ominus} \xrightarrow[\text{(Dimethyl formamide)}]{\text{DMF}} R{-}Cl + Br^{\ominus}$$



Ethyl bromide	n-Propyl bromide	Isobutyl bromide	neo-pentyl bromide

Relative Rate	Ethyl	*n*-Propyl	*Iso*-butyl	*Neo*-Pentyl
(S_N2)	1.0	0.69	0.33	0.000006

NOTE: **Thus, one may safely infer that the *S_N2 mechanism* is adequately supported by three lines of evidence:**

- ***kinetics*** • ***Stereochemistry*** **and** • ***Effect of Structure on Reactivity.***

20.2.1.7.1 Effect of Nucleophilicity upon the Rate of S_N2 Reaction

The term of **nucleophilicity** refers to—**'the tendency of the nucleophile to displace the, leaving functional moiety duly attached to the *substrate C-atom*'.**

In other words, ***nucleophilicity*** may also be defined as—**'the rate of attack of a nucleophile upon an electrophilic C-atom'.**

In a broader sense, it could be observed specifically that the so-called:

'species bearing the *nagative charge* and the base of a *conjugate acid* are shown to be relatively more efficient and strong nucleophiles'.

At this point in time, let us first of all examine certain basic data pertaining to the **S_N2 reactions of methyl iodide (CH_3I)** having the so-called **anionic nucleophiles** with altogether ***different basicity*** to observe and ascertain whether the *assumption is met duly in actual practice or not.*

Table: 20.1 Records some data for the reaction of **methyl iodide (CH_3I)** with an array of **divergent nucleophiles** in *methanol* (as solvent); and plotted subsequently in Fig. 20.5.

Table 20.1: The Dependence of S_N2 Reaction Rate Upon the Inherent Basicity of the Nucleophile.

$$\underset{\text{Nucleophile anion}}{Nuc:^{\ominus}} + \underset{\text{Methyl iodide}}{CH_3—I} \xrightarrow{25°C;\ CH_3OH;} \underset{\text{Methyl nucleophile}}{Nuc—CH_3} + \underset{\text{Iodide ion}}{I^{\ominus}}$$

S.No.	Name of Nucleophile	p*Ka* of Conjugate Acid*	*k* (Second Order Rate Constant, $M^{-1}\cdot s^{-1}$)	log *k*
1	**Methoxide** [CH_3O^-]	15.1	2.5×10^{-4}	– 3.6
2	**Phenoxide** [C_6H_5-O^-]	9.95	7.9×10^{-5}	– 4.1
3	**Cyanide** [CN^-]	9.4	6.3×10^{-4}	– 3.2
4	**Acetate** [CH_3COO^-]	4.76	2.7×10^{-6}	– 5.6
5	**Azide** [$N\equiv N=N^-$]	4.72	7.8×10^{-5}	– 4.1
6	**Fluoride** [F^-]	3.2	5.0×10^{-8}	– 7.3
7	**Sulphate** [SO_4^{2-}]	2.0	4.0×10^{-7}	– 6.4
8	**Nitrate** [NO_3^-]	– 1.2	5.0×10^{-9}	– 8.3

* **p*ka* values in water.**

[**Adapted From:** London GM: **Organic Chemistry,** 4th ed., Oxford University Press, Oxford (UK), 2002].

NOTE: **It may be observed critically that in this 'Table' the so-called '*nucleophilic atoms*' are all from the *second period* of the 'Periodic Table'.**

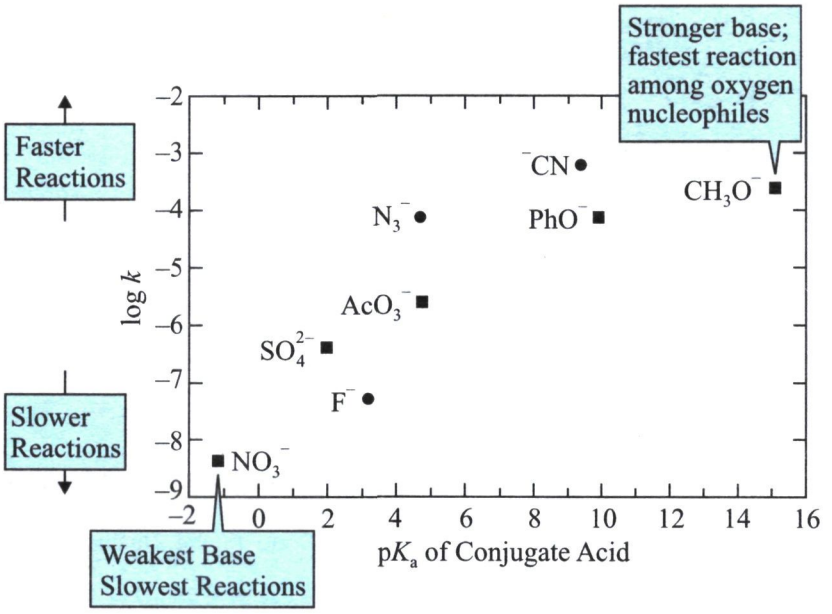


Fig. 20.5: The observed dependence of 'log *k*' in Methanol Related to the Different Nucleophiles with Methyl Iodide (CH_3I) upon the Inherent Basicity of the Nucleophile (*i.e.,* upon the pk_a of the Nucleophile's Conjugate Acid). The Nucleophilic Atoms in almost All Cases are from the *Second Period* of the Periodic Table.

NOTE: **The particular *Nucleophiles* wherein the *nucleophilic atom* is (O^-)–are shown explicitly in *'colour'*.**

Special Remarks: These essentially comprise:

1. The Fig. 20.5 vividly, depicts a ***very rough*** trend toward the so-called **'faster reactions'** having the ***more basic*** **nucleophiles** perceptively.
2. Restricting and focusing the attention to the ***'nucleophiles'***, which are shown as the **'O-anions'** (*coloured in Fig. 20.5*)—one may ultimately visualize and observe:
   "*the correlation of rate with basicity* in a more explicit and better way".
3. Nevertheless, one may take cognizance of the fact that the *Table: 20.1* practically covers more than ***sixteen*** **orders of different magnitude in basicity;** whereas, the effect observed upon the **reaction rate** duly covers a range of:
   "less than *six* orders of magnitude predominantly".

Important Observation: It has been duly observed that as and when the electron pairs of a nucleophile are actively involved in the **H-bonding phenomenon,** these are not at all available for:

'the so-called donation to the C-atom in an S_N2–reaction'.

Therefore, for the **S_N2 reaction** to occur prevalently:

"the H-bonds existing between the *'solvent'* and and the *'nucleophile'* should be cleaved by all means (as illustrated in *Fig. 20.6*)".

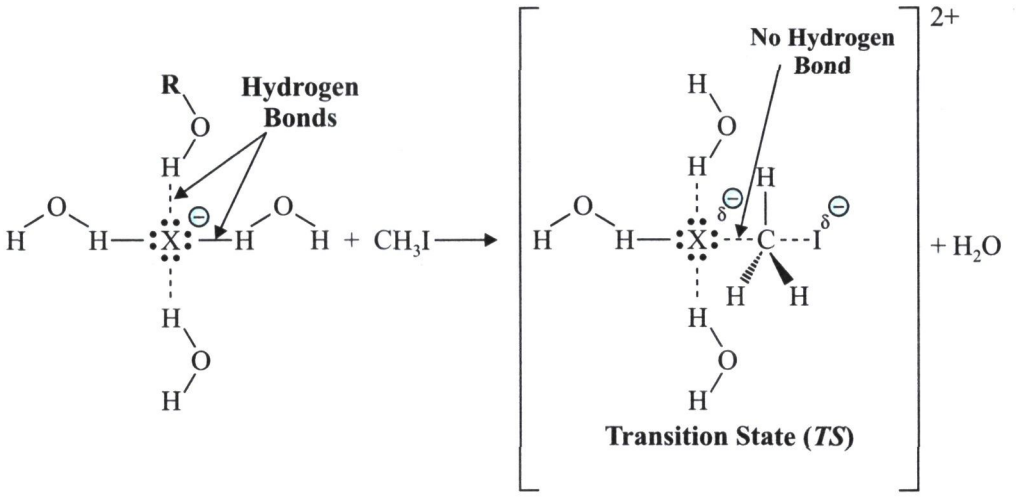


Fig. 20.6: The S_N2-Reaction of Methyl Iodide (CH_3I) Involving a Halide Nucleophile $\left[:\ddot{X}:^{\ominus}\right]$ in a Protic Solvent (*viz.*, CH_3OH) Requires breaking an H-Bond to the Nucleophile. Thus, when $:\ddot{X}:^{\ominus}$ = $F^{\ominus}$, the H-Bond is Strong, but when $:\ddot{X}:^{\ominus}$ = $I^{\ominus}$, it is Weak. Hence, more Energy is Required to Reach the so-called Transition State when $:\ddot{X}:^{\ominus}$ = $F^{\ominus}$; and Consequently, the Overall Reaction is Slower in nature.

Remarks: It is, however, pertinent to state here that **more energy** is certainly needed to cleave a **strong H-bond** to the respective **F^- ion** than is required to break a comparatively **weak H-bond** to the respective **iodide ion (I^-)**. Besides, the *extra energy* is duly reflected in a **greater free energy of activation** *i.e.,* the **energy barrier;** and consequent, the ultimate reaction of the **fluoride ion ($F^{\ominus}$)** is found to be **slower** perceptively.

[A] Basicity and Nucleophilicity

Basicity refers to the inherent tendency of the ***base*** in the critical process of **abstracting a proton**. In fact, it relates to the so-called:

'measure of *thermodynamic* phenomenon';

whereas, the **nucleophilicity** refers to the crucial tendency of:

'the inherent tendency, of the *nucleophile* to displace the leaving functional group'.

In addition, it more or less concerns a typical and systematic **kinetic investigative study** of the ensuing ***substitution reaction*** perceptively.

Example: The **hydroxyl (OH^-)** moiety designates a relatively **stronger base** *vis-a-vis* **cyanide or nitrile [CN^-]** moiety; and, therefore, possesses certainly a ***much greater affinity*** for a **'proton (H^+)'.** Thus, quite contrarily the **cyanide (CN^-)** proves to be a **strong nucleophile;** and hence, categorically helps to displace the so-called **'leaving group'** more rapidly.

As we move from ***left to right*** hand side in the **Periodic Table,**—we may explicitly take cognizance of the fact that:

"*nucleophilicity decreases* predonimantly; whereas, *electronegativity* increases perceptively"

Exception*:** There is an **absolute exception** in the specific instance of the ***halides, ***basicity***, and ***nucleophilicity***. Besides, these are found to be **not related directly to the nucleophilicity profile;** and hence, follows the following stated order:

$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$$

whereas, the so-called **reverse order** is critically followed by the underlying **basicity profile** perceptively:

$$F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$$

Importantly, the aforesaid **obvious contradictions** may be expatiated by the critical observation and fact that:

'the exact size of 'atom' gets enhanced while moving down from *top to bottom in a column* in the Periodic Table'.

Interestingly, with the increment in the ***size of the atom*** one may also observe that the distance between the ***valence shell electrons*** and the ***nucleus*** gets increased proportionately,—thereby affording.

'an *increased polarizability*, which subsequently helps in the specific distortion of the so-called *electron cloud* of the atom of the *nucleophile* with it attacks largely'.

Remarks: These essentially include:

1. Based on the above reasons the **halide (X^-)** gets duly overlapped effectively having the **'back lobe'** being gradually **rehybridizing** the ***sp^3* hybrid orbitals**. Perhaps this actually renders in—**poor basicity of most large-sized halides**.
2. Besides, the **attack of iodide** critically engages the so-called ***partial bond formation*** occurring at relatively **large distances**. Thus, the so-called **'electron cloud'** of the **nucleophile** is invariably *extended toward the C-atom*, but the same could not be observed in the particular case of **fluoride ion (F^-)**.

[B] Electronegativity and Nucleophilicity

Based on the scientific evidences and logical explanations it has been duly established that both **electronegativity** and **nucleophilicity** are ***inversely proportional*** to each other. Thus, we have the following **important observations,** namely:

- **Electronegativity designates the affinity for electrons;**
- **Nucleophilicity gets decreased from *left-to-right* during a specific period;**
- **Higher the electronegativity of a *nucleophile*—lesser would be the availability of electrons on it for the donation to the respective *electrophilic substrate*,**
- **Lesser would be the *tendency of the electrophile* to displace the so-called '*leaving functional group*' from the substrate;** and
- **Reactivity of the ensuing '*Bulky Group*' appears to be quite less *vis-a-vis* to '*Less-bulky Group*' perceptively.**

[C] Leaving Group Effects in the S_N2 Reaction

In many typical instances, when an **alkyl halide (CH_3X)** is intended to be used as a ***starting material* in an S_N2 reaction,**—one may possibly do have a choice of the ***leaving group***. Alternatively, an **alkyl halide (CH_3X)** could be available instantly as an **alkyl chloride (R—Cl)**, **alkyl bromide (R—Br)**, or **alkyl iodide (R—I)**. Hence, in such a case, the **halide** that eventually reacts *most rapidly* and enjoys the *most preferred* recognition.

Nevertheless, the overall reactivities of the **alkyl halides** may be critically predicted based solely upon:

"close analogy existing between *S_N2-reactions* and Bronstead acid base reactions".

Thus, the overall **S_N2 reactivity** exclusively depends upon the ensuing ***carbon*-halogen bond energy**—that particularly follows the **same trend** *i.e.*, the **alkyl iodides (CH_3I)** are the most ***reactive alkyl halides*** and the **alkyl fluorides (R—F)** happen to be the ***least reactive***.

Thus, we may express the **Relative Reactivities in S_N2 Reactions** as stated under:

R—F < R—Cl < R—Br < R—I

NOTE: **In other words,—the best leaving groups in the S_N2 reaction are those that ultimately react to give the weakest bases.**

Salient Features: They essentially comprise:

1. **Fluoride (F^-)** represent the ***strongest base*** **of the halide ions;** as a result the **alkyl fluorides** do represent the *least reactive* of the **alkyl halides in the so-called S_N2-reactions.**
2. **Alkyl fluorides (R-F)** do react so sluggishly (slowly) that they are found to be *almost useless* as the **leaving groups in the S_{N2}—reactions.**
3. On the contrary, the respective **chloride, bromide, and iodide ions** are observed to be ***much less basic than the fluoride ion (F^-).***
4. The **alkyl chlorides, alkyl bromides,** and **alkyl iodides** do possess the ***acceptable reactivities*** in **most typical S_N2 reactions** (and the **alkyl iodides** are the most reactive of these species).

[D] Effect of Solvents on S_N2 Solvents [Protic and Aprotic Solvents]

The **nucleophiles** are regarded to be the ***'polar species'***; and, therefore, the **polar solvents** (*viz.*, **ethanol, ethyl acetate, water, dimethyl ketone** etc.) are mostly preferred in the **S_N2 reactions.**

The **aprotic solvents** (*viz.*, **THF_2, sulfolane, acetonitrile** etc.) fail to *solvate the anions* since these are incapable of forming the **H-bonds** with the so-called **anionic nucleophiles**; and hence, the ***polar aprotic solvents*** do critically give rise to the **'fact reaction rate'** perceptively.

Polar Aprotic Solvents: They include: **DMF** (*dimethyl formamide*), **DMSO** (*dimethyl Sulfoxide*) etc.

[E] Solvent Effect: [Effect of Solvation Upon the Rate of S_N2 Reaction]

The term **'solvation'** may be defined as—**'the extent to which the particular *nucleophilic specie* gets duly surrounded by the solvent molecules'.**

In other words, it serves as a *crucial barrier* between the ***two*** **entities**: • **Nucleophile** and • **Substrate.** Perhaps it could be the so-called *valid reason* for the same *i.e.*, **within the solvent,**— the *nucleophile* is invariably surrounded by **solvent molecules,** such as: ***water*** or ***alcohol*** that eventually forms the **H-bonds** perceptively with an ***'anionic nucleophile'*** thereby preventing it to attack specifically upon the substrate,—as shown in Fig. 20.7.

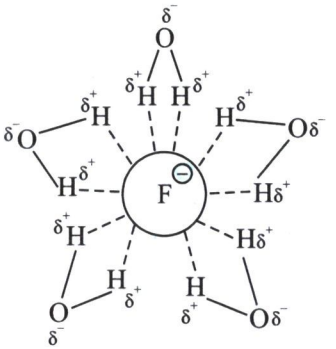


Fig. 20.7: Diagrammatic Representation of the Solvation of $F^{\ominus}$ Nucleophiles.

Remarks: These essentially include:

1. In such an instance, one may observe vehemently that:

***'nucleophilicity* is duly suppressed by *solvation'*.**

2. Hence, for a **solvated nucleophile** (*anion*) to enable it to attack upon the **substrate** exclusively,—one may essentially need a certain quantum of energy to afford the *cleavage of some bonds with the solvent molecules*; and hence, virtually **strip off certain solvent molecules**.
3. Importantly, the typical **'smaller ions'** do get solvated more rapidly and conveniently *via-a-vis* the **'larger ions'**.

20.2.1.8 Unimolecular Nucleophilic Substitution (S_N1) [Substitution by Ionization]

First and formost it should be understoon explicitly that the **S_N1 reaction** (*i.e.*, **Unimolecular nucleophilic substitution**) usually proceeds by the **ionization phenomenon** predominantly. However, the prevailing bondage existing between:

• **Substrate** and • **Leaving Functional Moiety,**

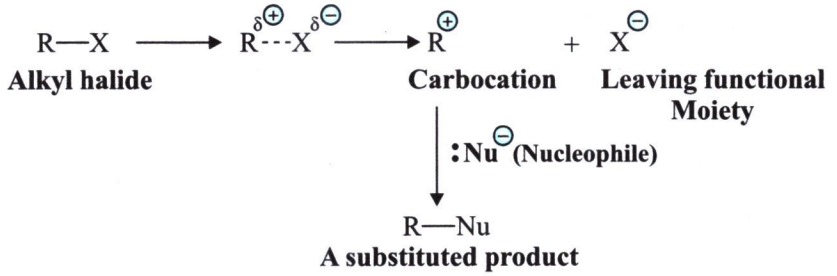
gets ***dissociated heterolytically*** thereby giving rise to the formation of the so-called:

➢ **electrophilic carbocation;** and

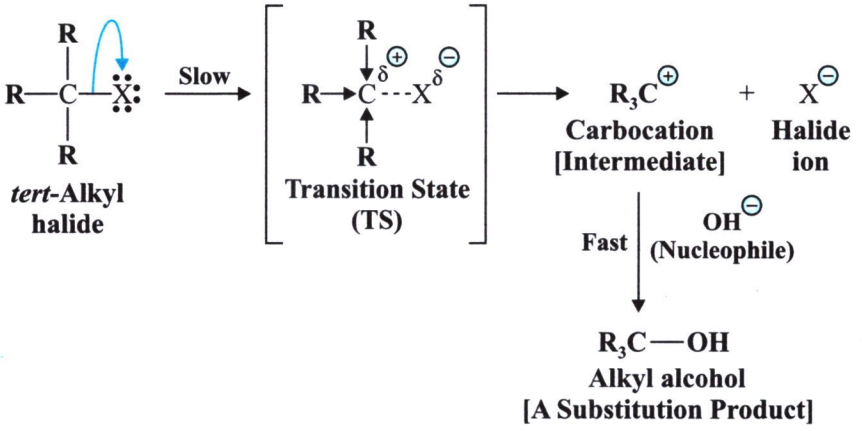
➢ **leaving functional moiety.**

Nevertheless, the **carbocation** obtained in this manner gets duly combined with the so-called **Lewis Acid** (*i.e., an **electron donor***) or **nucleophile** to provide the desired **substituted product**.

Example: Following is a typical example that shows the **S_N1** reaction *via* the conversion of an **alkyl halide (RX)** to a **substituted product (RN_4),**—as depicted under:



***Mechanism of S_N1 Reactions*:** It would be possible to expatiate the underlying mechanism of the **S_N1 reaction** by considering the following **generalized example**:

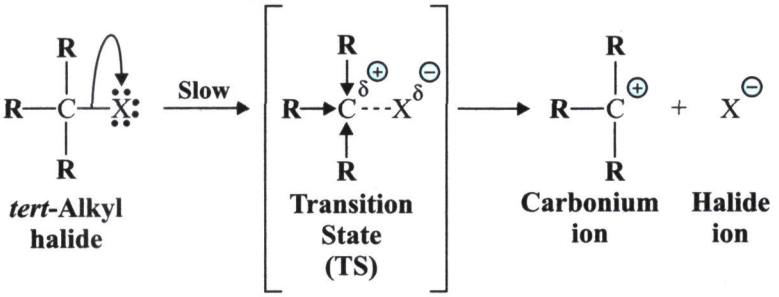


The aforesaid **generalized reaction** essentially involve the following ***three* sequential steps,** namely:

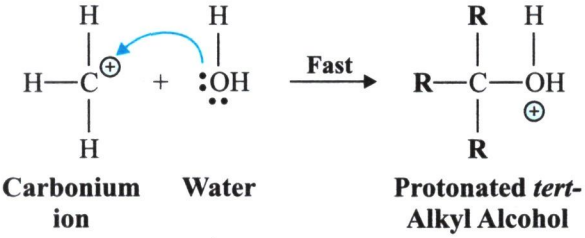
Step-1*:** The so-called typical **ionization phenomenon** or **heterolysis** process pertaining to the **C-X bond** critically involves the *hydrolysis* of the said **(C-X) bond**, based upon the **differences in the ensuing *electronegativities of **both 'C' and 'X' atoms** thereby giving rise to the formation of:

- **a carbocation, and**
- **a leaving functional group,**

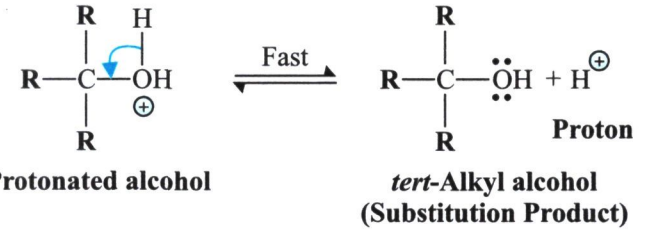
that invariably get detached (dissociated) as an ***'anion'***, as shown below:



***Step-2*:** Exclusive combination of the **'Nucleophile' (*carbonium ion*)** with the respective **water mole,**—as given under:



***Step-3*: Acid-base reaction of the Protonated Alcohol** occurs as stated under:



Comments: The **step-3** essentially involves so-called **'deprotonation'** of the ensuing *protonated alcohol* to result into the formation of the **substitution product (*tert*-alkyl alcohol).**

***Kinetics of S_N1-Reaction*:** Importantly, the **kinetics of S_N1 reaction** between the ***tert*-alkyl halide [R_3C—X]** and the **nucleophile (carbonium ion)** usually yields the **following product**:

$$\frac{dx}{dt} = K\,[R_3X]$$

***Points to Ponder*:** They usually comprise:

1. The very ***first* step** of the mechanism critically engages the heterolysis of the **C—X bond** so as to give the **nucleophile (carbonium ion)**,—that relates specifically to the **rate-determining step** perceptively.
2. The *subsequent steps* show the formation of carbonium ion (*i.e.*, the *nucleophiles*) which get combined almost instantly with the **base ($X^{\ominus}$)** to yield the **desired product (*tert*-alkyl alcohol)**.

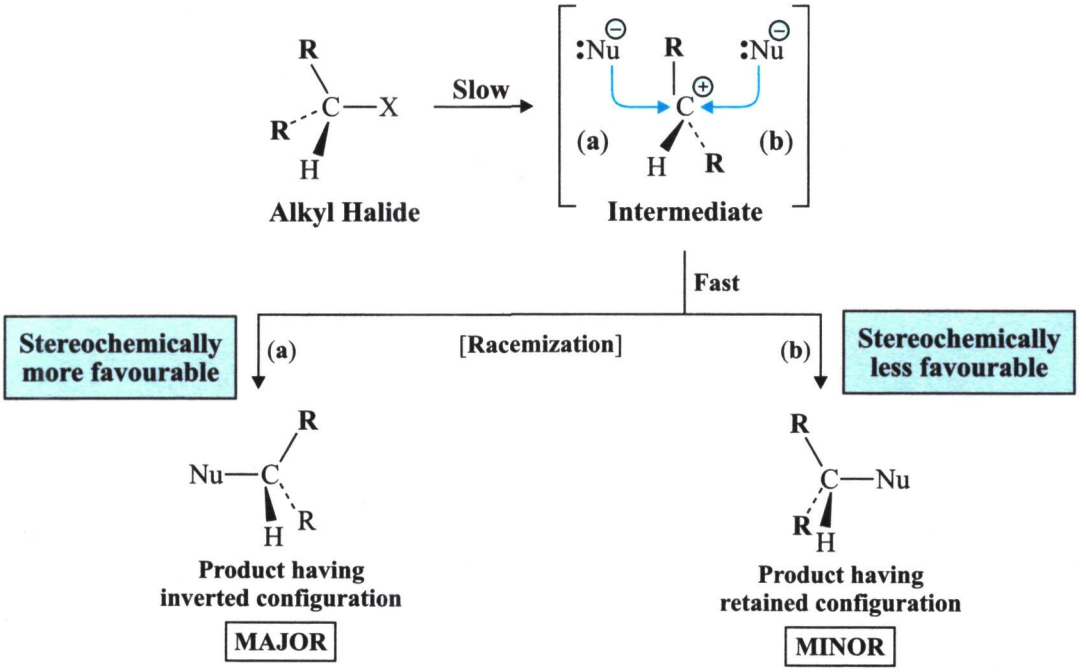
NOTE: **Interestingly, the rate determining *first step* (Step-1) of the *S_N1-reaction* certainly has no dependence, whatsoever, upon the ensuing concentration of the '*base*'; and, hence, its prevailing concentration of the '*base*' is not being considered at all *i.e.*, only the concentration of the '*reactant*' is usually taken into account.**

The Stereochemical Aspects of S_N1 Reaction

The stereochemical aspects of the **S_N1 reaction** is invariably expatiated by the help of **'racemization' phenomenon**. Importantly, the ensuing **S_N1 reaction** coming into play particularly at:

"a stereocenter of an *optically active* alkyl halide ultimately leads to racemization phenomenon perceptively,"

—that actually takes place by virtue of an anticipated attack of the **nucleophile** (*carbonium ion*) on both sides of the **planar achiral carbocation intermediate,**—as depicted below:



- The **'Inverted Configuration'** product is usually obtained as the ***"major product"*** in the **S_N1 reaction**; and
- The **'Retained Configuration'** product is invariably accomplished as the ***"minor product"*** in the **S_N1 reaction**.

The Status of Resultant Enantiomers

It has been observed critically and perceptively that the status of the ***two*** **resultant enantiomers** are as given under:

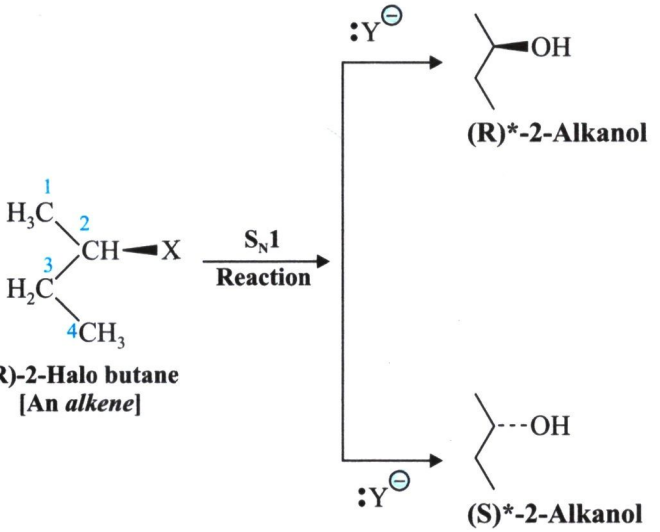
- **mostly occur in an *uneven quantities*;** and
- **Configuration of the *major enantiomer* (*i.e.,* having an *inverted configuration*) is largely found to be opposite to that of the *reactant* or *substrate i.e.,* the alkyl halide.**

The aforesaid facts do ascertain that:

'*inversion* in configuration dominates over *retention* in configuration'.

In addition, the **nucleophile** (*carbonium ion*) shows a clear cut preference to attack upon the ***carbon atom*** present in the **carbonium ion** from the side other than to which the ensuing **leaving functional moiety** is duly attached.

Thus, the so-called ***'anion'*** portion of the **ion pair** (*consisting of both the carbonium and anion* pair) virtually shields the side of the **C-atom** to which it is attached; and hence, these sequence of events may be illustrated with the aid of the following **specific example**:



20.2.2 Nucleophilic Aromatic Substitution

It has been amply proven and suggested that neither of the proposed **major mechanisms** for the so-called ***Nucleophilic Substitution*** specifically in the ***saturated*** **organic compounds** is found to be:

'accessible for substitution on the *Aromatic Rings*'.

Important Points: These essentially comprise:

1. First and foremost a ***back-side*** S_N2 **reaction** is invariably prevented by the so-called **geometry of the benzene ring**. Thus, the ***rear lobe*** of the sp^3 **orbital** is directed toward the centre of the **benzene ring**.

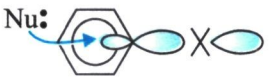
2. Therefore, an ***'inversion mechanism'*** is prevented exclusively by the **'geometry of the benzene ring'**.

* **'R' and 'S'-Specification of Configuration:** Thje most general and useful way usually suggested is the usage of the ***prefixes R and S***, according to a precedure proposed by **RS Cahn**.

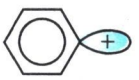
Comments: It clearly explains that an—S_N1 **mechanism** is found to be ***extremely expensive*** in terms of **'energy'** since a ***cation*** located strategically upon a **benzene ring** is fairly ***unstable*** in nature.

3. Thus, an ***aryl carbocation*** is duly localized in an sp^2 **orbital,** which happens to be ***orthogonal*** **to the π-system;** and hence, there prevails absolutely ***no stability*** due to the **π-electrons.**

We may have the following expression:



Back-side Approach of the Nucleophile with inversion is impossible



Phenyl cation is a high-energy intermediate

Various **organic chemistry researchers** have proposed many ***mechanisms*** by which the overall net ***nucleophilic aromatic substitution*** may take place.

Let us now look into the following *two* important mechanisms, namely:

- **Nucleophilic Aromatic Substitution by the Addition Elimination Mechanism** and,
- **Nucleophilic Aromatic Substitution by the Elimination—Addition Mechanism**

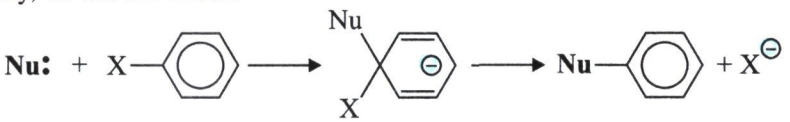
which shall now be discussed in the sections that follows:

20.2.2.1 Necleophilic Aromatic Substitution by the Addition—Elimination Mechanism

Various researchers have proposed the **addition-elimination mechanism*** which categorically makes use of one of the so-called:

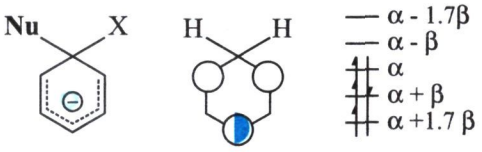
'vacant *π orbitals* for the bonding interaction with the nucleophile (carbonium ion)'.

Thus, it allows the addition of the *nucleophile* to the **aromatic ring** without causing the displacement of any of the *prevailing substituents*. However, in a situation when the **attack comes into play** at a position duly occupied by a ***potential*** **leaving functional group,** the overall net substitution may take place *via* a **second step** wherein the so-called **leaving functional group** is *pushed out* ultimately, as shown under:



Nucleophile **Aryl Halide** **Addition Intermediate**

In the above reaction, the ensuing ***'addition intermediate'*** is observed to be **isoelectronic** with a ***pentadienyl anion***,—as shown under:



* **Reviews:** Bemasconi CF. In: *MTP Int. Rev Sci. Organic Series*, **Vol. 3.**, Zollinger H (Ed.), Butterworths, London (UK), 1973, Zoltewiez JA: *Top Curr. Chem.*: **59**: 33, 1975.

Important Points:

1. In this case, the **HOMO** is ψ_3, that essentially possesses its inherent **electron density** located primarily at the ***C-atoms***:

   'located at the *ortho-* and *para*-to the respective position of substitution'.
2. Hence, the **addition intermediate** gets strongly stabilized by the help of an **electron withdrawing group (EWG)** located strategically at the so-called ***ortho*-or *para*-to the precise side of substitution**.
3. The **nitro (NO_2) moiety** exhibits the ***most powerful effect***; however, the **cyano (CN)** and **carbonyl (>C=O)** functional groups do also exert an *equally favourable effect perceptively*.
4. In a broader sense, the **nucleophilic aromatic substitution** shows an **energetically demanding reaction**, even when the so-called **electron attracting substituents (EAS)** are duly present; thereby the ensuing **aromatic π-system** gets disrupted predominantly by the process.

NOTE: **Interestingly, in the absolute absence of an EWG,—the *nucleophilic aromatic substitution* comes into play solely under the influence of *extreme reaction parameters*.**

Role of the Potential Leaving Functional Group: Importantly, the precise **role of the potential leaving functional group** is being employed gainfully in the critical determination of:

'the reaction rate is certainly different *vis-a-vis* the S_N2 and S_N1 substitution of the alkyl moieties'.

Obviously, in such cases, the observed ***bond strength*** is invariably found to be the **predominant factor**; and hence, the ensuing ***order of reactivity of the halogenes*** is as stated under:

$$I > Br > Cl > F$$

Besides, in the **nucleophilic aromatic substitution**—the crucial formation of the **addition intermediate** (see *section: 2.2.1*) is usually the so-called ***rate-determining step***; and, therefore, in the particular instance of the **cleavage of C—X bond** fails to affect the ***rate of reaction***. Hence, in such a situation the **order of reactivity** is given by:

$$F > Cl > Br > I^*$$

Importantly, the above stated **order of reactivity of the halogens** is virtually caused due to the ***polar effect of the halogens perceptively***.

NOTE: **The so-called *stronger bond dipoles* intimately associated with the distinctly *more electronegative halogens* do favour the addition intermediate step; and thus, affords a definite enhancement in the overall net rates of reaction grossly.**

The Meisenheimer Complexes: Amazingly, the **addition intermediates** (see *section 2.2.1*) are also called as ***Meisenheimer complexes***—that may:

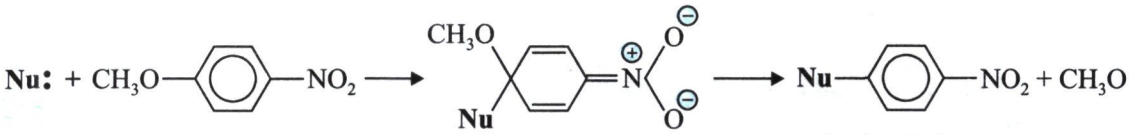
- **invariably be detected spectroscopically,** and
- **also isolated occasionally**.**

* Bartali G and Todesco PE: *Acc Chem Res*, **10**: 125, 1977.

** Bermascom CF: *Acc Chem Res*, II: 147, 1978.

Especially in the typical instance of such **'adducts'** being stabilized by the **nitro (NO_2)** moieties, the resulting **addition intermediates** are mostly obtained as ***strongly-coloured products***.

Thus, we may have the following expression:



Meisenheimer complex [Strongly Coloured Product]

Remarks: It may be observed that the **range of nucleophiles** which may duly take part in the **nucleophilic aromatic substitution** is found to be very much akin to the so-called:

'range of those nucleophiles which participate in the S_N2 reactions',

and thus, essentially comprises an array of **functional moieties** *viz.*,

- **Alkoxides** • **Amines** • **Fluoride ion** • **Phenoxides** and • **Sulphides.**

Points to Ponder:

1. In the particular case where the reaction, with **aromatic amines** and **1-chloro-2, 4-dinitrobenzene** occur, the value of **p** (*i.e.*, momentum of the particle) stands at **– 4.0**,—which vehemently indicates that:

'an appreciable build-up of the *+ve charge* takes place at the N-atom present in the transition state, (TS)*.

2. It may be observed that the **substitution by carbaanions** appears to be rather less prevalent. Perhaps it could be due to the fact that there are apparantly and frequently certain *unavoidable complications* which may result from the respective *electron transfer processes* having critically the so-called ***'nitraromatics'*** (or **aryl nitrites**).

3. The observed solvent effects upon the ensuing **nucleophilic aromatic substitutions** are very much akin to those discussed (earlier) for the **S_N2 reactions**.

4. Besides, certain highly specific chemical entities, such as:

- **Dipolar aprotic solvents,****
- **Crown ethers,***** and
- **Phase transfer catalysts,******

which would certainly increase the ***rate of substitution*** simply by providing the so-called: **"nucleophilic in a *reactive state* having a Weak Solvation".**

---

* Ikramudeen TM *et. al.*: *J Ind Chem. Soc.*, **66**: 342, 1989.

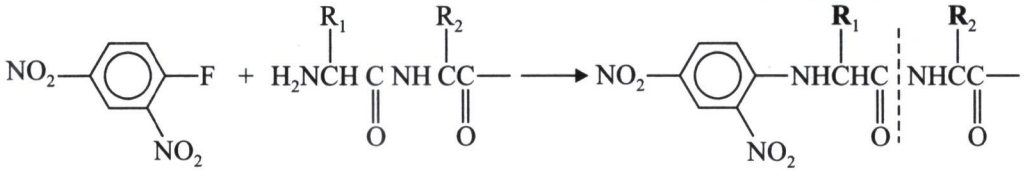
** Prato M *et. al.*: *Gazz Chim Ital*, **114**: 413, 1984.

*** Abramovitch A and Newman A (Jr.): *J Org. Chem.*, **39**: 3690, 1974.

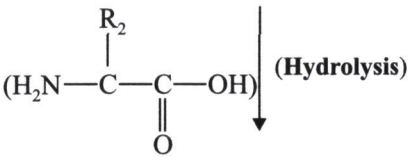
**** Makosza M *et. al.*: *Tetrahedron*, **30**: 1723, 1974.

Historically Significant Typical Examples of the Aromatic Nucleophilic *Substitution*: Such a substitution is particularly shown by the **reaction of amines with 2,4-dinitrofluorobenzene**. Sanger (1949)* used this reaction to develop an altogether **new method** for the crucial *identification* of the so-called—'**N-terminal amino acid present in proteins**, and thus, the process virtually paved the way for:

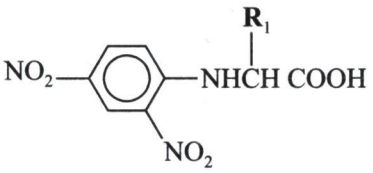
'**structural characterization of proteins and other Biopolymers,**—as depicted under:



2,4-Dinitrofluor benzene | **N-Terminal amino acid** | **N-Terminal amino acid adduct (In protein)**



(Eliminated) (X)



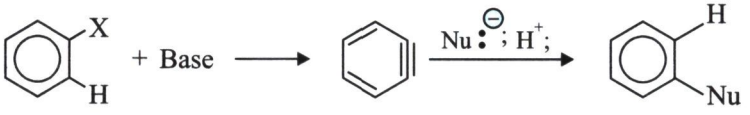
A N-Terminal acid

The interaction between **2,4-dinitrofluorobenzene** and **N-terminal amino** acid yields the respective **N-terminal amino acid adduct** (*in protein*), which on ***hydrolysis*** gives rise to the formation of an **N-terminal acid** with the elimination of a **substituted α-amino carboxylate (X)**.

20.2.2.2 Nucleophilic Aromatic Substitution by the Elimination-Addition Mechanism

In the 'specific **elimination-addition mechanism** one may explicitly observe the involvement of an **extremely unstable intermediate** invariably termed as: ***Dehydrobenzene*** or ***Benzyne*****.

It may be expressed as given below:



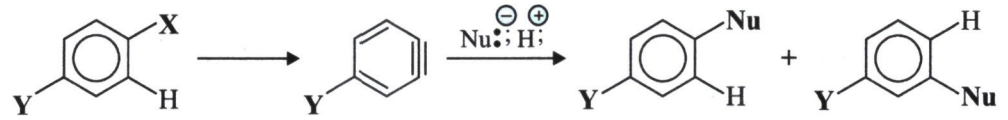
Phenyl halide | **Dehydrobenzene [or Benzyne] [An extremely unstable intermediate]** | **Nucleophilic addition mechanism**

* Sanger F: *Biochem J.*, **45**: 563, 1949.

** Wenk HH *et. al.*: *Angew Chem. Int. Ed. Engl.*, **42**: 502, 2002.

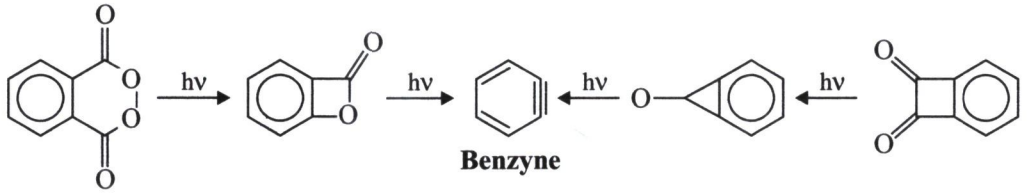
Comments: A characteristic feature of the aforesaid **mechanism** being the ***substitution profile*** in the **end product.**

However, the so-called **entering nucleophile** may not every time gain a legitimate entry right at the **C-atom** to which the leaving **functional moiety** was duly bound since it would eventually ***add on to the triply bonded C-atom (C≡C)***, as given under:



Thus, we may observe vividly the **benzyne** ***spectroscopically*** in an *inert matrix* at **very low temperatures***.

Hence, in order to carry out an elaborated investigative study the ***molecule*** may be generated **photolytically**,—as illustrated under:



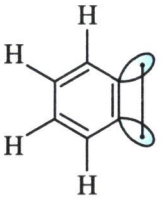
Remarks: Hence, the *bonding episode* in **benzyne** is obviously regarded to be very much akin to **benzene**; however, an *additional weak bond* duly present in the **plane of the ring** generated by virtue of:

'overlap of the *two* sp^2 orbitals'.**

Warmuth (1997)*** based the comparison of the **NMR characteristic features** *vis-a-vis* the **molecular orbital (MO)** pointed out that:

"*π-conjugation* being maintained rigidly and *benzyne* forms a *strained but aromatic molecule*".***

Thus, we obtained the following **strained aromatic molecule**:



* Rasdziszewski JG *et al.*: *J Am. Chem. Soc.*, **114**: 52, 1992.

** Simmons HE, *J Am. Chem. Soc.*, **83**: 1657, 1961.

*** Warmuth R: *Agnew Chem. Int. Ed. Engl.* **36**: 1347, 1997.

**** Jiao H *et al.*: *Agnew Chem. Int., Int Ed., Engl.* **36**: 2761, 1997.

20.2.3 Electrophilic Aliphatic Substitution

As we have already taken cognizance of the fact that in the *aromatic systems*—**proton (H^+)** also serves as the **leaving functional moiety** in the so-called **aliphatic systems**; however, its reactivity solely rests upon the ensuing **acidity profile** perceptively.

Following are the *two* recognized **mechanisms** for the **electrophilic substitution** in an **'Aliphatic System'**:

"S_N1, S_N2 (Front), S_N2 (Back), and S_Ei".

20.2.3.1 Biomolecular Mechanisms [S_E2 and S_Ei]

The **electrophilic aliphatic bimolecular mechanisms** do essentially involve the **transition state (TS)** that is associated prevalently with:

- **the simultaneous cleavage of bond,** and
- **the newer bond formation.**

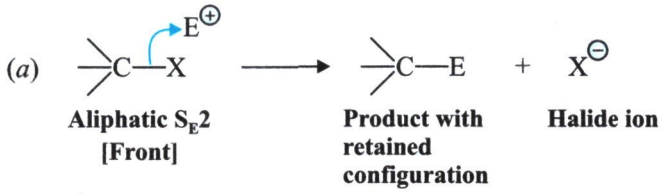
It has been duly observed that the ***attacking agent*** (*i.e.*, an **electrophile**),—does attack the **substrate** most prevalently either:

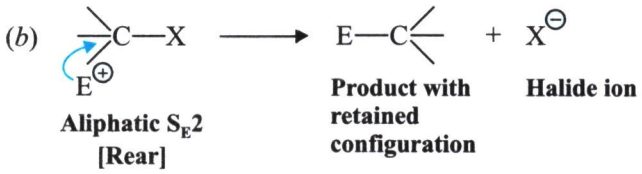
- ➢ **from the *'front side'***, or
- ➢ **from the *'rear side'***.

In this manner, the **electrophile** critically brings forth:

"the vacant *p*-orbital for overlapping with the central C-atom".

These expressions may be expatiated as under:





NOTE: **The IUPAC designation of *S_E2 (Front)* and *S_E2 (Rear)* are *DEAE*.**

Rear attack of the *electrophile* usually gives rise to the formation of an **'Inversion in Configuration'**; whereas, the **front attack** duly results in a **'Retention in Configuration'**.

Important Observations

These essentially comprise:

1. As and when the **electrophile** exerts its *attack from the front side*, **S_Ei (Internal Electrophilic Substitution)** may also be observed.

2. The **electrophile** perceptively aids in the *removal of the ensuing leaving functional moity* due to the specific **formation of a bond with it** *i.e.,* the ***simultaneous formation*** of:

'an altogether newer C—Y bond'.

NOTE: **The IUPAC designation of S_Ei *mechanism* is cyclo $D_EA_ED_nA_N$.**

3. All the ***three*** **aforesaid mechanisms** *viz.,* **S_E2 (Front), S_E2 (Rear),** and **S_Ei (Internal Electrophilic Substitution)** are critically observed to be:

- ***second*** **order reactions,** and
- **differentiation amongst them may be accomplished solely on the basis of** ***stereochemistry*****.**

4. The **S_E2 (Rear)** invariably comes into being only in **inversion of configuration**; whereas, **S_E2 (Front)** and **S_Ei** duly results in **retention in configuration.***

Besides, the **S_E2 (Front)** and **S_Ei** may not be distinguished at all even with the help of **stereochemistry**.

20.2.3.2 The S_E1 Mechanism [Unimolecular Aliphatic Electrophilic Substitution]

The mechanism critically involves ***two*** **phenomena one after the other** *viz.,* ***Ionization*** **followed by** ***combination*****,**—as shown below:

$$R{-}X \xrightarrow{\text{Slow}} :R^{\ominus} + X^{\oplus}$$

$$:R^{\ominus} + E^{\oplus} \longrightarrow R{-}E$$

Remarks: The IUPAC designation of S_E1 reaction is given by:

$$D_E + A_E$$

The **S_E1 reaction** undergoes rapidly with the ***substrates*** *i.e.,* the **carbanions**,—that are *not stabilized by resonance* at all, and hence, are found to be mostly **non-polar in character**. However, the **stereochemistry of S_E1 reaction** exclusively depends on both:

- **structure of carbanion,** and
- **geometry of carbanion.**

Importantly, the so-called **'Planar Carbanion'** virtually gives rise to the phenomenon of **racemization**; whereas, the **'Pyramidal Carbanion'** invariably results in the so-called **retention in configuration**—provided it holds the **structure in tact**.

NOTE: **In a situation, when the *Pyramidal Carbanion* is not capable of holding its inherent structure,—it would ultimately give rise to the phenomenon of '*Racemization*' perceptively.**

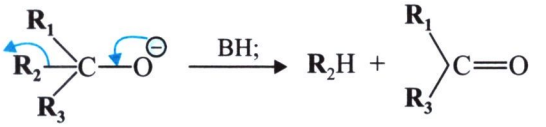
Cram *et al.* (1952)** Critically observed that the alkoxide ($R_3C{\cdot}O^{\ominus}$) **cleavage reaction** involves the ***specific*** **retention and inversion** *i.e.,* it may not be quite necessary that:

"the '*Planar Carbanion*' results in the racemization process".

* Baired *et al.*: *J. Am. Chem. Soc.*, **98**: 5539, 1976.

** Cram DJ. *et al.*: *J. Am. Chem. Soc.*, **74**: 5829, 1952.

Thus, we may have the following expression:



Planar carbanion [An Alkoxide] **A ketone**

R_2 = *tert*-alkyl group

Various Factors Grossly Affecting Rate of Aliphatic Electrophilic Substitution: The survey of literature reveals largely that there are ***three*** **recognized cardinal factors** which do affect the overall net rate of the **aliphatic electrophilic substitution** predominantly, such as:

(*a*) **The substrate:** Importantly, whenever the ***electron-donating functional moieties*** are duly present upon the so-called **'substrate C-atom'**, it apparently ***reduces the*** **rate of S_E1 reaction** particularly; whereas, the corresponding **electron-withdrawing groups (EWGs)** do enhance the **rate of S_E1 reaction** significantly.

S_E2 (Rear) Mechanism: Shows the reactivity of the alkyl moieties as stated under:

Methyl (CH_3) > Ethyl (C_2H_5) > Propyl (C_3H_7) > Iso-propyl [$(CH_3)_2CH$]

i.e., very much akin to **S_N2** reaction*.

S_E2 (Rear) reaction essentially involves the so-called ***backside attack***, and hence, is influenced by the **steric hindrence** due to the *functional moieties* attached to the respective **substrate C-atom**.

(*b*) **Leaving Functional Moieties:** Based on the fact that **electrophilic substitution** involves prominently the ***ionization phenomenon*****;** and hence, the ensuing **polarity profile of C—X bond** does effect the so-called **'*rate of reaction*'** perceptively.

In a specific instance, when the *leaving functional moiety* happens to be **metallic** in character,—the nature of ***other*** **moiety** duly attached to the **metal** predominantly effects the **rate of reaction.**

In another situation, when the **functional moiety** duly attached to **metal** appears to be definitely **more electronegative in character**, the ensuing polarity of the so-called **carbon-metal bondage** gets reduced significantly; and hence, the **rate of reaction** gets **retarded perceptively**.

Nevertheless, when the **metals** designate the ***leaving functional moieties*****,**—the **S_E1 mechanism would be always preferred**, and when it represents the **C-leaving group**,—the **S_E2** or **S_Ei mechanism would be favoured** predominantly.

(*c*) **Solvation (The Solvent Effect):** It has been proven and established beyond any reasonable doubt that the **solvation** phenomenon effects the **stereochemistry** of the ***chemical entities*** **(compounds)** largely. Cram et. al. (1952) proposed elegantly that simply by **changing the solvent profile,** one may critically lay hands on to an array of products that eventually:

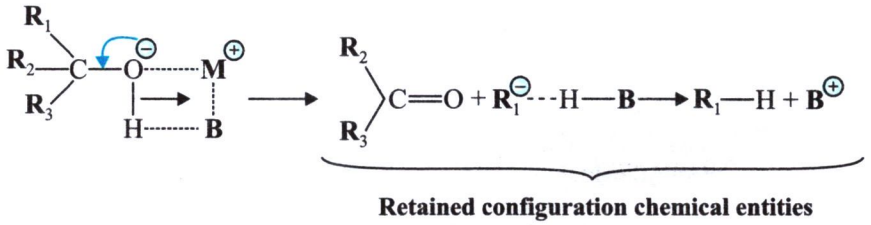
"range from *60% inversion* to *99% retention of configuration* (including racemization)"

since the **carbanion** gets adequately ***solvated***.

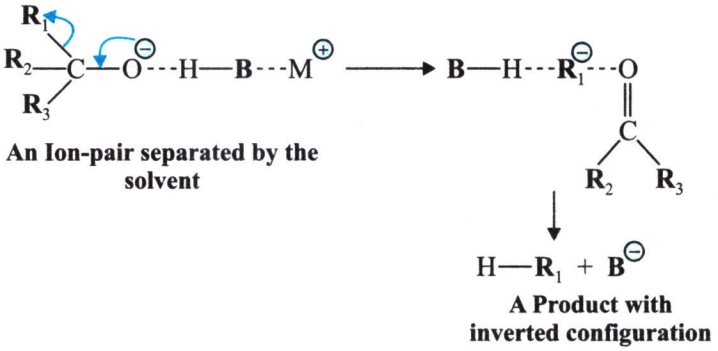
However, in the **non-polar solvents** *viz.,* **Benzene** or **Dioxane**, one may largely observe the existence of the **alkoxide ion [$R_3C{\cdot}O^{\ominus}$]**—as the so-called an **'*ion-pair*'** duly solvated by **BH**.

* Davis *et al.*: *J. Am. Chem. Soc.*, **93**: 4048, 1971.

The above may be expressed as under:



Fate in Protic Solvents: In the **protic solvents** (*viz.*, **water, methanol**), the ensuing **'carbanion'** gets duly solvated by the **leaving functional moiety** from the **opposite side** specifically; and thereby forms a product having an **inverted configuration,**—as shown under:



Fate in Aprotic Solvents: A variety of **aprotic solvents** *viz.*, **DMSO (dimethyl sulphoxide),** invariably results in the **racemization phenomenon.**

20.2.4 Electrophilic Aromatic Substitution

We have already observed the so-called enormous characteristic reactions of **benzene**, wherein the ***substitution*** gets involved primarily—thereby the **benzene-ring system** is duly preserved due to ***resonance stabilization*** phenomenon.

Reagents and Mechanisms Associated with Reactions of Benzene: These essentially include:

1. The **benzene ring** critically has a ***cloud of π-electrons*** both above and below the plane of the **benzene ring**, as depicted in Fig: 20.6.

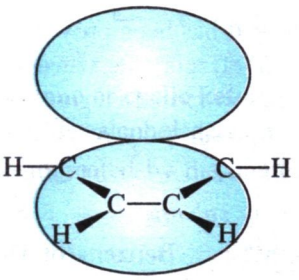


Fig. 20.6: Diagrammatic Representation of Benzene Ring: The π-cloud being a Source of Electrons.

EXPLANATIONS

Amazingly, *via* resonance phenomenon (in **benzene**) these π-electrons do get more intimately involved in ***holding together the C-nuclei*** in comparison to the respective **π-electrons** of a **carbon-carbon double bond (C=C)**. Furthermore, while comparing with the ensuing ***s*** **electrons** these **π electrons** are found to be held loosely; and hence, are mostly available to a *reagent* which is dire need of **'electrons'**.

Benzene Ring: A Source of Electrons: It is, however, pertinent to state here that:

'based on its typical reaction profiles the benzene ring does serve as a potential *source of electrons i.e.,* it behaves as a *base*.

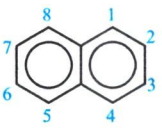
Besides, the various *chemical entities* **(compounds)** with which **benzene** reacts are indeed found to be quite **deficient in electrons** *i.e.,* they do belong to the particular class of **electrophilic reagents** or **acids**.

NOTE: **Since we are fully aware of the *typical reactions of the alkenes* that perceptively relate to the so-called *electrophilic addition reactions*; and, therefore, in the same vein the *typical reactions of the benzene ring* do refer to the *electrophilic substitution reactions* categorically.**

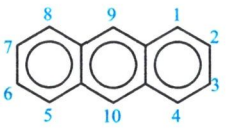
Important Points: These essentially comprise:

1. Importantly, these reactions are duly observed to be *highly characteristic* not pertaining to ***benzene*** itself, but also of the ***benzene ring*** generally found in ***several*** **aromatic rings as well** *viz.,*

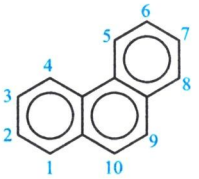
- **Benzenoid Aromatic Compounds**



Naphthalene
$[C_{10}H_8]$



Anthracene
$[C_{14}H_{10}]$



Phenanthfene
$[C_{14}H_{10}]$

- **Non-Benzenoid Compounds,** *i.e.,* the *aliphatic organic compounds*.

2. Interestingly, the **electrophilic aromatic substitution** critically embraces a ***broad-spectrum* of reactions**, such as:

- **Friedel-Craft's Reactions,**
- **Halogenation,**
- **Nitration, and**
- **Sulphonation.**

which have undergone by approximately most **'aromatic rings'** (as stated above).

3. However, the reactions, for instance:

- **Diazo-Coupling,** and
- **Nitrosation,**

that have undergone exclusively by such ***'ring systems'*** having a **high reactivity profile**.

4. Besides, an array of such **typical characteristic reactions,** namely:

- **Desulphonation,**
- **Isotopic exchange,** and
- **Several ring-closure reactions,**

that are clearly seem to be unrelated are precisely observed to be duly and gainfully viewed as reactions belong to the class of electrophilic **aromatic substitution** appears to be generally *unequatated* by so-called other kind of **organic reactions**.

Variants in Electrophilic Aromatic Substitution

Following are ***ten*** **cardinal variants** in ***electrophilic aromatic substitution,*** namely:

• **Nitration** • **Sulphonation** • **Halogenation** • **Friedel-Crafts Alkylation** • **Fridel-Crafts Acylation** • **Protonation** • **Nitrosation** • **Diazo Coupling** • **Kolbe Reaction** and • **Reimer Tiemann Reaction.**

which shall now be treated briefly in the section that follows:

(*a*) ***Nitration*:** Let us look into the following reaction:

$$\underset{\text{Benzene}}{ArH} + HONO_2 \xrightarrow{H_2SO_4;} \underset{\substack{\text{A Nitro}\\ \text{compound}}}{Ar{-}NO_2} + H_2O$$

Comments:

(*i*) **Ar = Aryl** *i.e.,* any **aromatic moiety** with attachment directly to **ring C-atom.**

(*ii*) $NO_2^{\oplus}$–Electrophile *i.e.,* the formation of the ***electrophile*** takes place as given under:

$$HONO_2 + H_2SO_4 \rightleftharpoons \underset{\substack{\text{Hydronium}\\ \text{ion}\\ \text{[Cation]}}}{H_3O^{\oplus}} + \underset{\substack{\text{Bisulphate}\\ \text{ion}\\ \text{[Anion]}}}{2HSO_4^{\ominus}} + \underset{\substack{\text{Nitronium}\\ \text{ion}\\ \text{[Cation]}}}{NO_2^{\oplus}}$$

Remarks: The *resonance energy* of the **Cation** may not be higher as that of the **benzene** itself; however, due to the **elimination of a proton ($H^{\oplus}$)** the ensuing molecule may revert to the **benzenoid form** perceptively. Thus, the **proton ($H^{\oplus}$)** is never released in the ***'free state'*** as such, but gets removed by the presence of certain **base.**

Fig. 20.7 clearly shows the formation of the **σ-complex (II),** that gets preceded by the formation of its **transition state (TS)** from the so-called **reactant;** however, in the **transition state (TS) I**—the newly formed ***covalent bond*** is formed **incompletely**. Furthermore, the **complex II**, now gives rise to the formation of the ***products*** *via* the **transition state (TS) III.**

Obviously, one may visualize the so-called ***generalized picture*** of the **electrophilic aromatic substitution** may be illustrated most effectively by the help of the **nitration reactions** perceptively.

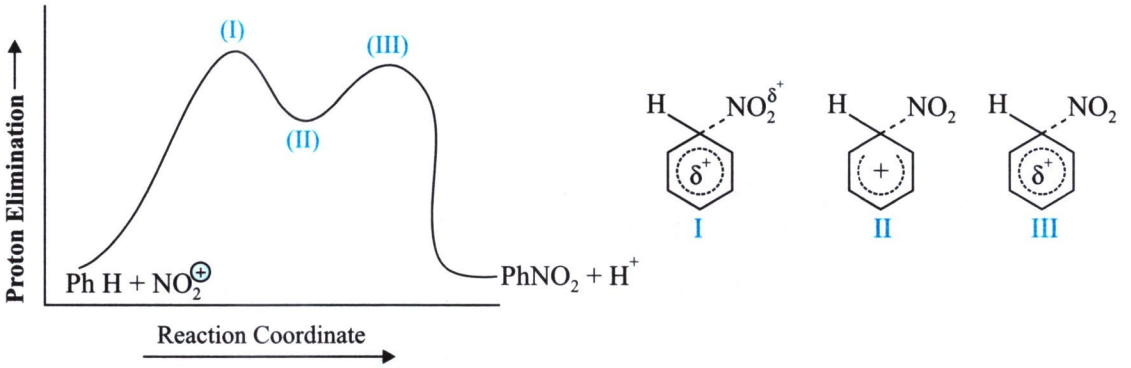


Fig. 20.7: Various Transition States I, II and III: Showing the Graphic Representation between Proton Elimination and Reaction Coordinate.

Explanations

The **complex II** subsequently generates the ensuing products *via* the **transition state (TS) III**. It is indeed quite feasible to have the generalized picture of the adequately illuminated version by the aid of **nitration reactions**. ***Kinetic studies*** of the nitration of **nitrobenzene** in H_2SO_4 have revealed explicitly that this reaction happens to be:

- **First order in nitrobenzene,** and
- **First order in nitric acid.**

(*b*) ***Sulphonation*:** We may consider the following reaction:

$$\underset{\textbf{Benzne}}{ArH} + HOSO_3H \xrightarrow{SO_3} \underset{\textbf{Sulphonic acid}}{AR{-}SO_3H} + H_2O$$

Here, the **electrophile** is SO_3.

Thus, the formation of **electrophile** is given by

$$2H_2SO_4 \rightleftharpoons \underset{\textbf{Hydronium ion}}{H_3O^{\oplus}} + \underset{\textbf{Hydronium sulphite ion}}{HSO_3^{\ominus}} + SO_3$$

(*c*) ***Halogenation*:** Following *two* reactions show the **halogenation** reactions:

$$(i)\ ArH + Br_2 \xrightarrow{Fe} \underset{\textbf{Aryl bromide}}{Ar{-}Br} + HBr$$

$$(ii)\ ArH + Cl_2 \xrightarrow{Fe} \underset{\textbf{Aryl chloride}}{Ar{-}Cl} + HCl$$

Here, the **chloride ion [$Cl^{\ominus}$]** designates the **electrophile**.

Production of the **electrophile** is shown by the following reaction:

$$Cl_2 + FeCl_3 \rightleftharpoons \underset{\textbf{Perchloro-ferric chloride}}{FeCl_4^{\ominus}} + Cl^{\ominus}$$

(*d*) ***Friedel-Craft's Alkylation*:** It is shown by the following reaction:

$$\underset{}{ArH} + \underset{\text{Acyl chloride}}{RCOCl} \xrightarrow{AlCl_3} \underset{\text{Aryl ketone}}{Ar-COR} + HCl$$

Here, the **electrophile** is represented by $\mathbf{R^{\oplus}}$.

The critical production of **electrophile** takes place as shown under.

$$RCl + AlCl_3 \rightleftharpoons \underset{\text{Alkyl cation}}{R^{\oplus}} + \underset{\text{Perchloro aluminium chloride}}{AlCl_4^{\ominus}}$$

(*e*) ***Friedel-Craft's Acylation*:** The reaction given below illustrates the **Friedel-Craft's acylation**:

$$\underset{}{ArH} + \underset{\text{Alkyl chloride}}{RCl} \xrightarrow{AlCl_3} \underset{\text{Alkyl benzene}}{Ar-R} + HCl$$

Here, the **electrophile** is $RCO^{\oplus}$

Formation of the **electrophile** occurs as given below:

$$RCOCl + AlCl_3 \rightleftharpoons \underset{\text{Perchloro-aluminium chloride}}{AlCl_4^{\ominus}} + RCO^{\oplus}$$

(*f*) ***Protonation*:** **Protonation** may be depicted by the reaction:

$$\underset{\text{Benzene sulphuric acid}}{ArSO_3H} + \underset{\text{Protonium}}{H^{\oplus}} \xrightarrow{H_2O} \underset{\text{Benzene}}{Ar-H} + H_2SO_4 \qquad \textbf{Desulphonation}$$

$$\underset{}{ArH} + \underset{\text{Deuterium ion}}{D^{\oplus}} \xrightarrow{D_2O} \underset{\text{Deuterzated benzene}}{Ar-D} + H^{\oplus} \qquad \textbf{Hydrogen Exchange}$$

In the **protonation** reaction the **electrophile** is $\mathbf{H^{\oplus}}$ ***i.e.*, proton**.

(*g*) ***Nitrosation*:** This reaction may be shown by the following expression:

$$\underset{}{ArH} + \underset{\text{Nitrous acid}}{HONO} \longrightarrow \underset{\text{Nitroso compound}}{Ar-N=O} + H_2O \qquad \textbf{Holds good for highly reactive ArH}$$

Here, the **electrophile** is $NO^{\oplus}$; and the formation of the **electrophile** occurs as shown below:

$$HONO + HCl \rightleftharpoons H_2O + \underset{\text{Nitroso cation}}{NO^{\oplus}} + Cl^{\ominus}$$

(*h*) ***Diazo Coupling*:** The **diazo coupling** reaction may take place as given under:

$$ArH + Ar_1{-}\overset{\oplus}{N}{\equiv}N\cdot X^{\ominus} \longrightarrow Ar{-}N{=}N\,Ar_1 + HX$$

Aryl diazonium salt — **An Azo compound** — **Holds good for highly reactive ArH**

Here, the **electrophile** is $\mathbf{ArN_2^{\oplus}}$.

(*i*) ***Kolbe Reaction*:** In this particular instance the **electrophiles** is designated duly by:

$$\overset{\delta^-}{O}{=}\overset{\delta^+}{C}{=}\overset{\delta^-}{O}$$ **Holds good for Phenols only**

(*j*) ***Reimer-Tiemann Reaction*:** Here, the **electrophile** is $\ddot{C}\,Cl_2$

Thus, the formation of **electrophile** takes place as shown below:

$$HCCl_3 + NaOH \rightleftharpoons \ddot{C}\,Cl_2 + H_2O + NaCl$$

Trichloro methane — **Electrophile** — **Holds good for phenols only**

ELECTROPHILIC AROMATIC SUBSTITUTIONS: REGIOSELECTIVITY *VIS-A-VIS* RELATIVE REACTIVITY OF MONOSUBSTITUTED BENZENES

In a broader perspective, we invariably come across *two* different types of groups, namely:

- **activating groups,** and
- **deactiviting groups.**

which shall now be discussed briefly in the sections that follows:

- ***Activating Groups:*** A *group* is usually classified as the **'activating group'**, if the ***drug*** being attached to it is found to be ***more reactive*** *vis-a-vis* **benzene** itself.
- ***Deacting Group*:** A *group* when attached to the **benzene ring** is found to be ***less reactive*** *vis-a-vis* **benzene** itself, is termed as the **deactivating group**.

Comparison of Reactivities between Benzene and Substituted Benzene: The actual comparison of the aforesaid reactivities is solely based upon the following ***two*** **aspects mainly**:

- **time required,** and
- **severity of parameters.**

➢ ***Time Required*:** The precise and exact **time required** for the ensuing (*intended*) reactions to take place under **similar experimental parameters** may be measured.

Example: **Toluene** ($\mathbf{C_6H_5CH_3}$) reacts with fuming **sulphuric acid** ($\mathbf{H_2SO_4}$) within a span of **~ 1/10th - 1/20th the total time required by benzene**. Thus, **toluene** is indeed found to be *more reactive than benzene*; and hence, the **methyl** ($\mathbf{-CH_3}$) **group** is known as the **activating group**.

➢ ***Severity of Parameters:*** The **severity of parameters** essentially needed for the *comparable reactions* to take place very much within the ***same span of time*** may be observed explicitly.

Example: **Benzene** gets ***nitrated*** very much within **60 minutes at 60°C** by making use of an admixture **conc. $\mathbf{H_2SO_4}$ and conc. $\mathbf{HNO_3}$**. Besides, the usual comparable nitration of **nitrobenzene** ($\mathbf{C_6H_5NO_2}$) does need the treatment at **90°C** using **fuming $\mathbf{HNO_3}$** and **Conc. $\mathbf{H_2SO_4}$**. Thus, **nitrobenzene** is obviously *less reactive than* ***benzene***; and hence, the **nitro** ($\mathbf{-NO_2}$) **group** designates a **deactivating group**.

* These are: ***Slow*** **rate-determining step** and ***Fast*** **step**.

Mechanism of Electrophilic Aromatic Substitution

There are ***two*** **cardinal steps*** that are actually engaged in expatiating the *precise mechanism* of the **electrophilic aromatic substitution**.

Let us now look at the following ***two*** **cardinal steps**, namely:

1. • ***Slow*-Rate determining step,** and
   • ***Fast*** **step.**

2. $ArH + Y^{\ominus} \longrightarrow Ar^{\oplus}(H)(Y)$ **Slow : Rate-determining step**

$Ar^{\oplus}(H)(Y) + :Z \longrightarrow Ar—Y + H:Z$ ***Fast*** **: step**

rather than shown in just ***one step*** **only**,—as given under:

(La) $ArH + Y^{\oplus} \longrightarrow [Ar^{\cdots}(H)^{\cdots}(Y)]^{\oplus} \longrightarrow Ar—Y + H^{\oplus}$

At this point in time a critical question may arise that:

'one of these *two* steps: the *first* is found to be much slower than the *second*'.

Remarks: A good number of **aromatic chemical entities** (*compounds*) duly labelled with **deuterium (D_2)** or **tritium (T_2)** were subjected to:

- **Fridel-Crafts alkylation,**
- **Nitration,** and
- **Bromination**

***Inference*:** The aforesaid studies revealed that in all these reactions either **Deuterium (D_2) or Tritium (T_2)** gets duly replaced at;

"the same *rate* as Protium (or Hydrogen)—one may not observe any so-called *Isotopic Effect* at all".

NOTE: **In fact, these findings were adequately supported by *series of investigative studies* carried out by Lars Melander and extended by several other researchers.**

Special Comments: It is pertinent to state here that in a situation when the ***substitution*** involved a **'single step'** (as depicted in, **1a**), this very step should obviously represent the so-called ***'rate-determining step'***. Since, it essentially engages the specific cleavage of the prevailing **C—H bond,** hence one may observe an ***Isotope Effect*** perceptively.

Besides, in case, the **step (2)** pertaining to the above stated **2-step sequence** were **slow** indeed *vis-a-vis* the above **Step (1)** to afford the respective *overall net rate*,—one would again anticipate an ***Isotope Effect*** predominantly.

NOTE: **Nevertheless, in reality the *sulphonation* does exhibit a negligible *Isotope Effect*. Besides, in *sulphonation*—the overall rate is controlled mainly by *step (1)*.**

Complete Absence of *Isotope Effects* Suggests Both: 2-Step Nature of Electrophilic Aromatic Substitution and Relative Speeds of the Step Involved: The particular attachment of the **electrophile** to a *C-atom present in the ring system* is regarded to be the rather *difficult step* indeed,—as depicted in Fig. 20.8. Furthermore, it would be still a herculian task to ascertain whether the aforesaid **C-atom** does carry either a **Protium (or Hydrogen)** or **Deuterium (D_2)**.

Interestingly, the very ***next step*** *i.e.,* the crucial loss of an **H^+-ion** appears to be rather quite convenient and easy. Even though this phenomenon comes into play **more sluggishly** for **D_2** than for **H**; and thus, ultimately produces no apparent difference at all. In addition, it is absolutely immaterial whether the overall speed is either ***slightly faster*** or ***slightly slower***—it exhibits absolutely little effect upon the **overall net rate**.

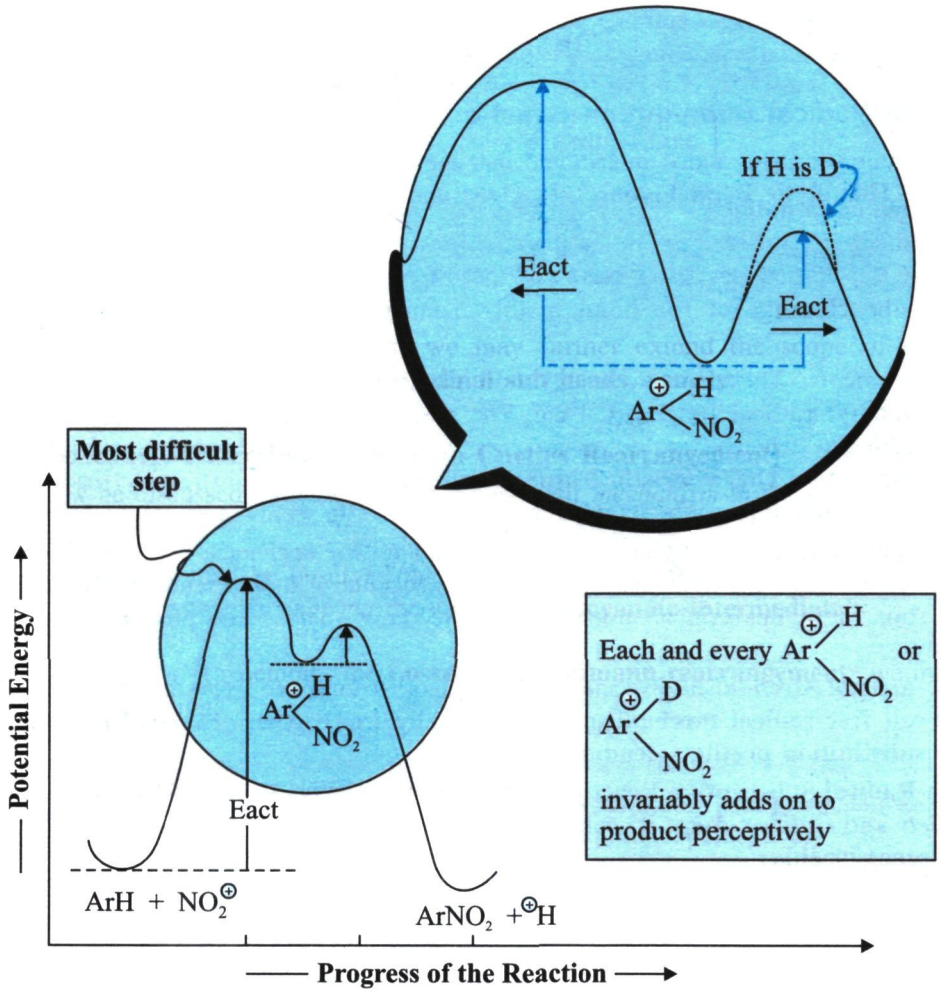
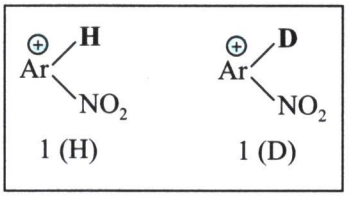


Fig. 20.8: The Nitration of Carbocation Relates to Rate-Controlling Step; Which takes place quite Rapidly Even when Protium (H) or Deuterium (D) is at Point of Attack. All Carbocations go on to the Product. Since there is total absence of Isotope Effect; and hence, Nitration Remains Irreversible.

EXPLANATIONS

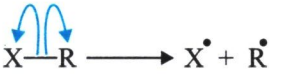
The closer look at the ***inset of Fig: 20.8*** shows explicitly that each and every **carbocation** so generated **[whether 1 (H) or 1 (D)]** usually adds on to the product vehemently; and since the ***existing*** **energy barrier to the right** (*i.e.,* ahead of **carbocation**)—whether ***slightly higher for*** **Deuterium (D) or** ***slightly lower for*** **Proteum (H)**—is observed to be still significantly lower in comparison to the **barrier to the left** (*i.e.,* behind the **carbocation**).

Importantly, the barrier located strategically behind the **carbocation** is the **Eact** for the reverse of **step (1)**. Amazingly, the so-called **reverse reaction** which should be reasonably lower than **Step (2)** provided **step (1)** is expected to be a **rate-determining step in reality**.



20.2.5 Free Radical Substitution Reaction

It has been amply proven and demonstrated that the so-called **'Free-Radical'** formation critically involves the **Homolytic Bond Fission,**—as given under:



Thus, the **cleavage of the bond** in this manner is usually termed as ***homolytic*** **fission** (or ***homolysis***).

Free Radicals*:** These are invariably **odd electron molecule** *viz.,* **Methyl radical [$CH_3^{\bullet}$], Triphenyl methyl radical [$(C_6H_5)_3C^{\bullet}$]** etc. The majority of the ***Free Radicals are found to be **neutral** ***electrically*** (whereas, we do come across a few ***free radical*** **ions**). Besides, most of them do possess ***additional*** **characteristic features,** and are found to be extremely reactive. However, whenever a **free radical** is ***stable***, its inherent **stability profile** seems to be solely due to ***resonance***.

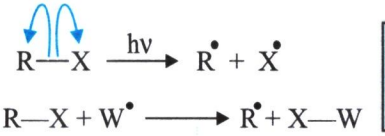
Paramagnetic*:** The **free radicals** are indeed ***paramagnetic in character *i.e.,* do possess essentially a *small but permanent magnetic moment* perhaps on account of the presence of the **odd** *(unpaired)* **electron**. Amazingly, this critical property duly ascertains (detect) the presence of **free radicals** vehemently.

Free-Radical Mechanism*:** We may consider another vital and important characteristic feature of the so-call **free-radical mechanism** that eventually leads to an ***abnormal orientation **in the aromatic substitution profile splendidly**.

Free-Radical Substitution Reaction: Involving the Cleavage of Bond Existing between the *Alkyl Moiety* and *Halide Group*: It enables to give rise to the production of **free-radicals** very much in the presence of either:

- **Sun Light** or **Heat**

It may be expressed as under:



S_N1: Unimolecular Substitution Homolytic

where $W^{\bullet}$ = Formed duly from a compound known as initiator;

$R^{\bullet}$ = Formed usually produces the desired product either:

- **due to substitution, as shown below:** or

$$R^{\bullet} + Y{-}W \longrightarrow R{-}Y + W^{\bullet}\ (SH_2)$$

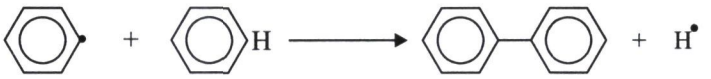
- **due to combination with either of the *two* free-radicals leading ultimately to product:**

$$R^{\bullet} + Y^{\bullet} \longrightarrow R{-}Y$$

Free-Radical Substitution Reaction: Illustrated by Reaction Involving Substraction of *Proton* (H^+) from *Methyl Moiety (of Toluene)* by *Bromine Atom*: It may be illustrated explicitly as given below:

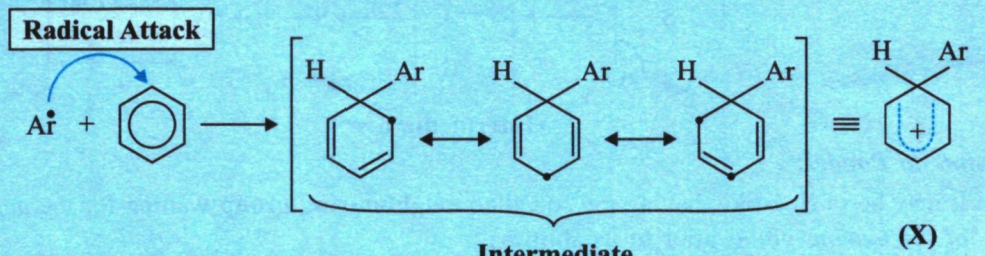


In a specific instance, where **R** is ***aromatic***—one may observe an ***ordinary*** **substraction mechanism,**—as depicted under:



Phenyl radical **Benzene** **Diphenyl** **Hydrogen radical**

Remarks: It has bee duly observed that the underlying **mechanism of an aromatic substrate** is quite identical to that of the ***electrpphilic*** **and** ***nucleophilc*** **aromatic substitution,** whereby the **'radical'** attack the **Benzene Ring** perceptively,—as shown under:



Intermediate
[*Stabilized by Resonance*]

20.2.6 Neighbouring Group Participation

It is also known as the **'Intramolecular Nucleophilic Attack'**. Based on the foregoing *discussions*, *explanations*, and *conclusions* one may observed critically that the **Nucleophilic Substitution Reactions** invariably come into play with the help of:

"some highly specific stereochemistry *viz., Racemization* (as in S_N1 reaction); and also with Inversion in Configuration (as in S_N2 reaction)".

Manus *et al.* (1976)* proposed that in certain typical cases the **retention in configuration** is duly observed thereby ascertaining the ground reality that the most probable reason for the same is—**'neighbouring, group participation'**.

* Manus M *et al.*: **Neighbouring Group Participation, Vol.1,** Plenum, New York, 1976.

S_N1 and S_N2–Like Migration: Let us have a closer look at the **migration process** being involved based upon the ***same view point***—as we had already seen in the concentration with the **Hoffman Rearrangement** (dicussed earlier).

EXPLANATIONS

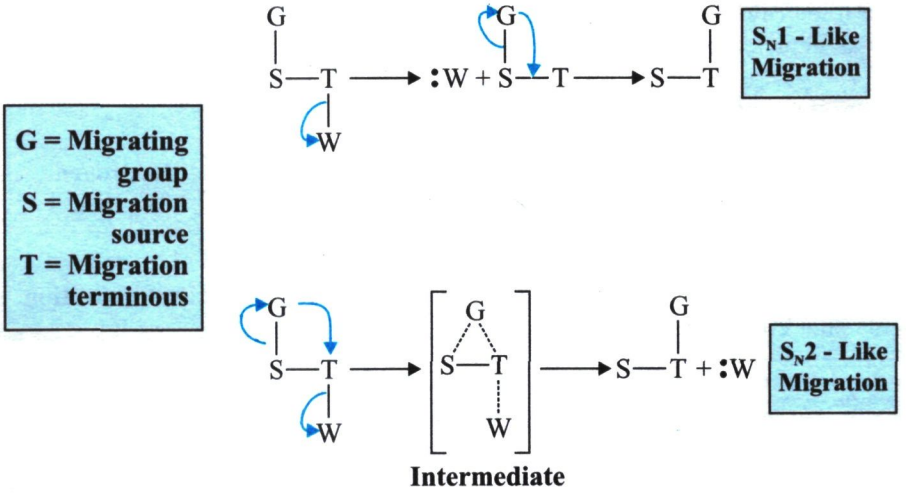
It has been amply proven and established that:

'an electron-deficient C-atom most abundantly produced by the critical departure of a leaving moiety that takes up the bonding electrons along with it'.

Since the **migrating moiety** happens to be a ***'nucleophile'***; and hence, a rearrangement of this type tantamounts to:

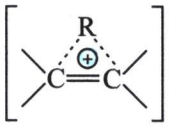
"Intramolecular Nucleophilic Substitution".

Therefore, the rearrangement may be of ***two*** **different kinds** ***viz., S_N1*** **and** ***S_N2*****-like Migration,**— as shown under:



Points to Ponder:

1. It may be of **S_N1-like,** having the so-called **neighbouring group** waiting for the *departure of the leaving group* prior to its shifting.
2. It could be **S_N2-like,** having the ensuing **neighbouring group** typing to push out the so-called **leaving group** by virtue of a ***single-step reaction***; and this sort of help is usually termed as—**anchimeric assistance**.

***Anchimeric Assistance*:** Obviously, the **bridged ion** *e.g.*,  essentially contains

three **partial bonds** duly generated from only ***one pair of electrons***.

Importantly, the very idea and concept of the so-called ***'bridged carbonium ions'*** was put forward by Nevell *et. al.* (1939), but it should be admitted squarely that the very existence of such an **ion** has not yet been established fully when the ***migrating moiety*** happens to be an **alkyl group**. Besides, the formation of these **bridged ions** p0a0rticularly in the **1, 2-shifts** serves as a beautiful

example of the so-called—**'neighbouring group participation'**. However, when the ultimate ***'rate-of-rearrangement'*** gets enhanced by virtue of this effect, the said rearrangement is invariably termed as—**'Anchimeric Assistance'** (Winstein *et al.,* 1953).

Interestingly, in a rearrangement, wherein a nearby group carries electrons in an *electron-deficient atom*, and then ***stays there***. But in several occasions it so happens, that a **group brings electrons** and then ***goes back to where it initially came from***. Thus, it virtually affords:

'the neighbouring group effect predominantly'.

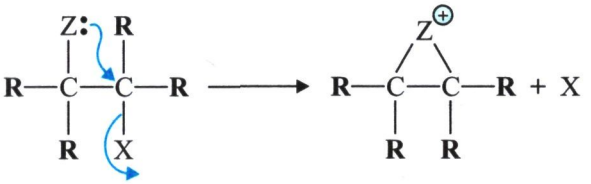
Hence, the so-called ***intramolecular effects*** duly exerted upon a reaction *via* **direct participation** *i.e.,* through definite movement to:

'within the *bonding distance*-by a group located near the centre'.

Mechanism: In both the above sited cases related to S_N1 and S_N2 **like migration (rearrangment)**—the prevailing ***electron-rich group*** brings the ***electron*** to the ***electron-deficient electrophile C-atom,*** and after staying there for a while **shifts back to the original position** perceptively.

Thus, we may have the following expression:

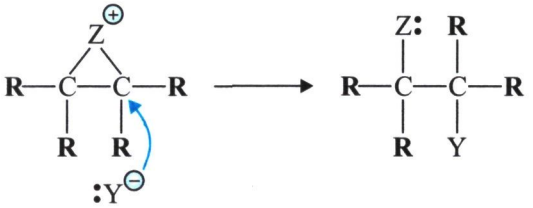
Step-1:



where, **Z** = Nucleophilic neighbouring group,
X = Leaving functional group

Step-2*:** It critically involves the attack of an ***'external electrophile' upon the **bridged-intermediate** so as to yield the resulting **substitution product**. Thus, ultimately the ***neighbouring moiety*** does retain its **original position and status**, and also its ***configuration*** **about the C-atom undergoing nucleophilic substitution** vehemently thereby rataining it.

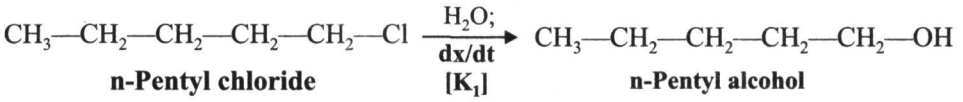
The reaction may be expressed as under:



SPECIAL NOTE: **It has been duly observed that the participation of the so-called '*neighbouring moiety*' in the particular *rate determining step* gets duly enhanced the ensuing *rate-of-reaction* predominantly; and this effect is usually called as—*anchimeric assistance* as explained earlier.**

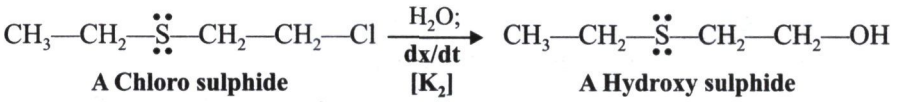
Following are the *two* different **'Relative Rate of Reactions'**:

When the Relative Rate of Reaction = 1:



n-Pentyl chloride **n-Pentyl alcohol**

When the Relative Rate of Reaction = 700:



A Chloro sulphide **A Hydroxy sulphide**

Remark: The above *two* different reactions explicitly reveals that the value of $\mathbf{K_2}$ is more than $\mathbf{K_1}$.

Suggested Reading

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Chapter 21

Elimination Reactions

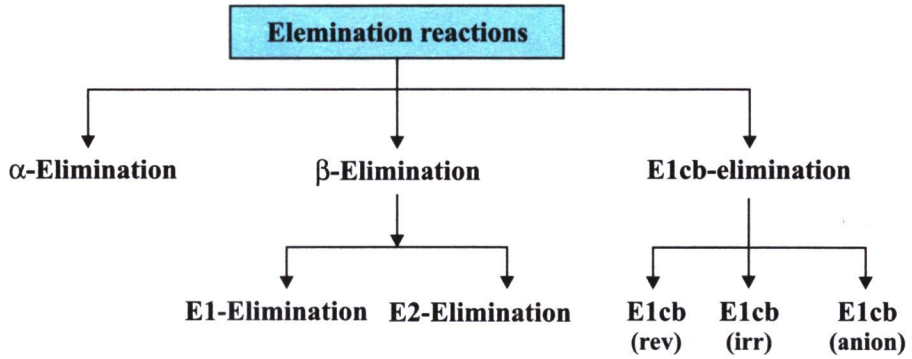
LESSONS AT A GLANCE

21.1 Introduction
- 21.1.1 Dehydrohalogenation
- 21.1.2 Dehydrosulphonation
- 21.1.3 Eliminations of Quaternary Ammonium Hydroxides

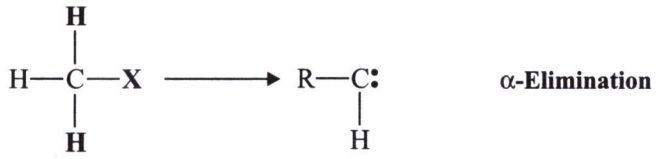
21.2 Elimination Reaction Variants
- 21.2.1 β-Elimination Reactions—Unimolecular [or E_1-Elimination]
- 21.2.2 β-Elimination Reactions—Bimolecular [or E_2-Elimination]

21.1 INTRODUCTION

In usual practice, the **elimination reactions** invariably proceed by the actual loss of either ***two*** **atoms** or ***two*** **moieties** from a molecule. However, in a broader perspective the **elimination reaction may be classified judiciously** into the following categories—that depends solely upon the precise **C-atom** where the **H-atom** is eliminated.



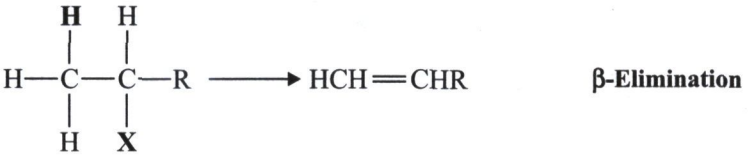
❑ ***α-Eliminations*:** These are known as the **1,1-eliminations**—that critically involves the ***elimination*** of an **H-atom** and the leaving moiety from the **same C-atom**—as shown under:



❑ ***β-Eliminations*:** They are also termed as: **1,2-eliminations**—that predominantly involves the ***eliminations*** of an **H-atom** from the **β-C-atom** thereby giving rise to the formation of an **unsaturated bond**. In a broader perspective, the **β-eliminations** may be illustrated explicitly by the so-called ***acid-catalyzed*** **dehydration** of:

• **Alcohols** • **Solvolytic Reactions and** • **Base-induced Elimination Reactions,**

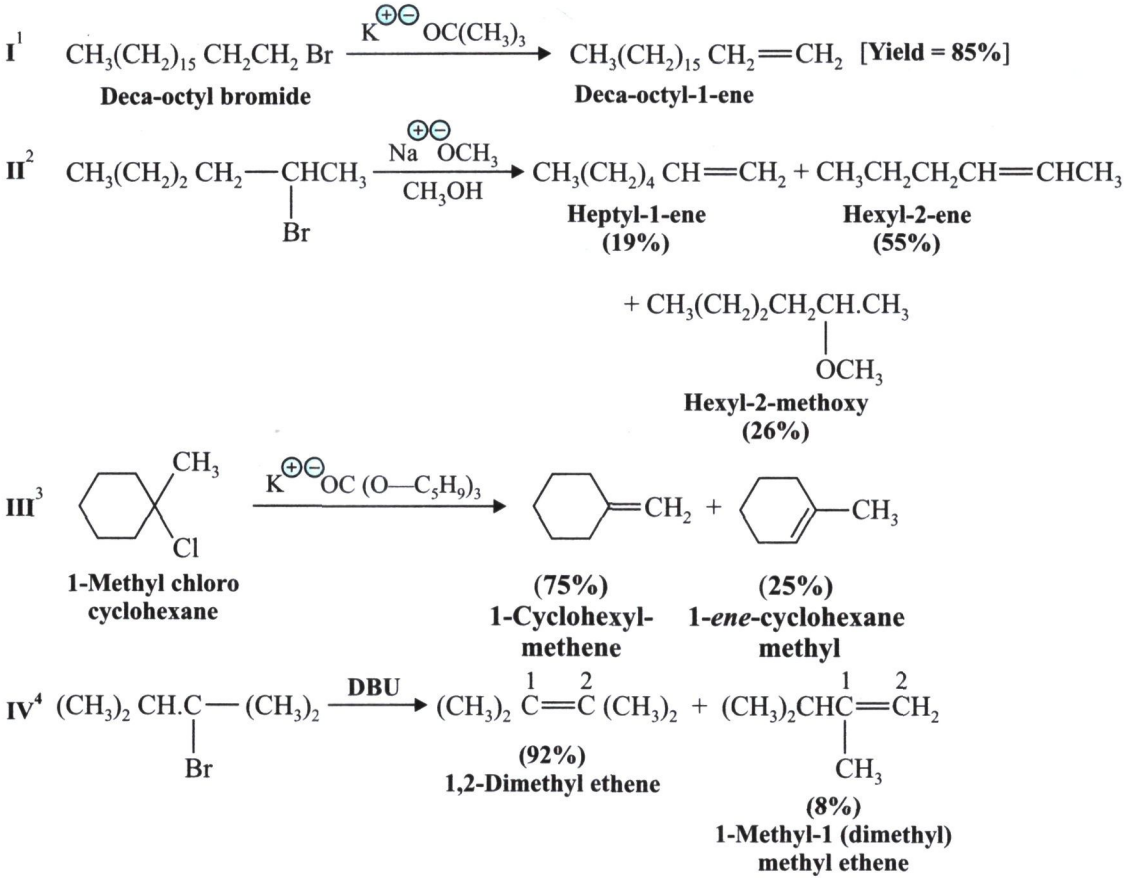
from **'alkyl halides'**, **'sulphonates'** etc., and **Hoffmann Elimination Reactions,**—as depicted below:



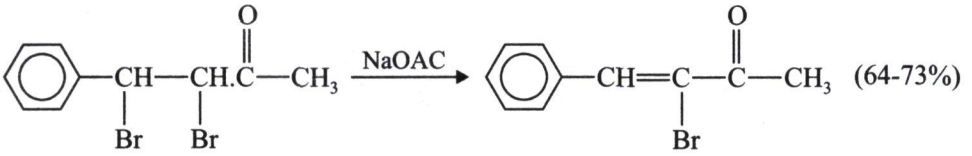
Representative Examples of β-Elimination Reaction: A few selected and representative examples of the **β-elimination reactions** have been enumerated as under in the following ***two*** **types of organic reactions,** namely:

• **Dehydrohalogenation,** and • **Dehydrosulphonation.**

21.1.1 Dehydrohalogenation



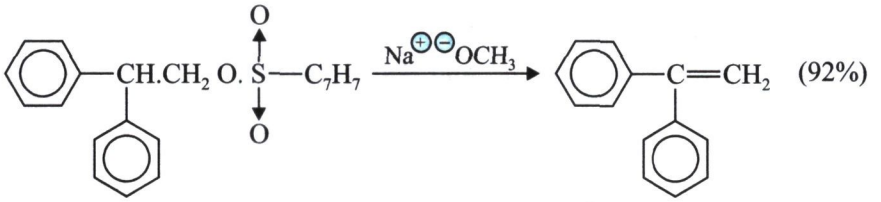
V[5]



1-Phenyl-1,2-dibromide ethyl methyl ketone **2-Bromo-phenyl ethene-methyl ketone**

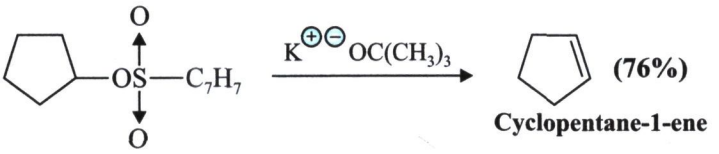
21.1.2 Dehydrosulphonation

VI[6]



Diphenyl ethene

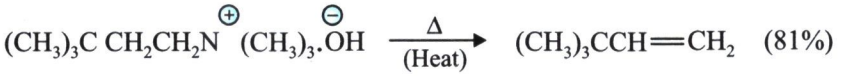
VII[7]



Cyclopentane-1-ene

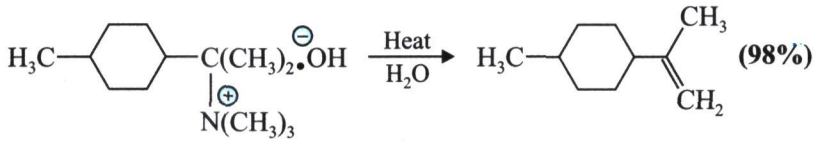
21.1.3 Eliminations of Quaternary Ammonium Hydroxides

VIII[8]



A Trimethyl ammonium hydroxide **1-Trimethyl methane ethene**

IX[9]



A Cyclohexyl trimethyl ammonium hydroxide **1-Methyl-(4-cyclohexy (methyl) ethene)**

1. Veeragn P *et al.*: *J Am Chem. Soc.*, **86**: 3072, 1964.
2. Bartsch RA and Bunnett JF: *J Am. Chem Soc.*, **90**: 408, 1968.
3. Acharya SA and Brown HC: *J Chem. Soc. Chem. Commun.*, 305, 1968.
4. Wolkoff JP: *J Org., Chem.*, **47**: 1944, 1982.
5. Cornwell NR *et al.*: *Org. Syn.*, **111**: 135, 1953.
6. Hamrick PJ and Hanser CR: *J Org Chem.*, **26**: 4199, 1961.
7. Cuyder CH and Soto AR: *J Org. Chem.*, **19**: 742, 1964.
8. Cope AC and Ross DL: *J Am. Chem. Soc.*, **83**: 3854, 1961.
9. King LC *et al.*: *J Org Chem.*, **21**: 1232, 1956.

EXPLANATIONS

All the above ***Entries from 1 to 9***—shall now be explained explicitly as under:

❑ ***Entry* 1:** It represents a typical **dehydrohalogenation** reaction which critically involves absolutely no issue of either:

- **regioselectivity episode,** or
- **stereoselectivity profile.**

However, with the specific **primary reactants**—the so-called **major competing reaction** is indeed the ***substitution reaction***.

Obviously, the **base** employed duly in **Entry-1 [$K^{\oplus}$ · $^{\ominus}$O-*tert*-Bu]** certainly favours the ***elimination* phenomenon** *vis-a-vis* the ***substitution* phenomenon**, when being elegantly compared with the so-called:

'less-branched alkoxide species predominantly'.

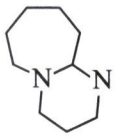
❑ ***Entry* 2:** It illustrates prominently the *two* main issues pertaining to • **regiochemistry** and • **stereochemistry—**which may eventually come into being, even with the help of:

➢ **a comparatively simpler reactant,** and

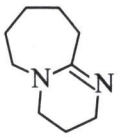
➢ **exhibiting explicitly that *substitution* may compete elegently having *elimination* in an *unhindered system*.**

❑ ***Entry* 3:** It clearly shows the usage of a ***very hindered*** **alkoxide [$K^{\oplus}$ · $^{\ominus}$OC (O—$C_5H_9)_3$]** so as to favour vehemently the ***less-substituted product***. Therefore, the so-called ***strong organic bases viz.*, 1, 3-diazabicyclo [4, 3, 0] undecene (DBU)*** and **1, 3-diazabicyclo [3, 2, 0] nonene (DBN)****—that may also effect the process of ***dehydrohalogenation*** (as depicted in ***Entry* 4**).

In addition, the said ***two* bases** (**DBU** and **DBN**) are found to be specifically effective for such **reactants** which are ***ionized*** rather easily and conveniently, for instance: ***tertiary* Halides (R_3X)**.



DBU



DBN

❑ ***Entry* 5:** In this particular instance, wherein the so-called **'carbanion-stabilizing effect'** of a ***carbonyl* (>C=*O*) *moiety*** does facilitate the **elimination pehnomenon** by the help of:

- **a comparatively 'weak base';** and
- **controls *regiochemistry by protonation of the α-C-atom*.**

❑ ***Entries* 6 and 7:** These represent particularly the **tosylate [CH_3—$6H_4$—$SO_3^{\ominus}$] eliminations**. In a broader perspective, the **tosylates** do provide a relatively **higher quantum of substitution** *vis-a-vis* the **halides*****.

---

* Oediger H and Moeller F: *Angew Chem. Int. Ed. Engl.*, **6**: 76, 1967; Wolkoff P: *J. Org Chem.*, **47**: 1944, 1982.

** Oediger H *et al.*: *Chem. Ber.*, **99**: 2012, 1966.

*** Veeravagu P *et al.*: *J Am. Chem. Soc.*, **86:** 3072, 1964.

❑ *Entries* **8 and 9:** In fact, they represent the *examples* of the well-known ***Hoffmann Elimination Reaction***—that implies a typical instance wherein the so-called:

"relatively *weak* and *bulky leaving moiety* (*viz.*, trimethylamine) critically leads to a preference for the *formation of the less-substituted alkene*".

21.2 ELIMINATION REACTION VARIANTS

The **elimination reactions** are of ***four* different variants,** such as:

- ❑ **β-Elimination Reactions—Unimolecular [or E_1-Elimination],**
- ❑ **β-Elimination Reaction—Bimolecular [or E_2-Elimination],**
- ❑ **E1cb—Elimination Reactions [or Conjugate Base Unimolecular Elimination], and**
- ❑ **Internal Elimination [Ei],**

which shall now be discussed, individually at length in the section that follows:

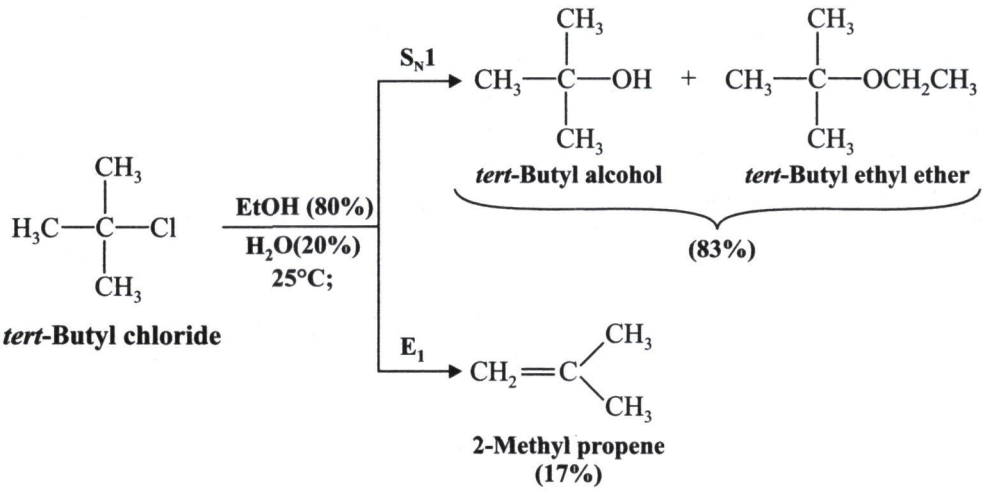
21.2.1 β-Elimination Reactions—Unimolecular [or E_1-Elimination]

Let us take the specific example whereby the **elimination** may eventually take the course of an altogether **different pathway** *i.e.*, by treating ***tert*-Butyl Chloride [$(CH_3)CCl$]** using *80% (ups) ethanol* at **25°C.**

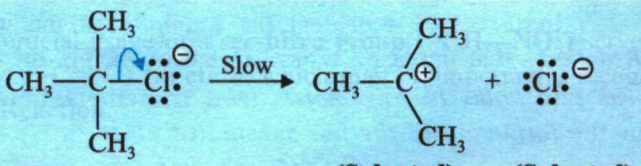
Example: Thus, we may critically observe *two* divergent situations:

- **substitution products: giving an yield 83%;** and
- **elimination product (2-methyl propene): giving an yield of only 17%.**

The aforesaid ***two* types of products** may be expressed vividly as under:



Remarks: Based on the aforesaid *two* reactions *viz.*, S_N1 and E_1, one may observe critically that in either of the ***two* instances** results into the formation of a ***tert*-butyl cation [$(CH_3)C^{\oplus}$].** Obviously, it also serves as the so-called-**'rate-determining step'** for both the said reactions; and hence, duly ascertains the underlying fact that both these reactions are **unimolecular** in nature:

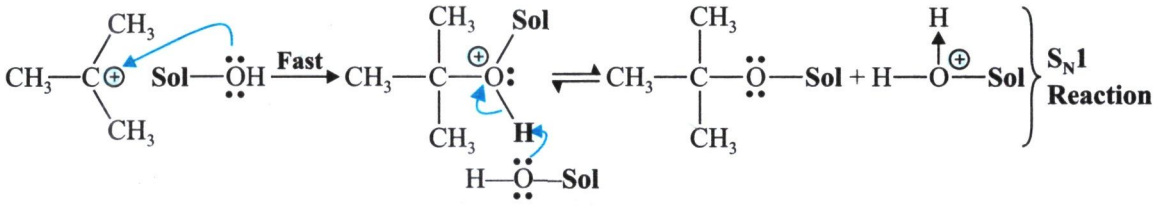


The *Fast* Step: The actual event that eventually leads to either ***substitution*** or ***elimination*** depends exclusively upon the ***next step*** *i.e.,* **the *fast* step**. In case, a solvent molecule reacts as a **nucleophile** specically at the **positive C-atom** of the **'*tert*-butyl cation'**,—the ultimate product must be either:

- ***tert*-Butyl alcohol** or
- ***tert*-Butyl ethyl ether,**

and, therefore, the reaction is definitely S_N1 perceptively.

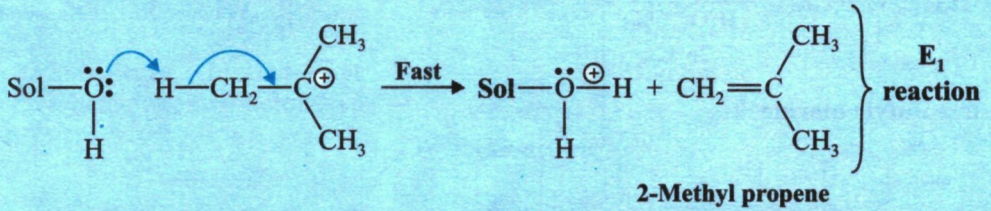
The above may be further expatiated as expressed below:



Sol = H— or CH_3CH_2—

Comments: Nevertheless, if a **solvent molecule** does act as a **'base'** and helps to remove **one of the β-H-atoms** as a **proton ($H^{\oplus}$)**, the resulting product is **2-methylpropene**; and hence, the reaction is E_1.

In a broader sense, the so-called E_1 **reaction** invariably accompanies the S_N1**-reactions** perceptively,—as stated under:



The Saytzeff Rule *Vs* Hoffmann Rule: The direction in which the E_1 **reactions** occur, right from the ***intermediate*** **carbocation**, more than one **substituted alkenes** are duly obtained and **the *product alkene*** that actually need to be taken into consideration as the so-called **Principal Product** is ultimately being decided by **Saytzeff Rule** *i.e.,* it implies that ***more* substituted akene is usually preferred** *vis-a-vis* the **major product** [—as already shown above under: S_N1 **(83%) and** E_1 **(17%) yields.**

When the product of ***Saytzeff Elimination*** gets destabilized by the aid of **inherent steric hindrence of a serious type,** one may critically observe an ***exception*** **to the Saytzeff Rule** *i.e.*, the **Hoffmann Rule** is considered to be applicable predominantly.

The E_1-Mechanism: In true sense, one may regard $\mathbf{E_1}$ is a model to expatiate the specific kind of ***chemical elimination reaction***. $\mathbf{E_1}$ actually refers to the **unimolecular Elimination**; and hence, essentially possess the following specifications, namely:

1. It relates indeed to a **2-step process of elimination** *viz.*, ***Ionization*** and ***Deprotonation***.

- ***Ionization*: *i.e.,*** the *carbon-halogen* bond undergoes cleavage to render the formation of a **carbocation intermediate**; and
- ***Deprotonation*:** of the **carbocation entity**.

2. E_1-typically occurs with ***tert*-alkyl halides**, but is also possible with certain ***secondary*** **alkyl halides**.

3. Rate of reaction is largely influenced by the *actual concentration of the alkyl halide* being used since the ***formation of the carbocation*** is the **'slowest step'** [(*i.e.,* the *rate-determining step*)—that eventually implies the ***First*-order kinetics** (*unimolecular*)].

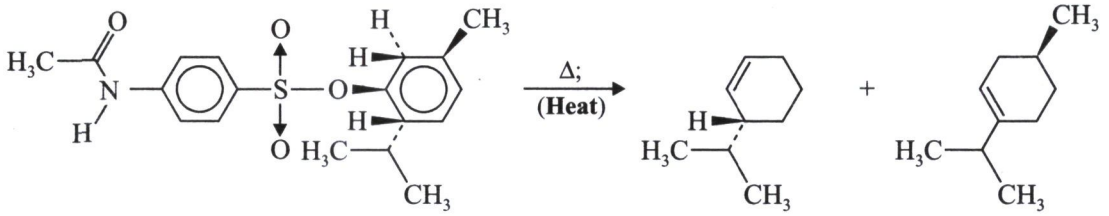
4. $\mathbf{E_1}$ reaction usually comes into play in the **absolute absence of a base or presence of only a weak base** (*plus acidic medium and high temperature*).

5. Interestingly, the **$\mathbf{E_1}$ reactions** do exhibit a close competition with the **$\mathbf{S_N1}$ reactions** since they significantly *do share a common* ***carbocationic intermediate*** (as stated above).

6. However, a ***secondary*** **Deuterium isotope** effect, being **slightly more than 1** (*usually 1-1.5*) is observed perceptively,

7. $\mathbf{E_1}$ reaction does not require any sort of **'antiperiplanar'** obligation. ***Antiperiplanar***: Only the ***axial*** **C—H bonds** in the *α-position* may be in such an **antiperiplanar position** with regard to the **trajectory of the H-nucleophile only** provided the **nucleophile** attacks *via* a **transition state (TS)**.

Example: Following is the typical example showing the ***'pyrolysis'*** of a certain **sulphonate ester of menthol**—as stated under:

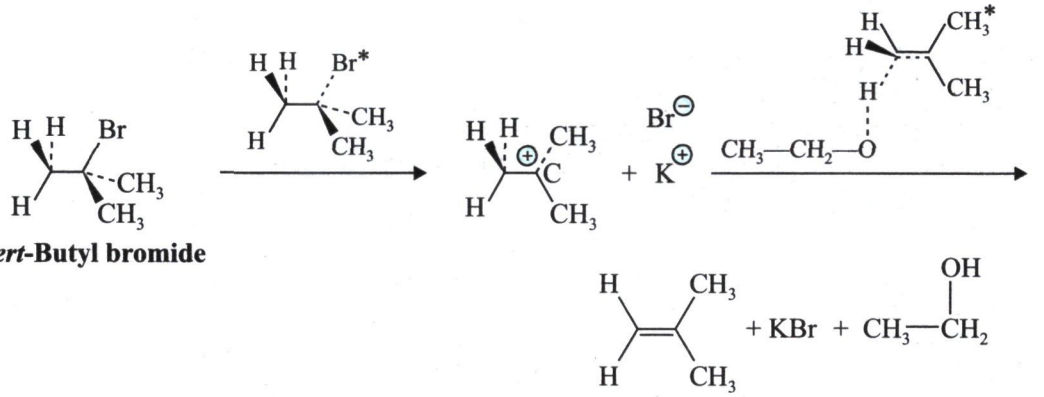


A Suphonate ester of Menthol **Product [A]** **Product [B]**

Comments: The reaction **product (A)** is duly obtained from the so-called **anti-periplanar elimination** phenomenon; whereas, the presence of **product (B)** implies a **positive indication** that an **$\mathbf{E_1}$-mechanism** is taking place predominantly.*

* Nash JJ *et. al.*: **Pyrolysis of Aryl Sulphonate Esters in the Absence of Solvent**, *J Chem. Edu.*, **85** (4): 552, 2008

8. Carbocationic Rearrangement Reactions: Another (*Scheme 2*) reaction being the **carbocationic rearrangement reactions**—which may be examplified by the typical reaction of ***tert*-Butyl bromide** with freshly prepared **potassium ethoxide** in absolute ethanol,—as depicted under:



***tert*-Butyl bromide**

Remarks: Thus, the **E_1 elimination** reactions do come into play with ***highly substituted* alkyl halides** due to the following *two* cardinal reasons:

- The ***highly substituted*** **alkyl halides** are invariably ***bulky*** in nautre-thereby limiting the room for the **E_2-one step mechanism**; and hence, the ***two*** **step E_1-mechanism** is always favoured preferentially.
- The ***highly substituted*** **carbocations** are observed to be much **more stable** *vis-a-vis* the **methy/*pri*-substituted cations**; and thus, such a **stability profile** provides an ample scope and time for the so-called **2-step E_1-mechanism** to take place elegantly.

21.2.2 β-Elimination Reactions—Bimolecular [or E_2-Elimination]

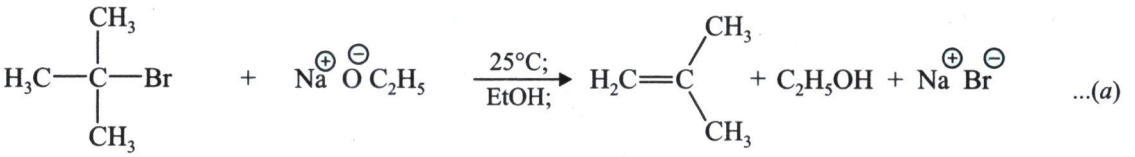
During the 1920s **Sir Christopher Ingold** duly put forward a model to explain a peculiar kind of **chemical reaction:** the **E_2 mechanism**. Here, the **E_2-stands** for the **Bimolecular Elimination**. Thus, the ensuing reaction essentially involves a ***single step*** wherein both substrate and the **bass** take part in the reaction.

In other words, the **mechanism** engages critically:

'Carbon-hydrogen and Carbon-halogn bonds'

that eventually undergo a cleavage to form a **double bond (C=C)** or **π-bond**. This **reaction** involves a ***base-promoted β-elimination***—that relates critically to the ***second*** **important reaction of 'Alkyl Halides'**.

Example: **Elimination of the elements of HBr from *tert*-Butyl bromide:**



...(*a*)

***tert* - Butyl bromide** **Sodium ethoxide** **Dimethyl ethene** **Ethanol** **Sodium bromide**

Let us now consider the following ***six*** vital and important aspects of the **E_2-elimination reaction,** namely:

- **Rate Law and Mechanism of E_2-Reaction,**
- **Leaving-Group Effects on the E_2-Reaction,**
- **Deuterium Isotope Effects in the E_2-Reaction,**
- **Stereochemistry of the E_2-Reacton,**
- **Regioselectivity of the E_2-Reaction** and
- **Internal Elimination (E_i)**

which shall now be treated separately in the sections that follows:

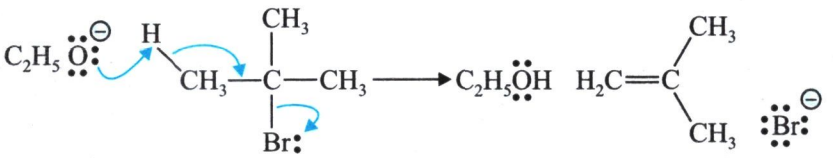
21.2.2.1 Rate Law and Mechanism of E_1-Reaction

It is indeed the **base-promoted β-elimination reactions**—that critically follow the course of a **rate law** which being ***second*** **order overall** and ***first*** **order in each reaction** perceptively.

We may have the following expression:

$$\boxed{\text{Rate} = k\,[(CH_3)C{-}Br]\,[C_2H_5CO^{\ominus}]} \qquad ...(b)$$

Hence, following is the **most probable mechanism** that stands quite consistent to the ***rate law,***—and may be expressed as under:



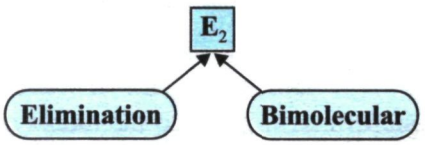
***tert*-Butyl bromide** ...(*c*)

Remarks: In fact, this kind of **mechanism**—essentially involves the so-called ***concerted removal*** of a **β-proton ($H^{\oplus}$)**:

- **by the aid of a *'base'*,** and
- **loss of a halide ion ($X^{\ominus}$),**

and hence, is termed as an **E_2-mechanism.**

Besides, all such reactions that usually take place by the **E_2-mechanism** are commonly known as the **E_2-reactions**. The precise and exact meaning of the so-called ***'nickname'*** **E_2**—is as stated under:



21.2.2.2 Leaving-Group Effects on the E_2-Reaction

It is, however, pertinent to state here that in the **mechanism of the E_2-reaction**, the most pivotal role of the **leaving halide moiety** is *more or less the same* as it is prevalent in the **S_N2-reaction**. Thus, it could be observed most elegantly that:

"its bond to C-atom is undergoing a cleavage; whereas, it critically takes on an *additional electron pair* to form the respective *halide ion* (X^-)".

As a result, it may not be surprising at all to find that the ensuing rates of **S_N2- and E_2-reactions** are duly affected vehemently almost in a similar manner—as **'changing the halide leaving moiety'**.

Thus, we may express the so-called—Relative Rates of the **E_2-reactions** as stated below:

$$\boxed{R—Cl < R—Br < R—I} \qquad ...(d)$$

Remarks: Based on the above observations we may infer that as in the **S_N2-reaction,**—the overall prevailing *reactivity difference* between the **alkyl bromides** and **alkyl iodides** is not great. In general, the **'alkyl bromides'** are invariably employed in the laboratory for carrying out the **E_2-reactions** so as to accomplish:

- **best optimum compromise of both reactivity and cost-effectiveness,** and
- **in commercial scale (large-scale reactions) are performed with *cheaper alkyl chlorides*.**

21.2.2.3 Deuterium Isotope Effects in the E_2-Reactions

It may be observed prominently that the underlying **mechanism in *Eqn. (c)*** suggests that a **proton** ($H^{\oplus}$) is being removed meticulously in:

'the prevailing *Transition State (TS)* of the ensuing E_2-reaction'.

Thus, we may further ascertain and test the said aspect of the **mechanism** by the help of:

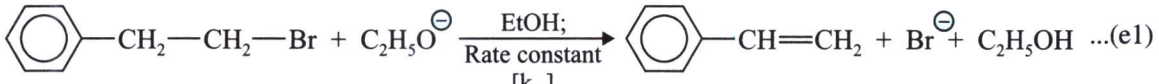
'a means whereby an H-atom is duly transferred in the so-called rate-limiting step of a reaction being studied',

i.e., a chemical entity (compound) wherein that H-atom gets replaced by its corresponding ***'isotope'*** **Deuterium**—which usually will react rather more sluggishly in the **same reaction**. Importantly, such an effect pertaining to the so-called:

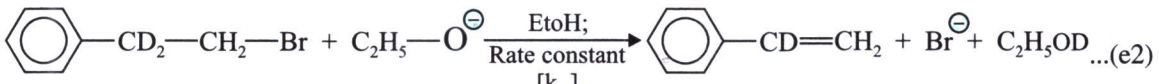
"isotopic substitution on the rates of reaction",

is invariably known as—**'primary Deuterium isotopic effect'**.

Example: The above episode may be expatiated further by taking into consideration the following **E_2-reaction of 2-phenyl-1-bromoethane being 'k_H'**; whereas, the rate constant for the reaction of its respective **β-Deuterium analogue being 'k_D'**,—as expressed under:



...(e1)



...(e2)

Primary Deuterium Isotopic Effect: It refers to the ratio k_H/k_D, and usually such **'isotopic effect'**—do fall within the range of **2.5-8** only. However, the k_H/k_D for the **Eqn. (e) is 7.1**.

Comments: Thus, the critical observation of the ensuing **primary** isotope effect having the aforesaid **magnitude** illustrates explicitly that the ensuing **'bond'** to a **β-H-atom** is meticulously broken in the so-called **rate-limiting step** of this reaction perceptively.

Theoretical Basis of Primary Isotope Effect: The fundamental theoretical basis for the primary isotope effect rests predominantly upon the so-called **relative strengths** of both ***C—H* and *C—D* bonds.**

Obviously in the very ***starting material***, the ensuing **'bond'** to the **heavier D** happens to be ***stronger*** *vis-a-vis* the **'bond'** to the **lighter isotope H**. Nevertheless, in the so-called **transition states (TS)** for both the aforesaid reactions one may observe specifically that—

- **the bond from H or D to sustain a rough approximation only;** and
- **the *'isotope'* undergoing an actual transfer virtually never gets bonded to anything (*i.e.*, it adopts an *'in fight'* strategy).**

Comments: Thus, one would safely infer that:

- **since there exists *'no bond'*,—hence there prevails no *bond-energy difference* existing between the *two* isotopes;**
- **the compound having the *C-D bond* commences usually at a lower-energy level *vis-a-vis* the compound having the *C—H bond*;** and
- **ultimately acquires relatively *more-energy level* so as to accomplish the desired *transition state (TS)* perceptively—as shown in Fig. 21.1.**

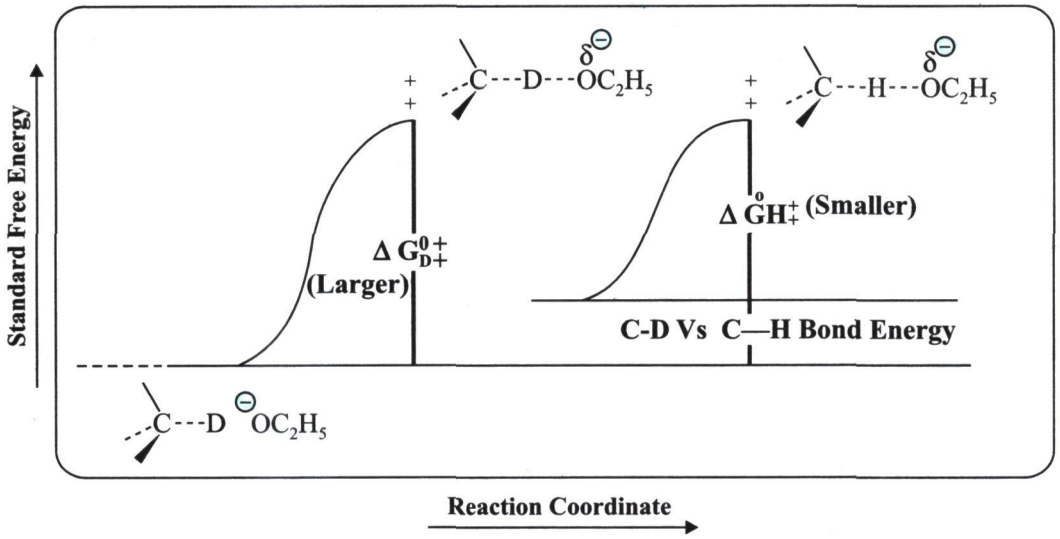


Fig. 21.1: Diagrammatic Representation of the Primary Deuterium Isotope Effect Showing the Stronger C-D Bond.

[The actual difference between the bond energies of C-H and C-D Bonds being largely exaggerated for the sake of illustration explicitly].

EXPLANATIONS

1. Obviously, the ***energy barrier*** or the ***free-energy*** of activation—pertaining to the chemical entity (compound) having ***C-D bond*** is found to be certainly greater perhaps due to the fact that:

'the overall net *rate-of-reaction* is smaller'.

2. In addition, it may be understood clearly that a **primary deuterium isotopic effect** is invariably observed only when:

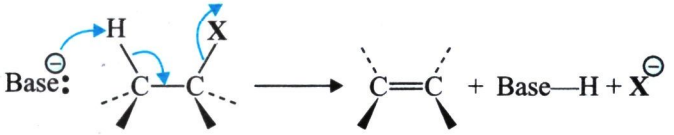
   "the hydrogen which gets transferred in the rate-determining step is duly substituted by *Deuterium* (D)".

3. Interestingly, the corresponding substitution of *other H-atoms* with **Deuterium (D)** virtually shows either *little or absolutely no effect upon the rate of reaction.*

21.2.2.4 Stereochemistry of the E_2-Reaction

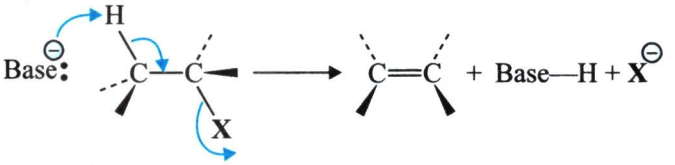
In a broader sense, an ***elimination reaction*** may come into play by the help of ***two*** **altogether *divergent* stereochemical manners** with respect to the ***elimination of H—X*** from a general ***'Alkyl Halide'***,—as depected under:

(*a*) *Syn* - Addition



...(f1)

(*b*) *anti* - Elimination



...(f2)

Remarks: These essentially include:

1. ***syn*-Elimination:** In this episode the **H** and **X** usually leave the so-called **alkyl-halide molecule** from the **same sides**.
2. ***anti*-Elimination:** In this case, the **H** and **X** invariably leave the ***alkyl-halide molecule*** from the ***opposite sides***.

NOTE: **It may also be observed critically that the *syn*-elimination is conceptually almost the reverse of a *syn*-addition; and *anti*-elimination is conceptually the reverse of an *anti*-addition.**

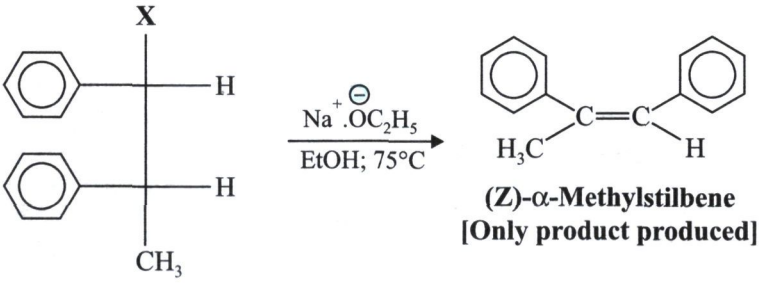
Investigation of Stereochemistry: In fact, the **investigation of the stereochemistry** of an ***elimination reaction*** essentially needs that:

'both α-and β-C-atoms necessarily be the 'stereocentres',"

in either of the starting **alkyl halide** and **product alkene**.

Therefore, in all such instances, one may take cognizance of the fact based on experimental results that **a majority of the E_2-reaction are *stereoselective* in nature** *viz.*, shows ***anti*-elimination**.

Example: The above analogy may be exemplified as under:



...(g1)

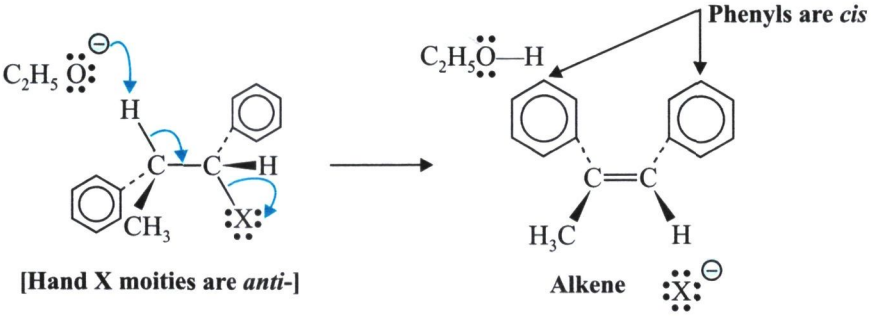
(X = Br, Cl)
[Fischer Projection]

(Z)-α-Methylstilbene
[Only product produced]

Hence, in order to ascertain fully that it is an ***anti*-elimination reaction**, we may draw the so-called—**'*alkyl-halide molecule*'** in such a conformation wherein:

"H-atom and Halogen (X)-atom intended to be eliminated are *anti*—,*i.e.*, located strategically at a *dihedral angle of 180°*".

It may be shown explicitly as under:



...(g2)

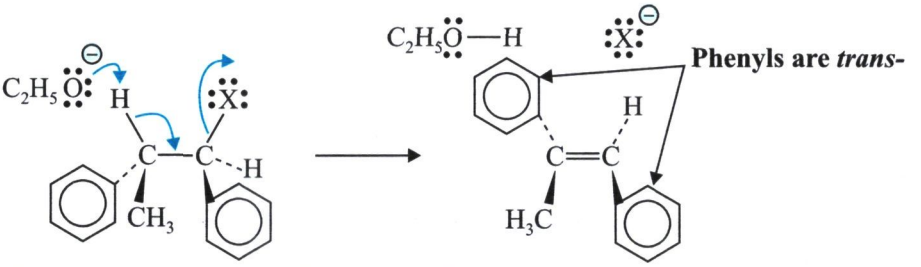
[Hand X moities are *anti*-]

Alkene

Remarks: It may be observed critically that both **H** and **X** (*halogen*) are eliminated specifically from these positions, whereas, the **phenyl moieties** are duly present on the **same side (*cis*=) of the molecule**; and, therefore, should usually and up in a ***cis*-relationship** (*configuration*) in the ultimate product **'alkene'**.

***Points to Ponder*:** It is, however, pertinent to state here that the so-called ***syn*-elimination** may eventually give rise to the other **alkene stereoisomer** (Y), but **not observed in reality**.

We may express the above episode as under:



...(g3)

[H and X Moities are *syn*]

[Not-observed in reality]

Preference for *anti*-Elimination: In true sense, the ***anti*-elimination** is preferred overwhelmingly for ***three* good reasons**, namely:

- ***First*:** The ***syn*-elimination** takes place usually *via* a typical **transition state (TS)**, which essentially possesses a so-called ***'eclipsed conformation'***—as illustrated in Fig. 21.2 (*a*); whereas, the ***anti*-elimination** comes into play *via* a **transition state (TS)** that critically has a ***staggered conformation***—as depicted in *Fig. 21.2 (b)*.

Comments: Since the ***'eclipsed conformations'*** are observed to be unstable, the **transition state (TS)** related to ***syn*-elimination** is certainly found to be relatively **less stable** *vis-a-vis* the **transition state (TS)** for the ***anti*-elimination.**

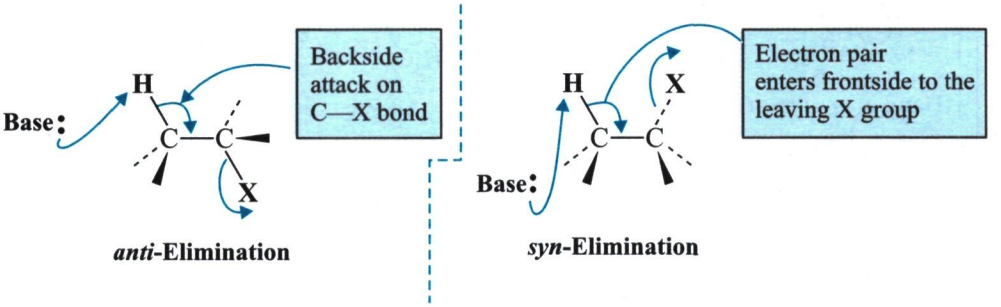
Thus, as a result, the ***anti*-elimination** is found to be much faster in nature.

- ***Second*:** The second prominent reason refers to the ***anti*-elimination** phenomenon which is regarded to be the most preferred modality; besides, both the ***'base'*** and the ***'leaving moiety'*** do exist on the **opposite sides of the molecule** prevalently,—out of each other's way.
- ***Third*:** The ultimate **calculations** pertaining to the so-called ***transition-state energies*** by exclusively making use of the **'molecular orbital theory'** do exhibit obviously that:

  "*anti*-elimination is certainly much more favourable",

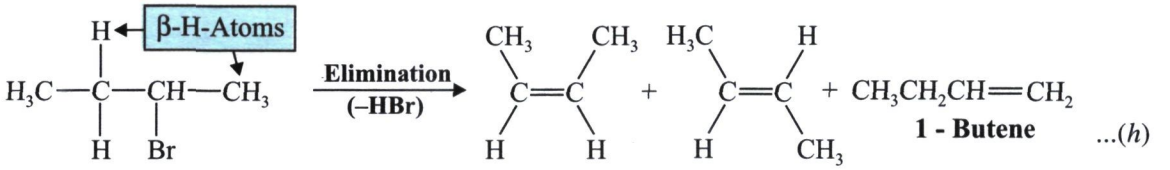
  the overall reasoning does relate to the underlying fact that an ***anti*-elimination** phenomenon does involve specifically the—**'all backside electron displacements predominantly'**—as the so-called ***S_N2 reaction***.

  The above expression of thoughts may be expatiated as under:



21.2.2.5 Regioselectivity of the E_2-Reaction

It has been duly established that as and when an **'alkyl halide'** possesses more than one specific type of **β-H-atom,** ***more than one alkene product*** may be formed,—as given under:



...(*h*)

2-Bromobutane ***cis*-2-Butene** ***trans*-2-Butene**

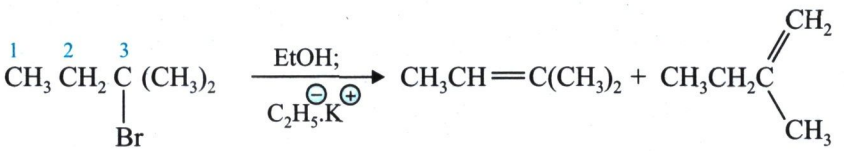
The above reactions critically focuses upon which of the **most probable reaction products** is generally preferred and why.

Salient Features: These essentially comprise:

1. Formation of Most Stable Alkene Isomer: In a particular instance when we use only the so-called ***simple*** **alkoxide bases** *viz.*, **methoxide [CH_3O^-], ethoxide [$C_2H_5O^-$],**—the most preferred product of an **E_2-reaction** is invariably the **most stable alkene isomers.**

Comments: We have already observed that the **'most stable alkene isomer'**—do belong to the class having the so-called ***most alkyl branches*** at the **specific C-atoms** of the **olefinic** (or *double*) **bond.**

However, these **isomers** are, in fact, duly obtained in *largest and optimized quantum*, and may be expressed as under:



...(i)

3-Dimethyl propyl bromide (An alkyl branded halide) | **(Potassium ethoxide)** | **(Yield = 70%)** | **(Yield = 30%)**

2. Besides, it may also be observed explicitly that in the above reaction,—the ***'alkene isomer'*** so formed in relatively **smaller quantum** would be most favoured with respect to the **statistical grounds** perceptively.

In other words, ***six*** **equivalent H-atoms** may be duly lost right from the **alkyl halide** (so formed) to result the formation of this **alkene**; however, out of the whole lot only ***two*** **H-atoms** could be eliminated actually to yield the **'other *alkene*'**.

NOTE: **Importantly, the *other alkene* is the one obtained in major quantum that shows that *certain other factor (s)* is also functioning simultaneously.**

3. It is, however, pertinent to state here that the inherent observed predominance of the corresponding—**'more stable alkene isomer'** fails to be delivered right from the so-called ***equilibration of the alkenes***—themselves,—since the:

"alkene products are indeed found to be more stable under the existing parameters of the reaction".

Remarks: As we know that once the **product mixture** is duly formed, ***does not alter*** the so-called:

'distribution pattern of the resulting products',

—that eventually should reflect directly upon the relative rates at which they are generated in its normal course. Therefore, we have left with no other choice than to:

'look for the logical and acceptable explanation related to the transition—state theory'.

4. The **transition state (TS)** for the ensuing **E_2-reaction** may be observed as a structure that critically lies somewhere between the **alkyl halide (R—X)** and **alkene**. In addition, it may be

visualized that to the extent the so-called—**'transition state (TS)'** actually resembles the **alkene**, it virtually gets stabilized by means of the ***same factors*** which stabilize the **alkenes**; and hence, the **branching of the double bond** designates one such factor predoninantly.

5. Besides, a typical reaction which may actually result ***two*** **alkene products** distinctly does relate to ***two*** **different reactions** that are found to be in **close competition to each other** *i.e.,* with its ***own transition state (TS)***. Thus, ***two*** **separate situations may arise**:

- ***First*: having certain more prevalent branching at the so-called developing double bond—showing the *faster reaction*;** and
- ***Second*: the reaction having transition state (TS) of *lower energy profile*; and thereby more product is obtained *via* the transition state (TS) perceptively.**

The Zaitsev's Rule: The **Zaitsev's Rule** refers to an **elimination reaction which forms predominantly the most highly branched alkene isomers**. It is sometimes also termed as **Zaitsev Elimination** after **Alexander M Zaitsev [1841-1910]**—a Russian chemist—who observed critically the aforesaid phenomenon in **1875**. Thus, very much akin to the well-known **Markownikoff's Rule** solemnly, describes the ***regioselectivity*** **of hydrogen—halide addition** to the **'alkenes'** the **Zaitsev Rule** also describes the ***regioselectivity*** **of the elimination reactions** perceptively. Besides, just like the **Markownikoff's Rule**, the **Zaitsov Rule** is exclusively a descriptive rule; and hence, it fails to make any sort of effort so as to expatiate this **transition state (TS)** at all.

Remarks: In a broader perspective, whenever an **alkyl halide** possesses **more than one type of β-H-atom**,—a mixture of alkenes is obtained prevalently in its **E_2-reaction**. The actual formation of a mixture definitely suggests that the ultimate yield of the **intended *alkene* isomer** gets reduced articulately. Besides, since the **'*alkenes*'** duly present in such mixtures do represent:

"the *isomers* of closely related chemical structure",

they do eventually possess identical **boiling points**, and hence, are rather **difficult to seggregate**. As a result, the **optimized utility of E_2-elimination** for the actual ***preparation of alkene*** usually takes place when the **alkyl halide (R—X)** critically bears **only one type of β-H-atom** plus **only one alkene product is possible eventually.**

21.2.2.6 Internal Elimination (Ei)

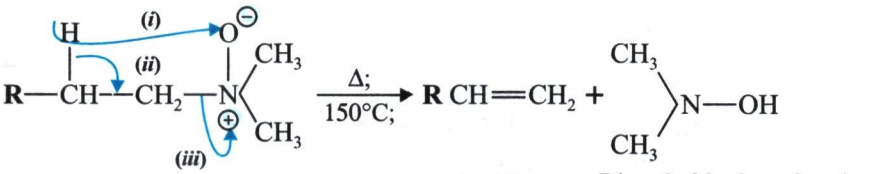
It is also known as—**Pyrolytic *syn*-Elimination**. Importantly, these reactions invariably come into play *via* a ***concerted reaction profile***; and subsequently, through a so-called **cyclic-transition state** that essentially involves the critical:

"intramolecular proton transfer followed by its elimination to yield an '*alkene*',"

Mechanism of Internal Elimination (Ei): It may be observed critically that the ultimate knock-out of the **leaving moiety** as well as the **proton ($H^{\oplus}$)** from the same **side of the olefinic (C=C) bond** (*i.e.,* the ***syn*-elimination**) is caused exclusively on account of the prevalent—**'cyclic transition state (TS)'**. Importantly, they are predominantly the so-called **thermal eliminations**; and hence, do come into play in:

- **Acetates [$CH_3COO^{\ominus}$]** • **Amine Oxides [$-\overset{\oplus}{N}(Me)_2$]** and • **Xanthates [$RO-\overset{\overset{S}{\|}}{C}-S\ Na$]**

Thus, we may have the following expression:



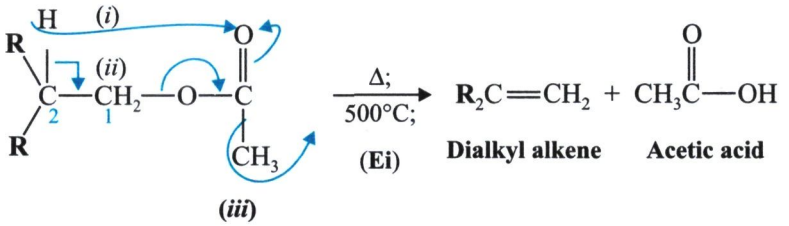
where, (*i*) : Depicts removal of a proton ($H^{\oplus}$)

(*ii*) : Shifting of a covalent bond to form a **π-system**; and

(*iii*) : Elimination of the **'Leaving Moiety'**.

21.2.2.6.1 Internal Elimination (Ei) in Isomerization of Enol into a Carbonyl Compound [Cope Reaction]

It may be exemplified as under:



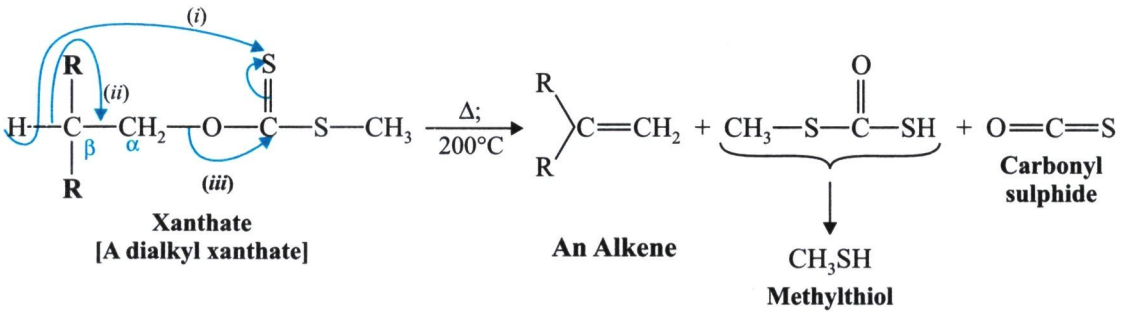
2-Dialkyl propyl acetate

[(*i*), (*ii*) and (*iii*)—are as explained above]

Thus, 2-alkyl propyl acetate undergoes **internal elimination (Ei)** at 500°C to yield a mole each of **dialkyl alkene** and **acetic acid**.

21.2.2.6.2 Internal Elimination (Ei) in Xanthates

It may be expatiated as given under:



Thus, a mole of **xanthate** on being subjected to the **internal elimination (Ei)** at 200°C yields a mole each of an **'alkene'** and a **carbonyl disulphide**, while the latter cleaves into a mole each of **methyl thiol** and a **carbonyl sulphide** respectively.

Remarks: These essentially include:

1. In a situation, when the **conjugate moiety** is absent at the **β-C-atom** (*shown above*),—the resulting composition of the **end-product** is determined by the **H-atoms** that are readily available at such **β-C-atoms**. However, in the presence of a definite **conjugate moiety** located strategically at the **β-C-atom** (*see in the above example*),—the **elimination** does proceed to produce meticulously the so-called ***Conjugate Olefin*** perceptively.

NOTE: The 'IUPAC'—designatin of Ei-reaction is represented by $D_E D_N A_n$.

2. **Evidence of Ei-Reaction:** The distinct and concrete evidence for the existence of the **Ei-reaction actually comes from the kinetics** *viz.*,
   - ***First* order kinetics:** Here, only one specific molecule of the substrate gets involved intimately in the ensuing reaction since there is absolutely little critical effect due to the so-called-***'free radical inhibitors'***. Therefore, no **'free-radical mechanism'** is involved at all; and hence, the *entire investigative study* of the aforesaid mechanism depicts evidently the so-called:

     'critical involvement of the *syn*-elimination'.
   - **The Ei-Reaction:** It essentially follows the ***syn*-stereochemistry**. Thus, an ***erythro*-isomer** particularly results into a ***trans*-olefin;** whereas, a ***threo*-isomer** yields a ***cis*-olefin.**

NOTE: However, in a respective *'cyclic structure'*, the specific prompt availability of the *cis*-hydrogen atom only on one side affords *elimination in that particular direction.*

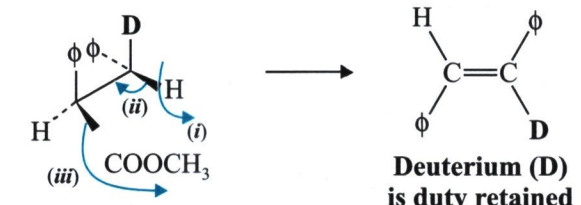
21.2.2.6.3 Elimination of the Leaving Moiety

It is vividly demonstrated by showing the so-called—

'retention of Deuterium (D) in the end-product obtained duly from the *erythro*-isomer perceptively; whereas, the reaction with *threo*-isomer,—the Deuterium (D) is not retained at all and gets eliminated'.

Example: The above conceptualized thoughts and analogy may be duly demonstrated by the help of the following glaring example that crucially involves the *'erythro'*—and *'threo*—isomers' of **1-acetoxy-2-deutero-1, 2-diphenyl ethane**, wherein the only gross difference being the ensuing ***configuration of deuterium (D) and hydrogen (H)*** around the **C-atom**,—as shown under:

(*a*) ***erythro*-Isomer**



***erythro*-isomer**
[H is *syn* wrt acetoxy]

Deuterium (D) is duty retained

(*b*) ***threo*-Isomer**



***threo*-isomer**
[Deuterium (D) is *syn*-wrt acetoxy]

[Deuterium (D) is eliminated]

[**where**: (*i*) = Elimination; (*ii*) = Shifting of σ-Bond to form π-Bond; and (*iii*) = Removal of the'*Leaving Moiety*']

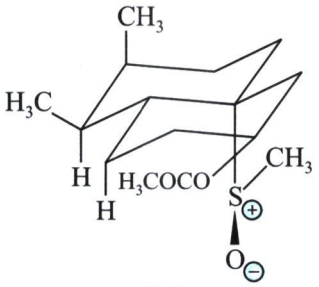
The Stereochemical Aspect of Internal Elimination (Ei): Based on the theoretical considerations arrived due to an array of experimental evidences it has been observed critically that the **'*syn*-elimination'** may also be regarded to involve—***'a pair of steroidal molecules'*: *viz.*,**

- **3 β-acetoxy-(R)-5α-methyl sulphinyl-cholestane (A);**
- **3 β-acetoxy-(S)-5α-methyl sulphinyl cholestane (B);**

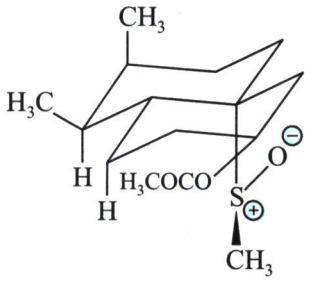
that critically differ with respect to the inherent strategical positions of:

- **Oxygen (O)** and • **Methyl (CH_3) moiety,**

around the **sulphur (S)** atom,—as shown under:



[A]



[B]

- **Pyrolysis** of **[A]** afford the **elimination** to **all the *four* sides**; whereas, the **pyrolysis** of **[B]** result the **elimination** to **all the *six* sides**.
- Orientation of the **Ei-reactions** may be eventually decided by the established **Hoffmann's Rule** (*i.e., **solely based upon the actual availability of the β-H-atoms in the chemical entity***).

Suggested Reading

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❑❑❑

Chapter 22

Electrocyclic Reactions

LESSONS AT A GLANCE

22.1 Introduction
22.2 Interconversions of Dimethylcyclohexadienes and 2,4,6-Octatrienes
22.3 Thermal Cyclization of Substituted Butadienes
22.4 Electrocyclic Reactions in Organic Synthesis

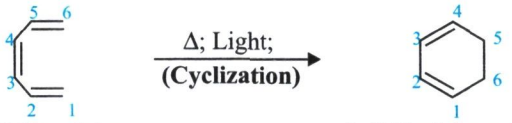
22.1 INTRODUCTION

The fundamentals of the **electrocyclic reactions** essentially lies on the fact that under the critical influence of either **heat** or **light**,—a **conjugated polyene system** may be subjected to the phenomenon of ***'isomerization'*** to result in the formation of a **'cyclic compound'** having a single bond existing between the:

'terminal C-atoms of the original conjugated system'.

The above episode could be possible perhaps due to the disappearance of the **double bond** and subsequent shifting of the ***residual double bonds*** from their respective positions.

Example: It may be explicitly demonstrated when **1,3,5-hexatriene** gives rise to the production of **1,3-cyclohexadienes,**—as given below:



1, 3, 5-Hexatriene **1, 3-Cyclohexadiene**

Interestingly, the so-called **'reverse process'** may also occur, whereby a ***single-bond gets duly cleaved*** and a **'cyclic compound'** obtained with an ***open chain*** **polyene**.

Example: **Cyclobutenes** are duly converted into respective—**'Butadienes'**:

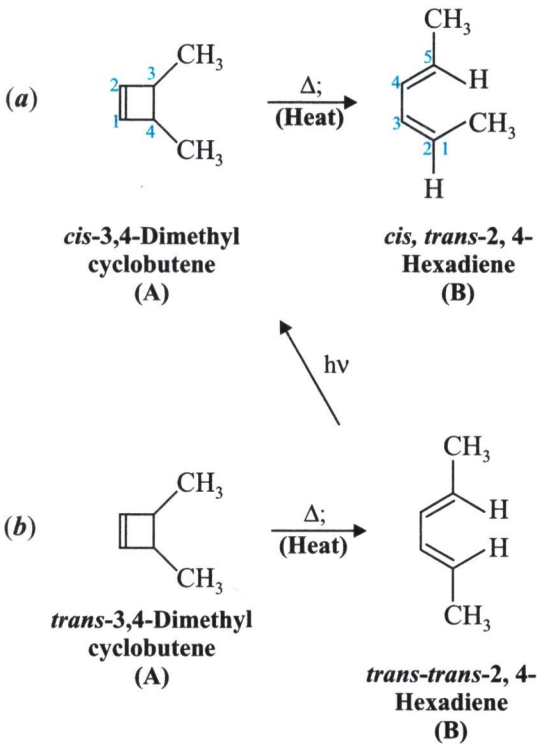


Cyclobutene **1, 3-Butadiene**

In short, such ***classical*** **interconversions** are invariably termed as—**Electrocyclic Reactions**.

Importance of Electrocyclic Reactions*:** It may be worthwhile to state here that it is the actual underlying ***electrochemistry **of electrocyclic reactions** which is of immense interest and utility to an **organic chemist**. Thus, one should have certain **appropriately substituted molecules**.

❑ **Interconversion of 3, 4-Dimethylcyclobutene (A) and 2, 4-Hexadiene (B):** Let us look into the following ***two*** **interconversions**, namely:



EXPLANATIONS

These essentially include:

1. It is known that **cyclobutene** does exist as: ***cis*-and *trans*-isomers.**
2. The **hexadiene** exists in ***three*** **distinct forms**, namely:
   - ***cis*-form** - ***cis*, *trans*-form** and - ***trans*, *trans*-form.**
3. Importantly, the ***cis*-cyclohexadiene** usually gives only one of the aforesaid ***three*** **isome dienes**; whereas, the ***trans*-cyclobutene** produces an altogether **different isomer**,—as shown above.
4. Therefore, the reaction elegantly designates a so-called:

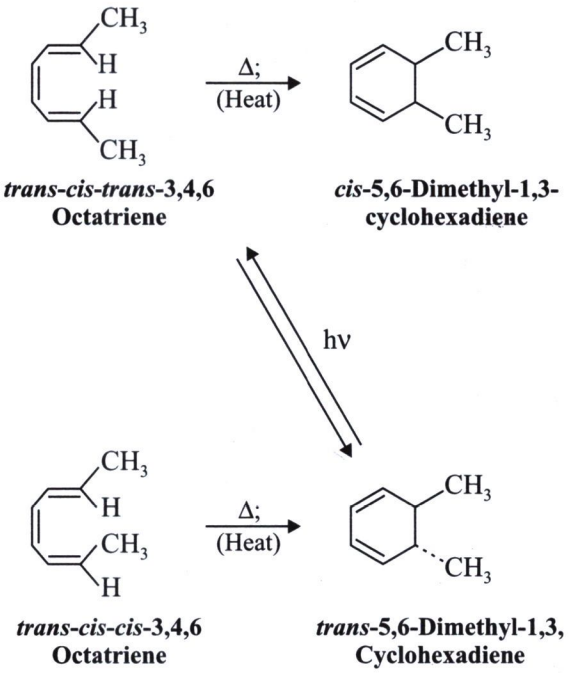
   "completely stereoselective and completely stereospecific".
5. Besides, the critical and specific—**'photochemical cyclization'** of the resulting ***trans*, *trans*-diene** provides a ***different cyclobutene*** right from the one from which the so-called ***'diene'*** is generated by virtue of the ***theremal*-ring opening*** **phenomenon.**

---

* That is, **heat-promoted**.

22.2 INTERCONVERSIONS OF DIMETHYLCYCLOHEXADIENES AND 2,4,6-OCTATRIENES

The above **interconversions** are also found to be both **stereoselective** and **stereospecific**,—as depicted under:



***trans-cis-trans*-3,4,6 Octatriene** — ***cis*-5,6-Dimethyl-1,3-cyclohexadiene**

***trans-cis-cis*-3,4,6 Octatriene** — ***trans*-5,6-Dimethyl-1,3, Cyclohexadiene**

Remarks: In this particular case, two, **thermal** and **photochemical reactions** distinctly ***differ in stereochemistry***. However, if we closely serutinize the aforesaid structures, we may observe the following cardinal aspects vividly:

- **stereochemistry of the trienecyclohexadiene *interconversions* is observed to be just the *opposite* to that of the respective *diene-cyclobutene interconversions*;**
- **importantly—the so-called *thermal reaction e.g., cis*-methyl groups usually present in the *cyclobutene* get changed to *cis*-and *trans*-in the corresponding *diene*, whereas, the *cis*-methyl group present critically in the cyclohexadiene are found to be *trans*- and *trans*-in the so-called related '*triene*'.**

Mechanism of Thermal Reactions: First of all let us examine the **thermal cyclization** of a ***disubstituted butadiene* [RCH=CH—CH=CHR]**. Fig. 22.1 illustrates the **1, 3-butadiene configuration of π-electrons** both in the **ground state** (*low energy state*) and the ***first* excited state** (*high-energy state*):

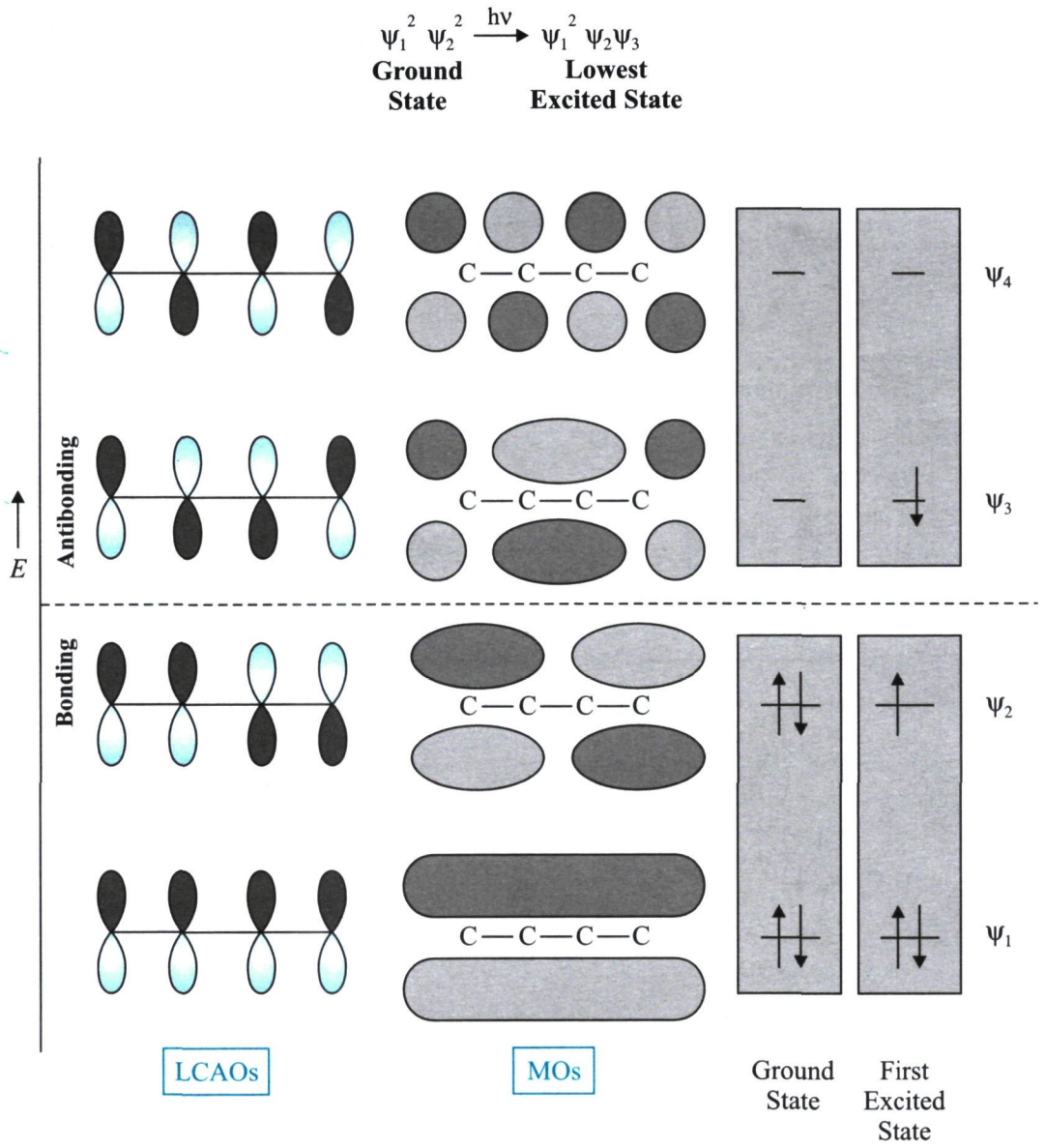


Fig. 22.1: The Typical Example of 1, 3-Butadiene: Showing the Configuration of π-Electrons in both Ground State and First Excited State.

[***Adapted From***: Morrison RT *et. al*: **Organic Chemistry**, 7th ed., Pearson Prentice Hall, New Delhi, 2012.]

Based on Fig. 20.1, one may critically take cognizance of the fact that the **highest occupied molecular orbital (HOMO)** of a ***conjugated diene*** is ψ_2.

Obviously the **electrons** present specifically in the *orbital* shall eventually create the bond which closes the ring ultemately. Nevertheless, the bond formation essentially needs ***overlap***; and hence, in this instance:

"the overlap of lobes upon the C-atoms: *C-1* and *C-4*, of the diene,—as depicted in the front C-atoms in Fig. 20.2".

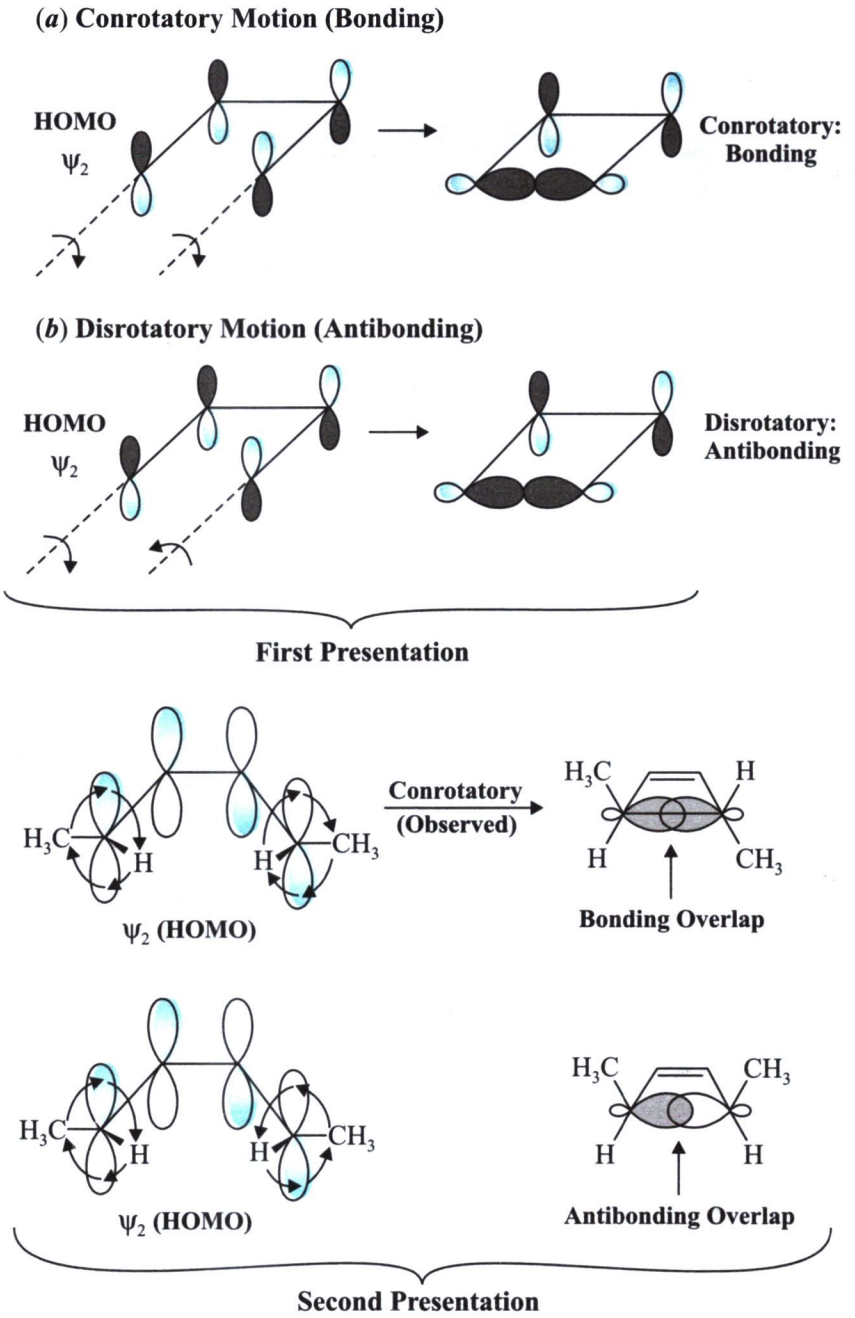
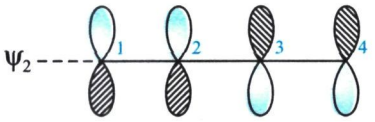


Fig. 22.2: Diagrammatic Representation of Thermal Cyclization of a 1,3-Butadiene to the Corresponding Cyclobutene. (*a*) The Conrotatory Motion Leads to Bonding; and (*b*) Disrotatory Motion Leads to Antibonding.

***Conjugated Diene*:** It may be shown explicitly as under



The HOMO of *Ground State*

Conjugated diene

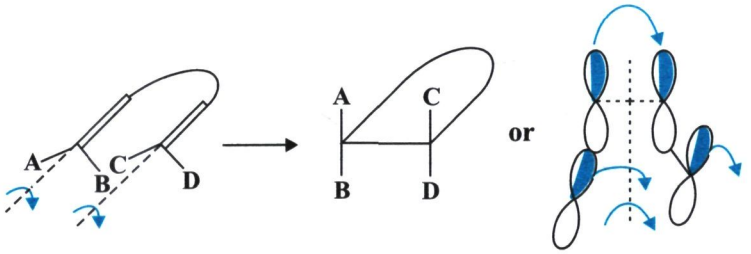
Comments: Thus, for bringing these ***'lobes'*** into position to accomplish perfect overlap there should be **actual rotation** around ***two*** **bonds:**

- **C (1)—C (2) and**
- **C (3)—C (4).**

The above mentioned rotation may be brought into effect in *two* **different manners,** such as:

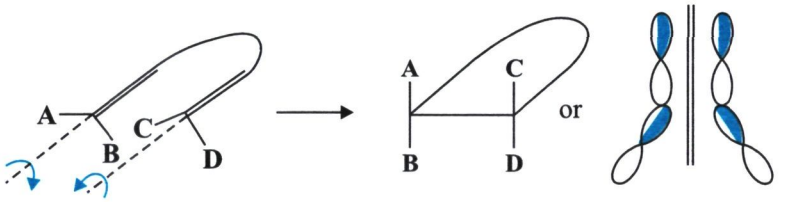
- **Conrotatory Motion:** In this case, the **bonds invariably rotate in the same direction,**—as shown under:

Conrotatory



NOTE: **In a *Conrotatory process* the observed symmetry about the *C2-axis* of rotation is being adequately maintained throughout the reaction.**

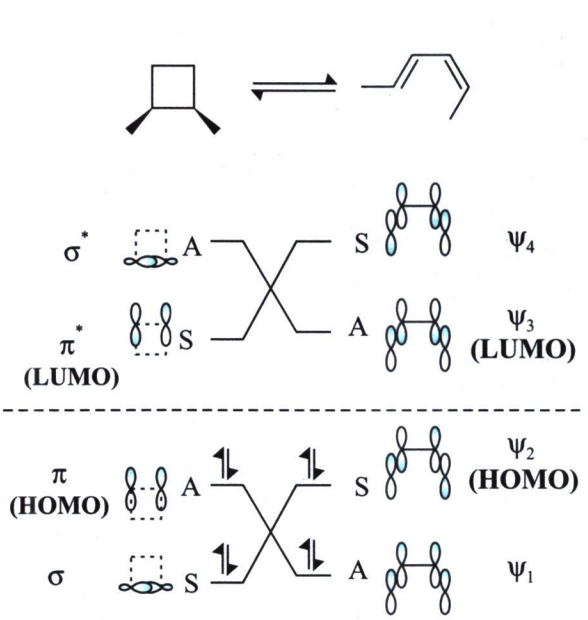
- **Disrotatory Motion:** In this instance, the **bonds rotate in opposite direction,**—as depicted below:



NOTE: **In a disrotatory process the symmetry about the *reflection plane* is duly maintained throughout the reaction.**

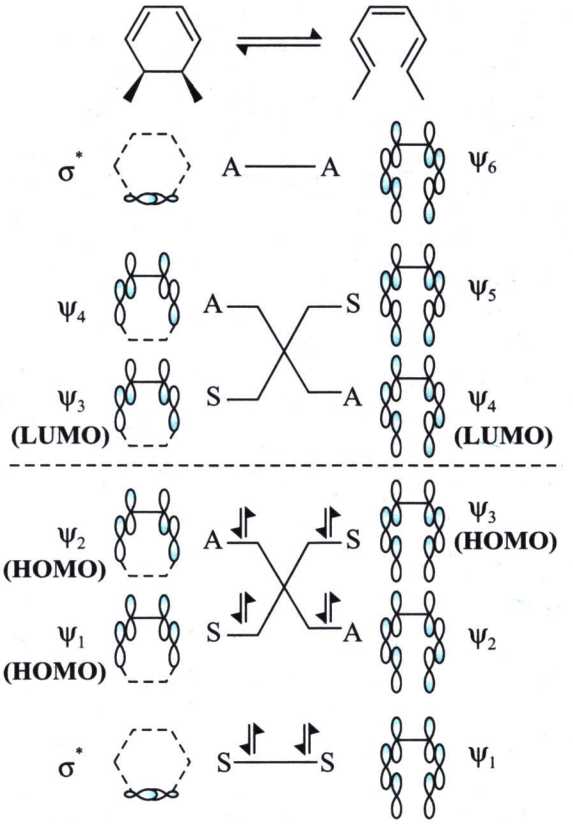
Fig. 20.3 illustrates the **'Correlation Diagrams'**—that eventually connect the so-called ***molecular orbitals*** of the reactant to those of the product having the ***same symmetry***,—may now be constructed explicitly for the ***two*** **distinct phenomenon***.

* **The Conservation of Orbital Symmetry,** *Acc Chem Res.*, **Vol. 1,** pp: 17-22, 1968.



Correlation Diagram for the allowed Conrotatory ring opening of 3, 4-dimethylcyclobutene

LUMO = Lowest Unoccuied Moleculr Orbital
HOMO = Highest Occupied Molecular Orbital



Correlation Diagram for the allowed Disrotatory ring opening of 5,6-dimethylcyclohexa-1,3-diene

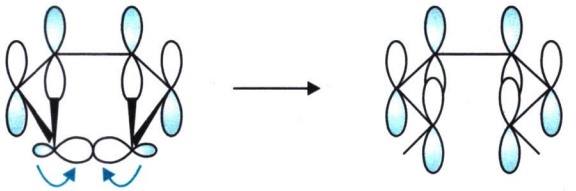
S = symmetric to symmetry element
A = antisymmetric to symmetry element

Fig. 22.3: Illustrates the Correlation Diagrams Indicating only a **Conrotatory Ring Opening** of 3,4-Dimethylcyclobutene; whereas, only a **Disrotatory Ring Opening** of 5, 6-Dimethylcyclohexa-1,3-diene.

Comments: These essentially include:

1. In both ring-opening episodes (*viz.*, **Conrotatory** and **Disrotatory**) the **symmetry is allowed perceptively**.
2. Besides, in these particular cases the so-called **optimized orbital overlap** take place in the **transition state (TS)** exclusively.
3. As a result, the **product(s)** so obtained would certainly be in a:
   "*ground state* (low-energy form) rather than an *excited state* (high-energy form)".

Frontier Molecular Orbital Theory (FMOT): According to the **FMOT**—the ***sigma (σ) bond*** present strategically in the **ring system** shall open in such a manner that the **resulting orbitals** will possess more or less the **some symmetry** as that of the **HOMO** of the end-product*,—as shown under:



HOMO of Hexatriene



HOMO of Butadiene

Remarks: Amazingly, for the **5, 6-dimethyl cyclohexa-1, 3-diene,** only a **Disrotatory** mode would eventually result in its ***p*-orbitals** essentially possessing the *same kind of symmetry* as that of the **HOMO of hexatriene**. Thus, for the respective: **3, 4-dimethylcyclobutene**, only a **Conorotatory** mode would result in the so-called ***p*-orbitals** possessing the **identically symmetry as the HOMO of butadiene.**

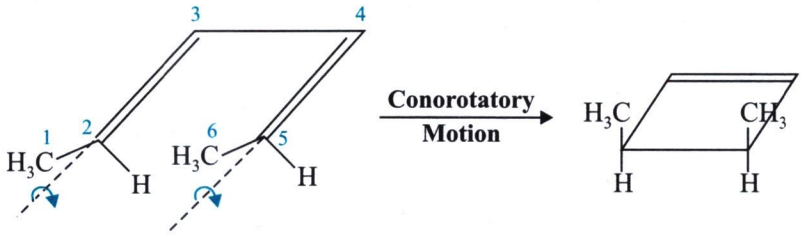
22.3 THERMAL CYCLIZATION OF SUBSTITUTED BUTADIENES

It has been proven and established that the **Conrotatory Motion** which gives rise to:

'the stereochemistry being observed actually'

Fig. 22.4 shows the **thermal cyclization of the substituted butadienes** and also the ***visualized stereochemistry*** depicting the **Controrotatory Motion** explicitly

(*a*) **Conrotatory Motion [*cis*, *trans*-2, 4-Hexadiene]**

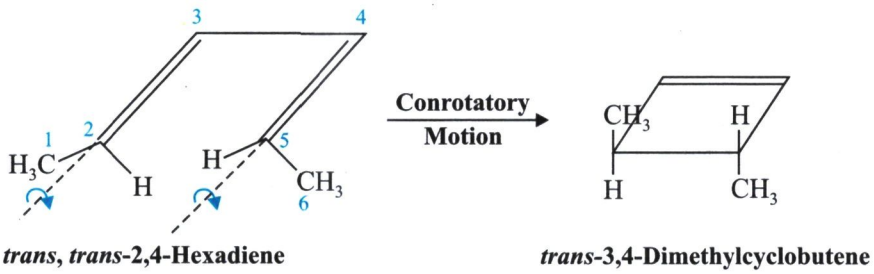


***cis*, trans-2,4-Hexadiene** ***cis*-3,4-Dimethylcyclobutene**

(Contd...)

* Fleming I: **Frontier Orbitals and Organic Chemical Reaction**, John Wiley and Sons Ltd., New York, 1976.

(*b*) **Conrotatory Motion [*trans*, *trans*-2, 4-Hexadiene]**



***trans*, *trans*-2,4-Hexadiene** ***trans*-3,4-Dimethylcyclobutene**

Fig. 22.4: Diagrammatic Representation of Thermal Cyclization of Substituted Butadiene: Showing Stereochemistry Acertaining the Conrotatory Motion.

Mechanism of Photochemical Reactions: In the spectacular ***ring-opening phenomenon*** of ***trans*-3,4-dimethylcyclobudiene** being performed strictly under the influence of the so-called **photochemical parameters**—the resulting **Electrocyclization** will come into play *via* the **Disrotatory Mode** elegantly instead of the **Conrotatory Mode**,—as may observed explicitly in the following **correlation diagram** [*Fig. 22.5*]—for the permitted **excited state ring opening reaction.**

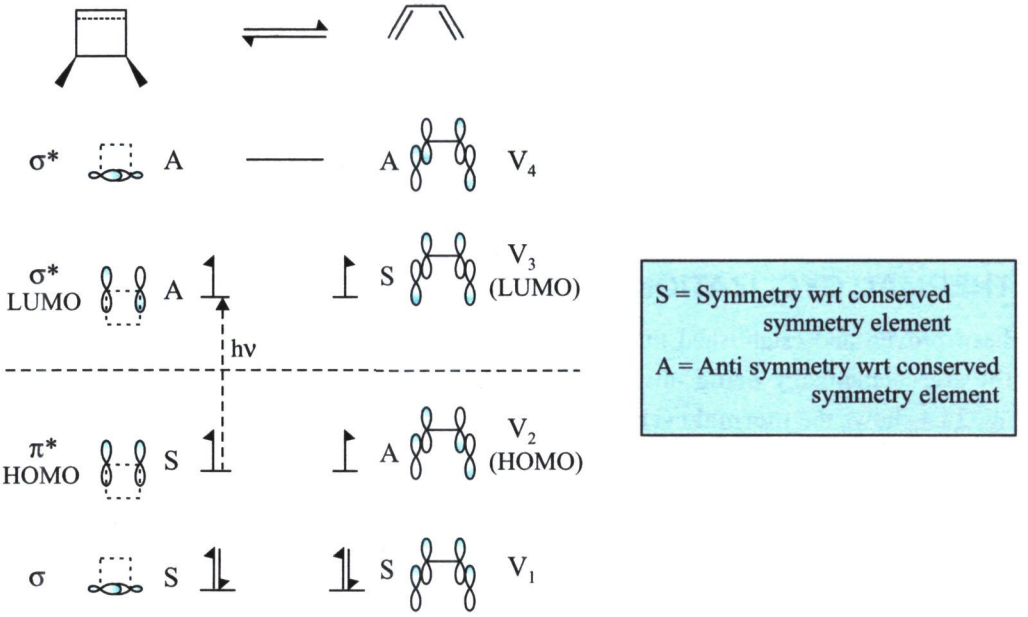
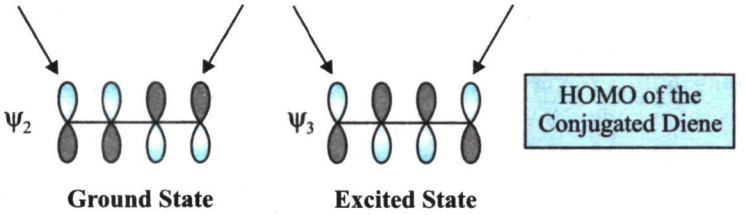


Fig. 22.5: The Correlation Diagram for the Excited State Disrotatory Ring-Opening Cis-3,4-Dimethyl cyclobutene.

Opposite Stereochemistry in the Photochemical Reaction: It has been duly observed that—**'upon absorption of light the *Butadiene* gets converted into the respective excited state (as *shown in Fig. 22.1*), wherein one electron from ψ_2 has been raised to ψ_3'.**



Remarks: From the aforesaid representation, we may critically observe that the so-called maximised orbital is ψ_3; hence, it is the electron here which we are actually concerned with. However, ψ_3 (*i.e.*, the *relative symmetry* of the **end C-atoms** is found to be just opposite to that in ψ_2.

Therefore, it is now the so-called ***Disrotatory Motion*** which predominantly holds together the specific lobes belonging to the ***same phase***; and hence, the **stereochemistry** gets reversed perceptively,—as could be seen in Fig. 22.6.

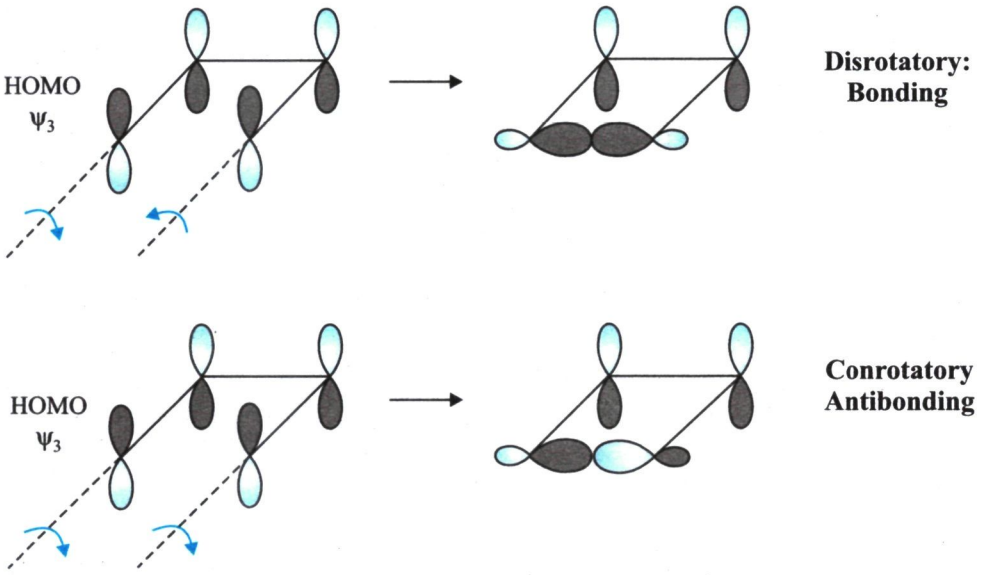


Fig. 20.6: The Photochemical Cyclization of 1, 3-Butadiene to Cyclobutene. The Disrotatory Motion Ultimately Leads to Bonding and **Conrotatory Motion** Leads to Antibonding Phenomenon.

Thermal Cyclization of Disubstituted Hexatriene [RCH=CH—CH=CH—CH=OH]: Let us now examine the **thermal cyclization of disubstituted hexatriene**—the so-called ***electronic configuration*** of which is being shown in an elaborated manner in Fig. 20.7.

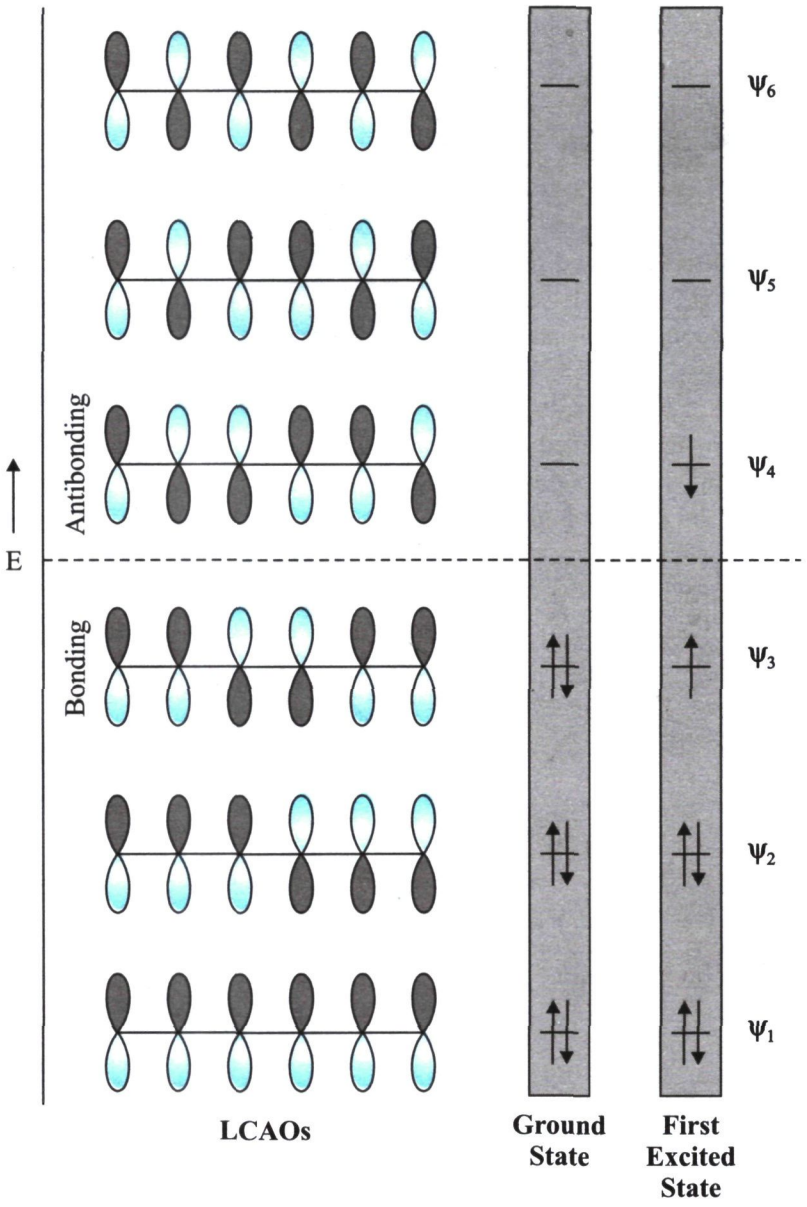


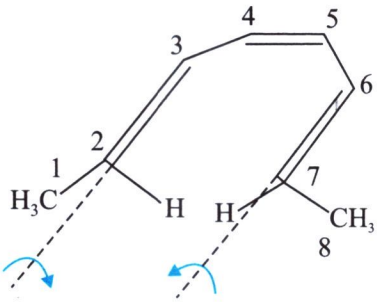
Fig. 22.7: The Configuration of Electrons as Shown in 1,3,5-Hexatriene with the π-Electrons in Ground State and the First Excited State.

EXPLANATIONS

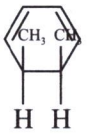
1. The **HOMO** of a *disubstituted hexatriene* related to the **ground state** of the **hexatriene is** ψ_3.
2. In case, a comparison of this is duly made with the **HOMO for the ground state of Butadiene** (ψ_2 in *Fig. 22.1*),—one may critically observe that the ***relative symmetry*** about the **terminal C-atoms** is just opposite in the said ***two*** **cases** explicitly.

3. Amazingly, the **Hexatrene** in the ***ground state*** (low energy level), the respective **Disrotatory Motion** that elegantly leads to *bonding* (as depicted in the *two* following observed stereochemistry showing the so-called ***Disrotatory Motion*** with regard to the **Thermal Cyclization of Substituted Hexatrienes**:

(A_1)



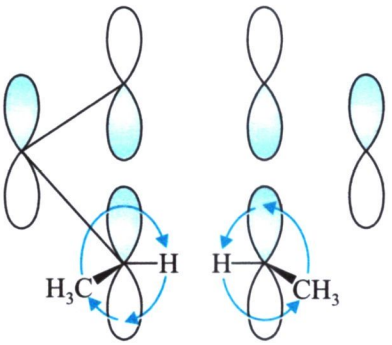
Disrotatory Motion →



***trans, cis, trans*-2,4,6-Detabutene**

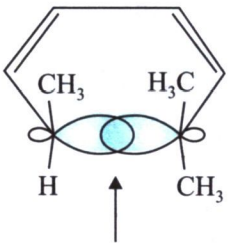
5, 6-*cis*-Dimethyl-1,3-cyclohexadiene

(A_2)



ψ_3 **(HOMO)**

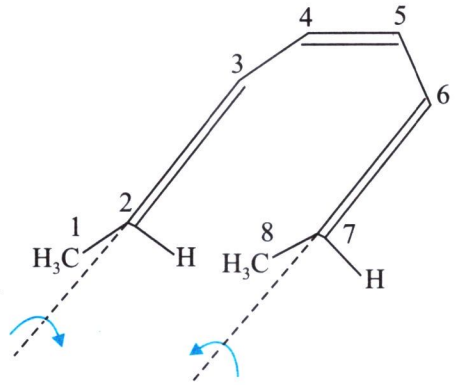
Disrotatory Motion →



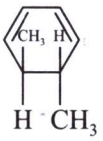
Bonding Overlap

***cis*-5,6-Dimethyl-1,3-cyclohexadiene**

(B_1)



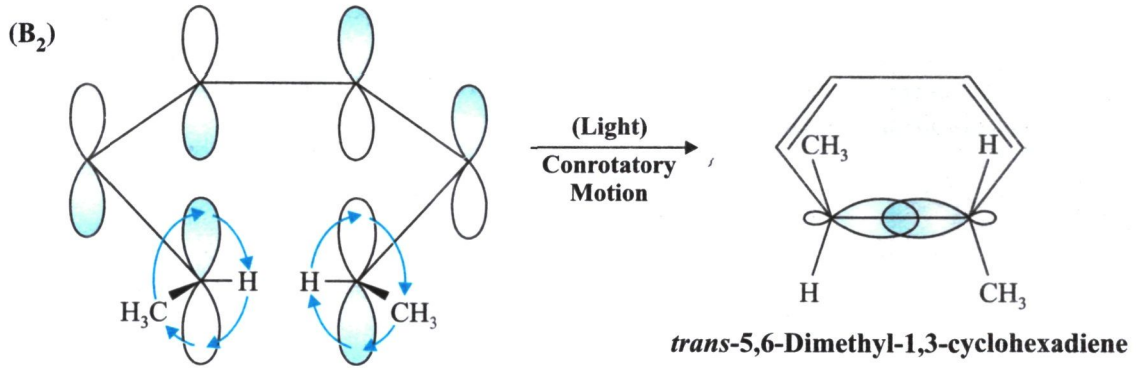
Disrotatory Motion →



***trans, cis, cis*-2,4,6-Detabutene**

5, 6-trans-Dimethyl-1,3-cyclohexadiene

(Contd...)



ψ_4 (HOMO of Excited State)

trans-5,6-Dimethyl-1,3-cyclohexadiene

Remarks: These essentially include:

1. In the ***excited state*** **of hexatriene,** ψ_4 designates the **HOMO**; and thus, once more we encounter a **'*reversal of symmetry*'**—which ascertains the so-called **Conrotatory Motion** as the most favoured phenomenon.
2. **Since the *actual* number of pairs of π electrons in the polyene gets enhanced, one may critically observed the *relative symmetry* about the terminal C-atoms present in the HOMO alternates at a regular fashion.**
3. Besides, the ensuing symmetry duly present in the **HOMO** of.

   "the very *first excited state* remain invariably opposite to that in the *ground state* perceptively'

22.4 ELECTROCYCLIC REACTIONS IN ORGANIC SYNTHESIS

The survey of literature reveals several vital and important **organic synsthesis** which are solely based upon the so-called ***Electrocyclic Reactions***.

Following are the ***two*** **classical examples**, namely:

- **Conrotatory Thermal Ring Opening of Benzocyclobutene,** and
- **Endiandric Acids.**

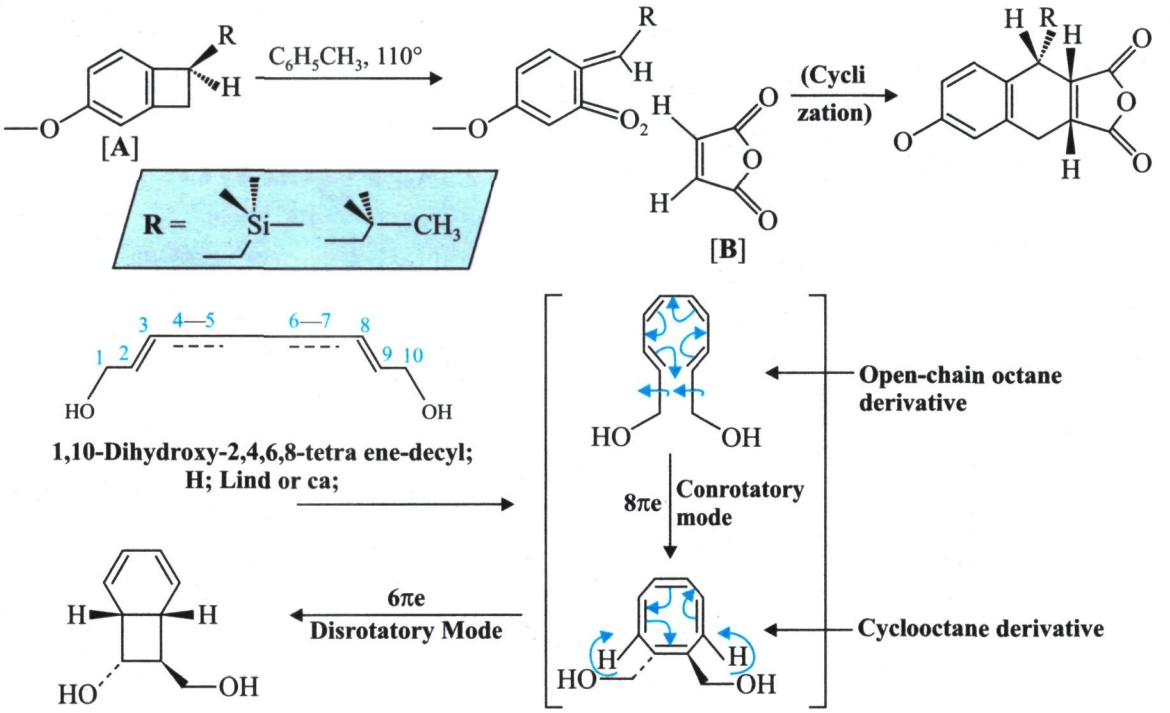
❑ In the first case,—the **reaction product** is found to be extremely *unstable in nature*: ***O*-quinodimethane**. Interestingly, the said molecule may be trapped meticulously in an ***endo*-addition** having a rather strong **'dienophile'** *viz.*, ***Maleic Anhydride*** **(B)** to the respective **Diets-Alder adduct**.

However, the actual yield for the *ring-opening* of the **benzocyclobutane (A)** solely depends on the nature of the **substituent 'R'***. In a solvent medium of **Toluene** and at **110°C** (reaction temperature)—the overall yield enhances starting from **methyl** *to* **iso-butyl methyl** *to* **trimethylsilylmethyl**. Thus, the increased rate of reaction for the **trimethylsilyl compound** may be duly expatiated by means of the **silicon-hyperconjugation** as:

"β-C-Si bond weakens the inherent cyclobutane *C-C bond* by the donations of electrons".

* Yuji Matsuya *et al.*: *J. Am. Chem Soc.*, **128** (2): 412-413, 2006.

Thus, we may have the following expressions:



Remarks: They essentially include:

The ***Asymmetric*** **Electrocyclic Reactions** do ensure an ever-growing highly specific emerging field in the domain of so-called—

"Contemporary Organic Synthesis".

Highlights—essentially comprise:

- **4π-Standinger β-Lactam Synthesis*,** and
- **4π-Nazarov Reaction**.**

The *two* aforeasaid reactions are controlled by the use of a **'Chiral Auxiliary'**. However, the **4π-Nazarov reaction** has been duly carried out by making use of:

- ***Chiral*** **Lewis Acid** • **Bronsted Acids** and • **Chiral Amines.**

Suggested Reading

Arnason JT *et al.*: **Phytochemistry of Medicinal Plant**, 2nd ed., Sringer Verlag, New York, 1995.

Fleming Ian: **Frontier Orbitals and Organic Chemical Reactions**, Wiley and Sons Ltd., New York, 1976.

London GM: **Organic Chemistry**, 4th ed., Oxford University Press, Oxford (UK) 2002.

https://en.wikipedia.org/wiki/Electrocyclic Reaction.

❑❑❑

* http:/www.Organic Chemistry.org/named reactions/standinger synthesis. shtm.,

** Thompson AG *et al.*: **Asymmetric Electrocyclic Reactions,** *Chem. Soc. Rev.*, **40**: 4217-4231, 2011.

Chapter 23

Thermodynamics of Organic Reactions

LESSONS AT A GLANCE

23.1 Introduction
23.2 Kinetic *vs* Thermodynamic Control of Product Composition
23.3 Kinetic Profiles of Organic Reactions
23.4 Effect of Catalyst Upon the Kinetics of Reaction
23.5 Kinetic Control *vs* Thermodynamic Control of a Typical Chemical Reaction

23.1 INTRODUCTION

In a broader sense, one may consider the **Chemical Reactions** as the ***equilibrium phenomena*** wherein the prevailing largeness of the attained equilibrium constant [K_{eq}],—that indicates the so-called ***feasibility*** **of a reaction**. Interestingly, a realatively large observed value of [K_{eq}] implies explicitly such *prevalent aspects* as:

- **high-feasibility of the reaction,** and
- **non-productive reactions rendering the value of K_{eq} to be *'zero'*.**

Equilibrium Constant [K_{eq}]—It is indeed closely related with the known ***Gibb's Free Energy Change*** **(ΔG)*** pertaining to the reaction by **van Hoff's Isotherm,****—as stated under:

$$\boxed{\Delta G = -RT \text{ in } K_{eq.}} \qquad ...(a)$$

where, **T** = Absolute temperature (*i.e.*, at which the reaction occurs), and
R = Universal Gas Constant

Hence, under the **Standard Parameters**, we have:

---

* **Gibb's Free Energy Change (ΔG):** The **standard-free-energy change (ΔG°)**, we mean that the products and reactions are taken as being in their standard states. Thus, the **free-energy change** is usually termed as the **Gibb's Free Energy Change (ΔG)**.

** **van Hoff's Isotherm:** It relates to the idea and concept that certain conformations of moleculars are favoured originates from the work of ion Hoff JH (1901) for his remarkable work on **Organic Reaction.**

$$\Delta G = \Delta G^\circ$$
$$\Delta G^\circ = -RT \ln K_{eq} \quad \ldots(b)$$

In the above **Eqn. (*b*),** we may observe that:

$$K_{eq} > 0$$

because both **R** and **T** are always **positive**. Therefore, the so-called **Gibb's Free-Energy Change [ΔG]** is found to be ***negative*** specially for all such reactions. Since **ΔG is *negative***, we may critically observe that the aforesaid reaction is certainly **spontaneous** in its iherent character.

Relation of ΔG to ΔH (Change in Enthalpy) and ΔS (Change in Entropy): Furthermore, it has been duly observed that the **Gibb's Free-Energy Change (ΔG)** is related perceptively to the following *two* vital and important factors, namely:

- **Change in Enthalpy (ΔG),** and
- **Change in Entropy (ΔS),**

by the following equation:

$$\Delta G = \Delta H - T\Delta S \quad \ldots(c)$$

where, T = Fixed temperature

❑ ***Exothermic Reactions*:** Importantly, for the **exothermic reactions** the **change in enthalpy (ΔH)** is equal to ***negative***; and if the actual number of *moles of the* ***products*** duly produced is found to be greater **than the number of moles of the *reactants*,—ΔS** is also **positive**. Hence, in such reactions, one may critically observe that:

"ΔG is always '*negative*' at all temperatures T".

The status of the **exothermic reactions (ΔH = negative)**—in a situation when the actual number of moles of the products obtained is found to be lesser than the ensuing number of moles of the reactants,—**ΔS** is **negative**.

NOTE: **The above kind of the *exothermic reactions* do become quite possible and feasible particularly at *low tempertures* only.**

❑ **Endothermic Reactions:** Amazingly, for the **endothermic reactions** the **change in enthalpy (ΔH)** is found to ***positive***; and hence, the ensuing reactions do become feasible at **high temperature** only.

Interestingly, the so-called **endothermic reactions** with **ΔS = negative**—are never found to be ***feasible at all***. Therefore, the actual ***feasibility* of an organic reaction** is exclusively based upon the prevailing—**'thermodynamic conditionality, ΔG; and hence, is temperature dependent.**

23.2 KINETIC *vs* THERMODYNAMIC CONTROL OF PRODUCT COMPOSITION

In a broad perspective, it may be observed and concluded that the so-called:

"product composition obtained duly at the end of the reaction may be controlled, governed, and monitored by the underlying equilibrium thermodynamics of the system".

If the above dictum holds good,—the ensuing ***composition of product*** is solely governed by the following *two* aspects:

- **thermodynamic control,** and
- **stability difference between the competing product.**

In true sense, it is critically provided by the **Gibb's Free Energy change (difference) [ΔG]**—that eventually determines the **product composition** squarely.

Alternatively, the accomplished **product composition** may be solemnly controlled and governed by the so-called:

"competing rates of formation of the products—invariably termed as the—'*Kinetic Control*'".

Fig. 23.1 illustrates various typical examples of the **reaction** under the jurisdiction of **kinetic** and **thermodynamic control** *viz.*, (*a*) $\Delta G_B^{\ddagger} < \Delta G_A^{\ddagger}$; (*b*) $\Delta G_A^{\ddagger} < \Delta G_B^{\ddagger}$; and (*c*) alternative mechanism for product equilibrium.

Thus, *three* situations arise perceptively—that will be treated separately as under:

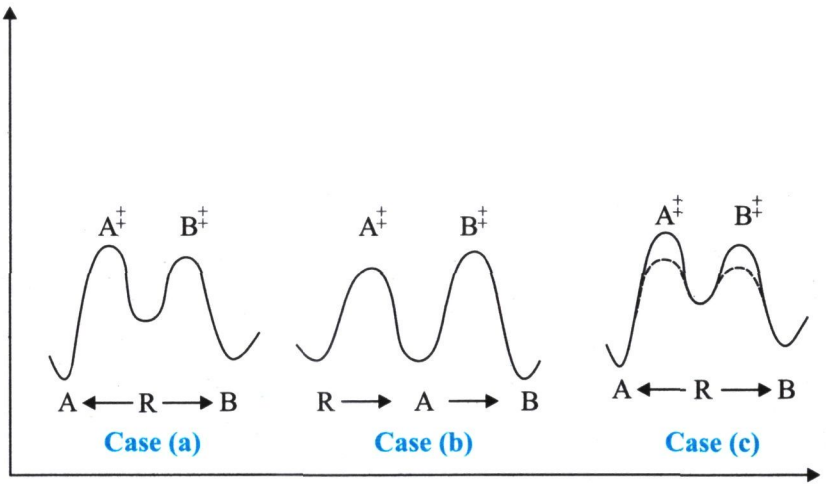


Fig. 23.1: Examples of Reactions Under Kinetic and Thermodynamic Control: (*a*) $\Delta G_B^{\ddagger} < \Delta G_A^{\ddagger}$; (*b*) $\Delta G_A^{\ddagger} < \Delta G_B^{\ddagger}$; (*c*) Alternative Mechanism for Product Equilibrium.

Case* (*a*):** The **$\Delta G^{\ddagger}$'s** formation pertaining to the respective ***transition states **$A^{\ddagger}$** and **$B^{\ddagger}$** from the **reactant R** are found to be significantly much less *vis-a-vis* the **$\Delta G^{\ddagger}$'s** for the subsequent formation of **$A^{\ddagger}$** and **$B^{\ddagger}$** from **A** and **B** respectively.

- In case, the latter ***two*** **$\Delta G^{\ddagger}$s** are considerably large enough so that the respective competitively formed products **B** and **A** fail to return to **R**,—the observed **ratio of the products A** and **B** towards the *end of the reaction* may not actually depend on their **relative stabilities**,—but solely upon the so-called:

  "relative rates of formation".
- Besides, the formation of **A** and **B** is found to be ***irreversible*** **effectively** under these typical circumstances.
- The overall *reaction energy profile* in **'*Case* (*a*)'** indeed corresponds to this situation and suggests a **typical case of the kinetic control.**

- The relative quantum of products **A** and **B** mostly depend on the so-called ***relative activation barries***: $\Delta G_A^{\ddagger}$ and $\Delta G_B^{\ddagger}$; and certainly not on the **relative stability of the products A** and **B**.

Comments: Fig. 23.1 depicts explicitly that $\Delta G_B^{\ddagger} < \Delta G_A^{\ddagger}$; and hence, the major product would be **B**,—even though it is found to be rather less stable than **A**.

Case (b)*:** It designates critically a situation of ***two **successive reactions**. The **lowest** $\Delta G^{\ddagger}$ is actually meant for the formation of $A^{\ddagger}$ **from R** (*reactant*). However, the $\Delta G^{\ddagger}$ for the **formation of** $B^{\ddagger}$ **from A** is not found to be larger at all. In true sense, the ***system*** **in (*b*)** might be duly monitored or governed by either:

- **Kinetic** or • **Thermodynamic factors.**

Thus, we may have:

➢ Conversion of **R to A** shall be slightly fastor *vis-a-vis* the **conversion of A to B**;

➢ When the *reaction parameters* are adjusted meticulously, it could be a lot easier and possible for **A to accumulated duly**, and hence, may not proceed on to yield the **more stable product B**;

➢ Under these prevailing circumtances:

- **A should be the overall '*dominant product*'; and**
- **The reaction would be under the *kinetic control* perceptively;**

➢ Under **more energetic parameters** *e.g.,* at a higher temperature range **A** shall be duly *transformed into B*; and hence, under these conditionalities the overall reaction would be under the **thermodynamic control**; and

➢ finally, **A** and **B** will *equilibrate*; and thus, the ***product ratio*** shall solely depend upon the so-called resultant **equilibrium constant by** ΔG for the reaction: $\mathbf{A} \rightleftharpoons \mathbf{B}$.

Case (*c*): Here, the **solid-reaction energy profile** duly represents almost a *similar situation* of **kinetic control** [as depicted in *Fig. 23.1 (a) above*], wherein the resulting **Product B** (which being *thermodynamically less stable*) is obtained since $\Delta G^{\ddagger} < \Delta G^{\ddagger}$. Besides, the ***dotted-line*** (or *dashed*) **energy profile** designates an altogether divergent set of parameters given for the **same transformation** phenomenon *viz.,*

➢ **addition of a catalyst,** or

➢ **change of solvent,**

which significantly minimises the ensuing energy of $A^{\ddagger}$ and $B^{\ddagger}$,—in such a manner that:

'the actual *interconversion* of A and B is fast perceptively'.

Remarks: It would certainly give rise to the formation of the ***more stable*** **product A**, even though the so-called observed barrier to the **formation of B** usually remains at a ***lower ebb***. Amazingly, under these circumstances one would find the reaction to be:

"under the legitimate Thermodynamic Control".

Structural and Mechanistic Basis Pertaining to the Relationships Between Kinetic *Vs* Thermodynamic Control.

It may be observed that the **α-H atoms** of the *methyl (CH_3) moiety* are indeed found to be ***less* hindered sterically** *vis-a-vis* the **α-H atoms** of the **butyl (CH_3—CH_2—CH_2—CH_2) moiety**. Consequently, the critical removal of a so-called **methyl H-atom** (as a **proton**) is observed to be much *faster* than the corresponding removal of a **butyl H-atom (proton)**.

Importantly, the aforesaid **'effect'** is magnified adequately when the ***base*** is found to be—**'bulky sterically'**; and, therefore, is specifically sensitive to the so-called ensuing **steric environment** of the available **competing H-atoms**.

Thus, one may invariably encounter ***two* different situations**, namely:

(*a*) **When the *Base* is very strong:** In this case, the ***enolate*** will never get converted to the respective *ketone*, since the '*enolate*' happens to be **too weak a base so as to regain the proton (H^+)**. Obviously, these parameters actually correspond to *Fig: 23.1 (a);* and thus, designated a case of **'Kinetic Control'**.

(*b*) **When the *Base* is weaker:** In a situation, when a weaker base is employed or when the **solvent** is ***protic*** in nature, the ensuing **proton (H^+)** may be duly:

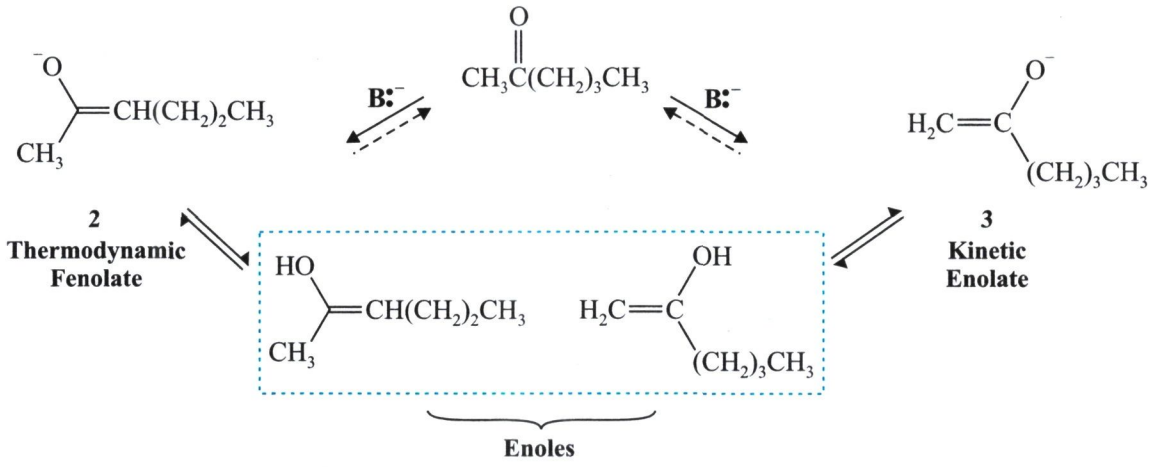
'transferred reversible between the *isometric enolates* and the base'*.

Obviously, under these circumstances so-called **more stable-enolate** would be specifically **dominant** in character since the respective **enolates** are in a ***state of equilibrium***.

Thus, we may take cognizance of these aspects:

- the more ***substituted enolate 2*** (see structures below) happens to be the more stable of the pair, and
- it fairly relates to (*c*) in *Fig. 23.1*

i.e., the so-called ***product* (enolate)** equilibration comes into play *via* **rapid proton (H^+) exchange;** whereas, in the **protic solvents** the aforesaid exchange may usually take place *via* the **enols**.



* Since the inherent **base strengths** of both ***'enolate'*** and ***'base'*** are fairly comparable to each other.

23.3 KINETIC PROFILES OF ORGANIC REACTIONS

The scientific evidences and their interpretations do reveal squarely that:

'every reacting system does possess an inherent tendency to oppose (counter) any change in it'.

In fact, the said **'tendency'** both governs and controls the so-called actual ***rate of a reaction*** perceptively. Thus, we may conceptualize and endorse the following critical observations predominantly:

- Higher being the inherent tendency to resist any possible change,—the slower would be the *Organic Reaction*;
- Above mentioned typical aspect of the *Organic Reaction* is virtually governed by the *conditionality of* time; and is usually termed as—*Kinetics of a Reaction*; and
- Kinetics of an *Organic Reaction* is found to be absolutely *concentration dependent.*

Thus, the **concentration dependence** of an **Organic Reaction** may be expressed as under:

$$aA + bB \rightleftharpoons dD + eE$$

And also expressed by the **Rate of Reaction** as stated under:

$$\text{Rate of the Reaction} = K\,[A]^{n_1}\,[B]^{n_2}$$

where, $n_1 + n_2$ = Order of the reaction

K = Magnitude of the rate constant (determines the *fastness* of **organic reaction**).

NOTE: **The higher is the value of '*K*',—the faster would be the reaction.**

Remarks: These essentially include:

1. For a ***thermodynamically feasible*** **organic reaction** *i.e.,* a reaction wherein the **ΔG = negative,**—there must also be an *appropriate pathway* for the **organic reaction** *via* which the so-called:

"electron reorganization with respect to the reactant molecules may occur to yield the desired product molecules".

2. It would be fairly appropriate and logical to predict that: **"such an effective *electron reorganization of the reaction molecules* may obviously involve certain typical *state-of-the system* which happens to be *higher-in-energy level* in comparison to either of the reactant or the product molecules".**

Therefore, the aforesaid *typical state* is invariably termed as the—**Transition State (TS) of the Organic Reaction**. Consequently, higher being the **energy level of the TS** *vis-a-vis* the **reactant molecule,**—The ***slower would be the reaction rate*** ultimately.

Thus, the **organic reaction** of this type may be expressed as:

$$A + B - C \longrightarrow A - B + C$$

Comments: In a specific instance, when the ensuing **B-C bond** is found to be reasonably stronger in comparison to the respective **A—B bond**, the so-called **Transition State (TS)** belongs to the ***higher-energy in the*** **organic reaction episode**.

3. **The Activation Energy:** It has been duly proven and established that the observed **energy difference, E_{TS}—$E_{reactant}$,** is usually known as the **'activation energy', $\Delta E^{\ddagger}$ (or $\Delta H^{\ddagger}$)**, of the reaction. It is, however, pertitent to state here that unless and until the:

"reactant molecules do attain this extra energy ($\Delta H^{\ddagger}$), the actual collisons amongst them may not lead to any sort of *electron reorganization i.e.,* the assumed organic reaction".

NOTE: **Hence, the accomplished quantum of the '*activation energy*' $\Delta H^{\ddagger}$, is solely responsible for the ultimate *rate-of-reaction*; and hence, ΔG has absolutely no control whatsoever on this state.**

4. **The Multistep Reaction:** In the specific case when a **multistep reaction** is involved,—the **overall product of one step** does critically act as a ***reactant*** for the ensuing **successive step** predominantly.

Hence, in between the *two* **transition states (TSs)**—only one such intermediate would be generated finally. Thus, *energy profile* of the **organic reaction**, such:

***"intermediation formation* is solely indicated by an 'Energy Well' or '*Energy Minimum*'".**

Importantly, the so-called depths of these **'Energy Wells'** do indicate explicitly the observed—**'stability of the intermediates'**. Hence, it may be safely concluded and generalized that:

'for an *n-step reaction*,—there would be n-energy hills (TSs), and *n-1 energy wells* (or intermediates)'.

NOTE: **Amazingly, the step of the reaction with respect to the so-called '*tallest-energy hill*' [*i.e.,* highest energy of transition state (TS)]—is, in fact, the *slowest step*; and hence, the rate of this step virtually determines the *overall rate of the reaction* perceptively. It is, therefore, termed as the *rate-determining step*.**

23.4 EFFECT OF CATALYST UPON THE KINETICS OF REACTION

In a broader perspective, the so-called ***'catalyzed reaction'*** are found to be relatively faster *vis-a-vis* the ***'uncatalyzed reactions'*** since the **catalyst** being employed provides predominantly.

"an alternative route of the reaction of lower activation energy".

It is, however, pertinent to state here that the ***'catalyst'*** may not be able to alter the inherent feasibility of a reaction since it **fails to change the value of ΔG** (*i.e.,* **Gibb's Free Energy Change**).

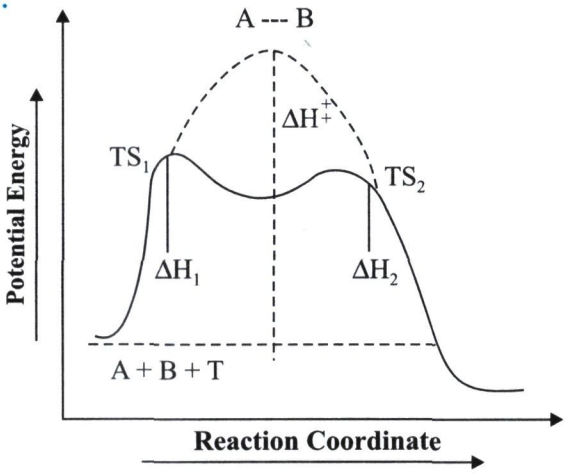
The aforesaid expression of thought and concept may also be expatiated based on the fact that a ***catalyst cannot alter the status and position of the equilibrium of an*** **Organic Reaction**.

Obviously, a ***'catalyst'*** may be able to afford a:

'reduction in the magnitude of the *activation energy* of the reaction',

and in turn helps in establishing the ***attained equilibrium at a rather faster rate***.

Example:



$+ \Delta H_2 < \Delta H^{\ddagger}$

We may express the above sequence of transformations as under:

$$A + B + T \longrightarrow A \text{ ..... } B \text{ ..... } T \longrightarrow A - B - T \longrightarrow$$

Intermediate

$$\mathbf{TS_1}$$

$$A \text{ ..... } B \text{ ..... } T$$

$$\mathbf{TS_2}$$

T = Catalyst; and TS = Transition State

23.5 KINETIC CONTROL *vs* THERMODYNAMIC CONTROL OF A TYPICAL CHEMICAL REACTION

The underlying concept and analogy related to **the kinetic control *vs* the thermodynamic control** in a ***typical*** **chemical reaction** may be explicitly exemplified by:

'the addition of hydrogen bromide (HBr) to 1, 3-butadiene'.

However, the above episode seems to be rather intersting in an altogether aspect as well *i.e.*, the **'temperature'** being a vital and important criteria with respect to the so-called *relative quantum* of **1,2- and 1,4-addition products** which we obtain eventually are found to be **absolutely independent of temperature of the reaction parameters**.

Interestingly, such **addition reactions** do exhibit altogether different reaction modalities at:

- **low temperature** and - **higher temperature.**

❑ ***Low Temperature*:** Thus, at a **low temperature [–80°C]**, the interaction between 1, **3-butadiene** and **hydrogen bromide (HBr)**, in the total ***absence of peroxides***—the **major reaction** that occurs is that of the **1, 2-addition**. Thus, under these reaction parameters we may obtain:

- **nearly 80% of the 1, 2-product;** and
- **merely 20% of the 1, 4-product.**

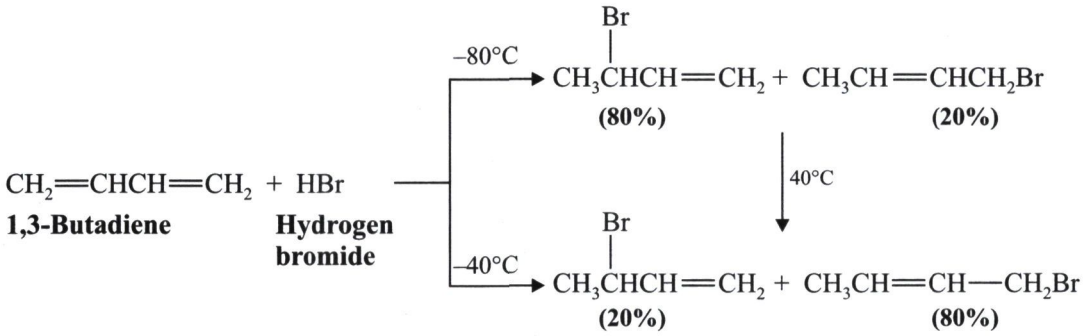
❑ ***High Temperature*:** In this case, at a **high temperature [+ 40°C]**, the *on-going reaction gets altogether* **reversed**. Thus, the ensuing **major reaction** that eventually takes place is **1,4-addition**; and hence, one may ultimately obtain:

- **approximately 80% of the 1, 4-product;** and
- **merely 20% of the 1, 2-product.**

Important Observations: It is worthwhile to state at this point in time that:

"when the mixture duly accomplised at *lower temperature* is gradually raised to the *higher temperature*,—the so-called *relative* quantum of the two reaction products do change perceptively".

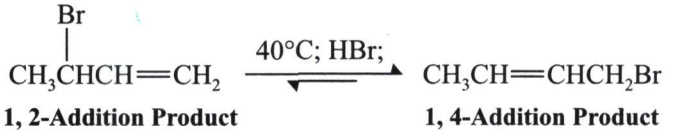
1. Importantly, the ***newly formed*** **reaction mixture** eventually comprises almost the **same proportion of products**—as duly provided by the reaction being performed meticulously at the **higher temperature**. The various interactions may be duly expressed as under:



2. Besides, it may also be ascertained and demonstrated that:

"at the *higher temperature* and also in the presence of HBr, the *1,2-addition product* gets duly rearranged to the 1,4-product thereby an equilibrium does exist between the said products".

Thus, we may express the reactions as given under:



Remarks: Since the **equilibrium** vehemently favours the **1,4-addition product,**—hence: **"that product should be definitely more stable'.**

3. Reactions of HBr with 1,3-Butadiene: We may critically observe a ***striking illustration*** in the manner the **reactions of HBr with 1,3-butadiene** come into play,—whereby we may determine specifically the net outcome of a **chemical reaction**. Thus, in *one instance* by making use of:

- **the relative rates of competing reactions,** and
- **in another case-based on the observed relative stabilities of the final product.**

Thus, we may come across *two* **distinct situations**, namely:

- **At Lower Temperature:** We may see that the ***relative quantum of the ensuing* 'products-of—addition** are determined adequately by the so-called:

  "relative rates at which the *two* additions take pace *i.e.*, the actual *1,2-addition occurs much faster;* and hence, the resultant *1,2-addition product* appears to be the major product".

- **At Higher Temperature:** We may observe critically that the so-called relative quantum of the products are duly determined by the position of an equilibrium status being attained perceptively. Thus, the altimate resultant:

  "1,4-addition product tends to be *more stable*; and hence, obtained as the *major product*".

Fig. 23.2 represents diagrammatically—the above mentioned behavioural pattern of:

• **1,3-Butadiene** and • **Hydrogen Bromide,**

which could be understood more explicitly provided one may have a close look and examine the said diagram.

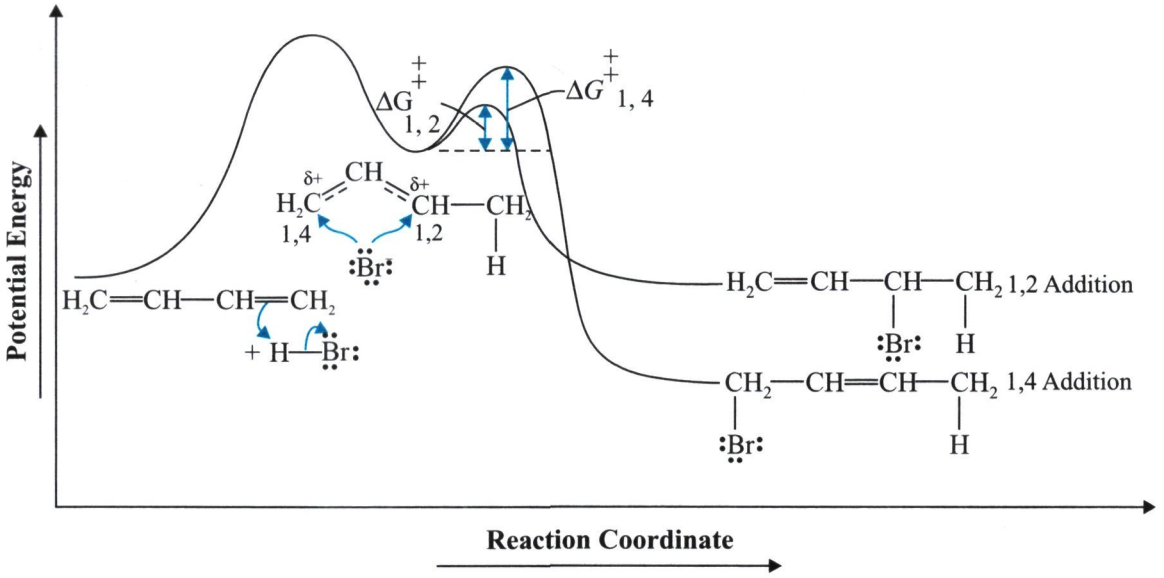
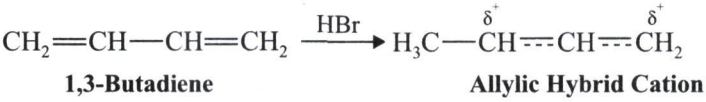


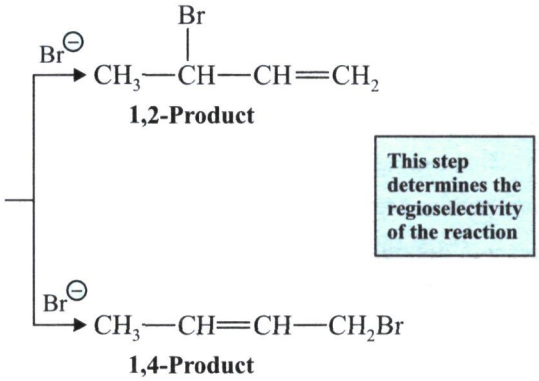
Fig. 23.2: The Representation of a Schematic Free-Energy *Vs* Reaction Coordinate Diagram for the 1,2- and 1,4-Addition of HBr to 1,3-Butadiene.

Explanations

Following is the cardinal step that virtually helps to determine the *overall outcome of the reaction* based on the step wherein the so-called—**Hybrid Allylic Cation** critically combines with a **bromide ion [Br^-],**—as stated under:



1,3-Butadiene **Allylic Hybrid Cation**



Importantly, the presence of an **allylic carbocation** is found to be common to both the ***aforesaid pathways*** *viz.*,

- **1,2-Addition;** and
- **1,4-Addition.**

Nevertheless, the actual **energy barrier** for the attack of the **bromide ion [$Br^{\ominus}$]** located strategically upon the **allylic cation** to give rise to the formation of the so-called ***1,2-addition product*** is observed to be quite less than that to yield the corresponding ***1,4-addition product***. Besides, the ***1,2-addition product*** is favoured kinetically also; whereas, the ***1,4-addition product*** is observed to be rather **more stable**; and hence, it would be the ultimate **thermodynamically favoured product**.

Fig. 23.2 reveals critically that for the aforesaid step: "the *free-energy of activation* that virtually leads to the *1,2-addition product* is found to be comparatively less *vis-a-vis* the free-energy leading to the **1,4-addition product**—which is certainly more stable.

Again we are confronted with ***two*** **distinct situations,** namely:

(*a*) **At Low Temperature:** Here, a relatively *larger fraction of collisions* do occur between the **intermediate ions** (*i.e.*, having energy to cross the so-called *lower barrier*)—thereby leading to the ultimate **1,2-product**. Perhapes that could be the valid reason why only a very ***few small fraction of collisions*** does possess enough energy level to cross the *higher barrier* (*i.e.*, leading to the **1,4-product** perceptively).

***Key Point*:** Indeed in either case, the phenomenon of **product formation** is critically the most essential **irreversible episode**—irrespective of the **barrier** it happens to cross to low **temperature (– 80°C)**, since:

"there is an absolute *lack of energy* available so as to lift precisely either products right out of its deep potential, energy valley".

Because **1,2-addition** occurs much faster, the **1,2-product** duly predominates; and hence, the ensuing reaction is said to be under: **Kinetic Control** or **Rate Control**.

(*b*) **At High Temperature:** In this particular instance, the so-called **intermediate ions** do exhibit ***sufficient level-of-energy*** to cross over **both barriers** with great ease and fervour.

Importantly, one may take cognizance of the fact that:

"at higher temperatures both the reactions are reversible".

In addition, availability of enough energy even proves to be able to take the resulting products back over their so-called *energy barriers* right to the *intermediate level of both*:

- **allylic hybrid cations** $[H_3C—\overset{\delta^+}{C}H{=}{=}CH{=}{=}\overset{\delta^+}{C}H_2]$; and
- **bromide ions** $[Br^-]$.

Therefore, under the aforesaid **experimental parameters** *i.e.,* at *higher temperatures*:

"the so-called *relative proportions* of the products fail to reflect the relative heights of the energy barriers thereby leading from the—*allylic cation to ultimate products*".

In other words, **they instead do reflect the relative stabilities of the products themselves.**

Remarks: Since the obtained **1,4-product** is found to be definitely more stable,—it is duly formed at the cost of the respective **1,2-product** generously which may be due to the so-called:

"overall change from *1,2-product* to *1,4-product* which is being favoured energetically".

In fact, such a reaction is broadly recognized to be under either:

- **thermodynamically control,** or
- **equilibrium control.**

Suggested Reading

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Chapter 24

Addition Reactions

LESSONS AT A GLANCE

24.1 Introduction
24.2 Electrophilic Addition Reactions [Addition of Hydrogen Halides (HX) to Alkenes]
  24.2.1 Mechanism and Markovnikov's Rule
24.3 Nucleophilic Addition Reactions to Alkenes and Alkynes
  24.3.1 Mesomeric Delocalization
  24.3.2 Negative Inductive Effect

24.1 INTRODUCTION

Addition reactions do occur invariably in *chemical entities* **(compounds)** having **π-electrons** that are present in:

- **Carbon-carbon double (or olefinic) bonds [*alkenes*]; *or***
- **Carbon-carbon triple bonds [*alkynes*]**; or
- **Carbon-oxygen double bonds [*aldehydes (—CHO) or ketone (>C=O)*].**

In general, the **addition reactions** are of ***two* distinct types,** namely:

➢ **Electrophilic Addition to *Alkenes* and *Alkynes*;** and

➢ **Nucleophilic Addition to *Aldehydes* and *Ketones*.**

NOTE: **It is worth while to state here that in an *addition reaction* the product does contain practically all of the inherent elements belonging to the *two* reacting species.**

24.2 ELECTROPHILIC ADDITION REACTIONS [ADDITION OF HYDROGEN HALIDES (HX) TO ALKENES]

It is an established fact and reality that the electrons that are duly present in the ***π-bond*** are found to be susceptible specifically to the so-called **electron-seeking reagents** perceptively. Hence, such reagents are usually said to be—**'electrophilic'** (or ***electron seeking***); and hence, are termed as the **'Electrophiles'**.

The **electrophiles** do essentially comprise—***Positive Reagents*** *viz.*, **protons (H^+)**; ***Neutral Reagents*** *viz.*, **bromine* (Br_2)**; and the ***Lewis Acids***, *viz.*, **BH_3, BF_3 and $AlCl_3$**.

* Since it can be **polarized** so that one terminal is ***positive***.

Besides, the **metal ions** which normally contain **vacant orbital** also behave critically as the **'electrophiles'** *viz.,*

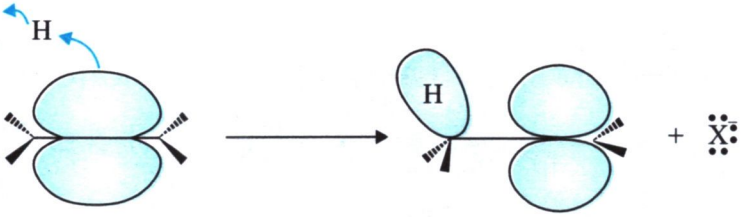
- **Silver Ion (Ag^+)** - **Mercuric Ion (Hg^{2+})** and - **Platinum Ion (Pt^{2+}).**

Example: **Hydrogen halides (HX)** do react with **alkenes** by the active donation of a **proton (H^+)** to the respective **π-bond**. In other words, the **proton** makes use of the ***two* inherent electrons of the π-bond** to give rise to the formation of a **σ-bond to one of the C-atoms** perceptively.

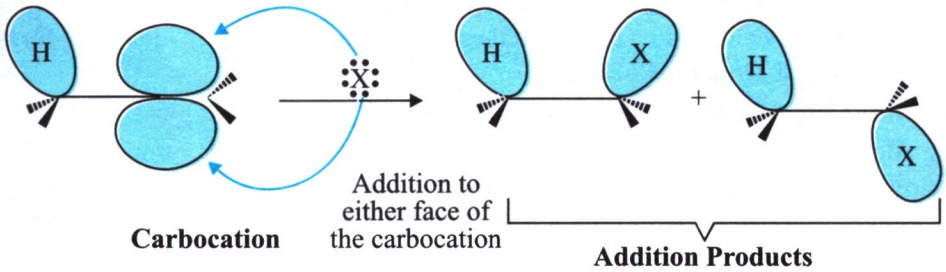
Thus, it leaves a **vacant *p*-orbital** plus a **+ve charge present on the C-atom**. Consequently, the overall result could be observed prominently due to:

"the formation of a *carbocation* and a *halide* ion from the corresponding *Alkene* and *Hydrogen Halide (HX)*".

The aforesaid conversion of an '*Alkene*' into '*Carbocation*' may be depicted as under:

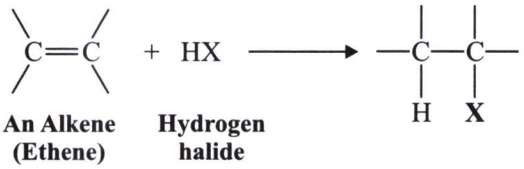


Consequently, the ensuing **carbocation** being highly reactive may then get combined with the **halide ion (X^-)** by critically ***accepting one of its electron pairs***, as illustrated below:



24.2.1 Mechanism and Markovnikov's Rule

The **hydrogen halides** *viz.,* **HI, HBr, HCl and HF** are added to the *double bond* (or *olefinic bond*) of **alkenes**,—as shown under:



***Modus Operandi*:** In general, the aforesaid **additions** are sometimes brought about either by:

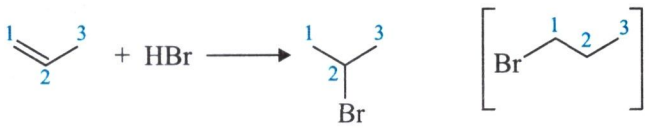
- **dissolving the *hydrogen halide (HX)* in a solvent *viz.,* acetic acid (CH_3COOH) or dichloromethane (CH_2Cl_2);** or
- **bubbling the *gaseous HX* directly into the *alkene*,** or
- **using the *alkene* itself as the *solvent*.**

Addition of **HX** to an **'unsymmetrical alkene'** may take place conceivably in ***two*** **distinct ways**; however, one of the products predominates invariably.

Example:

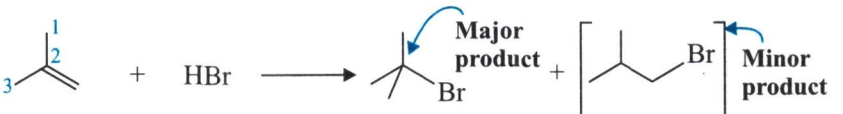
1. Addition of HBr to propene: would conceivably give rise to either **1-bromopropane** or **2-bromopropane;** and thus, the latter is obtained as the ***major product***.

Thus, we may have the following expressions:



1-Propene **2-Bromopropane** **1-Bromo propane**
(*Maximum*) **(*Small*)**

2. Interaction of 2-Methylpropane with HBr: would eventually yield ***two*** **main products** *viz.*, **2-Bromo-2-methylpropane (A)** and **1-Bromo-2-methyl propane (B)**, as given under:



2-Methylpropene Hydrogen bromide **[A]** **[B]**

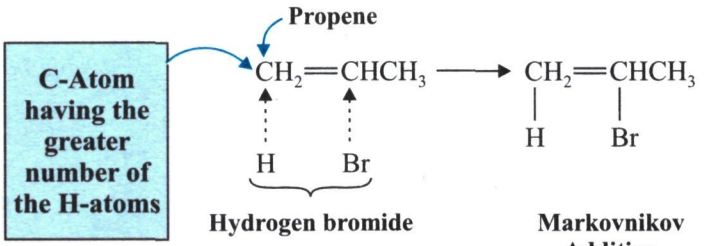
❑ Markovnikov's Rule:

Based on an array of such highly specific and typical examples ultimately led the ***Russian chemist*: Valdimir Markovnikov** (1870) to put forward the widely known and equally famous **Markovnikov's Rule** in the domain of ***Organic Chemistry***.

The **Markovnikov's Rule** may be defined as:

"the addition of *HX* to an *alkene*,—the H-atom adds on to the C-atom of the double bond that already has the greater number of H-atoms".

The perfect addition of **HBr** to **propene** (an *alkene*) illustrates explicitly the **Markovnikov's Rule,**—as stated under:

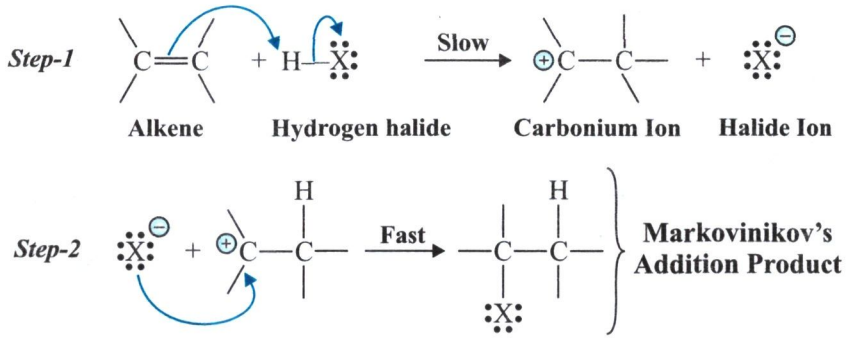


Hydrogen bromide **Markovnikov Addition Product**

NOTE: **Based on the above reaction (and *all such reactions*) that critically illustrate the *Markovnikov's Rule* are invariably termed as *Markovnikov Additions*.**

❑ Mechanism For Markovnikov Reaction:

The **mechanism for Markovnikov reaction** may be expatiated in ***two*** **distinct steps** using the **'addition of hydrogen halide (HX) to an alkene'**,—as given below:



Both **steps 1 and 2** are self-explanatory.

Rate-Determining Step*:** It is, however, important to state here that the most important step is: **Step-1**, since it is the so-called **rate-determining step**. Interestingly, in **Step-1** the ***alkene critically donates a pair of electrons particularly to the corresponding ***proton*** of the **HX** (*hydrogen halide*); and hence, ultimately forms a **'carbocation'**.

Fig. 24.1 explicitly illustrates the above **step-1** which happens to be extremely **endergonic*** in nature; and, therefore, possesses a relatively **high-free energy of activation** perceptively. As a

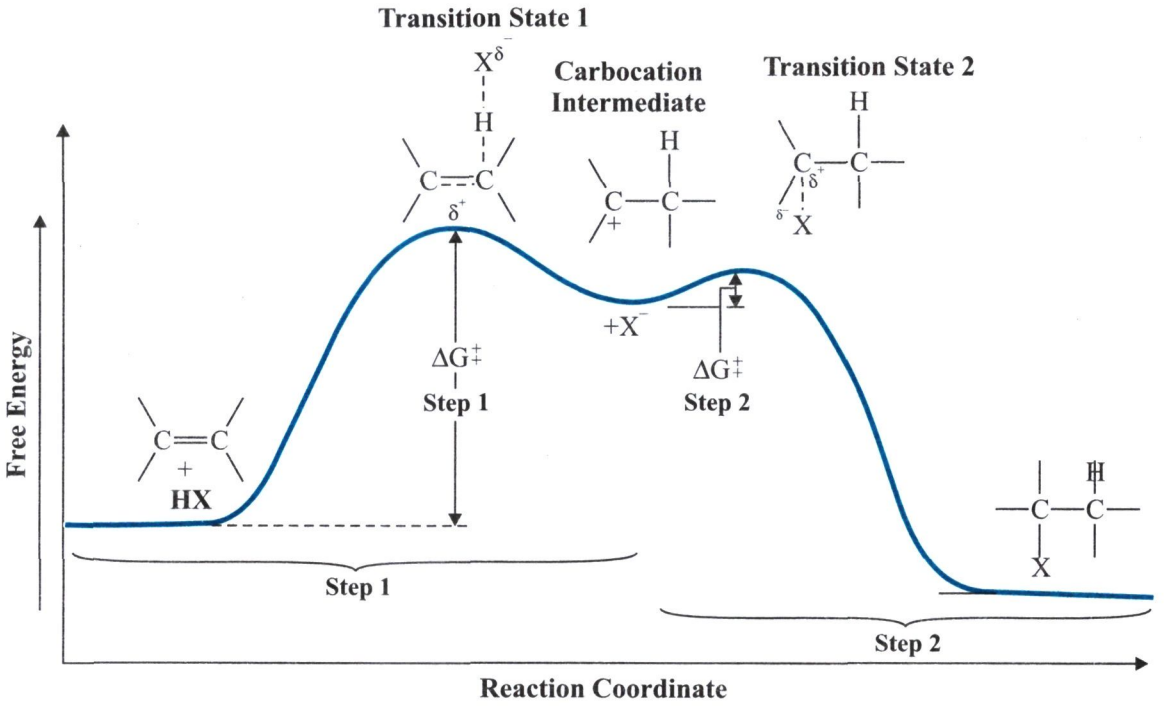


Fig. 24.1: Diagrammatic Representation of Free-Energy Profile for the Addition of HX to an Alkene. The Free-Energy of Activation for **Step-1** is much Higher than for **Step-2**.

* **Endergonic:** It refers to a typical **non-spontaneous process** in which the ***free-energy*** is either absorbed or a process that needs an *energy input* to make it happen ultimately.

** **Exergonic:** It relates to a **spontaneous process** from which the ***free-energy*** gets released finally.

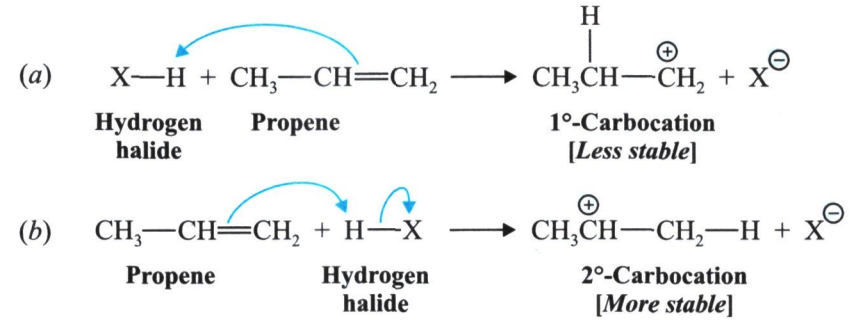
result, the **Step-1** takes its course rather **slowly**. Nevertheless, in **Step-2** the prevailing extremely reactive carbocation gets duly stabilized by associating with a **halide ion** (X^-). Consequently, this **exergonic**** step does possess indeed a ***very low free-energy of activation;*** and hence, takes its course **very rapidly**.

❑ Theoretical Considerations of Markovnikov's Rule

First and foremost let us assume that, in case, the **alkene** which is being subjected to the critical and specific addition of a **hydrogen halide (HX)** and happens to be an ***asymmetrical alkene*** *viz.,* **propene [$CH_3CH{=}CH_2$]**, then the **Step-1** might possibly and conceivably lead to ***two*** **altogether divergent carbocations:**

➢ **1°—Carbocation:** Less stable; and ➢ **2°—Carbocation:** More stable.

The *two* reactions may be expressed as under:



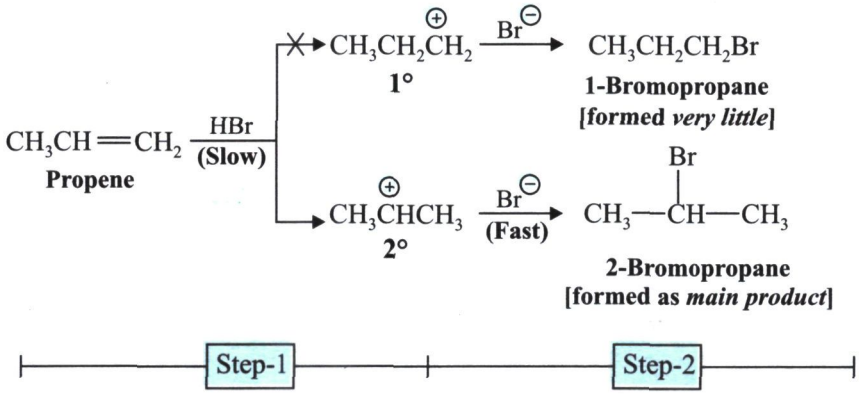
Remarks: These essentially comprise:

1. These ***two*** **carbocations** [*viz.,* **1° and 2°-carbocations**—as shown in *(a) and (b) above*].
2. The so-called ***secondary*** **(2°) carbocation** is certainly more stable; and hence, it is the *greater stability of the secondary carbocation* that ultimately leads to the precise and exact prediction of the overall addition by the **Markovnikov's Rule.**

Furthermore, the critical ***addition*** of **HBr to propene** *viz.,* the reaction invariably follows the under-mentioned course of reaction whereby these ***two*** **products of reaction** are duly obtained:

- **1-Bromopropane** [formed *very little*]; and
- **2-Bromopropane** [formed as *main product*].

These reactions may be expressed as under:



Comments:

1. Obviously, the ***main product*** of the above interaction between **propene and hydrogen bromide (HBr)** is ***2-bromopropane*** since the so-called ***more stable*** **secondary carbocation** is duly accomplished preferentially in the very ***first*** **step** itself.
2. Besides, the ensuing ***more stable*** **carbocation predominates** overwhelmingly since it is duly formed in a ***faster*** **modality**.

Fig. 24.2 illustrates explicitly the so-called ***Free-Energy Diagrams*** pertaining to the addition of **HBr to propane**. Thus, it enables us to understand the intricacies of the entire episode to be true if we do examine critically the so-called ***Free-Energy Diagrams*** in Fig. 24.2.

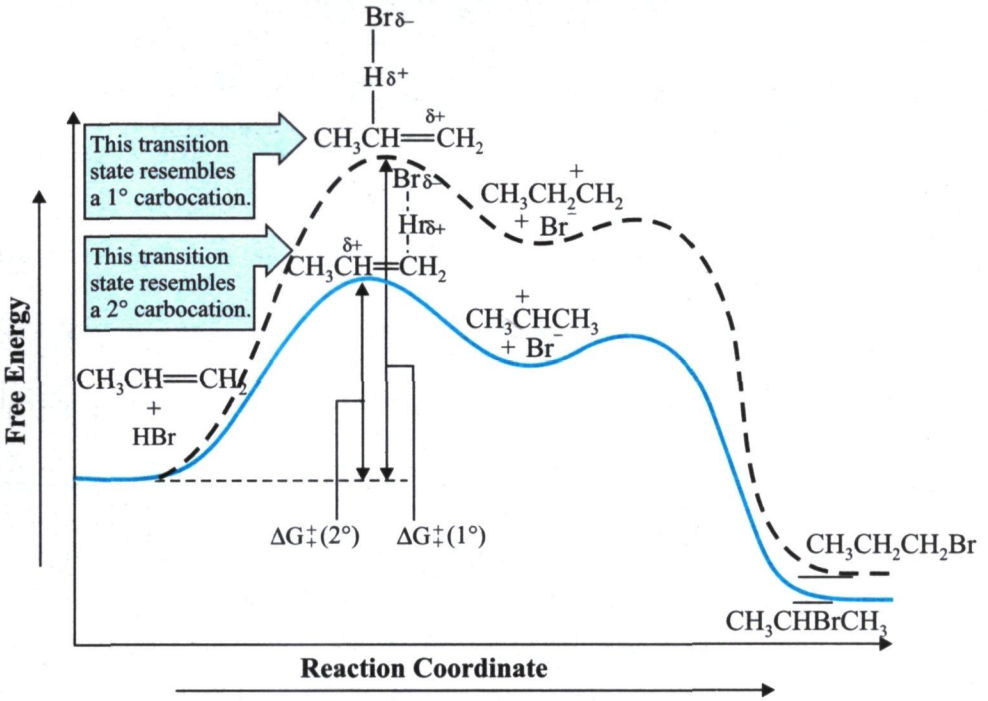


Fig. 24.2: The Free-Energy Diagrams for the Addition of HBr to propane [$\Delta G^{\ddagger}(2°) < \Delta G^{\ddagger}(1°)$].

Explanations

The various aspects in Fig. 24.2 may be explained as under:

1. In **Fig. 24.2** the specific reaction that virtually leads to the ***secondary (2°)*** **carbocation** (and finally to **2-bromopropane**) does possess the definite ***lower*** **free-energy of activation**.

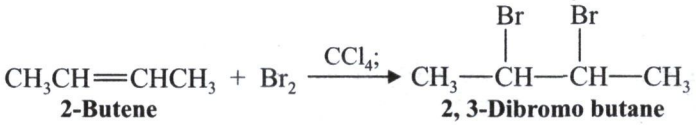
NOTE: **Perhaps the path followed by the reaction is quite true and reasonable since its *transition state (TS)* resembles the *more stable carbocation* perceptively.**

2. The reaction that actually leads to the ***primary (1°)*** **carbocation** (and finally to **1-bromopropane**) possess critically a ***higher*** **free-energy of activation** since its **transition state (TS)** very much resembles a definite ***less stable primary*** **(1°) carbocation**.

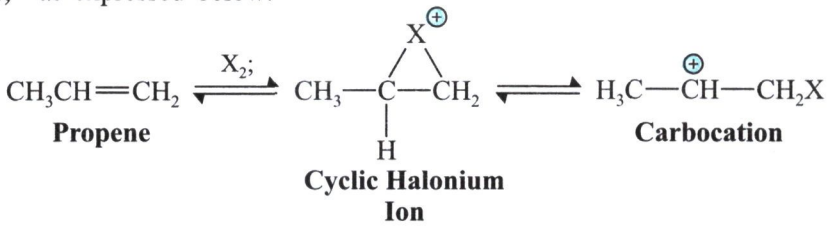
NOTE: **Amazingly, the *second reaction* is found to be much slower; and hence, fails to complete with the *first reaction*.**

❑ Addition of Halogens to Alkenes

(*a*) **Addition of Bromine (Br_2) to Alkenes [Bromination]:** The **alkenes** upon the addition of **bromine (Br_2)** get duly converted into the respective **dibromide**; and thus, the reaction is performed in the presence of an ***inert* solvent** (*viz., carbon tetrachloride*, **CCl_4**),—as given under:



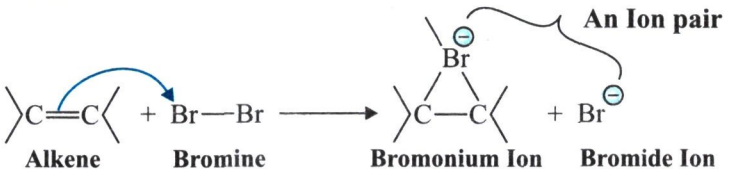
Mechanism of Bromination: Importantly, the **bromination** of ***alkenes*** do provide the typical examples of ***Electrophilic Additions***; and hence, usually proceed *via* the **positively charged intermediates,**—as expressed below:



NOTE: **Mechanism related to the addition of *halogens to alkene* is usually known as—*Biomolecular Electrophilic Additions* [AdE_2].**

Interestingly, **AdE_2 (Bimolecular Electrophilic Addition)** critically involves the following ***two* cardinal steps 1 and 2**:

***Step* 1: The critical transfer of Bromide ion (Br^-) released from a Bromine Molecule (Br_2) to the respective '*Alkene*':**

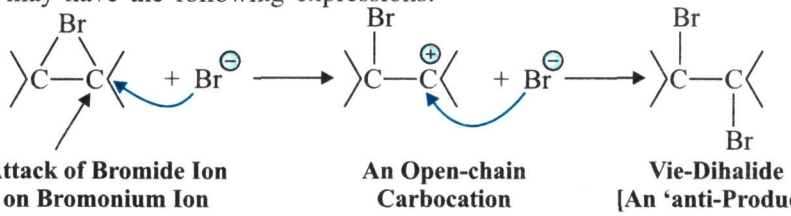


Thus, one may observe the formation of an **Ion-Pair** [from an ion each of *Bromonium* and *Bromide*].

***Step* 2: The attack of Bromide ion (Br^-) from the back side of a Bromonium ion to yield the *Vic-dihalide* [an '*anti*'-Product]. The Bromonium ion thus formed gets duly:**

- **Cleaved (opened) by the attack of the Bromide Ion (Br^-), to give an open-chain Carbocation,** and
- **on further attack of the Bromide Ion (Br^-) yields the *Vic-dihalide* [an '*anti*'-Product]*.**

Thus, we may have the following expressions:



* Roberts JD and Kimball KE: *J Am. Chem. Soc.*, **59**: 947, 1937.

❑ Stereochemical Investigative Study of Bromination

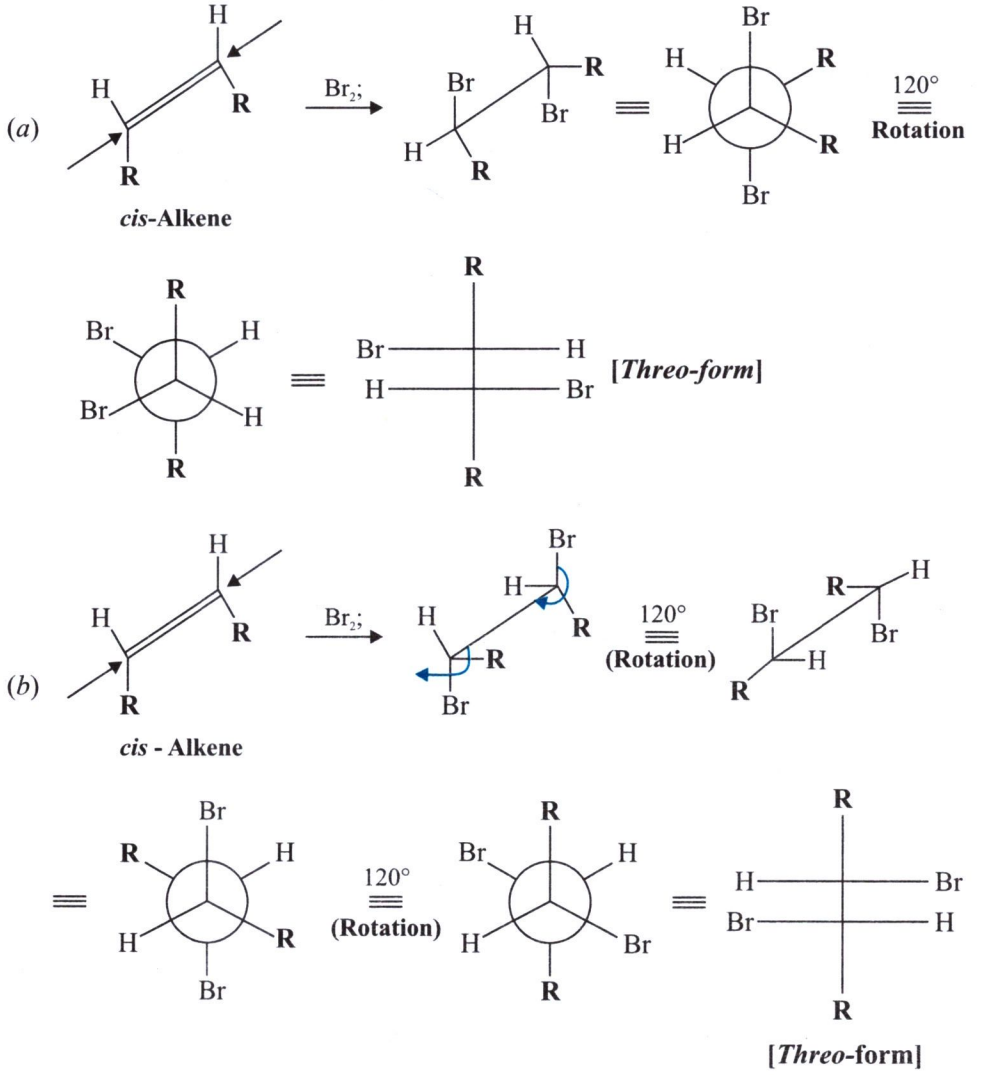
Based on the scientific revelations and authentication it has been duly revealed that the **stereochemical investigative study of bromination** suggests vehemently the **'addition'** to be ***'anti'*-stereospecific** in nature.

Remarks: Importantly, the crucial formation of the following ***two*** **products**

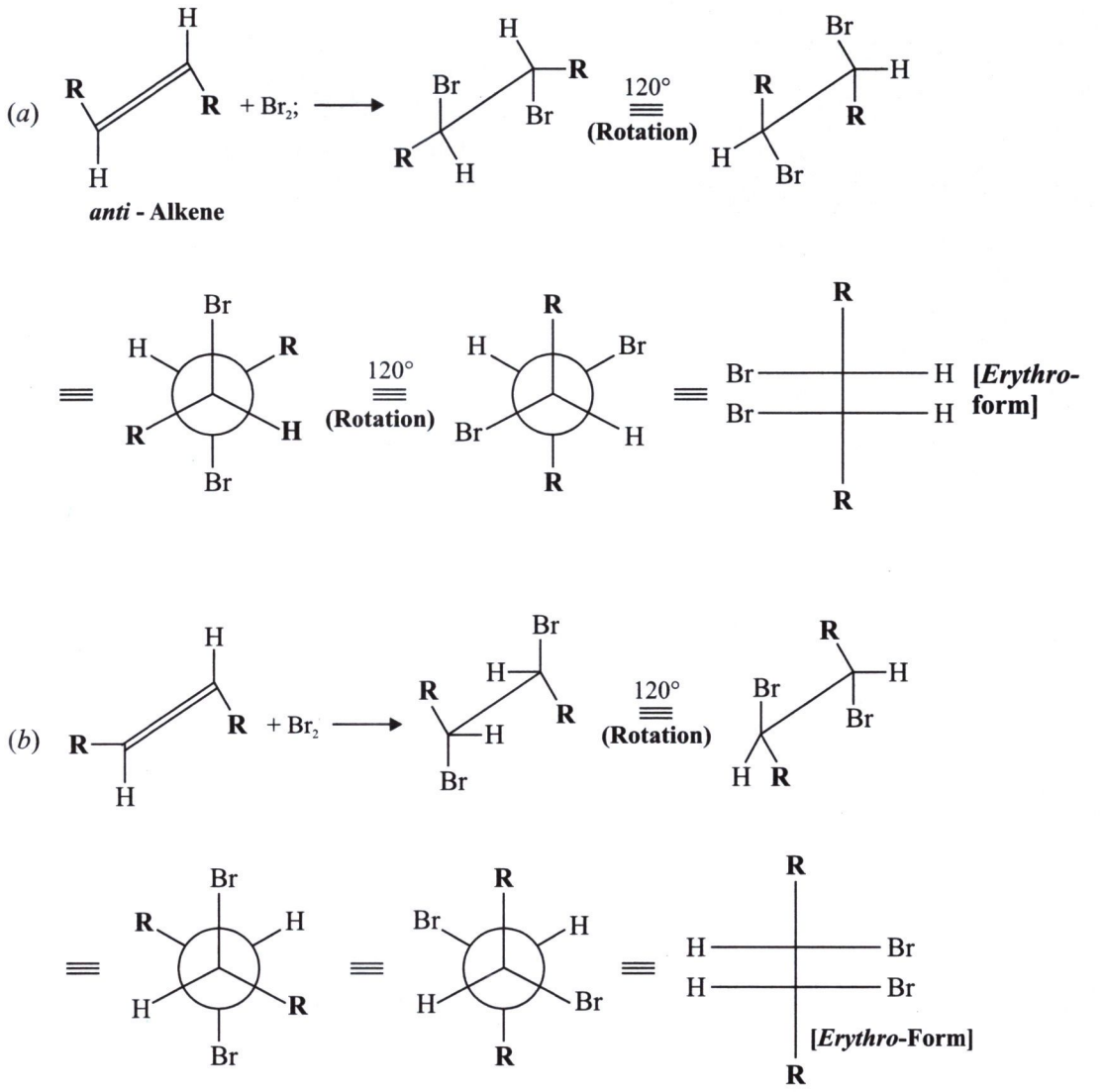
- ***Threo-d, l*-dibromide (racemic) is obtained from *cis*-Alkene: [Scheme-I] and**
- ***Erythro-d, l*-dibromide (meso) is resulted from the *Bromination* of *trans*-Alkene: [Scheme-II]**

Nevertheless, the formation of these products do provide ample solid evidence very much in favour of the above cited **mechanism**.

***Scheme* I: Formation of Recemic Threo-*d*, *l*-Dibromide**

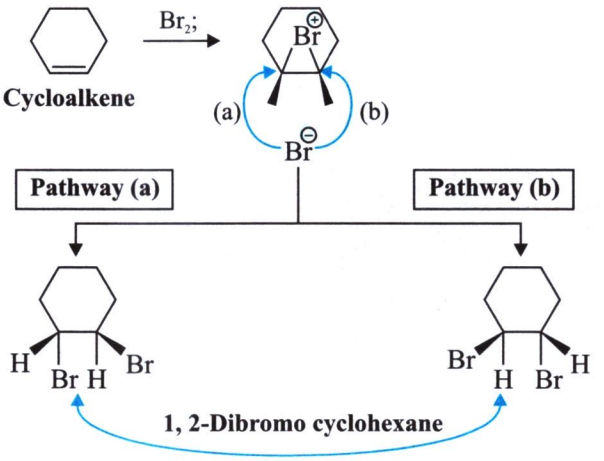


Scheme **II: Formation of *Meso Erythro d, l*-Dibromide**



❑ Bromination of Cycloalkene

It has been proven and demonstrated that the **bromination of cycloalkene** relates to a **stereospecific *anti*-addition**, and it may be expressed as under:

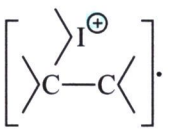


Remarks: Freeman (1975)* based on his kinetic studies revealed elegantly that the **bromination of an alkene** refers to a ***third order*** **kinetics** thereby providing an ***ample*** **satisfying evidence** for the above mentioned mechanism.

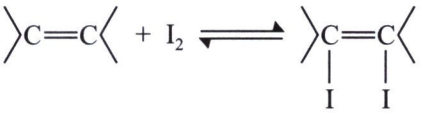
Thus, we have the following relationship:

$$\boxed{\text{Rate} = K\,[\text{Alkene}]\,[Br]^2}$$

(*b*) **Addition of Iodine (I_2) to Alkene [Iodination]:** Interestingly, the addition of **iodine to alkene (*iodination*)** represents broadly a so-called ***reversible reaction*** that specifically involves:

"electrophilic attack of *iodine* upon the *Carbon-Carbon double bond (C=C)*—thereby leading to the formation of a *cyclic intermediate i.e.*, the Iodinium Ion  .

Thus, we have:



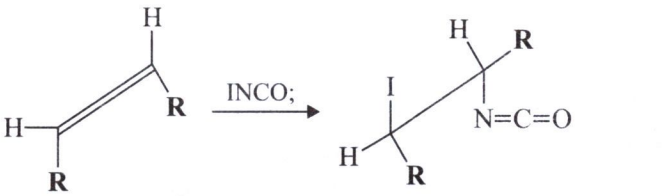
Anti*-stereospecificity Observed in '*Iodination*':** It is worthwhile to state here that the ***stereochemistry of iodination of alkene has not yet been proven with concrete scientific evidences; however, the so-called ***anti*-stereospecificity** may be observed explicitly as and when:

"an *Iodine-containing chemical entity* (compound) is being incorporated to *alkene i.e.*, addition of Iodine Isocyanate (INCO) to *cis*-and *trans*-alkene give rise to the formation of both *threo*-and *erythro*-3-iodoalkyl isocyanates".**

Hence, we may express the conversion of ***cis*-alkene** to ***threo*-3-iodoalkyl isocyanate (A)** in the presence of *iodine isocyanate (INCO)*; and also the conversion of the ***trans*-alkene** to *erythro*-3-iodoalkyl **isocyanate (B)** with **INCO**, as stated under:

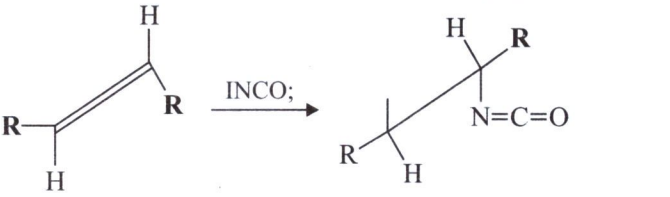
* Freeman F: *Chem. Rev.*, **75**: 439, 1975.

** Hasser A and Healthcock CC: *Tetrahedron Lett.*, 1125, 1964.



cis - **Alkene** ***Three* -3- Iodoalkyl isocyanate**

(A)



trans- **Alkene** ***Erythro* -3- Iodoalkyl isocyanate**

(B)

(*c*) **Addition of Fluorine (F_2) to Alkene [Fluorination]:** It has been well established that—'a radical phenomenon is involved perceptively in the addition of fluorine (F_2) to alkene'.

Thus, **fluorine (F_2)** is being incorporated to ***alkene*** in a perfect **non-stereospecific manner**, but with an absolute overall preference to the ***cis*-adduct**.

Points to Ponder:

1. However, the ***low temperature*** **addition** is generally found to be:
   - **'*ionic*' in nature,** and
   - **complete devoid of any formation of *rearranged product*.***
2. **Fluorination (F_2)** is supposed to involve critically the so-called **'carbocation intermediate'** since *Fluorine (F_2)* is known to be:

   "an extremely poor '*neighbouring-group participant*',"

and hence, there is a clear cut evidence that the involvement of a **bridging intermediate** does not exist at all.

❑ Electrophilic Addition to Bicyclic Alkene

The addition to the so-called **Bicyclic Alkene** *viz.,* **Norbornene**, ***trans*-2,3-Dichlorobornane**, ***syn*-Dichlorobornene**, ***cis*-2, 3-Dichlorobornane** etc., prevalently undergoes the ***electrophilic addition*** *via* an altogether different mechanism that is certainly found to be totally divergent from that of an—**'acyclic alkene'**; and thus, gives rise to the production of a ***mixture of reaction products*** perceptively.

Example: **Electrophilic addition** of *chlorine* (Cl_2) to **'Norbornene'** gives ***syn*-, *anti*-, and several rearranged reaction products** (Kwari and Takeshita, 1963)**.

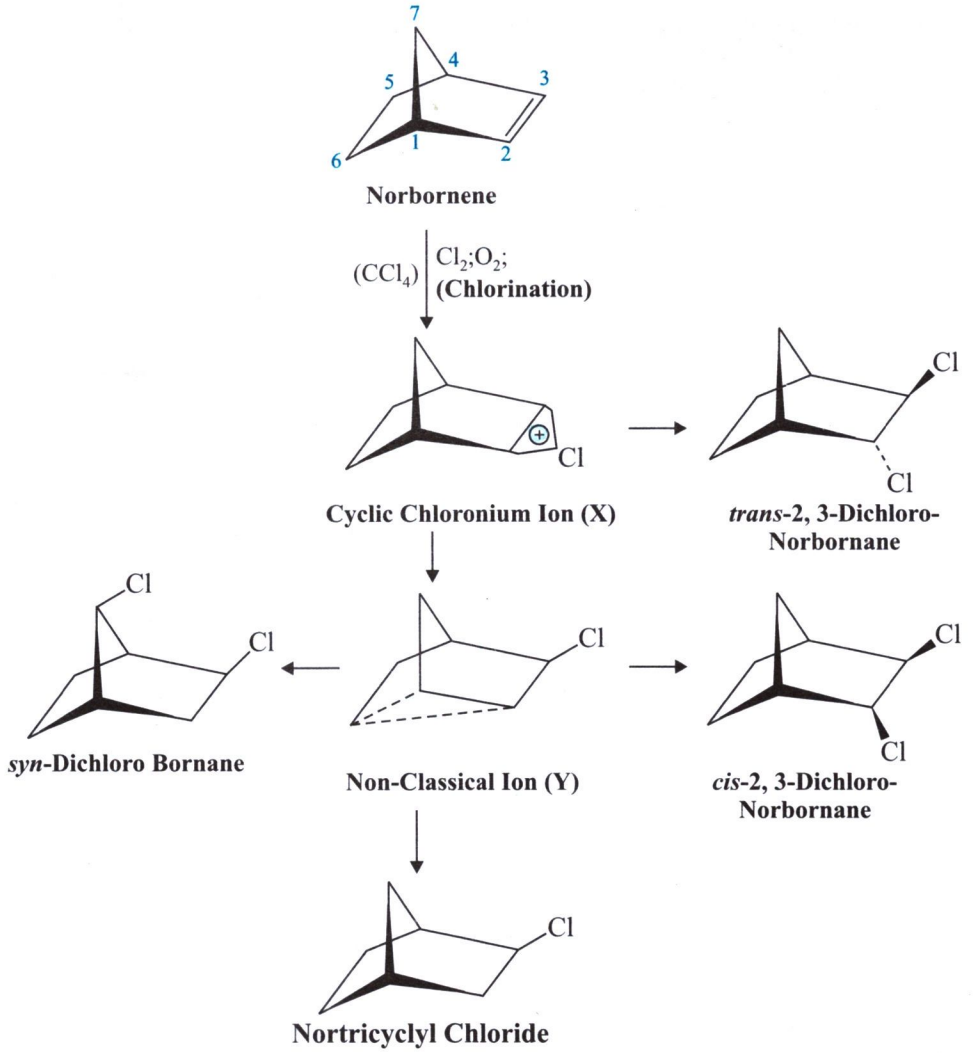
However, the formation of ***three*** **resulting products** may be duly accounted for; and hence, associated intimately with the critical involvement of ***two*** **ions** as the generated **'intermediates'** *viz.,*

* Merritt RF: *J Org. Chem.*, 31: 3871, 1966, *ibid*: *Am J Chem. Soc.*, **89**: 606, 1967.

** Kwai H and Takeshita T: *J Org. Chem.*, **28**: 670, 1963.

- **Cyclic chloronium ion (X);** and
- **Non-classical ion (Y).**

Thus, the formation of ***syn*-, *anti*-, and rearranged reaction products** may be shown as given under:



❑ Factors Governing Rate of Electrophilic Addition

There are *two* vital and important factors governing the ***Rate* of Electrophilic Addition,** namely:

- **Effect of Substituents,** and
- **Addition to Conjugate Dienes,**

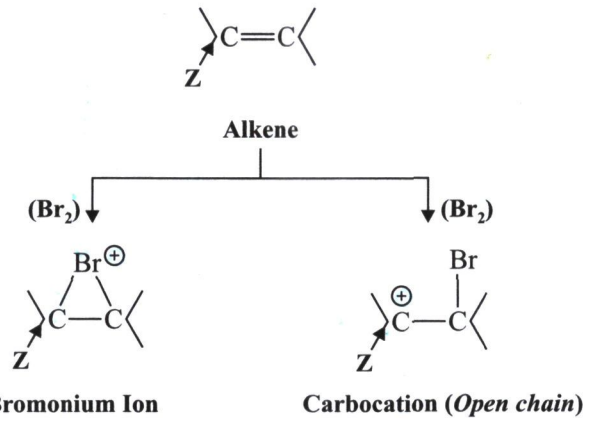
which shall now be discussed individually in the sections that follows:

(*a*) **Effect of Substituents:** Importantly, the **bromination** essentially involves the crucial role played by the so-called—***'Bromonium Ion'*, which being an intermediate +vely charged ion,**—formation of which actually serves as the—***Rate Determining Step***.

Besides, it has been duly ascertained that the very presence of the ***Electron-Donating Groups [EDGs]*** would help in a big way towards the ultimate **stabilization profile of the transition state (TS);** and thereby speed up the ***Rate of Electrophilic Addition*** predominantly; whereas, the same would be eventually slowed down by the so-called: ***Electron-Withdrawing Groups (EWGs).***

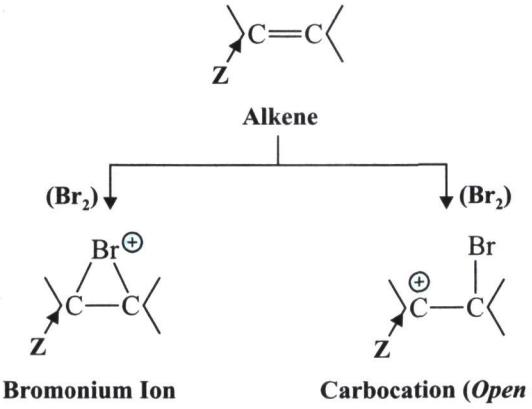
Thus, we may have the following expressions:

➢ **Electron Donating Groups [EDGs]**



Z = Electron Donating Group

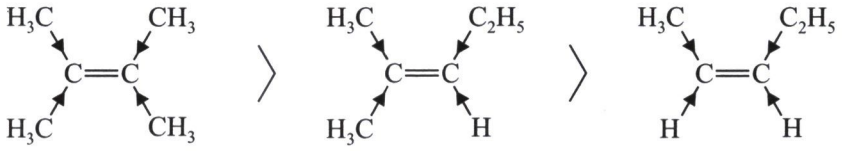
➢ **Electron Withdrawing Groups [EWGs]**



Z = Electron with drawing Group

Important Observations: Following are the ***two*** **important observations** with regard to the respective **effect of substituents** upon the **rate of electrophilic addition.**

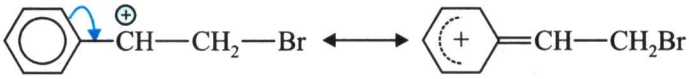
❑ The undermentioned order actually reveals the overall effect of the specific introduction of **Electron-Donating Groups [EDGs]** in the so-called **Transition State (TS)** upon the resulting observed **rate of addition reaction:**



Rate = 9.25×10^5 > Rate = 1.19×10^5 > Rate = 4.16×10^3

❑ It may also be observed critically that the ***phenyl moiety*** also helps in enhancing the so-called **rate of electrophilic addition** solely by virtue of the so-called:

"resonance stabilization of the '*Intermediate*' accomplished".

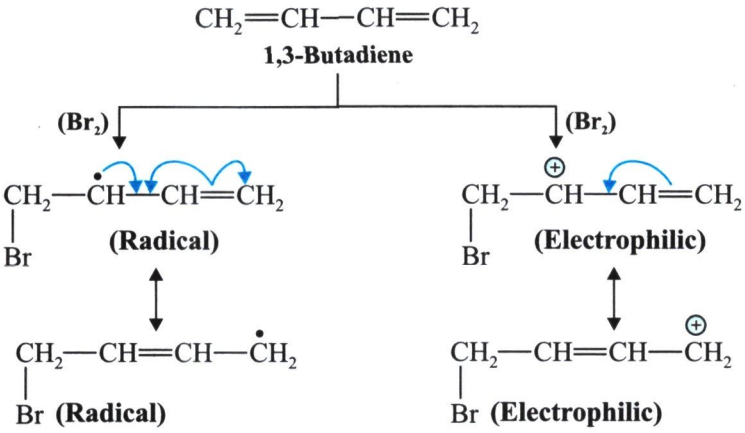


A Resonance Hybrid

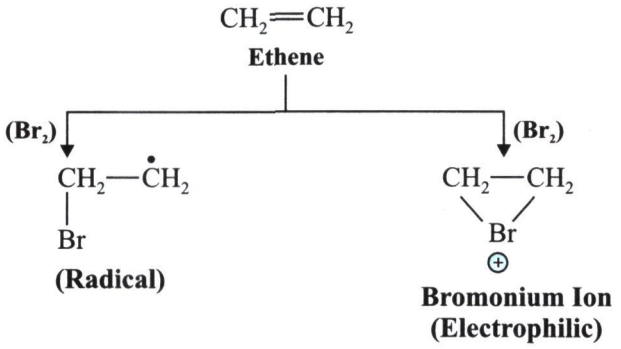
(*b*) **Addition to Conjugate Dienes:** Based on the secientific evidences and logical explanations it has been duly established that:

"conjugate dienes (*viz.*, Butadiene) are found to be rather more stable than the so-called *ordinary dienes* since the allylic-type intermediate are duly stabilized due to the critical *delocalization of electrons* more *vis-a-vis* the non-conjugate diene".

➢ **Addition to Conjugate Diene**



➢ **Addition to Alkene**



24.3 NUCLEOPHILIC ADDITION REACTIONS TO ALKENES AND ALKYNES

In a broader perspective, one may rightly take cognizance of the fact that:

"addition of a *Nucleophile* to the 'alkenes' as such does not take place at all; however, the presence of an appropriate *Leaving Group viz.*, aldehyde (CHO), Carbonyl (COR), ester (COOR), amide ($CONH_2$), nitrile (CN), nitro (NO_2) etc., may render the *alkene* to undergo the so-called Nucleophilic Addition Reaction".

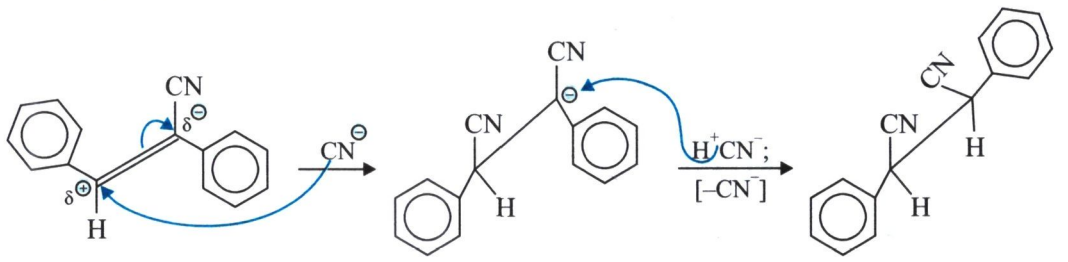
Besides, these aforesaid substituents do have a tendency to minimize the inherent **π-electron density** significantly at the typical ***alkene* C-atoms**; and hence, overwhelmingly favours the approach of a **nucleophile [$Y^{\ominus}$]**—by critically delocalizing the negative charge of the so-called ***'Carbanion Intermediate'*** perceptively. Thus, in order to afford a more effective and plausible delocalization of the ***negative charge*** the following *two* crucial means are being *adopted*, *practiced*, and *carried out*, namely:

- **Mesomeric Delocalization,** and
- **Negative Inductive Effect,**

which would be explicitly dealt with under the so-called **Nucleophilic Additon**,—as given under:

24.3.1 Mesomeric Delocalization

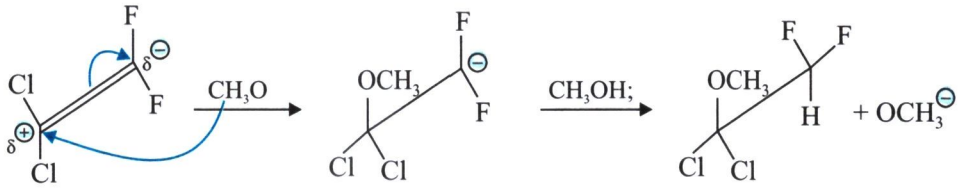
It is duly expressed as under:



1, 2-Diphenyl-1-cyano-ethene | **1, 2-Diphenyl-1,2-dicyano ethane carbanion** | **1, 2-Diphenyl-1,2-dicyano ethane**

24.3.2 Negative Inductive Effect

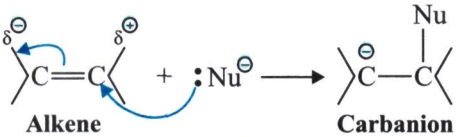
It may be expatiated as given below:



1-Difluoro-2-dichloro ethene | **2-Dichloro methoxy 1-difluoro ethane carbanion** | **1-Difluoro-2-dichloro methoxy ethane**

Mechanism of Nucleophilic Addition: The underlying ***mechanism of the* nucleophili addition** essentially involves the following ***two* cardinal** and sequential steps:

***Step* 1: Coversion of a Alkene to Carbanion**



Alkene | **Carbanion**

[Attack of Nucleophile on Electron Deficient Atom]

***Step* 2: Formation of Nucleophilic Addition Product**



Carbanion **Nucleophilic addition product**

[**Addition of Electron Deficient specie to Electron-Rich C-Atom**]

Remarks: These essentially include:

1. The ***first* step** of the ***mechanism of nucleophilic addition*** being the specific incorporation of a **nucleophile** to ***one of the double bonded C-atoms*** thereby giving rise to the formation of a **'carbanion'** that eventually gets combined with a ***positively charged specie*** to produce a **nucleophilic addition product** (see **step-2 above**).
2. However, the **IUPAC** designation of the so-called **Nucleophilic Addition** is either:

$\boxed{A_N + A_g}$ or $\boxed{A_N + A_H}$

Preferential Formation of More Stabilized Carbanion: It may be observed that the ensuing ***orientation of the* addition of an 'Unsymmetrical Adduct'**, such as:

$\boxed{HY}$ or $\boxed{XY}$

where, $Y^{\ominus}$ = Represents a **Nucleophile.**

That is, either **HY** or **XY** with reference to an **unsymmetrically substituted *alkene*** is usually defined as:

"preferential formation of the more *Stabilized Carbanion*".

Example: The *two* most glaring examples in this regard are:

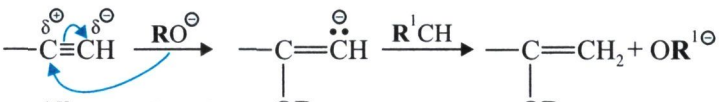
- **Friedel-Craft Acylation,** and
- **Cannizaro's Reaction,**

that are related to the **Nucleophilic Addition Reactions**. Besides, the frequently encountered ***powerful nucleophiles*** *viz.*, an **alkoxide ion [CH_3O^-, $C_2H_5O^-$]** duly present in an alcoholic medium, **may not need actually any *'catalyst'* to attack on the alkynes [CH≡CH];** whereas, the corresponding ***weak* nucleophiles do eventually require *catalyst* *viz.*, Hg^{2+} ions.**

Therefore, we may categorically illustrate the **Nucleophilic Addition** at the ***'Alkynes'*** by the aid of the following ***two* classical examples:**

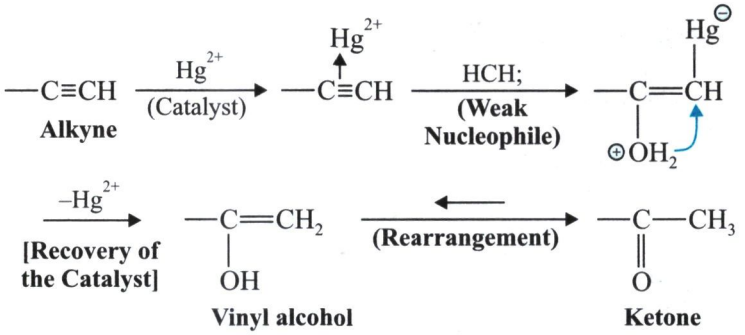
- **Nucleophilic Addition of Strong Nucleophile in Alkyne,** and
- **Nucleophilic Addition of Weak Nucleophile in Alkyne (in the presence of a *Catalyst*).**

***Scheme*-1: Nucleophilic Addition of Strong Nucleophile in Alkyne**



Alkyne **Alkoxide** **Carbanion**

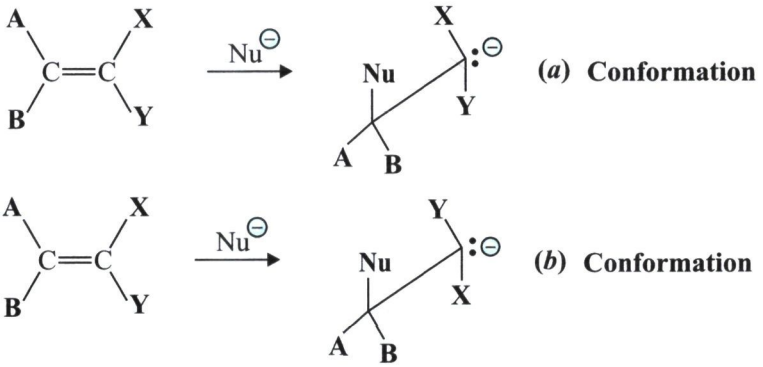
Scheme-2: **Nucleophilic Addition of Weak Nucleophile in Alkyne (in the presence of a *Catalyst*)**



Thus, an **alkyne** yields a **ketone** in the presence of a **catalyst**.

Carbanion Mechanism Initiates Nucleophilic Addition: If it holds good indiscriminately, the so-called **addition reaction** must be by all means a **non-stereo specific one**.

Thus, one may take the following illustration to extend the discussion a step further to the stereochemistry dictum; and hence, following are the **E** and **Z** forms of a compound **ABC=CXY**:



Remarks: Importantly, both the above **conformations (*a*) and (*b*)** are observed to be not only **most favourable** but also yield the **same product** on being subjected to the ***nucleophilic attack*** perceptively. Thus, it would serve as one of the ***two* possible diastereoisomers;** and hence, the said reaction is very much **stereoselective in nature**. However, the resulting ***cis*-and *trans*-isomers** fail to produce **different isomers;** and, therefore, is **not stereospecific in character**.

Example: Following are the *two* classical examples of **Nucleophilic Addition,** namely:

- **Michael Condensation*,** and
- **Cyanoethylation**.**

Marcantioni *et. al.* (2006)*** recently explored the **diastereoselective synthesis** of the ***tertiary* alcohols** by performing the critical **nucleophilic addition** of:

"the α-substituted β-keto esters".

* Kamimura A *et al.*: *J Org. Chem.*, **55:** 2437, 1990.

** Ballini R et al.: *Synthesis*, 231, 1988.

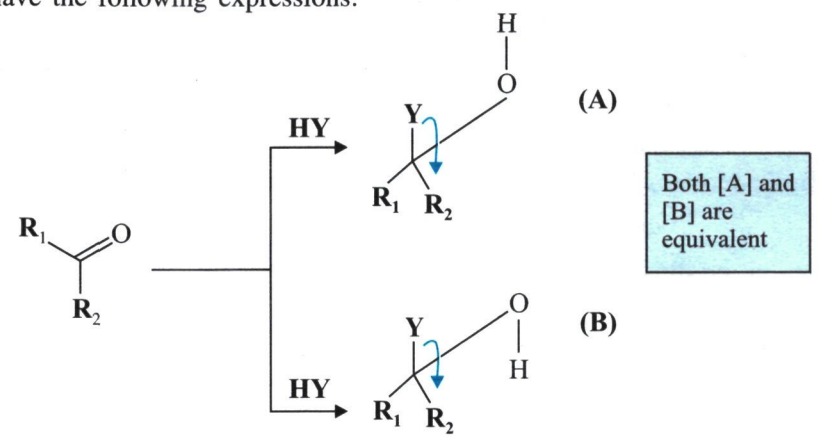
*** Marcantioni E *et al.*: *ARKIVOC*, 175-180, 2006.

❑ Stereoselectivity of Nucleophilic Addition to the Carbonyl Compounds

At the very outset it may be understood that the **nucleophilic addition of HY to the carbonyl bond (>C=O)**,—yield an array of **alternate products** that are found to be:

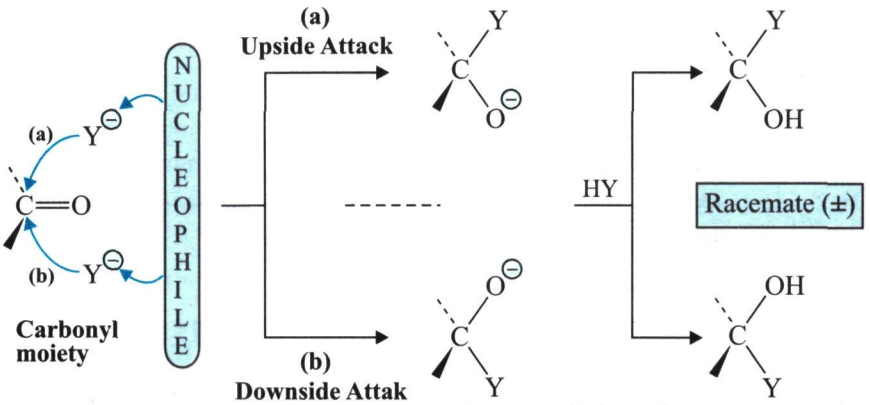
"identical by virtue of the free rotation about the carbonyl (>C=O) bonds *i.e.*, the reaction products are not either *cis*-or *trans*-".

Let us have the following expressions:



Importantly, it has been duly proven and ascertained that the further careful attack of the **Nucleophile $Y^{\ominus}$** critically renders the ***Carbon to a Chiral Centre*** (*i.e.*, the C-atom becomes **asymmetric in character**).

Therefore, the targeted attack of the **nucleophile ($Y^{\ominus}$)** upon the **carbonyl (>C=O) moiety** ultimately yield the **racemate (±)**,—as depicted in the following expression:



Remarks:

1. It has been duly observed that the attack of the **nucleophile ($Y^{\ominus}$)** either from **upside (*a*)** or from **downside (*b*)** upon the **chiral centre** (*i.e., carbon of carbonyl moiety*) are found to be equal **statistically**.
2. In a situation, when ***two*** **chiral alkyl moieties** are duly attached to the **carbonyl C-atom**,—the resulting two forms of the carbonyl compound critically comprising:

   "the asymmetric α C-atoms are not the same—thereby ruling out the scope of formatin of a *racemate* (±)".

Diastereo Selective Reactions: 1,2-Asymmetric Induction [Cram's Rule]*: Interestingly, in the **stereoselective reactions**, a specific reagent may virtually differentiate the so-called ***stereoheterotopic units*** of a **substrate**. Thus, in a specific instance when the **stereoheterotopic unit** happens to be an ***enantiotopic centre***—the reaction is known as:

"Enantiotopos—Differentiating Reaction".

If it has an **Enantiotopic Face,** the reaction is called as:

"Enantio face—Differentiating Reaction".

In the same vein, if the **stereoheterotopic unit** designates a so-called ***diastereotopic centre,***—the ensuing reaction is **diastereotopos-differentiating reaction;** and hence, for a *reaction* located strategically at a **diastereotopic face** it is invariably known as:

"diastereo face—differentiating reaction".

Furthermore, in the **diastereoselective reactions** one may critically observe the formation of ***two*** **diastereoisomers** usually in an *unequal proportion* by carrying out the intended reaction of an ***achiral reagent*** either with:

- **diastereotopic centre** or
- **diastereotopic face.**

NOTE: **Based on the aforesaid scientific evidences it has been duly inferred that the control and management of either:**

- ***Stereodifferentiation*** **or**
- ***Stereoselectivity,***

is exerted perceptively by the *chiral centre* already present in the substrate.

Another school of thought believes vechemently that if the reaction is **reversible** then we may have predominantly *two* or more reaction products that are ***fairly*** **stable thermodynamically;** whereas, for the so-called **irreversible reactions** (usually performed with **Grignard's Reagent** and **Lithium Aluminium Hydride [$LiAlH_4$],**—one may lay hands on to the ***favourable product*** rather quickly. It is, however, pertinent to state at this point in time that:

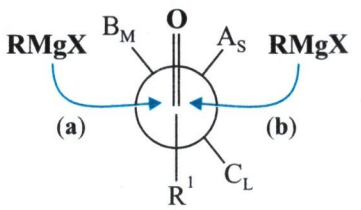
"the desired (intended) product is solely decided by the Cram's Rule".

Therefore, the **Cram's Rule** significantly predicts the precise and exact **diastereoisome** which is generated from the ***addition reaction*** to the corresponding **carbonyl (>C=O) bond of ketones** essentially consisting of the **asymmetric α-C-atom**.

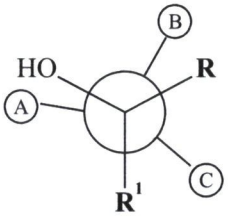
Example: Let us look into the following example wherein the **Grignard's Reagent [RMgX]** to perform **irreversible reactions** in chemical entities having predominantly the **carbonyl (>C=O) bond of ketones**, so as to obtain **'*Major*'** and **'*Minor*'** products.

* G. am. DJ and Abdel Hafez CA: *J. Am. Chem. Soc.*, **74**: 5852, 1952; Gram DJ and Kopecky KR, *ibid*, **81:** 2748, 1959; Erman WE and Flantt JJ: *J Org. Chem.*, **27**: 1526, 1962.

IRREVERSIBLE REACTIONS



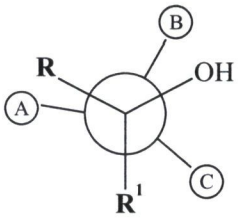
(a) Favourable Stereo-chemically



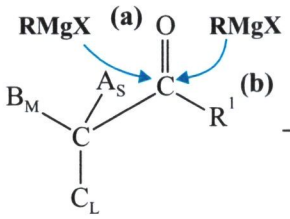
Major product

Predominates Grossly

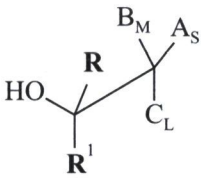
(b)



Minor product



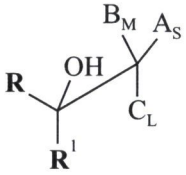
(a)



Major Product

Predominates Grossly

(b)



Minor Product

Key to Abbrevations

A,B,C	=	Substituents	**RMgX**	=	Grinard's Reagant
B,M,L	=	Size of substituent	**(a)**	=	Upside the carbonyl e-atom
A_s	=	Small substituent	**(b)**	=	Downside the carbonyl e-atom
B_M	=	Medium substituent			
C_L	=	Large substituent			

Remarks:

1. The **Cram's Rule** predicts rightly which **diastereoisomer** formed duly by the ***addition reaction*** to the respective **Carbonyl (C=O) bond** of **'ketones'** comprising the so-called **asymmetric α-carbon atom,**—that would predominate squarely.
2. In the aforesaid example one may observe specifically that the **O-atom** present in the *carbonyl (C=O) moiety* readily orients itself in between the available both ***small* and *medium* sized substituents** [*i.e.*, $\mathbf{A_s}$ **to** $\mathbf{A_m}$]. In this way, it enables the attack of the ***nucleophile*** which is largely influenced by the ***steric factor*** *i.e.*, ensuing ***nucleophile*** does attack perceptively:

   'on the side of the plane that is adequately substituted with the small sized functional moieties'.
3. Therefore, the so-called **relative proportion of the diastereoisomers** so produced are usually *governed and controlled* by ***two* important factors,** namely:
   - **steric control aspect;** and
   - **product control profile.**
4. Interestingly, the so-called ***'major product'*** is formed generously right from the **attack of the nucleophile** obviously from the relatively **less-hindered side;** and hence, the *two* guiding factors are found to be **contradicting each other profoundly**.
5. The **Cram's Rule** makes it quite feasible and possible to *find and determine precisely*: **"which *product* would be formed in the *major quantum* or we may conclude intelligently that the *most preferred reaction* should occur *via* the *thermodynamically stable* and *less-crowded transition state (TS)*".**

Points to Ponder*:** Amazingly, beyond the so-called ***steric control and ***product control*** profiles—there are quite a few equally vital and important factors that do influence largely the stereoselectivity of **Nucleophilic Addition,** such as:

- **Dipole-Dipole Interactions,**
- **Complex Formation,** and
- **Hydrogen-Bond Formation.**

Suggested Reading

Bruckner R: **Advanced Organic Chemistry**, Academic Press, Harcourt (India) Pvt. Ltd., New Delhi, 2003.

Carey FA and Sundberg RJ: **Advanced Organic Chemistry Part A and B,** 5th ed., Springer International, New Delhi, 2015.

Cook and Carruthers [Eds]: **Progress in Organic Chemistry, Vol. 6,** Butterworths, London (UK), 1964.

Morrison RT *et. al.*: **Organic Chemistry,** 7th ed., Pearson-Prentice Hall, New Delhi, 2012.

Raphael R: **Acetylenic Compounds in Organic Synthesis**, Butterworth, London (UK), 1955.

❑❑❑

SECTION 5

Some Novel Reactions in Organosilicon Chemistry

Chapter 25. Accelerated Organic Synthesis with Organosilicon Compounds

Chapter 25

Accelerated Organic Synthesis with Organosilicon Compounds

LESSONS AT A GLANCE

25.1 Introdouction
- 25.1.1 Aims and Objectives
- 25.1.2 Selection Criteria for Silylating Agents
- 25.1.3 The Taft Equation
- 25.1.4 Applications of Taft's Parameter

25.2 Organosilicon Polymers

25.3 Comprehensive Account on Accelerated Organosynthesis with Organosilicon Compounds
- 25.3.1 Allyolsilanes and Related Nucleophiles
- 25.3.2 Enantio Selective Allylation
- 25.3.3 Extended Allylsilane Chemistry
- 25.3.4 [3 + 2] Annulation Approaches
- 25.3.5 Organosilanes in Cross-Coupling Reactions
- 25.3.6 The Brook Chemistry [Brook Rearrangement]
- 25.3.7 Biological Applications of Organosilanes

25.1 INTRODUCTION

A survey of literature reveals that in the recent past the enormous usage of the **Organosilicon Compounds** in the domain of **organic chemistry** has virtually gained a tremendous ground so as to occupy a coveted status as:

"an ever-increasing potential and vital field".

Amazingly, an array of altogether newly research-based products:

- **Silylating Agents,** and
- **Organosilicon Compounds,**

have duly bear recognized across the globe.

Silylating Agents*: The silylating agents** refer to such agents that are being employed intelligently to replace the so-called 'active-H-atom of a chemical species having the ***silyl moiety **[—SiRR′R″]**.

Examples: A host of common **functional moieties** *viz.*, **hydroxy (-OH), carboxylate (-COOH), amino ($-NH_2$), amide ($-CONH_2$),** and **thiol (-SH)** are duly converted into:

- **-OSiRR′R″** • **-COOSiRR′R″** • **-NHSiRR′R″** • **-CONHSiRR′R″** and
- **-SSiRR′R″** respectively.

25.1.1 Aims and Objectives

In a broader perspective, the ***critical replacement of the*** **active hydrogens** substantially ***reduces*** the so-called:

- **reactivity of a functional moiety,** and
- **minimizes significantly the polar interactions profile,**

for instance—the **hydrogen bonding episode**.

Nevertheless, these replacement may be carried out actually for several good reasons, but certainly and typically do fall under one or more of the following aims/objectives perceptively, namely:

(*i*) **Protecting a Reactive Functions Moiety During One or More Chemical Reactions.**

(*ii*) **Improving Grossly the Selectivity of a Chemical Reaction.**

(*iii*) **Improving the overall Stability During Distillation.**

(*iv*) **Improving Solubility in Polar and/or Non-Polar Solvents.**

(*v*) **Increasing Volatility by Decreasing or Eliminating the Hydrogen-Bonding.**

Table: 25.1 records *eleven* most prevalent **Silylating Agents** that are almost being employed on an ***industrial scale***.

Table 25.1: The Commonly Used Silylating Agents Being Used on an Industrial Scale.

S.No.	Grade	Formula	Molecular Weight (g. mol^{-1})	d	n_D	Boiling Point [0°C/mm Hg]	Flash Point (0°C)
1	**KA-31**	Na_3SiCl	108.6	0.85	1.387	57	15
2	**HMDS**	$Me_3SiNHSiMe_3$	101.4	0.77	1.408	126	17
3	**BTSU**	$Me_3SiNHCONHSiMe_3$	204.4	—	—	(212)*	—
4	**BSTFA**	$Me_3SiOC(CF_3)$=$NSiMe_3$	257.4	0.07	1.381	46/17	34
5	**TMST**	$Me_3SiOSO_2CF_3$	222.3	1.23	1.363	140	40
6	**TESC**	Et_3SiCl	150.7	0.89	1.429	145	39
7	**HBSC**	i-Bu_3SiCl	234.9	0.88	1.446	101/10	87
8	**TBMS**	*tert*-$BuMe_2SiCl$	150.7	—	—	125	28
9	**TIPSC**	i-Pr_3SiCl	192.8	0.91	1.452	59/8	63
10	**TDSC**	$TxMe_2SiCl$**	178.8	0.91	1.449	55/10	49
11	**CIPS**	Cl (i-$Pr)_2SiOSi$ (i-$Pr)_2Cl$	315.4	1.01	1.453	108/14	110

* **Melting Point (°C)**

** **Tx = Thexyl**

25.1.2 Selection Criteria for Silylating Agents

Following are the ***two*** **cardinal** factors which solemnly help in the **Selection Criteria** for the ***silylating agents*** that find their enormous utility as stated earlier, such as:

- ***First*: Reactivity:** It virtually refers to the **type of by-product, price factor** and **availability** are quite often do play an important role that should always be taken into consideration whenever an attempt is made to undertake the critical development of a ***synthetic process*** **(ultimately scaled-up to an industrial scale).**
- ***Second*: Stability:** It relates certainly to the so-called:

  "stability of the resultant silylated functional moiety",

  which is mostly determined by the prevailing:

  —"combined steric-bulk of the alkyl moieties attached intimately to *Silicon* (*Si*) (R, R′, and R″)".

Important Observations

In a broader sense, since the ***steric bulk*** of the **alkyl moieties** get enhanced perceptively,—the ensuing **stability of the silylated functional moieties** also get increased accordingly.

NOTE: **For the sake of convenience, the observed *stability* of a silylated functional moieties may be determind with great ease and fervour by making use of the *Taft's Parameters viz.*, as those listed in Table: 25.2.**

Nevertheless, the proper selection criteria for the **silylating agents** may also be largely influenced by the aid of **'Additional Reactivity'** profile.

Example: The **1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (CIPS) Cl (i-Pr)$_2$SiOSi(i-Pr)$_2$Cl** is a ***bi-functional silylating agent*** which is found to be grossly effective in the **synthesis of nucleosides** being used as the **anti-HIV Drugs.**

Table 25.2: Steric Parameter E_6^{Si}: Taft's Parameter*

S.No.	R	ESSi	S.No.	R	ESSi
1	**Methyl**	0	7	***Sec*-Butyl**	– 0.704
2	**Ethyl**	– 0.261	8	**Cyclohexyl**	– 0.767
3	**n-Propyl**	– 0.315	9	**Me_3CCH_2**	– 0.589
4	**n-Butyl**	– 0.348	10	**Et_2CH**	– 0.816
5	**Iso-Butyl**	– 0.400	11	***tert*-Butyl**	– 1.670
6	***iso*-Propyl**	– 0.677	12	**Tx (Thexyl)**	– 1.899

Thus, we may have the following expression:

$$\mathbf{R\bullet}\ (CH_3)_2\ SiCl \xrightarrow[(\text{In Acridine})]{\text{Aq. Dioxane;}} \mathbf{R\bullet}\ (CH_3)_2\ SiOH + HCl$$

[where: R = An Aliphatic Moiety, (log k_{ul})/2.1 = E_S^{Si}]

* Shimizu N *et al.*: *Chem. Lett*, 1263-66, 1992.

25.1.3 The Taft Equation

Definition: The **Taft Equation** refers to a ***structure-activity relationship (SAR)*** pertaining to the so-called **Aliphatic Compounds**. The *model reaction* usually observed in the ***basic hydrolysis of esters*** *viz.*,

- **Esters (X—CH_2—COOR):** In this case, the methylene moiety (—CH_2—) does act as an **insulating moiety** for any resonance between the *two* prevailing groups: **halide (—X)** and **ester (—COOR)**. However, the precise and exact nature of **halide (—X)** critically upon the **rate of the ensuing—'hydrolytic reaction'**, therefore, is chiefly:
  - ➢ **polar (inductive),** and ➢ **steric (only to a smaller degree).**

We may have the following reaction:

$$\underset{\textbf{(An Ester)}}{X—CH_2—COOR} \xrightarrow{NaOH_{aq.}} X—CH_2—COONa + \underset{\textbf{Alcohol}}{ROH}$$

Therefore, an ***equation*** may be expressed as given under:

$$\log\left(\frac{K}{K_H}\right)_{Base} = p^*\sigma^* + E_s$$

where, E_s = Contribution of the *steric factor.*

Remarks: Taft specifically eliminated this factor from the observation that for the observed ***acid-catalyzed hydrolysis*** **of esters the *p*-value** *i.e.,* the **slope of the graph is indeed quite small,** and this clearly means that for the so-called **acid-catalyzed reaction,**—the ***first factor*** **for $p^*\sigma^*$ may be neglected (or ignored) completely.**

Therefore, we may have the following expression:

$$\log\left(\frac{K}{K_H}\right)_{Base} = p^*\sigma^* + \log\left(\frac{K}{K_H}\right)_{Acid}$$

or

$$\log\left(\frac{K}{K_H}\right)_{Base} - \log\left(\frac{K}{K_H}\right)_{Acid} = p^*\sigma^*$$

That is:

$$\log\frac{(K/K_H)_{Base}}{(K/K_H)_{Acid}} = p^*\sigma^*$$

or

$$\log\frac{(K)_{Base}/(K)_{Acid}}{(K_H)_{base}/(K_H)_{Acid}} = p^*\sigma^*$$

Thus, the **LHS** is very much akin to **log K/K_H** for which ***Taft Equation*** takes the following form:

$$\log\frac{K}{K_H} = p^*\sigma^*$$

where, **σ^*** = Taft Substitution constant containing exclusively the **inductive polar** factors of the substituents duly present in the **saturated C-compounds**.

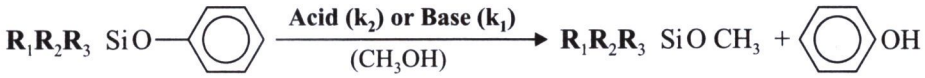
25.1.4 Applications of Taft's Parameter

First of all let us consider the following expression based on Taft's Equation:

$$[\Sigma E_S^{Si} = E_S^{Si}(R_1) + E_S^{Si}(R_2) + E_S^{Si}(R_3)]$$

Since the plots of **log (k)** *vs* Σ_S^{Si} explicitly show **Linear Relationships;** hence, the relative stability of **'silylated compounds'** may be determined quite easily and conveniently.

We may have the following relationship:



Phenol

Based on the aforesaid scietific evidences and interpretations, we may reasonably lay hands on the following ***two*** **classical examples:**

(*a*) **Base-Catalyzed Methanolysis of Trialkylphenoxysilanes,** and

(*b*) **Acid-Catalyzed methanslysis of Trialkyl phenoxysilanes.**

25.1.4.1 Base-Catalyzed Methanolysis of Trialkylphenoxysilanes

The following Fig. 25.1 shows explicitly the **Linear Relationship** plot between the **log k_1.** (*i.e.,* **second order rate constant**) *Vs* **Taft's constant.**

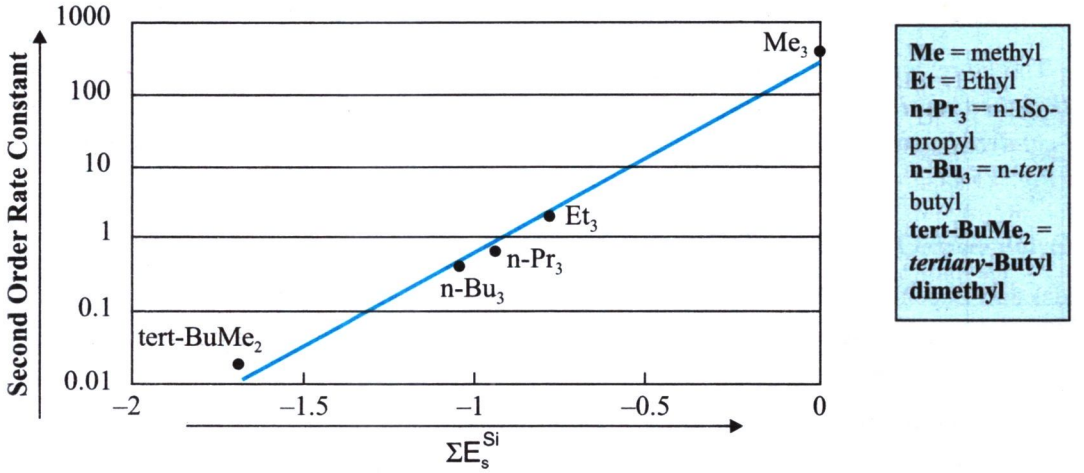


Fig. 25.1: Linear Relationship showing the Base-Catalysed Methanolysis of Trialkylphenoxysilanes.

Explanations

The various aspects in Fig. 25.1 may be explained as under:

1. The *second order* **Rate Constant (k_1)** is found to be maximum for **Me_3 (~ 500)** followed by **Et_3 (~ 3), n-Pr_3 (~ 0.9), n-Bu_3 (~ 0.6),** and **tert-$BuMe_2$ (~ 0.02).**
2. A **vivid linearity** does prevail between the entities starting from ***tert*-$BuMe_2$** and **Me_3.**
3. Hence, it fully ascertains and justifies the **base-catalyzed methanolysis of trialkylphenoxysilanes.**

25.1.4.2 Acid-Catalyzed Methanolysis of Trialkylphenoxysilanes

Fig. 25.2 illustrates clearly the **Linear Relationship** plot between the **log k_2** (*i.e.*, second order rate constant) *Vs* **Taft's Constant**. Importantly, the **n-Bu_3** and ***tert*-$BuMe_2$** spots do not follow the **linearity** completely.

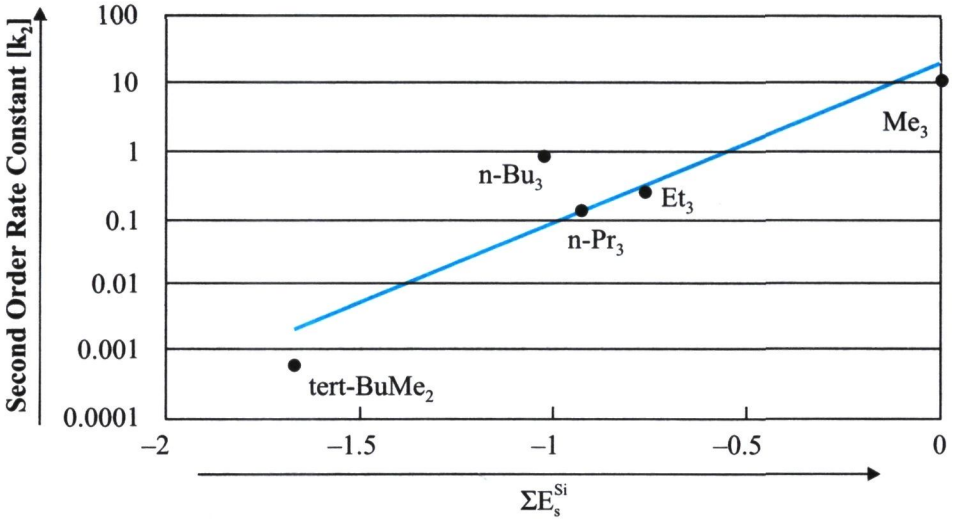


Fig. 25.2: Linear Relationship Depicting the Acid-Catalyzed Methanolysis of Trialkylphenoxysilanes.

Therefore, one may explicitly arrive at the *ultimate conclusion* that the ***methanolysis of trialkylphenoxysilanes*** **do not** adhere to the **total linear relationship** specifically in the ***acid-catalyzed*** **process**; whereas, the same is almost followed rigidly in a ***base-catalyzed*** **process** (see *Fig. 25.1*).

25.2 ORGANOSILICON POLYMERS

Friedel and Ladenburg (1874)—based on their earlier observations indicated that:

'the ultimate *complex products* are accomplished by heating together'

- **alkylsilanoids [$R_2Si(OH)_2$** and
- **Alkylsilanetriols [$RSi(OH)_3$].**

However, Kipping* was the very first *investigative researcher* who realized vehemently that:

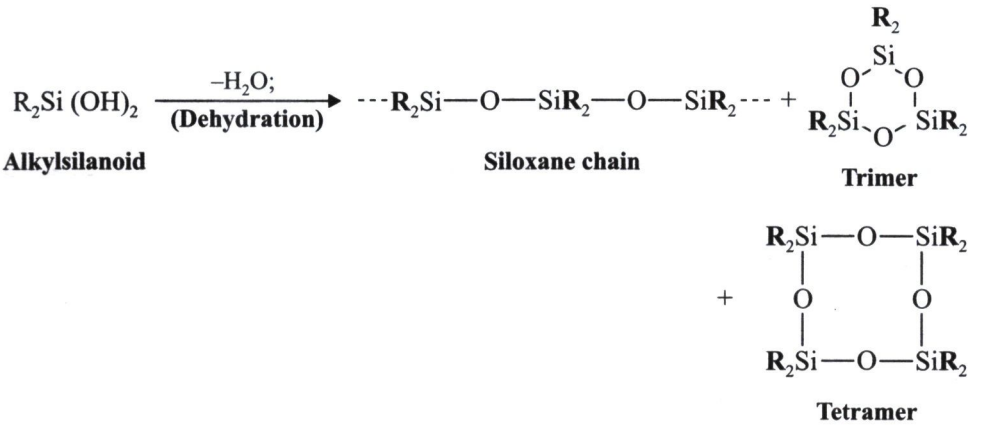
"these substances are really the so-called *intermolecular condensation products* of the 'silanols' (1908)".

In the recent past, both *American* and *Russian* manufacturers were pioneer in the proper utilization of the aforesaid polymerization—**'for the gainful preparation of the products of great interest and utility'**.

***Dehydration of Dialkylsilanediol*:** It invariably leads to a **long-chain anhydrides** and the **cyclic polymers** *viz.*, specifically the so-called: **Trimer** and **Tetramer**.

* Kipping FS (1863-1940); b. Manchester (UK); Ph.D.; Nottingham, *J. Chem. Soc.*, 849, 1951.

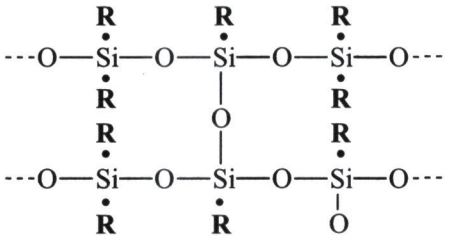
We may have the following expression:



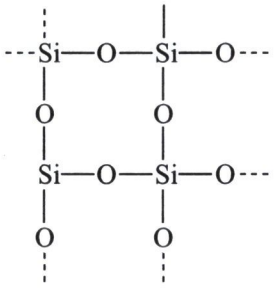
The **3D-Polymers** are duly obtained from the respective **polymerization** of an **alkylsilanetriol**—wherein each **Si-stom** is:

"critically bound into a completely cross-linked rigid structure resembling to that of Silica (Si)".

Importantly, the ensuing **'intermediate polymers'** essentailly comprising *occasional cross-links* (as may be observed in the **siloxane resin formulated**),—are duly obtained by the *copolymerization* of an **Alkylsilanetriol** and a **Dialkylsilanediol**.



The *Siloxane* network



The Silica [Silicon dioxide]

Remarks: These essentially include:

1. When **'R'**—designates either **Methyl (CH_3)** or **Ethyl (C_2H_5)**, the corresponding **'resins'**—are found to be **extremely stable** to both:
   - **Heat** and **Oxygen (O_2),**

   and hence, they are well-suited for extensive usage in the **'electrical insulation'** purposes.
2. Preparation of ***'Silicone Rubber'*** is usually carried out from the **long-chain polymer of *Dimethylsilanediol***, wherein the so-called **cross-links,** are being introduced meticulously during the ***'curing phenomenon'*** (normally accomplished by *controlled oxidation process*).

Examples:

1. **Methylsilicone Rubber** offers the inherent added advantage *vis-a-vis* the so-called **Natural Rubber** (*obtained from the plant-exudate product*) plus the **Other Synthetic Products** in terms of its supermacy due to the following cardinal reasons:
   - **more stability profile to heat,**
   - **better stability to chemical reagents,** and
   - **mostly remains '*flexible*' at very low temperatures.**
2. **Linear Polymers of Dimethylsiloxane:** having the prevalent terminal ***trimethylsilyl moieties*** are found to be extremely **'Valuable Oils'** since they do change their ***viscosity*** much more slowly in comparison to the respective **'Hydrocarbon Oils'** do.

❑ **The Silicone Tetrahalides:** Evidence from the literature reveals that the most readily available *starting materials* for the preparation of the **'monomer'** are the **Silicone Tetrahalides.**

Kipping (1951)* first and foremost introduced the use of the **Grignard reagent** for the preparation of the desired **alkyl silanols.**

Thus, we may have the following reactions:

$$SiCl_4 + \mathbf{R}MgX \longrightarrow \mathbf{R}SiCl_3 \xrightarrow{H_2O} \mathbf{R}Si(OH)_3$$

$$\mathbf{R}SiCl_3 + \mathbf{R}MgX \longrightarrow \mathbf{R}_2SiCl_2 \xrightarrow{H_2O} \mathbf{R}_2Si(OH)_2$$

Comments: The aforesaid reactions cannot be controlled/monstired to ***one specific stage***; and, therefore, the resultant product is an admixture of such substances that essentially do comprise:

"right from *one* to *four* alkyl moieties".

Direct Synthesis of R_2SiCl_2 [Dialkyl dichlorosilane]: Rochow (1940)** proposed a direct synthesis by making use of the ***vapour-phase reaction*** of:

"alkyl halides with *Silicon (Si)* at high temperature under the catalytic action of *Cu* or *Ag*".

Thus, we may have the following reaction:

$$Si + 2\,RCl \longrightarrow R_2SiCl_2$$

Silicon **Alkyl halide** **Dialkyldichlrosilane**

NOTE: **Interestingly, again we may lay hands on to an admixture of the so-called—'*related organosilicon halides*'; and hence, the usual separation could be accomplished by distillation.**

* Kipping FS: *J. Chem. Soc.*, 849, 1951.

** Rochow EG: b. 1909: Newark N.J., Ph.D., Cornell General Electric Co., Harvood Univ.

25.3 COMPREHENSIVE ACCOUNT ON ACCELERATED ORGANOSYNTHESIS WITH ORGANOSILICON COMPOUNDS

Preamble: Having understood the fundamentals of **Organosilicon Compounds** let us have a comprehensive account on the so-called accelerated organosynthesis with them in a systematic and elaborative manner.

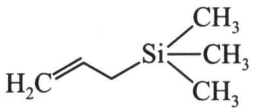
Therefore, it would be worthwhile to extend the discussion with appropriate *explanations*, *exemplifications*, and *delibrations* with respect to the following important aspects, namely:

(*i*) **Allylsilanes and Related Nucleophiles,**
(*ii*) **Enantioselective Allylation,**
(*iii*) **Extended Allylsilane Chemistry,**
(*iv*) **Annulation Approaches,**
(*v*) **Organosilanes in Cross-Coupling Reactions,**
(*vi*) **Brook Chemistry,**
(*vii*) **Low-Coordinate Silicon Compounds,**
(*viii*) **Silyl Protecting Groups,** and
(*ix*) **Biological Applications of Organosilanes,**

which shall now be treated briefly and individually in the sections that follows:

25.3.1 Allylsilanes and Related Nucleophiles

Let us look into a typical example related to the particular class of **'allylsilanes'** *viz.*, **Allyltrialkylsilanes** and considering the specific example of **allyltrimethylsilane (X)**:

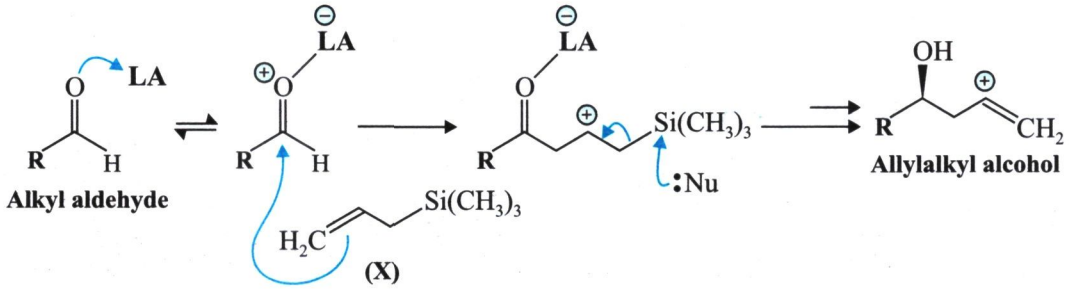


Allyl trimethylsilane (X)

It is a rather cheap and available on a large-scale.

Mayr *et al.* (1989)* observed critically that **allyltrimethylsilane** is *not* a **strong nucleophile.** Therefore, the intended reaction with the **aldehydes [—CHO]** invariably requires an ***external*** **Lewis Acid (LA)****.

Thus, we may have the following expression:

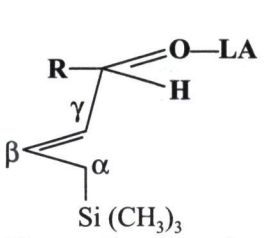


* Mayr H *et al.*: *An gew Chem. Int., Ed. Engl.*, **33**: 938-957, 1994, Mayr H *et al.*: *J. Chem. Soc., Chem Common*, 91-92, 1989.

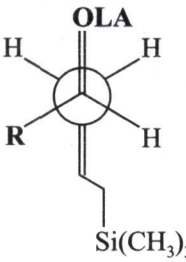
** Ueno M *et al.*: *Eur J. Org. Chem.*, 1965-68, 2005.

Mechanisms

1. The aforesaid reaction proceeds meticulously *via* an **anti-S_E2' reaction pathway***,—as given under:



The reaction proceeds via the γ-C-Atom

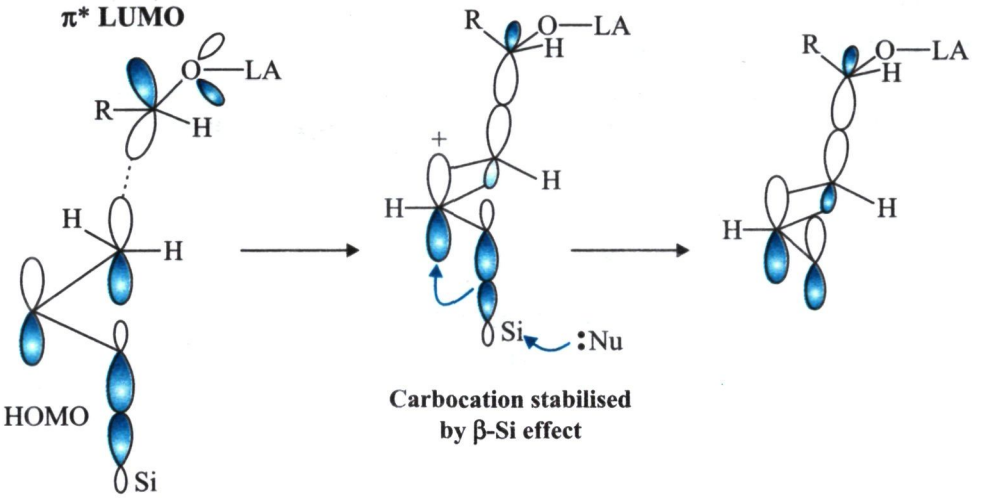


An Open transition state (TS)

A complete range of staggered reactive conformations need to be accounted for strictly

2. An alternative **mechanism** has also been put forward which is solely based upon the **LUMO** and **HUMO** concepts.

Example: It can be explicitly exemplified by citing the **silyl group remote from reacting centre (I)** being converted to the corresponding **carbocation stabilized by β-Si effect (II)**, which finally yields the **allylalkyl alcohol**,—as given under:



Silyl group remote from reacting centre

Carbocation stabilised by β-Si effect

25.3.2 Enantio Selective Allylation

The scope of **Enantioselective Allylation** is a broad spectrum, and hence, it needs to be studied and explored under the following *sub-heads*, namely:

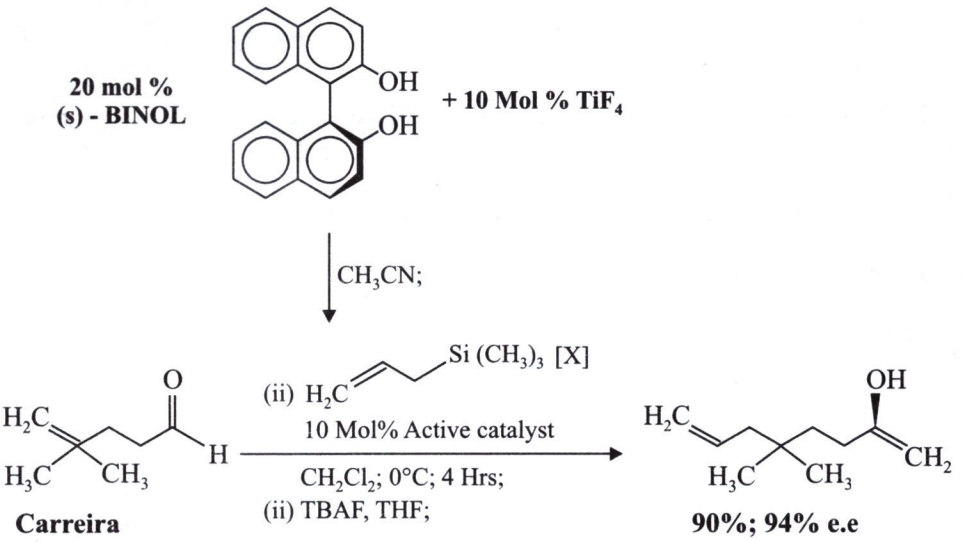
- **Aldehydes** • **Imines** • **Stereoselective Crotylation** • **Allyltri-chlorosilanes** • **Chiral Phosphoramides** • **Chiral Lewis Base Catalysts** • **Strain Induced Lewis Acidity** • **Leighton's Allylsilanes** and • **Enantioselective Allylation of Imines,**

which will now be discussed separately in the sections that follows:

* Tietze LF *et al.*: *J. Am. Chem. Soc.*, **128**: 11483—11495, 2006.

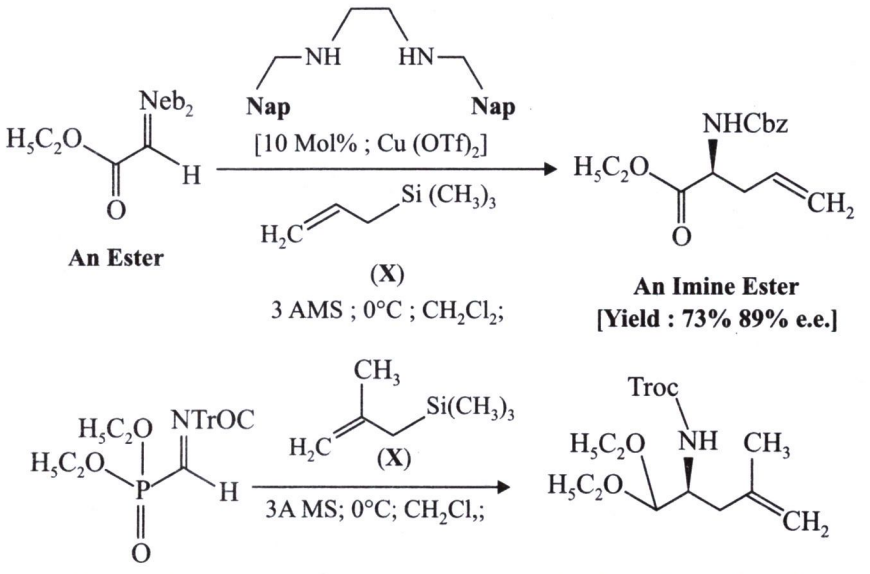
25.3.2.1 Aldehydes

In the **enantioselective allylation of aldehydes** the crucial use of a ***chiral* Lewis acid** is made intelligently so as to accomplish a distinct differentiation in the ensuing ***enantiotopic faces of the electrophile****.



25.3.2.2 Imines

Kiyohara *et al.* (2006)** carried out the so-called **enantioselective allylation of imines**,—as shown below:



* Gautheir G R *et al.*: *Angew-Chem. Intl Ed. Engl.*, **35**: 2363-65, 1996.

** Kiyohara H *et al.*: *Anglew Chem. Int. Ed.*, **45**: 1615-17, 2006.

25.3.2.3 Stereoselective Crotylation

Hoffmann (1982)* reported that the **Type II Alkylating Agents** have usually not been employed so abundantly in order to afford the:

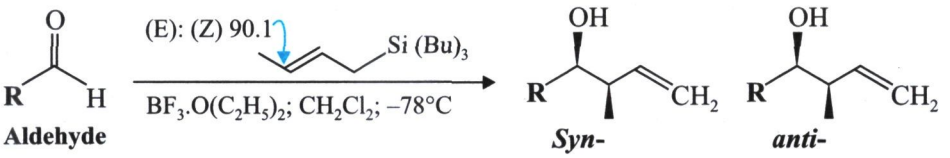
"stereoselective crotylation of Aldehydes",

and hence, the reactions with **crotylsilanes** [$CH_3CH{=}CH{-}CH_2Si(CH_3)_3$]—are indeed found to be **specifically very rare.****

Hence, the analogous reaction with **crotylsilanes** is invariably found to be ***syn*-selective** in nature***.

NOTE: **As on date, the so-called fairly *effective enantioselective variants* have not yet been developed.*****

We may have the following expression:



R = Ph [⬡], Syn : anti - (98.2) : 85%
R = Cy [$CH_3CH{=}CHCH_2$], Syn : anti-(94:6): 88%

Thus, we may obtain different proportions of ***syn*: *anti*-products** using. **R=Ph** or **R=CR** as given above; and thus, the **stereoselective crotylation** seems to be occurring perceptively.

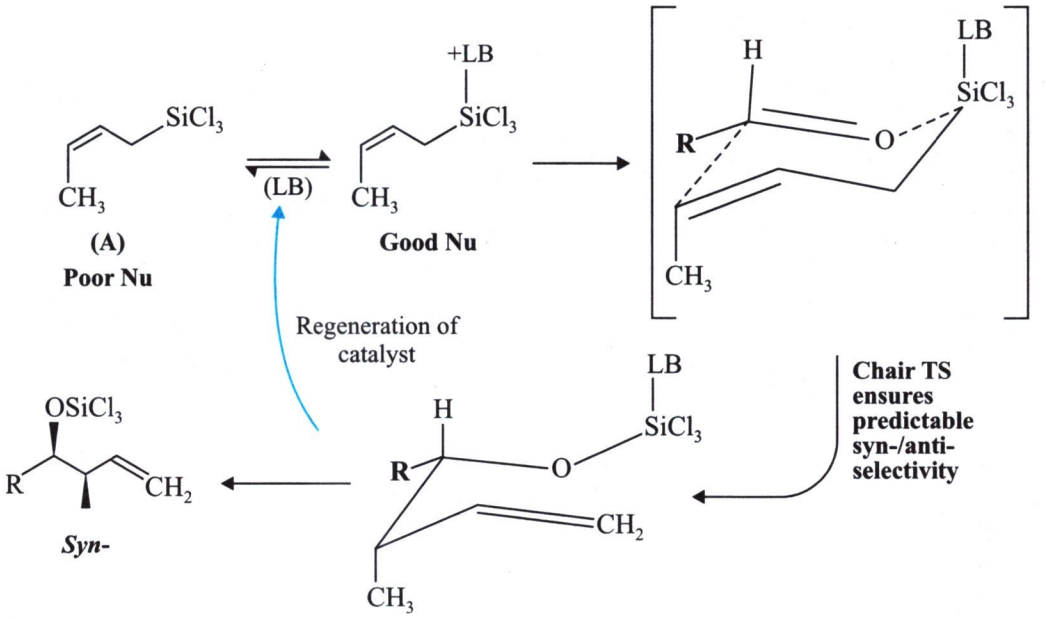
25.3.2.4 Allyltrichlorosilanes

In reality, based on their own, the **allyltrichlorosilanes** are duly recognized to be the so-called—**'poor alkylating agents'**.

Nevertheless, their **overall reactivity** may be ***enhanced significantly*** when being employed in the presence of **dimethyl formamide (DMF)******. In this way, **DMF** acts as a **Lewis base activator******* *i.e., Si may expand duly its valence state perceptively—as states earlier*. The above observation has, in fact, paved the way for the possibility of utilizing the ***chiral* Lowis bases** in order to affect the ***enantioselective allylation*** of the **'aldehydes'** by the help of **allyltrichlorosilane (A)**, —as stated under:

---

* Hoffmann RW: *Angew Chem. Int. Ed. Engl.*, **21**: 555-66, 1982.
** Aoki S *et al.*: *Tetrahedron*, **49**: 1783-92, 1993.
*** Keek GE *et al.* : *J Org. Chem.*, **59**: 7889-96, 1994.
**** Kabayashi S *et al.*: *J. Org. Chem.*, **59**: 6620-28, 1994.
***** Garronski J. *et al.*: *Chem. Rev.*, **108**: 5227-52, 2008.

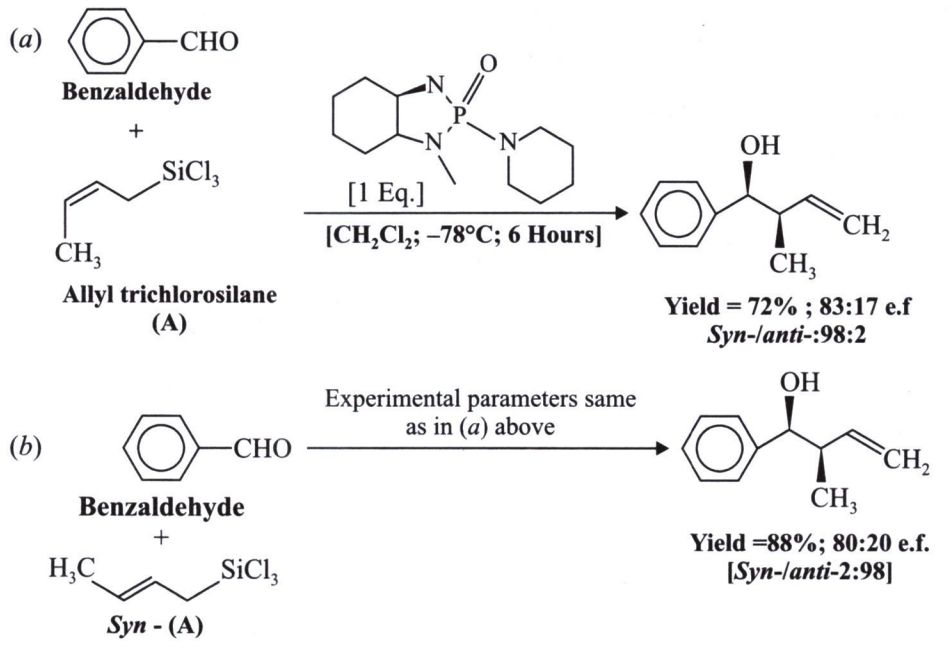


25.2.5 Chiral Phosphoramides

Denmark *et al.* (2006)* was pioneer with regard to exploit the so-called ***chiral*** **Lewis bases** predominantly as the vital and important ***catalysts*** for carrying out:

"the selective crotylation of aldehydes with allyltrichlorosilanes".

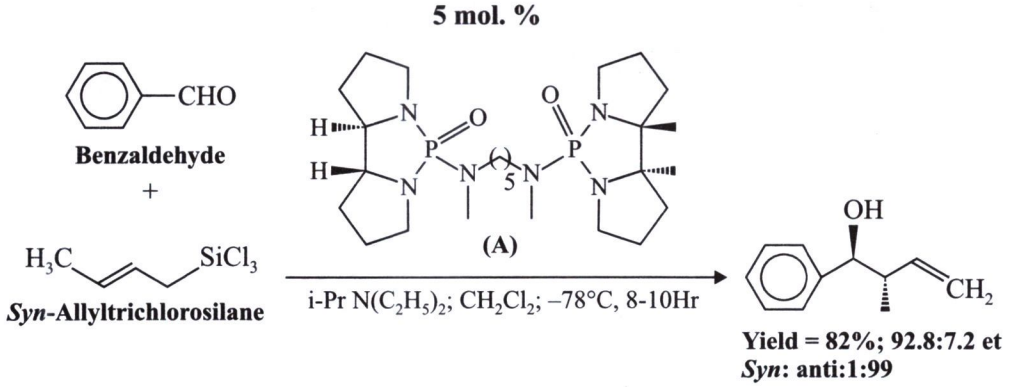
Thus, we may have the following expressions.



* Denmark SE *et al.*: *J. Org. Chem.*, **71**: 1523-1536, 2006.

Development of Improved Catalysts Based on a *Bis*-Phosphoramide Scaffold*: Both careful and systematic analysis of the **mechanism of the reaction** and **consideration of the reactive transition state (TS) structures** have ultimately led to the **development** of improved catalysts based duly upon a ***bis*-phosphoramide** scaffold to a great extent.

We may, however express the reaction between **benzaldehyde** and ***syn*-allyltrichlorosilane** in the critical presence of a ***bis*-phosphoramide (A)** scaffold under certain specific experimental parameters,—as stated under:

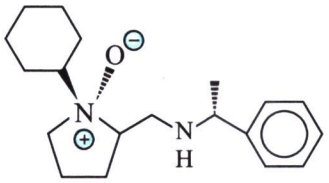


Remarks: It has been observed that the **'aliphatic aldehydes'** are ***not good substrates for the reaction***. Hence, under the **reaction parameters** the quick generation of the **α-chloro silyl ether** takes place. However, the critical incorporation of **mercuric chloride ($HgCl_2$)**—as an ***'additive'*** does improve grossly the overall yield of the **allylation phenomenon** perceptively, but with the ***mutual compromise of the* enantioselectivity profile** prefile predominantly.

25.3.2.6 Chiral Lewis Base Catalysts

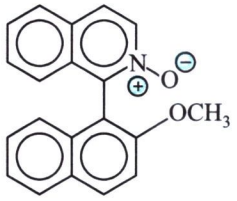
Following are a few known and recognized ***chiral* Lewis base catalyst**, such as:

- **Amine Oxides***



*Simonini V *et al.* : Synlett, 1061-65, 2008

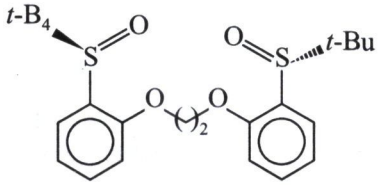
- **Pyridine N-Oxides and Related Systems****



**Hrdina R et al. : Chem Commun,2314-16,2009.

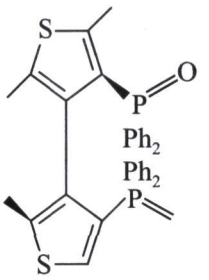
* Denmark SE *et al.*: *Chem. Commun*, **107**: 170, 2003.

❑ **Sulphoxides***



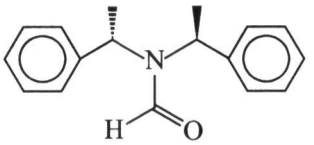
*Massa A *et al.* : *Tetrahedron* (Asymmetry) *20* : 202-204, 2009.

❑ **Diphosphine Oxides****



**Simonini v *et al* : *Adv synth catal.*, *350*:561-64,2008.

❑ **Formamides*****



***Iseki K *et al.* : Tetrahedron 55:977-988, 1999.

25.3.2.7 Strain-Induced Lewis Acidity

It has already been observed how the **stereoselectivity of an allylation** may be either:

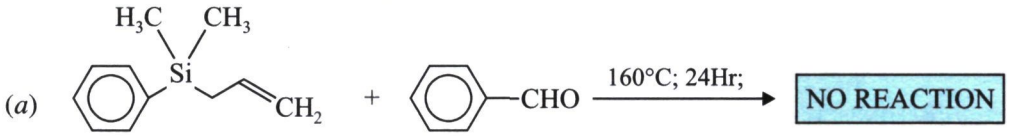
- **Improve upon** or • **Predicted critically,**

by precisely **pushing the reaction forward** so as to proceed through a ***closed chair-like* transition state (TS)**—by rendering the **'Si-atom'** more **Lewis acidic perceptively**.

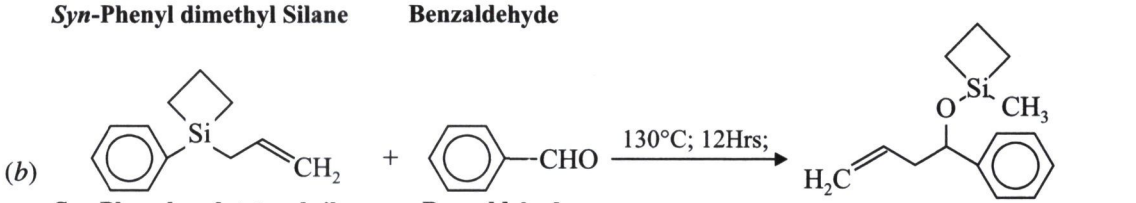
Alternatively, one may also adopt the path of the so-called enhancing:

"the *Lewis acidity* of the *Si-centre* in order to include the Si-atom enclosed duly in a *small ring system*"*.

Let us look into the following *two* expressions:



***Syn*-Phenyl dimethyl Silane** **Benzaldehyde**

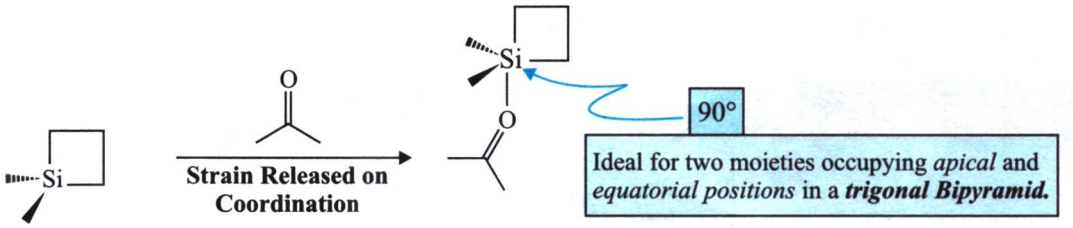


***Syn*-Phenyl cyclotetrayl silane** **Benzaldehyde** **A Phenyloxy cyclo tetrayl silane [Yield = 85%)**

* Matsumoto K *et al.*: *J. Org. Chem.*, **59**: 7152-56, 1994.

Comments: The **phenylcyclotetraylsilane** forms an ***oxy*-derivative** with **benzaldehyde** up to a yield of **85%; [see in (*b*) above]** whereas, the corresponding **opon-chain phenyldimethylsilane [see in (*a*) above]** fails to react completely.

Strain-Released on Coordination: Interestingly, the strain is duly released on coordination of the ensuing ***cyclotetraylsilane*** to obtain the following **adduct**,—as shown under:

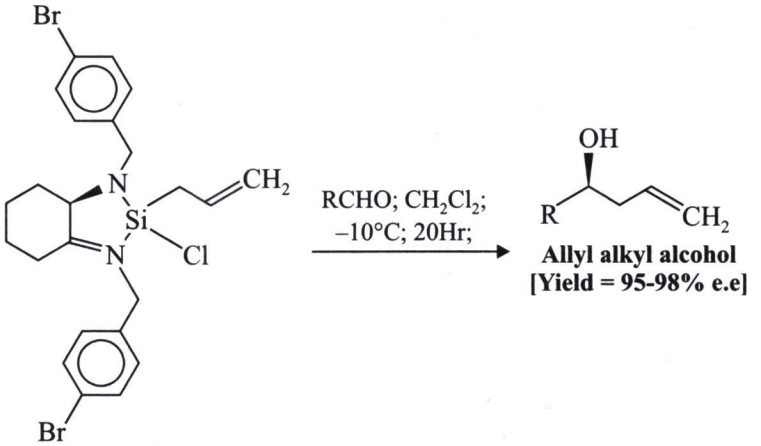


Cyclotetraylsilane

25.3.2.8 Leighton's Allylsilanes

Leighton has rightly introduced a broad range of **allylsilanes** wherein the **Si-atom** is contained duly within a **5-membered ring system**. Besides, the ***long* Si-N** and ***short* C-N bonds** critically ensure the **'*silacycle*'** is still **strained perceptively**. The electronegative **N and Cl substituents** further increases the **Lewis acidity profile** of the **Si-Centre***.

The reaction may be expressed as under:



Reagents: crystalline, shelf-stable, and easy to prepare

Allyl alkyl alcohol [Yield = 95-98% e.e]

Thus, the **5-membered ring system** breaks down to yield **an-open chain allylalkyl alcohol**.

25.3.2.9 Enantioselective Allylation of Imines

Evidence from the literature reveals that **Leighton** made an intelligent usage of a related class of:

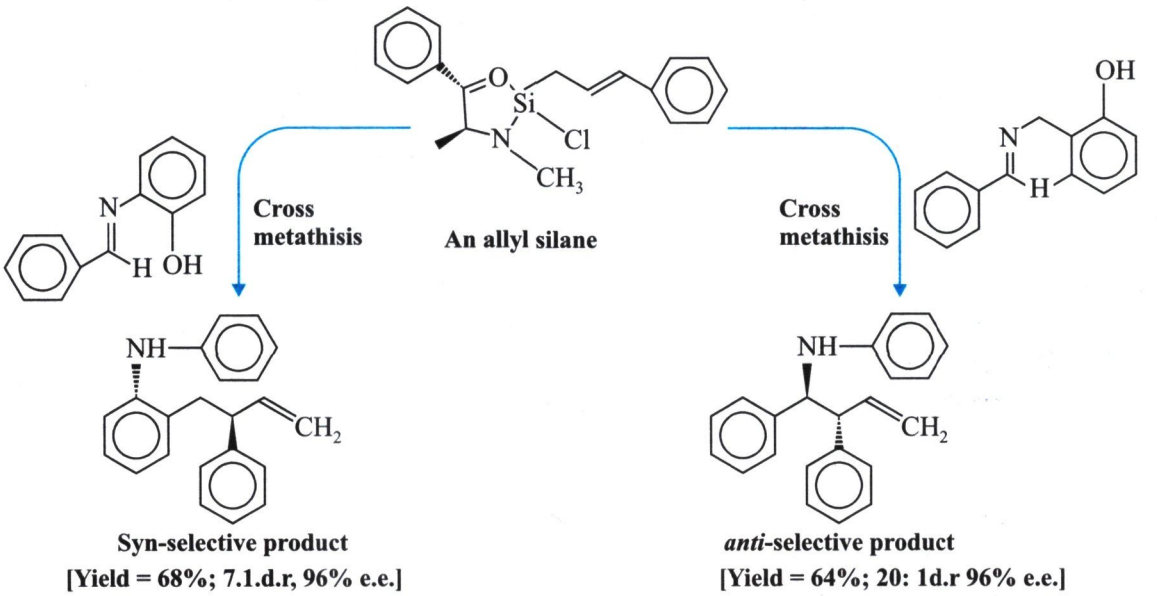
"Chiral γ-substituted allylsilanes",

* Zhang X *et al.*: *Angew Chem Int Ed.*, **44**: 938-941, 2005; Burns N Z *et al.*; Angew Chem Int Ed., **45**: 3811-3813, 2006.

which may be prepared readily from the so-called ***simple allylsilane*** by means of the ***cross-metaltusis***, in the specific domain of:

'enantioselective imine allylation'*.

The above may be expressed as under:



NOTE: **It is, however, pertinent to state here that the *precise choice of N-substituent* in the *'imine'* virtually determines the *diastereoselectivity of the reaction* preceptively*.**

25.3.3 Extended Allylsilane Chemistry

The following aspects in the **extended allylsilane chemistry** shall be discussed briefly in the sections that follows:

(*a*) **Substrate-Controlled Stereoselective Allylations in Ring Synthesis,**

(*b*) **Allylsilanes in Multicomponent Reactions,**

(*c*) **Intramolecular Hosomi Sakurai Reaction,** and

(*d*) **Reactions of Allylsilanes with Other Electrophiles.**

25.3.3.1 Substrate-Controlled Stereoselective Allylations in Ring Synthesis

Based on the scientific revelations and concrete evidences have indeed ascertained the fact that:

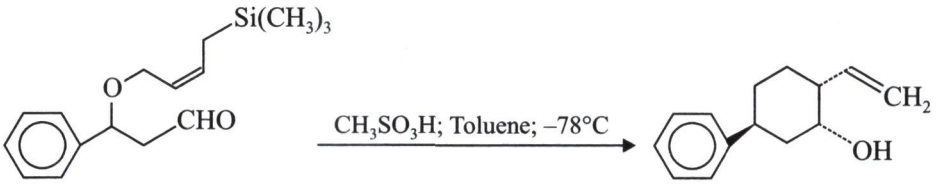
"intramolecular allylation does provide an excellent opportunity for generating the rings in organic compounds".

Important Observations

It may be grossly observed that since cyclisation mostly occurs *via* the so-called well-defined **transition states (TSs)**—the *overall net levels of stereochemistry might prove to be not only excellent, but also of great utility in organic chemistry.*

* Huber JD. *et al.*: Anglw Chem. Int. Ed., **47**: 3037-3039, 2008.

Let us consider the following expression:



Open-chain trimethyl silane aldehyde

Ring formation [Yield = 88%; d.e>95%]

Remarks: However, the **Bronsted Acids** are not being used frequently as ***activators*** for reactions that critically involves the ***allylsilanes*** perhaps due to the **propensty of these reagents** so as to undergo the **phenomenon of protodesilylation.**

In this particular instance, the specific use of **Lewis Acid activators** ultimately led to a ***reduction in the diastereoselectivity*** profile perceptively*.

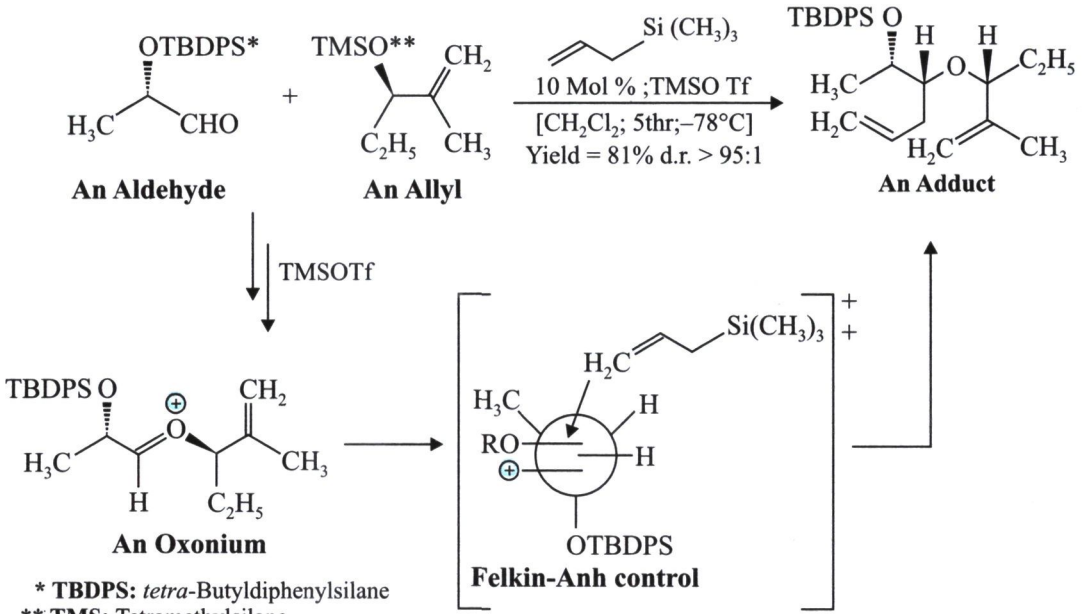
25.3.3.2 Allylsilanes in Multicomponent Reactions

It has been duly observed that the **Lewis-or Bronsted-*Acid-Mediated*** **reaction** of:

- **Alcohols** or **Ethers,**

with **aldehydes (-CHO)** or **ketones (>C=O)** affords the so-called **'Oxacarbenium Cations'**. Besides, these ***reactive*** **electrophiles** do react rather rapidly with the **'allylsilanes'**; and thus, the **inter—and intramolecular variants** have been duly reported**.

Thus, we may have the following reactions:



An Aldehyde **An Allyl** **An Adduct**

An Oxonium **Felkin-Anh control**

* **TBDPS:** *tetra*-Butyldiphenylsilane
** **TMS:** Tetramethylsilane

* Jervis PJ *et al.*: *Org Lett.*, **8**: 4649-52, 2006.

** Ullapu PR *et al.*: *Anglew ChemInt Ed.*, **48**: 2196-2000, 2009; Zhang Y *et al. Org lett*, **II**: 3366-69, 2009.

25.3.3.3 Intramolecular Hosomi Sakurai Reaction

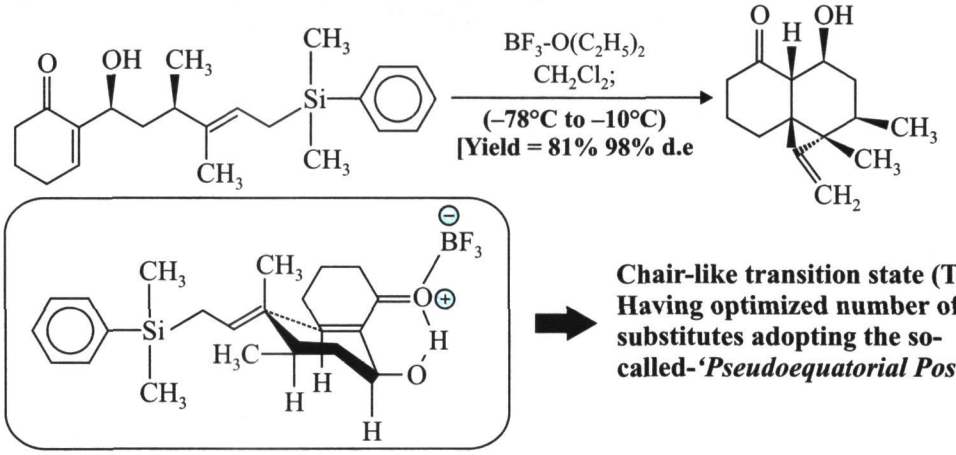
It has been proven beyond any reasonable doubt that under the influence of **Lewis-acid activation**, the ***allylsilanes*** are found to be:

"definitely *good nucleophiles* for the respective *conjugate addition reactions* to yield α,β-unsaturated carbonyl compounds".

Schauss made use of an extended ***intramolecular version*** of the aforesaid reaction in a **classical synthesis** of:

'*trans*-Decalinscaffold found in the Clerodane Diterpenoid Natural Products'*.

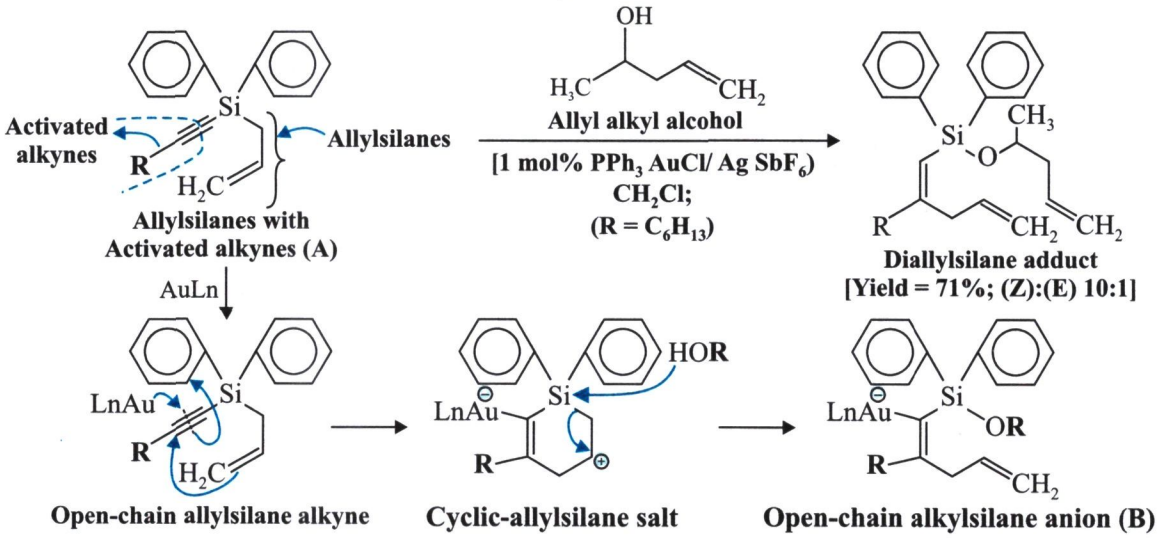
The conjugate addition reaction of **allylsilanes** and **α,β-unsaturated carbonyl compounds** yielding a ***substituted*** **biphenyl product** is given as under:



Chair-like transition state (TS) Having optimized number of substitutes adopting the so-called-*'Pseudoequatorial Positions'*

25.3.3.4 Reactions of Allylsilanes with Other Electrophiles

These are also referred to as the **activated alkynes****.



* Stevens BD *et al.*: *J. Org. Chem.*, **70**: 4375-79, 2005; Rodgen SA *et al.*: *Anglew Chem Int Ed.*, **45**: 4929-32, 2006.

** Park S *et al.*: *J. Am. Chem. Soc.*, **128**: 10664-665, 2006.

Remarks: The **allylsilane** with *activated alkynes* **(A)** in the presence of allylalkyl alcohol and other stated reagents yield a **diallylsilane adduct** upto a yield of **71% (having Z:E:: 10:1)**.

Besides, the **product (A)** with *AuLn* give an **open-chain allylsilane**—gets converted to a **cyclic allylsilane salt**—and further transforms again into an **open chain allylsilane anion (B)**. The resulting **product (B)** ultimately gives rise to the formation of **di-allylsilane adduct** (*as stated earlier*).

25.3.4 [3 + 2] Annulation Approaches

The **[3 + 2]—annulation approaches** do serve as the most viable and appropriate means of an array of important accelerated organic synthesis with the help of certain highly specific **organosilicon compounds**, such as:

(*a*) **Allylsilanes in the Annulation Reactions,**

(*b*) **Roush's Synthesis of Asimicin,** and

(*c*) **[3 + 2]—Annulation Route to Pyrrolidines,**

which shall now be described separately in the sections that follows:

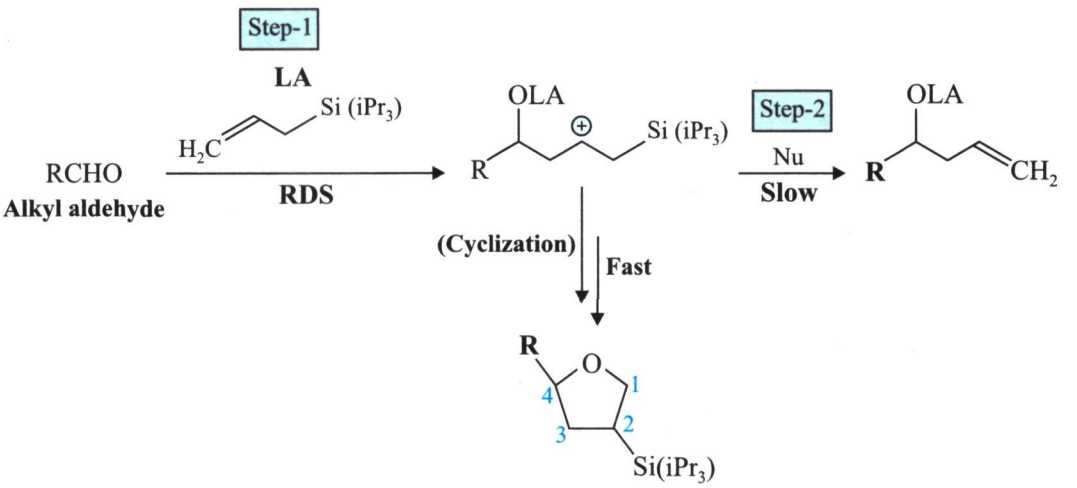
25.3.4.1 Allylsilanes in the Annulation Reactions

In the recent past, the allylation of aldehydes tends to be:

"a typical step-wise phenomenon, proceeding *via* a carbocationic intermediate perceptively".

Nevertheless, it has been duly established that normally the **attack of an external nucleophile upon the particular silyl moiety** in this intermediate is found to be quite rapid and fast, and thereby leads to a—**'homoallylic alcohol product'**.

The reactions involved may be expressed as under:



4-Alkyl-2-isopropyl tetrahydrofuran silane

Remarks: These essentially comprise:

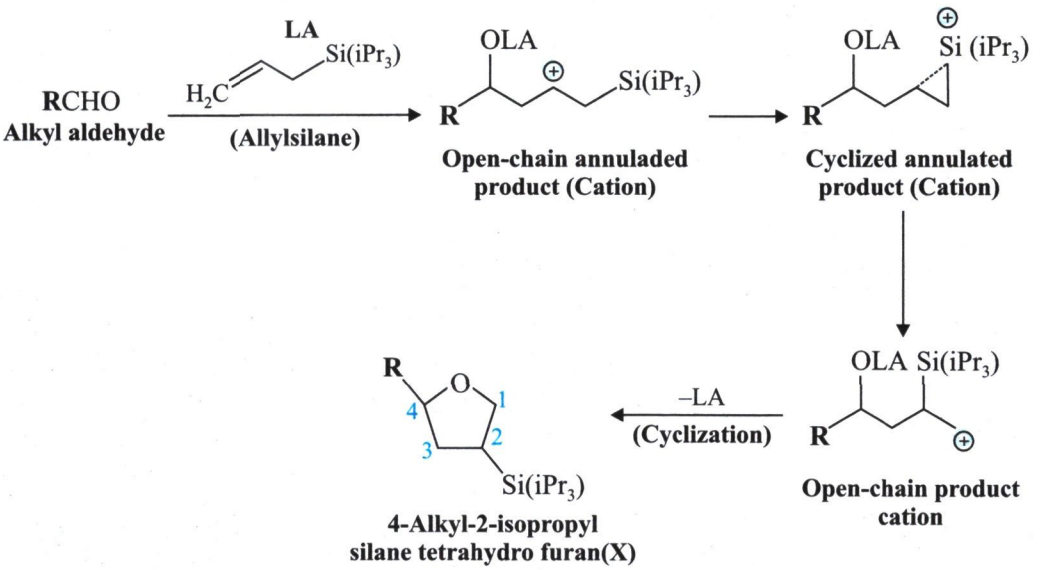
1. Nevertheless, if *step-2* of the aforesaid **allylation reaction** may be ***slowed down*** or ***disfavoured*** articulately,—the **alternative reaction pathways** may be followed thereby leading to the formation of altogether **divergent products perceptively.**
2. Interestingly, perhaps one of the easiest means to **redirect the allylation reaction** is duly accomplished.

   'to replace critically the *methyl* (CH_3) *substituents* located strategically upon the *silyl moiety* with rather bulkier moieties'.
3. Consequently, in the aforesaid instance—the so-called:

   "intramolecular trapping of a Carbocationic Intermediate definitely provides the ring products predominantly".

Formation of the Tetrahydrofuran Product: As we know that the ultimate ***product outcome*** is rather found to be **substrate dependent** predominantly; and hence, the critical formation of a ***tetrahydrofuran product*** seems to be specifically common*.

NOTE: **Importantly, the said overall outcome certainly needs the rearrangement of the so-called *initially formed cationic* intermediate.**

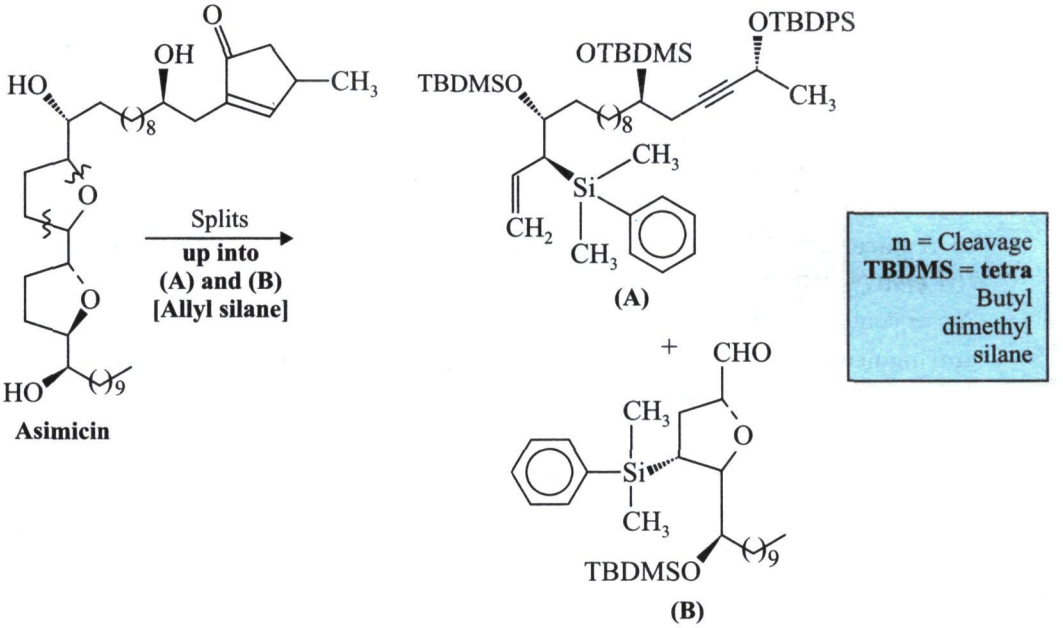


The various steps involved in the formation of the so-called **tetrahydrofuran product (X)** from *alkylaldehyde and allylsilane* is self-explanatory.

25.3.4.2 Roush's Synthesis of Asimicin

Rousch made use of the **[3 + 2] annulation of allylsilanes and aldehydes** in carrying out the synthesis of the ***two*** **tetrahydrofuran rings** present in ***'asimicin'***.

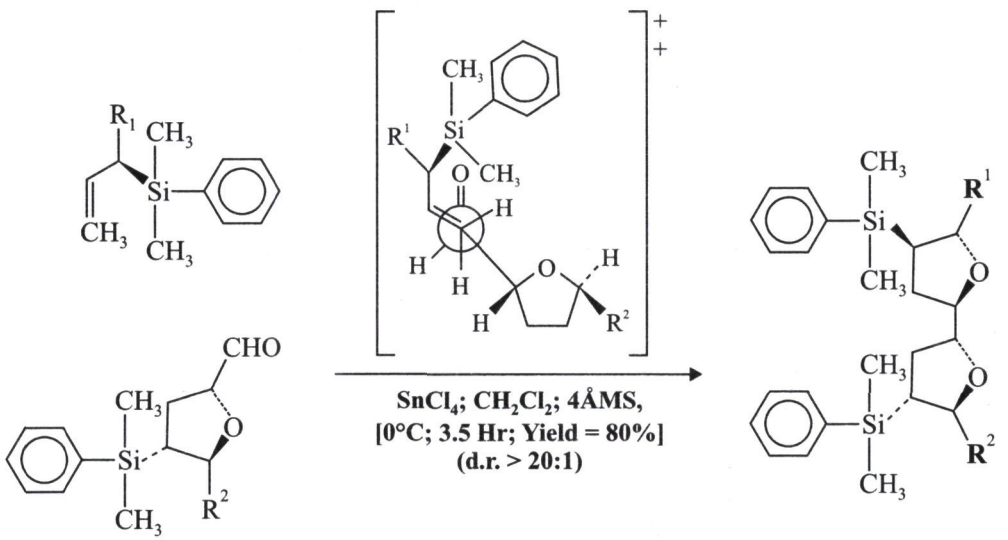
* Bates RH *et al.*: *Org. Lett.*, **10**: 4343-46, 2008.



Keek *et al.* (1995)* proposed vehemently the existence of an excellent **diastereoselectivity** of **Roush's synthesis of *asimicin***, which was eventually attributed solely to:

"the matched facial selectivity associated with using a *chiral allylsilane* (*anti*-S_E2') and *stannic chloride* ($SnCl_4$)—*chelated chiral aldehyde* specifically reacting *via* a *syn*-synclinal transition state (TS)".

Thus, we may have the following expressions:



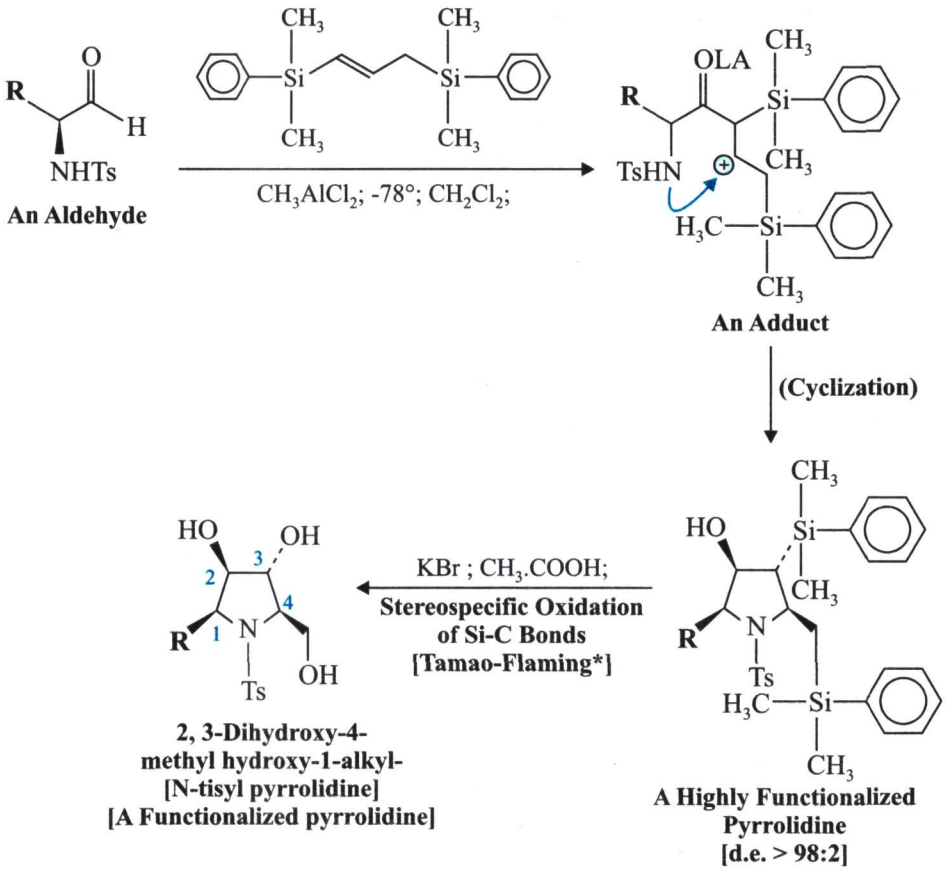
* Keek GE *et al.*: *J. Am. Chem. Soc.*, **117**: 6210-6223, 1995.

25.3.4.3 [3 + 2] Annulation Routes to Pyrrolidines

Based on the scientific evidences it has been duly ascertained that a **1,2-silyl shift** of the ensuing '***silyl moiety***' located in the **initially formed *carbocationic intermediate*** is observed to be sometimes not-so-necessary, since in **Sonfai's synthesis**, pertaining to highly functionalised pyrrolidines, loherein the inherent sulphonamide does function as the so-called:

"internal nucleophile trap"*.

The course of sequential reactions involved may be expressed as under:



25.3.5 Organosilanes in Cross-Coupling Reactions

The critical involvement of the **organosilanes** in the **cross-coupling reactions** in the domain of ***organic reactions***; and hence, it would be further explored with regard to the following ***four* important aspects**, namely:

(*a*) **Disconnection,** (*b*) **Hiyama Coupling,**

(*c*) **Denmark Modifications,** and (*d*) **Biaryl Synthesis**

which shall now be discussed briefly and individually in the sections that follows:

* Romero A *et al.*: *Org. Lett.*, **8**: 2127-30, 2006; Dressei M *et al.*: *Chem. Eur J.*, **14**: 3072-77, 2008.

** Fleming T: *Chemtracts Org. Chem.*, **9**: 1-64, 1996; Jones R *et al.*: *Tetrahedron*, **52**: 7599-7662, 1995.

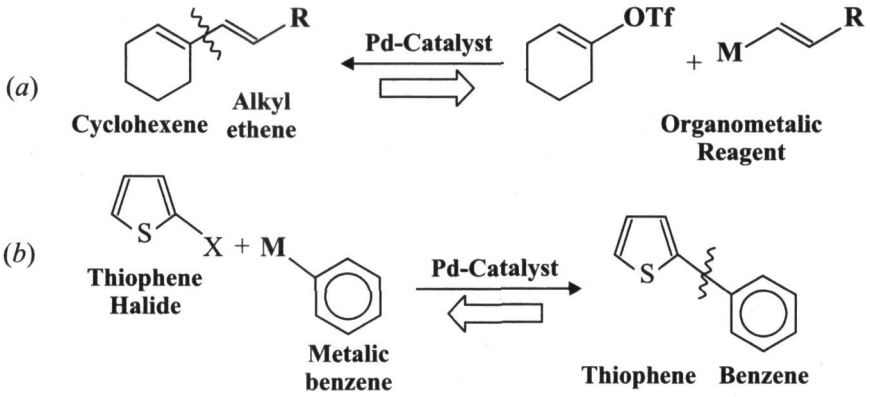
25.3.5.1 Disconnection

It is worthwhile to state here that the so-called Pd-catalysed cross-coupling strategies invariably need an—**'electrophilic' coupling partner**, preferentially:

- **an *Organohalide* [or *Pseudohalide*] (*viz., Sulphanate, Phosphate, Diazonium sp. etc.*);** and
- **a *'Nucleophilic Coupling Partner'***

The most commonly employed ***Organometalic Reagents*** essentially comprise are: **Si-Species, B, Sn, Cu, Zn, Mg, Zr**.

Following are *two* classical examples elaborating the phenomenon of **Disconnection**:



Remarks: All such reactions that essentially make use of the **organosilanes*** in this specific kind of;

"cross-coupling strategies",

are invariably termed as the—**"Hiyama Couplings".**

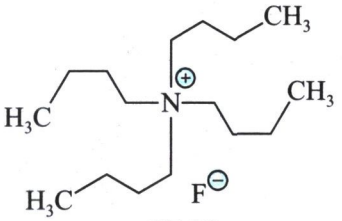
25.3.5.2 Hiyama Coupling

Based on the fundamental fact that due to the low polarization of the **C-Si bond** the so-called:

"Organosilanes are found to be relatively *unreactive nucleophilic coupling partners* for the Pd (0)-catalyzed cross-coupling reactions".

Consequently, the aforesaid reactins are invariably carried out in the critical presence of the ***'activator'*** *i.e.,* typically a **fluoride source** *viz.,*

- **Tetrabutylammonium Fluoride (TBAF)**



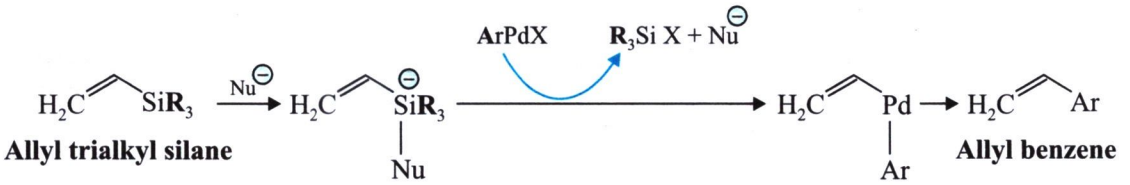
TBAF

* That is, ***syn*-Allyltrichlorosilane** H_3C $SiCl_3$

Therefore, in the very presence of an ***'activator'***—the ensuing reaction comes into play rather more rapidly perhaps due to:

"*in situ* formation of the *Pentacoordinate Siliconate Species*—that eventually undergoes the phenomenon of *'transmetallation'* more readily"

Thus, we may have the following expressions:



Remarks: The *substituents* located strategically on the **silyl moiety [SiR_3]** are also found to be equally vital and important. However, the **silanes**, (*viz.*, **allyltrialkyl silane**) critically having the **electron-withdrawing groups (EWGs)** invariably tend to be most useful:

$(CH_3)_2FSi$—(but not F_3Si—) are fairly good, as are the so-called alkoxysilanes [$(CH_3)_2(RO)Si$—and $CH_3(RO)_2Si$—better than $(RO)_3Si$—]*.

25.3.5.3 Denmark Modifications

In a broader perspective the **Denmark modifications** essentially make use of a wide range of ***Bases*** including:

- **NaO^tBu [NaO—$C(CH_3)_3$]**
- **NaH and**
- **Ca_2CO_3.**

Importantly, the **potassium oxytrimethyl silane [$KOSi(CH_3)_3$]** is mostly considered to be a rather **Mild Alternative**.

NOTE: **Nevertheless, in all typical instances the so-called *'reactive species'* is duly represented by the respective *'silanolate'*.**

***The Mechanistic Investigative Studies*:** An extensive and intensive **mechanistic investigative studies** have, in fact, revealed an altogether different and divergent explicit—**'Mechanistic Pathway'** specially for the aforesaid:

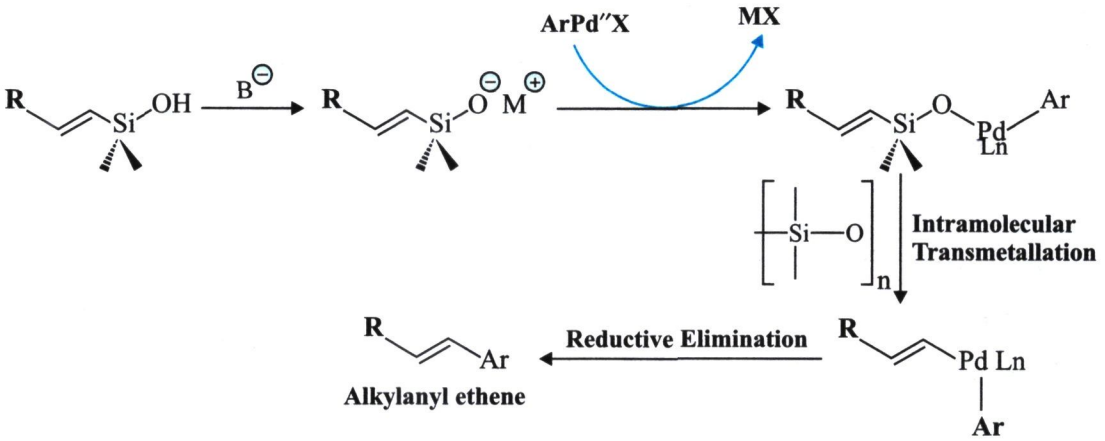
"base-mediated Hiyama Coupling".

It is, however, pertinent to state here that the **specific reaction** does not require the formation of a so-called **'pentavalent siliconate species'**. In other words, the ensuing ***transmetallation*** **pehnomenon** does proceed in a ***direct intramolecular modality*** critically upon:

"an intermediate *tetracoordinate* Pd″ species".

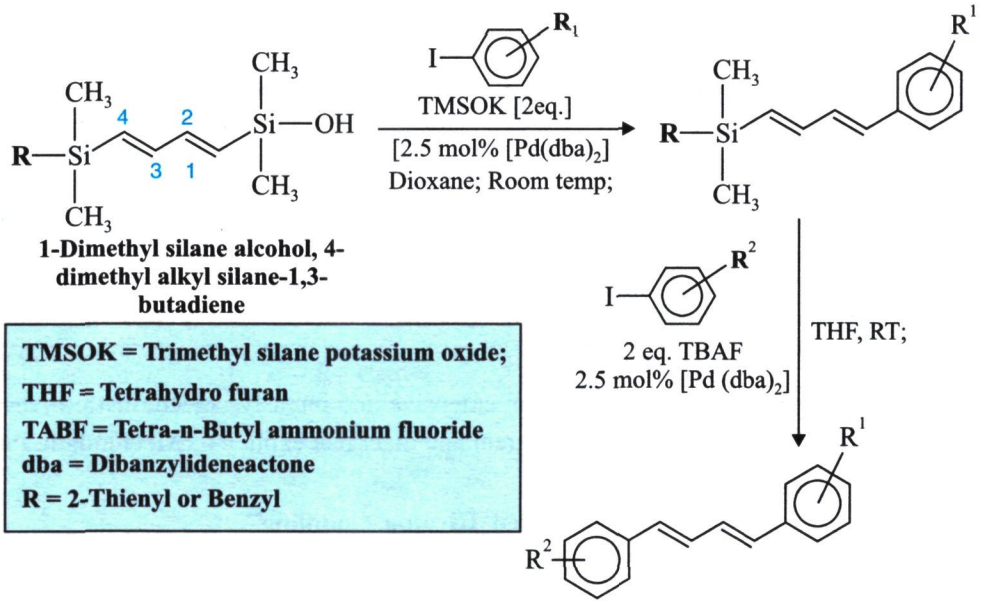
* Chaband *et al.*: *Eur J. Org. Chem.*, 3173-99, 2004.

Thus, we may have the following expressions:



Applications of Different Activity of Organosilanes in Sequential Hiyama Coupling Reactions*:

Tietze *et al.* (2006) carried out an exhaustive study with regard to the different activity of the **organosilanes** which could be further explored in the ensuing sequential **Hiyama Coupling Reactions**—as given under:



1-Dimethyl silane alcohol, 4-dimethyl alkyl silane-1,3-butadiene

TMSOK = Trimethyl silane potassium oxide;
THF = Tetrahydro furan
TABF = Tetra-n-Butyl ammonium fluoride
dba = Dibanzylideneactone
R = 2-Thienyl or Benzyl

25.3.5.4 Biaryl Synthesis

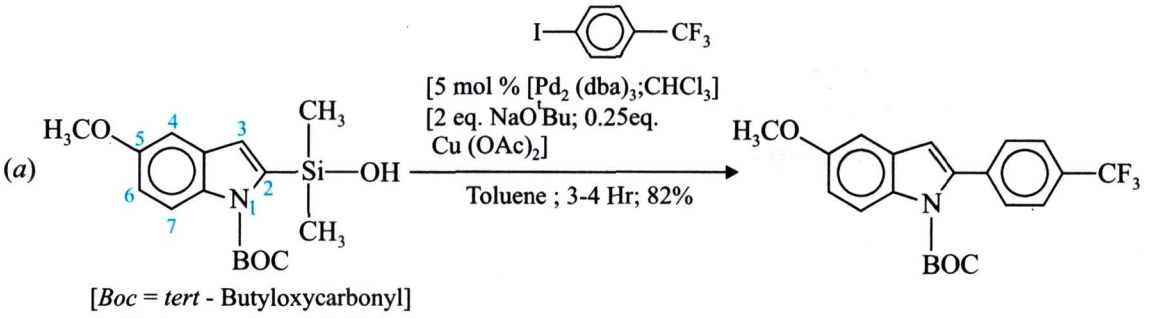
Kiyahara *et al.* (2006)** first and foremost proposed the **Hiyama Couplings** that have been employed to prepare **biaryls**—including (after due optimization):

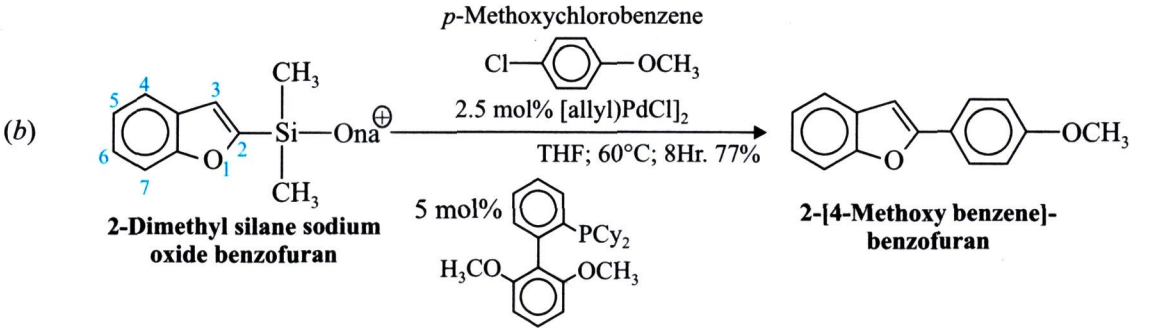
'challenging specifically the 2-aryl heterocycles'.

* Tietze LF *et al.*: *J. Am. Chem. Soc.*, **128**: 11483-95, 2006.

** Kiyohara H *et al.*: *Anglew Chem. Int. Ed.*, **45**: 1615-1617, 2006.

We may express the various reactions as given under:



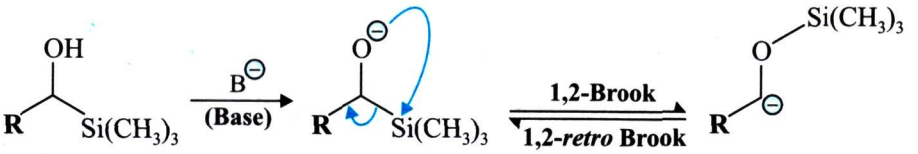


Remarks: Interestingly, these **Hiyama Couplings** do essentially need very careful **optimization of the reaction parameters**. However, the prevalent choice of the ***shielding moiety*** located strategically upon the **indole N-atom**—enables the pre-forming the **sodium silanolate** prior to commencement of the reaction; and subsequent judicious choice of the **Pd=Catalyst** and **ligand**, and also in certain typical cases the inclusion of a ***copper salt***—need to be taken into account.

25.3.6 The Brook Chemistry [Brook Rearrangement]

Mayr *et al.* (1994, 1989)* observed vehemently that both **Si-F and Si-O bonds** are indeed significantly ***stronger*** in comparison to the respective **Si-H and Si-C bonds**. Since the observed *difference in bond strength* may prove to be a reasonably strong—**'driving force for the ensuing Chemical Reactions'**; and hence, has been specifically exploited extensively to produce critically the so-called—**'Carbocations'** from the the corresponding ***'alkoxides'*** *via.* **The Brook rearrangement**.

The various reactions may be expressed as under:



* Mayr H *et al.*: *Angew Chem. Int. Ed. Engl.* **33**: 938-957, 1994; *ibid, J. Chem. Soc. Chem. Commum.*, 91-92, 1989.

Remarks: The **Brook rearrangement** is reversible in nature. Besides, the precise and exact position of the **equilibrium** solely depends on an array of important factors, such as:

- **polarity of solvent,**
- **anion-stabilizing ability of the C-substituents,** and
- **actual strength of the *oxygen-metal bond*.**

NOTE: **Importantly, the *original report* was related to the *[1,2]-rearrangement*, the reaction is rather general in nature. A range of *[1,n]-silyl moiety* to the *oxygen migrations* have been duly reported, and on being subjected to through investigation shown to proceed *via* the so-called-*intramolecular silyl moiety transfer* perceptively.**

The **Brook chemistry** has been intelligently extended to the following ***two* important aspects**, *viz.*,

(*a*) **Retro Brook Rearrangements,** and

(*b*) **One-Pot Synthesis of 2,3-Disubstituted Thiophenes,**

which shall now be described briefly in the sections that follows:

25.3.6.1 Retro Brook Rearrangements

In reality, when the Retro Brook rearrangements are being used in its ***Reverse Sense***,—it critically provides a *gainful procedure* for the unique preparation of **'organosilanes'**.

$\mathbf{C_{OX}}$ carefully made use of the so-called **1,4-retro-Brook rearrangement** to generate predominantly:

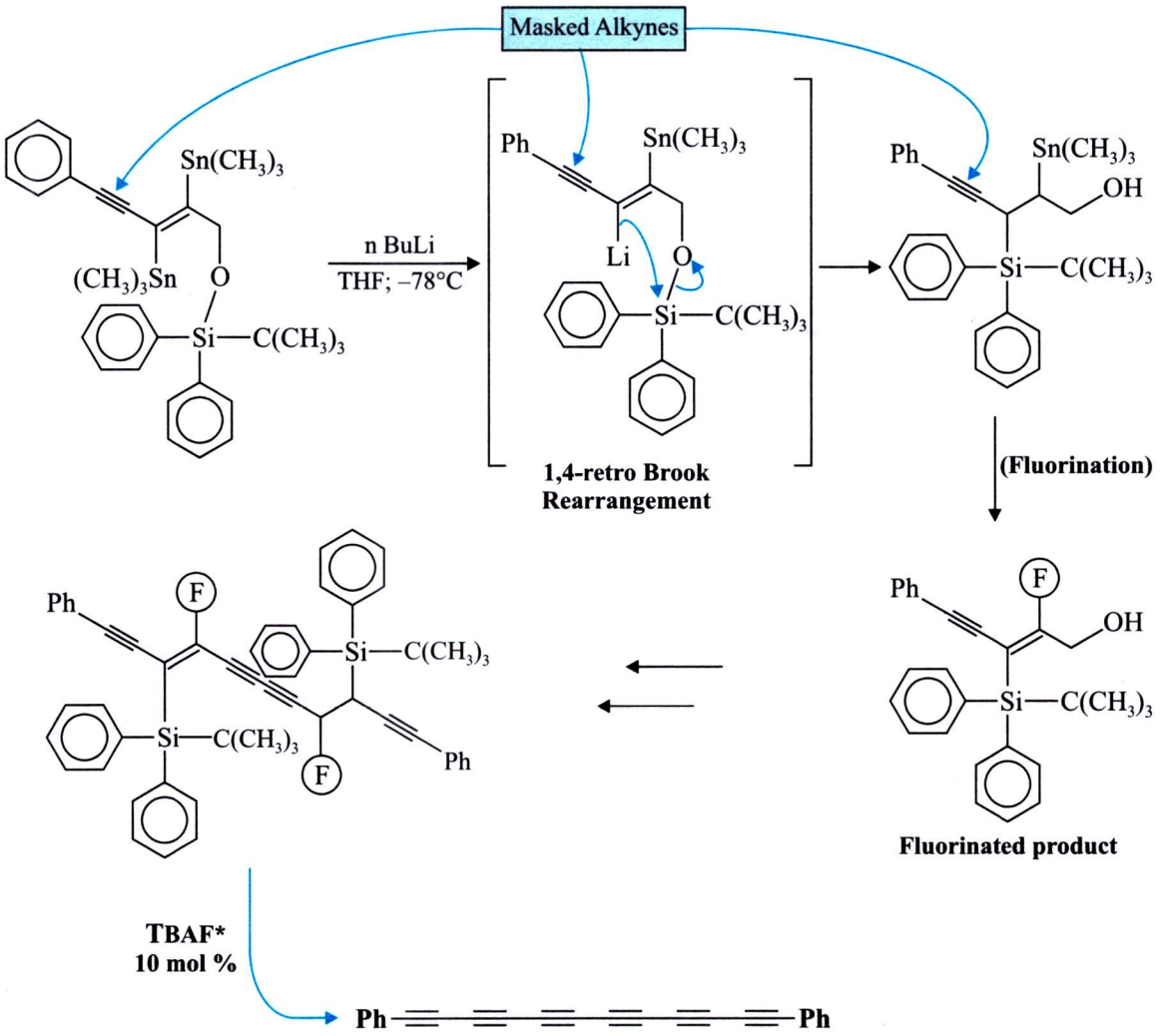
"stereodefined tetrasubstituted β-halovinylsilanes",

that eventually do serve as the ***masked alkynes*** for the intended ***oligoyne* assemblage** perceptively.

Besides, the **intramolecular silyl moiety transferance** permitted the so-called addition of **bulky silyl moieties**,—that would be rather not-so-easy a task to enable the introduction of the desired—**standard intermolecular trapping methods** in a big way*.

Let us consider the **following sequential steps** towards an attempt to understand the **Retro-Brook Rearrangement** in an elaborated manner:

* Simpkins SM E *et al.*: *Chem Commun*, 4036-37, 2007: Welter MD *et al.*; *Chimie*, **12**: 366-377, 2009; Nakazaki A *et al.*: *Angew-Chem Int. Ed.*, **45**: 2235-38, 2006.



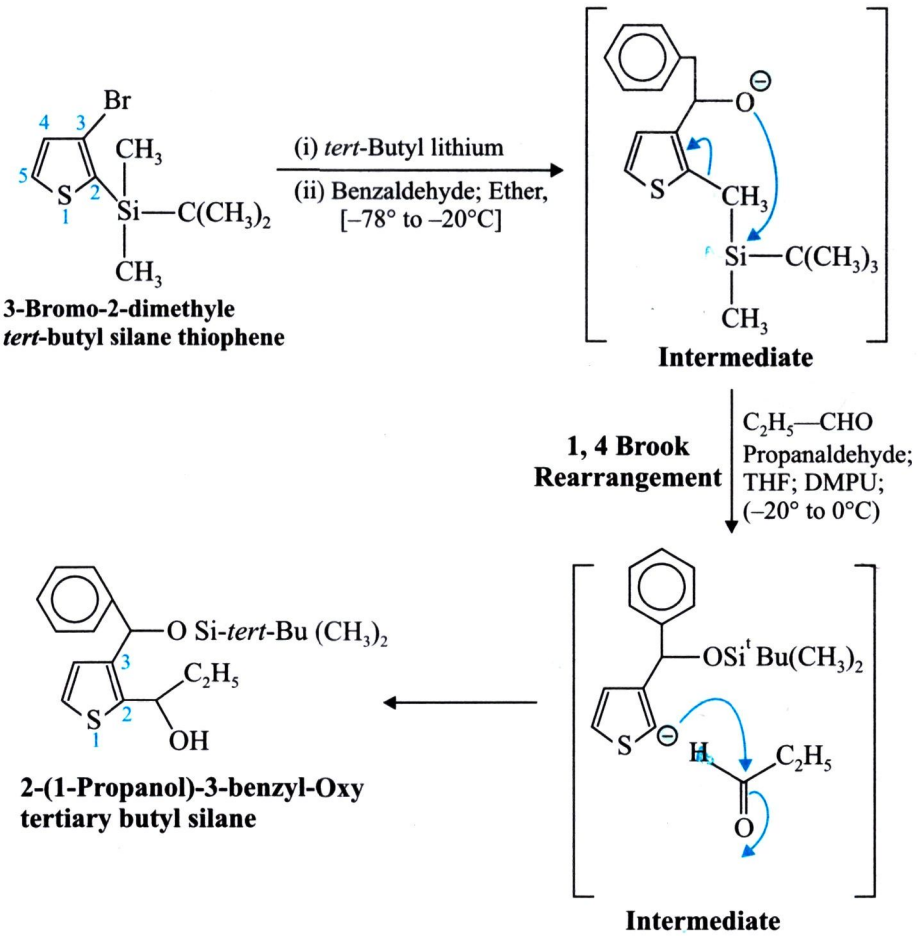
25.3.6.2 One-Pot Synthesis of 2,3-Disubstituted Thiophenes

The survey from the literature reveals that the critical inclusion of **DMPU** as a co-solvent was indeed quite important to ensure a smooth production of **1,4-Brook rearrangement***.

The various reactions involved may be expressed as under:

* **TBAF**: tetra-n-Butylammonium fluoride.

** Unger R *et al.*: *Eur J. Org. Chem.*, 1749-1766, 2009.



3-Bromo-2-dimethyle *tert*-butyl silane thiophene

2-(1-Propanol)-3-benzyl-Oxy tertiary butyl silane

The various steps of reactions are self-explanatory.

25.3.7 Biological Applications of Organosilanes

The various vital and **biological applications of the organosilanes** will be studied in terms of the following aspects, namely:

- **Bioactive Organosilanes,**
- **Silanediols as Protease Inhibitors,**
- **Silanediol Inhibitors of Angiotensin Converting Enzymes (ACE),** and
- **Silanediol Synthesis,**

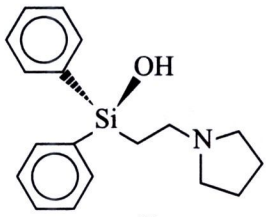
which shall now be discussed briefly and individually in the section that follows:

25.3.7.1 Bioactive Organosilanes

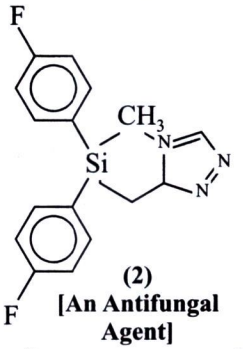
Even though we have enough concrete evidence with respect to the ***close similarity*** **of Silicon and Carbon**, the so-called **Si-containing organic compounds** are indeed found to be relatively rare in the domain of ***Biological Chemistry Research Programmes***. Nevertheless, the observed **Bioactive Organosilanes**—are invariably known; and hence, in certain instances have been duly commercialized to an appreciable extent.

Example: Following are the ***four*** **most prominent Bioactive Organosilanes**—namely:

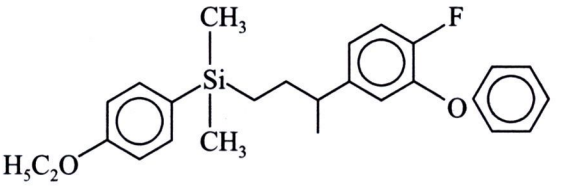
- **Muscarinic Receptor Agonist (1)**
- **Flusilazole (2)**
- **Silafluofen (3)** and
- **Pe4 (4) (*i.e.*, a photodynamic agent for application in Cancer Treatment).**



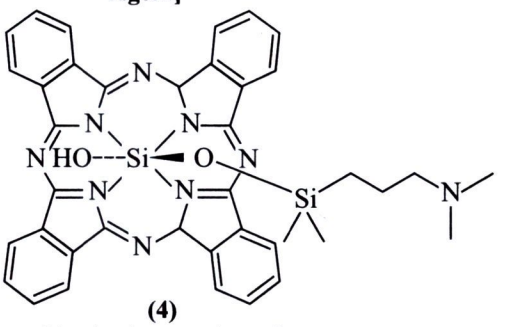
(1)
[Muscarinic Receptor Antagonist]



(2)
[An Antifungal Agent]



(3)
[An Insecticide]



(4)
[An Anticancer Agent]

25.3.7.2 Silanediols as Protease Inhibitors

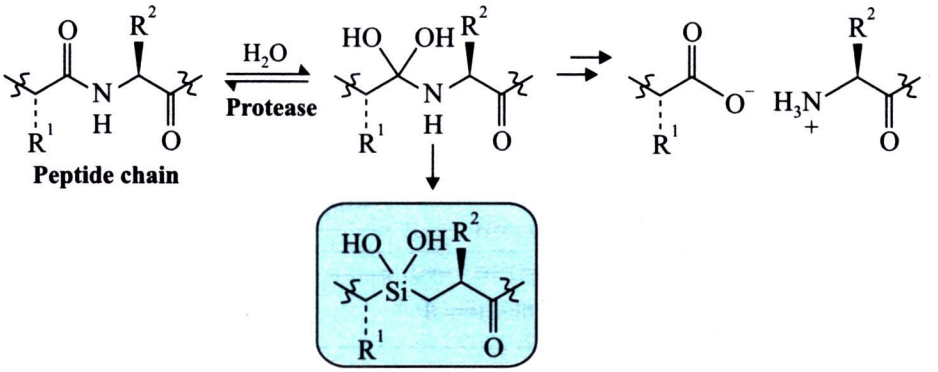
The **'proteases'** refer to the enzymes which catalyze the ensuing ***hydrolysis of a peptide bond***. It has been duly demonstrated that the following *two* enzymes:

- **aspartic acid proteases,** and
- **metalloproteases,**

do catalyze the addition of a water molecule to the so-called—**'amide carbonyl moiety'** perceptively.

Amazingly, the molecules which invariably mimic the so-called **'hydrated form'** of the specific ***hydrolyzing-amide bond*** should, therefore, possess the ability to be used as the classical inhibitors of the said ***two*** **classess of enzymes**.

The reactions involved may be expressed as under:



Remarks: Importantly, the **'Silanediols'** have recently come to the limelight as the so-called:

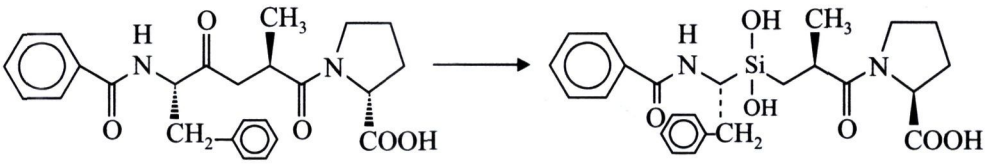
"potentially useful *isosteres* of the *tetrahedral intermediate* in the aforesaid type of hydrolysis reaction".

Nevertheless, based on their inherent propensity to ***oligomerise*** to the respective ***siloxanes*** may be controlled meticulously (*viz.*, by **typical steric blockade**); and therefore, these are observed to be potentially very ***attractive stable hydrate replacements*** because they are more or less **'neutral'** at the **physiological pH***.

25.3.7.3 Silanediol Inhibitors of Angiotensin-Converting Enzymes (ACE)

Sieburth first and foremost prepared the classical ***silanediol analogue*** of a known **ACE-inhibitor** (Kim *et al.*, 2005)*.

We may express the reactions as given under:



An ACE-Inhibitor
[IC_{50} 1.0nm]

A Silanediol Analogue
[IC_{50} 3.8nm]

Remarks: The above sited synthesis of the so-called **'Silanediol'** is indeed noteworthy.

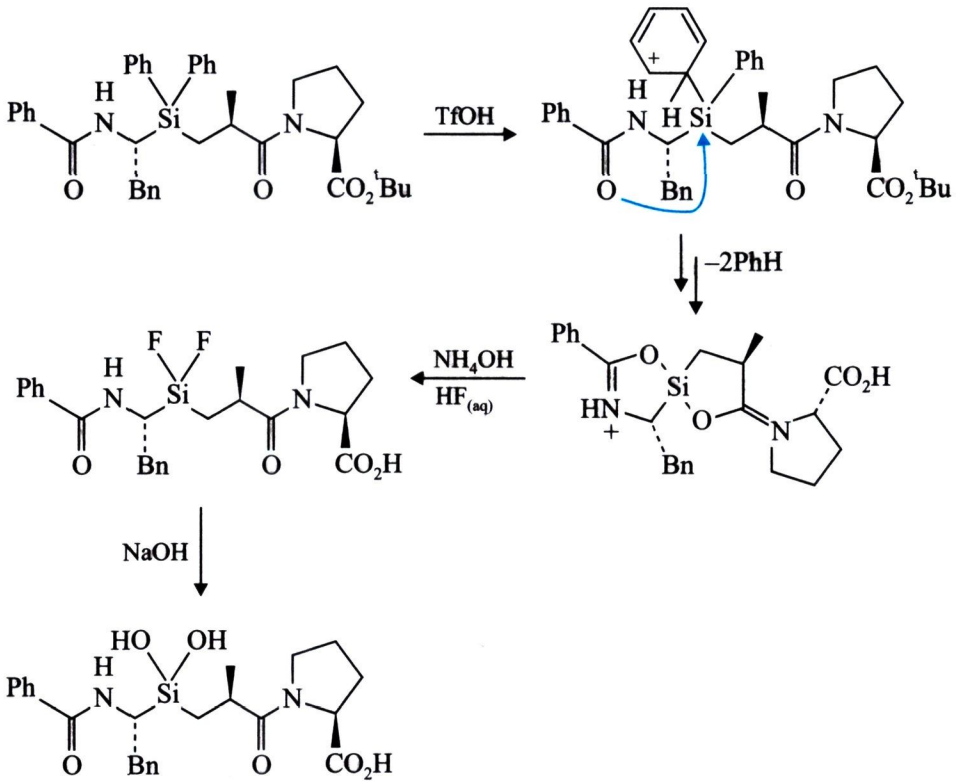
NOTE: **The observed *inhibitory activity* of the *'Silanediol'* analogue compares favourably with the *keto*-lead.**

25.3.7.4 Silanediol Synthesis

The **silanediol synthesis** could be expatiated explicitly with the help of the following sequence of reactions involving *four* important steps:

* Sieburth S McN *et al.*: *Eur J Org Chem.*, 311-322, 2006; Kim J *et al.*: *J. Org Chem.*, **70**: 5781-89, 2005; Nielsen L *et al.*: *J Am. Chem Soc.*, **130**: 13145-51, 2008.

** Kim J *et al.*: *J. Org. Chem.*, **70**: 5781-5789, 2005.



SOME IMPORTANT CONCLUSIONS

The **chemistry of organosilicon compounds** is rich and diverse and finds application in many aspects of **modern organic synthesis**. Most of it, however, can still be rationalised by considering the basics:

- **Electronegativity:** Si is more electropositive than C and H;
- **Size:** Si is a relatively large and polarisable atom compared with C, H, O etc;
- **Electron Configuration:** $1s^2$, $2s^2$, $2p^6$, $3s^2$, $3p^2$;
- **Position in Periodic Table:** Period 3, therefore capable of expanding its valence state;
- **Stereoelectronics:** C—Si bond is good at stabilising β-positive charge; and
- **Bond Strengths:** Si—O and Si—F bonds are significantly stronger than Si—C and Si—H bonds.

Suggested Reading

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Zhou H *et al.*: *Angew Chem. Int Ed.*, **48**: 5355-57, 2009.
Zhou S *et al.*: *Chem Commun*, 4883-85, 2009.



APPENDICES

Appendix 1. Glossary

Appendix 2. Substitutive Nomenclature of Organic Compounds

Appendix 3. Infrared Absorptions of Organic Compounds

Appendix 4. Proton NMR-Chemical Shifts in Organic Compounds

Appendix 5. ^{13}C NMR Chemical Shifts in Organic Compounds

Appendix 6. Summary of Synthetic Methods

Appendix 7. Reactions Used to Form Carbon-Carbon Bonds

Appendix 8. Typical Acidities and Basicities of Organic Functional Groups

Appendix 9. Claisen and Cope Related Rearrangements

Appendix 10. Abbreviations Used in Claisen and Cope Related Rearrangements

Appendix 1

Glossary

Absolute configuration: The three-dimensional structure of a chiral compound. The configuration is designated by R or S.

Absorption band: A peak in a spectrum that occurs as a result of absorption of energy.

Acetal:

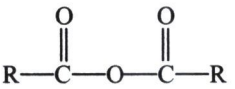


Acetoacetic ester synthesis: Synthesis of a methyl ketone using ethyl acetoacetate as the starting material.

Achiral (optically inactive): An achiral molecule has a superimposable mirror image and does not rotate the plane of polarized light.

Acid: A substance that donates a proton or accepts a pair of electrons.

Acid anhydride:



Acid-base reaction: A reaction in which an acid donates a proton to a base.

Acid catalyst: A catalyst that increases the rate of a reaction by donating a proton.

Acid-catalyzed reaction: A reaction catalyzed by an acid.

Acid dissociation constant: A measure of the degree to which an acid dissociates.

Activating substituent: A substituent that increases the reactivity of an aromatic ring. Electron-donating substituents activate aromatic rings toward electrophilic attack, and electron withdrawing substituents activate aromatic rings toward necleophilic attack.

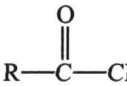
Activation energy: The minimum energy which reacting species must possess in order to be able to form an 'activated complex', or 'transition state', before proceeding to the products. [The activation energy (Ea) may be derived from the temperature dependence of the reaction rate using the Arrhenius equation].

Active site: A pocket or cleft in an enzyme where the substrate is bound.

Acyclic: Noncyclic.

Acyl group: A carbonyl group bonded to an alkyl group or to an aryl group.

Acyl halide:



1,2-Addition (direct addition): Addition to the 1- and 2-positions of a conjugated system.

1,4-Addition (conjugate addition): Addition to the 1- and 4-positions of a conjugated system.

Addition polymer (chain-growth polymer): Made by adding monomers to the growing end of a chain.

Addition reaction: A reaction in which atoms or groups are added to the reactant.

Alcohol: (ROH) a compound with an OH group in place of one of the hydrogens of an alkane.

Alcoholysis: Reaction with alcohol.

Aldaric acid: A dicarboxylic acid with an OH group bonded to each carbon. Obtained by oxidizing the aldehyde and primary alcohol groups of an aldose.

Aldehyde: 

Alditol: A compound with an OH group bonded to each carbon. Obtained by reducing an aldose or a ketose.

Aldol addition: A reaction between two molecules of an aldehyde (or two molecules of a ketone) that connects the α-carbon of one with the carbonyl carbon of the other.

Aldol condensation: An aldol addition followed by elimination of water.

Aldonic acid: A carboxylic acid with an OH group bonded to each carbon. Obtained by oxidizing the aldehyde group of an aldose.

Aldose: A polyhydroxyaldehyde.

Aliphatic compound: A non-aromatic organic compound.

Alkaloid: A natural product with one or more nitrogen hetero atoms found in the leaves, bark, or seeds of plants.

Alkane: A hydrocarbon that contains only single bonds.

Alkene: A hydrocarbon that contains a double bond.

Alkoxymercuration: Addition of alcohol using a mercuric salt of a carboxylic acid as a catalyst.

Alkylation reaction: A reaction that adds an alkyl group to a reactant.

Alkyl halide: A compound with a halogen in place of one of the hydrogens of an alkane.

Alkyl substituent (alkyl group): Formed by removing a hydrogen from an alkane.

Alkyl tosylate: An ester of para-toluenesulphonic acid.

Alkyne: A hydrocarbon that contains a triple bond.

Allene: A compound with two adjacent double bonds.

Allyl group: $CH_2{=}CHCH_2^-$

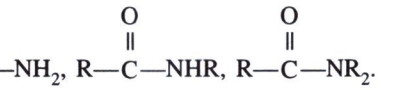
Allylic carbon: an sp^3 carbon adjacent to a vinyl carbon.

Allylic cation: A compound with a positive charge on an allylic carbon ($CH_2{=}CH{-}\overset{\oplus}{C}H_2$).

Alpha olefin: A monosubstituted olefin.

Alternating copolymer: A copolymer in which two monomers alternate.

Ambident nucleophile: A nucleophile with two nucleophilic sites.

Amide: 

Amine: A compound with a nitrogen in pace of one of the hydrogens of an alkane (RNH_2, R_2NH, R_3N).

Amine inversion: A compound containing an sp^3 hybridized nitrogen with a nonbonding pair of electrons that rapidly turns inside out.

Amino acid: An α-aminocarboxylic acid. Naturally occurring amino acids have the L configuration.

Aminolysis: Reaction with an amine.

Amino sugar: A sugar in which one of the OH groups is replaced by an NH_2 group.

Amphoteric compound: A compound that can behave either as an acid or as a base.

Anchimeric assistance (intramolecular catalysis): Catalysis in which the catalyst that facilitates the reaction is part of the molecule undergoing reaction.

Angle strain: The strain introduced into a molecule as a result of its bond angles being distorted from their ideal values.

Angular methyl group: A methyl substituent at the 10- or 13-position of a steroid ring system.

Anion-exchange resin: A positively charged resin used in ion exchange chromatography.

Anionic polymerization: Chain-growth polymerization in which the initiator is a nucleophile; the propagation site therefore is an anion.

Annulation reaction: A ring-forming reaction.

Annulene: A monocyclic hydrocarbon with alternating double and single bonds.

Anomeric carbon: The carbon in a cyclic sugar that is the carbonyl carbon in the open-chain form.

Anomeric effect: The preference for the axial position shown by certain substituents bonded to the anomeric carbon of a six member ring sugar.

Anomers: The specific term used to describe carbohydrate stereoisomers differing only in configuration at the hemi-acetal carbon atom, that is, two cyclic sugars that differ in configuration only at the carbon, that is, the carbonyl carbon in the open-chain form.

Antarafacial bond formation: Formation of two σ bonds from opposites sides of the π system.

Antarafacial rearrangement: Rearrangement in which the migrating group moves to the opposite face of the π system.

Anti addition: An addition reaction in which the two added substituents add to opposite sides of the molecule.

Anti-aromatic: A cyclic and planar compound with an uninterrupted ring of π orbital-bearing atoms containing an even number of pairs of π electrons.

Antibiotic: A compound that interferes with the growth of a microorganism.

Antibodies: Compounds that recognize foreign particles in the body.

Antibonding molecular orbital: A molecular orbital that results when two atomic orbitals with opposite signs interact. Electrons in an antionding orbital decrease bond strength.

Anti conformer: The most stable of the staggered conformers.

Anti elimination: An elimination reaction in which the two substituents eliminated are removed from opposite sides of the molecule.

Anti-periplanar: Parallel substituents on opposite sides of a molecule.

Antiviral drug: A drug that interferes with DNA or RNA synthesis in order to prevent a virus from replicating.

Applied magnetic field: The externally applied magnetic field.

Aprotic solvent: A solvent that does not have a hydrogen bonded to an oxygen or to a nitrogen.

Arene oxide: An aromatic compound that has had one of its double bonds converted to an epoxide.

Aromatic: A cyclic and planar compound with an uninterrupted ring of π orbital-bearing atoms containing an odd number of pairs of π electrons. An aromatic molecule or ion possesses aromaticity. Aromaticity is the special property of planar (or nearly planar) cyclic, conjugated systems having $(4n + 2)$ conjugated π (pi) electrons. The delocalization of the $(4n + 2)$ π (pi) electrons gives them special stability. For benzene, the most common aromatic system ($n = 1$, therefore 6 π (pi) electrons), the aromaticity confers the characteristic reactivity of electrophilic substitution.

Aroyl group: A carbonyl group attached to an aromatic ring.

Arrhenius equation: relates the rate constant of a reaction to the energy of activation and to the temperature at which the reaction is carried out ($k + Ae^{-Ea/RT}$).

Asymmetrical ether: An ether with two different substituents bonded to the oxygen.

Asymmetric molecular orbital: A molecular orbital in which the left half is not a mirror of the right half.

Atomic number: Tells how many protons (or electrons) the neutral atom has.

Atomic orbital: An orbital associated with an atom.

Atomic weight: The average mass of the atoms in the naturally occurring element.

Aufbau principle: States that an electron will always go into the available orbital with the lowest energy.

Auxochrome: A substituent that, when attached to a chromophore, alters the λ_{max} and intensity of absorption of ultraviolet/visible radiation.

Avogadro's constant: The number of particles (atoms or molecules) in one mole of any pure substance. [6.023×10^{23}].

Axial bond: A bond of the chair form of cyclohexane that is perpendicular to the plane in which the chair is drawn (an up-down bond).

Aziridine: A three-member ring compound in which one of the ring atoms is a nitrogen.

Azo linkage: a—N=N—bond.

Back side attack: Nucleophilic attack on the side of the carbon opposite to the side bonded to the leaving group.

Bactericidal drug: A drug that kills bacteria.

Bacteriostatic drug: A drug that inhibits the further growth of bacteria.

Baeyer-Villiger oxidation: Oxidation of aldehydes or ketones with H_2O_2 or peracids to form carboxylic acids or esters, respectively.

Banana bond: The σ bonds in small rings that are weaker as a result of overlapping at an angle rather than overlapping head-on.

Base[1]: A substance that accepts a proton or donates a pair of electrons.

Base[2]: A heterocyclic compound (a purine or a pyrimidine) in DNA and RNA.

Base catalyst: A catalyst that increases the rate of a reaction by removing a proton.

Basicity: Describes the tendency of a compound to share its electrons with a proton.

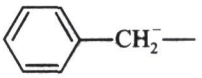
Beer-Lambert law: Relationship among the absorbance of UV/Vis light: the concentration of the sample, the length of the light path, and the molar absorptivity.

Bending vibration: A vibration that does not occur along the line of the bond.

Benzoyl group: A benzene ring bonded to a carbonyl group.

Benzylic carbon: An sp^3 hybridized carbon bonded to a benzene ring.

Benzylic cation: A compound with a positive charge on a benzylic carbon.

Benzyl group: 

Benzyne intermediate: A compound with a triple bond in place of one of the double bonds of benzene.

Bicyclic compound: A compound that contains two rings that share at least one carbon.

Bifunctional molecule: A molecule with two functional groups.

Bimolecular reaction (second-order reaction): A reaction whose rate is dependent on the concentration of two reactants.

Biochemistry (biological chemistry): The chemistry of biological systems.

Bioorganic compound: An organic compound that is found in biological systems.

Biosynthesis: Synthesis in a biological system.

Birch reduction: The partial reduction of benzene to 1,4-cyclohexadiene.

Block Copolymer: A copolymer in which there are blocks of each kind of monomer.

Blue shift: A shift to a shorter wavelength.

Boat conformation: The conformation of cyclohexane that roughly resembles a boat.

Boiling point: The temperature at which a liquid vapourizes.

Bonding molecular orbital: A molecular orbital that results when two atomic orbitals with the same sign interact. Electrons in a bonding orbital increase bond strength.

Bond length: The internuclear distance between two atoms at minimum energy (maximum stability).

Brand name (proprietary name, trade name): Identifies a commercial product and distinguishes it from other products. Only the owner of the registered trademark can use it.

Bridged bicyclic compound: A bicyclic compound in which rings share two nonadjacent carbons.

Bronsted acid: A substance that donates a proton.

Bronsted base: A substance that accepts a proton.

Buffer: An acid and its conjugate base.

Carbanion: A compound containing a negatively charged carbon.

Carbene: A species with a carbon that has a nonbonded pair of electrons and an empty orbital (H_2C:).

Carbocation: A compound containing a positively charged carbon.

Carbocation rearrangement: The rearrangement of a carbocation to a more stable carbocation.

Carbohydrate: A sugar, a saccharide. Naturally occurring carbohydrates have the D configuration.

α-Carbon: A carbon adjacent to a carbonyl carbon.

Carbon acid: A compound that contains a carbon that is bonded to a relatively acidic hydrogen.

Carbonyl addition (direct addition): Nucleophilic addition to the carbonyl carbon.

Carbonyl carbon: The carbon of a carbonyl group.

Carbonyl compound: A compound that contains a carbonyl group.

Carbonyl group: A carbon doubly bonded to an oxygen.

Carbonyl oxygen: The oxygen of a carbonyl group.

Carboxyl group: COOH

Carboxylic acid: R-COOH

Carboxylic acid derivative: A compound that is hydrolyzed to a carboxylic acid.

Carboxyl oxygen: The singly bonded oxygen of a carboxylic acid or an ester.

Catalyst: A species that increases the rate at which a reaction occurs without being consumed in the reaction. Because it does not change the equilibrium constant of the reaction, it does not change the amount of product that is formed.

Catalytic hydrogenation: The addition of hydrogen to a double or a triple bond with the aid of a metal catalyst.

Chair conformation: The conformation of cyclohexane that roughly resembles a chair. It is the most stable conformation of cyclohexane.

Chemical exchange: The transfer of a proton from one molecule to another.

Chemically equivalent protons: Protons with the same connectivity relationship to the rest of the molecule

Chemical shift: The location of a signal in an NMR spectrum. It is measured downfield from a reference compound (most often TMS).

Chichibabin reaction: The reactin of pyridine with sodium amide to form 2-aminopyridine (and some 4-aminopyridine).

Chiral (optically active): A chiral molecule has a non-superimposable mirror image.

Chiral auxiliary: An enantiomerically pure compound which, when attached to a reactant, causes a product with particular configuration to be formed.

Chirality centre: An atom bonded to four different groups.

Cholesterol: A steroid that is the precursor of all other steroids.

Chromatography: A separation technique in which the mixture to be separated is dissolved in a solvent and the solvent passed through a column packed with an adsorbent stationary phase. A series of related techniques exist for the separation of a mixture of compounds by their distribution between two phases. In gas-liquid chromatography the distribution is between a gaseous and a liquid phase. In column chromatography the distribution is between a liquid and a solid phase.

Chromophore: The part of a molecule responsible for an ultraviolet or visible spectrum.

Cine substitution: Substitution at the carbon adjacent to the carbon that was bonded to the leaving group.

***cis*-Fused:** Two cyclohexane rigns fused together such that, if the second ring were considered to be two substituents of the first ring, one substituent would be in an axial position and the other would be in an equatorial position.

***cis* Isomer:** The isomer with identical substituents on the same side of the double bond.

***cis-trans* Isomers:** Geometric isomers.

Claisen condensation: A reaction between two molecules of an ester that connects the α-carbon of one with the carbonyl carbon of the other and eliminates an alkoxide ion.

Claisen rearrangement: A [3, 3] sigmatropic rearrangement of an allyl vinyl ether.

α-Cleavage: Homolytic cleavage of an alpha substituent.

Clemmensen reduction: A reaction that reduces the carbonyl group of a ketone to a methylene group using Zn (Hg)/HCl.

Combination band: Occurs at the sum of two fundamental absorption frequencies ($\nu_1 + \nu_2$).

Combinatorial library: A group of structurally related compounds.

Combinatorial organic synthesis: The synthesis of a library of compounds by covalently connecting sets of building blocks of varying structure.

Common intermediate: An intermediate that two compounds have in common.

Common name: Nonsystematic nomenclature.

Competitive inhibitor: A compound that inhibits an enzyme by competing with the substrate for binding at the active site.

Complete racemization: Formation of a pair of enantiomers in equal amounts.

Complex carbohydrate: Contains two or more sugar molecules linked together.

Concerted reaction: A reaction in which all the bond-making and bond-breaking processes occur in one step.

Condensation polymer (step-grwoth polymer): Made by combining two molecules while removing a small molecule (usually water or an alcohol).

Condensation reaction: A reaction combining two molecules while removing a small molecule (usually water or an alcohol).

Conducting polymer: A polymer that can conduct electricity down its backbone.

Configuration: The three-dimensional structure of a chiral compound. The configuration is designated by R or S.

Configurational isomers: Stereoisomers that cannot interconvert unless a covalent bond is broken. *Cis-trans* isomers and optical isomers are configurational isomers.

Conformation: The three-dimensional shape of a molecule at a given instant.

Conformational analysis: The investigation of the various conformations of a compound and their relative stabilities.

Conformers (conformational isomers): Different conformations of a molecule.

Conjugate acid: A compound accepts a proton to form its conjugate acid.

Conjugate base: A compound loses a proton to form its conjugate base.

Conjugated double bonds: Double bonds separated by one single bond.

Conrotatory ring closure: Achieves head-to-head overlap of π orbitals by rotating the orbitals in the same direction.

Conservation of orbital symmetry theory: A theory that explains the relationship between the structure and configuration of the reactant, the conditions under which a pericyclic reaction takes place, and the configuration of the product.

Constitution: The number and type of atoms in a molecule.

Constitutional isomers (structural isomers): Molecules that have the same molecular formula but differ in the way the atoms are connected.

Contributing resonance structure: A structure with localized electrons that approximates the true structure of a compound with delocalized electrons.

Convergent synthesis: A synthesis in which pieces of the target compound are individually prepared and then assembled.

Cope elimination reaction: Elimination of a proton and a hydroxylamine from an amine oxide.

Cope rearrangement: A [3,3] sigmatropic rearrangement of a 1,5-diene.

Copolymer: A polymer formed using two or more different monomers.

Corrin ring system: A porphyrin ring system without one of the methine bridges.

COSY spectrum: A 2-D NMR spectrum that shows coupling between sets of protons.

Coupled protons: Protons that split each other. Coupled protons have the same coupling constant.

Coupling constant: The distance (in hertz) between two adjacent peak of a split NMR signal.

Coupling reaction: A reaction that joins two alkyl groups.

Covalent bond: A bond created as a result of sharing electrons.

Covalent catalysis (nucleophilic catalysis): Catalysis that occurs as a result of a nucleophile forming a covalent bond with one of the reactants.

Cram's rule: The rule used to determine the major product of a carbonyl addition reaction in a compound with a chirality centre adjacent to the carbonyl group.

Cross-conjugation: nonlinear conjugation.

Crossed (mixed) aldol addition: An aldol addition in which two different carbonyl compounds are used.

Cross-linking: Connecting polymer chains by intermolecular bond formation.

Crown ether: A cyclic molecule that contains several ether linkages.

Crown-guest complex: The complex formed when a crown ether binds a substrate.

Cryptand: A three-dimensional polycyclic compound that binds a substrate by encompassing it.

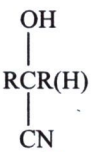
Cryptate: The complex formed when a cryptand binds a substrate.

Crystallites: Regions of a polymer in which the chains are highly ordered.

Cumulated double bonds: Double bonds that are adjacent to one other.

Curtius rearrangement: Conversion of an acyl chloride into a primary amine using $^{-}N_3$.

Cyanohydrin:



Cycloaddition reaction: A reaction in which two π-bond-containing molecules react to form a cyclic compound.

[4 + 2] Cycloaddition reaction: A cycloaddition reaction in which 4 π electrons come from one reactant and 2 π electrons come from the other reactant.

Cycloalkane: An alkane with its carbon chain arranged in a closed ring.

Deactivating substituent: A substituent that decreases the reactivity of an aromatic ring. Electron-withdrawing substituents deactivate aromatic rings towards electrophilic attack, and electron-donating substituents deactivate aromatic rings towards nucleophilic attack.

Deamination: Loss of ammonia.

Decarboxylation: Loss of carbon dioxide.

Degenerate orbitals: Orbitals that have the same energy.

Dehydration: Loss of water.

Dehydrohalogenation: Elimination of a proton and a halide ion.

Delocalization energy (resonance energy): The extra stability a compound achieves as a result of having delocalized electrons.

Delocalized electrons: Electrons that are shared by more than two atoms.

Deoxygenation: Removal of an oxygen from a reactant.

Deoxyribonucleic acid (DNA): A polymer of deoxyribonucleotides.

Deoxyribonucleotide: A nucleotide in which the sugar component is D-2-deoxyribose.

Deoxy sugar: A sugar in which one of the OH groups has been replaced by an H.

DEPT ^{13}C NMR Spectrum: A series of four spectra that distinguishes among $—CH_3$, $—CH_2$ and —CH groups.

Detergent: A salt of a sulphonic acid.

Deuterium kinetic isotope effect: Ratio of the rate constant obtained for a compound containing hydrogen and the rate constant obtained for an identical compound in which one or more of the hydrogens have been replaced by deuterium.

Dextrorotatory: The enantiomer that rotates polarized light in a clockwise direction.

Diastereomer: A configurational isomer that is not an enantiomer.

Diastereotopic hydrogens: Two hydrogens bonded to a carbon that, when replaced in turn with a deuterium, results in a pair of diastereomers.

1,3-Diaxial interaction: The interaction between an axial substituent and the other tow axial substituents on the same side of the cyclohexane ring.

Diazonium ion: ArN_2^+ or RN_2^+

Diazonium salt: A diazonium ion and an anion $ArN_2^+X^-$.

Dieckmann condensation: An intramolecular Claisen condensation.

Dielectric constant: A measure of how well a solvent can insulate opposite charges from one another.

Diels-Alder reaction: A [4 + 2] cycloaddition reaction.

Diene: A hydrocarbon with two double bonds.

Dienophile: An alkene that reacts with a diene in a Diels-Alder reaction.

Dihedral angle: The angle between groups attached on adjacent carbon atoms when viewed in a Newmann projection.

β-Diketone: A ketone with a second carbonyl group at the β-position.

Dimer: A molecule formed by the joining together of two identical molecules.

Dipole-dipole interaction: An interaction between the dipole of one molecule and the dipole of another.

Dipole moment (μ): A measure of the separation of charge in a bond or in a molecule.

Direct displacement mechanism: A reaction in which a nulceophile displaces the leaving group in a single step.

Direct substitution: Substitution at the carbon that was bonded to the leaving group.

Disaccharide: A compound containing two sugar molecules linked together.

Disconnection: Breaking a bond to carbon to give a simpler species.

Disproportionation: Transfer of a hydrogen atom by a radical to another radical with the result that an alkane and an alkene are formed.

Disrotatory ring closure: Achieves head-to-head overlap of *p* orbitals by rotating the orbitals in opposite directions.

Dissociation energy: The amount of energy required to break a bond/the amount of energy released when a bond is formed.

Dissolving metal reduction: A reduction using sodium or lithium metal dissolved in liquid ammonia.

Disulphide bridge: A disulphide (—S—S—) bond in a peptide or protein.

DNA (Deoxyribonucleic acid): A polymer of deoxyribonucleotides.

Double bond: A sigma bond and a pi bond.

Doublet: An NMR signal split into two peaks.

Doublet of doublets: An NMR signal split into four peaks of approximately equal height. Caused by splitting a signal into a doublet by one hydrogen and into another doublet by another (nonequivalent) hydrogen.

Drug: A compound that reacts with a biological molecule, triggering a physiological effect.

Eclipsed conformation: A conformation in which the bonds on adjacent carbons are parallel to each other as viewed looking down the carbon-carbon bond.

E-Conformation: The conformation of a carboxylic acid or carboxylic acid derivative in which the carbonyl oxygen and the substituent bonded to the carboxyl oxygen or nitrogen are on opposite sides of the single bond.

Edman's reagent: Phenyl isothiocyanate. A reagent used to determine the N-terminal amino acid of a polypeptide.

Effective magnetic field: The magnetic field that a proton 'senses' through the surrounding cloud of electrons.

Effective molarity: The concentration of the reagent that would be required in an intermolecular reaction for it to have the same rate as an intramolecular reaction.

E-Isomer: The isomer with the high-priority groups on opposite sides of the double bond.

Elastomer: A polymer that can stretch and then revert back to its original shape.

Electrocyclic reaction: A reaction in which a π bond in the reactant is lost so that a cyclic compound with a new σ bond can be formed.

Electromagnetic radiation: Radiant energy that displays wave properties.

Electron affinity: The energy given off when an atom acquires an electron.

Electronegative: Describe an element that readily acquires an electron.

Electronegativity: Tendency of an atom to pull electrons toward itself.

Electronic transition: Promotion of an electron from its HOMO to its LUMO.

Electron sink: Site to which electrons can be delocalized.

Electrophile: An electron-deficient atom or molecule.

Electrophilic addition reaction: An addition reaction in which the first species that adds to the reactant is an electrophile.

Electrophilic aromatic substitution: A reaction in which an electrophile substitutes for a hydrogen of an aromatic ring.

Electrophilic catalysis: Catalysis in which the species that facilitates the reaction is an electrophile.

Electropositive: Describes an element that readily loses an electron.

Electrostatic attraction: Attractive force between opposite charges.

Elemental analysis: A determination of the relative proportions of the elements present in a compound.

α-Elimination: Removal of two atoms or groups from the same carbon.

β-Elimination: Removal of two atoms or groups from adjacent carbonds.

El-Reaction: A first-order elimination reaction.

E2-Reaction: A second-order elimination reaction.

Elimination reaction: A reaction that involves the elimination of atoms (or molecules) from the reactant.

Empirical formula: The relative numbers of the different kinds of atoms in a molecule.

Enamine: An α, β-unsaturated tertiary amine.

Enantiomerically pure: Containing only one enantiomer.

Enantiomeric excess (optical purity): How much excess of one enantiomer is present in a mixture of a pair of enantiomers.

Enantiomers: Non-superimposable mirror-image molecules.

Enantioselective reaction: A reaction that forms an excess of one enantiomer.

Enantiotopic hydrogens: Two hydrogens bonded to a carbon that is bonded to two other groups that are nonidentical.

Endergonic reaction: A reaction with a positive $\Delta G°$.

Endo: A substituent is endo if it is closer to the longer or more unsaturated bridge.

Endothermic reaction: A reaction with a positive $\Delta H°$.

Enolization: Keto-enol interconversion.

Enthalpy: The heat given off ($-\Delta H°$) or the heat absorbed ($+\Delta H°$) during the course of a reaction.

Entropy: A measure of the freedom of motion in a system.

Enzyme: A protein that is a catalyst.

Epimerization: Changing the configuration at a chirality centre by removing a proton from it and then reprotonating the molecule at the same site.

Epimers: Monosaccharides that differ in configuration at only one carbon.

Epoxidation: Formation of an epoxide.

Equatorial bond: A bond of the chair form of cyclohexane that just out from the ring in approximately the same plane that contains the chair.

Equilibrium constant: The ratio of products to reactants at equilibrium or the ratio of the rate constants for the forward and reverse reactions.

Equilibrium control: Thermodynamic control.

Erythro enantiomers: The pair of enantiomers with similar groups on the same side when drawn in a Fischer projection.

Essential amino acid: An amino acid that humans must obtain from their diet because they cannot synthesize it or cannot syntehsize it in adequate amounts.

Ether: A compound containing an oxygen bonded to two carbons (ROR).

Excited-state electronic configuration: The electronic configuration that results when an electron in the ground-state electronic configuration has been moved to a higher-energy orbital.

Exergonic reaction: A reaction with a negative $\Delta G°$.

Exhaustive methylation: Reaction of an amine with excess methyl iodide resulting in the formation of a quaternary ammonium iodide.

Exo: A substituent is exo if it is closer to the shorter or more saturated bridge.

Exothermic reaction: A reaction with a negative $\Delta H°$.

Experimental energy of activation ($Ea = \Delta H^{\#} - RT$): A measure of the approximate energy barrier to a reaction. (It is approximate because it does not contain an entropy component).

Extrusion reaction: A reaction in which a neutral molecule (for example, CO_2, CO or N_2) is eliminated from a molecule.

Fat: A triester of glycerol that exists as a solid at room temperature.

Fatty acid: A long-chain carboxylic acid.

Fingerprint region: The right-hand third of an infrared spectrum where the absorption bands are characteristic of the compound as a whole.

First-order rate constant: The rate constant of a first-order reaction.

First-order reaction (unimolecular reaction): A reaction whose rate is dependent on the concentration of one reactant.

Fischer esterification: The reaction of a carboxylic acid with excess alcohol in the presence of an acid catalyst to form an ester.

Fischer projection: A method of representing the spatial arrangement of groups bonded to a chirality centre. The chirality centre is the point of intersection of two perpendicular lines; the horizontal lines represent bonds that project out of the plane of the paper toward the viewer, and the vertical lines represent bonds that point back from the plane of the paper away from the viewer.

Flagpole hydrogens (transannular hydrogens): The two hydrogens in the boat conformation of cyclohexane that are closest to each other.

Fourier transform NMR: A technique in which all the nuclei are excited simultaneously by a radio frequency pulse, their relaxation monitored, and the data mathematically converted to a spectrum.

Free energy of activation ($\Delta G^{\#}$): The true energy barrier to a reaction.

Free induction decay: Relaxation of excited nuclei.

Frequency: The velocity of a wave divided by its wavelength (in units of cycles/s).

Friedel-Crafts acylation: An electrophilic substitution reaction that puts an acyl group on a benzene ring.

Friedel-Crafts alkylation: An electrophilic substitution reaction that puts an alkyl group on a benzene ring.

Frontier orbital analysis: Determining the outcome of a pericyclic reaction using frontier orbitals.

Frontier orbitals: The HOMO and the LUMO.

Frontier orbitals theory: A theory that, like the conservation of orbital symmetry theory, explains the relationships among reactant, product and reaction conditions in a pericyclic reaction.

Functional group: The centre of reactivity in a molecule.

Functional group inter-conversion: Conversion of one functional group into another functional group.

Functional group region: The left-hand two-thirds of an infrared spectrum where most functional groups show absorption bands.

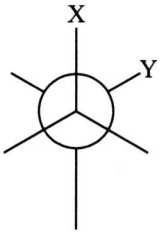
Furanose: A five-member ring sugar.

Furanoside: A five-member ring glycoside.

Fused bicyclic compound: A bicyclic compound in which the rings share two adjacent carbons.

Gabriel synthesis: Conversion of an alkyl halide into a primary amine using phthalimide as a starting material.

Gauche: X and Y are gauche to each other.



Gauche conformer: A staggered conformer in which the largest substituents are gauche to each other.

Gauche interaction: The interaction between two atoms or groups that are gauche to each other.

Gem-diol: A compound with two OH groups on the same carbon.

Geminal coupling: The mutual splitting of two nonidential protons bonded to the same carbon.

Geminal dihalide: A compound with two halogen atoms bonded to the same carbon.

Gene: A segment of DNA.

General-acid catalysis: Catalysis in which a proton is transferred to the reactant during the slow step of the reaction.

General-base catalysis: Catalysis in which a proton is removed from the reactant during the slow step of the reaction.

Geometric isomers: *cis-trans* (or *E-Z*) isomers.

Gibbs standard free energy change: The difference between the free energy content of the products and the free energy content of the reactants at equilibrium under standard conditions (1 M, 25°C, 1 atm).

Gilman reagent: A dialkylcopper reagent used to replace a halogen with an alkyl group.

Glycoside: The acetal of a sugar.

Glycosidic bond: The bond between the anomeric carbon and the alcohol in a glycoside.

Grignard reagent: The compound that results when magnesium is inserted between the carbon and halogen of an alkyl halide (RMgBr, RMgCl).

Ground-state electronic configuration: A description of which orbitals the electrons of an atom or molecule occupy when they are all in their lowest-energy orbitals.

Half chair conformation: The least stable conformation of cyclohexane.

Haloform reaction: The reaction of a halogen and HO^- with a methyl ketone.

Halogenation: Reaction with halogen (Br_2, Cl_2).

Halohydrin: An organic molecule that contains a halogen and an OH group on adjacent carbons.

Hard and soft acids and bases: A classification of acids and bases depending on their polarizability. [Hard bases include fluoride ions; soft bases include triphenylphosphine. Hard acids include Na^+, whilst an example of a soft, polarisable acid is Pt^{2+}; hard-hard and soft-soft interactions are favoured. Hardness and softness can be described in terms of the HOMO and LUMO interactions].

Haworth projection: A way to show the structure of a sugar; the five-and six-member rings are represented as being flat.

Heat-to-tail addition: The head of one molecule is added to the tail of another molecule.

Heat of combustion: The amount of heat given off when a carbon-containing compound reacts completely with O_2 to form CO_2 and H_2O.

Heat of formation: The heat given off when a compound is formed from its elements under standard conditions.

Heat of hydrogenation: The heat ($\Delta H°$) released in a hydrogenation reaction.

Heisenberg uncertainty principle: States that both the precise location and the momentum of an atomic particle cannot be simultaneoulsy determined.

Hell-Volhard-Zelinski (HVZ) reaction: Heating a carboxylic acid with Br_2 + P in order to convert it into an α-bromocarboxylic acid.

Hemiacetal:



Hemiketal:



Henderson-Hasselbalch equation: $pKa = pH + \log [HA]/[A^-]$.

Heptose: A monosaccharide with 7 carbons.

HETCOR spectrum: A 2-D NMR spectrum that shows coupling between protons and the carbons to which they are attached.

Heterocyclic compound (heterocycle): A cyclic compound in which one or more of the atoms of the ring are hetero atoms.

Heterogeneous catalyst: A catalyst that is insoluble in the reaction mixture.

Heterolytic bond cleavage (heterolysis): Breaking a bond with the result that both bonding electrons stay with one of the atoms.

Hexose: A monsosaccharide with six carbons.

High-energy bond: A bond that releases a great deal of energy when it is broken.

Highest occupied molecular orbital (HOMO): The molecular orbital of highest energy that contains an electron.

High-resolution NMR spectroscopy: NMR spectroscopy that uses a spectrometer with a high operating frequency.

Hofmann degradation: Exhaustive methylation of an amine, followed by reaction with Ag_2O, followed by heating to achieve a Hofmann elimination reaction.

Hofmann elimination (anti-Zaitsev elimination): A hydrogen is removed from the β-carbon bonded to the most hydrogens.

Hofmann elimination reaction: Elimination of a proton and a tertiary amine from a quaternary ammonium hydroxide.

Hofmann rearrangement: Conversion of an amide into an amine using Br_2/HO^-.

Homogeneous catalyst: A catalyst that is soluble in the reaction mixture.

Homolog: A member of a homologous series.

Homologous series: A family of compounds in which each member differs from the next by ome methylene group.

Homolytic bond cleavage (homolysis): Breaking a bond with the result that each of the atoms gets one of the bonding electrons.

Homopolymer: A polymer that contains only one kind of monomer.

Homotopic hydrogens: Two hydrogens bonded to a carbon that is bonded to two other groups that are identical.

Hormone: An organic compound synthesized in a gland and delivered by the bloodstream to its target tissue.

Hückel's rule: States that for a compound to be aromatic its cloud of electrons must contain $(4n + 2)$ π electrons, where n is an integer. This is the same as saying it must contain an odd number of pairs of π electrons.

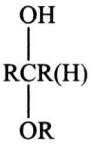
Hund's rule: States that when there are degenerate orbitals, an electron will occupy an empty orbital before it will pair up with another electron.

Hunsdiecker reaction: Conversion of a carboxylic acid into an alkyl halide by heating a heavy metal salt of the carboxylic acid with bromine or iodine.

Hybridization: The process whereby atomic orbitals of different type but similar energies are combined to form a set of equivalent hybid orbitals. These hybrid orbitals do not exist in the atoms but only in the formation of molecular orbitals by combining atomic orbitals from different atoms.

Hybridized orbital: An orbital formed by mixing (hybridizing) orbitals.

Hydrate (*gem*-diol):



Hydrated: When water has been added to a compound.

Hydration: Addition of water to a compound.

Hydrazone: $R_2C{=}NNH_2$

Hydride ion: A negatively charged hydrogen.

1,2-Hydride shift: The movement of a hydride ion from one carbon to an adjacent carbon.

Hydroboration-oxidation: The addition of borane to an alkene or an alkyne followed by reaction with hydrogen peroxide and hydroxide ion.

Hydrocarbon: A compound that contains only carbon and hydrogen.

α-Hydrogen: A hydrogen bonded to the carbon adjacent to a carbonyl carbon.

Hydrogenation: Addition of hydrogen.

Hydrogen bond: an unusually strong dipole-dipole attraction (5 Kcal/mol) between a hydrogen bonded to O, N, or F and the nonbonding electrons of an O, N, or F of another molecule.

Hydrogen ion (a proton): A positively charged hydrogen.

Hydrolysis: Reaction with water.

Hydrophobic interactions: Interactions between nonpolar groups. They increase stability by decreasing the amount of structured water (increasing entropy).

Hyperconjugation: Delocalization of electrons by overlap of carbon-hydrogen or carbon-carbon σ bonds with an empty *p* orbital.

Imine: $R_2C{=}NR$

Inclusion compound: A compound that specifically binds a metal ion or an organic molecule.

Induced dipole–induced dipole interaction: An interaction between a temporary dipole in one molecule and the dipole the temporary dipole induces in another molecule.

Inductive electron donation: Donation of electrons through a σ bond.

Inductive electron withdrawal: Withdrawal of electrons through a σ bond.

Infrared radiation: Electromagnetic radiation familiar to us as heat.

Infrared spectroscopy: Uses infrared energy to provide a knowledge of the functional groups in a compound.

Infrared (IR) spectrum: A plot of relative absorption versus wave number (or wavelength) of infrared radiation.

Initiation step: The step in which radicals are created, or the step in which the radical needed for the first propagation step is created.

Intermediate: A species formed during a reaction that is not the final product of the reaction.

Intermolecular reaction: A reaction that takes place between two molecules (same or different).

Internal alkyne: An alkyne with the triple bond not at the end of the carbon chain.

Intimate ion pair: The covalent bond that joined the cation and the anion has broken, but the cation and anion are still next to each other.

Intramolecular reaction: A reactin that takes place within a molecule.

Inversion of configuration: Turning the carbon inside-out like an umbrella in a windstorm so that the resulting product has a configuration opposite to that of the reactant.

Iodoform test: Addition of I_2/HO^- to a methyl ketone forms a yellow precipitate.

Ion-dipole interaction: The interaction between an ion and the dipole of a molecule.

Ion-exchange chromatography: A technique that uses a column packed with an insoluble resin to separate compounds on the basis of their charges and polarities.

Ionic bond: A bond formed through the attraction of two ions of opposite charges.

Ionization energy: The energy required to remove an electron from an atom.

Ionophore: A compound that binds metal ions tightly.

Iron protoporphyrin IX: The porphyrin ring system of heme plus an iron atom.

Isoelectric point (*pI*): The pH at which there is no net charge on an amino acid.

Isolated double bonds: Double bonds separated by more than one single bond.

Isomers: nonidentical compounds with the same molecular formula.

Isoprene rule: Head-to-tail linkage of isoprene units.

Isotactic polymer: A polymer in which all the substituents are on the same side of the fully extended carbon chain.

Isotopes: Atoms with the same number of protons but different numbers of neutrons.

Iterative synthesis: A synthesis in which a reaction sequence is carried out more than once.

IUPAC nomenclature: Systematic nomenclature.

Kekule structure: A model that represents the bonds between atoms as lines.

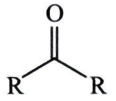
Ketal:



Keto-enol tautomerism (keto-enol interconversion): Interconversion of keto and enol tautomers.

Keto-enol tautomers: A ketone and its isomeric α, β-unsaturated alcohol.

Ketone:



Ketose: A polyhydroxyketone.

Kiliani-Fischer synthesis: A method used to increase the number of carbons in an aldose by one, resulting in the formation of a pair of C-2 epimers.

Kinetic control: When a reaction is under kinetic control, the relative amounts of the products depend on the rates at which they are formed.

Kinetic isotope effect: A comparison of the rate of reaction of a compound with the rate of reaction of an identical compound in which one of the atoms has been replaced by an isotope.

Kinetic product: The product that is formed the fastest.

Kinetic resolution: Separation of enantiomers based on the difference in their rate of reaction with an enzyme.

Kinetics: The field of chemistry that deals with the rates of chemical reactions.

Kinetic stability: Chemical reactivity, indicated by $\Delta G^{\#}$. If $\Delta G^{\#}$ is large, the compound is kinetically stable (not very reactive). If $\Delta G^{\#}$ is small, the compound is kinetically unstable (very reactive).

Kolbe-Schmitt carboxylation reaction: A reaction that uses CO_2 to carboxylate phenol.

Lactam: A cyclic amide.

Lactone: A cyclic ester.

Leaving group: The group that is displaced in a nucleophilic substitution reaction.

Le Chatelier's principle: States that if equilibrium is disturbed, the components of the equilibrium will adjust in a way that will offset the disturbance.

Levorotatory: The enantiomer that rotates polarized light in a counterclockwise direction.

Lewis acid: A substance that accepts an electron pair.

Lewis base: A substance that donates an electron pair.

Lewis structure: A model that represents the bonds between atoms as lines or dots and the valence electrons as dots.

Ligation: Sharing of nonbonding electrons with a metal.

Linear combination of atomic orbitals (LCAO): The combination of *p* atomic orbitals to produce a molecular orbital.

Linear conjugation: The atoms in the conjugated system are in a linear arrangement.

Linear synthesis: A synthesis that builds a molecule step by step from starting materials.

Lipid: A water-insoluble compound found in a living system.

Living polymer: A nonterminated chain-growth polymer that remains active. This means that the polymerization reaction can continue on addition of more monomer.

Lambda (λ) max: The wavelength at which there is maximum ultraviolet/visible absorbance.

Localized electrons: Electrons that are restricted to a particular locality.

Lock-and-key model: A model the describes the specificity of an enzyme for its substrate: the substrate fits the enzyme like a key fits a lock.

Lone pair electrons (nonbonding electrons): Valence electrons not used in bonding.

Long-range coupling: Splitting of a proton by a proton more than three σ bonds away.

Lowest unoccupied molecular orbital (LUMO): The molecular orbital of lowest energy that does not contain an electron.

Lucas test: A test that determines whether an alcohol is primary, secondary, or tertiary.

Magnetic anisotropy: The term used to describe the greater freedom of a π electron cloud to move in response to a magnetic field as a consequence of its greater polarizability compared with σ electrons.

Magnetic resonance imaging (MRI): NMR used in medicine. The difference in the way water is bound in different tissues produces the signal variation between organs as well as between healthy and diseased states.

Magnetogyric ratio: A property (measured in rad T^{-1} s^{-1}) that depends on the magnetic properties of a particular kind of nucleus.

Malonic ester synthesis: Synthesis of a carboxylic acid using diethyl malonate as the starting material.

Markovnikov's rule: The actual rule is: "when a hydrogen halide adds to an asymmetrical alkene, the addition occurs such that the halogen attaches itself to the sp^2 carbon of the alkene bearing the lowest number of hydrogen atoms". A more useful version is: the electrophile adds to the sp^2 carbon that is bonded to the greater number of hydrogens.

Mass number: The number of protons plus the number of neutrons in an atom.

Mass spectrometry: Provides a knowledge of the molecular weight, molecular formula and certain structural features of a compound.

Mass spectrum: A plot of the relative abundance of the positively charged fragments produced in a mass spectrometer versus their m/z values.

Materials science: The science of creating new materials to be used in place of known materials such as metal, glass, wood, cardboard and paper.

McLafferty rearrangement: Rearrangement of the molecular ion of a ketone. The bond between the α- and β-carbons breaks, and a γ-hydrogen migrates to the oxygen.

Mechanism-based inhibitor (suicide inhibitor): A compound that inactivates an enzyme by undergoing part of its normal catalytic mechanism.

Mechanism of a reaction: A description of the step-by-step process by which reactants are changed into products.

Melting point: The temperature at which a solid becomes a liquid.

Membrane: The material that surrounds the cell in order to isolate its contents.

Mercaptan (thiol): The sulphur analog of an alcohol (RSH).

Meso compound: A compound that contains chirality centres and a plane of symmetry.

Metabolism: Reactions living organisms carry out in order to obtain the energy they need and to synthesize the compounds they require.

Meta-directing substituent: A substituent that directs an incoming substituent meta to an existing substituent.

Metal-activated enzyme: An enzyme that has a loosely bound metal ion.

Metal-ion catalysis: Catalysis in which the species that facilitates the reaction is a metal ion.

Metalloenzyme: An enzyme that has a tightly bound metal ion.

Methine hydrogen: A tertiary hydrogen.

Methylene group: A CH_2 group.

1,2-Methyl shift: The movement of a methyl group with its bonding electrons from one carbon to an adjacent carbon.

Micelle: A spherical aggregation of molecules each with a long hydrophobic tail and a polar head, arranged so that the polar head points to the outside of the sphere.

Michael reaction: The addition of an α-carbanion to the β-carbon of an α,β-unsaturated carbonyl compound.

Mixed anhydride: An acid anhydride with two different R groups (RCO_2COR').

Mixed Claisen condensation: A Claisen condensation in which two different esters are used.

Mixed triacylglycerol: A triacylglycerol in which the fatty acid components are different.

Molar absorptivity: The absorbance obtained from a 1.00-M solution in a cell with a 1.00-cm light path.

Molecular modeling: Computer-assisted design of a compound with a structure similar to that of a compound with the desired activity.

Molecular modification: Changing the structure of a lead compound.

Molecular orbital: An orbital associated with a molecule.

Molecular orbital theory: Describes a model in which the electrons occupy orbitals as they do in atoms but with the orbitals extending over the entire molecule.

Molecular recognition: The recognition of one molecule by another as a result of specific interactions; for example, the specificity of an enzyme for its substrate.

Molozonide: An unstable intermediate containing a five-member ring with three oxygens in a row that is formed from the reaction of an alkene with ozone.

Monomer: A repeating unit in a polymer.

Monosaccharide (simple carbohydrate): A single sugar molecule.

Monoterpene: A terpene that contains ten carbons.

MRI scanner: An NMR spectrometer used in medicine for whole body NMR.

Multiplet: An NMR signal split into more than seven peaks.

Multiplicity: The number of peaks in an NMR signal.

Multistep synthesis: Preparation of a compound by a route that requires several steps.

Mutarotation: A slow change in optical rotation to an equilibrium value.

N + 1 Rule: An 1H NMR signal for a hydrogen with N equivalent hydrogens bonded to an adjacent carbon is split into N + 1 peaks. A ^{13}C NMR signal for a carbon bonded to N hydrogens is split into N + 1 peaks.

N-glycoside: A glycoside with a nitrogen instead of an oxygen at the glycosidic linkage.

N-Terminal acid: The terminal amino acid of a peptide (or protein) that has a free amino group.

Natural abundance atomic weight: The average mass of the atoms in the naturally occurring element.

Natural product: A product synthesized in nature.

Neurotransmitter: A compound that transmits nerve impulses.

Nicotinamide adenine dinucleotide (NAD^+): A coenzyme required in certain oxidation reactions. It is reduced to NADH, which can act as a reducing agent in another reaction.

Nicotinamide adenine dinucleotide phosphate ($NADP^+$): A coenzyme required in certain oxidation reactions. It is reduced to NADPH, which can act as a reducing agent in another reaction.

Nitration: Substitution of a nitro group (NO_2) for a hydrogen of a benzene ring.

Nitrile: A compound that contains a carbon-nitrogen triple bond ($R{\equiv}CN$).

Nitrosamine (N-nitroso compound): $R_2NN{=}O$.

NMR spectroscopy: The absorption of electromagnetic radiation to determine the structural features of an organic compound. In the case of ^{1}H NMR spectroscopy, it determines the carbon-hydrogen framework.

Node: That part of an orbital in which there is zero probability of finding an electron.

Nominal mass: Mass rounded to the nearest whole number.

Nonbonding molecular orbital: The *p* orbitals are too far apart to overlap significantly, so the molecular orbital that results neither favours nor disfavours bonding.

Nonpolar covalent bond: A bond formed between two atoms that share the bonding electrons equally.

Non-reducing sugar: A sugar that cannot be oxidized by reagents such as Ag^{+} and Cu^{+}. Non-reducing sugars are not in equilibrium with the open-chain aldose or ketose.

Normal alkane (straight-chain alkane): An alkane in which the carbons form a continuous chain with no branches.

Nucleic acid: The two kinds of nucleic acid are DNA and RNA.

Nucleophile: An electron-rich atom or molecule.

Nucleophilic acyl substitution reaction: A reaction in which a group bonded to an acyl or aryl group is substituted by another group.

Nucleophilic addition-elimination reaction: A nucleophilic addition reaction that is followed by an elimination reaction. Imine formation is an example: an amine adds to the carbonyl carbon and water is eliminated.

Nucleophilic addition reaction: A reaction that involves the addition of a nucleophile to a reagent.

Nucleophilic aromatic substitution: A reaction in which a nucleophile substitutes for a substituent of an aromatic ring.

Nucleophilic catalyst: A catalyst that increases the rate of a reaction by acting as a nucleophile.

Nucleophilicity: A measure of how readily an atom or molecule with a pair of non-bonding electrons attacks an atom except hydrogen.

Nucleophilic substitution reaction: A reaction in which a nucleophile substitutes for an atom or group.

Octet rule: States that an atom will give up, accept, or share electrons in order to achieve a filled shell. Because of filled second shell contains eight electrons, this is known as the octet rule.

Off-resonance decoupling: The mode in ^{13}C NMR spectroscopy in which spin-spin splitting occurs between carbons and the hydrogens attached to them.

Oil: a triester of glycerol that exists as a liquid at room temperature.

Olefin: an alkene.

Oligomer: A protein with more than one peptide chain.

Optical isomers: Stereoisomers that contain chirality centres. Optically active (chiral) rotates the plane of polarized light.

Orbital: The volume of space around the nucleus in which an electron in most likely to be found.

Orbital hybridization: mixing of orbitals.

Organic compound: A compound that contains carbon.

Organic synthesis: Preparation of organic compounds from other organic compounds.

Organometallic compound: A compound containing a carbon-metal bond.

Orphan drugs: Drugs for diseases or conditions that affect fewer than 2,00,000 people.

***ortho*/*para*-directing substituent:** A substituent that directs an incoming substituent *ortho* and *para* to an existing substituent.

Osazone: The product obtained by treating an aldose or a ketose with excess phenylhydrazine. An osazone contains two imine bonds.

Overtone band: Occurs at a multiple of the fundamental absorption frequency ($2v_1$, $3v_1$).

Oxidation: Loss of electrons by an atom or molecule.

Oxidation-reduction reaction (redox reaction): A reaction that involves the transfer of electrons from one species to another.

Oxidative cleavage: An oxidation reaction that cuts the reactant into two or more pieces.

Oxime: $R_2C{=}NOH$.

Oxirane (epoxide): An ether in which the oxygen is incorporated into a three-member ring.

Oxonium ion: A compound with a positively charged oxygen.

Oxyanion: A compound with a negatively charged oxygen.

Oxymercuration: Addition of water using a mercuric salt of a carboxylic acid as a catalyst.

Ozonide: The five-member ring compound formed as a result of rearrangement of a molozonide.

Ozonolysis: Reaction of a carbon-carbon double or triple bond with ozone.

Packing: The fitting of individual molecules into a frozen crystal lattice.

Paraffin: An alkane.

Parent hydrocarbon: The longest continuous carbon chain in a molecule.

Parent ion (molecular ion): Peak in the mass spectrum with the greatest m/z.

Partial hydrolysis: A technique that hydrolyzes only some of the peptide bonds in a polypeptide.

Partial racemization: Formation of a pair of enantiomers in unequal amounts.

Pauli exclusion principle: States that no more than two electrons can occupy an orbital and that the two electrons must have opposite spin.

Pentose: A monsosaccharide with five carbons.

Peptide: Polymer of amino acids linked together by amide bonds. A peptide contains fewer amino acid residues than a protein.

Peptide bond: The amide bond that links the amino acids in a peptide or protein.

Pericyclic reaction: A concerted reaction that takes place as the result of a cyclic rearrangement of electrons.

Peroxy acid: A carboxylic acid with an OOH group instead of an OH group.

Perspective formula: A method of respresenting the spatial arrangement of groups bonded to a chirality centre. Two bonds are drawn in the plane of the paper; a solid wedge is used to depict a bond that projects out of the plane of the paper toward the viewer, and a dashed line is used to represent a bond that projects back from the plane of the paper away from the viewer.

pH: The pH scale is used to describe the acidity of a solution ($pH = -\log [H^+]$).

pH-activity profile: A plot of the activity of an enzyme as a function of the pH of the reaction mixture.

Phase transfer catalysis: Catalysis of a reaction by providing a way to bring a polar reagent into a nonpolar phase so that the reaction between a polar and a nonpolar compound can occur.

Phase tranfer catalyst: A compound that carries a polar reagent into a nonpolar phase.

Phenylhydrazone: $R_2C{=}NNHC_6H_5$

Phosphoacylglycerol (phosphoglyceride): Formed when two OH groups of glycerol form esters with fatty acids and the terminal OH group forms a phosphate ester.

Phosphoanhydride bond: The bond holding two phosphoric acid molecules together.

Phospholipid: A lipid that contains a phosphate group.

Phosphoryl transfer reaction: The transfer of a phosphate group from the compound to another.

Photochemical reaction: A reaction that takes place when a reactant absorbs light.

Photosynthesis: The synthesis of glucose and O_2 from CO_2 and H_2O.

pi (π)-Bond: A bond formed as a result of side-to-side overlap of *p* orbitals.

pi-Complex: A complex formed between an electrophile and a π bond.

Pinacol rearrangement: Rearrangement of a vicinal diol.

pK_a: Describes the tendency of a compound to lose a proton ($pK_a = -\log K_a$, where K_a is the acid dissociation constant).

Plane of symmetry: An imaginary plane that bisects a molecule into a pair of mirror images.

Plasticizer: An organic molecule that dissolves in a polymer and allows that polymer chains to slide by each other.

Polar covalent bond: A bond formed by the unequal sharing of electrons.

Polarimeter: An instrument that measures the ratation of polarized light.

Polarizability: An indication of the case with which the electron cloud of an atom can be distorted.

Polarized light: Light that oscillates only in one plane.

Polar reaction: The reaction between a nucleophile and an electrophile.

Polyamide: A polymer in which the monomers are amides.

Polycarbonate: A step-growth polymer in which the dicarboxylic acid is carbonic acid.

Polyene: A compound that has several double bonds.

Polyester: A polymer in which the monomers are esters.

Polymer: A large molecule made by linking monomers together.

Polymer chemistry: The field of chemistry that deals with synthetic polymers; part of the larger discipline known as materials science.

Polymerization: The process of linking up monomers to form a polymer.

Polypeptide: Many amino acids linked by amide bonds.

Polysaccharide: A compound containing ten or more sugar molecules linked together.

Polyunsaturated fatty acid: A fatty acid with more than one double bond.

Polyurethane: A polymer in which the monomers are urethanes.

Primary alcohol: An alcohol in which the OH group is bonded to a primary carbon.

Primary alkyl halide: An alkyl halide in which the halogen is bonded to a primary carbon.

Primary amine: An amine with one alkyl group bonded to the nitrogen.

Primary carbocation: A carbocation with the positive charge on a primary carbon.

Primary carbon: A carbon bonded to only one other carbon.

Primary hydrogen: A hydrogen bonded to a primary carbon.

Primary radical: A radical with the unpaired electron on a primary carbon.

Prochirality centre: A carbon bonded to two hydrogens that will become a chirality centre if one of the hydrogens is replaced by deuterium.

Propagating site: The reactive end of a chain-growth polymer.

Propagation step: In the first of a pair of propagation steps, a radical (or an electrophile or a nucleophile) reacts to produce another radical (or an electrophile or a nucleophile) that reacts in the second propagation step to produce the radical (or the electrophile or the nucleophile) that was the reactant in the first propagation step.

pro-R-Hydrogen: Replacing this hydrogen with deuterium creates a chirality centre with the R configuration.

pro-S-Hydrogen: Replacing this hydrogen with deuterium creates a chirality centre with the S configuration.

pro-Chiral carbonyl carbon: A carbonyl carbon that will become a chirality centre if it is attacked by a group unlike any of the groups already bonded to it.

Protecting group: A reagent that protects a functional group from a synthetic operation that it would otherwise not survive.

Protic solvent: A solvent that has a hydrogen bonded to an oxygen or a nitrogen.

Proton: A positively charged hydrogen; a positively charged particle in an atomic nucleus.

Proton-decoupled ^{13}C NMR spectrum: A ^{13}C NMR spectrum in which all the signals appear as singlets because there is no coupling between the ^{13}C nucleus and its bonded hydrogens.

Proton transfer reaction: A reaction in which a proton is tranferred from an acid to a base.

Protoporphyrin-IX: The porphyrin ring system of heme.

Pseudo First-order reaction: A second-order reaction in which the concentration of one of the reactants is much greater than the other, which allows the reaction to be treated as a first-order reaction.

Pyranose: A six-member ring sugar.

Pyranoside: A six-member ring glycoside.

Pyridoxal-phosphate: The coenzyme required by enzymes that catalyze certain transformations of amino acids.

Quantum numbers: Numbers arising from the quantum mechanical treatement of an atom that describe the properties of the electrons in the atom.

Quartet: an NMR signal split into four peaks.

Quaternary ammonium ion: An ion containing a nitrogen bonded to four alkyl groups (R_4N^+).

Quaternary ammonium salt: A quaternary ammoruum ion and an anion ($R_4N^+X^-$).

Quaternary structure: A description of the way the individual polypeptide chains of a protein are arranged with respect to each other.

Racemic mixture (racemate, racemic modification): A mixture of equal amounts of a pair of enantiomers.

Radical: An atom or molecule with an unpaired electron.

Radical addition reaction: An addition reaction in which the first species that adds is a radical.

Radical anion: A species with a negative charge and an unpaired electron.

Radical cation: A species with a positive charge and an unpaired electron.

Radical chain reaction: A reaction in which radicals are formed and react in repeating propagating steps.

Radical inhibitor: A compound that traps radicals.

Radical initiator: A compound that creates radicals.

Radical reaction: A reaction in which a new bond is formed using one electron from one reagent and one electron from another reagent.

Radical substitution reaction: A substitution reaction that has a radical intermediate.

Rate constant: A measurement of how easy it is to reach the transition state of a reaction (to get over the energy barrier to the reaction).

Rate-determining step (rate-limiting step): The step in a reaction that has the transition state with the highest energy.

Rational drug design: Designing drugs with a particular structure to achieve a specific purpose.

R-Configuration: After assigning relative priorities to the four groups bonded to a chirality centre, if the lowest-priority group is on a vertical axis in a Fischer projection (or pointing away from the viewer in a perspective formula), an arrow drawn from the highest priority group to the next-highest-priority group goes in a clockwise direction.

Red shift: A shift to a longer wavelength.

Reducing sugar: A sugar that can be oxidized by reagents such as Ag^+ and Cu^+. Reducing sugars are in equilibrium with the open-chain aldose or ketose.

Reduction: Gain of electrons by an atom or molecule.

Reductive amination: The reaction of an aldehyde or a ketone with ammonia or with a primary amine in the presence of a reducing agent (H_2/Raney Ni).

Reference compound: A compound added to the sample whose NMR spectrum is to be taken. The positions of the signals in the NMR spectrum are measured from the position of the signal given by the reference compound.

Regioselective reaction: A reaction that leads to the preferential formation of one constitutional isomer over another.

Relative configuration: The configuration of a compound relative to the configuration of another compound.

Resolution of a racemic mixture: Separation of a racemic mixture into the individual enantiomers.

Resonance: A compound with delocalized electrons is said to have resonance.

Resonance contributor (resonance structure): A structure with localized electrons that approximates the true structure of a compound with delocalized electrons.

Resonance electron donation: Donation of electrons through *p* orbital overlap with neighbouring π bonds.

Resonance electron withdrawal: Withdrawal of electrons through *p* orbital overlap with neighbouring π bonds.

Resonance hybrid: The actual structure of a compound with delocalized electrons; it is represented by two or more structures with localized electrons.

Resonances: NMR absorption signals.

Retrosynthesis (retrosynthetic analysis): Working backward (on paper) from the target molecule to available starting materials.

rf-Flip radiation: Radiation in the radiofrequency region of the electromagnetic spectrum.

Ribonucleic acid (RNA): A polymer of ribonucleotides.

Ribonucleotide: A nucleotide in which the sugar component is D-ribose.

Ring current: The movement of π electrons around a benzene ring.

Ring-expansion rearrangement: Rearrangement of a carbocation in which the positively charged carbon is bonded to a cyclic compound and as a result of rearrangement the size of the ring increases by one carbon.

Ring-flip (chair-chair interconversion): The conversion of the chair conformer of cyclohexane into the other chair conformer. Bonds that are axial in one chair conformer are equatorial in the other chair conformer.

Ring-opening polymerization: A chain-growth polymerization that involves opening the ring of the monomer.

Ritter reaction: Reaction of a nitrile with a secondary or tertiary alcohol to form a secondary amide.

Robinson annulation: A Michael reaction followed by an intramolecular aldol condensation.

Rosenmund reduction: Reduction of an acyl chloride to an aldehyde using H_2 and a deactivated palladium catalyst.

Ruff degradation: A method used to shorten an aldose by one carbon.

Sandmeyer reaction: The reaction of an aryl diazonium salt with a cuprous salt.

Saponification: Hydrolysis of a fat under basic conditions.

Saturated hydrocarbon: A hydrocarbon that is completely saturated with hydrogen (contains no double or triple bonds).

Sawhorse projection: The sideways projection of a carbon-carbon single bond and the attached substituents. [It gives a clearer representation of stereochemistry than the Fischer projection. See also Newmann projection].

Schiemann reaction: The reaction of an aryl diazonium salt with HBF_4.

Schiff base: $R_2C{=}NR$.

s-cis-Conformation: The conformation in which two double bonds are on the same side of a single bond.

S-Configuration: After assigning relative priorities to the four groups bonded to a chirality centre, if the lowest-priority group is on a vertical axis in a Fischer projectin (or pointing away from the viewer in a perspective formula), an arrow drawn from the highest-priority group to the next-highest-priority group goes in a counterclockwise direction.

Secondary alcohol: An alcohol in which the OH group is bonded to a secondary carbon.

Secondary alkyl halide: An alkyl halide in which the halogen is bounded to a secondary carbon.

Secondary amine: An amine with two alkyl groups bonded to the nitrogen.

Secondary carbocation: A carbocation with the positive charge on a secondary carbon.

Secondary carbon: A carbon bonded to two other carbons.

Secondary hydrogen: A hydrogen bonded to a secondary carbon.

Secondary radical: A radical with the unpaired electron on a secondary carbon.

Secondary structure: A description of the conformation of the backbone of a protein.

Second-order rate constant: The rate constant of a second-order reaction.

Selection rules: The rules that determine the outcome of a pericyclic reaction.

Selenenylation reaction: Conversion of an α-bromoketone into an α,β-unsaturated ketone via formation of an α-phenylseleno ketone.

Semicarbazone: $R_2C{=}NNHCONH_2$

Separated charges: A positive and a negative charge that can be neutralized by the movement of electrons.

Sesquiterpene: A terpene that contains 15 carbons.

Shielding: Cause by electron donation to the environment of a proton. The electrons shield the proton from the full effect of the applied magnetic field. The more a proton is shielded, the farther to the right its signal appears in an NMR spectrum.

Sigma (σ) bond: A bond with a symmetrical distribution of electrons.

Sigmatropic rearrangement: A reaction in which a σ bond is broken in the reactant, a new σ bond is formed in the product, and the π bonds rearrange.

Simmons-Smith Reaction: Formation of a cyclopropane using CH_2I_2 + Zn(Cu).

Simple triacylglycerol: A triacylglycerol in which the fatty acid components are the same.

Single bond: A σ bond.

Singlet: An unsplit NMR signal.

S_N1-Reaction: A first-order nucleophilic substitution reaction.

S_N2-Reaction: A second-order nucleophilic substitution reaction.

S_NAr Reaction: A nucleophilic aromatic substitution reaction.

Soap: A sodium or potassium salt of a fatty acid.

Solid-phase synthesis: A technique in which one end of the compound being synthesized is covalently attached to a solid support.

Solvation: The interaction between a solvent and another molecule (or ion).

Solvent-separated ion pair: The cation and anion are separated by a solvent molecule.

Solvolysis: Reaction with the solvent.

Specific-acid catalysis: Catalysis in which the proton is fully transferred to the reactant before the slow step of the reaction.

Specific-base catalysis: Catalysis in which the proton is completely removed from the reactant before the slow step of the reaction.

Specific rotation: The amount of rotation that will be caused by a compound with a concentration of 1.0 g/mL in a sample tube 1.0 dm long.

Spectroscopy: Study of the interaction of matter and electromagnetic radiation.

Spin-coupled ^{13}C NMR: Spectrum a ^{13}C NMR spectrum in which each signal for a carbon is split by the hydrogens bonded to that carbon.

Spin-coupling: The atom that gives rise to an NMR signal is coupled to the rest of the molecule.

Spin-decoupling: The atom that gives rise to an NMR signal is decoupled from the rest of the molecule.

Spin-spin coupling: The splitting of a signal in an NMR spectrum described by the N + 1 rule.

α-Spin state: Nuclei in this spin state have their magnetic moments oriented in the same direction as the applied magnetic field.

β-Spin state: Nuclei in this spin state have their magnetic moments oriented opposite to the direction of the applied magnetic field.

Spirocyclic compound: A bicyclic compound in which the rings share one carbon.

Staggered conformation: A comformation in which the bonds on one carbon bisect the bond angle on the adjacent carbon when viewed looking down the carbon-carbon bond.

Stereochemistry: The field of chemistry that deals with the structures of molecules in three dimensions.

Stereoelectronic effects: The combination of steric effects and electronic effects.

Stereoisomers: Isomers that differ in the way the atoms are arranged in space.

Stereoselective reaction: A reaction that leads to the preferential formation of one stereoisomer over another.

Stereospecific reaction: A reaction in which the reactant can exist as stereoisomers and each stereoisomeric reactant leads to a different stereoisomeric product.

Steric effects: Effects due to the fact that groups occupy a certain volume of space.

Steric hindrance: Refers to bulky groups at the site of a reaction that make it difficult for the reactants to approach each other.

Steric strain (van der Waals Strain or van der Waals repulsion): The repulsion between the electron cloud of an atom or group of atoms and the electron cloud of another atom or group of atoms.

Steroid: A class of compounds that contains a steroid ring system.

Stork enamine: Reaction that uses an enamine as a nucleophile in a Michael reaction.

s-*trans*-Conformation: A conformation in which two double bonds are on opposite sides of a single bond.

Strecker synthesis: A method used to synthesize an amino acid: an aldehyde reacts with NH_3, forming an imine that is attacked by cyanide ion. Hydrolysis of the product gives an amino acid.

Stretching frequency: The frequency at which a stretching vibratin occurs.

Stretching virbation: A vibration occurring along the line of the bond.

Structural protein: A protein that gives strength to a biological structure.

α-Substituent: A substituent on the opposite side of a steroid ring system as the angular methyl groups.

β-Substituent: A substituent on the same side of a steroid ring system as the angular methyl groups.

α-Substitution reaction: A reaction that puts a substituent on an α-carbon in place of an α-hydrogen.

Substrate: The reactant of an enzyme-catalyzed reaction.

Subunit: an individual chain of an oligomer.

Sulphide (thioether): The sulphur analog of an ether (RSR).

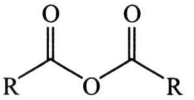
Sulphonate ester: The ester of a sulphonic acid (RSO_2OR).

Sulphonation: Substitution of a hydrogen of a benzene ring by a sulphuric acid group ($—SO_3H$).

Suprafacial bond formation: Formation of two σ bonds from the same side of the π system.

Suprafacial rearrangement: Rearrangement in which the migrating group remains on the same face of the π system.

Symmetrical anhydride: An acid anhydride with identical *R* groups.



Symmetrical ether: An ether with two identical substituents bonded to the oxygen.

Symmetric molecular orbital: A molecular orbital in which the left half is a mirror image of the right half.

Symmetry-allowed pathway: A pathway that leads to overlap of inphase orbitals.

Symmetry-forbidden pathway: A pathway that leads to overlap of out-of-phase orbitals.

***syn*-Addition:** An addition reaction in which the two added substituents add to the same side of the molecule.

***syn*-Elimination:** An elimination reaction in which the two substituents eliminated are removed from the same side of the molecule.

***syn*-Periplanar:** Parallel substituents on the same side of a molecule.

Synthetic equivalent: The reagent actually used as the source of a synthon.

Synthetic polymer: A polymer that is not synthesized in nature.

Synthetic tree: An outline of the available routes to get to the desired product from available starting materials.

Synthon: A fragment of a disconnection.

Target molecule: The desired end product of a synthesis.

Tautomerism: Interconversion of tautomers.

Tautomers: Isomers that differ in the location of a double bond and a hydrogen.

Terminal alkyne: An alkyne with the triple bond at the end of the carbon chain.

Termination step: Two radicals combine to produce a molecule in which all the electrons are paired.

Terpene: A lipid, isolated from a plant that contains carbon atoms in multiples of 5.

Terpenoid: A terpene that contains oxygen.

Tertiary alcohol: An alcohol in which the OH group is bonded to a tertiary carbon.

Tertiary alkyl halide: An alkyl halide in which the halogen is bonded to a tertiary carbon.

Tertiary amine: An amine with three alkyl groups are bonded to the nitrogen.

Tertiary carbocation: A carbocation with the positive charge on a tertiary carbon.

Tertiary carbon: A carbon bonded to three other carbons.

Tertiary hydrogen: A hydrogen bonded to a tertiary carbon.

Tertiary radical: A radical with the unpaired electron on a tertiary carbon.

Tertiary structure: A description of the three-dimensional arrangement of all the atoms in a protein.

Tetrahedral bond angle: The bond angle (109.5°) formed by adjacent bonds of an sp^3 hybridized carbon.

Tetrahedral carbon: An sp^3 hybridized carbon; a carbon that forms covalent bonds using four sp^3 hybridized orbitals.

Tetrahedral intermediate: The intermediate formed in a nucleophilic acyl substitution reaction.

Tetraterpene: A terpene that contains 40 carbons.

Tetrose: A monosaccharide with four carbons.

Thermodynamic control: When a reaction is under thermodynamic control, the relative amounts of the products depend on their stabilities.

Thermodynamic product: The most stable product.

Thermodynamics: The field of chemistry that describes the properties of a system at equilibrium.

Thermodynamic stability: Is indicated by $\Delta G°$. If $\Delta G°$ is negative, the products are more stable than the reactants. If $\Delta G°$ is positive, the reactants are more stable than the products.

Thermoplastic polymer: A polymer that has both ordered crystalline regions and amorphous noncrystalline regions.

Thermosetting polymer: Cross-linked polymers that, after they are hardened, cannot be remelted by heating.

Thiirane: A three-member ring compound in which one of the ring atoms is a sulphur.

Thin-layer chromatography: A technique that separates compounds on the basis of their polarity.

Thioester: The sulphur analog of an ester. R(CO)SR.

Thioether (sulphide): The sulphur analog of an ether (RSR).

Thiol (mercaptan): The sulphur analog of an alcohol (RSH).

Tosylation: A reaction which introduces the toluence-4-sulphonyl group into a molecule. [Generally by reaction of an alcohol with tosyl chloride to give the tosylate ester].

Threo enantiomers: The pair of enantiomers with similar groups on opposite sides when drawn in a Fischer projection.

Tollens test: An aldehyde can be identified by observation of the formation of a silver mirror in the presence of Tollens reagent (Ag_2O/NH_3).

Torsional strain: The repulsion felt by the bonding electrons of one substituent as they pass close to the bonding electrons of another substituent.

Trademark: A registered name, symbol, or picture.

Transamination: A reaction in which an amino group is transferred from one compound to another.

Transcription: The synthesis of mRNA from a DNA blueprint.

Transesterification reaction: The reaction of an ester with an alcohol to form a different ester.

***trans*-Fused:** Two cyclohexane rings fused together such that if the second ring were considered to be two substituents of the first ring, both substituents would be in equatorial positions.

Transimination: The reaction of a primary amine with an imine to form a new imine and a primary amine derived from the original imine.

***trans*-Isomer:** The isomer with identical substitutent on opposite sides of the double bond.

Transition state: The highest poin on a hill in a reaction coordinate diagram. In the transition states, bonds in the reactant that will break are partially broken and bonds in the product that will form are partially formed.

Transition state analog: A compound that is structurally similar to the transition state of an enzyme-catalyzed reaction.

Translation: The synthesis of a protein from an mRNA blueprint.

Transmetallation: Metal exchange.

Triacylglycerol: The compound formed when the three OH groups of glycerol are esterified with fatty acids.

Triene: A hydrocarbon with three double bonds.

Trigonal planar carbon: An sp^2 hyvbridized carbon.

Triose: A monosaccharide with three carbons.

Tripeptide: Three amino acids linked by amide bonds.

Triple bond: A σ bond plus two π bonds.

Triplet: An NMR signal split into three peaks.

Triterpene: A terpene that contains 30 carbons.

Twist-boat (skew-boat) conformation: A conformation of cyclohexane.

Ultraviolet light: Electromagnetic radiation with wavelengths ranging from 180 to 400 nm.

Ultraviolet/visible spectroscopy: The absorption of electromagnetic radiation to determine information about conjugated systems.

Umpolung: Reversing the normal polarity of a functional group.

Unsaturated hydrocarbon: A hydrocarbon that contains one or more double or triple bonds.

Valence electron: An electron in an unfilled shell.

Valence shell electron pair repulsive (VSEPR) model: Combines the concept of atomic orbitals with the concept of shared electron pairs and the minimization of electron pair repulsion.

van der Waals forces (London forces): Induced dipole-induced dipole interactions.

van der Waals radius: A measure of the effective size of an atom or group. A repulsive force occurs (van der Waals repulsion) if two atoms approach each other at a distance less than the sum of their van der Waals radii.

Vector sum: Takes into account both the magnitudes and the directions of the bond dipoles.

Vicinal dihalide: A compound with halogens bonded to adjacent carbons.

Vicinal diol (vicinal glycol): A compound with OH groups bonded to adjacent carbons.

Vinyl group: $CH_2{=}CH$

Vinylic carbon: A carbon in a carbon-carbon double bond.

Vinylic cation: A compound with a positive charge on a vinylic carbon.

Vinylic radical: A compound with an unpaired electron on a vinylic carbon.

Visible light: Electromagnetic radiation with wavelengths ranging from 400 to 780 nm.

Vitamin: A substance needed in small amounts for normal body function that the body cannot synthesize or cannot synthesize in adequate amounts.

Vulcanization: Increasing the flexibility of rubber by heating it with sulphur.

Walden inversion: A Walden inversion occurs at a tetrahedral carbon atom during an S_N2 reaction when the entry of the reagent and the departure of the leaving group are synchronous. The result is an inversion of configuration at the centre under attack.

Wavelength: Distance from any point on one wave to the corresponding point on the next wave (in units of mm).

Wavenumber: The number of waves in 1 cm.

Wax: An ester formed from a long-chain carboxylic acid and a long chain alcohol.

Wedge-and-dash structure: A method of representing the spatial arrangement of groups bonded to a chirality centre. Wedges are used to represent bonds that point out of the plane of the paper toward the viewer, and dashed lines are used to represent bonds that point back from the plane of the paper away from the viewer.

Williamson ether synthesis: Formation of an ether from the reaction of an alkoxide ion with an alkyl halide.

Witting reaction: The reaction of an aldehyde or a ketone with a phosphonium ylide, resultng in formation of an alkene.

Wolff-Kishner reduction: A reaction that reduces the carbonyl group of a ketone to a methylene group using NH_2NH_2/HO^-.

Woodward-Fieser rules: Allow the calculation of the λ_{max} of the $\pi \rightarrow \pi^*$ transition for compounds with four or fewer conjugated double bonds.

Woodward-Hoffmann rules: A series of selection rules for pericyclic reactions.

Ylide: A compound with opposite charges on adjacent, covalently bonded atoms with complete octets.

Zaitsev's rule: The more stable alkene product is obtained by removing a proton from the β-carbon that is bonded to the fewest hydrogens.

Z-Conformation: The conformation of a carboxylic acid or carboxylic acid derivative in which the carbonyl oxygen and the substituent bonded to the carboxyl oxygen or nitrogen are on the same side of the single bond.

Ziegler-Natta catalyst: An aluminum-titanium initiator that controls the stereochemistry of a polymer.

Z-Isomer: The isomer with the high-priority groups on the same side of the double bond.

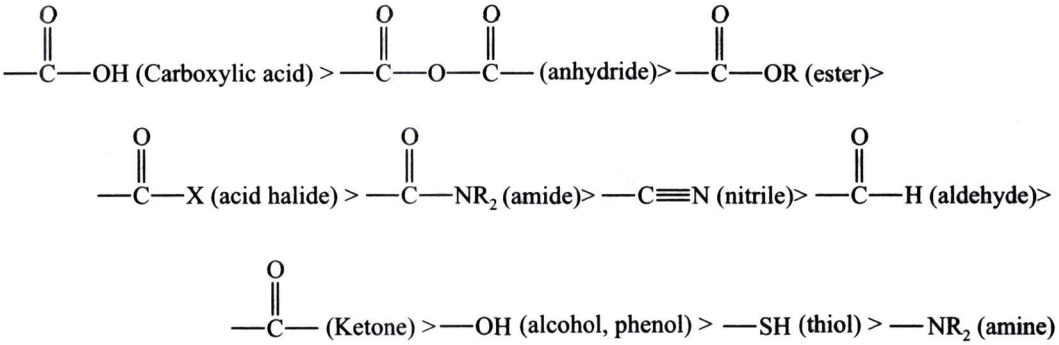
Zwitterion: A compound with a negative charge and a positive charge on non-adjacent atoms.

Appendix 2

Substitutive Nomenclature of Organic Compounds

The substitutive name of an organic compound is based on its *principal group* and *principal chain*.

The *principal group* is assigned according to the following priorities:



The *principal chain* is *identified* by applying the following criteria in order until a decision can be made.

1. Maximum number of substituents corresponding to the principal group.
2. Maximum number of double and triple bonds considered together.
3. Maximum length.
4. Maximum number of substituents cited as prefixed.

A *principal chain* is *numbered* by applying the following criteria in order unitl there is no ambiguity. Where multiple numbers are possible, comparisons are made at the first point of difference.

1. Lowest number for the principal group cited as a suffix, that is, that group on which the name is based.
2. Lowest numbers for multiple bonds, with double bonds having priority over triple bonds in case of ambiguity.
3. Lowest numbers for other substituents, taking into account the "first point of difference" rule (Sec. 2.4C, Rule 8).
4. Lowest number for the substituent named as a prefix that is cited first in the name.

The *name* is *constructed* starting with the hydrocarbon corresponding to the principal chain.

1. Cite the principal group by its suffix and number; its number is the last one cited in the name.
2. If there is no principal group, name the compound as a substituted hydrocarbon.
3. Cite the names and numbers of the other substituents in alphabetical order at the beginning of the name.

These lists cover most of the cases cited in the text. (See Study Problems 8.1-8.3 for illustrations). For a more complete discussion of nomenclature, see, *Nomenclature of Organic Chemistry, 1979 Edition*, by the International Union of Pure and Applied Chemistry, published by Pergamon Press.

In 1993, the IUPAC published *A Guide to Nomenclature of Organic Compounds Recommendations 1993*, R. Panico, W. H. Powell, and Jean-Claude Richer (senior editor), Blackwell Science. This publication advocated one major change that affects the nomenclature of relatively simple compounds. This change involves the way that principal groups are cited. The *1993 Recommendations* cite the principal group or multiple bond position with a number preceding the suffix itself, whereas the *1979 Recommendations* (followed in this text) cite the principal group or multiple bond position with a number preceding the hydrocarbon name. These differences are best illustrated by example.

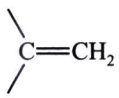
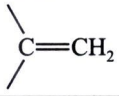
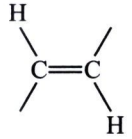
	$H_2C{=}CHCH_2CH_2CH_3$	$HOCH_2CH_2CH_2CH_2CH_3$	$HOCH_2CH_2CH_2CH{=}CH_2$
1979 Recommendations:	**1-pentene**	**1-pentanol**	**4-penten-1-ol**
1993 Recommendations:	**pent-1-ene**	**pentan-1-ol**	**pent-4-en-ol**

NOTE: **The 1993 *Recommendations* have not yet been generally adopted. Thus, names that adhere to either set of recommendations are acceptable.**

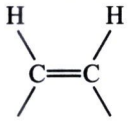
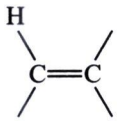
Appendix 3

Infrared Absorptions of Organic Compounds

This table presents a summary of the important infrared absorptions discussed in this text. For more detailed tables, the reader may wish to consult more specialized texts such as *Infrared Absorption Spectroscopy*, by Koji Nakanishi and Philippa H. Solomon, San Francisco: Holden-Day, 1977; or *Organic Structure Analysis*, by Philip Crews, Jaime Rodriguez, and Marcel Jaspars, 1998, Oxford University Press, Chapter 8.

Types of Absorption	Frequency, cm^{-1} (Intensity)*	Comment
	Alkanes	
C—H stretch	2850-3000 (m)	occurs in all compounds with aliphatic C—H bonds
	Alkenes	
C=C stretch —CH=CH_2	1640 (m)	
	1655 (m)	
Others	1660-1675 (w)	not observed if alkene is symmetrical
=C—H stretch	3000-3100 (m)	
=C—H bend		
—CH=CH_2	910-990 (s)	
	890 (s)	
	960-980 (s)	

* (s) = strong; (m) medium, (w) = weak.00000

	675-730 (s)	position is highly variable
	800-840 (s)	
	Alcohols and Phenols	
O—H stretch	3200-3400 (s)	
C—O stretch	1050-1250 (s)	also present in other compounds with C—O bonds: ethers, esters, etc.
	Alkynes	
C≡C stretch	2100-2200 (n)	not present or weak in many internal alkynes
≡C—H stretch	3300 (s)	present in 1-alkynes only
	Aromatic Compounds	
C=C stretch	1500, 1600 (s)	two absorptions
C—H bend	650-750 (s)	
overtone	1660-2000 (w)	
	Aldehydes	
C=O stretch ordinary	1720-1725 (s)	
α,β-unsaturated	1680-1690 (s)	
benzaldehydes	1700 (s)	
C—H stretch	2720 (m)	
	Ketones	
C=O stretch ordinary	1710-1715 (s)	increases with decreasing ring size (Table 21.3)
α,β-unsaturated	1670-1680 (s)	
aryl ketones	1680-1690 (s)	
	Carboxylic Acids	
C=O stretch ordinary	1710 (s)	
benzoic acids	1680-1690 (s)	
O—H stretch	2400-3000 (s)	very broad
	Esters and Lactones	
C=O stretch	1735-1745 (s)	increases with decreasing ring size (Table 21.3)

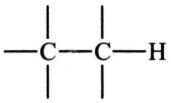
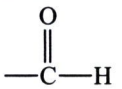
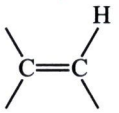
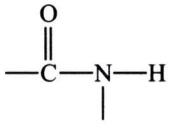
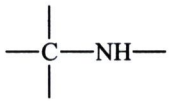
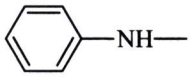
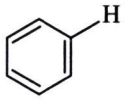
	Acid Chlorides	
C=O stretch	1800 (s)	second weaker band sometimes observed at 1700-1750
	Anhydrides	
C=O stretch	1760, 1820 (s)	two bands; increases with decreasing ring size in cyclic anhydrides
	Amides and Lactams	
C=O stretch	1650-1655 (s)	increases with decreasing ring size (Table 21.3)
N—H bend	1640 (s)	
N—H stretch	3200-3400 (m)	doublet absorption observed for some primary amides
	Nitriles	
C≡N stretch	2200-2250 (m)	
	Amines	
N—H stretch	3200-3375 (m)	several absorptions sometimes observed, especially for primary amines

Appendix 4

Proton NMR Chemical Shifts in Organic Compounds

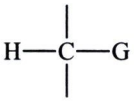
This appendix is subdivided into a table of chemical shifts for protons that are *part* of functional groups and a table of chemical shifts protons that are *adjacent to* function groups.

A. PROTONS WITHIN FUNCTIONAL GROUPS

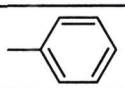
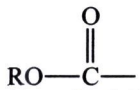
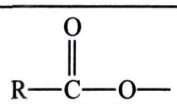
Group	Chemical shift, ppm	Group	Chemical shift, ppm
	0.7-1.5		9-11
	4.6-5.7		7.5-9.5
—O—H	varies with solvent and with acidity of O—H		0.5-1.5
—C≡C—H	1.7-2.5		2.5-3.5
	6.5-8.5		

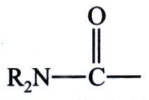
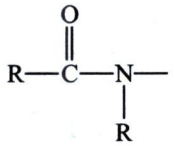
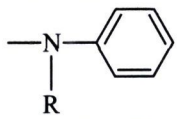
B. PROTONS ADJACENT TO FUNCTIONAL GROUPS

In this table, a range of chemical shifts is given for protons in the general environment



in which G is a group listed in column 1, and the two other bonds are to carbon or hydrogen. The remaining columns give the approximate chemical shifts for methyl protons (H_3C—G), methylene protons (—CH_2—G), and methine protons (—$\overset{|}{C}H$—G), respectively. This shifts in the following table are typical; some variation with structure of a few tenths of a ppm can be expected. Note that the chemical shifts of methine protons are usually further downfield than those of methylene protons, which are further downfield than methyl protons. Each additional carbon substitution increases chemical shift by 0.3-1.0 ppm.

Group, G	Chemical shift of H_3C—G, ppm	Chemical shift of —CH_2—G, ppm	Chemical shift of —$\overset{|}{C}H$—G, ppm
—H	0.2		
—CR_3	0.9	1.2	1.4
—F	4.3	4.5	4.8
—Cl	3.0	3.4	4.0
—Br	2.7	3.4	4.1
—I	2.2	3.2	4.2
—CR=CR_2 (R = H, alkyl)	1.8	2.0	2.3
—C≡CR (R = alkyl, H)	1.8	2.2	2.8
	2.3	2.6	2.8
RO—(R = alkyl, H)	3.3 (R = alkyl)	3.4	3.6
	3.5 (R = H)		
RO—(R = aryl)	3.7	4.0	4.6
RS—(R = alkyl, H)	2.4	2.6	3.0
	2.1 (R = alkyl) 2.6 (R = aryl)	2.4 (R = alkyl) 2.7 (R = aryl)	2.6 (R = alkyl) 3.4 (R = aryl)
	2.1	2.2	2.5
	3.6 (R = alkyl) 3.8 (R = aryl)	4.1 (R = alkyl, aryl)	5.0 (R = alkyl, aryl)

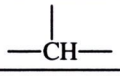
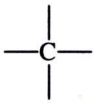
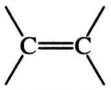
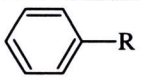
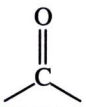
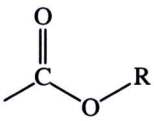
 (R = alkyl, H)	2.0	2.2	2.4
 (R = alkyl, H)	2.8	3.4	3.8
$-NR_2$ (R = alkyl, H)	2.2	2.4	2.8
 (R = alkyl, H)	2.6	3.1	3.6
N≡C—	2.0	2.4	2.9

Appendix 5

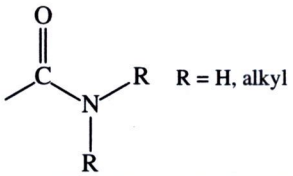
^{13}C NMR Chemical Shifts in Organic Compounds

This section is divided into a table of chemical shifts for carbons within functional groups, and a table of chemical shifts for alkyl carbons adjacent to functional groups. A typical range of shifts is given for each case.

A. CHEMICAL SHIFTS OF CARBONS WITHIN FUNCTIONAL GROUPS

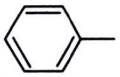
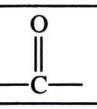
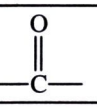
Group	Chemical shift range, ppm
$-CH_3$	8-23
$-CH_2-$	20-30
	21-33
	17-29
	105-150*
$-C\equiv C-$	66-93*
	125-150*
	200-220
	170-180

* Alkyl substitution typically increases chemical shift.

 R = H, alkyl	165-175
—C≡N	110-120

B. CHEMICAL SHIFTS OF CARBONS ADJACENT TO FUNCTIONAL GROUPS

In most cases, alkyl substitution on the carbon increases chemical shift. Thus, methyl carbons will have shifts in the low end of the range; tertiary and quaternary carbons will have shifts in the upper end of the range.

Group G	Chemical shift range, —C—
$R_2C{=}CR-$	14-40
HC≡C—	18-28
	29-45
F—	83-91
Cl—	44-68
BR—	32-65
I—	5-42
HO—	62-70
RO— R = alkyl, H	70-79
 R = alkyl, H	43-50
 R = alkyl, H	33-44
R_2N- R = alkyl, H	41-51 (R = H) 53-60 (R = alkyl)
N≡C—	16-28

Appendix 6

Summary of Synthetic Methods

The following methods are listed in order of their occurrence in the text; the section reference follows each reaction in parentheses. Thus, a review at any point in the text is possible by considering the methods listed for earlier sections.

Don't forget that in many cases a method can be applied to compounds containing more than one functional group. Thus, catalytic hydrogenation can be used to convert phenols into alcohols, but it is listed under "Synthesis of Alkanes and Aromatic Hydrocarbons" because the actual transformation is the formation of $—CH_2—CH—$ groups from —CH=CH— groups; the presence of the —OH group is incidental.

Reaction summaries for each chapter are found in the Study Guide.

A. SYNTHESIS OF ALKANES AND AROMATIC HYDROCARBONS

1. Catalytic hydrogenation of alkenes (4.9A)
2. Protonolysis of Grignard or related reagents (8.8B)
3. Cyclopropane formation by the addition of carbenoids to alkenes (Simmons-Smith reaction; 9.8 B)
4. Catalytic hydrogenation of alkynes (14.6A)
5. Friedel-Crafts alkylation of aromatic compounds (16.4E)
6. Catalytic hydrogenation of aromatic compounds (16.6)
7. Stille reaction of aryl triaflates and aryl-or alkylstannanes to form substituted aromatic hydrocarbons (18.9B)
8. Wolff-Kishner or Clemmensen reductions of aldehydes or ketones (19.12)
9. Reaction of aryldiazonium salts with hypophosphorous acid (23.10A)

B. SYNTHESIS OF ALKENES

1. β-Elimination reactions of alkyl halides or sulfonates (9.5, 10.3A, 17.3B)
2. Acid-catalyzed dehydration of alcohols (10.1)
3. Catalytic hydrogenation of alkynes (gives *cis*-alkenes when used with internal alkynes; 14.6A)
4. Reduction of alkynes with alkali metals in liquid ammonia (gives *trans*-alkenes when used with internal alkenes; 14.6B)
5. Diels-Alder reactions of dienes and alkenes to give cyclic alkenes (15.3, 25.3)
6. Heck reaction of aryl halides and alkenes to give aryl-substituted alkenes (18.5)
7. Witting reaction of aldehydes and ketones (19.13)
8. Aldol condensation reactions of aldehydes or ketones to give α,β-unsaturated aldehydes or ketones (22.4)
9. Hofmann elimination of quaternary ammonium hydroxides (23.8).

C. SYNTHESIS OF ALKYNES

1. Alkylation of acetylenic anions with alkyl halides or sulfonates (14.7B)
2. b-Elimination reactions of alkyl dihalides or vinylic halides (18.2)

D. SYNTHESIS OF ALKYL AND ARYL HALIDES

1. Additin of hydrogen halides to alkenes (4.7, 15.4A)
2. Addition of halogens to alkenes to give vicinal dihalides (5.1)
3. Peroxide-promoted addition of HBr to alkenes (5.5)
4. Synthesis of dihalocyclopropanes by addition of dihalomethylene to alkenes (9.8A)
5. Reaction of alcohols with HBr, thionyl chloride, or phosphorus tribromide (10.2, 10.3D, 17.1)
6. Reaction of sulfonate esters or other alkyl halides with halide ions (10.3A, 17.4)
7. Halogenation of aromatic compounds (16.4A)
8. Allylic and benzylic bromination of alkenes or aromatic hydrocarbons (17.2)
9. α-Halogenation of aldehydes, ketones, or carboxylic acids (22.3A,C)
10. Synthesis of aryl halides by the reaction of cuprous chloride, cuprous, bromide, or potassium iodide with aryldiazonium salts (Sandmeyer and related reactions; 23.10A)

E. SYNTHESIS OF GRIGNARD REAGENTS AND RELATED ORGANOMETALLIC COMPOUNDS

1. Reaction of alkyl or aryl halides with metal (8.8A)
2. Preparation of acetylenic Grignard reagents by metal-hydrogen exchange (14.7A)
3. Preparation of alkyl-and aryl stannanes by reaction of Grignard reagents with trialkylstannyl chlorides (18.9B)
4. Preparation of lithium dialkylcuprates by reaction of alkyllitium reagents with cuprous halides (21.10B)

F. SYNTHESIS OF ALCOHOLS AND PHENOLS

(Syntheses apply only to alcohols unless noted otherwise)

1. Acid-catalyzed hydration of alkenes (used industrially, but generally not a good laboratory method; 4.9B)
2. Synthesis of halohydrins from alkenes (5.1B)
3. Oxymercuration-reduction of alkenes (5.3A)
4. Hydroboration-oxidation of alkenes (5.3B)
5. Ring-opening reactions of epoxides (11.4A, B)
6. Reaction of ethylene oxide with Grignard reagents (11.4C)
7. Reduction of aldehydes or ketones (19.8, 22.9, 27.7D)
8. Reaction of aldehydes or ketones with Grignard or related reagents (19.9, 22.10A)
9. Reduction of carboxylic acids to primary alcohols (20.10)
10. Reductin of esters to primary alcohols (21.9A)
11. Reaction of esters with Grignard or related reagents (21.10A)
12. Aldol addition reactions of aldehydes or some ketones to give β-hydroxy aldehydes or ketones (22.4)
13. Reaction of diazonium salts with water to give phenols (23.10A)
14. Synthesis of phenols by the Claisen rearrangement of allylic aryl ethers (25.4B)

G. SYNTHESIS OF GLYCOLS

1. Acid-catalyzed hydrolysis of epoxides (11.4B)
2. Reaction of alkenes with osmium tetroxide or alkaline potassium permanganate (11.5)

H. SYNTHESIS OF ETHERS AND ACETALS

1. Alkylation of alkoxides or phenoxides with alkyl halides or alkyl sulfonates (Williamson synthesis; 11.1A, 18.6B, 27.6)
2. Alkoxymercuration-reduction of alkenes (11.1B)
3. Acid-catalyzed dehydration of alcohols (11.1C)
4. Acid-catalyzed addition of alcohols to alkenes (11.1C)
5. Acetal formation by the acid-catalyzed reaction of alcohols with aldehydes or ketones (19.10A, 27.5)

I. SYNTHESIS OF EPOXIDES

1. Oxidation of alkenes with peroxycarboxylic acids (11.2A).
2. Cyclization of halohydrins (11.2B)

J. SYNTHESIS OF DISULFIDES

1. Oxidation of thiols (10.9, 26.9A)

K. SYNTHESIS OF ALDEHYDES

1. Ozonolysis of alkenes (of limited utility because carbon-carbon bonds are broken; 5.4)
2. Oxidation of primary alcohols (10.6A)
3. Oxidative cleavage of glycols (of limited utility because carbon-carbon bonds are broken; 11.5B, 27.7C)
4. Hydroboration-oxidation of alkynes (14.5B)
5. Reduction of acid chlorides (21.9D)
6. Aldol addition reactions of aldehydes to give β-hydroxy aldehydes (22.4)
7. Aldol condensation reactions of aldehydes to give α,β-unsaturated aldehydes (22.4)
8. Synthesis of aldoses from other aldoses by the Kiliani-Fischer synthesis (27.8) and the Ruff degradation (27.9B)

L. SYNTHESIS OF KETONES

1. Ozonolysis of alkenes (of limited utility because carbon-carbon bonds are broken; 5.4)
2. Oxidation of secondary alcohols (10.6A)
3. Oxidative cleavage of glycols (of limited utility because carbon-carbon bonds are broken; 11.5B)
4. Mercuric-ion catalyzed hydration of alkynes (14.5A)
5. Friedel-Crafts acylation of aromatic compounds (16.4F)
6. Oxidation of phenols to quinones (18.7)
7. Reaction of acid chlorides with lithium dialkylcuprates (21.10B)
8. Aldol condensation reactions of ketones to give α,β-unsaturated ketones (22.4)
9. Claisen and Dieckmann condensation reactions of ester to give β-keto esters (22.5A, B)
10. Crossed Claisen condensation reactions of esters to give β-diketones (22.5C)

11. Acetoacetic ester synthesis (22.7C)
12. Conjugate addition reactions of α,β-unsaturated ketones (22.8), including addition of lithium dialkylcuprate reagents (22.10B)

M. SYNTHESIS OF SULFOXIDES AND SULFONES

1. Oxidation of sulfides (11.8)

N. SYNTHESIS OF CARBOXYLIC AND SULFONIC ACIDS

(Syntheses apply only to carboxylic acids unless noted otherwise)

1. Ozonolysis of alkenes (of limited utility because carbon-carbon bonds are broken; 5.4)
2. Oxidation of primary alcohols (10.6B)
3. Oxidation of thiols to sulfonic acids (10.9)
4. Sulfonation of aromatic compounds to give arylsulfonic acids (16.4D)
5. Side-chain oxidation of alkylbenzenes (17.5)
6. Oxidation of aldehydes (19.14)
7. Reaction of Grignard or related reagents with carbon dioxide (20.6)
8. Hydrolysis of carboxylic acid derivatives, especially nitriles (21.7, 21.11. 26.4C)
9. Haloform reaction of methyl ketones (of limited utility because this reaction breaks carbon-carbon bonds; 22.3B)
10. Malonic ester synthesis (22.6A, 26.4B)
11. Strecker synthesis of amino acids (26.4C)

O. SYNTHESIS OF ESTERS

1. Reaction of alcohols and phenols with sulfonyl chlorides (for sulfonate esters; 10.3A, 18.9B)
2. Acid-catalyzed esterification of carboxylic acids with primary or secondary alcohols (20.8A, 26.5)
3. Alkylation of carboxylic acids with diazomethane (20.8B)
4. Alkylation of carboxylate salts with alkyl halides (20.8B)
5. Reaction of acid chlorides, anhydrides, or esters with alcohols and phenols (21.8, 27.6)
6. Claisen and Dieckmann condensation reactions of esters to give β-keto esters (22.5A, B)
7. Alkylation of ester enolate ions; includes malonic ester synthesis, acetoacetic ester synthesis, and direct alkylation (22.7)
8. Conjugate addition reactions of α,β-unsaturated esters (22.8, 22.10B)

P. SYNTHESIS OF ANHYDRIDES

1. Reaction of carboxylic acids with dehydrating agents (20.9B)
2. Reaction of acid chlorides with carboxylate salts (21.8A)

Q. SYNTHESIS OF ACID CHLORIDES

1. Reaction of carboxylic or sulfonic acids with thionyl chloride, phosphorus pentachloride, or related reagents (20.9A)
2. Synthesis of sulfonyl halides by chlorosulfonation of aromatic compounds (20.9A)

R. SYNTHESIS OF AMIDES

1. Reaction of acid chlorides, anhydrides, or esters with amines (21.8, 26.5)
2. Condensation of amines and carboxylic acids with dicyclohexylcarbodiimide (26.7)

S. SYNTHESIS OF NITRILES

1. Formation of cyanohydrins from aldehydes and some ketones (19.7A, B, 27.8)
2. Reaction of alkyl halides or alkyl sulfonates with cyanide ion (21.11)
3. Conjugate addition of cyanide ion to α,β-unsaturated carbonyl compounds (22.8A)
4. Reaction of cuprous cyanide with aryldiazonium salts (23.10A)

T. SYNTHESIS OF AMINES

1. Reduction of amides (21.9B)
2. Reductin of nitriles to primary amines (21.9C)
3. Direct alkylation of ammonia or amines (of limited utility because of the possibility of over-alkylation: 23.7A, 26.4A)
4. Reductive amination of aldehydes and ketones (23.7B)
5. Aromatic substitution reactions of aniline derivatives (23.9)
6. Gabriel synthesis of primary amines (23.11A)
7. Reduction of nitro compounds (23.11B)
8. Curtius and Hofmann rearrangements (23.11C)

U. SYNTHESIS OF NITRO COMPOUNDS

1. Nitration of aromatic compounds (16.4C)

Appendix 7

Reactions Used to Form Carbon-Carbon Bonds

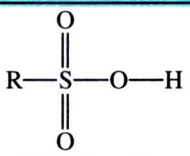
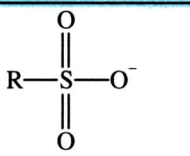
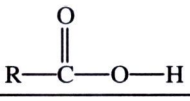
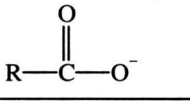
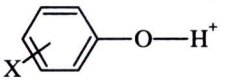
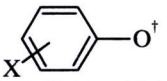
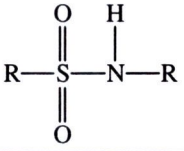
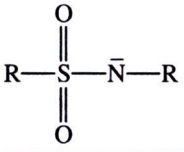
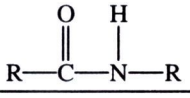
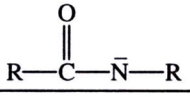
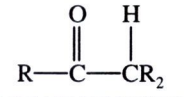
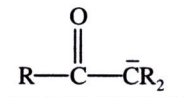
Reactions that form carbon-carbon bonds have central importance in organic chemistry, because these reactions can be used to form carbon chains or rings. These reactions are listed in the order that they are discussed in the text. The section reference follows each reaction in parentheses.

1. Cyclopropane formation by addition of carbenese or carbenoids to alkenes (9.8)
2. Reaction of Grignard reagents with ethylene oxide (11.4C)
3. Reaction of acetylenic anions with alkyl halides or sulfonates (14.7B)
4. Diels-Alder reactions (15.3, 25.3)
5. Friedel-Crafts alkylation (16.4E) and acylation reactions (16.4F)
6. The Heck reaction of alkenes with aryl halides (18.5F)
7. The Stille reaction of organostannanes with aryl triflates (18.9B)
8. Cyanohydrin formation (19.7, 26.4C, 27.8)
9. Reaction of Grignard and related reagents with aldehydes and ketones (19.9)
10. The Wittig alkene synthesis (19.13)
11. Reaction of Grignard and related reagents with aldehydes and ketones (20.6)
12. Reaction of Grignard and related reagents with esters (21.10A)
13. Reaction of lithium dialkylcuprates with acid chlorides (21.10B)
14. Reaction of cyanide ion with alkyl halides or sulfonates (21.11)
15. Aldol addition and condensation reactions (22.4)
16. Claisen and related condensation reactions (22.5)
17. Malonic ester synthesis (22.7A, 26.4B)
18. Alkylation of ester enolate ions with alkyl halides or sulfonates (22.7B)
19. Acetoacetic ester synthesis (22.7C)
20. Conjugate-addition reactions of cyanide ion (22.8A) or enolate ions (22.8C) to α,β-unsaturated carbonyl compounds
21. Conjugate addition of lithium dialkylcuprate reagents to α,β-unsaturated carbonyl compounds (22.10B)
22. Reaction of aryldiazonium salts with cuprous cyanide (23.10A)
23. Fischer and Reissert indole syntheses (24.4)
24. Skraup quinoline synthesis (24.5E)
25. Formation of rings by electrocyclic reactions (25.2)
26. Claisen rearrangement (25.4B)

Appendix 8

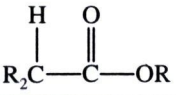
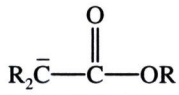
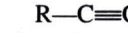
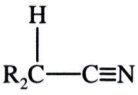
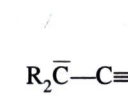
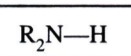
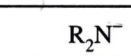
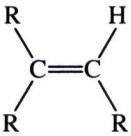
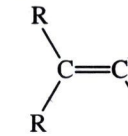
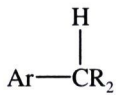
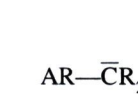
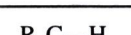
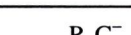
Typical Acidities and Basicities of Organic Functional Groups

A. ACIDITIES OF GROUPS THAT IONIZE TO GIVE ANIONIC CONJUGATE BASES

Functional group	Structure*	Structure of conjugate base	Typical pK_a
sulfonic acid			< 1 (strong acid)
carboxylic acid			3-5
phenol			9-11
thiol	R—S—H	R—S$^-$	9-11
sulfonamide			10
amide			15-17
alcohol	R—O—H	R—O$^-$	15-19
aldehyde, ketone			17-20

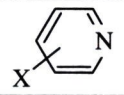
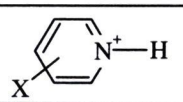
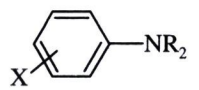
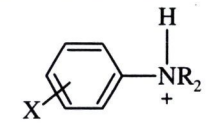
* In the structures, R = alkyl or H.

† X = general ring substituent group.

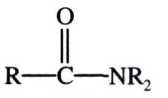
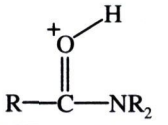
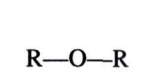
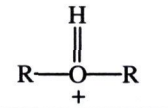
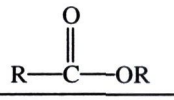
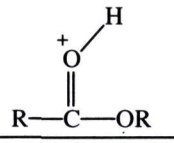
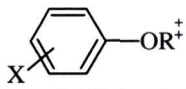
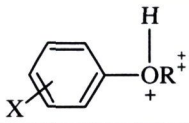
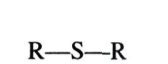
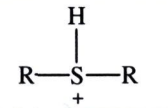
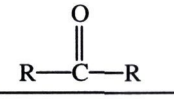
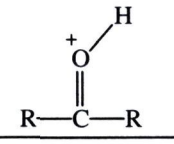
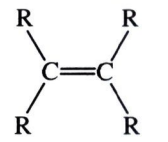
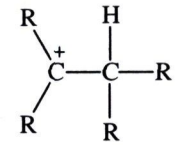
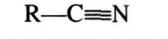
ester			25
alkyne			25
nitrile			25
amine			32
alkene			42
benzylic alkyl group			42
alkane			55-60

B. BASICITIES OF GROUPS THAT PROTONATE TO GIVE CATIONIC CONJUGATE ACIDS

One should be careful to distinguish between the behaviour of a particular functional group as an acid and the same functional group as a base. For example, when an alcohol acid acts as an acid, it loses the RO—H proton to form an alkoxide (see table in part A of this section). When it acts as a base, it *gains* a proton to form $R\overset{+}{O}H_2$. These are very different processes with different pK_a values. When we discuss the *acidity* of an alcohol, the relevant pK_a is that for the alcohol itself (see table in part A). This same pK_a describes the *basicity* of the alkoxide, RO^- ,which is the conjugate base of the alcohol. When we discuss the *basicity* of the alcohol itself, the relevant pK_a is the value for the acidity of $R\overset{+}{O}H_2$, given in the following table.

Functional group	Structure*	Structure of conjugate acid	Typical conjugate acid pK_a
alkylamine	R_3N	$R_3\overset{+}{N}—H$	9-11
pyridine			5
aromatic amine			4-5

* In the structures, R = alkyl or H.

amide			– 1
alcohol, ether			– 2 to – 3
ester, carboxylic acid			– 6
phenol, aromatic ether†			– 6 to – 7
thiol, sulfide			– 6 to – 7
aldehyde, ketone			– 7
alkene			– 8 to – 10
nitrile			– 10

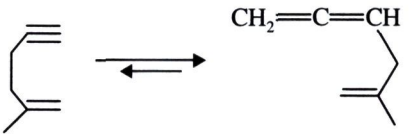
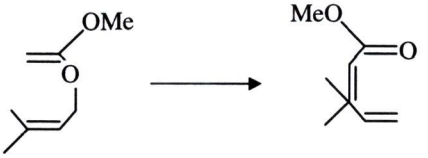
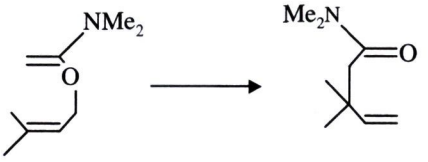
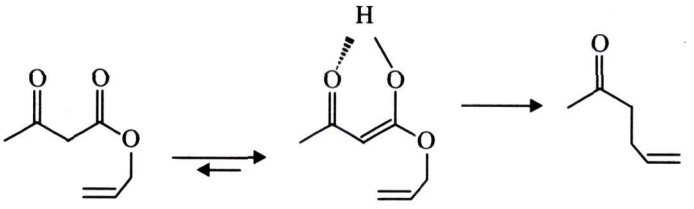
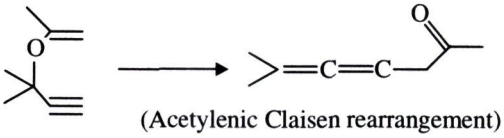
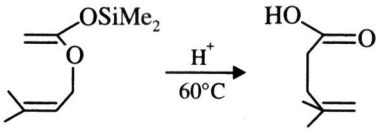
† A phenol or aromatic ether can be protonated on a ring carbon if the resulting carbocation can be strongly stabilized by the substituent groups.

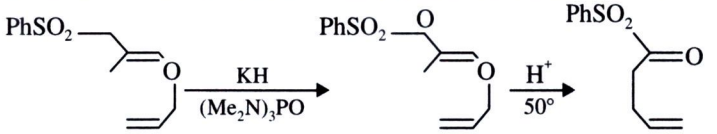
‡ X = general ring substituent group.

* In the structures, R = alkyl or H.

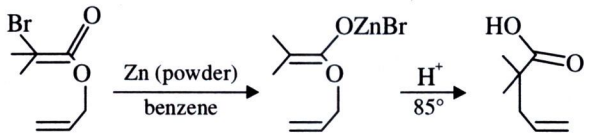
Appendix 9

Claisen and Cope Related Rearrangements

Rearrangement/Reaction	Discoverer
1. 	Hunstmann-Boerwoosley (1965)
2. 	Johnson (1970)
3. 	Eschenmoser (1964)
4.  (Rearrangement followed by decarboxylation)	Carroll (1940)
5.  (Acetylenic Claisen rearrangement)	Saucey-Marbet (1960)
6. 	Ireland (1972)

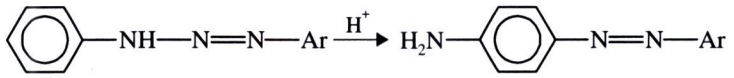
7. 

(Anion-accelerated Claisen rearrangement) — Denmark (1982)

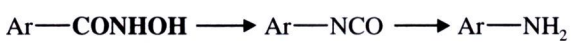
8. 

(Reformatsky-claisen rearrangement) — Baldwin-Walker (1973)

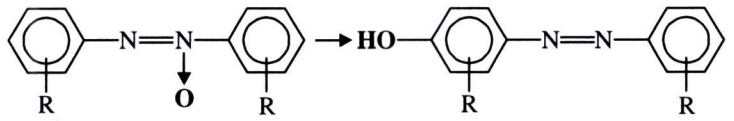
Rearrangements Involving the Shifting to an Aromatic Carbon

9. 

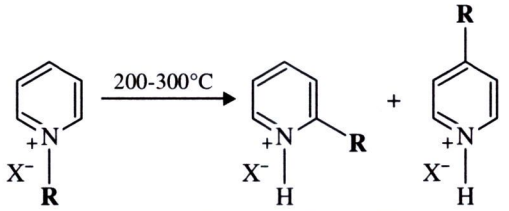
Griess-Martins (1866)

10. 

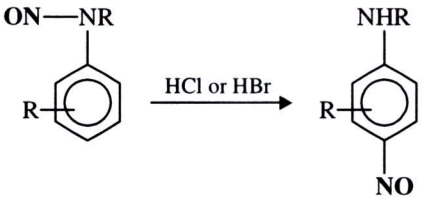
(Degradation) — Lössen (1872)

11. 

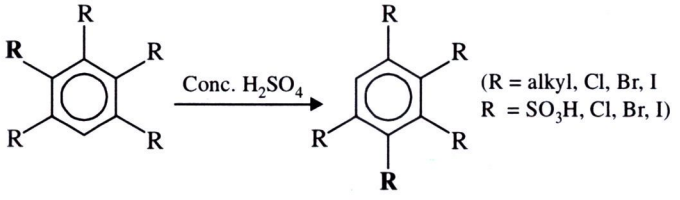
Wallach (1880)

12. 

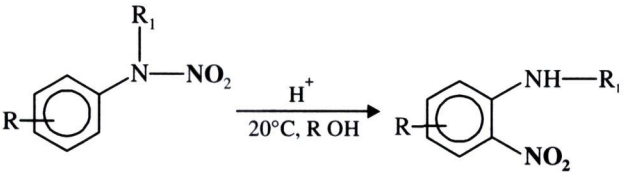
R = alkyl group; X^- = halide — Ladenburg (1884)

13. 

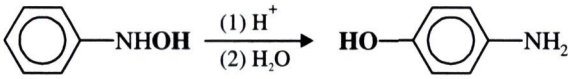
Fischer-Hepp (1886)

14. 

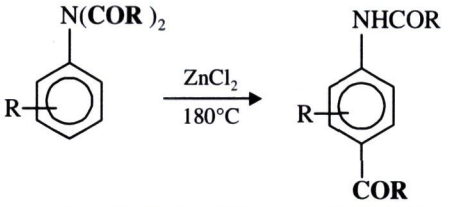
(R = alkyl, Cl, Br, I
R = SO_3H, Cl, Br, I) — Jacobsen (1886)

15. 

Bamberger (1893)

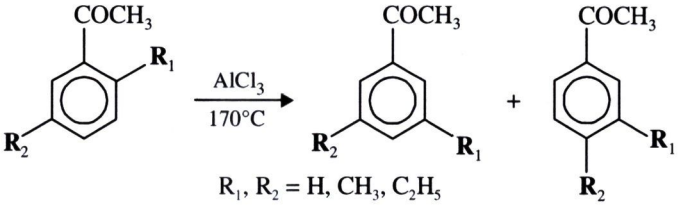
16. 

Bamberger (1894)

17. 

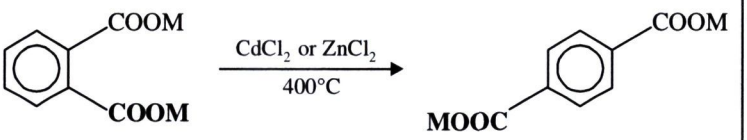
R = H, Cl, Br, CH_3; **R** = alkyl, C_6H_5

Chattaway (1904)

18. 

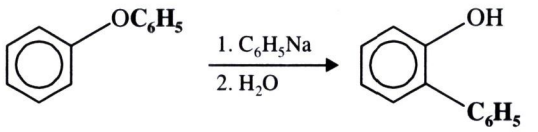
R_1, R_2 = H, CH_3, C_2H_5

Baddeley (1944)

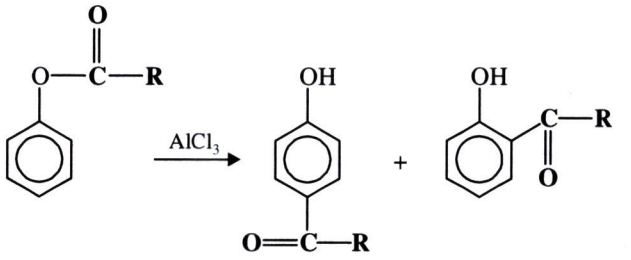
19. 

M = Na, K

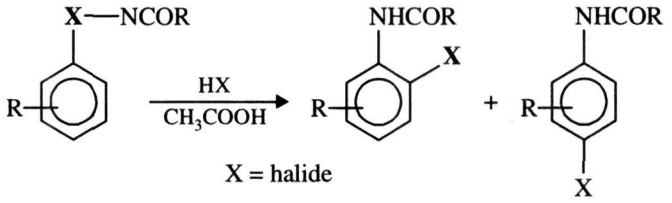
Henkel (1952)

20. 

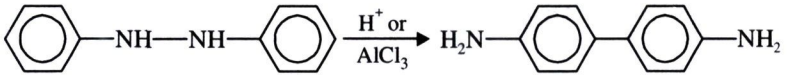
Lüttringhaus (1938)

21. 

Fries (1908)

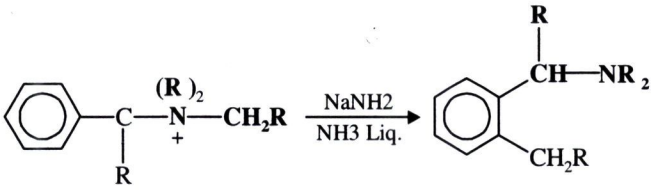
22. 

Orton (1909)

23. 

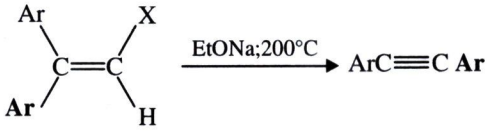
Hydrazobenzene **Benzidine**

Pummerer (1921)

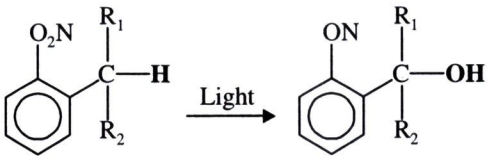
24. 

Sommelet-Hauser (1937, 1953)

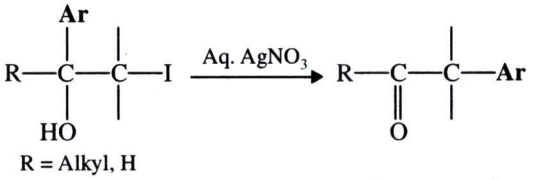
Rearrangements Involving the Shifting to a Non-Aromatic Carbon

1. 

Fritsch-Buttenberg-Wiechell (1894)

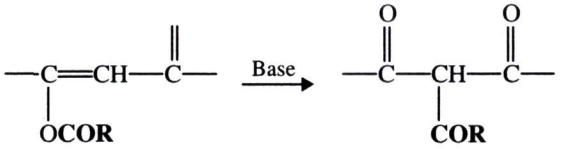
2. 

Ciamician (1901)

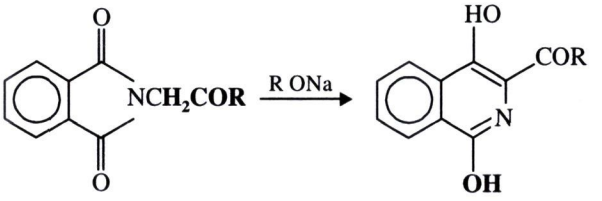
3. 

R = Alkyl, H

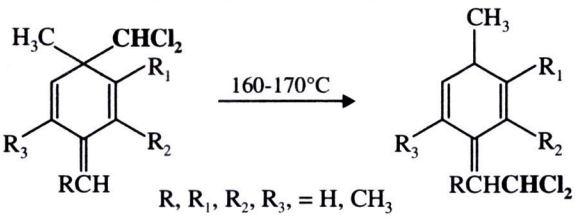
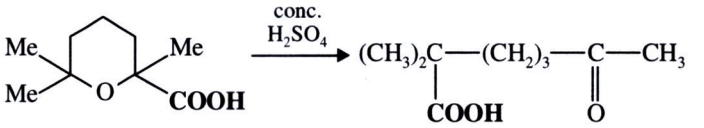
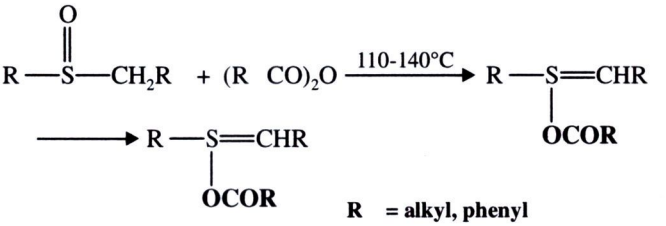
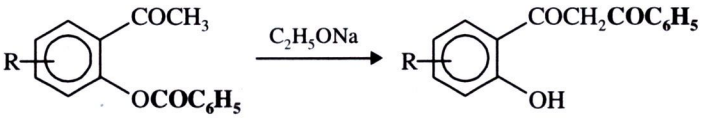
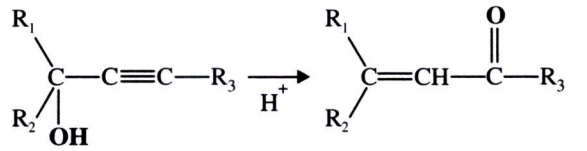
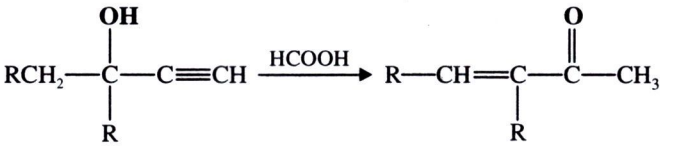
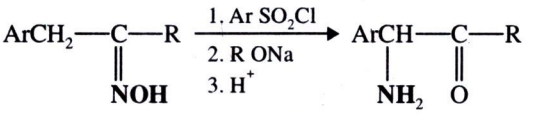
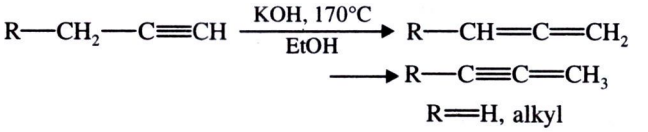
Tiffeneau (1907)

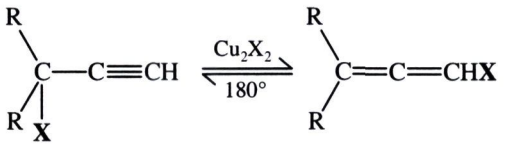
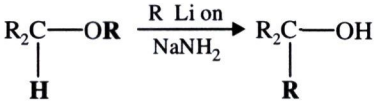
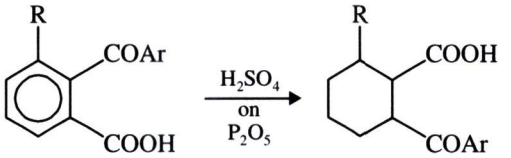
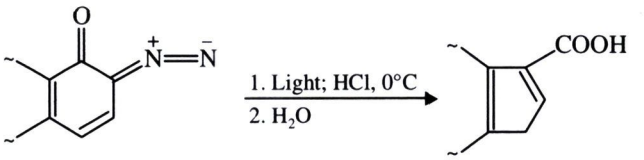
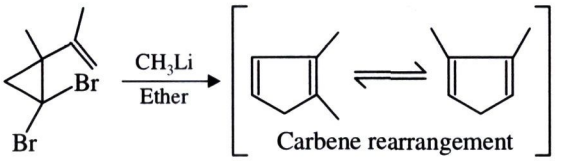
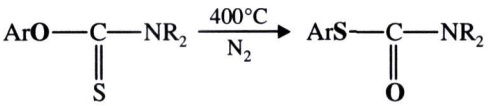
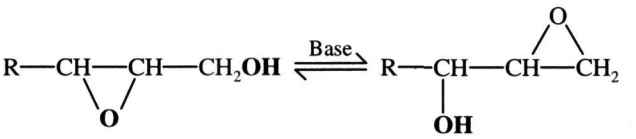
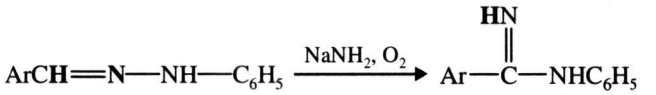
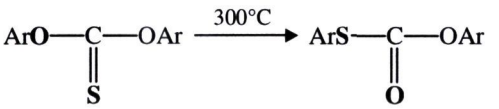
4. 

Claisen-Haase (1900)

5. 

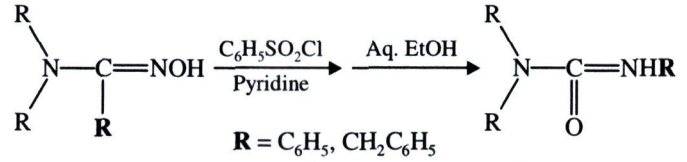
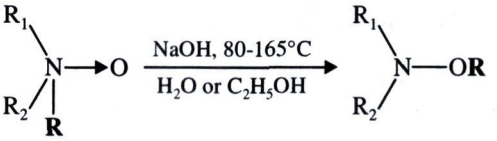
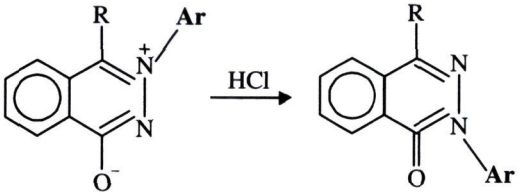
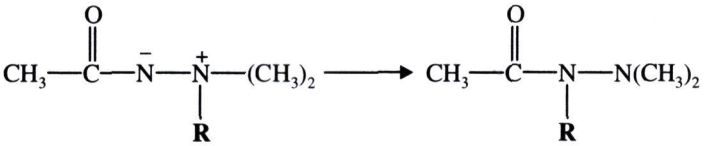
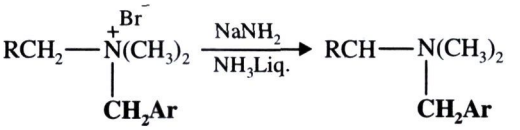
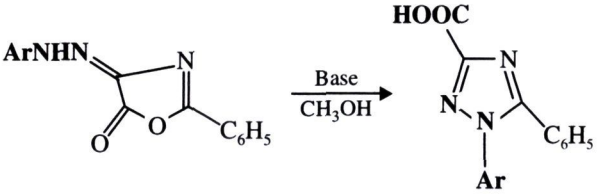
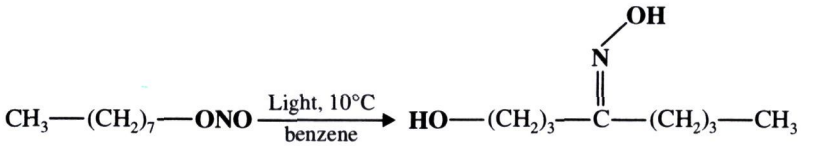
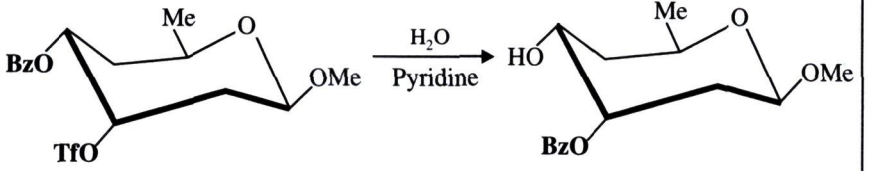
Gabriel (1900)

6.	 R, R_1, R_2, R_3, = H, CH_3	Auwers (1907)
7.		Rupe (1908)
8.	 **R = alkyl, phenyl**	Pummerer (1909)
9.	 (R = alkyl, hydroxyl, alkoxyl)	Baker-Venkataraman (1933)
10.		Meyer-Schuster (1922)
11.		Rupe (1926)
12.	 R = $ArArCH_2$	Neber (1926)
13.	 R=H, alkyl	Favorskii (1935)

14.		Favorskii-Favorskya (1935)
15.		Wittig (1942)
16.		Hayashi (1927)
17.		Süs (1944)
18.		Doering-Moore-Skattebol (1967)
19.		Newman-Kwart (1966)
20.		Payne (1962)
21.		Rober (1954)
22.		Schönberg (1944)

Rearrangements Involving the Shifting to a Heteroatom

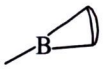
1. $ArAr_2C—NHOH \xrightarrow{PCl_5,\ Et_2O} Ar_2C{=}N—Ar + ArArC{=}N—Ar$	Stieglitz (1913)

2.	 **R** = C_6H_5, $CH_2C_6H_5$	Tiemann (1891)
3.	 R_1, R_2 = Aryl Alkyl; **R** = $ArCH_2$, Ar_2CH,	Meisenheimer (1919)
4.		Rowe (1926)
5.	 R = $C_6H_5CH_2$–, CH_2 = CH—CH_2	Wawzonek (1960)
6.		Stevens (1928)
7.		Sawdey (1957)
8.		Barton (1960)
9.	 Triflate rearrangement (BZ and Tg stand for benzoyl and triflate respectively)	Binkley (1986)

Appendix 10

Abbreviations Used in Claisen and Cope Related Rearrangement

Polymer Support

A	adenosine
Ac	acetyl
AIBN	2, 2′-azobisisobutyronitrile
Alpine-borane®	*B*-isopinocampheyl-9-borabicyclo [3.3.1]-nonane
Ar	aryl
B:	generic base
	9-Borobicyclo [3.3.1]-nonylboryl
9-BBN	9-borabicyclo [3.3.1] nonane
[bimim] $Cl.2AlCl_2$	1-butyl-3-methylimidazolium chloroaluminuminate (a Lewis acid ionic liquid)
BINAP	2, 2'-bis (diphenylphosphino)-1, 1′-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
t-Bu	*tert*-butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
m-CPBA	*m*-chloroperoxybenzoic acid
CuTC	copper thiophene-2-carboxylate
DABCO	1,4-diazabicyclo [2.2.2] octane
dba	dibenzylideneacetone
DBU	1, 8-diazabicyclo [5.4.0] undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5, 6-dicyano-1, 4-benzoquinone
DEAD	diethyl azodicarboxylate
Δ	solvent heated under reflux

$(DHQ)_2$-PHAL	1,4-bis (9-*O*-dihydroquinine)-phthalazine
$(DHQD)_2$-PHAL	1,4-bis (9-*O*-dihydroquinidine)-phthalazine
DIAD	diisopropyl azodidicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMA	*N*, *N*-dimethylacetamide
DMAP	4-*N*, *N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*, *N*-dimethylformamide
DMFDMA	*N*, *N*-dimethylformamide dimethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulfoxonium methylide
DMT	dimethoxytrityl
dppb	1,4-bis (diphenylphosphino) butane
dppe	1,2-bis (diphenylphosphino) ethane
dppf	1,1'-bis (diphenylphosphino) ferrocene
dppp	1,3-bis (diphenylphosphino) propane
DTBA	di-*tert*-butylazodicarbonate
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E1	unimolecular elimination
E2	bimolecular elimination
E1cB	2-step, base-induced β-elimination *via* carbanion
EAN	ethylammonium nitrate
EDDA	ethylenediamine diacetate
ee	enantiomeric excess
Ei	two groups leave at about the same time and bond to each other as they are doing so.
Eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMTTA	1,1,4,7,10,10-hexamethyltriethylenetetramine
hv	irradiation with light
IMD	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide

LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	metal
Mes	mesityl
Ms	methanesulfonyl
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	N-iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
Nos	nosylate (4-nitrobenzenesulfonyl)
Nu	nucleophile
N-PSP	*N*-phenylselenophthalimide
N-PSS	*N*-phenylselenosuccinimide
Ⓟ	Polymeric backbone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	para-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
$PyPH_2P$	diphenyl 2-pyridylphosphine
Pyr	pyridine
Red-Al	sodium bis (methoxy-ethoxy) aluminium hydride (SMEAH)
Salen	*N*, *N*′-disalicylidene-ethylenediamine
SET	single electron transfer
SM	starting material
SMEAH	sodium bis (methoxy-ethoxy) aluminum hydride (Red-Al)
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic substitution on an aromatic ring
TBABB	tetra-*n*-butylammonium bibenzoate
TBAF	tetra-*n*-butylammonium flouride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEOC	trimethysilylethoxycarbonyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anhydride
TFP	tri-2-furylphosphine
THF	tetrahydroforan
TIPS	triisopropylsilyl
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMG	tetramethylguanidine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSCI	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Tol	toluene or tolyl
Tol-BINAP	2,2′-bis (di-*p*-tolylphosphino)-1, 1′-binaphthyl
TosMIC	(*p*-tolylsulfonyl) methyl isocyanide
Ts	tosyl
TsO	tosylate
UHP	urea-hydrogen peroxide
UV	Ultraviolet
X_C	Chiral auxiliary

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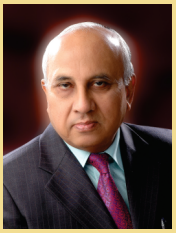

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