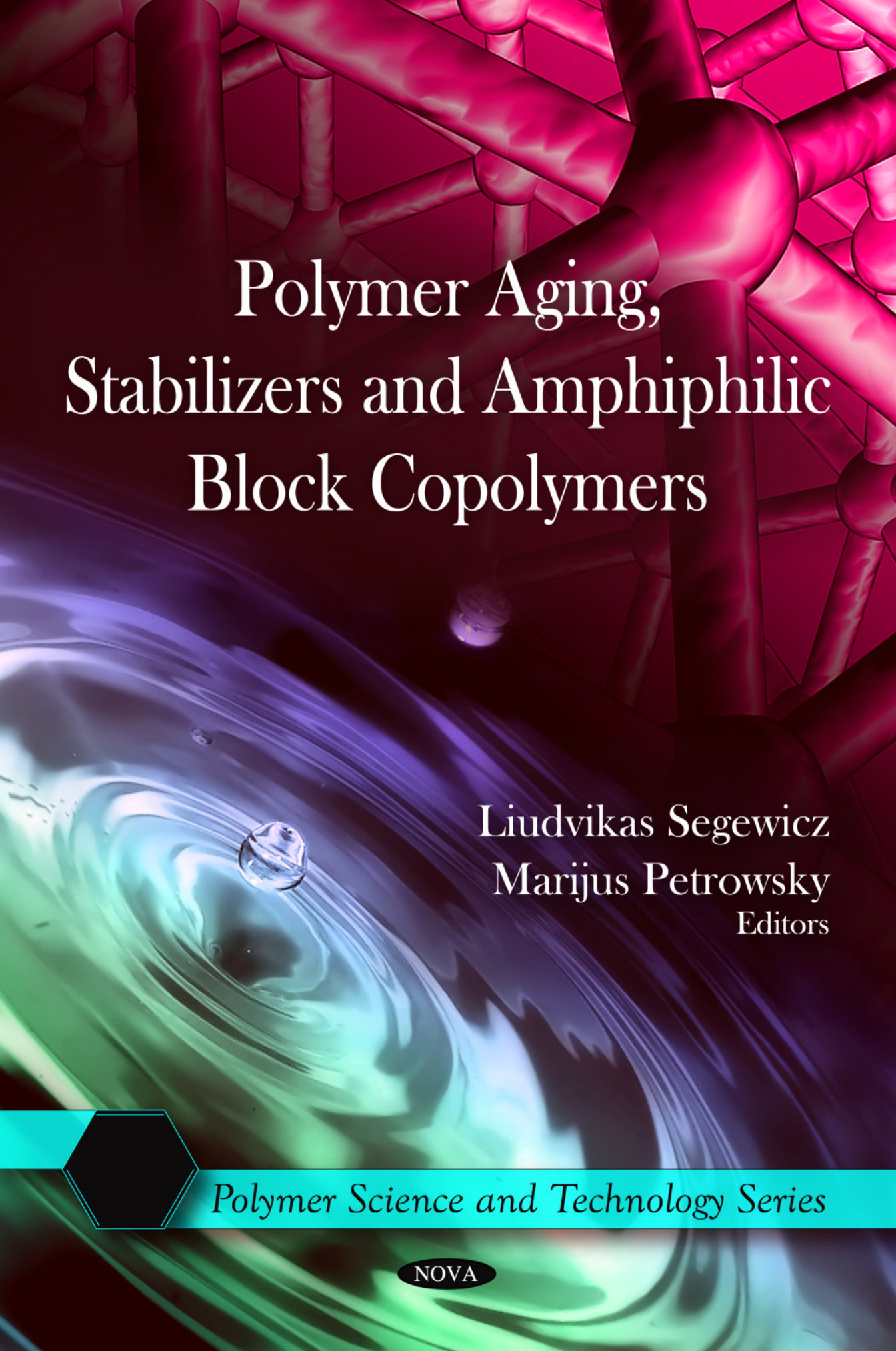




Polymer Aging, Stabilizers and Amphiphilic Block Copolymers

Liudvikas Segewicz
Marijus Petrowsky
Editors



Polymer Science and Technology Series

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POLYMER AGING, STABILIZERS AND AMPHIPHILIC BLOCK COPOLYMERS

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POLYMER AGING, STABILIZERS AND AMPHIPHILIC BLOCK COPOLYMERS

**LIUDVIKAS SEGEWICZ
AND
MARIJUS PETROWSKY
EDITORS**

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PREFACE

Double hydrophilic block copolymers (DHBCs) constitute a novel class of water-soluble macromolecules with potential utilization in a wide range of applications. In this book, the current developments in the field of double hydrophilic block copolymers are discussed. In particular, synthetic strategies leading to the preparation of DHBCs are described. Moreover, their aqueous solution behavior is examined in respect to their ability to self assemblage, due to changes in the solution temperature, and/or pH, as well as due to complexation. This book also reviews the contribution of soluble polymer-supported ligands and insoluble polymer-supported ligands to asymmetric catalysis in various fields by means of nitrogen containing ligands complex with metal as asymmetric catalyst. Furthermore, the authors propose new surfactants or alternative synthetic procedures, and new stabilization systems for polymeric nanoparticles. Other chapters in this book examine the effects of physical aging near the surface region of glass polymers, the application of Hindered Amine Stabilizers (HAS) as a state-of-the-art approach to protection of carbon-chain polymers, the molecular self-assembly of block copolymers and recent developments in the field of various amphiphilic block copolymers, and future perspectives in the field of DHBCs regarding general polymer science and nanotechnology issues.

Chapter 1 - The molecular self-assembly is induced by variation in the surroundings, such as temperature, pressure, pH, salt formation, and noncovalent bond cross-linking. The block copolymers are molecularly converted in situ from the nonamphiphilic copolymers completely dissolved in a solvent to amphiphilic copolymers due to these stimuli. Therefore, the association and dissociation of the isolated copolymers are reversibly controlled by such stimuli. The induced self-assembly has advantages over direct self-assembly of amphiphilic copolymers in molecular designing. There is no dependence on the balance of solvophilic and solvophobic moieties when designing the copolymers. Thus, a better selection of the driving force can be provided. The advantages also include the fact that a variety of amphiphilic copolymers can be created from one nonamphiphilic copolymer in situ by selecting the stimuli.

Chapter 2 - A novel kind of biodegradable thermosensitive composite hydrogel was successfully prepared in this work, which was a flowing sol at ambient temperature and became a non-flowing gel at body temperature. The composite hydrogel was composed of poly(ethylene glycol)-poly(ϵ -caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG, PECE) and Pluronic F127 copolymer. By varying the composition of above two copolymers, *in vivo* degradation rate and *in vitro* drug release behavior could be controlled. Histopathological study of tissue at injection site showed no significant inflammatory reaction and toxicity,

which means that the composite hydrogel might serve as a safe candidate as *in situ* gel-forming controlled drug delivery system.

Chapter 3 - This paper reviews the recent progress made in insoluble polymer supported amino alcohols, amino thiols, oxazolines, salens, sulphonamides, oxazaborolidines and diamines ligands. This paper deals also with various approaches of stabilization of the catalytic system by immobilization of the chiral catalyst onto the polymer by the way of immobilization of the chiral ligand. Different types of ligand immobilization are presented: pendant ligands anchored on a polymer prepared by a polymer reaction, ligands on the backbone prepared by copolymerization and molecular imprinting technique. Examples of their use, performance and recyclability in a variety of enantioselective reactions such as alkylation and reductions of C=O bonds (hydrogenation, hydrogen transfer reduction) reduction of C=N bonds, C-O bond formations (epoxidation, dihydroxylation), C-C bond formations (Diels Alder, cyclopropanation, aldolisation, allylic substitution) and oxidation ... are presented.

Chapter 4 - In the last 20 years, the synthesis of nanoparticles with defined size and shape has been studied with strongly growing interest, leading to a multitude of synthetic approaches and strategies. Whereas the synthesis of the nanocrystals has been studied in great detail, far less effort has been directed towards the stabilization of the obtained materials against agglomeration. This is surprising as the stabilization determines their dispersibility in various solvents, which is a crucial parameter for most applications. For conventional colloids, the classical theories of electrostatic, steric and electrosteric stabilization are well established, but application of these theories to the stabilization of small nanomaterials leads to some peculiarities and at the same time has some limitations, which is known from experimental experience but has not been studied in a systematic fashion yet.

One important conclusion from the theories is that short organic molecules sufficiently serve to provide steric stabilization of nanoparticles less than about 50 nm in size, without a need for long-chain polymeric stabilizers. This concept has been successfully applied using commercial metal oxide nanoparticles in the 50 nm size range, and it is even possible to tailor nanoparticle dispersions with respect to their rheological properties by adjustment of the stabilizer size. Through proper choice of the stabilizer, nanoparticle slurries with high solids content but at the same time low viscosity can be realized, which is highly advantageous for applications especially in the field of ceramic processing.

For ultrasmall nanoparticles in the sub-10-nm regime, the picture is somewhat different. On the one hand, the dispersions of such particles in a stabilized state show very special properties on the verge to molecular solutions, rendering them highly relevant for applications and thus their preparation highly important. On the other hand, due to the lack of suitable model materials, the fundamentals of interaction and stabilization of such small nanoparticles remains largely in the dark. Only a small number of reports were specifically directed to address these problems and systematically investigate the effects of stabilizer chemistry and structure as well as solvent influence. A brief overview of these studies is provided to show that first concepts have been presented, but the general applicability of these concepts still remains to be seen, and to demonstrate the substantial need for further research in this field in order to develop concepts for the rational stabilization and preparation of dispersions with tailored nanoparticle interactions and thus tailored properties.

Chapter 5 - Aiming to gain further insight into the complexity of drug/polymeric micelle interaction phenomena, the present chapter investigated the incorporation of the poorly water-

soluble topical antibacterial agent triclocarban (TCC) into polymeric micelles of the branched pH/temperature-responsive poly(ethylene oxide)-poly(propylene oxide) block copolymers Tetronic® 1107 (MW = 15 kDa, 70 wt% PEO) and 1307 (MW = 15 kDa, 70 wt% PEO). Solubility extents showed a sharp increase of up to 4 orders of magnitude. Due to the pH-dependent character of both the carrier and the drug, studies were performed under different pH conditions. Due to a more efficient poloxamine aggregation at higher pH-values, a clear increase in the solubilization capacity was apparent under these conditions. However, ionization of TCC at pH 12.7 constrained the formation of hydrogen bonds between the urea moieties and the polyether chain, leading to a decrease in solubility above this pH. The size and size distribution of drug-loaded micelles was evaluated by Dynamic Light Scattering (DLS). Findings indicated the increase in the size of the aggregates with the incorporation of the drug. The morphology of the nanostructures was visualized by transmission electron microscopy (TEM). The stability of the systems over time was also evaluated. Finally, the antibacterial activity of different TCC/poloxamine complexes was assayed on different bacteria collections. For example, while a poloxamine-free TCC aqueous solution (pH 7.4) was not effective on *Staphylococcus aureus*, a 10% drug-containing T1307 system inhibited the bacterial growth to some extent. These results supported the release of the drug from the polymeric reservoir. However, as opposed to previous reports, overall findings indicated the limited intrinsic activity of TCC against the investigated pathogens.

Chapter 6 – Generally, surfactants are used as stabilizers of interfaces or particles and their applications are very wide, from foams or adhesion modifiers to the orientation of chemical reactions.

Siloxane surfactants are known for their ability to decrease the surface tension of liquids in such extent that is comparable only with some fluorinated compounds, which are thought to exhibit potential toxicological problems. On the other hand, polysiloxanes are unique by their set of properties, like for example low glass transition temperature, hydrophobic behavior, transparency to visible and UV light, high permeability to various gases (especially oxygen), physiological inertness, excellent blood compatibility (low interaction with plasma proteins). In addition, their chemistry is very versatile, and as a result, a very broad range of siloxane-organic compounds can be synthesized, including amphiphilic macromers or polymers.

The most commonly known siloxane surfactants are the so called „silicone polyethers”, but other nonionic, as well as ionic surface active agents have been prepared and used over the years in cosmetics, textile conditioning, foam stabilization, coatings or agriculture.

Recent developments in this research field and especially our experimental results on the synthesis, properties and applications of siloxane-containing surfactants will be reviewed. Our main interest is to propose new surfactants or alternative synthetic procedures, and new stabilization systems for polymeric nanoparticles. Carbohydrate modified (poly)siloxanes with different architectures have particularly been studied and tested, due to their biocompatibility and bioavailability.

Chapter 7 - The ability of amphiphilic block copolymers to modulate multi drug resistance related processes has been demonstrated the first time more than 10 years ago. Nowadays, the efflux pump inhibitory activity of amphiphilic block copolymers is used in two main areas. First, to improve the transport of efflux pump substrates across the blood brain barrier (BBB) and second, in cancer therapy. It has been shown that in the presence of amphiphilic block copolymers higher concentrations of certain anticancer drugs, which are

known as efflux pump substrates, can be found in the brain. Within the current chapter, recent developments in the field of amphiphilic block copolymer mediated efflux pump inhibition are discussed. Besides presenting data from *in vitro* and *in vivo* studies, also the mechanisms involved in efflux pump inhibition are addressed. In addition, the influence of hydrophilicity/lipophilicity of various amphiphilic block copolymers as well as factors such as micelle formation on the efflux pump inhibitory activity are explained.

Chapter 8 - The effects of physical aging near the surface region of glassy polymers are studied via the relaxations of (1) surface topographic features created by rubbing, and (2) the rubbing induced birefringence (RIB). Extensive experimental results are presented to show that physical aging processes that would have drastic effects on the relaxations of bulk polymers have little effects on the relaxations of rubbed surfaces. We also found that surface topographic features, such as ditches and ridges created by rubbing, relax at temperatures at about 20 °C below the bulk glass transition temperature of the polystyrene for the molecular weight of 442 kg/mol, even though the Laplace Pressure driving the relaxation is 1/500 of the yield limit. The relaxation of RIB in polystyrene (PS), its derivatives with modified side group, and polycarbonate (PC), involves only the length scale of the order of an individual segment. A phenomenological model based on individual birefringence elements is proposed for the RIB relaxation. The relaxation times (RT's) of the elements are found to be independent of the thermal or stress history of the samples, either before or after the formation of the birefringence. The RT's are also independent of the molecular weight, rubbing conditions, and film thickness, while the RT's distribution function does depend on the molecular weight and rubbing conditions. The model provides quantitative interpretations that agree very well with all the reported experimental results, and sheds important light to the novel behaviors of the RIB relaxation. The absence of physical aging effects is probably due to the combined effects of small length scale of the RIB relaxation, and the accelerated aging speed in the near surface region. This is consistent with the mobility enhancement in the surface layer previously reported in the literature.

Chapter 9 - Double hydrophilic block copolymers (DHBCs) constitute a novel class of water-soluble macromolecules with potential utilization in a wide range of applications. The exceptional combination of features, coming from their block copolymer structure and their ability to be stimuli responsive, establishes this class of copolymers as a core of intense research interest, aiming at elucidating aspects regarding their targeted synthesis, solution behavior and application possibilities. In this chapter, the current developments in the field of double hydrophilic block copolymers are discussed. In particular, synthetic strategies leading to the preparation of DHBCs are described. Moreover, their aqueous solution behavior is examined in respect to their ability to self assemble, due to changes in the solution temperature, and/or pH, as well as due to complexation. Additionally, the potential applications of DHBCs in mineralization processes, nanomedicine, nanotechnology and so on are mentioned. Finally, future perspectives in the field of DHBCs regarding general polymer science and nanotechnology issues, as well as open scientific questions, on synthesis and solution behavior of this class of materials, are also discussed.

Chapter 10 - Polyesters are heterochain macromolecular substances characterized by the presence of carboxylate ester groups in the repeating units of their chains. Predominant in terms of volume and products value are those based on poly(ethylene terephthalate) (PET), long established as basis of fibers, films, molding plastics and containers for liquids, and

poly(butylene terephthalate) (PBT) largely used to produce fibers as well as for special applications in motor and electric industry.

Chapter 11 - Application of Hindered Amine Stabilizers (HAS) is the state-of-the-art approach to protection of carbon-chain polymers such as polyolefins and polystyrene or blends containing these against weathering. During outdoor exposure, the polymers lose their material properties due to solar radiation-triggered photooxidation. The complex mechanism of the stabilization involving cyclic oxidation-triggered transformation of HAS is outlined. Monitoring of the formation of the HAS-developed key transformation products, HAS-related nitroxides, responsible within the regenerative mechanism for the effective stabilization was used to confirm the heterogeneous character of photooxidation of two carbon-chain polymers, polypropylene and a specific polyethylene copolymer. Depth profiles of nitroxides were monitored in a long-term photooxidation regime using Electron Spin Resonance Imaging (ESRI) technique. The shape of concentration profiles of the nitroxides accumulated in the equilibrium state upon filtered Xenon lamp-equipped Weather-Ometer exposure was interpreted in terms of the oxygen diffusion limited oxidation and radiation penetration in oxidation-stressed polymer surfaces. The data indicate differences in the character of the heterogeneous process in dependence on the polymer matrix and on the used stabilizer system based on secondary HAS and *O*-alkylhydroxylamine HAS and/or HAS combination with UV absorbers. Imaging of nitroxides is a precise tool for marking heterogeneous oxidation of polyolefins.

Chapter 1

RESEARCH AND REVIEW AND STUDIES INDUCED SELF-ASSEMBLY OF DIBLOCK COPOLYMERS

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1. INDUCED SELF-ASSEMBLY BY ELECTRON TRANSFER

The molecular self-assembly is induced by variation in the surroundings, such as temperature [1-4], pressure [5-9], pH [10-14], salt formation [13-18], and noncovalent bond cross-linking [19-21]. The block copolymers are molecularly converted in situ from the nonamphiphilic copolymers completely dissolved in a solvent to amphiphilic copolymers due to these stimuli. Therefore, the association and dissociation of the isolated copolymers are reversibly controlled by such stimuli. The induced self-assembly has advantages over direct self-assembly of amphiphilic copolymers in molecular designing. There is no dependence on the balance of solvophilic and solvophobic moieties when designing the copolymers. Thus, a better selection of the driving force can be provided. The advantages also include the fact that a variety of amphiphilic copolymers can be created from one nonamphiphilic copolymer in situ by selecting the stimuli.

Electron transport systems perform important functions concerning respiration and energy metabolism in eucaryotes [22, 23]. The electron transport reactions occur at the mitochondria inner membrane formed by electron transport proteins [24] and the lipid bilayer built up by the self-assembly of phospholipids as vital surfactants [25, 26]. The electron transport proteins include redox catalysts such as nicotinamide, iron [27, 28], and quinones [29]. The electrons produced by these redox reactions transfer through the lipid bilayer. While the relationship between the electron transport mechanisms and the molecular self-assembly in vivo has been clarified, control of the self-assembly by electron transport has been applied for an artificial polymeric surfactant.

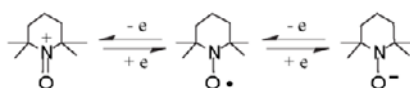


Figure 1-1-1. Redox system of TEMPO

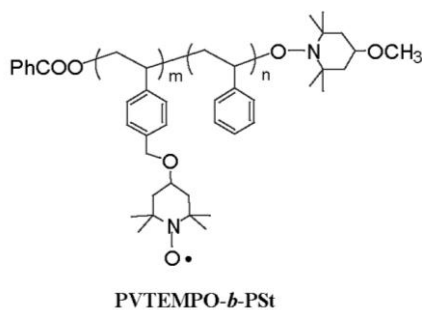


Figure 1-1-2. The PVTEMPO-*b*-PSt diblock copolymer.

1.1. Oxidation-Induced Micellization

Oxidation-induced micellization of a diblock copolymer was determined for a diblock copolymer containing 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) on the side chains [30]. TEMPO is a stable nitroxyl radical known as a spin trapping reagent [31], a spin label reagent [32], and a mediator for living radical polymerization [33, 34]. TEMPO forms a redox system in which the radical is converted into the oxoammonium cation (OA) by one-electron oxidation and is converted into the aminoxy anion (AA) by one-electron reduction [35] (Figure 1-1-1). The oxidation of TEMPO into the OA is caused by chlorine [36], bromine [37], copper (II), and iron (III) [38], while the reduction into AA is brought about by hydrazobenzene [39], quinones [40], and ascorbic acid [41, 42]. The OA salt serves as a one-electron oxidizing agent for amines [35, 36], sulfides [35, 43], and organometallic compounds [44] to produce their radical cation salts or radical intermediates. The OA salt also acts as a two-electron oxidizing agent for converting an alcohol into an aldehyde or ketone [45]. The salts such as the OA chloride, nitrate, trifluoroborate, and hexafluoroantimonate are easily prepared by disproportionation of TEMPO in ether by the acids [46].

The oxidation-induced micellization was attained using poly(4-vinylbenzyloxy-TEMPO)-*block*-polystyrene (PVTEMPO-*b*-PSt) diblock copolymer obtained by the reaction of 4-hydroxy-TEMPO and PVBC-*b*-PSt (Figure 1-1-2). The molecular weight of copolymer was $M_n(\text{PVTEMPO-}b\text{-PSt}) = 31,200\text{-}b\text{-}49,400$. The PVTEMPO-*b*-PSt diblock copolymer showed no self-assembly in carbon tetrachloride, a nonselective solvent. Dynamic light scattering demonstrated that the copolymer self-assembled into micelles when chlorine gas was added to the copolymer solution. An excess of chlorine (1.94 equivalents relative to the TEMPO) was added in order to complete the reaction with the TEMPO when it was taken into consideration that part of the chlorine gas would escape. The hydrodynamic diameter (D_H) of the micelles was estimated to be 49.5 nm by cumulant analysis, while that of the isolated copolymer was 15.6 nm. Figure 1-1-3 shows the scattering intensity distribution vs the hydrodynamic diameter of the copolymer before and after the reaction. The scattering intensity distribution was obtained by the Marquadt analysis [47]. The scattering intensity distribution of the micelles completely took the place of the unimer distribution by the reaction with chlorine.

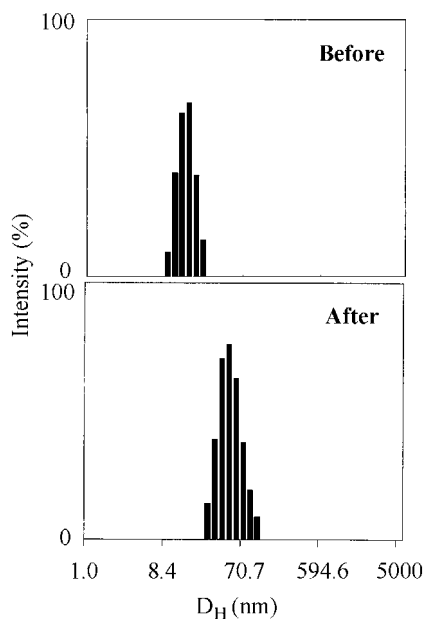


Figure 1-1-3. Scattering intensity distribution of the hydrodynamic diameter for before and after the reaction with the chlorine. [PVTEMPO-*b*-PSt] = 1.71×10^{-3} g/mL.

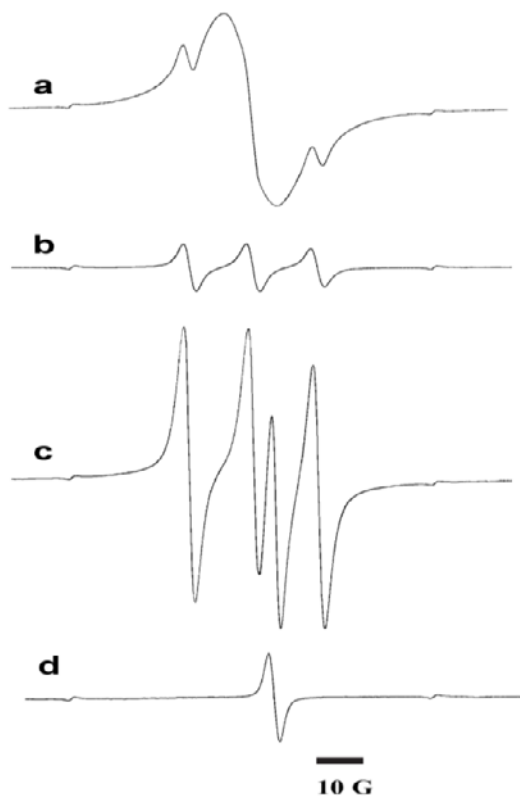


Figure 1-1-4. ESR spectra of PVTEMPO-*b*-PSt in CCl_4 before (a) and after (b) the reaction with the chlorine, and after the reaction with TMPD (c), and of Wursters' blue chloride separately prepared (d).

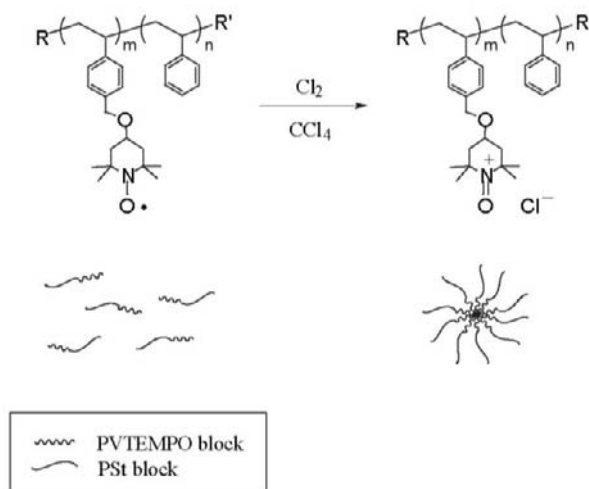


Figure 1-1-5. Micellization of PVTEMPO-*b*-PSt by the chlorine.

ESR studies verified that the radical concentration of the TEMPO in the copolymer decreased due to the reaction with chlorine. Figure 1-1-4 shows the ESR spectra of the copolymer before and after the reaction. Before the reaction with chlorine, a broad signal was observed due to the random orientation, probably caused by the restriction of the mobility of the TEMPO supported on the side chains. They should undergo a strong interaction with each other. After the reaction, the broad signal changed to a characteristic triplet attributed to the isotropy along with a decrease in the signal intensity. The g values of the radicals before and after the reaction were 2.0066 and 2.0064, respectively. This negligible difference in the g values indicates that they are identical radicals originating from the TEMPO. The initial concentration of the TEMPO radical was estimated to be 2.30 mM based on the molar ratio of the VTEMPO unit to the St (VTEMPO/St = 0.186/0.814). The radical concentration after the reaction with 1.94 equivalents of chlorine was estimated to be 6.76×10^{-2} mM on the basis of the integral curves obtained from the differential curves of the radicals. Ninety-seven percent of the TEMPO was consumed by 1.94 equivalents of the chlorine and only 3% of the TEMPO remained unreacted.

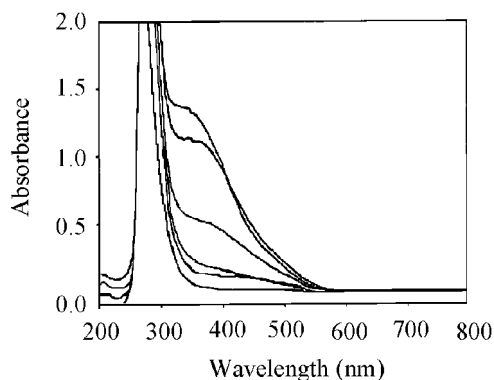


Figure 1-1-6. Variation in the UV absorbance of the PVTEMPO-*b*-PSt copolymer during the micellization. The chlorine to the VTEMPO unit was 0, 0.13, 0.28, 0.58, 1.11, and 1.94 equivalents from the bottom.

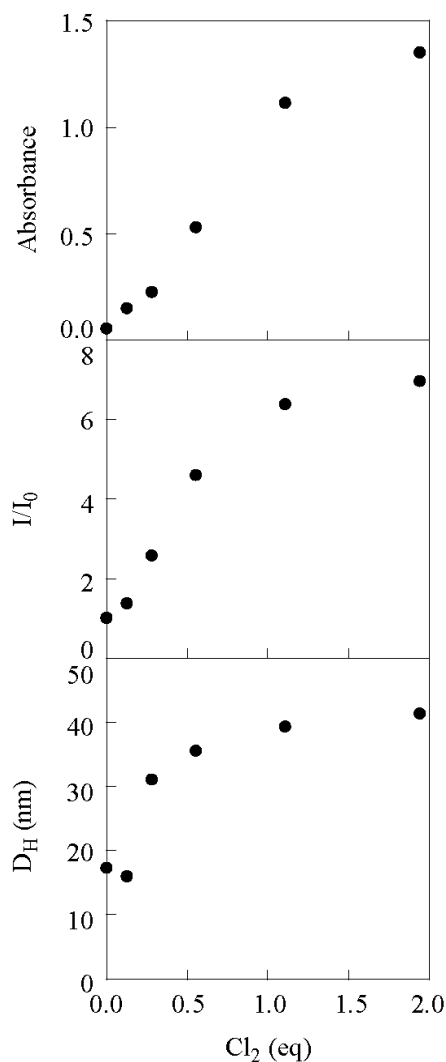


Figure 1-1-7. The variation in UV absorbance at 360 nm, relative scattering intensity (I/I_0), and hydrodynamic diameter (D_H) of PVTEMPO-*b*-PSt vs amount of the chlorine.

UV analysis revealed that as the TEMPO were oxidized into the OA chloride (OAC), the block copolymer became amphiphilic in nature, and hence the polymers underwent micellization (Figure 1-1-5). OA salts are insoluble in carbon tetrachloride; however, in good solvents, such as acetonitrile, the salts show absorption at 360 nm. As can be seen in Figure 1-1-6, the absorption at 360 nm increased as a result of increasing the chlorine. The increase in the absorption at 360 nm indicates an increase in the OAC. Figure 1-1-7 shows the plots of the absorbance at this wavelength, the relative scattering intensity (I/I_0), and the hydrodynamic diameter of the copolymer vs the amount of chlorine. The absorbance increased with an increase in the amount of chlorine, while the scattering intensity and hydrodynamic diameter remained almost constant over 1.11 equivalents of chlorine. It was assumed that no reaction except for the oxidation of the TEMPO by chlorine to the OAC occurred, and the degrees of oxidation of the TEMPO to the OAC were estimated at each

amount of chlorine. The oxidation degrees were determined based on the UV absorbance and the conversion at 1.94 equivalents by the ESR analysis. Figure 1-1-8 shows the variation in the scattering intensity and hydrodynamic diameter of the copolymer vs the oxidation degree. The hydrodynamic diameter rapidly increased at a 16% oxidation degree. Only 16 % of the OAC induced the micellization. The scattering intensity also rapidly increased at the 16% oxidation degree; however, it increased almost proportionally with an increase in the oxidation degree. The continuous increase in the scattering intensity over 16% should be based on increases in the aggregation number or the number of micelles. This consequence was supported by the results for the dependence of the scattering intensity on the copolymer concentration. Figure 1-1-9 shows the plots of the scattering intensity and hydrodynamic diameter of the micelles vs the copolymer concentration. Whereas the micellar size was almost independent of the copolymer concentration, the scattering intensity increased with increasing copolymer concentration. The number of micelles increased as a result of increasing copolymer concentration, causing an increase in the scattering intensity.

TEM observations confirmed that the POAC-*b*-PSt copolymer self-assembled into spherical micelles (Figure 1-1-10). The size of the micelles was almost equal to that estimated by the dynamic light scattering. In common cases, some micelles show a smaller size in the TEM image than in light scattering due to swelling of the micelles in solution. The POAC-*b*-PSt micelles may have difficulty swelling in carbon tetrachloride, because the micelles have the salts with low affinity for the solvent in the micellar cores, resulting in a slight difference in micellar size between that in light scattering and that in TEM.

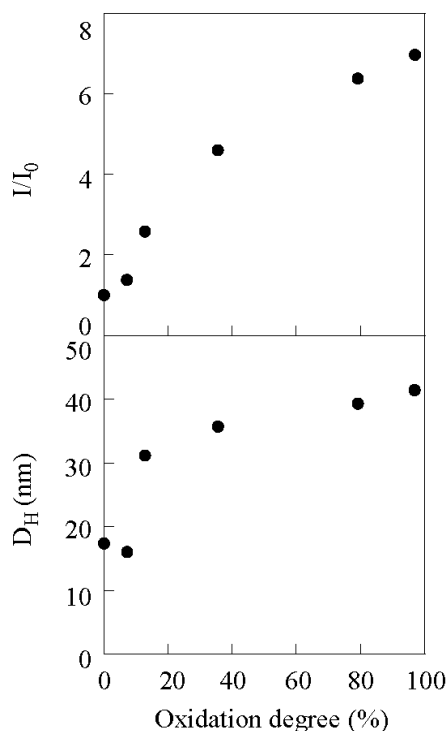


Figure 1-1-8. The plots of relative scattering intensity and hydrodynamic diameter of PVTEMPO-*b*-PSt vs the degree of oxidation.

The POAC-*b*-PSt copolymer seemed not to be very thermally stable, because the orange color of the OAC gradually faded out over room temperature, although the micellar structure was maintained even after the color disappeared. However, below 0°C the micellar solution retained the orange color for several hours.

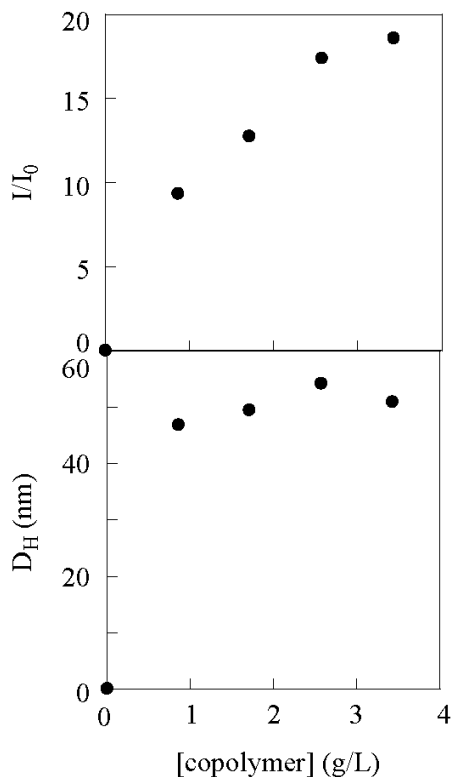


Figure 1-1-9. The plots of the relative scattering intensity and hydrodynamic diameter of PVTEMPO-*b*-PSt vs copolymer concentration.

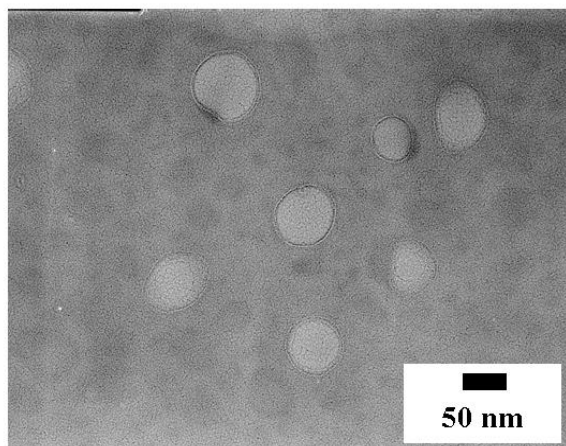


Figure 1-1-10. A TEM image of the POAC-*b*-PSt micelles.

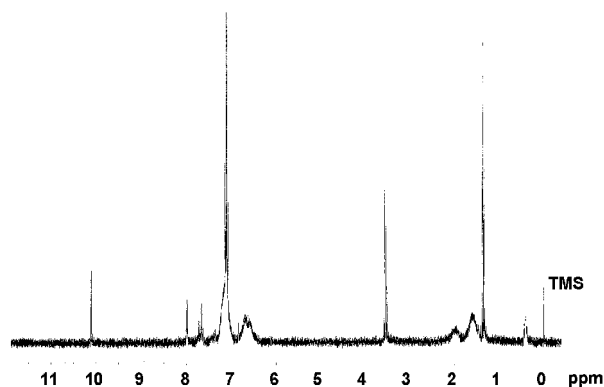


Figure 1-1-11. A ^1H NMR spectrum of the POAC-*b*-PSt micelles after the reaction with benzyl alcohol. Solvent: CCl_4 with benzene- d_6 as the lock solvent and diethyl ether as the standard to estimate the conversion.

The micelles served as an oxidizing agent for converting benzyl alcohol into benzaldehyde. When 1 equivalent of benzyl alcohol relative to the VTEMPO unit was added to the POAC-*b*-PSt micellar solution in carbon tetrachloride, the orange solution became colorless. ^1H NMR demonstrated the quantitative formation of benzaldehyde. Figure 1-1-11 shows the ^1H NMR spectrum of the reaction mixture. Signals originating from benzaldehyde are observed at 7.72, 8.00, and 10.13 ppm. The signals at 1.30 and 3.54 ppm are attributed to diethyl ether added as a standard to estimate the conversion into benzaldehyde. The conversions were determined from the ratio of the signal intensity at 10.13 ppm to that at 3.54 ppm, with the results after 20 and 45 min being 91 and 97%, respectively. The 97% conversion of benzyl alcohol into benzaldehyde confirms that the VTEMPO units were almost quantitatively converted to the OAC by the chlorine. The signals based on the blocks containing the pendant groups were not observed even after the oxidation of benzylalcohol, indicating that the copolymer maintains the micellar structure after the reaction. The light scattering revealed that no changes occurred in the micellar size and in the relative scattering intensity after the reaction. The OAC served as a two-electron oxidizing agent for benzyl alcohol, converting to the insoluble hydroxylamine-hydrochloride salt. Consequently, no dissociation of the micelles occurred due to the oxidation. It can be deduced that the micelles oxidized benzyl alcohol in the cores and released soluble benzaldehyde from the cores maintaining the micellar structure (Figure 1-1-12).

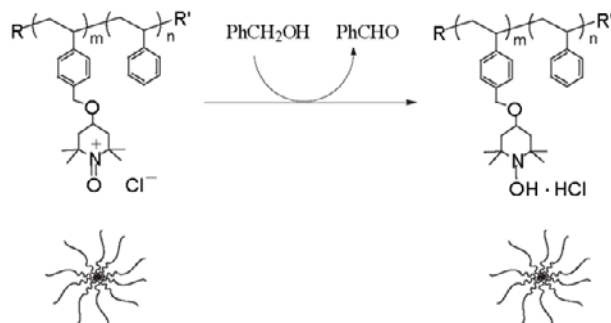


Figure 1-1-12. Oxidation of benzyl alcohol into benzaldehyde by the POAC-*b*-PSt micelles.

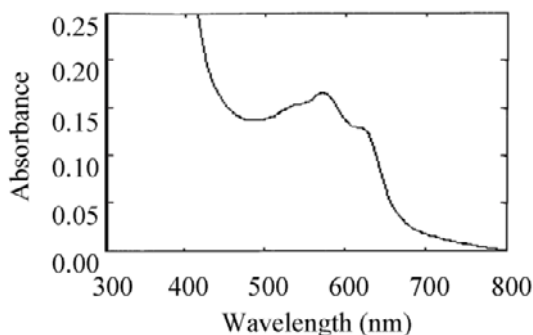


Figure 1-1-13. The UV spectrum of Wurster's blue chloride produced through the oxidation of TMPD by the POAC-*b*-PSt micelles.

The POAC-*b*-PSt micelles also oxidized *N,N,N',N'*-tetramethyl-1,4-phenylenediamine (TMPD) to produce Wurster's blue chloride. As 1 equivalent of TMPD relative to the VTEMPO unit was added to the micellar solution prepared by 1.94 equivalents of chlorine, the solution with orange colored micelles immediately turned purple. Figure 1-1-13 shows the UV spectrum of the micellar solution after the reaction. The characteristic absorption of Wurster's blue [48] was confirmed at 536, 574, and 624 nm. It was suggested that the Wurster's blue chloride was generated in the micellar cores by a one-electron transfer from TMPD to the OAC, because the insoluble Wurster's blue chloride was dissolved into carbon tetrachloride.

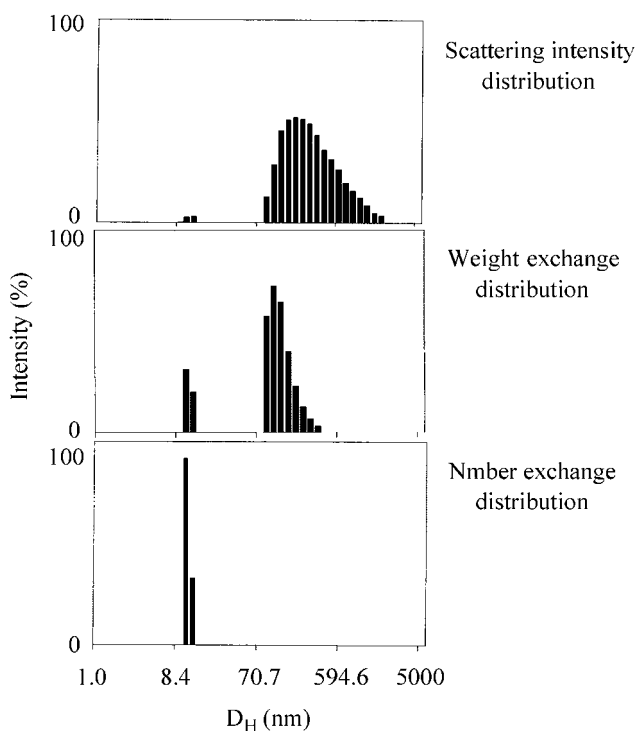


Figure 1-1-14. Scattering intensity distribution, weight exchange distribution, and number exchange distribution of the hydrodynamic diameter of the copolymer after the reaction with TMPD.

The one-electron transfer mechanism from TMPD to the oxoammonium salt was supported by the ESR analysis. As can be seen in Figure 1-1-4c, the signal intensity of the TEMPO increased due to the reaction with TMPD. The g value of the signal was 2.0063, showing good agreement with that before the reaction ($g = 2.0064$). In the triplet signal, another sharp signal was discerned. This singlet signal had a g value of 2.0034. We separately prepared Wurster's blue chloride in carbon tetrachloride by the reaction of TMPD with chlorine. Wurster's blue chloride was obtained as an insoluble black precipitate by the direct oxidation of TMPD by chlorine in carbon tetrachloride; however, the radical salt was unstable by itself and was rapidly decomposed thus losing its radical nature. Figure 1-1-4d shows the ESR spectrum of Wurster's blue chloride. Wurster's blue chloride alone showed a singlet signal with $g = 2.0034$ in carbon tetrachloride. The identification of g values verified that Wurster's blue chloride was produced from the reaction of TMPD and the POAC-*b*-PSt micelles and was solubilized within the micellar cores.

The Marquadt analysis also revealed that the POAC-*b*-PSt micelles were dissociated into the PVTEMPO-*b*-PSt copolymer by the reaction with TMPD. Figure 1-1-14 shows three different distributions of the hydrodynamic diameter of the copolymer; i.e., the scattering intensity distribution, weight exchange distribution, and number exchange distribution. The scattering intensity distribution showed the formation of huge particles over 500 nm, in addition to particles with a size similar to that of the POAC-*b*-PSt micelles. The huge particles should be attributed to the insoluble Wurster's blue dropped from the micelles, because the resulting solution gradually became a white suspension, thus losing the purple color. However, there were not many huge particles, because the distribution of the huge particles was not seen in the weight exchange distribution. On the other hand, the unimer distribution slightly discerned in the scattering intensity distribution was clearly observed in the weight exchange distribution. The number exchange distribution showed only the unimer distribution, suggesting that most of the micelles were dissociated into unimers by the reaction with TMPD.

TEM observations showed that the POAC-*b*-PSt micelles reverted into PVTEMPO-*b*-PSt unimers. Figure 1-1-15 shows a TEM image of the copolymer after the reaction with TMPD. It is observed that larger particles with cores and smaller particles almost without cores co-exist. The larger particles were expected to originate from the micelles including Wurster's blue. The larger particles are still bigger than the POAC-*b*-PSt micelles and have a somewhat distorted shape compared with the micelles. The distortion of the shape should be caused by the copolymer associating through a weak force. This weak association of the copolymer is also reflected in the fact that Wurster's blue chloride gradually dropped out of the micelles. The many small particles were considered to be the isolated copolymers, because the average size of the particles was 17.0 nm, almost the same size as the unimer determined by light scattering. Furthermore, unimers separating from the large particles were also observed. (Figure 1-1-16). It was deduced that the POAC-*b*-PSt micelles oxidized TMPD to the Wurster's blue chloride, reverting into the PVTEMPO-*b*-PSt copolymers (Figure 1-1-17). Most of the copolymers reverted into the isolated copolymers, while some of them still surrounded the Wurster's blue particles to solubilize them.

1.2. Reduction-Induced Micellization

While the oxidation-induced micellization was based on the OAC/TEMPO system using chlorine as the oxidizing agent, the reduction-induced was attained through the TEMPO/HA system using phenylhydrazine as the reducing agent [49].

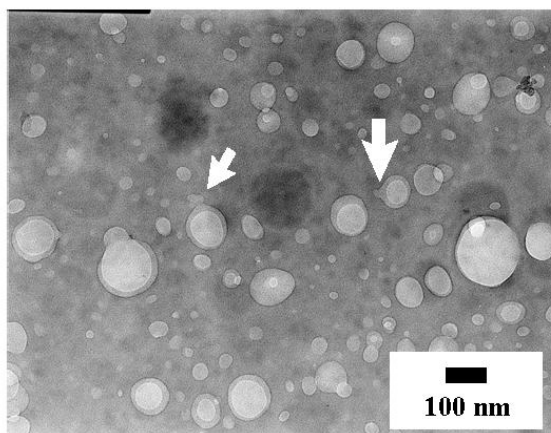


Figure 1-1-15. A TEM image of the POAC-*b*-PSt copolymer after the reaction with TMPD.

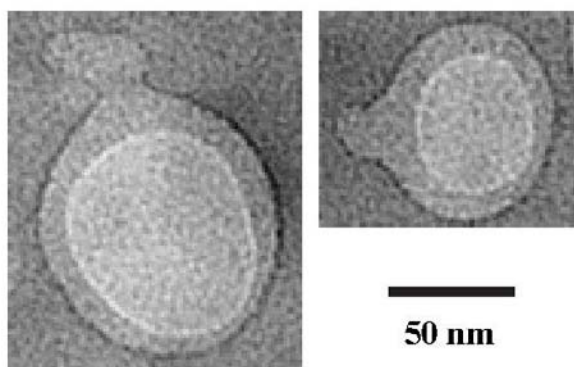


Figure 1-1-16. TEM images of PVTEMPO-*b*-PSt separating from the micelles.

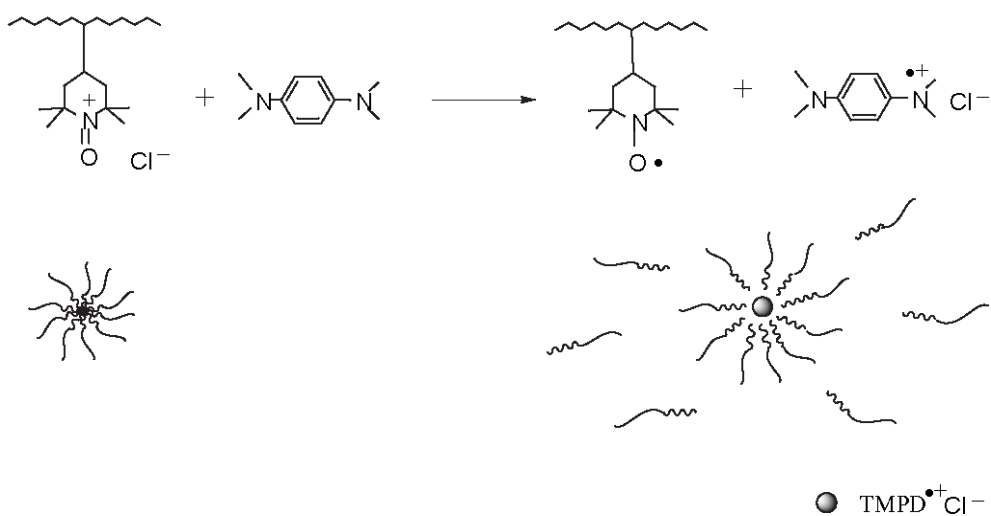


Figure 1-1-17. The reaction of TMPD by the POAC-*b*-PSt micelles.

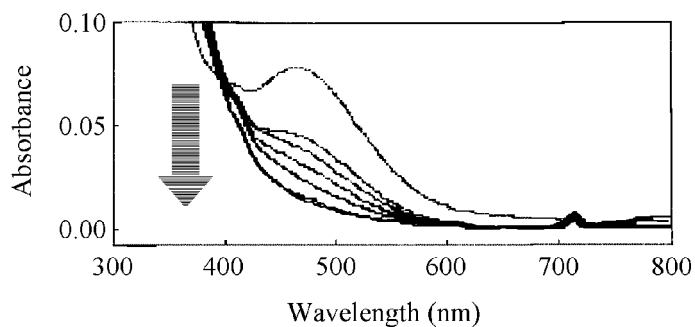


Figure 1-2-1. Variation in the UV absorbance as phenylhydrazine was added to the copolymer solution in benzene. The PH/TEMPO ratios were 0, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 from the top.

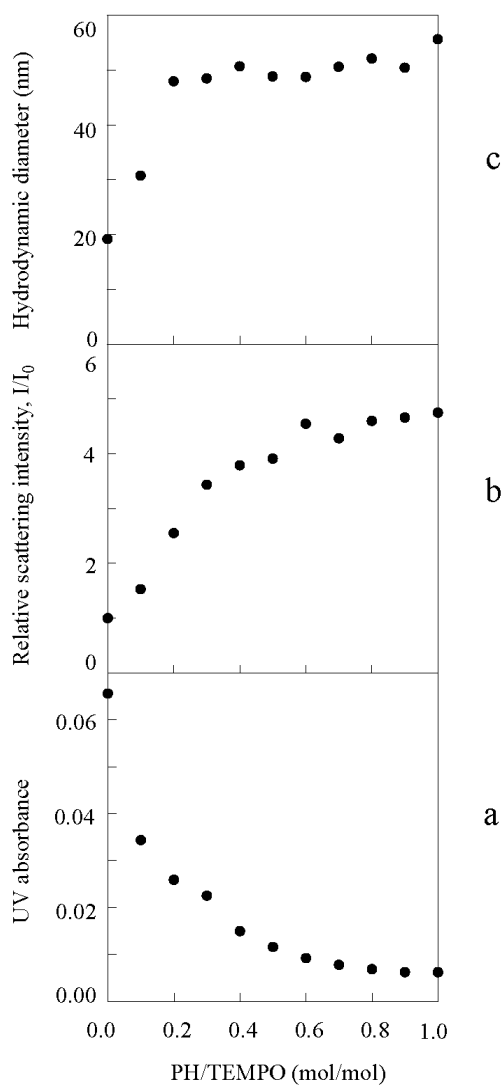


Figure 1-2-2. Plots of the UV absorbance at 500 nm (a), relative scattering intensity (b) and hydrodynamic diameter (c) vs the PH/TEMPO ratio.

TEMPO is red in color and has a UV absorption around 470 nm. This radical is reduced by phenylhydrazine to the colorless hydroxylamine [50]. The PVTEMPO-*b*-PSt diblock copolymer showed an absorption with a λ_{max} value at 467 nm based on the TEMPO radical. It was found that the red color of the copolymer solution in benzene faded out as phenylhydrazine was added to the solution. Figure 1-2-1 shows the variation in the UV absorption of the copolymer with the addition of the phenylhydrazine. The absorbance based on TEMPO decreased with an increase in the molar ratio of the phenylhydrazine to the VTEMPO unit (PH/TEMPO). The absorbance plotted at 500 nm versus the PH/TEMPO ratio is shown in Figure 1-2-2a. The absorbance continued to decrease up to 0.8 and was almost constant above it. The absorbance did not reach zero even at 1.0 due to the long foot of the large absorption peak observed at 240-390 nm. The formation of the hydroxylamine was also confirmed by the ^1H NMR measurement of the copolymer in CDCl_3 in the presence of phenylhydrazine. Signals based on the tetramethyl protons of the hydroxylamine derivative of TEMPO were observed at 1.18 and 1.26 ppm.

Light scattering studies demonstrated that the scattering intensity of the copolymer solution was inversely correlative to the variability in the UV absorbance. Figure 1-2-2b shows the variation in the relative scattering intensity versus the PH/TEMPO ratio. The scattering intensity increased with an increase in the ratio and became almost constant over 0.8. The increase in the scattering intensity suggests the formation of micelles. The hydrodynamic diameter of the copolymer also increased with the increase in the PH/TEMPO ratio (Figure 1-2-2c). The diameter of the copolymer rapidly increased with the addition of a small amount of phenylhydrazine and became steady over 0.2. Whereas the scattering intensity became constant over the PH/VTEMPO ratio of 0.8, the hydrodynamic diameter was constant over 0.2. This difference in the variability between the hydrodynamic diameter and scattering intensity can be accounted for by the fact that the increase in the hydrodynamic diameter indicates the formation of micelles, while the increase in the scattering intensity exactly means an increase in the number of the micelles. The formation of the micelles by the addition of only a 0.2 ratio of the PH/TEMPO suggests that the micellization occurred before all the TEMPO radicals were converted into the hydroxylamine. The hydrogen bonding among the hydroxyl groups should have effectively caused the micellization in the nonpolar solvent.

The Marquadt analysis of the scattering intensity distribution of the copolymer also revealed the micelle formation. The PVTEMPO-*b*-PSt copolymer showed no self-assembly in benzene, because both the blocks of PVTEMPO and PSt were solvophilic to benzene. Therefore, PVTEMPO-*b*-PSt existed as isolated copolymers, that is, unimers in the absence of phenylhydrazine. The hydrodynamic diameter of the unimers was estimated to be 19.2 nm based on the Marquadt analysis. Figure 1-2-3 shows the scattering intensity distributions obtained at the PH/VTEMPO ratios of 0.1 and 1.0. The scattering intensity distribution in the absence of phenylhydrazine could not be obtained due to the very low scattering intensity. It is obvious that the distribution of the unimers was shifted to the higher side of the hydrodynamic diameter at the 1.0 ratio, although part of the distributions overlapped. The micellar size was estimated to be 55.6 nm.

It has been reported that hydroxylamine is oxidized to TEMPO by oxygen [34]. To the micellar solution containing the hydroxylamine was added oxygen by bubbling after the hydroxylamine was converted into the aminoxy anions by sodium hydride in order to facilitate the oxidation by oxygen. As oxygen was added to the micellar solution, the UV absorbance due

to the TEMPO radicals increased. The hydroxylamine in the copolymer was converted into TEMPO by the oxygen, although the radicals immediately reverted to the hydroxylamine again due to the presence of phenylhydrazine in the solution. In addition, this experiment was performed at the PH/TEMPO ratio of 0.5 in order to minimize the influence of the hydrazine.

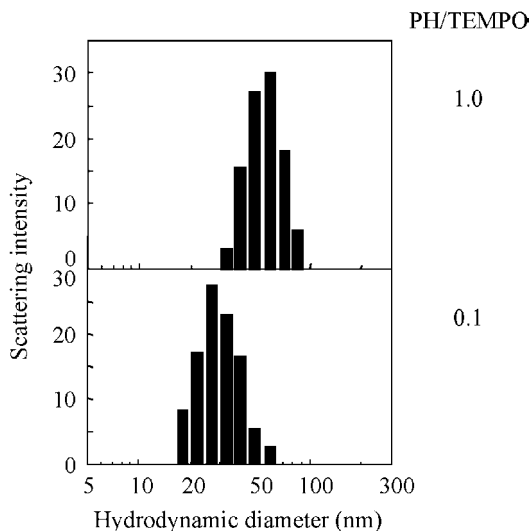


Figure 1-2-3. Scattering intensity distribution of the hydrodynamic diameter of the copolymer at the 0.1 and 1.0 PH/TEMPO ratios.

1.3. Disproportionation-Induced Micellization

TEMPO is disproportionated into the OA and the AA by the acids [46]. The disproportionation of TEMPO also promoted the micellization of the PVTEMPO-*b*-PSt copolymer [51]. The series of micellizations using the TEMPO redox systems indicate that the electron transport becomes a trigger that causes self-assembly of molecules, in addition to external triggers such as temperature, pressure, pH, salt formation, and noncovalent bond cross-linking.

PVTEMPO-*b*-PSt shows no self-assembly in 1,4-dioxane because both blocks are solvophilic to the solvent. Dynamic light scattering studies demonstrated that the copolymer formed micelles in this solvent by the addition of hydrochloric acid. Figure 1-3-1 shows variation in the hydrodynamic diameter and scattering intensity of the copolymer as the hydrochloric acid was added to the copolymer solution. The hydrodynamic diameter rapidly increased at a 0.8 molar ratio of hydrochloric acid to the VTEMPO unit (HCl/VTEMPO). This suggested that the micellization started at 0.8. The hydrodynamic diameter gradually continued to increase over 0.8 and almost became a constant at 1.6. At the complete micellization, the copolymer formed micelles with the hydrodynamic diameter of 53.8 nm, estimated by the cumulant analysis. The scattering intensity also started increasing at 0.8. The disagreement of the variation in the scattering intensity with that of the hydrodynamic diameter was based on the fact that the scattering intensity was attributed to the aggregation number of the micelles. Figure 1-3-2 shows the scattering intensity distribution obtained by

the Marquadt analysis for the hydrodynamic diameter of the copolymer before and after the addition of the hydrochloric acid. The Marquadt method is much better than the cumulant in analyzing the intensity distribution of the hydrodynamic diameter for polymers with comparatively narrow molecular weight distributions. The distribution of the hydrodynamic diameter for the isolated copolymers, that is unimers, was observed around 30 nm. The distribution of the micelles at the HCl/VTEMPO ratio of 2.0 was observed around ca. 55 nm. The unimer distribution was completely shifted to the micellar distribution, indicating that all the unimers were engaged in forming the micelles.

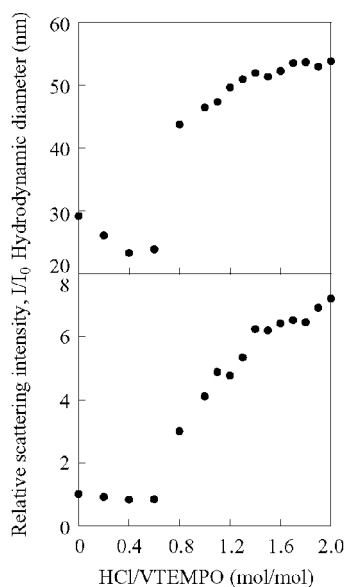


Figure 1-3-1. Variation in the hydrodynamic diameter and scattering intensity of the PVTEMPO-*b*-PSt copolymer vs. HCl/VTEMPO. [PVTEMPO-*b*-PSt] = 1.71 g/L.

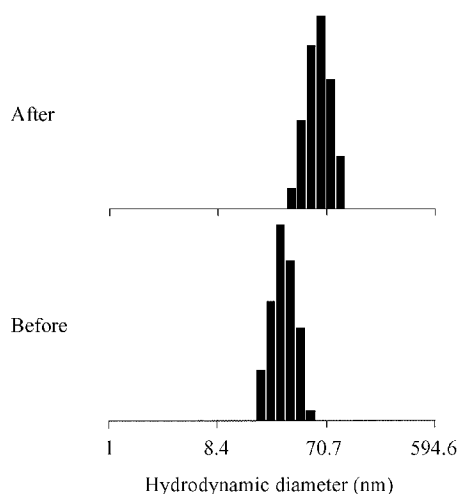


Figure 1-3-2. Scattering intensity distribution of the hydrodynamic diameter for PVTEMPO-*b*-PSt before and after the reaction with HCl at HCl/VTEMPO of 2.0. [PVTEMPO-*b*-PSt] = 1.71 g/L.

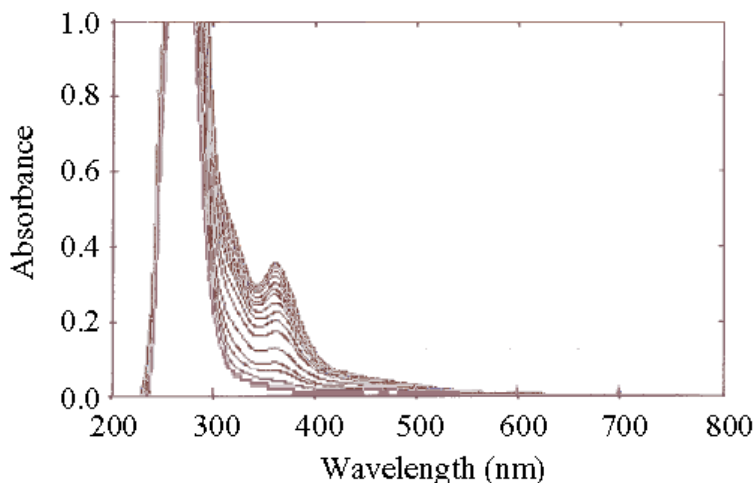


Figure 1-3-3. Variation in the UV absorbance of the PVTEMPO-*b*-PSt copolymer during the micellization. HCl/VTEMPO from the bottom = 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, and 2.0. [PVTEMPO-*b*-PSt] = 1.71 g/L.

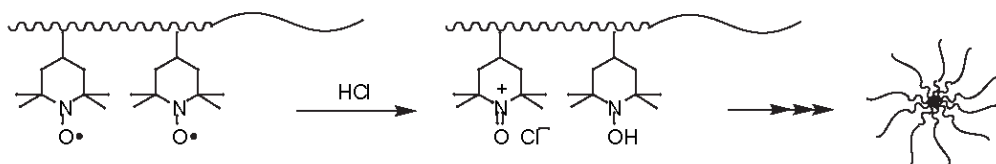


Figure 1-3-4. Micellization of PVTEMPO-*b*-PSt by the disproportionation of TEMPO.

A UV analysis confirmed that the oxoammonium chloride was formed in the micellar cores via the disproportionation using hydrochloric acid. Figure 1-3-3 shows the variability in the absorbance of the copolymer solution during the micellization. The oxoammonium chloride derived from 4-methoxy-TEMPO was insoluble in 1,4-dioxane, however, in a good solvent such as acetonitrile, the oxoammonium chloride showed an absorption at 360 nm. The hydroxylamine is soluble in the solvent, but had no UV absorption. The absorbance at 360 nm increased with an increase in the amount of HCl. This observation implies that the insoluble oxoammonium chloride was dissolved in the micelles by being supported on the core blocks. The increase in the absorbance indicates an increase in the amount of the oxoammonium chloride in the micellar cores. The disproportionation of TEMPO proceeded into the oxoammonium chloride and the hydroxylamine as the amount of the hydrochloric acid increased (Figure 1-3-4).

ESR studies demonstrated that the radical concentration of the TEMPO in the copolymer decreased with the increasing HCl. The ESR spectra of the copolymer during the micellization are shown in Figure 1-3-5. The copolymer showed broad signals before the addition of HCl. The broad signals are based on the random orientation caused by the restriction of the mobility of the TEMPO supported on the polymer side chains. The broad signals gradually changed to the typical triplet of TEMPO as the HCl increased. It is considered that the number of TEMPO molecules decreased as the disproportionation proceeded, resulting in the fact that the interaction among the TEMPO molecules was

reduced and showed the original triplet. In fact, the signal intensity decreased with this change in the signal, although the g values were almost constant throughout the micellization. The radical concentrations were estimated on the basis of the integral curves obtained from these differential curves in the ESR. Figure 1-3-6 shows the variation in the TEMPO concentration during the micellization. The radical concentration decreased as the HCl increased and became constant over a 1.6 HCl/VTEMPO ratio. It was found that 40 mol% of the TEMPO radicals remained unreacted. This result suggests that the micellization hindered the TEMPO disproportionation due to the fact that the remaining TEMPO was isolated in each of the micellar cores. However, the disproportionation continued to proceed unless the micellization was completed, because the TEMPO concentration continued to decrease even over the HCl/TEMPO ratio of 0.8 at which the micellization started.

TEM observations demonstrated that spherical micelles were formed by the disproportionation-induced micellization. The TEM image of the micelles is shown in Figure 1-3-7. The micelles did not have completely spherical outlines, suggesting that the micelles were constructed with a weak association force. This weak association should be caused by non-quantitative disproportionation and by the presence of the soluble hydroxylamine in the cores. The diameter of the micelles was ca. 72.7 nm in the TEM image. This micellar size was larger than that estimated by the dynamic light scattering. This difference may be accounted for by the fact that the micelles expanded by an increase in the repulsion among the OA cations when the solvent was removed.

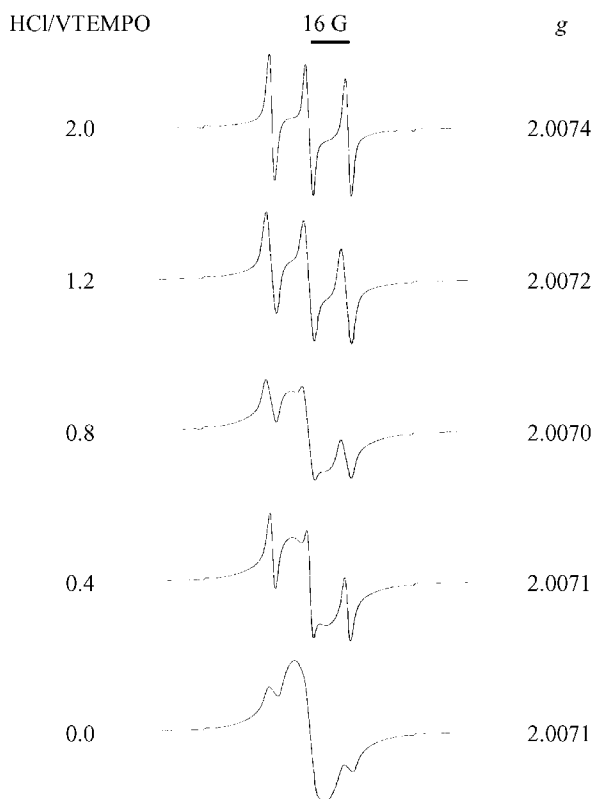


Figure 1-3-5. ESR spectra of PVTEMPO-*b*-PSt. [PVTEMPO-*b*-PSt] = 1.71 g/L.

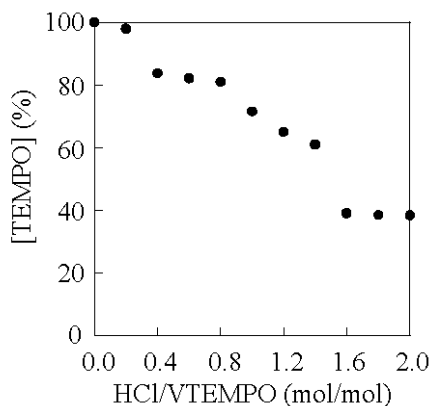


Figure 1-3-6. Plots of the radical concentration of the TEMPO vs. HCl/TEMPO.

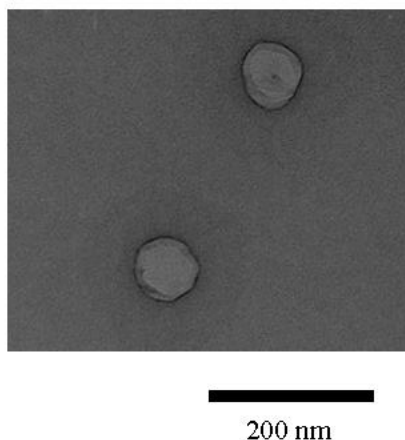


Figure 1-3-7. A TEM image of the micelles obtained by the disproportionation.

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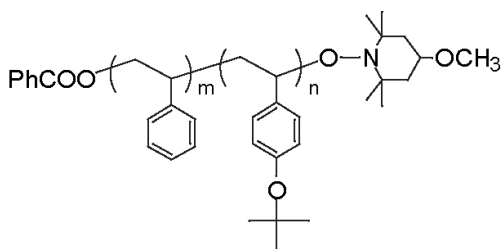
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2. INDUCED SELF-ASSEMBLY BY PHOTOLYSIS

Light is a handy, easily available, and environmentally clean stimulant to cause self-assembly. In vivo, the photoreceptor proteins in animal eye cells change their high-dimensional structure by receiving photons [1], while artificial polymers responsive to light contain photochromic compounds such as azobenzene [2-4], spiropyran [5,6], stilbene [7-9], cinnamate [10], and triphenylmethane leuco residues [11]. The polymers reversibly change their structure through the cis-trans isomerization, dimerization, and conformational changes of the photochromic compounds. This reversible behavior is manipulated by UV wavelength of the compounds or sometimes temperature. Compared to these reversible reactions required as a function of the on-off switches, irreversible reactions are convenient to fix the spatial structure changed by photo irradiation. The structure change effects by the photo irreversible reaction have been investigated on the photolysis of diazosulfonates [12-14], 1-iminopyridinium ylides [15], [4(4'-alkoxybenzoyl)phenylmethyl]phosphonic acids [16], and didecyl-2-methoxy-5-nitrophenyl phosphate [17]. The former three kinds of surfactants lose their surface-active ability by photolysis, resulting in the destruction of the micelles and vesicles. On the other hand, didecyl-2-methoxy-5-nitrophenyl phosphate formed vesicles by the photolysis.

The self-assembly induced by the photolysis was determined for a poly(4-*tert*-butoxystyrene)-*block*-polystyrene diblock copolymer (PBSt-*b*-PSt) [18] (Figure 2-1). In this photolysis-induced self-assembly, a diblock copolymer produced by the photolysis formed micelles. This new way of molecular self-assembly induced by photoirradiation has the potential to produce new applications for optical memory materials and optical devices using the photoirreversible reaction.



PBSt-*b*-PSt

Figure 2-1. The PBSt-*b*-PSt diblock copolymer.

The PBSt-*b*-PSt diblock copolymer shows no self-assembly in dichloromethane since the PBSt and PSt blocks are solvophilic to it. Light scattering studies have demonstrated that the copolymer is self-assembled into micelles in dichloromethane by irradiation in the presence of a photoacid generator. Figure 2-2 shows the variation in the hydrodynamic diameter (D_H) and the relative scattering intensity (I/I_0) of the copolymer with the molecular weight of

$M_n(\text{PBSt-}b\text{-PSt}) = 15,000\text{-}b\text{-}97,000$ during the irradiation using bis(alkylphenyl)iodonium hexafluorophosphate (BAI) as a photoacid generator. The molar ratio of BAI to the BSt unit was 0.38. The hydrodynamic diameter and scattering intensity showed a good correlation. They increased at 4.5 h and became constant over 5 h, indicating that the micellization was completed over 5 h. The hydrodynamic diameter of the micelles averaged 63.0 nm, while that of the isolated copolymer, which is a unimer, was 16.6 nm based on the cumulant analysis. The observation of the jump and the constant state within the short time period suggests the rapid micellization due to the strong aggregation force.

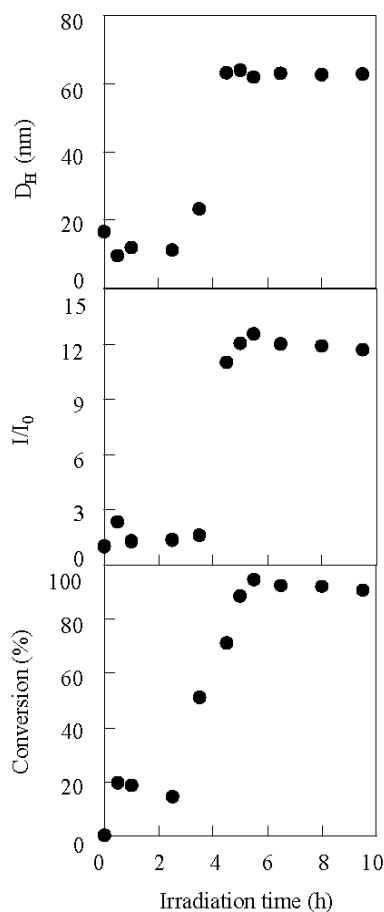


Figure 2-2. The variation in the hydrodynamic diameter (D_H), relative scattering intensity (I/I_0), and conversion of the copolymer during the irradiation using BAI. $M_n(\text{PBSt-}b\text{-PSt}) = 15,000\text{-}b\text{-}97,000$, $[\text{copolymer}]_0 = 3.30 \text{ g/L}$.

The variation in the scattering intensity distribution of the hydrodynamic diameter also supported the formation of the micelles by the rapid association. Figure 2-3 shows the scattering intensity distribution obtained by the Marquadt analysis. The distribution was shifted to the higher side of the hydrodynamic diameter over time by the irradiation. The slight shift in the distribution at 3.5 h implies that aggregates with a lower aggregation number were formed during the first stage and those associated into micelles, rather than that the unimers inserted step by step into the micelles.

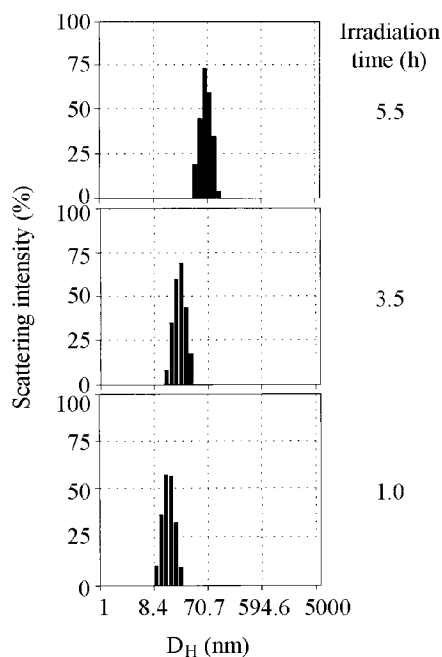


Figure 2-3. Scattering intensity distributions of the hydrodynamic diameter of the copolymer. $[\text{copolymer}]_0 = 3.30 \text{ g/L}$

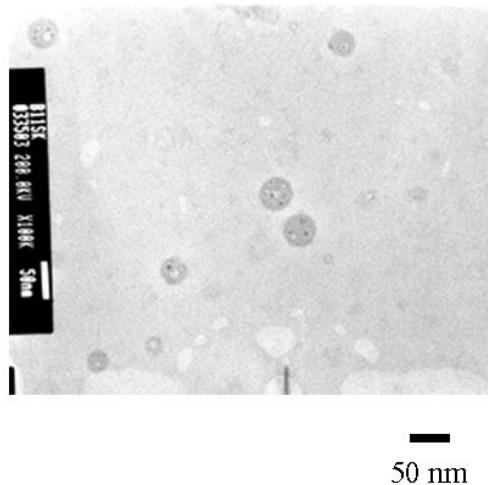


Figure 2-4. A TEM image of the micelles. $\text{Mn}(\text{PBSt-}b\text{-PSt}) = 15,000\text{-}b\text{-}97,000$,

TEM observation confirmed the formation of spherical micelles through the irradiation. The TEM image of the micelles is shown in Figure 2-4. The diameter of the micelles was estimated to average 40.6 nm based on the TEM. Compared to the micellar size determined by the cumulant analysis, the TEM exhibited a smaller diameter of the micelles than the dynamic light scattering. The estimation of the micelles as the smaller size can be accounted for by the fact that the micelles in the solution contracted when isolated in air.

The irradiation of the copolymer in the absence of BAI and the dark reaction in its presence produced no changes in the hydrodynamic diameter and scattering intensity. These two control experiments suggest that the structure of PBSt-*b*-PSt was changed by the irradiation on BAI. The ^1H NMR confirmed that the micellization was caused by the elimination of the *tert*-butyl groups in the copolymer. Figure 2-5 shows the ^1H NMR spectra of the copolymer before and after the irradiation. The ^1H NMR measurements were performed in 1,4-dioxane- d_8 . Signals at 1.29 ppm based on the *tert*-butyl groups were hardly observed after the irradiation. The disappearance of the signals implies that the *tert*-butyl groups were eliminated from the copolymer. PBSt-*b*-PSt should have been converted into poly(4-vinyl phenol)-*block*-PSt (PVPh-*b*-PSt) by the hydrolysis of the *tert*-butoxy groups with the photoacid generator as a catalyst (Figure 2-6), based on the mechanism of the hydrolysis of poly(4-*tert*-butoxystyrene) [19]. A signal based on the hydroxyl groups of the PVPh blocks could not be discerned due to the fact that it overlapped with the signals of the aromatic protons and had too low an intensity. In addition, it is clear that the disappearance of the butyl proton signals and no observation of the hydroxyl signal were not based on the self-assembly of the copolymer into micelles. This is because PVPh-*b*-PSt showed no self-assembly in 1,4-dioxane- d_8 and existed as unimers. The conversion of the BSt units into the VPh units was estimated based on the signal intensity of the *tert*-butyl protons to that of the aromatic protons at 6.3-7.7 ppm. The time-conversion plots are shown in Figure 2-2. The conversion started increasing at an earlier stage than the scattering intensity. The scattering intensity jumped when the conversion reached 50%, indicating that the micellization was dependent on the degree of the VPh unit formation.

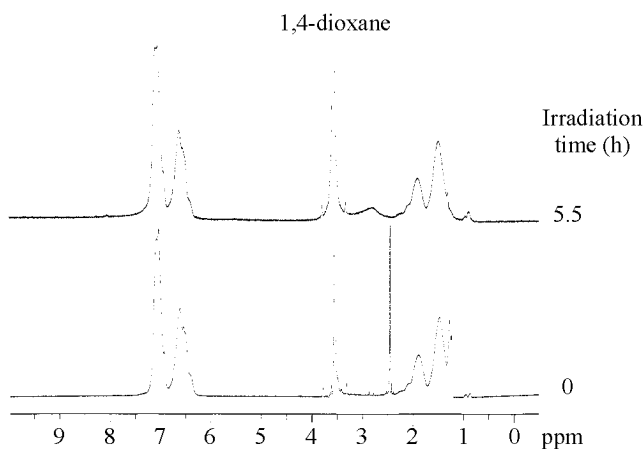


Figure 2-5. ^1H NMR spectra of the copolymer before (bottom) and after the irradiation (upper, the irradiation time = 5.5 h). Solvent: 1,4-dioxane- d_8 .

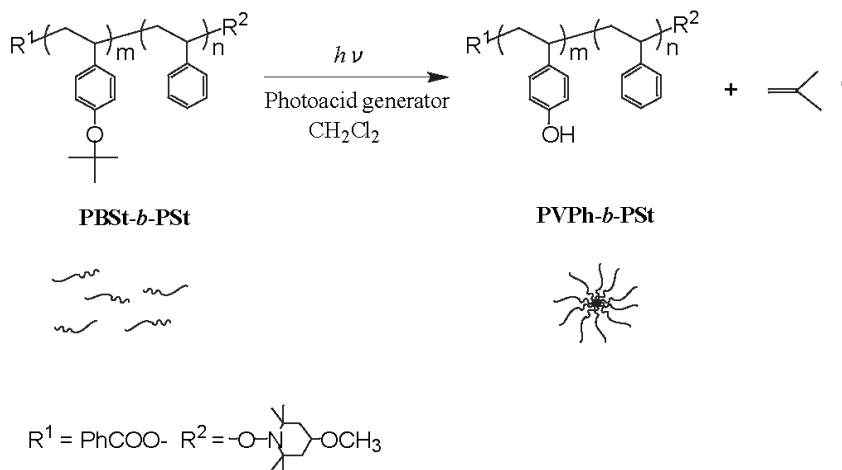


Figure 2-6. The micellization induced by photolysis of PBSt-*b*-PSt.

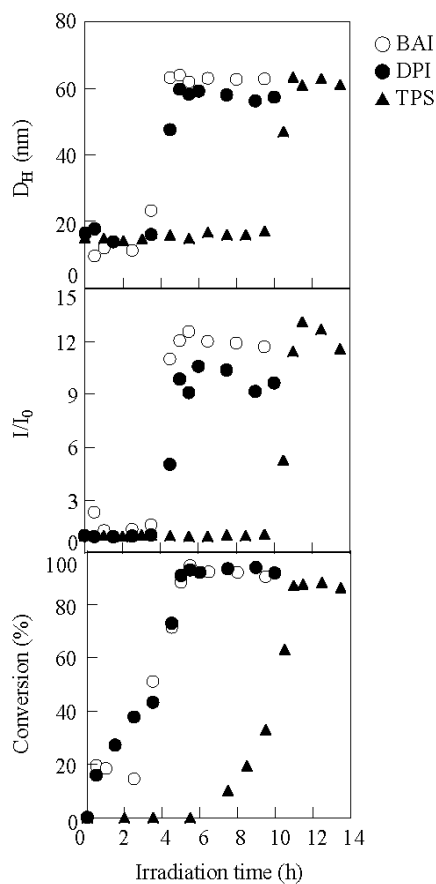


Figure 2-7. The variation in the hydrodynamic diameter, scattering intensity, and conversion of the copolymer during the irradiation in the presence of BAI (○), DPI (●), and TPS (▲). [copolymer]₀ = 3.30 g/L. Photoacid generator/BSt unit = 0.38.

The study of the micellization using different kinds of photoacid generators demonstrated that the micellization, coupled with the conversion, were dependent on the ability of the photoacid generator. The micellization by the irradiation was evaluated using diphenyliodonium hexafluorophosphate (DPI) and triphenylsulfonium triflate (TPS). Figure 2-7 shows the variation in the hydrodynamic diameter, scattering intensity, and conversion during the irradiation by BAI, DPI, and TPS. The conversion for DPI started increasing slightly earlier than that for BAI, although there is a negligible difference in the transition of the scattering intensity and hydrodynamic diameter. On the other hand, TPS needed a longer irradiation time to promote the micellization as compared to BAI and DPI. This difference in promoting the micellization was clarified on the basis of the UV analysis of the photoacid generators. Figure 2-8 shows the UV spectra of the photoacid generators and the PBSt-*b*-PSt copolymer, coupled with the illumination intensity of the irradiation versus the wavelength for the high-pressure mercury lamp. It is considered that the irradiation reaction of the photoacid generators occurred around 290 nm, because at this wavelength, the absorption of the photoacid generator overlapped at a highest proportion with the illumination intensity of the lamp without any obstruction by the copolymer. The absorbance of the photoacid generators decreased in the order of BAI > DPI > TPS. In particular, TPS had a slight absorption at 290 nm. It can be deduced that the difference in the absorption intensity among the photoacid generators was reflected in the irradiation time needed to initiate the micellization.

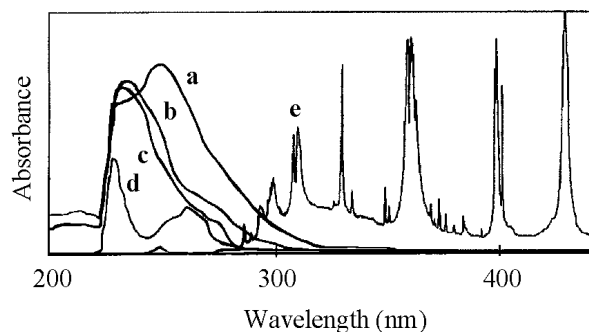


Figure 2-8. UV spectra of BAI (a), DPI (b), TPS (c), and PBSt-*b*-PSt (d) with the illumination intensity of the irradiation of the high-pressure mercury lamp (e). Solvent: dichloromethane. $M_n(\text{PBSt-}b\text{-PSt}) = 15,000\text{-}b\text{-}97,000$.

The efficiency of the micellization was also dependent on the concentration of the photoacid generator. Figure 2-9 shows the variation in the hydrodynamic diameter, scattering intensity, and conversion during the irradiation in the presence of DPI at the DPI/BSt molar ratios of 0.38 and 1.00. More sharply and earlier jumping was observed at 1.00, indicating that the micellization was promoted more effectively at 1.00. Consequently, the irradiation time needed for the micellization was manipulated by the concentration of the photoacid generator.

The block length of the copolymer had an effect not only on the micellar size and scattering intensity, but also on the conversion. For the identical PBSt block length ($M_n = 15,000$), the effect of the PSt block length on the micellization was explored. Figure 2-10 shows the variation in the hydrodynamic diameter, scattering intensity, and conversion during the irradiation using copolymers with the different PSt block lengths: $M_n = 63,000$ and

170,000. Regarding the hydrodynamic diameter and the scattering intensity, it was observed that the copolymer with the shorter PSt block showed a transition at an earlier stage than that with the longer PSt. The copolymer with the shorter PSt more easily aggregated into micelles. The shorter PSt sample produced smaller micelles with a higher aggregation number due to the shorter length of the PSt blocks. The conversion of the shorter PSt sample also started increasing slightly earlier than that for the longer sample. The reason why the shorter PSt sample initiated the micellization more earlier is also based on the faster conversion.

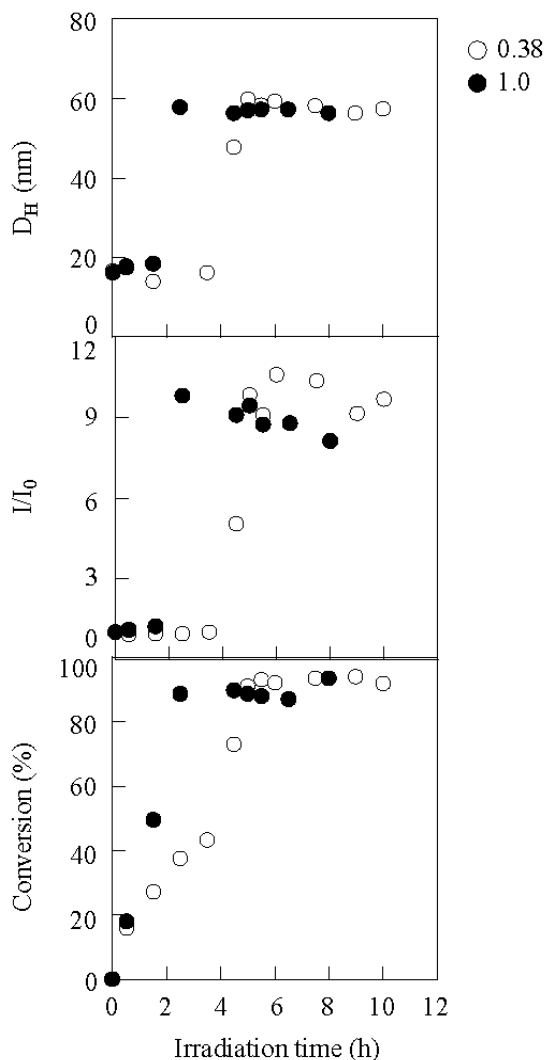


Figure 2-9. The variation in the hydrodynamic diameter, scattering intensity, and conversion during the irradiation at 0.38 (O) and 1.00 (●) of DPI/BSt. [copolymer]₀ = 3.30 g/L, Mn(PBSt-*b*-PSt) = 15,000-*b*-97,000.

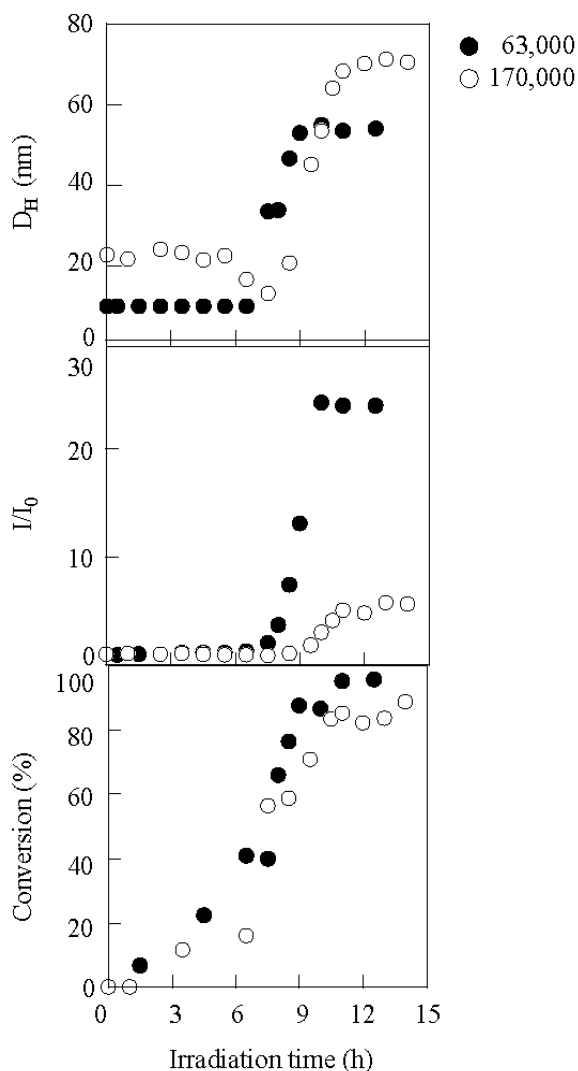


Figure 2-10. The variation in the hydrodynamic diameter, scattering intensity, and conversion during the irradiation using copolymers with $M_n(\text{PSt block}) = 63,000$ (●) and $170,000$ (○). $M_n(\text{PBSt block}) = 15,000$, $[\text{copolymer}]_0 = 3.30$ g/L, $\text{DPI/BSt} = 0.38$.

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Chapter 2

A NOVEL THERMOSENSITIVE COMPOSITE HYDROGEL BASED ON POLY(ETHYLENE GLYCOL)- POLY(E-CAPROLACTONE)-POLY(ETHYLENE GLYCOL) (PECE) COPOLYMER AND PLURONIC F127⁺⁺

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ABSTRACT

A novel kind of biodegradable thermosensitive composite hydrogel was successfully prepared in this work, which was a flowing sol at ambient temperature and became a non-flowing gel at body temperature. The composite hydrogel was composed of poly(ethylene glycol)-poly(ϵ -caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG, PECE) and Pluronic F127 copolymer. By varying the composition of above two copolymers, *in vivo* degradation rate and *in vitro* drug release behavior could be controlled. Histopathological study of tissue at injection site showed no significant inflammatory reaction and toxicity, which means that the composite hydrogel might serve as a safe candidate as *in situ* gel-forming controlled drug delivery system.

Keywords: Thermosensitive, Composite Hydrogel, Degradation, Pluronic, Drug Release.

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1. INTRODUCTION

Cancer is one of the most severe diseases and causes millions of death each year in the world. More than 1 million new cancer cases and 500,000 deaths from cancer are projected to occur in 2008 in USA [1]. Chemotherapy, as conventional cancer treatment, was widely used in clinical. However, conventional chemotherapy had severe side effects, which are very painful for patients to tolerate. Novel controlled drug delivery systems (DDS) are intended to deliver drugs at predetermined rates for predefined periods of time, which might overcome the shortcomings of conventional drug formulations, therefore could diminish the side effects and improve the life quality of the patients [2-3]. Thus, a suitable controlled drug delivery system is extremely important for chemotherapy. An optimal controlled drug delivery system should sustained release drugs in an extended period, and should be biodegradable, biocompatible, and non-toxic.

Hydrogels are a special series of materials that could absorb a considerable amount of water while maintaining their three-dimension integrity in water. Over the past decades, the stimuli-sensitive copolymer hydrogel has attracted increasing attention owing to their smart responsibility to the environmental stimulus including chemical substances and changes in temperature, pH, or electric field [4-10]. Especially, the biodegradable thermosensitive physical crosslinked hydrogels consisted of hydrophobic and hydrophilic blocks have been extensively studied owing to their smart responsibility to the environmental stimulus, biodegradability, and biocompatibility. Therefore, biodegradable thermosensitive hydrogels, which might have potential biomedical applications, have been investigated as *in situ* gel-forming system, such as controlled drug delivery, tissue repair, and cell encapsulation [11-23]. In previous contributions, many biodegradable thermosensitive hydrogels have been studied, such as poly(ethylene glycol)-poly(D,L-lactic acid-co-glycolic acid) (PEG-PLGA) copolymers [24-27], poly(ethylene glycol)-poly(L-lactic acid) (PEG-PLLA) copolymers [10, 28], chitosan derivatives [29-32], methylcellulose, polyphosphazene, and etc.

Poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) triblock copolymer (PEG-PPG-PEG), known as Pluronic or Poloxamer, has been extensively studied as a potential drug delivery vehicle due to their excellent biocompatibility and thermosensitivity [33-34]. These copolymers have been widely used as emulsifiers, wetting agents, and solubilizers [35]. However, due to weak hydrophobicity of PPG block and high PPG content, the Pluronic copolymer forms a fast-eroding gel and can not persist longer than a few hours *in vivo*, which greatly restricted its application as *in situ* gel-forming systems.

In our previous study, we prepared a new kind of biodegradable and injectable thermosensitive poly(ethylene glycol)-poly(ϵ -caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG, PECE) hydrogel controlled drug delivery system that undergoes sol-gel-sol transition. *In vitro* drug release behavior and *in vivo* gel formation and degradation test upon subcutaneous injection of PECE hydrogel in the mice model were also conducted [36]. PEG and PCL are materials that are biocompatible and have been used in several FDA-approved products [37-42]. And PCL is lack of toxicity and has great permeability [43]. Due to combination of great advantages of PEG and PCL, the PECE copolymer might have great potential application in biomedical field.

In this study, we prepared a new kind of biodegradable and injectable composite hydrogel based on PECE and Pluronic F127 copolymer. The composite hydrogels are free-flowing sol at room temperature and becomes gel at body temperature, and the influence of composition of the composite hydrogel on the sol-gel-sol transition was investigated. We wonder whether composite hydrogel with different composition would result in different drug release rate and *in vivo* gel degradation rate. Therefore, *in vitro* drug release behavior and *in vivo* gel formation and degradation test were conducted in this paper. The result showed that by altering the composition of composite hydrogel, *in vitro* drug release rate and *in vivo* gel degradation rate could be controlled, which was very important for their further application as injectable *in situ* gel-forming controlled drug delivery system.

2. MATERIALS AND METHODS

2.1. Materials

Poly(ethylene glycol) methyl ether (MPEG, $M_n=550$, Aldrich, USA), ϵ -caprolactone (ϵ -CL, Alfa Aesar, USA), Pluronic F127 (Sigma, USA), hexamethylene diisocyanate (HMDI, Aldrich, USA), stannous octoate ($\text{Sn}(\text{Oct})_2$, Sigma, USA), bovine serum albumin (BSA, BR, BoAo Co. Ltd, China), and VB_{12} (Sigma, USA) were used without any further purification. All the materials used in this article were analytic reagent (AR) grade and used as received, except BSA.

BALB/c mice, at weight of $20 \pm 2\text{g}$, were used for *in vivo* gel formation and degradation test. The animals were purchased from the Laboratory Animal Center of Sichuan University. The animals were housed at controlled temperature of $20\text{--}22^\circ\text{C}$, relative humidity of 50–60% and 12h light-dark cycles. Free access to food and water was allowed. All the animals would be in quarantine for a week before treatment. All animal care and experimental procedures were conducted according to Institutional Animal Care and Use guidelines.

2.2. Synthesis and Characterization of PECE Copolymer

PECE copolymer was synthesized as described in our previous work according to Figure 1. Briefly, PEG-PCL diblock copolymer was prepared by ring opening polymerization of ϵ -CL initiated by MPEG using stannous octoate as catalyst; PEG-PCL-PEG triblock copolymer was synthesized by coupling PEG-PCL diblock copolymer using HMDI as the coupling agent [18, 36]. The just-obtained PECE copolymer was first dissolved in AR grade dichloromethane, and reprecipitated from the filtrate using AR grade excess cold petroleum ether. Then the mixture was filtered and vacuum dried to constant weight at room temperature. The purified copolymer was kept in air-tight bags before further use.

The obtained PECE copolymer was characterized by FTIR (NICOLET 200SXV, Nicolet, USA), ^1H -NMR (Varian 400 spectrometer, Varian, USA), and GPC (Agilent 110 HPLC, USA).

2.3. Preparation of Composite Hydrogel

Preparation of composite hydrogels was described in Figure 2. Different amount of Pluronic F127 copolymer were dissolved in icy cold deionized water to a transparent solution, and PECE solution at different concentration were prepared by dissolution of PECE copolymer in deionized water at a designated temperature then cooled to 4°C. Subsequently, the two prepared solutions were mixed together under mild agitation to obtain a homogeneous liquid solution. The final solution contained a given concentration and composition of the two copolymers to form different composite hydrogel samples. The composite hydrogel prepared in this work were listed in Table 1.

Table 1. The composite hydrogel prepared in this work

Code	PECE: Pluronic F127 (w/w)	Phase Transition behavior	The concentration region with phase transition behavior (Wt%)
S1	100:0	Sol-gel-sol	15% to 35%
S2	70:30	Sol-gel-sol	25% to 35%
S3	50:50	Sol-gel-sol	20% to 35%
S4	30:70	Sol-gel-sol	20% to 35%
S5	0:100	Sol-gel-sol	15% to 35%

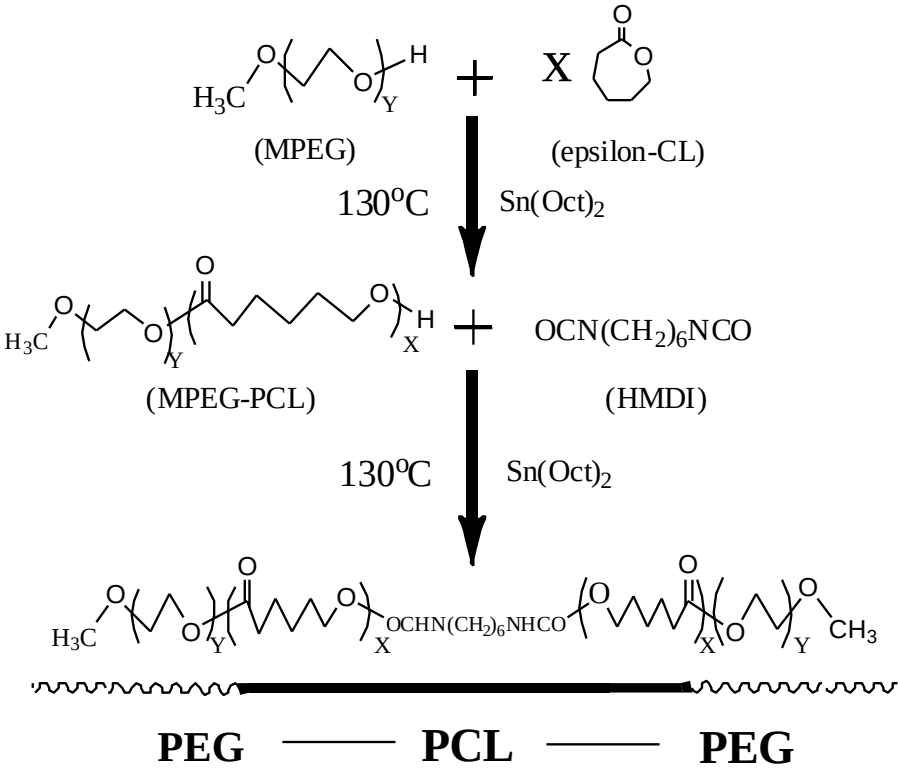


Figure 1. Synthesis scheme of PECE copolymer

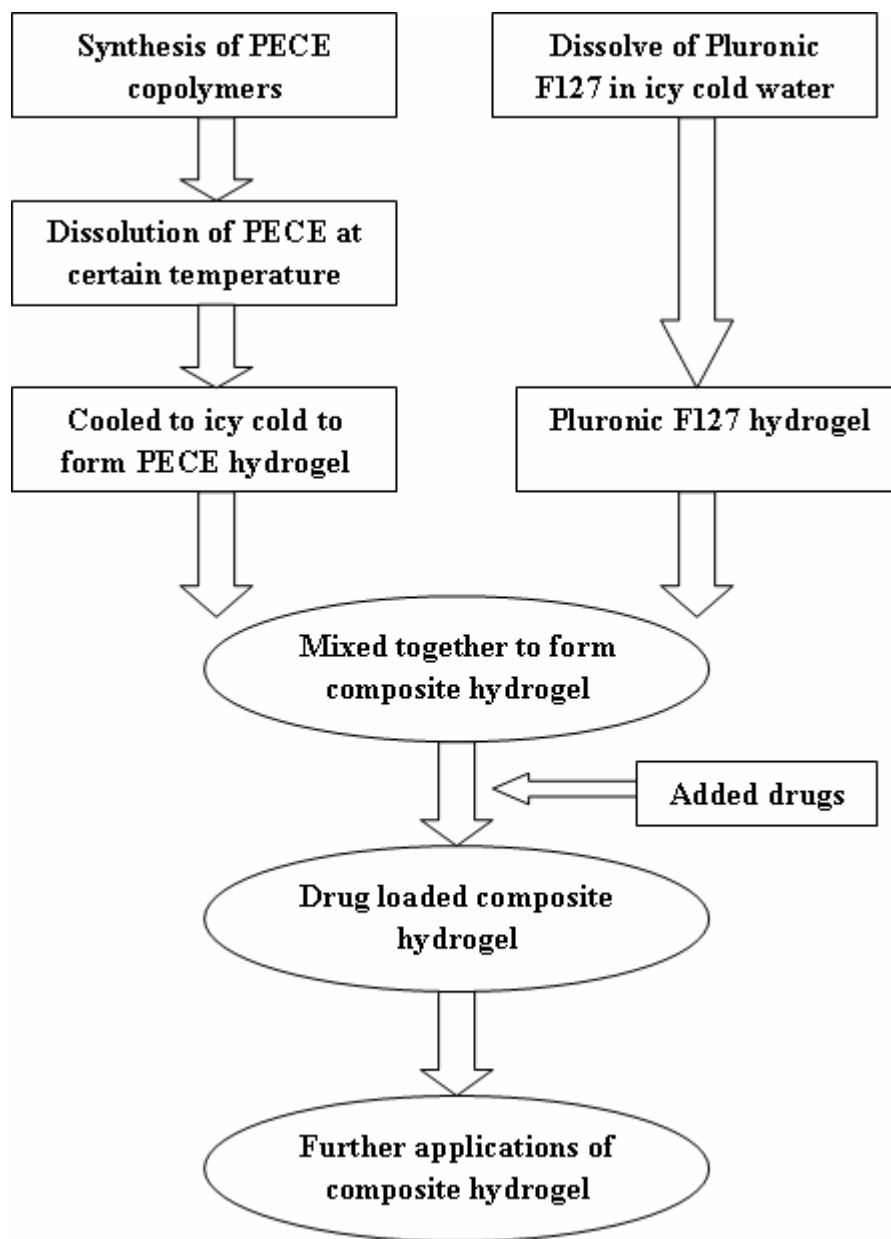


Figure 2. Preparation of composite hydrogel.

2.4. Sol-Gel-Sol Phase Transition Behavior Study

Sol-gel-sol phase transition diagrams of composite hydrogel were recorded using test tube-inverting method [18, 36]. The sol-gel-sol transition was visually observed by inverting the vials, and conditions of sol and gel were defined as “flow liquid sol” and “no flow solid gel” in one minute respectively.

In this study, the volume of the composite hydrogel solution was kept 0.5 mL in total regardless of the concentration. After incubated in water bath at 0°C for 20 minutes, the hydrous samples were slowly heated at a rate of 0.5°C/min, from 0°C to the temperature when precipitation occurred.

2.5. Scanning Electron Microscopy (SEM) of Composite Hydrogel

SEM was employed to investigate morphology of composite hydrogel. The composite hydrogels were frozen in liquid nitrogen and lyophilized for 72 h. The hydrogels were sputtered with gold before observation. In this study, morphology of prepared composite hydrogels was examined on JEOL SEM (JSM-5900LV, JEOL, Japan).

2.6. In vitro Drug Release Behavior

Freshly prepared VB₁₂ loaded composite hydrogel were used to assay *in vitro* release behavior of hydrophilic drugs. In detail, 200μl of prepared VB₁₂ loaded composite hydrogel containing 1mg VB₁₂ were placed into 4 mL EP tubes and allowed to gel in an incubator at 37°C for 12 h. Then, the gels were immersed in 1 mL of PBS (pH=7.4) and were shaken at 100rpm at 37°C. At specific time intervals, all of the release media were removed and replaced by fresh release media. After centrifugation at 13000rpm for 10min, the supernatant of the removed release media were collected and stored at -20°C until analysis. The collected supernatants were detected on UV spectrophotometer at 362 nm to determine the concentration of VB₁₂.

BSA was used as model protein drug to determine the release behavior of protein or peptide from protein loaded composite hydrogel *in vitro*. The detail procedure was similar to the study of VB₁₂ release, but the initial drug loading amount were 4mg. The amount of BSA present in the supernatant was determined by bicinchoninic acid (BCA) assay and BCATM Protein Assay Kit (PIERCE, USA) was used. The SDS-polyacrylamide gel electrophoretic (PAGE) analysis was used to assay the stability of BSA during the release period.

2.7. In vivo Gel Formation and Degradation Study

In vivo gel formation and degradation tests were performed in BALB/c mice (20±2g). The composite hydrogel (S1, S2, S3, S4 and S5) at concentration of 30wt% were prepared. Then, each animal was subcutaneously injected with 0.5 mL of composite hydrogel solutions by a syringe with a 25 gauge needle. At predetermined time (2h, 6h, 1d, 3d, 7d, 10d, and 14d), the animals were sacrificed by cervical dislocation. And then the injection site was carefully cut open and the *in situ* formed gel was taken photo.

2.8. Histopathologic Study

Tissue samples of injection site were obtained after taken photo at each time point (2h, 6h, 1d, 3d, 7d, 10d, and 14d), which described in section 2.7. Control group was only given

similar volume of normal saline at the same time and same way. All the tissue samples were preserved in 10% buffered formaldehyde and were subsequently embedded in paraffin. Then, paraffin sections were stained with haematoxylin-eosin (HE) for histopathologic examination. In order to investigate the inflammatory reaction and toxicity of composite hydrogel at injection site, the histopathological changes of tissue at injection site were observed on light microscope. At day 14, composite hydrogels would be physiologically metabolized and removed from injection site. Therefore, we save the picture at day 14 as an illustration.

3. RESULTS AND DISCUSSION

3.1. Synthesis and Characterization of PECE Copolymer

The synthesis of PECE triblock copolymer has been described in our previous work [18, 36]. Briefly, ring-opening copolymerization of ϵ -CL onto MPEG was performed to synthesize PEG-PCL diblock copolymer using stannous octoate as catalyst. PEG-PCL diblock copolymer was then coupled using HMDI as coupling agent to produce the biodegradable PEG-PCL-PEG triblock copolymer. FTIR, $^1\text{H-NMR}$ and GPC were used to characterize the chemical structure of PECE copolymer (data not shown). The results of FTIR, $^1\text{H-NMR}$ and GPC indicated that the PECE triblock copolymer designed by controlling the feed composition was synthesized successfully.

The number-average molecular weight (M_n) and the PEG/PCL block ratios of PECE triblock copolymer synthesized in this work were calculated from $^1\text{H-NMR}$ spectra. The M_n of PECE triblock copolymer was 3408 and the PEG/PCL block ratios was 960/2448, which was consistent with theoretical value calculated from feed ratio ($M_n=3300$, PEG/PCL=1100/2200). M_n and polydispersity (PDI, M_w/M_n) of PECE copolymer determined by GPC were 4391 and 1.30 respectively.

3.2. Temperature-Dependent Sol-Gel-Sol Transition Behavior

The composite hydrogel prepared in this work were composed of PECE and Pluronic F127 hydrogel, which individually presented sol-gel-sol transition. Due to combination of PECE hydrogel and Pluronic F127 hydrogel, the composite hydrogel also showed sol-gel-sol transition.

As presented in Table 1, composite hydrogel based on PECE and Pluronic F127 copolymers from S1 to S5 showed temperature-dependent reversible sol-gel-sol phase transition. The composite hydrogels flowed freely at lower temperature, but became gelation at body temperature about 37°C (Figure 3).

Figure 4 presented the sol-gel-sol phase transition diagram of prepared composite hydrogel. When the copolymer concentrations are above the critical gelation concentration (CGC), composite hydrogel changed from “sol” phase to “gel” phase with increase in temperature to the lower critical gelation temperature (LCGT). With further increase of temperature to upper critical gelation temperature (UCGT), the sol phase occurs.

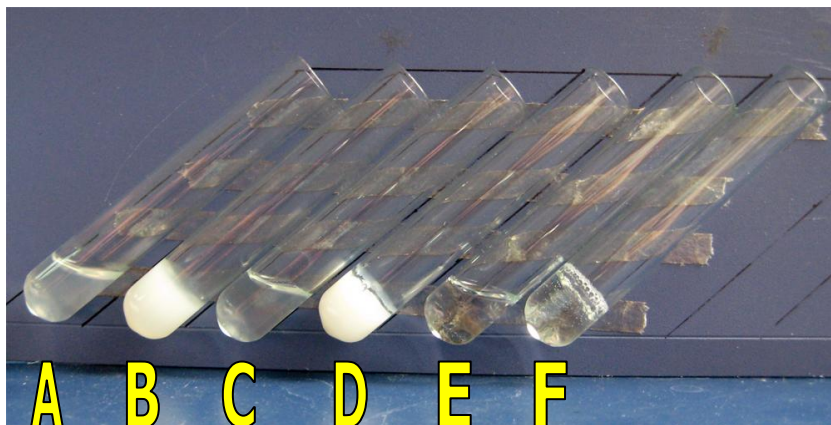


Figure 3. Photograph of composite hydrogel (30wt%). S1 at 10°C (A) and 37°C (B); S3 at 10°C (C) and 37°C (D); S5 at 10°C (E) and 37°C (F);

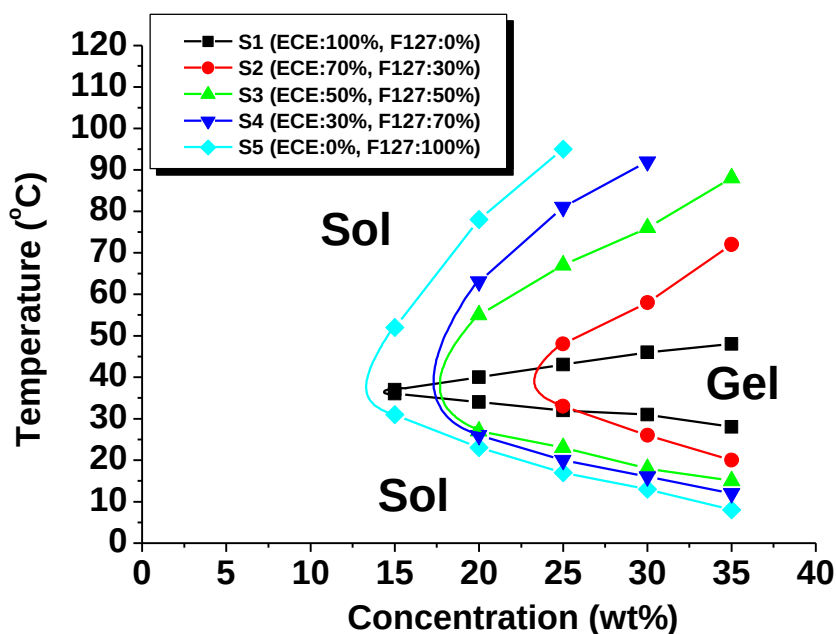


Figure 4. Sol-gel-sol transition phase diagram of composite hydrogel .

According to Figure 4, pure PECE hydrogel (S1) and pure Pluronic F127 hydrogel (S5) both have a CGC of approximately 15wt%, but S5 have a much wider gelation window than that of S1. The UCGT of S5 at the concentration of 30wt% and 35wt% was not detected in the temperature range of 0°C to 100°C.

The CGC of S2, S3, and S4 were 25wt%, 20wt%, and 20wt% respectively, which were much higher than that of two pure hydrogels. By mixing the two hydrogel together, the CGC of the composite hydrogel increased accordingly. CGC of S2 increased approximately 10wt% than that of S1, whereas CGC of S4 increased approximately 5wt% compared with that of S5. This phenomenon indicated that with regard to CGC the influence of Pluronic F127 hydrogel on PECE hydrogel was more dramatic than that of PECE hydrogel on Pluronic F127 hydrogel.

As shown in Figure 4, with increase in ECE hydrogel content in composite hydrogel, the UCGT decreased significantly, whereas the LCGT increased slightly. The UCGT of S5 hydrogel at concentration of 30wt% and 35wt% could not detected in the range of 0°C to 100°C, but the UCGT at concentration of 30wt% and 35wt% were detected in S4 and S3 hydrogel respectively due to the increase content of PECE hydrogel.

Therefore, it was obvious that sol-gel-sol transition behavior of composite hydrogel was depended on the composition of the PECE and Pluronic F127 hydrogel. In fact, by altering the composition of composite hydrogel, the temperature range of sol-gel-sol phase transition could be broadened to a certain extent, which might be very useful for their further application as injectable in situ gel-forming drug delivery system in different situation.

3.3. Morphology of Composite Hydrogel

Interior morphology of composite hydrogel was investigated by SEM. The composite hydrogels were frozen in liquid nitrogen and lyophilized for 72 h before the test. Figure 5-A, B and C showed the morphology of S1, S3 and S5 hydrogel respectively. All the hydrogel samples showed porous three-dimension structure, but the shape and mesh size of pores in the hydrogel were different. S1 showed approximately spherical pore with small mesh size, whereas S5 showed cylindrical-like shape with relatively larger mesh size compared to S1. S3 hydrogel, composed of 50% PECE hydrogel and 50% Pluronic F127 hydrogel, also showed spherical pore, but have a larger mesh size compared to pure PECE hydrogel (S1). The morphology of S3 hydrogel suggested that two compositions of S3 hydrogel both have great influence on S3 hydrogel interior structure.

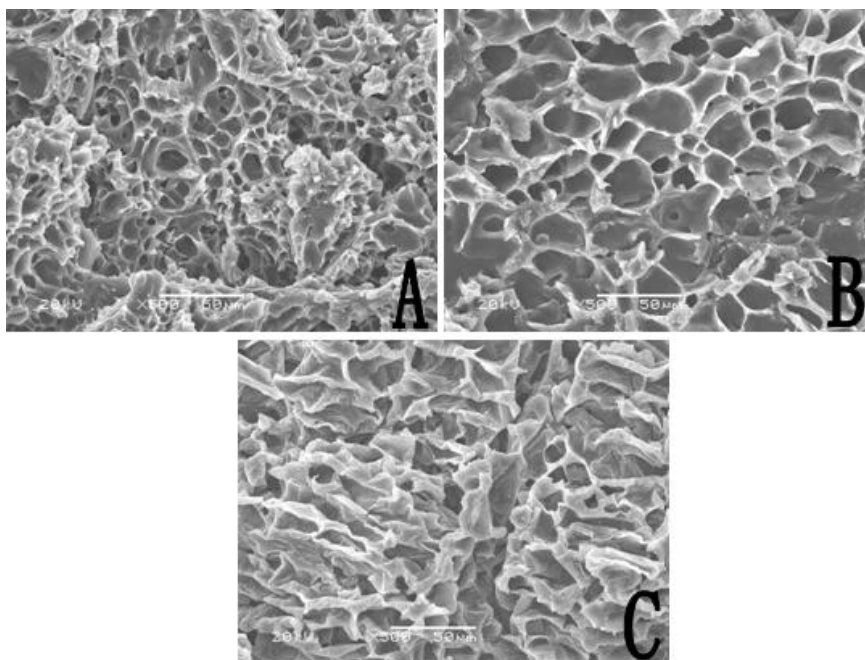


Figure 5. SEM photograph of composite hydrogel ($\times 500$). A: S1 hydrogel (30wt%); B: S3 hydrogel (30wt%); C: S5 hydrogel (30wt%)

3.4. In vitro Drug Release Profile of Composite Hydrogel

In vitro release profiles of VB₁₂ from VB₁₂ loaded composite hydrogel in PBS solution were investigated, and the results were shown in Figure 6. According to Figure 6, VB₁₂ could release from composite hydrogel in an extended period and the composition of composite hydrogel had great effect on VB₁₂ release profile. S5 hydrogel disappeared completely in PBS solution in 12h, whereas S1 and S3 hydrogel could maintain their integrity in the whole release period. VB₁₂ released faster and reached higher cumulative release rate (94.2%) from S5 hydrogel compared to S1 and S3 hydrogel. In S1 hydrogel, an initial burst release of 20.2% of loaded VB₁₂ occurred in the first one hour, followed by release of 82.9% in 7 days, whereas, in S3 hydrogel, the cumulative release rate of one hour and 7 days were 22.6% and 87.2% respectively.

In this study, BSA was used as a model drug to investigate *in vitro* release behavior of protein or peptide drugs from composite hydrogel, and the data were summarized in Figure 7. As presented in Figure 7-A, higher PECE hydrogel content in composite hydrogel resulted in slower release rate of BSA from composite hydrogel. The cumulative release rate of BSA from S1, S3, and S5 hydrogel were 32.7%, 46.1%, and 90.7% respectively. SDS-PAGE was performed to evaluate the stability of BSA in the *in vitro* release period. According to Figure 7-B, the major band for BSA appeared at about 67KD (lane2 to lane10) according to the protein marker, which means that BSA was stable in all the composite hydrogel and the whole release period.

Thus, composition of composite hydrogel substantially affected the drug release behavior of composite hydrogel, where higher Pluronic F127 content resulted in higher cumulative release rate and higher initial burst release rate. By altering the composition of PECE and Pluronic F127 copolymers in composite hydrogel, drug release rate could be varied and controlled.

3.5. In vivo Gel Formation and Degradation Behavior

The application of composite hydrogel as *in situ* gel-forming drug delivery system was tested by subcutaneous injection with 0.5 mL of hydrogel solution (from S1 hydrogel to S5 hydrogel, 30wt%) into BALB/c mice. In Figure 8, from A to E showed the photograph took at 1st day, 3rd day, 7th day, 10th day and 14th day after composite hydrogel injection respectively (From left to right: S4, S3, S2 and S1 hydrogel). F and G presented the photograph took at 2nd hour and 6th hour after S5 hydrogel injection.

The injectable sol state of composite hydrogel became gel in mice just in a few seconds and maintained its integrity *in vivo* in an extended period. The formed gel of S1 and S2 hydrogel were spherical shaped rather than spread to form sheet shaped. In the process of time after composite hydrogel injection, the *in vivo* formed gel decreased in size and finally disappeared due to the degradation. Hydrogels of S5, S4, S3, and S2 were disappeared *in vivo* at 6th hour, 7th day, 10th day, and 14th day after injection respectively. At 14th day after injection (Figure8-E), only a small mount of S1 hydrogel was found *in vivo*, which indicated that S1 hydrogel could sustain longer than 14days.

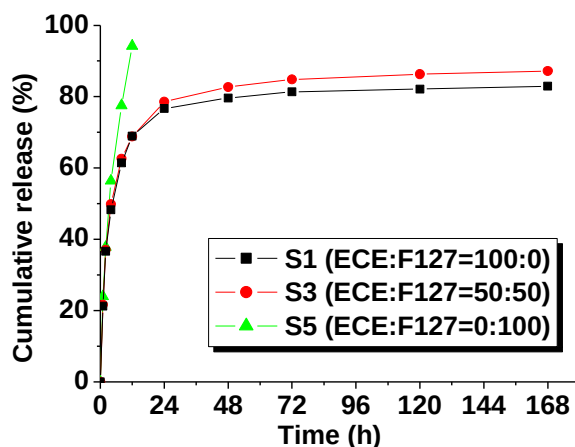


Figure 6. *In vitro* release behavior of VB₁₂ from composite hydrogel.

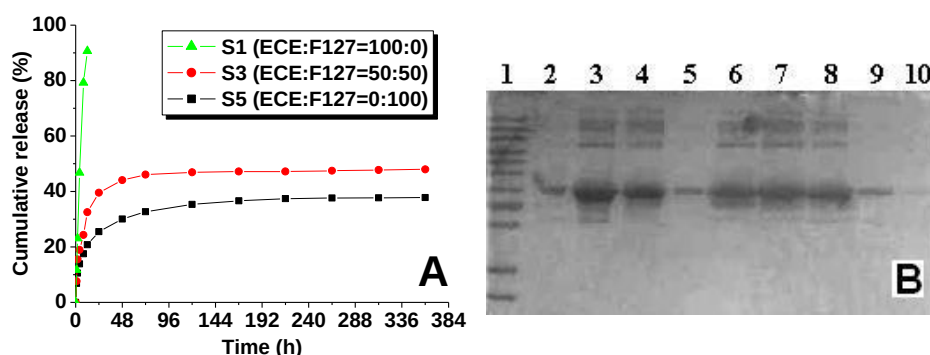


Figure 7. *In vitro* release behavior of BSA from composite hydrogel (A) and SDS-PAGE results of BSA *in vitro* release profile (B) (Lane 1: marker; Lane 2: BSA standard; Lane 3: S1 at 24th hour; Lane 4: S1 at 168th hour; Lane 5: S1 at 360th hour; Lane 6: S5 at 1st hour; Lane 7: S5 at 12th hour; Lane 8: S3 at 24th hour; Lane 9: S3 at 168th hour; Lane 10: S3 at 360th hour;).

According to Figure 8, we could find that the sustained time of the composite hydrogel *in vivo* could be controlled by altering the composition of above two hydrogel, which might be very useful for its potential application in injectable *in situ* gel-forming drug delivery system.

3.6. Histopathological Study

All samples were histopathological observed by light microscope, and no significant histopathological changes were observed due to composite hydrogels (Figure 9). As shown in Figure 9, the morphology of the composite hydrogel-treated tissue (Figure 9-B, C) did not show significant difference when compared with control group (Figure 9-A).

Histopathological study of tissue at injection site showed no significant inflammatory reaction and histopathological changes, which mean the composite hydrogel were non-toxicity and might serve as a safe candidate as *in situ* gel-forming drug delivery system.

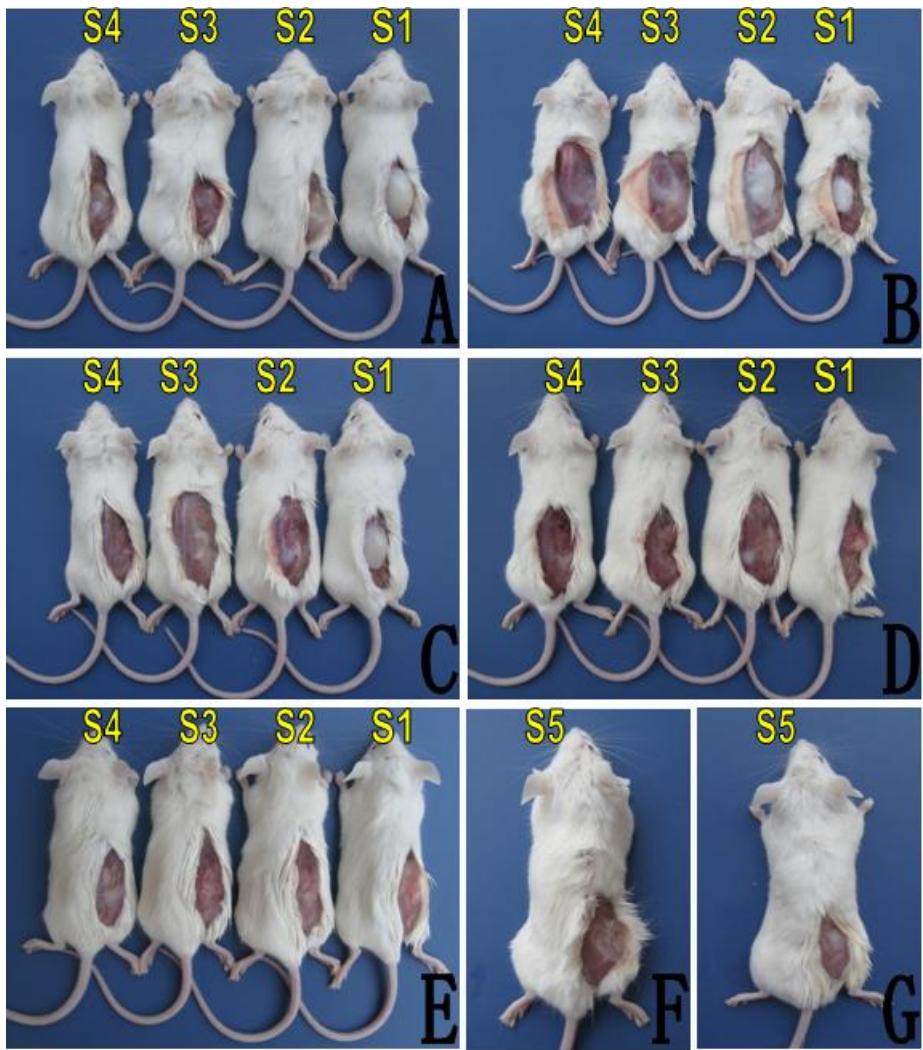


Figure 8. *In situ* gel formation and degradation behavior of composite hydrogels. From A to E showed the photograph took at 1d, 3d, 7d, 10d and 14d after injection respectively (From left to right: S4, S3, S2 and S1). F and G presented the photograph took at 2h and 6h after Pluronic F127 hydrogel injection.

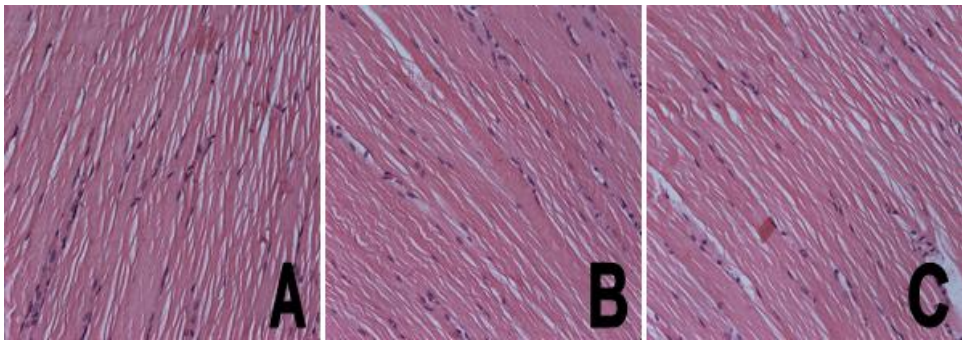


Figure 9. Photograph of tissue samples from injection site after composite hydrogel injection for 14d (×400). A: Control group; B: S3 hydrogel injection group; C: S1 hydrogel injection group.

4. CONCLUSION

A series of novel biodegradable and injectable thermosensitive composite hydrogel were successfully prepared. The obtained composite hydrogel underwent sol-gel-sol transition as temperature increased, which was a flowing sol at ambient temperature and became a non-flowing gel at physiological temperature, and the sol-gel-sol phase transition behavior of the copolymers aqueous solutions was determined using the test tube inverting method. By varying the composition of PECE and Pluronic F127 copolymers, the *in vivo* degradation rate and *in vitro* drug release profile of composite hydrogel could be controlled, which was very useful for its potential applications as an *in situ* gel-forming controlled drug delivery system. Histopathological study suggested the composite hydrogel is a safe candidate for its application in biomedicine fields.

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Chapter 3

NITROGEN-CONTAINING LIGANDS ANCHORED ONTO POLYMERS AS CATALYST STABILIZER FOR CATALYTIC ENANTIOSELECTIVE REACTIONS

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ABSTRACT

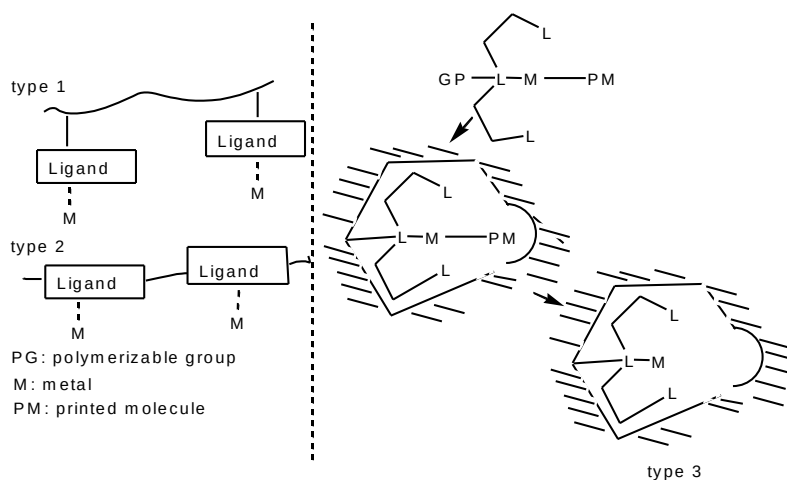
This paper reviews the recent progress made in insoluble polymer supported amino alcohols, amino thiols, oxazolines, salens, sulphonamides, oxazaborolidines and diamines ligands. This paper deals also with various approaches of stabilization of the catalytic system by immobilization of the chiral catalyst onto the polymer by the way of immobilization of the chiral ligand. Different types of ligand immobilization are presented: pendant ligands anchored on a polymer prepared by a polymer reaction, ligands on the backbone prepared by copolymerization and molecular imprinting technique. Examples of their use, performance and recyclability in a variety of enantioselective reactions such as alkylation and reductions of C=O bonds (hydrogenation, hydrogen transfer reduction) reduction of C=N bonds, C-O bond formations (epoxidation, dihydroxylation), C-C bond formations (Diels Alder, cyclopropanation, aldolisation, allylic substitution) and oxidation ... are presented.

1. INTRODUCTION

The need to develop effective methods for enantioselective synthesis is becoming ever more important as only a single enantiomer of a racemic bioactive compound is generally required for pharmaceuticals [1], agrochemicals [1,2], flavour [1,3] or fragrance [1,3]. Homogeneous asymmetric catalysis has been used to perform a variety of transformations

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under mild conditions with high enantioselectivity. As these fine and specialty chemicals are manufactured to meet high and well defined standards of purity compatible with the desired performance, chemical industry had to adopt efficient and clean technology [4]. From an industrial point of view, homogeneous methods remain impractical, particularly due to the high cost of the chiral metal catalysts (range of the chiral catalyst loadings from 1 to 10% and in some cases up to 30%) and the difficulty of their recovery and reuse. Thus, from an economic, environmental and technical point of view, homogeneous supported catalysis is preferable to homogeneous catalysis because of the handling, separation and recycling abilities [5]. Many approaches have been employed to immobilize the homogeneous catalyst. [6]. In the classical immobilization with organic polymer, the chiral ligand units are anchored onto polymers (type 1, Scheme 1). The incorporation of chiral ligands on the main chain of the polymers is another approach (type 2, Scheme 1) and is done by copolymerization of the chiral ligand with a linker. The last but less known approach consists in the use of an imprinted polymer (type 3, Scheme 1), an extensively used methodology to form artificial antibodies. The imprinted polymer is based on a copolymerization and a crosslinking of a polymer around a molecule used as a printed molecule (PM). This latter included into the polymer by means of an interaction with functional groups is then removed, thus leaving its imprint in the polymeric matrix. If a chiral PM is used, the formed chiral cavity is able to act as a center of molecular recognition [7].



Scheme 1.

The aim of this review is to discuss the contribution of soluble polymer-supported ligands and insoluble polymer-supported ligands to asymmetric catalysis in the field of reduction of C=O bonds, cyclopropanation, Diels-Alder, alkylation, allylation, dihydroxylations, epoxidation reactions, kinetic resolution of terminal epoxide by means of nitrogen containing ligands complexed with metal as asymmetric catalyst.

Each type of asymmetric homogeneous supported catalyst will be examined successively from the perspective of using phosphine-free nitrogen-containing ligands complexed with a metal.

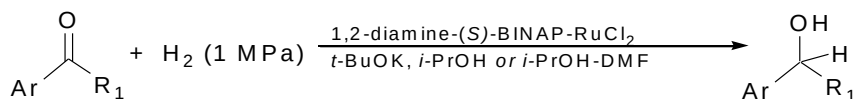
Results were analyzed in comparison to the results in the literature for similar systems.

2. REDUCTION OF C=O BOND

The three major catalytic reduction procedures which have emerged are enantioselective hydride reduction, hydrogenation and hydrogenation transfer reduction (HTR) close to the hydrosilylation which represent only few examples in asymmetric polymer-supported catalyst.

2.1. Hydrogenation

In homogeneous catalysis, various phosphines have been developed for asymmetric hydrogenation [8]. However, for hydrogenation of unfunctionalized ketone, a remarkably high reactivity emerges when the Ru compounds are further complexed with a 1,2 diamine ligand. Thus, the precatalyst $\text{RuCl}_2(\text{phosphine})_2(1,2\text{-diamine})$ combined with an inorganic base in isopropanol is considered as one of the most powerful systems for the hydrogenation of ketones (Scheme 2, *i*-PrOH as solvent) [9, 10].

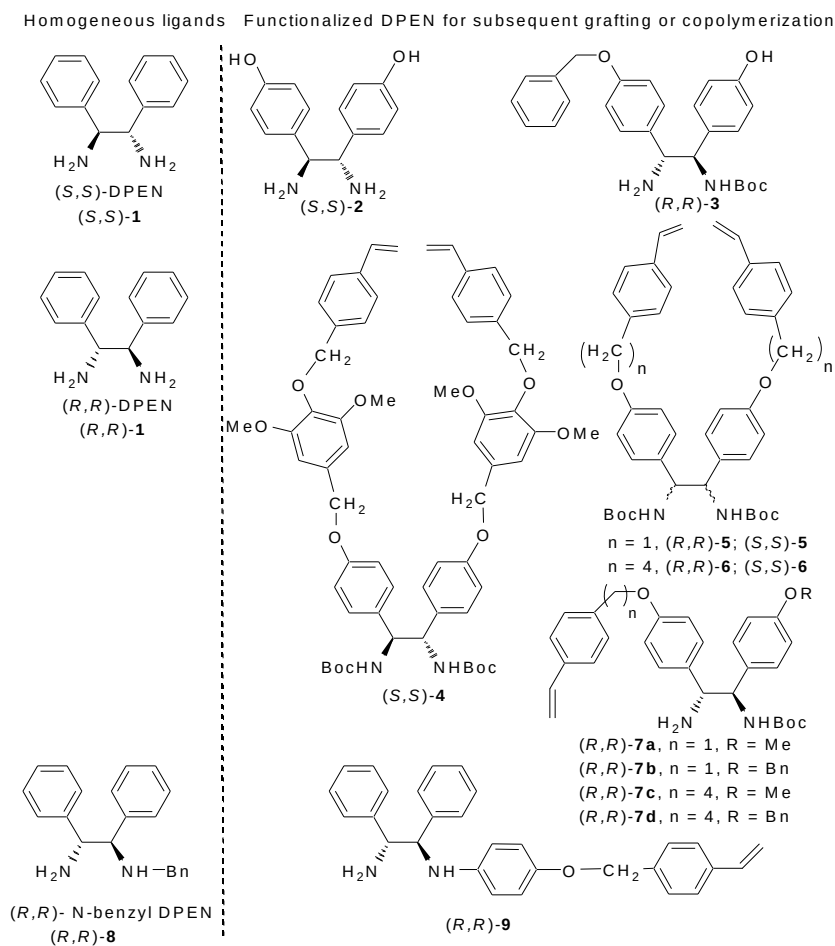


Scheme 2.

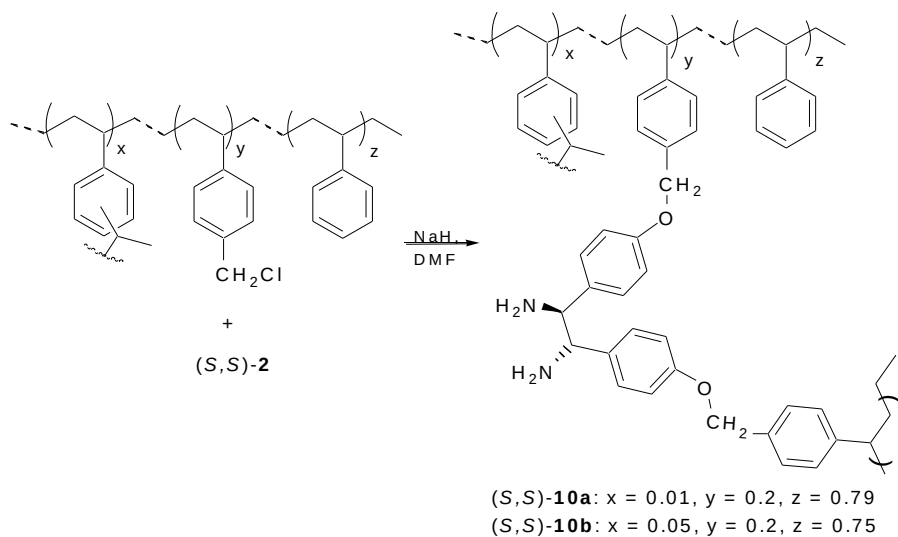
Close to polymer bound-BINAP/diamine ruthenium precatalyst [11], complexes of BINAP or their derivatives in the presence of polymer bound diamine have been employed. These catalytic systems have been mainly studied by Itsuno with immobilized diphenylethylenediamine (DPEN). As the use of *N*-substituted 1,2-diamine ligands decreased the catalytic activity of hydrogenation of simple ketones contrary to free diamine ligands, they have been less employed. However, *N*-substituted 1,2-diamine ligands are rather effective in the hydrogenation of α -substituted ketone, such as α -amido ketones. Thus, two types of immobilized DPEN have been performed. Functionalized DPEN for subsequent grafting onto polymer or copolymerization are presented (Scheme 3).

If free primary amines were maintained, grafting was realized by the modification of phenyl groups into phenolic ones [12, 13] and copolymerization by using a phenolic ether group containing a vinylphenyl functionality as monomer. ((*S,S*)-2, (*R,R*)-3 and (*S,S*)-4, -5, -6; (*R,R*)-5, -6, -7, -9 respectively (Scheme 3) [13, 14, 15].

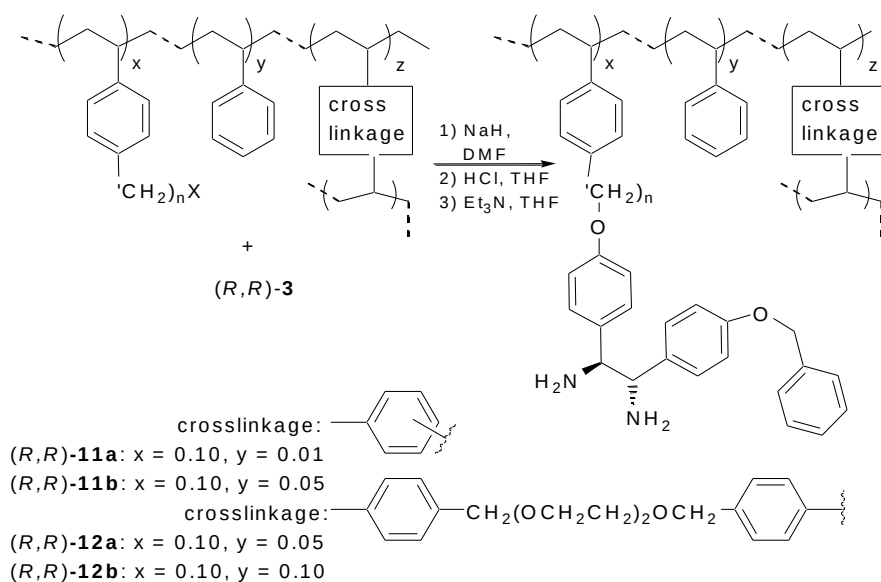
The first type of polymers was formed by reaction of the phenoxide derived from DPEN with 1% crosslinked chloromethylated polystyrene (Schemes 4 and 5). It has been observed that in the cases of higher content of chloromethyl group or a higher degree of crosslinking, some unreacted chloromethyl groups remain.



Scheme 3.



Scheme 4.



Scheme 5.

To perform the catalytic homogeneous-supported hydrogenation of acetophenone with precatalyst ((*S,S*)-10a, (*S,S*)-10b, (*R,R*)-11a, (*R,R*)-11b, (*R,R*)-12a or (*R,R*)-12b)-(*R*)-BINAP- RuCl_2 , it has been shown that the suitable solvent is a mixture of *i*-PrOH/DMF/ (1/1, v/v). If *i*-PrOH is employed alone, hydrogenation does not take place due to little swelling of the polymer catalyst (Scheme 2, Ar = Ph). Moreover, a lower degree of crosslinking gave better reactivity; higher ees and conversion are obtained (Table 1).

Table 1. Enantioselective hydrogenation of acetophenone with diamine polymer-supported-BINAP- RuCl_2

Ligand-BINAP- RuCl_2	Yield (%)	Ee (%)	Ref.
10a ^a	100%	73%	[12]
10b ^a	39%	68%	[12]
11a ^b	91%	70%	[13]
11b ^b	46%	67%	[13]
12a ^b	>99%	23%	[13]
12b ^b	70%	65%	[13]

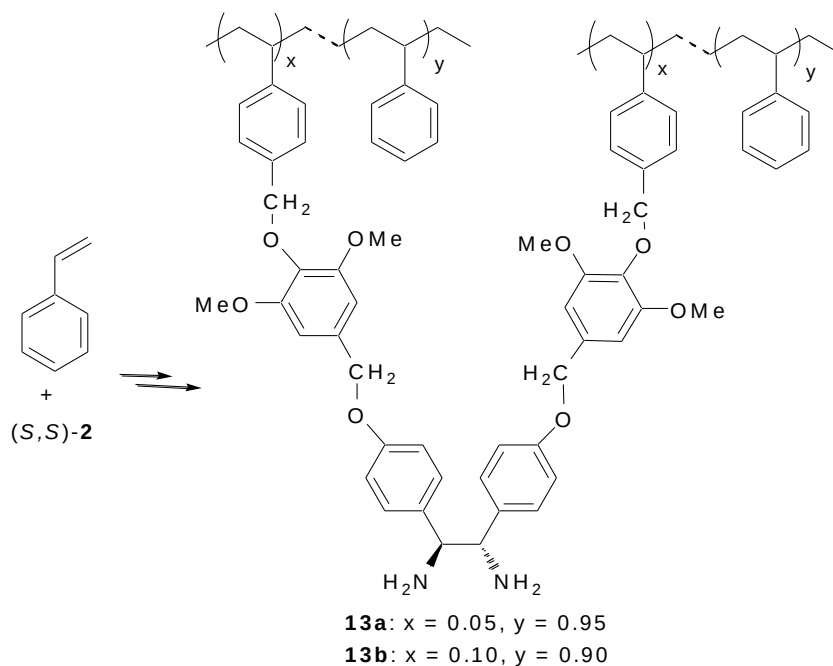
^aDiamine/BINAP/ RuCl_2 /ketone/*t*-BuOK : 1/1/1/200/20

^bDiamine/BINAP/ RuCl_2 /ketone/*t*-BuOK : 2/1/1/1000/20

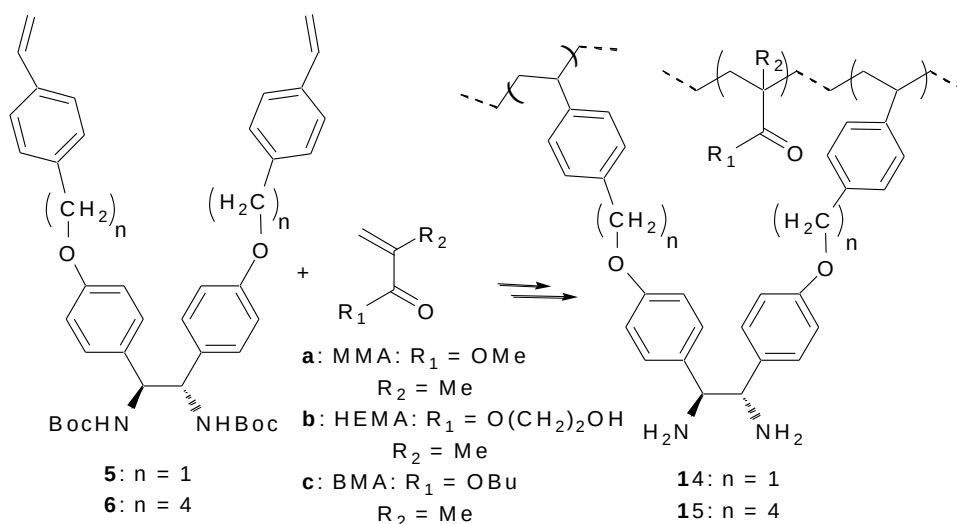
The best results are observed if xylBINAP is used instead of BINAP (ie 93% ee, 100% yield in the presence of 10a). The immobilized (*S,S*)-10a-(*R*)-BINAP- RuCl_2 can be reused at least four times without loss of activity and selectivity (from the first to the fourth reuse ee is about 73-74% with 100% yield) [12].

Enantioselectivities obtained with cocatalyst DPEN modified by a vinylphenyl group copolymerized under radical conditions (polymers 13 [14] and 14, 15 (Schemes 6 and 7) [15] and 16 (Scheme 8) [13] also exhibited almost the same level as those obtained from the low-

molecular-weight counterpart in solution system (73-80% and 80% ee respectively with conversions always >99% for polymer containing less than 5% DVB).

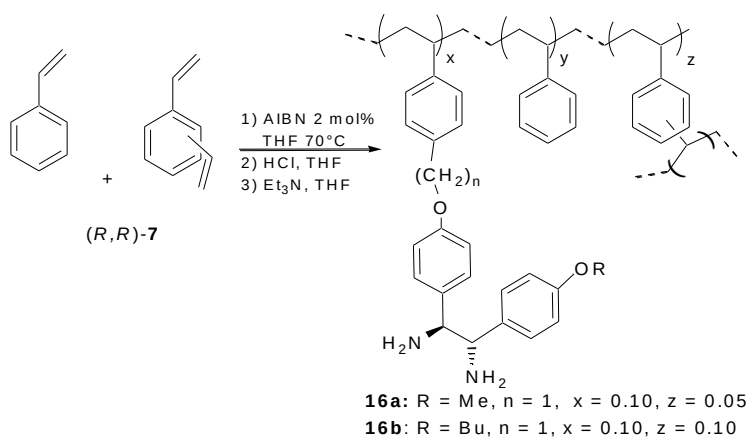


Scheme 6.



Scheme 7.

Catalytic systems derived from 13 and 14, 15 and 16a have successfully been recycled from four (for 13 [14]), 14 [15] and 15 [15]) to sixteen times (for 16a [13]) without any change of activity and selectivity. They were also tested with other aromatic ketones and high yields and enantioselectivities were observed (some examples are presented in Table 2).



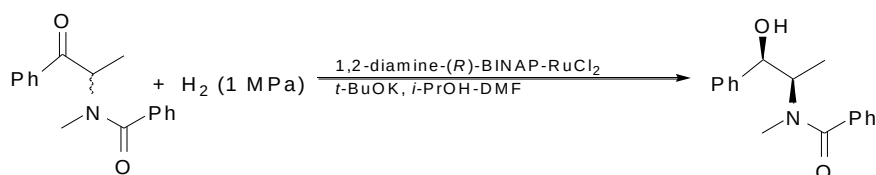
Scheme 8.

Table 2. Hydrogenation of several ketones with polymeric diamine/BINAP/RuCl₂ catalyst

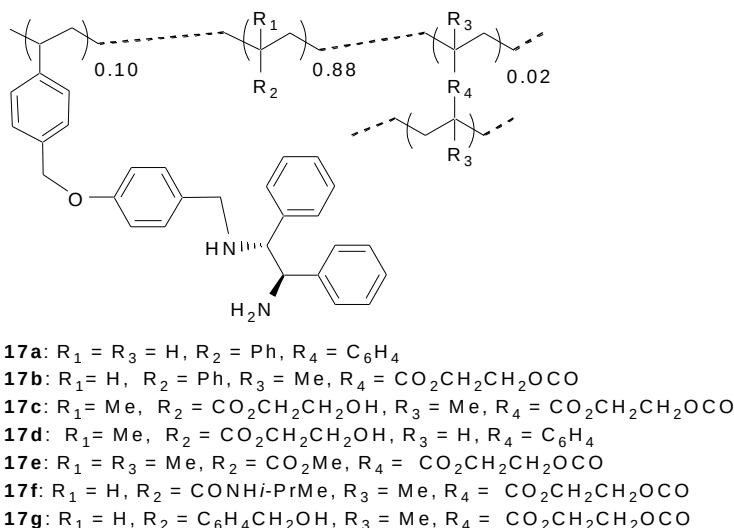
Ketone	Diamine	Time (h)	Conv. (%)	Ee (%) (config.)	Ref.
acetophenone	13a ^a or 13b ^a	18	100	77 (<i>R</i>)	[14]
	14a ^b	5	>99	78 (<i>R</i>)	[15]
	15c ^b	5	>99	79 (<i>R</i>)	[15]
propiophenone	13a ^a	4	100	82 (<i>R</i>)	[14]
	14a ^b	12	>99	84 (<i>R</i>)	[15]
	15c ^b	12	>99	83 (<i>R</i>)	[15]
	16a	24	99	82	[13]
1'-acetonaphthone	13a ^a	18	100	96 (<i>R</i>)	[14]
	14a ^b	12	>99	96 (<i>R</i>)	[15]
	15c ^b	12	>99	96 (<i>R</i>)	[15]
	16a ^c	24	>99	97	[13]

^aDiamine/BINAP/RuCl₂/ketone/*t*-BuOK : 2/1/1/1000/20^bDiamine/BINAP/RuCl₂/ketone/*t*-BuOK : 2/1/1/200/20^cDiamine/BINAP/RuCl₂/ketone/*t*-BuOK : 1/1/1/200/20

For the hydrogenation of the racemic α -(*N*-benzoyl-*N*-methylamino)propiophenone, (Scheme 9) polymers containing *N*-substituted DPEN were prepared by radical copolymerization of (*R,R*)-9 (Scheme 3) with various crosslinking agents (Scheme 10) [16].



Scheme 9.

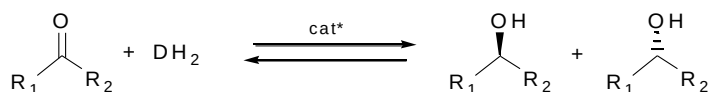


Scheme 10.

For the catalytic reduction, the solvent of choice was the mixture 1/1 (v/v) of *i*-PrOH/DMF (conditions for good swelling of the polymeric ligands 17). The polarity of the crosslinking agent has a direct influence on the results of the catalysis. The precatalyst obtained with 17a produced a low conversion (7%) and an excellent diastereoselection (>99%) for an enantiomeric excess of 61%. A slight improvement was observed for 17b formed with EGDMA a polar crosslinker (conversion: 10%, ee: 88%). Compared to them 17e present a better conversion (89%) with >99% of de and ee. The precatalysts prepared from 17c, 17d, 17f, 17g from better hydrophilic polymer support have exhibited excellent catalytic performance for this dynamic kinetic resolution of racemic α -amide ketone via hydrogenation to yield the corresponding *syn* β -amide alcohol (100% conversion, de >99% and ee ranging from 90 to >99%). In addition, the polymer-supported catalyst could be reused several times without loss of catalytic activity.

2.2. Hydrogenation Transfer Reduction

Hydrogenation transfer reduction (HTR) is defined as a reduction of mainly C=O and C=N bonds employing an hydrogen donor (DH₂) such as cyclohexene, cyclohexadiene, alcohols, formic acid or hydrazine, in the presence of a catalyst, avoiding all the risks inherent to molecular hydrogen (Scheme 11). For this reason and for a procedural simplicity, HTR can be regarded as an alternative for the asymmetric hydrogenation [17]. For HTR, the first heterogeneous catalytic systems were formed with homogeneous-supported phosphines, which were also oxygen sensitive contrary to amine ligands. Moreover, nitrogen-containing ligands could be easily polymerized.

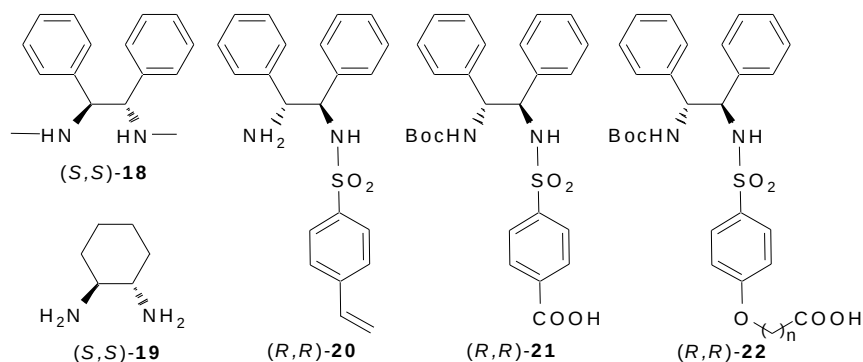


Scheme 11.

2.2.1. 1,2-diamine and derivatives

As for hydrogenation, most of the chiral ligands involved in heterogeneous HTR have been prepared starting from functionalized DPEN (Scheme 12).

In 1993, Lemaire found that *N,N*-dimethyl-1,2-diphenylethylenediamine (18) complexed with Rh could be employed as ligand for asymmetric HTR, leading to 67% ee and 100% for the reduction of acetophenone and methyl phenyl glyoxylate respectively [18]. Due to the presence of the amino groups, this C_2 diamine could be easily transformed into diurea and dithiourea derivatives.

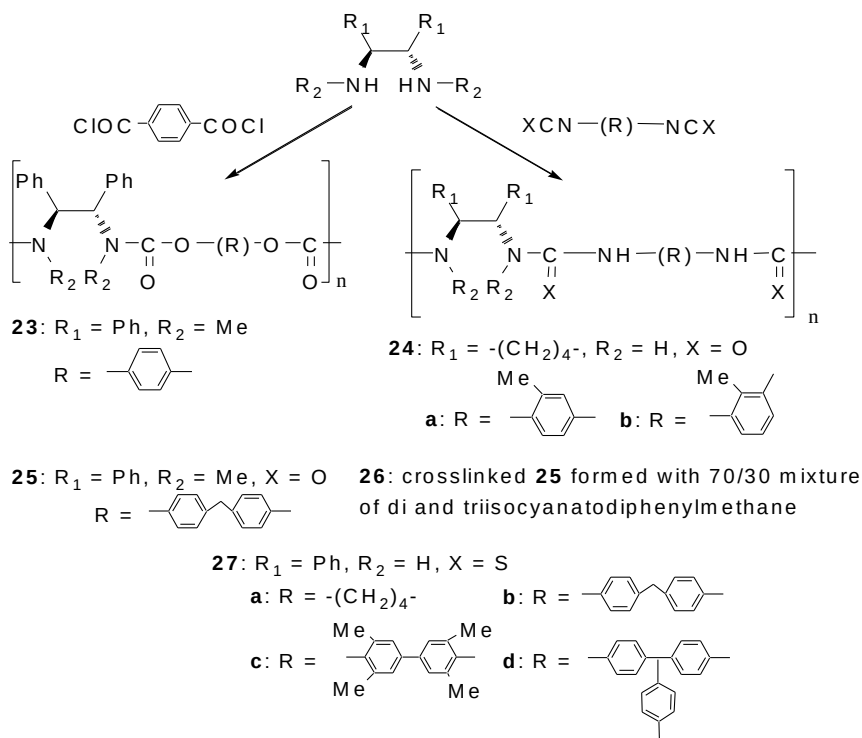


Scheme 12.

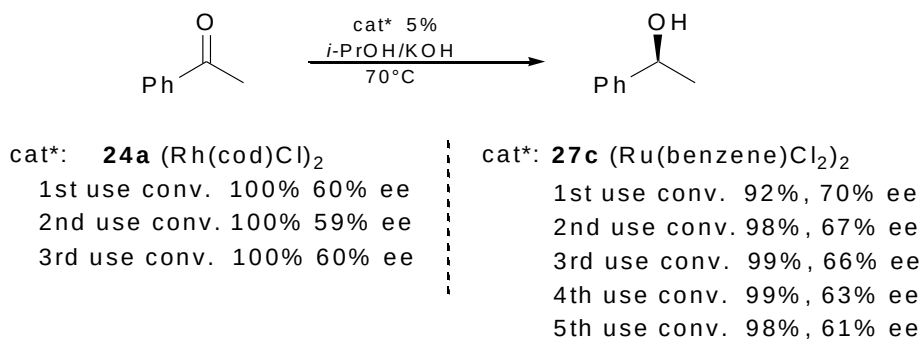
As good results for the asymmetric HTR of acetophenone were obtained (conversion 100% and 91% ee) with diurea [19], not only copolymerization of diamine 18 has been performed but 1,2-cyclohexyldiamine 19 was also used. Thus pseudo- C_2 polyamide 23, polyureas 24, 24 and 26 or polythioureas 27 were prepared by polycondensation with diacid chloride, diisocyanate [20] or dithioisocyanate respectively (Scheme 12) [21]. With rhodium complexes the conversions varied from 22% to 100% and ee from 0% to 60% for HTR with acetophenone at 70°C, in the presence of $[Rh(cod)Cl]_2$ with diamine polymer unit (23-26)/Rh ratio of 10, 2-propanol and KOH. Polyamide 23 proved to be useless (only 22% conversion and 28% ee) contrary to polyurea 25 which presents similar ee to those observed with diamine 18 when $(Rh(cod)Cl)_2$ was employed as the catalytic precursor for HTR (ie 100% conversion for both of them and 55% and 59% ee respectively). Polyureas 24a, 24b, 25 and crosslinked 26 led to better conversions, 80, 50, 97 and 100% with respectively 0, 13, 39 and 60% ee. Moreover, the chiral crosslinked polyurea 26 presented a slight increase in enantioselectivity over the monomer analog 18 (55% ee and 94% conversion under similar conditions) and the reaction rate appeared to be even higher than in the homogeneous phase. Catalytic system from 25 showed a capacity to recycle (Scheme 13) [20].

For thioureas, it has already been shown that under homogeneous conditions, they are better ligands than ureas, when using ruthenium complexes as precursors [22].

Thus, polythioureas were good candidates for the HTR reaction [21]. For polythioureas 27, studies of the DP were performed and it had been showed that DP depends on the ratio of the reagents. During the polymerization, a guanidine moiety could be formed, stopping the chain growing. To avoid its formation, dithioisocyanate must be used in excess.



Scheme 13.



Scheme 14.

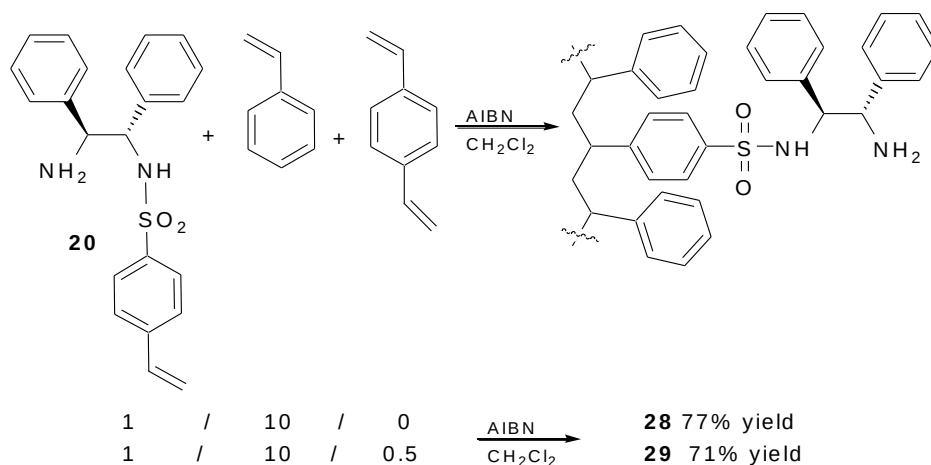
The HTR of various ketones was then performed in isopropanol with a substrate/ligand/*t*-BuOK/Ru ratio of 20/1.5/4/1. The chiral induction depended on the flexibility of the linker. The more flexible the linker, the less enantioselective the reaction: 31%, 70%, 70% and 65% ee for respectively **27a**, **27b**, **27c**, **27d** ruthenium complexes with conversion up to 90% for **27a**, **27b**, **27c** and only 47% for **27d**. For this latter ligand which was fully crosslinked, the decrease in conversion was due to the low accessibility of the catalytic site although a ligand/metal ratio of 8 had to be used.

The recovery and reusing of the **27c** polymeric catalyst has been performed with practically no loss of either catalytic activity or enantioselectivity (Scheme 14). These results could be

explained by the rigidity of the active site which is crucial for the selectivity and the stability of the catalytic system. Compared to the polyureas most of the polythioureas tested were more efficient.

Modification of 1,2-diphenylethylenediamine into *N-p*-toluenesulfonyl-1,2-diphenylethylenediamine (TsDPEN) led to one of the most selective ligand for the homogeneous HTR of ketones (97% ee for acetophenone) [23].

The heterogeneization of this ligand was first carried out with *N*-(vinylbenzene-*p*-sulfonyl)-1,2-diphenylethylenediamine (20), styrene and divinylbenzene as crosslinker (Scheme 15).



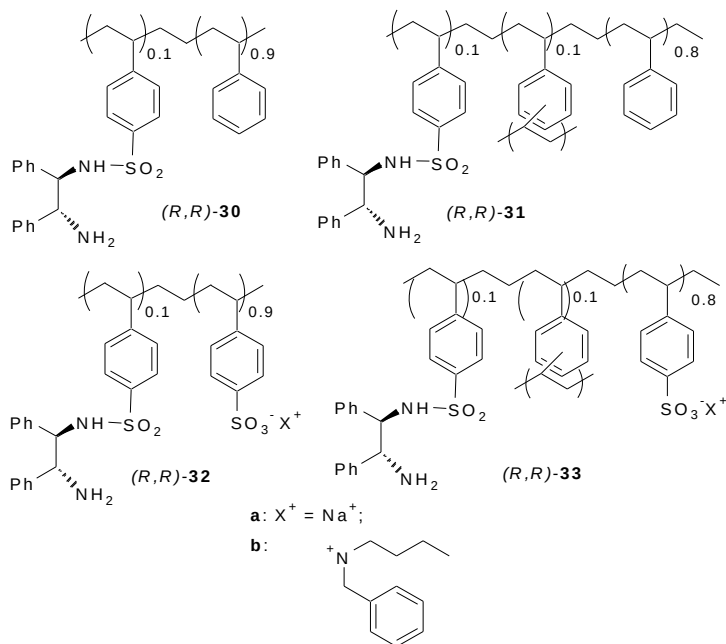
Scheme 15.

When tested as ligands for the Ir^{I} and Ru^{II} catalyzed HTR [24] of acetophenone, in presence of 2.5% of metal precursor and 2-propanol/base, at 70°C, Ir complexes led to higher ee (28: 92% and for the crosslinked 29: 94%) compared to the homogeneous analog for which only 75% of conversion and 89% ee were obtained. Nevertheless, the Ir catalyst was more efficient than ruthenium (Ir: 92% ee, Ru: 64% ee crosslinked Ir: 94% ee, crosslinked Ru: 84% ee), but for Ru the conversions were of about 20% in both cases. On the other hand the homogeneous Ir complex analog led to only 75% conversion at 89% ee. This difference could be explained by the formation of chiral microenvironments upon polymerization and stabilization of the reactive Ir complex.

Attempts to reuse the catalysts showed that the one containing Ru which is less selective is more stable upon reuse than the Ir derivative.

Itsuno [25] has also shown that polymer-supported DPEN monosulfonamides containing sulfonated pendent group (Scheme 16) are able to catalyze the HTR reduction of ketones in water with sodium formate as hydrogen donor (S/C = 100). However, TsDPEN immobilized on polystyrene crosslinked or not, polymer 30 and 31 respectively, shrank in water. Sodium *p*-styrene sulfonate was copolymerized with chiral *N*-(vinylbenzene-*p*-sulfonyl)-DPEN (20) under radical polymerization conditions with or without DVB leading respectively to ligand 32 and 33. Control of the balance hydrophilicity/hydrophobicity of the polymer support is carried out by changing the salt from Na^+ to quaternary ammonium. All of these polymers swelled in water, and their respective ruthenium, rhodium or iridium complexes were prepared. Compared to sodium salt polymer-supported catalyst from 32a and 33a, ammonium

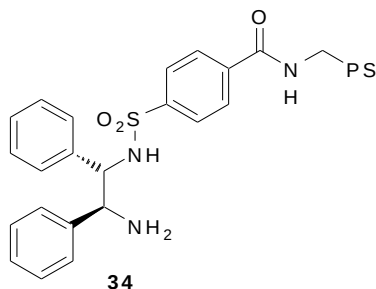
supported catalyst from 32b and 33b have produced the best results in terms of activity and selectivity for the reaction in aqueous media. Moreover, almost the same activity was observed for the reduction of acetophenone with the ammonium non crosslinked catalyst 32b prepared from $[\text{RhCl}_2\text{Cp}]_2$ and $[\text{RuCl}_2(p\text{-cymene})]_2$ (100% and 99% conversion; 98% and 98% ee respectively) while the catalyst from $[\text{IrCl}_2\text{Cp}]_2$ decreased both reactivity and enantioselectivity (77% conversion, 89% ee).



Scheme 16.

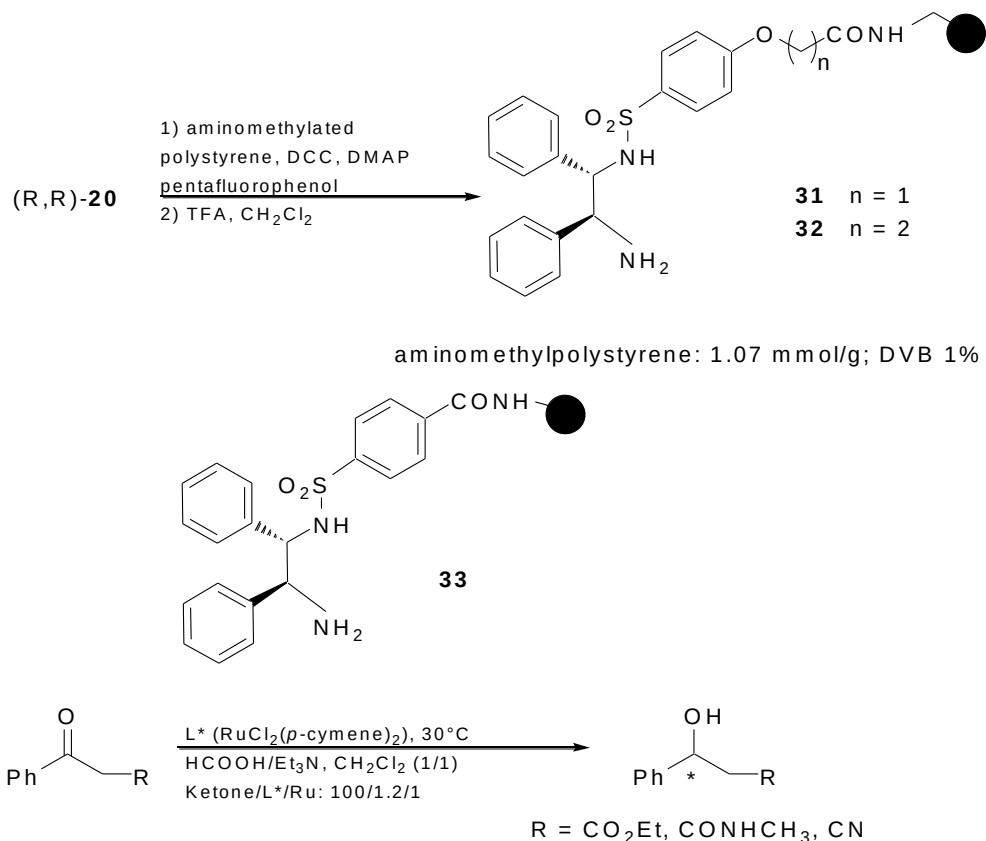
Enantioselectivities of 97-98% were obtained in five recycle runs by using (R,R)-33b derived catalyst.

Earlier, Bayston [26] has synthesized the polymer 34 (Scheme 17) starting from the aminostyrene Merrifield-type polymer. By means of ruthenium precursor, 88% conversion with 91% ee was obtained for reduction of acetophenone. Compared with the preceding ligand 29 complexed with ruthenium, better conversion and enantioselectivities are shown; these latter results were comparable with the Ir catalyst.



Scheme 17.

A similar heterogeneization of TsDPEN was made by Wang [27] with *N*-(carboxy, carbomethoxy or carboethoxy) benzene -*p*-sulfonyl)-1,2-diphenylethylenediamine (21 and 22 scheme 12). The acid function permitted the immobilization of the ligand to an aminomethylated polystyrene via an amide function (Scheme 18).

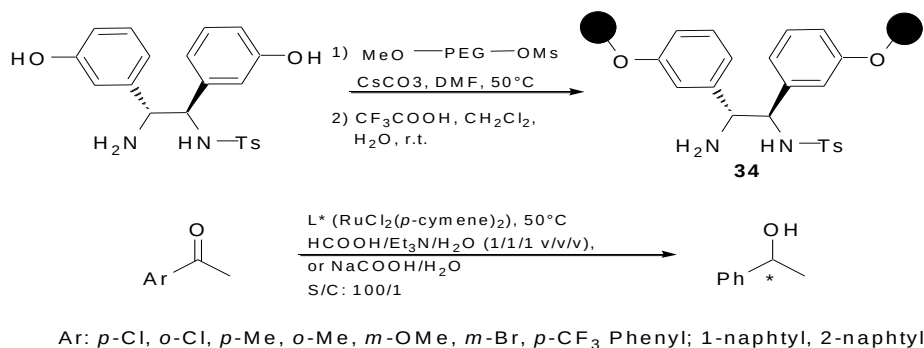


Scheme 18.

Ruthenium complexes of 31, 32 and 33 using the azeotrope triethylamine/formic acid as hydrogen donor permitted the reduction of β -keto ester, amide and nitrile with high conversion (> 95%) and ee (> 90%) (Scheme 18). The electronic character and the spacer length between the polystyrene part and the benzene ring had very little effect on the reduction outcome, for a same substrate conversion and ee are similar. Here also, it has been shown that the catalyst formed with ligand 32 could be reused at least three times without loss of activity and enantioselectivity.

Xiao proposed a poly(ethylene glycol)-supported ligand (34) in order to perform the HTR of aromatic ketones in water, using as hydrogen donor, the azeotrope triethylamine/formic acid [28] or sodium formate/water (Scheme 19) [29]. These ligands were formed by immobilization of TsDPEN by functionalization of the phenyl group by a hydroxy group in the *meta* position followed by a nucleophilic reaction with a monomethylether mesylate PEG (Mn 2000) (Scheme 19). The Ru-catalyst formed was soluble under the conditions of the reaction. It could be isolated from the reaction mixture by precipitation, though addition of a low polarity solvent,

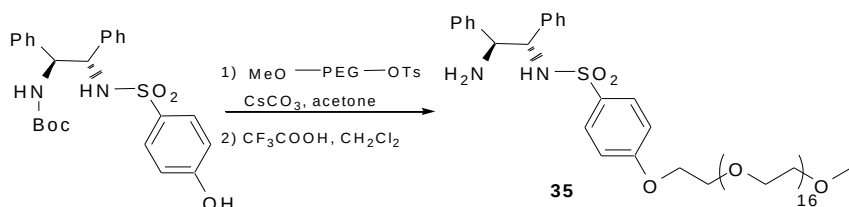
allowing recycling. Up to 80% ee and up to 85% ee were achieved with all of the ketones tested using the azeotrope triethylamine/formic acid or sodium formate/water systems respectively. Nevertheless, conversion depended on the structure of the ketone and mainly on the position of the withdrawing group of the aromatic group (Cl, OMe, CF₃).



Scheme 19.

For the sodium formate/water reduction system [29], several parameters were studied. A 20°C decrease of the temperature led to a slightly higher ee at a longer time. The lower the formate concentration, the slower the reduction is and the lower ee. Moreover, the reaction was not affected by the presence of a surfactant. The ligand itself probably acted as a phase transfer catalyst. The presence of an organic solvent, inducing a biphasic system, led to a slower reaction and a decrease in ee. Concerning the catalytic system stability, it appeared that in sodium formate/water medium, a possible decomposition occurred because catalytic recycle led quickly to loss of catalytic activity and ee, which was not the case when formate/water system was used: more than ten recycles with no loss of activity and enantioselectivity.

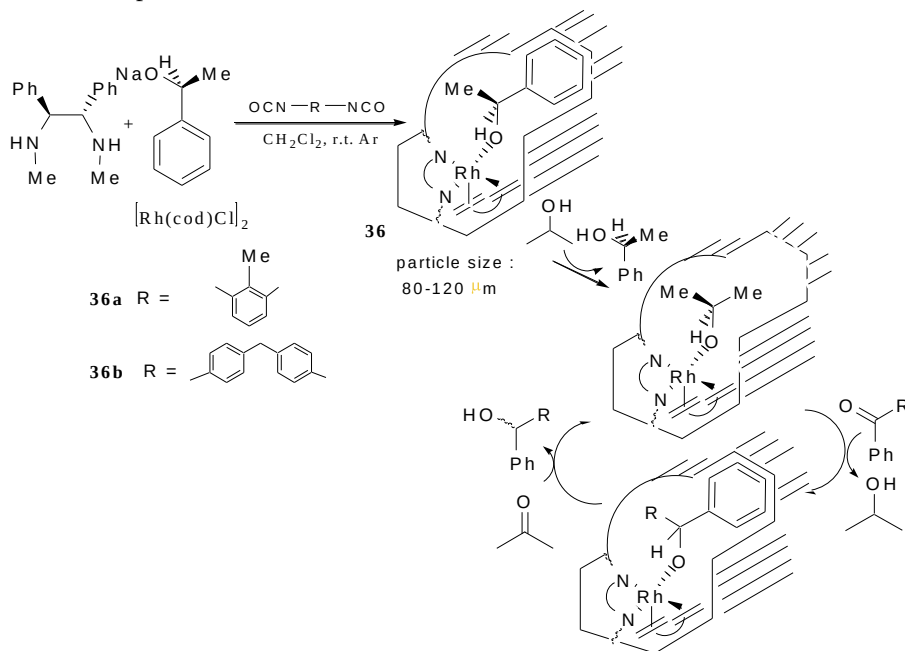
The same approach was involved in 2008 by Chan [30]. As an alternative method for attaching a PEG chain onto TsDPEN ligand, a PEG-750 (ie Mn = 750) was anchored at the *para*-position of an aryl sulphate group leading to polymer 35 in 51% overall yields starting from chiral DPEN (Scheme 20). Polymer 35 was examined in the Ru-catalyzed asymmetric HTR of acetophenone in water using HCOONa as the hydrogen donor at room temperature. Best ee (96%) was obtained with 5 equivalents of HCOONa and the high ratio of substrate to catalyst (S/C = 1000) led to slower reaction with a slight decrease in ee (90% ee). Other aryl ketones have been reduced. Compared with the precedent catalytic system formed with polymer 34, similar results were obtained in term of enantioselectivity. Once again, the catalyst could be easily recovered and reused at least eight times.



Scheme 20.

2.2.2. Imprinting technique for hydrogen transfer reduction with 1,2-diamines

In 1995, Lemaire [32] reported the immobilized transfer hydrogenation catalyst using a tetramine-rhodium complex **35** in order to study the effect of molecular imprinting. The upper rhodium complex was formed by copolymerization with a diisocyanide in the presence of sodium (*S*)-phenylethanolate (PM) leading to the imprinted polymers **36a** and **36b** (Scheme 21). The PM is then removed by adding 2-propanol. The resulting polymer as well as the non-templated polymer were tested in the transfer hydrogenation of acetophenone and phenylethylketone in the presence of 5 mol % of Rh-polymer with KOH/[Rh] ratio of 4 at 60°C. Results are presented in Table 3.



Scheme 21.

Table 3. Molecular imprinting effect in reduction by using Rh catalyst with templated and non-templated polymers 35a and 35b.

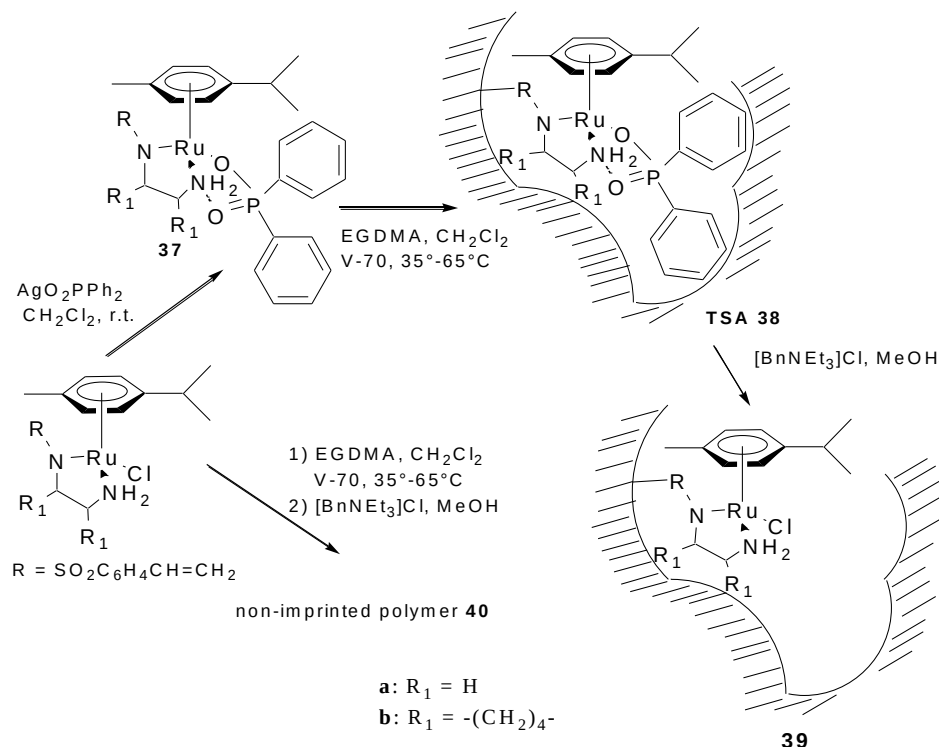
Substrate	Chiral polymer-Rh catalyst	Inductor configuration	Conv. (%)	Time (days)	Ee (%) (config.)
acetophenone	36a polymerized	(<i>R,R</i>)	44	1	33 (<i>S</i>)
acetophenone	36a (<i>S</i>) templated	(<i>R,R</i>)	42	1	43 (<i>S</i>)
acetophenone	36b polymerized	(<i>S,S</i>)	98	1	25 (<i>R</i>)
acetophenone	36b (<i>R</i>) templated	(<i>S,S</i>)	98	1	43 (<i>R</i>)
phenylethylketone	36b polymerized	(<i>S,S</i>)	96	6	47 (<i>R</i>)
phenylethylketone	36b (<i>R</i>) templated	(<i>S,S</i>)	91	9	67 (<i>R</i>)

In homogeneous catalysis using chiral diamine **18** complexed with Rh, the acetophenone was reduced quantitatively with 55% ee, in 7 days. In the case of polymerized complex **36a**, acetophenone reduction leads to 33% ee and with its templated analog 43% ee. With **36b**, an increase of about 20% ee is observed between polymerized and templated ligand. These increases in ee were ascribed to a favourable molecular imprinting effect of the PM, creating chiral pockets within the polymer network.

Nevertheless, in the case of sterically demanding substrates little or no reduction occurred, indicating a substrate stereospecificity different from that observed in homogeneous catalysis or when using catalyst precursor belonging to the polymer backbone [32]. For the reduction of acetophenone, crosslinked templated polymers were studied. Optimization of the crosslinking ratio led to the best compromise between activity and selectivity (70% ee for a crosslinking ratio of 50/50 of triisocyanate/diisocyanate) [33, 34].

This selectivity could be explained by a certain rigidity of the cavity, permitting good accessibility to the reaction sites.

This molecular imprinting technique was also used by Severin [35] [36] who proposed the synthesis of phosphonato complexes **37** (Scheme 22) in order to mimic the six membered cyclic transition structure suggested for HTR. This immobilized catalyst was prepared in a three step reaction (Scheme 22). In order to compare the effect of such polymeric organometallic transition state analog (TSA **38**), the polymer **40** was prepared (Scheme 22) by copolymerization of the non phosphonato complexed catalyst with ethylene glycol dimethacrylate (EGDMA) (Ru/EGDMA: 1/99). The ability of such polymers to catalyse the reduction of benzophenone was tested, using the azeotrope formic acid/ Et_3N as hydrogen donor.



Scheme 22.

The molecular imprinted polymer 39a was significantly more active than polymer 40a (TOF (40a) = 51.4 h^{-1} , TOF (39a) = 16.5 h^{-1}). With this enhancement of the rate of the reaction using the imprinting polymer, substantially higher specificity for benzophenone was observed when completion of HTR of an equimolar amount of benzophenone and a ketonic cosubstrate was performed. This behaviour was slightly larger for aliphatic ketones as compared to aromatic ketones. These results were consistent with the activity and selectivity using organometallic TSA as template with an imprinting technique. A similar study was made with the polymer including rhodium complexes coordinated with phosphinato ligands (polymer 38b) and the imprinted polymer 39b. After 6 hours, the reduction of acetophenone led to 81% yields and 95% ee, and ruthenium complexes gave up to 70% ee for the reduction of the ethyl phenyl ketone [37].

Due to the structurally defined transition state analogs, included in a polymer, a shape-selective cavity close to the catalytic active center was formed. This cavity is highly selective and an enhancement of the activity was observed.

Furthermore, it has also been shown that activity and selectivity depended on how the metal complex was attached to the polymer backbone: a rigid connection by two styrene side chains is superior [36].

2.2.3. Aminoalcohol and aminothiols as ligand

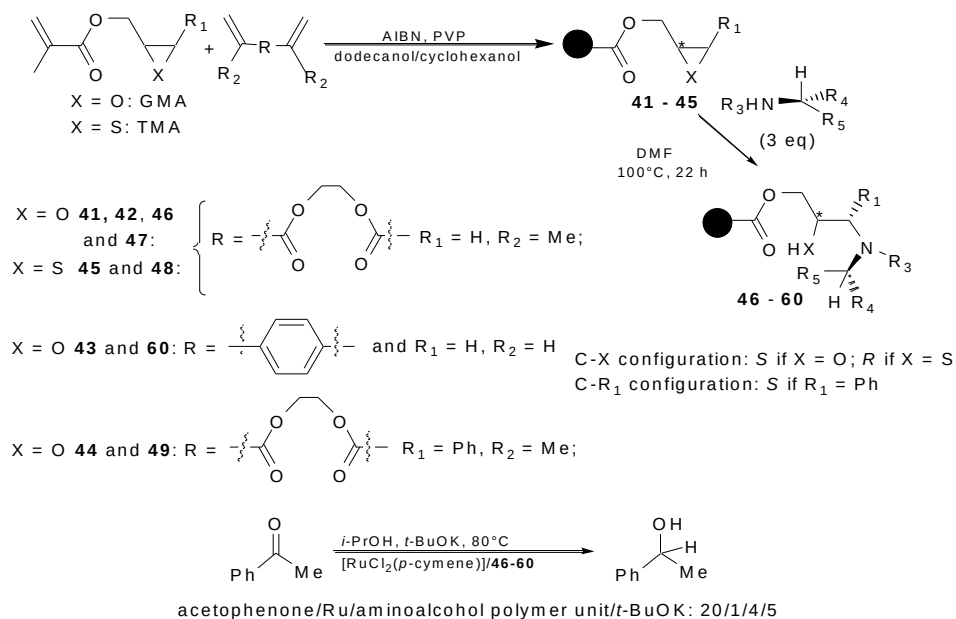
Chiral β -amino alcohols can also be used for homogeneous HTR of ketones and are known to be effective for reduction of aromatic ketones [38] but, only few examples of organic polymer-supported ligands have been reported.

Recently, poly((S)-glycidylmethacrylate-co-ethyleneglycol dimethacrylate) (41) (poly((S)-GMA-co-EGDMA)), [39][40] (poly((S)-PhGMA-co-EGDMA)) (42), [41] poly((S)-glycidylmethacrylate-co-divinylbenzene (poly((S)-GMA-co-DVB)) (43) [41] [42] and ((S)-thiiranylmethylmethacrylate-co-ethyleneglycol dimethacrylate) (44) [42] different precursor polymers were synthesized. They were formed by radical suspension polymerisation of enantiopure (S)-GMA (30 wt % for 41a or 70 wt % for 41b) with EGDMA or DVB (70 wt % for 43), or (S)-PhGMA (40 wt % for 42) with EGDMA or (S)-TMA (30 wt % for 45) with EGDMA in presence of AIBN, with a mixture of cyclohexanol/dodecanol (91/9 wt/wt) and 2% of aqueous polyvinylpyrrolidone (PVP) as stabilizer (Scheme 23). Chiral beads of 41 and 43 presented respectively a specific surface area of 82 and $275 \text{ m}^2/\text{g}$, and in both the cases, 2.11 mmol/g of epoxyde function. A specific area of $50 \text{ m}^2/\text{g}$ with 4.92 mmol/g of epoxyde function, a specific area of $35 \text{ m}^2/\text{g}$ with 1.83 mmol/g of epoxyde function and a specific area of $92 \text{ m}^2/\text{g}$ with 1.72 mmol/g of epoxyde function were respectively observed with 42, 44 and 45. The subsequent epoxide or episulfide ring opening with diverse amines led to the corresponding polyaminoalcohols and polyaminothiols. Their ruthenium complexes were applied to the HTR of benzophenone (Scheme 23).

It is noteworthy that the nature of the amine of the aminoalcohol played a crucial role. The best results in terms of conversion and enantioselection are obtained with polyaminoalcohols and polyaminothiols derived from methylamine and benzylamine (Table 4) [39].

It appeared that the efficiency of the catalyst depends on the nature and the proportion of the crosslinking agent (catalyst presenting 70% of EGDMA was more efficient than this with 30% of EGDMA and for DVB a decrease in conversion and ee was observed). It depended also on the specific surface, the nature of the ligand (aminoalcohol or aminothiol) and on the

steric hindrance (aminoalcohol and ligands from GMA compared with PhGMA were more efficient) (Table 4) [41]. Moreover, attempts to recycle ruthenium complexe of 46a led to a marked decrease in activity from 94 to 27% and lowered selectivity from 70 to 54%.



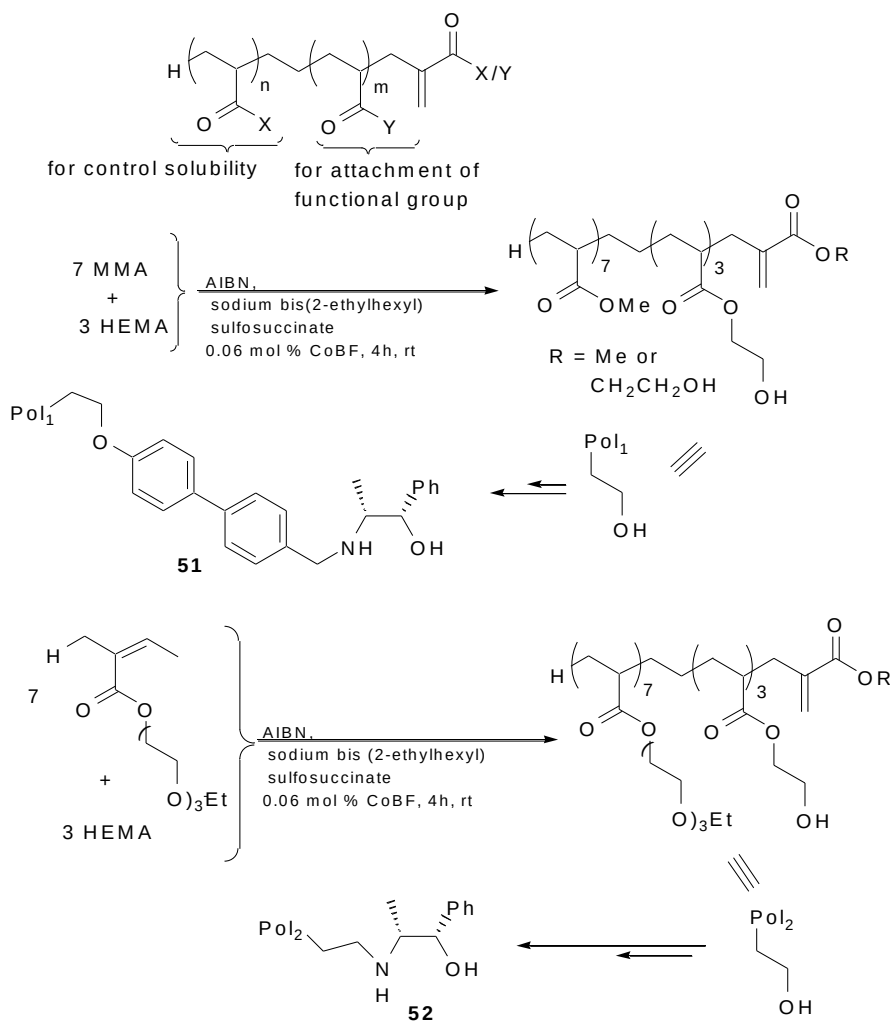
Scheme 23.

Table 4. HTR of acetophenone using several aminoalcohols and aminothiols (L*/Ru/Ketone/t-BuOH: 4/1/20/5, 80°C)

				Phenylethanol			
X (C-X config.)	R ₁ (C-R ₁ config.)	R ₅	Ligand	Functionality (mmol/g)	Time (h)	Conv. (%)	Ee (%) (config.)
O (S)	H	Ph	46a	1,46	3	94	71 (R)
O(S)	H	H	46b	0,85	1	95	65 (R)
O (S)	H	Ph	47a	2.90	72	51	57 (R)
S (R)	H	Ph	48a	1.11	22	55	50 (S)
S (R)	H	H	48b	0,90	22	50	39 (S)
O (S)	Ph (S)	Ph	49a	0.65	22	61	21 (R)
O (S)	Ph (S)	H	49b	0.51	72	<5	29 (R)
O (S)	H	Ph	60a	1.28	22	58	44 (R)

Wills [43] has tested a copolymer formed by a 7/3 methylmethacrylate and hydroxyethylmethacrylate ratio soluble in a range of organic solvent as backbone of a

norephedrine pendent polymer ligand, an aminoalcohol ligand selected for its good results in HTR of ketones when complexed with Ru^{II} (Scheme 24).

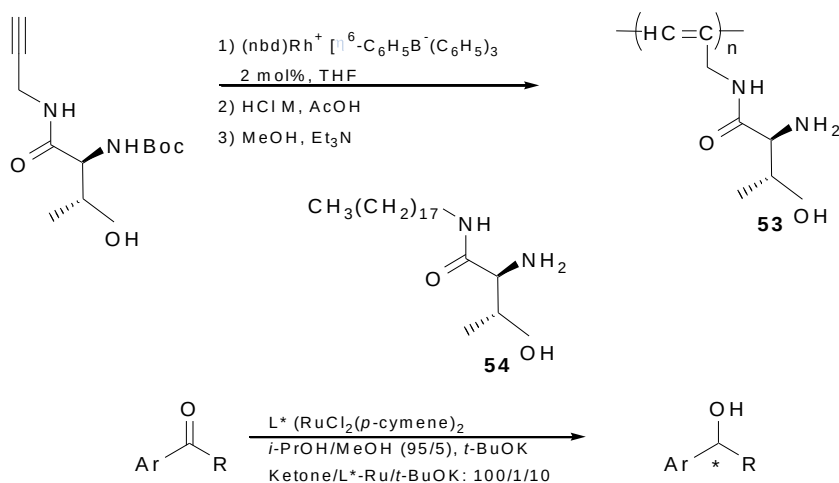


Scheme 24.

With ephedrine supported ligand 51, the best results were obtained for the HTR of acetophenone when 0.44 mol% of catalyst in dichloromethane is used (20% yield, 77% ee). Evaluation of ligand 52 for this reaction with 2 mol% of catalyst gave up to 85% yield with 81% ee. Three additions of acetophenone showed a deterioration of the catalytic system.

Few attempts have been made by Masuda to utilize the main chain chirality of polymers [44]. They reported the synthesis of an L-threonine-based helical poly(*N*-propargylamide)-Ru complex (53-Ru-complex) and evaluation of its catalytic activity in the asymmetric HTR of ketones (Scheme 25). The corresponding alcohols were obtained in 23–48% yields and the ee values were 12–36%; the highest ee was achieved in the reduction of 2-acetonaphthone. This reaction was achieved in homogeneous conditions with 54-Ru-complex and acetophenone led

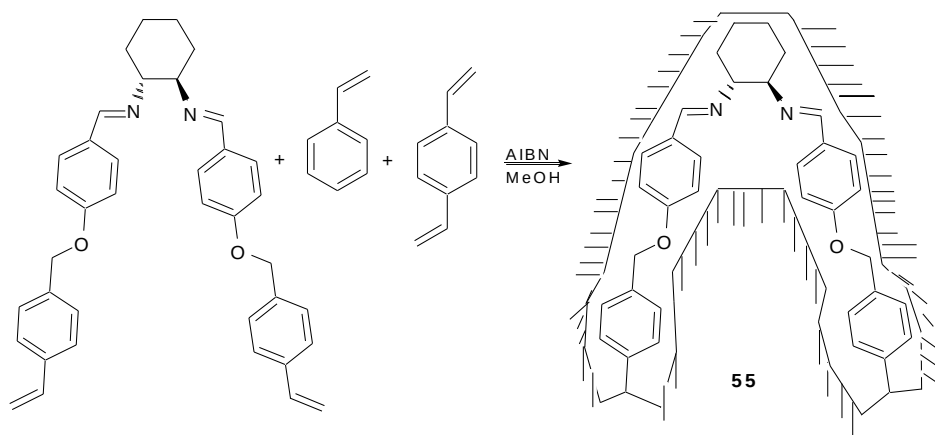
to phenylethanol with no ee. This suggested that the helical structure was effective to enhance the catalytic ability for chiral induction.



Scheme 25.

2.2.4. Diallyldimine ligand as ligand

One example of the use of heterogeneized dialldimine ligand 55 (Scheme 26) was reported for the asymmetric HTR of acetophenone [45]. Enantioselectivities of up to 70% were obtained for a degree of crosslinking of 71%. The rise of the degree of crosslinking to 100% gave no significant difference contrary to a crosslinking less than 71% which gave a decrease in enantioselectivity.



Scheme 26.

2.3. Enantioselective Hydride Reduction

The enantioselective hydride reduction of prochiral ketone is a well documented reaction which consists in the preparation of optically active alcohols. Thus, a large number of reducing agents and chiral catalysts have been developed.

Thus, from the beginning of the eighties, polymers containing chiral aminoalcohols and their derivatives were used as chiral auxiliaries for LAH [49], BH_3 [50] [51] or NaBH_4 [52].

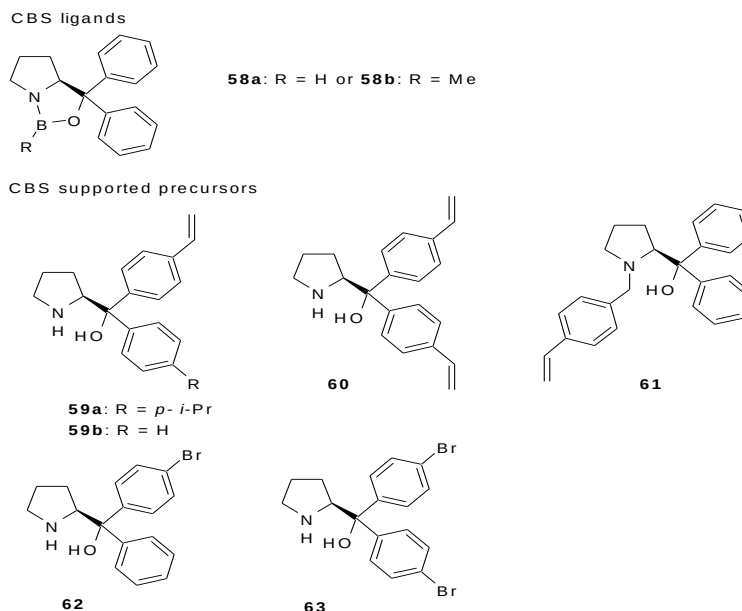
With the soluble polymer-supported catalyst 57 (Scheme 27), the reduction of acetophenone was performed in a continuous operated membrane reactor equipped with a nanofiltration membrane [54]. An enhancement of total TON from 10 to 560 (equivalent to 0.18 mol % catalyst for an average ee of 91% and an almost quantitative conversion) was observed. Excellent space-time yields of up to 1.4 kg per day were reached



More recently, several polymer versions of the efficient Corey-Bakshi-Shibata (CBS) catalyst have been prepared [47]. Different approaches have been used to bind the catalytic moieties to the polymer support: the diphenyl prolinol reacted with beads bearing benzene sulfonyl chloride residues (catalytic moieties bound to the nitrogen atom as part of a sulphonamide link), the diphenyl prolinol is bound to a polymer support or the aminoalcohol

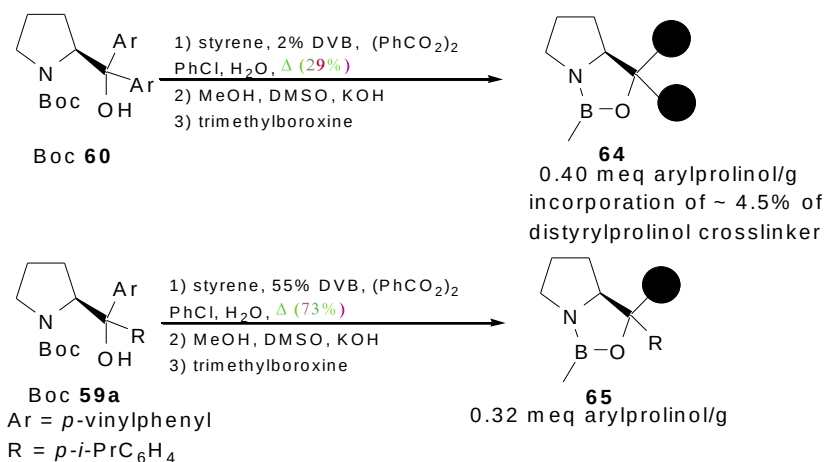
reacted with a polymer-supported boronic acid [55]. As in the last case the aminoalcohol is not supported, only the first two possibilities are reported.

In order to prepare polymer-supported CBS catalyst, monomeric precursors 59, 60 or 61 or bromides 62 and 63 have been synthesized (Scheme 28). The oxazaborolidine could be formed in situ or not before performing the hydride reduction of ketones.



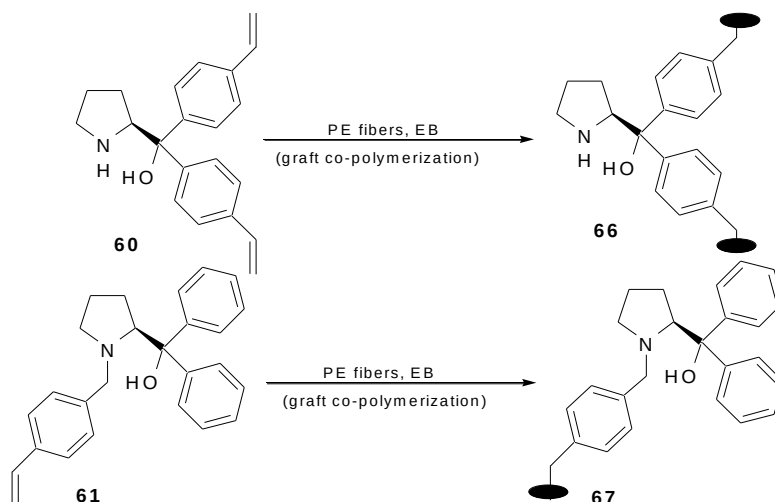
Scheme 28.

Shore [56] synthesized a pendent (64) and a crosslinked (65) CBS catalyst in bead form from monomeric precursors 59a and 60 respectively (Scheme 29) but also in monolith polymer form with a crosslinking level of 2% [57]. Monolith polymers were then cut to form CBS disks (64D and 65D) roughly 2 mm in height and 5 mm in diameter.



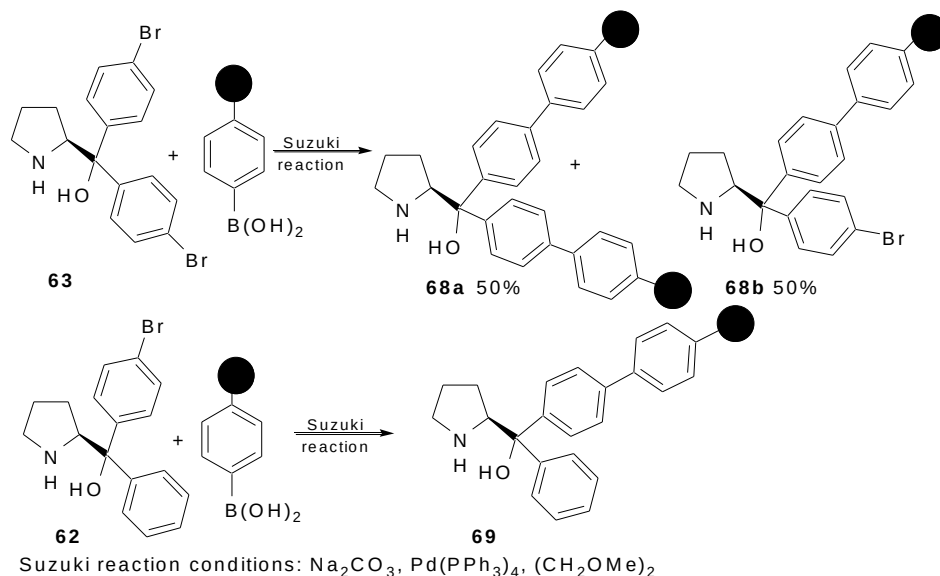
Scheme 29.

In 2004, Degni anchored chiral styrenic prolinol **60** and **61** on chemically inert polyethylene (PE) fibers by electron beam (EB) preirradiation, inducing graft copolymerization leading respectively to polymer **66** and **67** (Scheme 30) [58]. The corresponding oxazaborolidines were prepared in situ with borane from different sources: NaBH_4 in the presence of Me_3SiCl or $\text{BH}_3\cdot\text{Et}_2\text{O}$ and $\text{BH}_3\cdot\text{SMe}_2$.



Scheme 30.

Involving a Suzuki reaction, Hodge prepared “chemical robust” polymer-supported diphenyl prolinol based catalysts **68** and **69** from **62** and **63** and polystyrene boronic acid prepared via a direct lithiation of 1% crosslinking gel-type polystyrene beads (2.21 mmg/mol of boronic acid residue) (Scheme 31) [59].



Scheme 31.

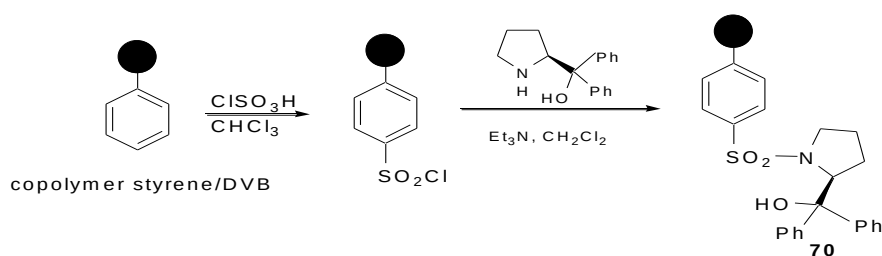
Comparative results for the reduction of acetophenone with these diverse oxazaborolidines are presented in Table 5.

Table 5. Reduction of acetophenone with several oxazaborolidines isolated or formed in situ from aminoalcohols and borane

Aminoalcohol or oxazaborolidine	Borane source	Mol %	T (°C)	Yield (%)	Ee (%)	Recycling (ee %)	Ref.
58a	BH ₃ .THF	5	r.t.	100	85	-	
64	BH ₃ .THF	5	r.t.	100	84	-	[56]
65	BH ₃ .THF	5	r.t.	100	62	-	[56]
64D	BH ₃ .THF	50	r.t.	97	99	3 (58)	[57]
65D	BH ₃ .THF	50	r.t.	100	63	-	[57]
58b	BH ₃ .SMe ₂	10	45	99	98	-	
66	BH ₃ .SMe ₂	10	45	90	95	1 (78)	[58]
67	BH ₃ .SMe ₂	10	45	99	44	-	[58]
68	BH ₃ .SMe ₂	30	22	> 95	94	16	[59]
69	BH ₃ .SMe ₂	30	22	> 95	96	8	[59]

In general, the crosslinked CBS (64, 64D or 66) afforded enantioselectivities almost identical to those of the CBS in homogeneous conditions (58a and 58b) and superior to the pendent-linker equivalent ligand (ie respectively 65, 65D and 67). These results could be ascribed to the superior swelling characteristics of the crosslinked catalyst in the solvent of the reaction which permits a better diffusion of the reagents into the catalyst [56-58]. For polymer 67, the weaker coordination with borane, due to the steric hindrance on the nitrogen atom, may be responsible of the slower catalysis. With 68 and 69 the results of the reaction were almost similar. After the 20th reuse, analysis of the polymeric mixture 68 showed that the overall weigh fell to 57% of its original value with an average loss per reaction of <3%. Moreover, nitrogen analysis was almost the same, suggesting that the catalyst groups were firmly bound and that the losses are probably due to physical attrition [59]. Concerning the reuse of the crosslinking polymer 64D, the recycle failed. This suggested a disassembly of the oxazaborolidine and a structural breakdown of the polymer itself [57].

Ketones [60], β -functionalized ketones [61] [62] and meso cyclic imide [63] have been enantioselectively reduced using polymer-supported chiral sulfonamides in presence of boranes (NaBH₄/Me₃SiCl or BH₃.SMe₂), leading in situ to the corresponding oxazaborolidine polymer-supported chiral sulphonamide 70 (Scheme 32).



Scheme 32.

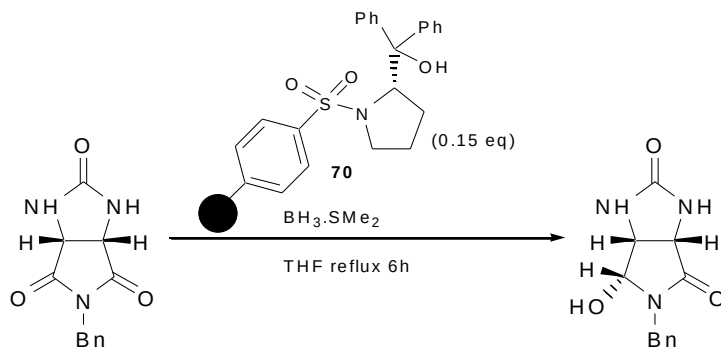
The reduction of unfunctionalized ketone was investigated at various conditions reactions: THF or toluene as solvent, 1% or 2% of crosslinking polystyrene resin and several degrees of functionalization.

The best results in terms of enantioselection (92.5%) and conversion (95%) were obtained in reflux toluene, with a catalyst amount of 15% polymer crosslinking of 2% and an aminoalcohol loading of 2.29 mmol/g. With lower degree of functionalization and 1% crosslinking the ee was of about 10 to 20% lower. The catalyst has been reused at least five times with minimal loss of catalytic performance. It is noteworthy that under these conditions, homogeneous supported catalyst showed better results than homogeneous catalyst. The best conditions were also involved successfully for the reduction of other ketones.

With the same polymer-supported chiral sulphonamide **70** (200-400 mesh, 2% DVB, 2.29 mmol/g functionalization) the reduction of several β -ketonitriles [61] and β -ketosulfones [62] were tested

It is noteworthy that aromatic β -ketonitriles and β -ketosulfones were reduced in good enantioselectivity (85-96% ee). Electron density (substituent in the *para* position) had little effect on enantioselectivity. For aliphatic β -ketonitriles or sulfones, both chemical yield and ee were lower compared to those obtained with aromatic analogs.

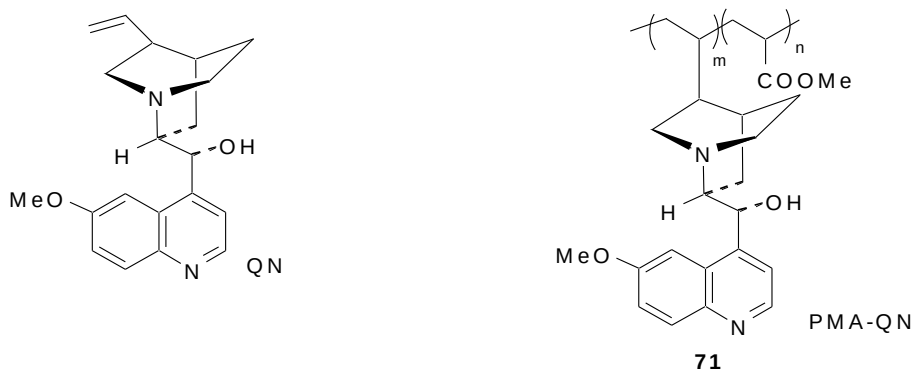
Meso-cyclic imide precursor of *d*-biotin has successfully been reduced with $\text{BH}_3\cdot\text{SMe}_2$ in the presence of polymer-supported sulphonamide catalyst **70** in THF under reflux for 6 hours. (Scheme 33) [63]. The enantioselective hydroxylactam was obtained in 91% yield with an ee > 98.5%. The recycling of the chiral supported-sulfonamide in the reduction of the *meso* precursor of *d*-biotin could be involved at least 5 times with non change in activity and enantioselectivity.



Scheme 33.

Recently, Wang [64] prepared by radical copolymerization a cinchona alkaloid copolymer: the methyl acrylate-co-quinine (PMA-QN (**71**)) (Scheme 34). Complexed with palladium(II), its catalytic activity in the heterogeneous catalytic reduction of aromatic ketones by sodium borohydride was studied. High yields in their corresponding alcohols are obtained but it is found that the efficiency of the catalyst depended on the nature of the solvent and the ketone which related to the accessibility of the catalytic active site. The optical yields in methanol and ethanol 95% were lower than in ethanol. This ability was attributed to a bad coordination between PMA-QN- PdCl_2 and sodium borohydride and a reaction rate which was very rapid. The stability of the chiral copolymer catalyst was studied

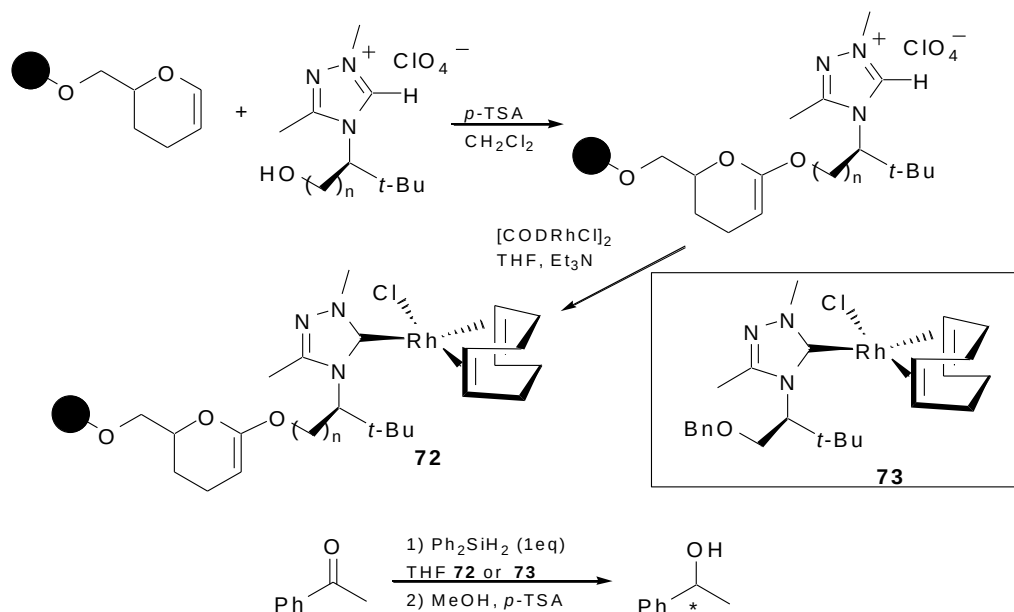
via the study of the recycling efficiency. Only 2 wt% loss of metal was observed after repeated use (at least 5 times) with only a little decrease in enantioselectivity.



Scheme 34.

2.4. Hydrosilylation with Ligands as Pendent Group

Asymmetric hydrosilylation of ketone had been studied in homogeneous supported catalyst with nitrogen containing ligands and only few examples have been reported. In 1998, Enders reported immobilized triazolium salts as precursors to chiral carbene-rhodium-catalyzed asymmetric hydrosilylation (Scheme 35). This Rh complex gave 24% ee compared to 17% ee for the homogeneous reaction (Scheme 34). The recycling of the solid supported catalyst **71** was successful with only slowly decreasing yields which were comparable to the yields of the homogeneous reactions with catalyst **72** [65].



Scheme 35.

3. REDUCTION OF C=N BOND

Although highly effective asymmetric reduction of carbonyl compounds has been extensively investigated, enantioselective reduction of imine derivatives to amines has been less studied, mainly in homogeneous supported catalysis [66].

With polymer containing nitrogen (2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenylpropan-1-ol [67], 2-piperazinemethanol), Itsuno [68] has shown that in stoichiometric conditions, oxime ethers could be reduced with borane with excellent ee (up to 99%).

More recently, in organocatalysis, Kočovský [69] has reported asymmetric reduction of imine with trichlorosilane catalyzed by an (*N*-methylvaline)-derived formamide anchored to a polymer. Under the best conditions, with 15 mol% of the catalyst enantiomeric excesses were about 85% and the catalyst could be reuse.

Then, in 2009, Itsuno [70] utilized for HTR of *N*-benzylimine the polymer-immobilized chiral ligands 31, 33a and 33b (Scheme 16) as their Ru^{II} complexes. These complexes were already used to catalyze the HTR reduction of ketones in water [25].

The HTR was carried out in organic solvent (dichloromethane) and in water using as hydrogen donor respectively the azeotrope HCOOH/Et₃N and HCOONa. Catalytic system with ligand 31 was effective for the HTR of *N*-benzyl imines in organic solvent. The corresponding amines were formed in good yields and ee (92-96% yields and 84-88% ee). In contrast, Ru^{II} complexes obtained from amphiphilic polymer 33a and 33b were found to be effective for the HTR of cyclic imines in water (50-95% yields 86-94% ee). The catalytic activity, in water, seemed to be controlled by the hydrophilic-hydrophobic balance in a polymer-supported catalyst.

4. CYCLOPROPANATION

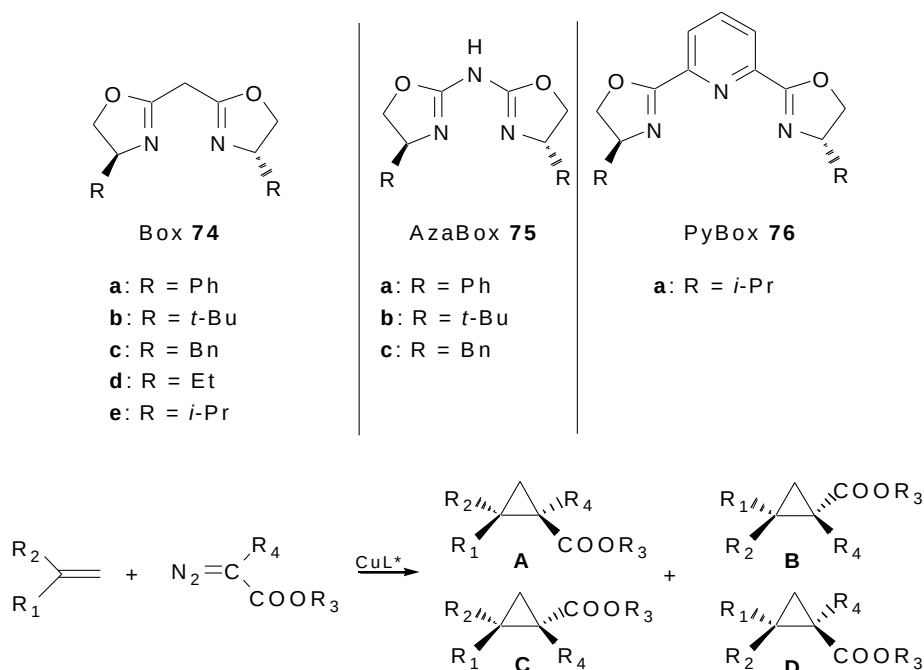
Highly functionalized cyclopropanes are important building blocks for obtaining numerous natural compounds (terpenes, pheromones), and compounds which are of high value in biological (ie: agrochemical active species) and medicinal chemistry. A wide number of methods have emerged in order to produce optically active cyclopropanes [71].

From all of them, highly enantioselective cyclopropanes are formed by asymmetric catalytic insertion of carbene to prochiral olefins. This method, first employed by Noyori in 1966 [72] consists in the metal-catalyzed decomposition of substituted diazo compounds in the presence of various prochiral alkenes.

Under homogeneous conditions [73], various chiral Schiff base-Cu(II or I) or Ru(II) complexes have been used as chiral catalyst precursors and from all of them the most efficient systems are formed with oxazolines and bis-oxazolines. Thus after their first use by Masamune [74], oxazoline-derived ligand have been extensively employed in homogeneous enantioselective catalytic reaction particularly in cyclopropanation [75]. Thus nitrogen-anchoring ligands on organic polymers are mainly formed by immobilized oxazolines.

4.1. Oxazolines Ligands

Bis-oxazolines (Box), azabis-oxazolines (azaBox) and pyridine bis-oxazoline (PyBox) with a C₂ symmetry form the great majority of various oxazoline-derived ligands which are used in immobilized catalytic cyclopropanation reactions (Scheme 36). For these reactions, immobilized ruthenium and copper complexes which are able to form carbene intermediates have been tested. Most of the time, the reaction involved styrene and ethyl diazoacetate (EDA). However other alkenes (diphenyl ethylene ...) and other diazo compounds (i.e. *tert*butyl and ethyl 2-phenyl diazoacetate) have also been investigated (Scheme 36).



Scheme 36.

First, heterogeneous catalytic systems involved *N*-anchoring ligands on inorganic supports such as zeolithes [76], clays [77]

Immobilization of the catalyst on organic support leading to insoluble or soluble polymers was made by grafting or copolymerization of the chiral ligand.

In all cases, the immobilization is performed via alkylation of the methylene bridge or of the nitrogen of the bridge (AzaBox, PyBox).

4.1.1. Insoluble supported-polymer Box as ligands

In 2000, Mayor [78] described the first immobilization of Box on insoluble polymer. For a same ligand, grafting and several methods of polymerization (Scheme 37) were reported in order to compare the catalytic efficiency of these supported ligands after their complexation with Cu. The study was based on immobilization of bis-(oxazoline) 74a-c (Scheme 36) and their corresponding Cu-complexes were tested in the cyclopropanation of styrene with EDA, a well known reaction in homogeneous catalysis [79].

The Box methylene bridge of 74a, [78, 80] 74b [78, 80, 81, 82] or 74c [78, 80] was first functionalized with two *p*-vinylbenzyl groups in order to perform homo-polymerization [78, 80] (polymer 79), or co-polymerization with styrene [78, 80, 81] (polymer 78), DVB [78, 80, 81, 82] (polymer 80_α) divinylbenzyl polyethylene glycol [80, 81, 82] (polymer 80_β) and divinylbenzyl resorcinol [80, 81] (polymer 80_γ) or dendrimers 80_δ (Scheme 2). The best results were observed with the homopolymer 79b (R = *t*-Bu) [78, 80]. This homopolymer 79 prepared by thermal polymerization [78] was able to coordinate a large amount of Cu and presented a better activity than the same homopolymer prepared in presence of AIBN (respectively 51% and 34% yield, 35/65 and 39/61 *trans/cis* ratio, 75% ee and 77% ee for the *trans* cyclopropane, 70% ee and 73% ee for the *cis* cyclopropane) [78].

For all the copolymers, the low efficiency of the copper complexes (cyclopropanation of styrene: yield up to 40%) may be explained by the non accessible core of polymer by Cu probably due to the high degree of crosslinking [78, 80]. But moderate to high ee were observed (up to 78% ee) and contrary to homopolymers, the *cis* cyclopropane is mainly formed. Attempts to use copolymers from monofunctionalized Box (Scheme 38) as ligand did not improve the efficiency (yield up to 16%); the diastereoselectivity is in favour of the *trans* stereoisomer. As for copolymer 80_α, yields obtained with 80_{β-δ}, do not exceed 35% and the diastereoselection gave mainly the *trans* cyclopropane. With 80_β the formation of *trans* isomer is up to 67% [81, 83]. The presence of oxygen atom in the crosslinking agents could induced more coordination with the metal. This effect is detrimental for the catalytic properties for the resulting Cu-loaded resin [81].

The homopolymer 79b could be reused up to five times without loss of ee but with a slight decrease in activity [80]

In order to avoid the non accessibility to the core of polymer by the metal due to excessive crosslinking, a monofunctionalization of the Box leading to Box pendant ligand 81 was performed [80] (Scheme 38). Unfortunately, the incorporation of copper into polymers 81 was not found to be improved (Cu loading: 0.07-0.08 mmol/g). Furthermore, a higher loading was observed with the less crosslinked polymer 81a. It is noteworthy that if the ligand 81c is transformed into a polymer with bisoxazoline moieties by treatment with MeLi and MeI, the results obtained for the cyclopropanation reaction were slightly worse than those obtained with 81c itself (yields 16% vs 16%; *trans/cis* ratio 60/40 vs 57/43, ee *trans* 23% vs 29%; ee *cis* 22% vs 34%).

Salvadori [84] showed that a copolymer structure presenting a single spacer, but flexible one linking the ligand moiety to the inert polystyrene backbone was effective with solution-like behaviour (Scheme 39).

For the cyclopropanation of styrene with EDA, Cu-polymerized 82 complexes afforded similar results than the non supported Box. In the first case 61% and 60% yield, 67/33 and 71/29 dr in favour of the *trans*, 93% and 94% ee were respectively observed. The catalytic system could be reused without loss of its catalytic properties. Moreover, it is noteworthy that the immobilization method did not influence the catalytic behaviour: catalytic systems formed with copolymerized (route A) [84] or graft methodology (route B) [85] were substantially equivalent (variation of about 1 to 2% of the yield, ee or dr).

In 2004, Yifei reported Merrifield (3.8 mmol/g) polymer-supported Box 74c-e [85] (Schemes 36 and 40) for the cyclopropanation of 1,1-diphenylethene with EDA.

The highest enantioselectivity of 85% ee with 82% yield was achieved by using 83d showing as in homogeneous conditions that the steric hindrance of the R group of the oxazoline had a great influence on the ee and the yield. Under recycling, the catalytic system led to an important decrease in enantioselectivity.

In order to restrict the conformational mobility of the groups on the bridge of the Box, a 1,3-dioxane group was introduced, then the Box was grafted onto a Wang resin (0.7 mmol Br/g) (Scheme 41) [86]. In that condition, only 0.26 mmol/g has been grafted onto the active site and the copper content was 0.018 mmol/g. The ligand 84 was evaluated in the cyclopropanation of styrene with EDA. The *trans* cyclopropane was obtained in 65% ee. The high ee was due to less steric hindrance between the two oxazoline groups, as the consequence of the chair conformation of the dioxane ring.

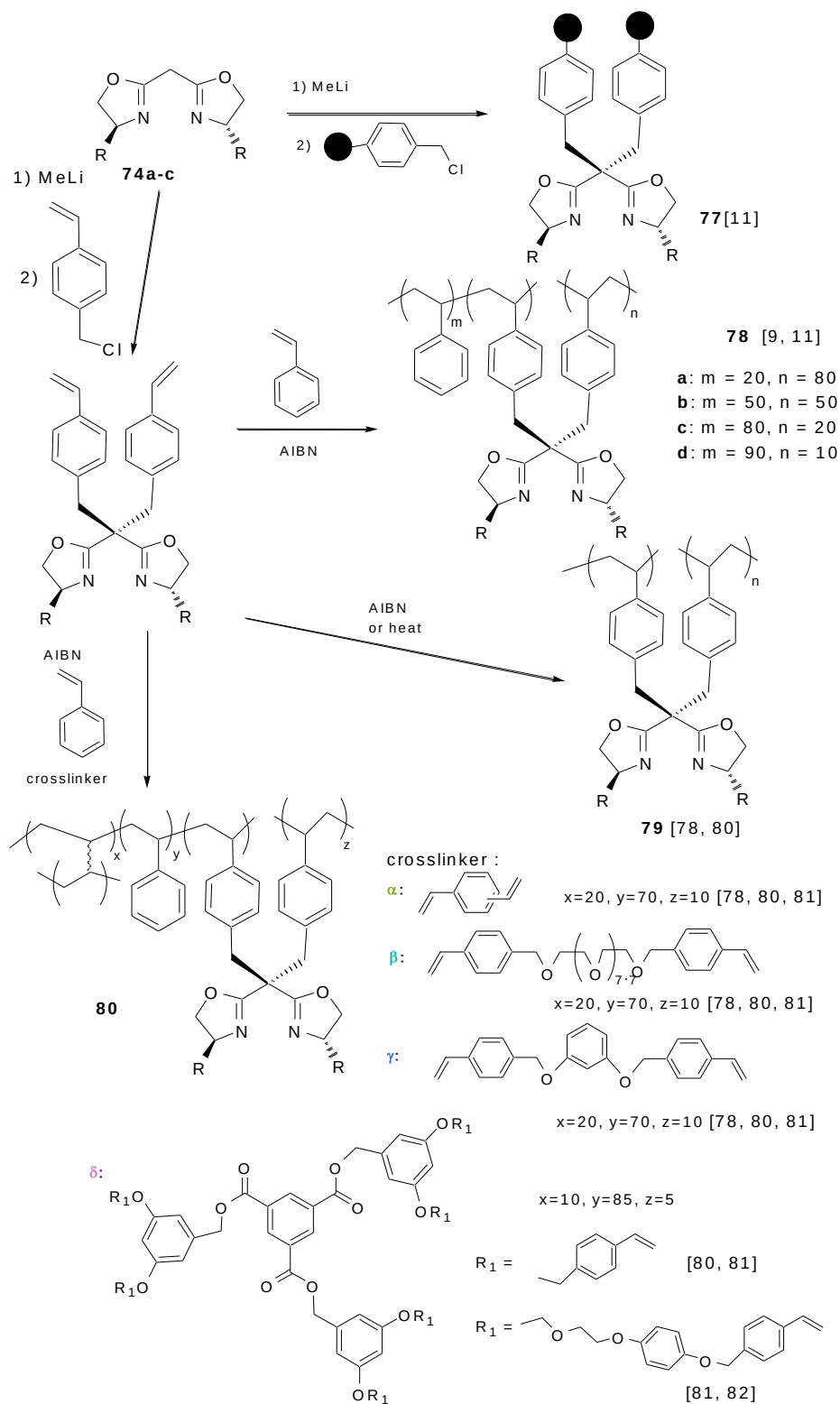
AzaBox as well as PyBox have the advantage towards Box to present a donor nitrogen atom in the bridge allowing to a higher coordinating ability. Thus a better stabilization and a better recoverability, with regard to their analogous Box ligand are observed. Additionally, AzaBox and PyBox ligands have only one link point in the bridge which makes grafting easier.

4.1.2. Insoluble supported-polymer AzaBOX as ligands

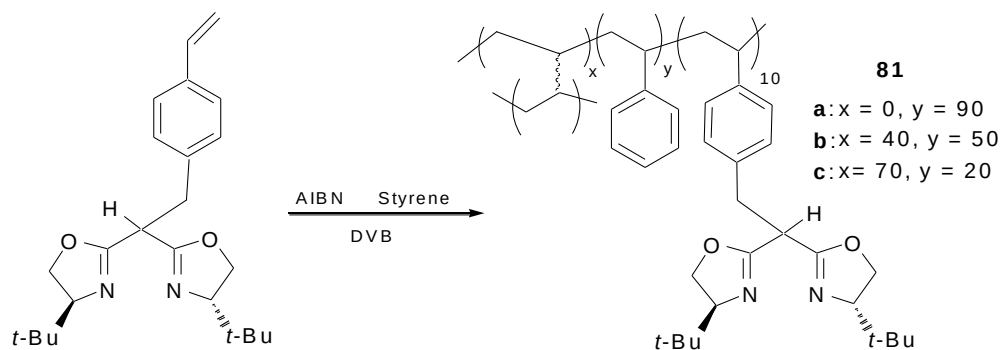
Recently, AzaBox ligands were attached to a TentaGel (polymer with a polystyrene backbone and PEG periphery) (87) or to polystyrene (88 and 89) by direct grafting of the ligand onto the polymer or by copolymerization of the ligand functionalized with a styryl group (Scheme 42) [87]. The corresponding catalyst presented a copper content of 0.2-0.3 mmol/g. Cyclopropanation of styrene and 1,1-diphenylstyrene with EDA was studied with 1-1.5 mol% of the catalyst. In these experiments, catalyst formed with copolymerized ligand 89 did not show any advantage over grafting ones. Moreover, Merrifield resin was a better support than TentaGel. With 87a the yield was up to 51% but its diastereoselection (64/34) and its ee (up to 62%) are lower than those obtained with 88 or 89 (yield up to 32%, dr 70/30, ee up to 88%) for the cyclopropanation of styrene.

4.1.3. Insoluble supported-polymer PyBox as ligands

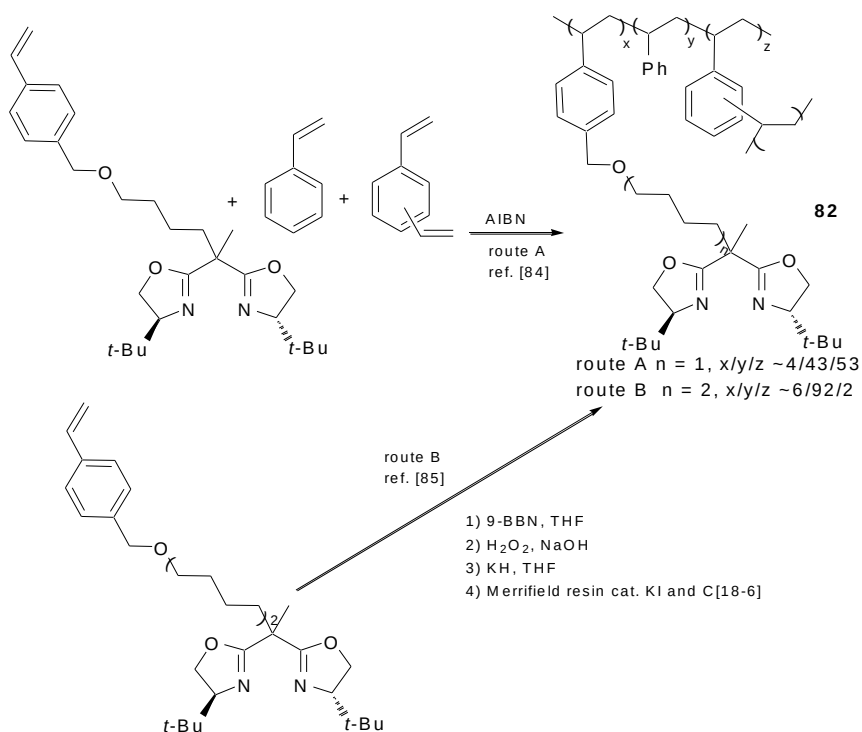
The first immobilization of PyBox was made by Mayoral [88] by means of radical copolymerization of 4-vinylPyBox with styrene and DVB in presence of AIBN and a porogen (toluene or a mixture toluene/dodecanol) (ligand 90 Scheme 43). PyBox was incorporated in the polymer with high yield from 75 to 95%. The corresponding Ru-complex was formed at about 50-60% showing that all the ligands were not accessible. The nature of the porogen solvent was important. A polymeric ligand prepared in presence of dodecanol gave a lower Ru functionalization and was detrimental to the *trans/cis* selectivity (77/23). The best catalytic system, high *trans/cis* selectivity (85/15) and ee (*trans*: 85%), was formed by the polymer prepared in toluene. However, it has been observed that with a lower crosslinking degree, dodecanol has less importance. The best catalysts were reused twice, but a marked decrease in both selectivities and activities were observed for the second recycle.



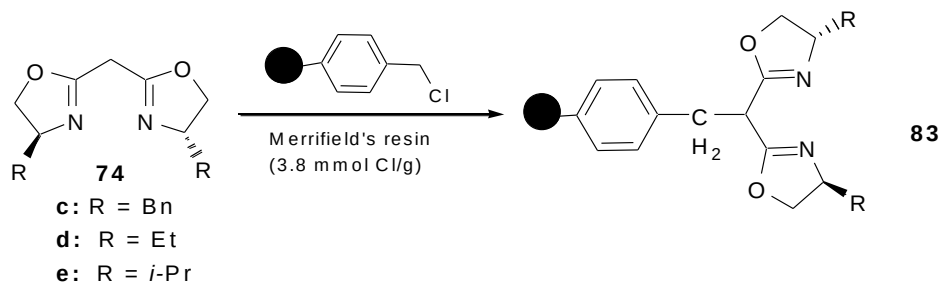
Scheme 37.



Scheme 38.



Scheme 39.



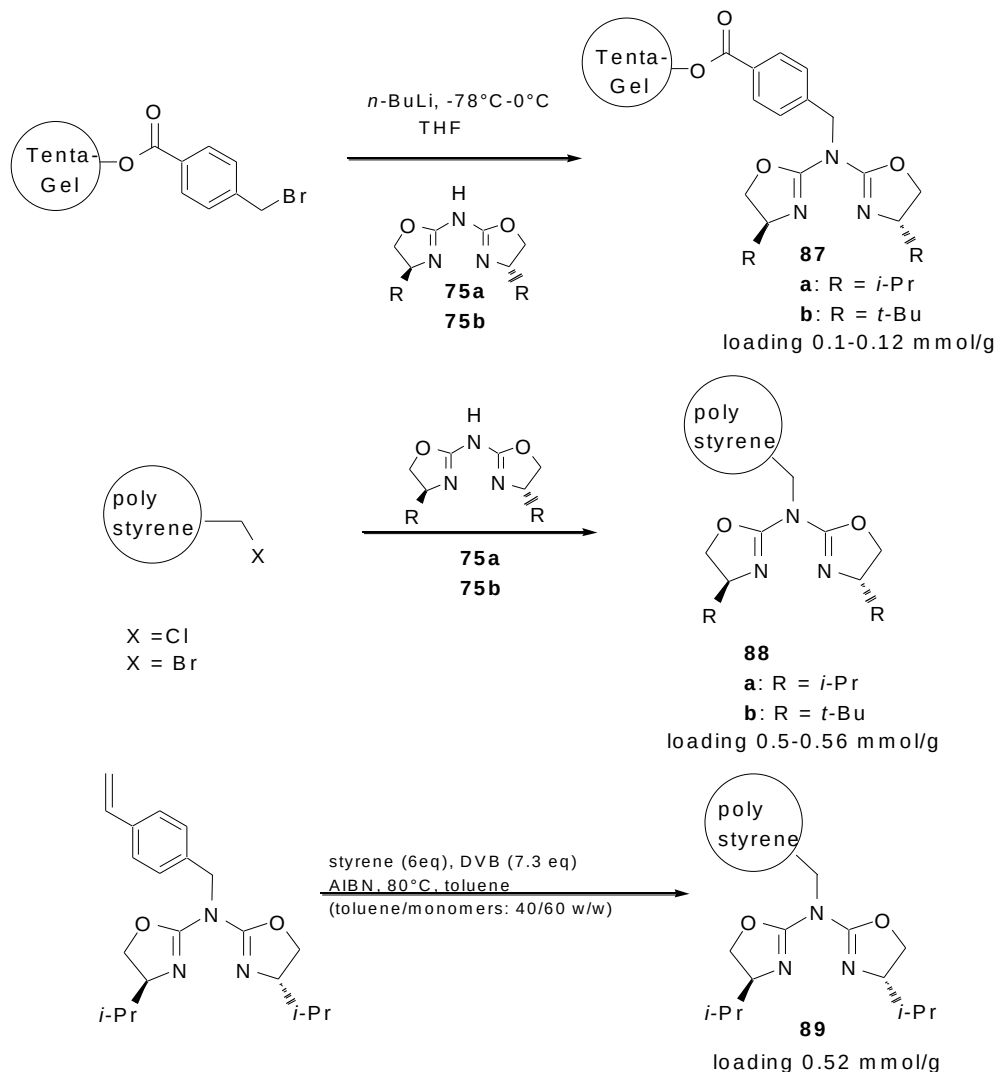
Scheme 40.



Mayoral [90] also demonstrated that the PyBox-Ru supported complexes on macroporous monolithic polymers were efficient catalysts for the cyclopropanation reaction. PyBox monolithic minireactors were prepared in a stainless column by radical copolymerization of 4-vinyl or 4-styryl PyBox in presence of styrene and DVB using 10% toluene/50% dodecanol as the precipitating porogeneous mixture (polymers 94 and 95 Scheme 44). To form the Ru complex, a solution of $[\text{RuCl}_2(p\text{-cymene})]_2$ was passed through the column at low flow then washed with dichloromethane to remove the non complexed Ru.

An increase of the flow rate induced a decrease of the cyclopropanation and a dimerization of EDA which is one of the poisons of the catalyst. Besides both region and enantioselectivities gave good values: 80/20 *trans/cis*, *cis* isomer $48 \pm 5\%$ ee, *trans* isomer $75 \pm 5\%$ ee. The catalyst could be used for several runs (4-6 times) without change in catalytic performance. Concerning the morphology of the catalyst, a slight decrease in catalytic

activity was found with ligand 95 containing an aryl spacer. If the crosslinking degree was higher (51% DVB instead of 20%), the activity and chemoselectivity were improved. The reaction performed without solvent provided an increase in both efficiency and chemoselectivity for a mixture styrene/EDA: 1/7 and minimize the dimerization of EDA. With scCO_2 as solvent, yields were about 25% but chemoselectivities and ee of both diastereoisomers rise. Moreover, the total number of turnover (TON) is greatly increased.

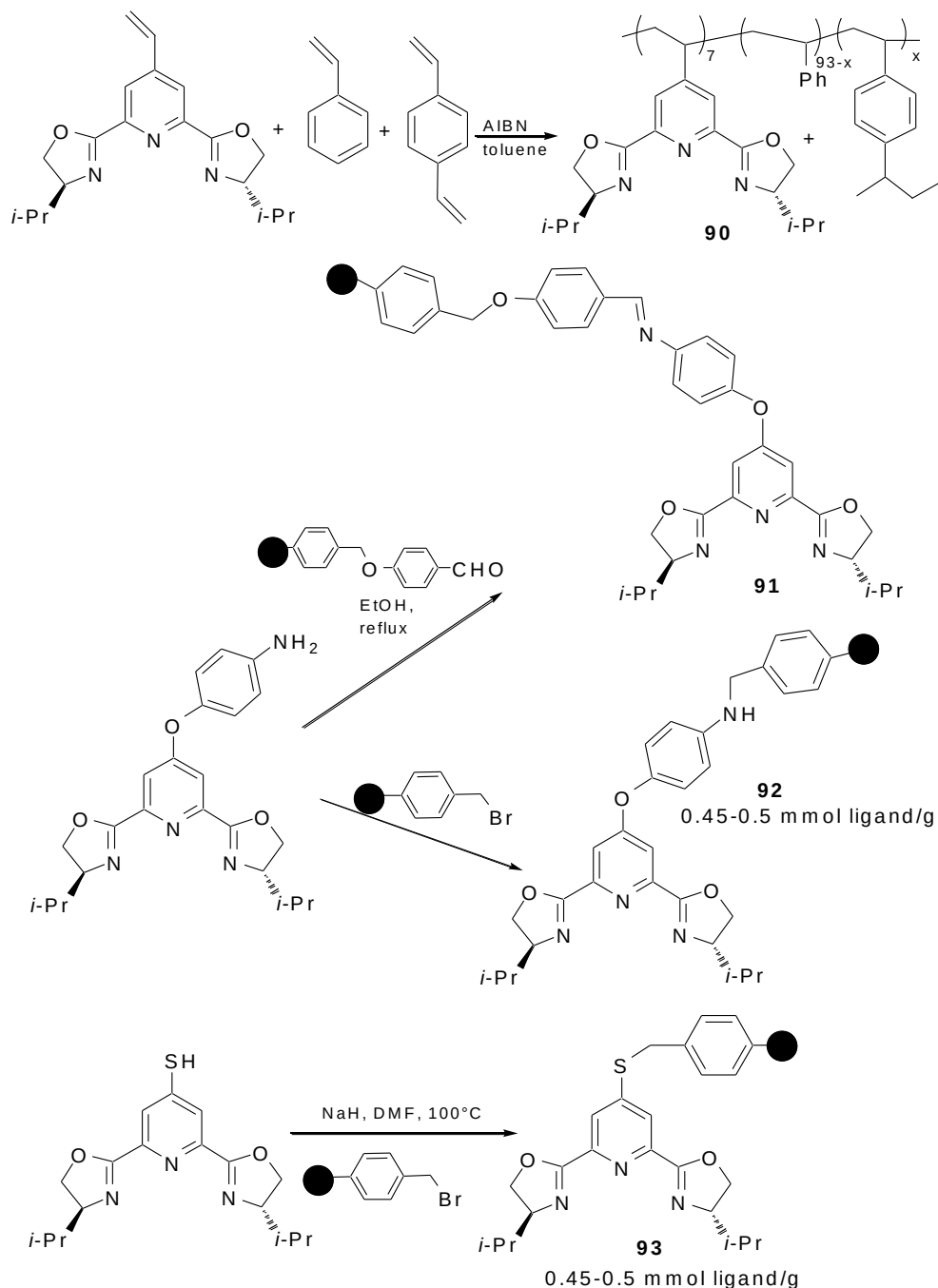


Scheme 42.

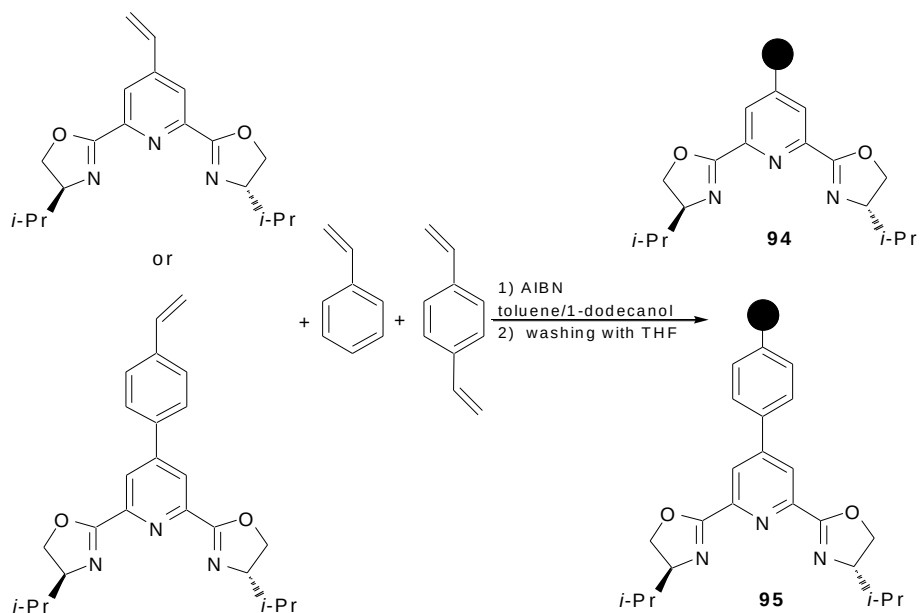
4.1.4. Immobilization of PyBox on natural polymers

Some natural polymers have also been used as support for Schiff base ligands. A starch support has also been used as support for a PyBox. A telomerized starch 96 [91] presenting a final double bound reacted with a thiol-PyBox in the presence of AIBN (Scheme 45) to form the corresponding immobilized PyBox. [92] Although the Ru-97 complex exhibited lower activity (up to 44% after the third reuse) and selectivity (*trans/cis*: 76/24 with 50% ee for the

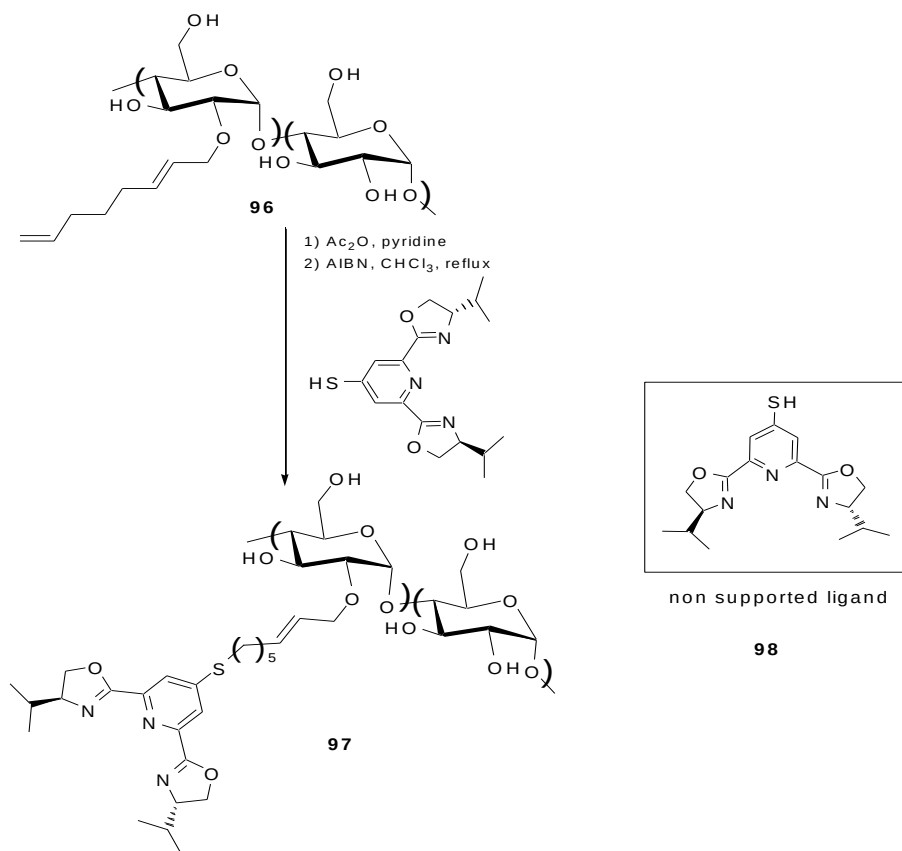
trans and 16% ee for the *cis*) towards the homogeneous complex formed with 98 (yield 67%, *trans/cis*: 89/11 with 77% ee for the *trans* and 63% ee for the *cis*) this supported catalyst showed better performance than that immobilized on silica [93]. These results pointed out a great influence of the support.



Scheme 43.



Scheme 44.



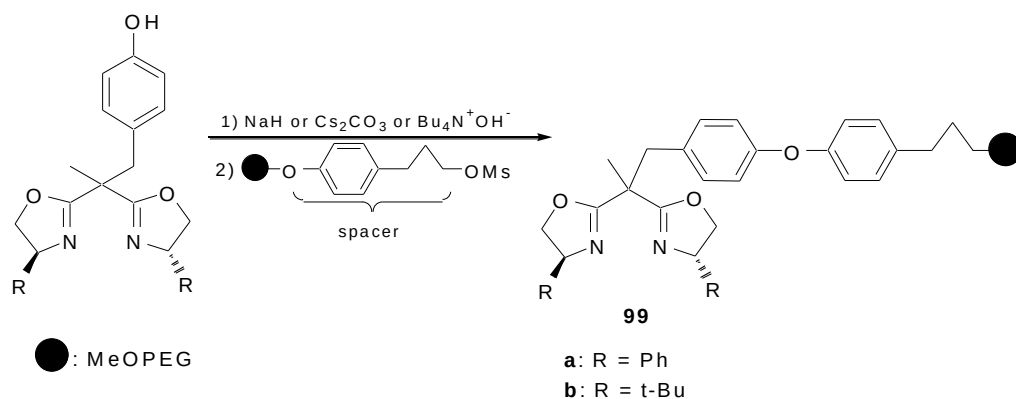
Scheme 45.

The homogeneous catalyst formed by reaction of non supported oxazoline 98 with RuCl_2 was very efficient, the ratio *cis/trans* was about 89/11 and enantioselectivities were 63% and 71% respectively. These values are lower than those achieved using 4H PyBox-Ru catalyst (88 and 70%) respectively, owing to the presence of a slightly electron-withdrawing group on the pyridine moiety of the ligand. The Ru-complex of the polymer supported ligand 97 exhibited lower activity and selectivity toward the cyclopropanation reaction of styrene. Three recycles were performed showing a *trans/cis* ratio and the enantioselectivity constants.

4.1.5. Soluble supported-polymer Box as ligands

Box 74a and 74b have also been immobilized onto the soluble polymer MeOPEG (a monomethylether of polyethylene glycol, $M_n > 2000$ Da) and employed as ligand in the Cu-catalyzed cyclopropanation of styrene and 1,1-diphenylethylene with EDA with up to 93% ee.

Taking into account the best parameters found with insoluble polymer, which were necessary to enhance the stereoselectivity of Box promoted reaction [94], i.e. disubstitution at the Box bridging atom and the necessity of introducing a spacer in order to separate the polymer moiety (PEG) to the ligand itself, Cozzi synthesized the supported polymers 99a and 99b (Scheme 46) [95]. With styrene, ligand 99b gave a *trans/cis* stereoselectivity in favour of the *trans* product (70%), the *trans* isomer presenting 87% ee. An increase of the yield (about 20%) was observed if the time of addition of EDA and of the reaction increased. In the same conditions, the results were inferior to those obtained with the *gem* dimethyl Box 74b but the two MeOPEG-supported catalysts presented similar behaviour. Recycling of the catalytic system was possible with marginal erosion of the catalytic activity and very limited loss in ee.

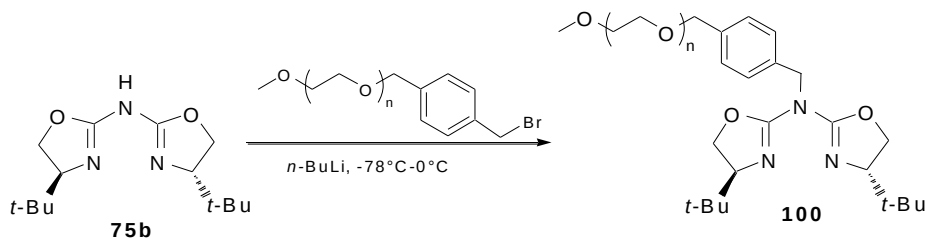


Scheme 46.

4.1.6. Soluble supported-polymer AzaBox as ligands

In 2000, Reiser [96] reported the first immobilization of aza-bis(oxazolines). Aza-bis(oxazoline) 74b has been easily grafted to a soluble polymeric support ((methoxy(polyethyleneglycol) MeOPEG 5000) in order to form soluble catalysts which could be recovered by precipitation. This polymer (100 Scheme 47) was obtained successfully (55% yield) if a benzylidene spacer linked to the PEG was employed. Complexed with Cu(II), this ligand was able to promote asymmetric cyclopropanation of styrene (Scheme 36: $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{Me}$, $R_4 = \text{H}$) and 1,1-diphenylethylene (scheme 36:

$R_1 = R_2 = \text{Ph}$, $R_3 = \text{Me}$, $R_4 = \text{H}$) with methyl diazoacetate in dichloromethane. With styrene, a diastereoselectivity in favour of the *trans* cyclopropane with a predominance of C over D was observed (C/B: 71/29, C: 91% ee B: 87% ee) with a yield of 69% (Scheme 36). Compared to the non-supported catalytic system (ligand 75b), the results in terms of diastereoselection and ee were 10% lower. The possibility of the reuse of this catalytic system was examined. 13 cycles were conducted without loss of ee, but to keep a good yield after the 10th use, it was necessary to reactivate the catalytic system with phenyl hydrazine.

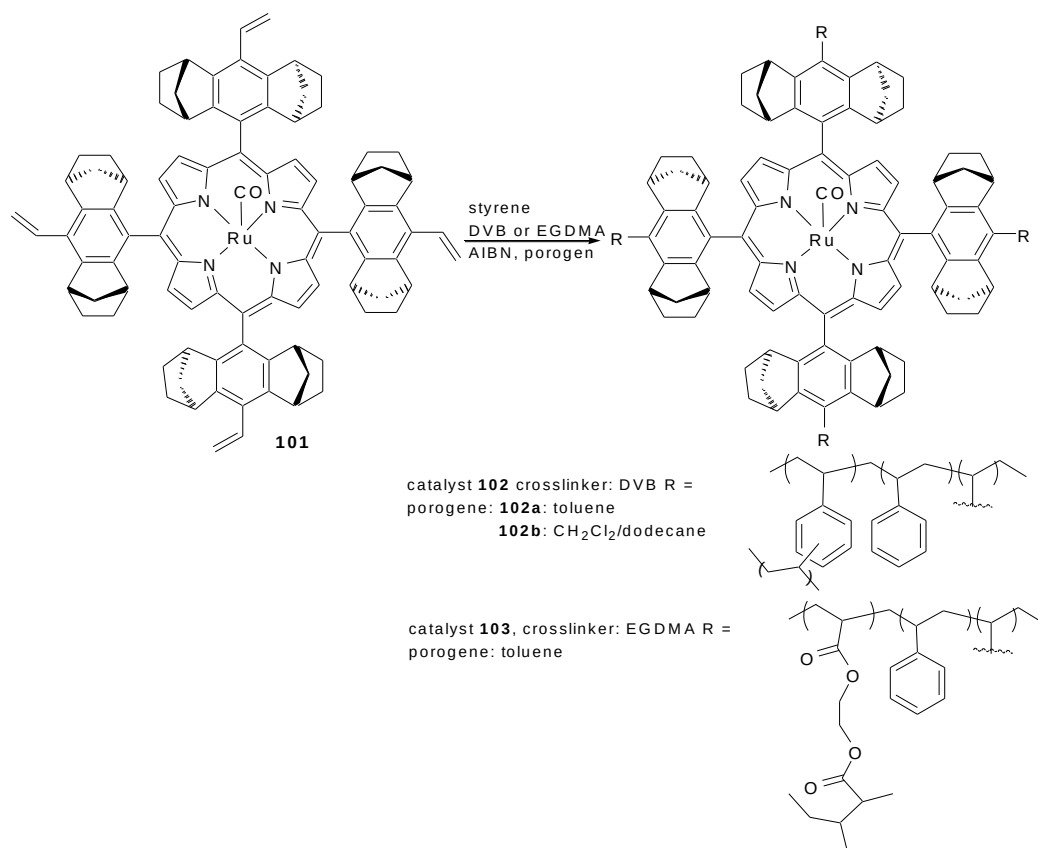


Scheme 47.

4.2. Porphyrins

More recently, chiral Ru-porphyrin polymers were used for catalytic asymmetric carbene transfer. A C₂-symmetric group containing two norbornane moieties fused to the central vinyl substituted benzene ring of a porphyrin was chosen in order to induce the chirality. Then the chiral ruthenium vinylporphyrin 101 was involved into radical copolymerization with styrene and DVB or EGDMA to lead respectively to monolithic resins chiral 102 and 103 which were crushed (Scheme 48).

In order to form cyclopropane esters and cyanocyclopropanes, EDA and diazoacetonitrile were respectively used in the cyclopropanation of various substituted styrenes. Although less enantioselective than their homogeneous counterpart, these catalysts in presence of EDA led to high stereoselectivities. For example with 102a, up to 92/8 for styrene and *p*-methoxystyrene and 97/3 for *p*-bromostyrene, in favour of the *trans* isomer were obtained. Yields were respectively 77%, 88% and 75%. The best ee (90%) was obtained with the *p*-bromo derivative. Moreover, diastereoselectivity and enantioselectivity were influenced by the nature of the porogenic solvent employed during the formation of the catalyst. Compared to 102b, better ee and diastereoselectivities were obtained with catalyst 102a (*trans/cis* ratio: 82/18 and 92/8; 82% ee and 71% ee respectively), these two catalysts having the same DVB/styrene ratio. This behaviour was attributed to the reduced accessibility of the catalytic sites, also evidenced with polymers prepared from higher DVB/styrene ratio. With 102 slightly lower results than those of 102a were observed. Concerning the cyclopropanation with diazonitrile, moderate activities from 35 to 53% yield and correct enantioselectivities around 70% were obtained, the best results being found with catalyst 102a. These catalysts were stable upon recovery and recyclability (no leach of metalloporphyrins) but a slight decrease in activity was observed [97].



Scheme 48.

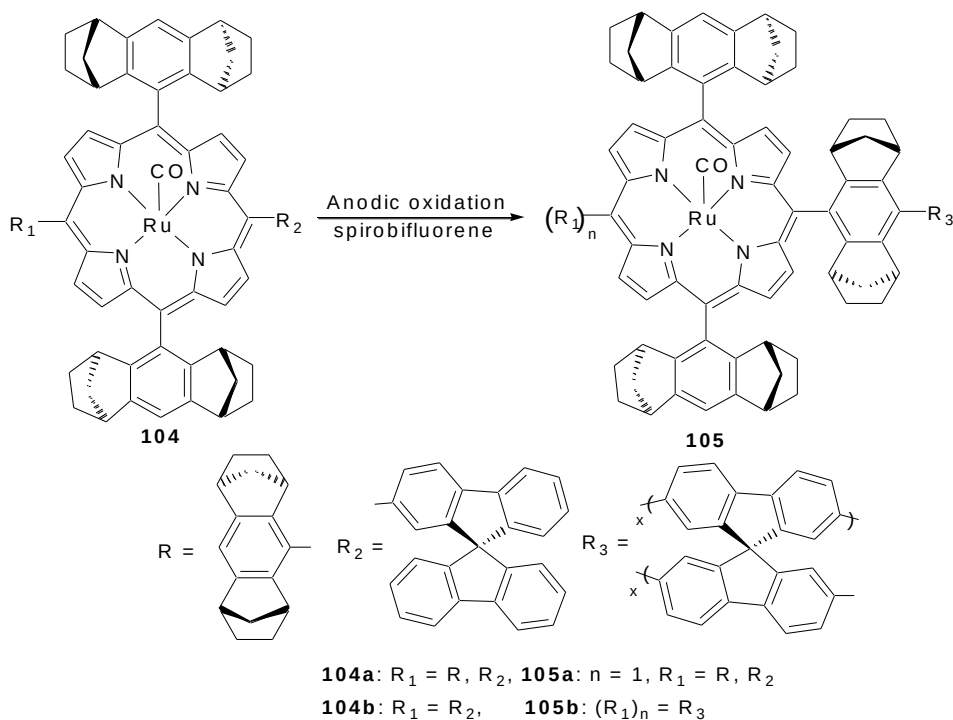
Supported metalloporphyrins have also been synthesized by electropolymerization leading to films of polymers. They were formed on the platinum working electrode during the oxidative electrosynthesis (Scheme 49) [98]. Contrary to the preceding catalysts **102** and **103**, these electropolymerized catalysts led to low enantioselectivities for the bench-mark reaction between styrene and EDA. Up to 53% ee at -40°C was reached in the presence of **105a**. Moreover, at room temperature, the reactions proceeded efficiently (yields 80-90%). Seven recycling of polymer **105a** were carried out without a significant decrease in enantioselectivity and activity.

4.3. Miscellaneous

Instead of Box ligand, carboxamidate coordinate with rhodium have been tested successfully for the cyclopropanation of some functionalized alkenes [99] (Scheme 50). The carboxamidate anchored to the NovaSyn Tentagel hydroxyl resin (TG) or Merrifield resin (Scheme 50) was treated with chiral dirhodium tetrakis[methyl 2-oxypyrrolidine-5(*S*)-carboxylate] (Rh₂((*S,S*)MEPY)₄) leading to the corresponding Rh-**106** and Rh-**107** precatalyst.

With these catalysts, intramolecular cyclopropanation of allyldiazoacetate was investigated (Scheme 51). Compared with homogeneous catalyst, yield of bicyclic lactone was similar to those obtained with the two catalysts i.e. 75% and 95% ee.

Catalyst with the Merrifield support (Rh-107) presented a yield of about 75% and a slight decrease in ee after 10 runs contrary to the TG one (Rh-106) which showed 10% of the yield and of about 20% ee decrease. Ligand loading had an influence only on the yield but not on the selectivity of the reaction. A similar study was performed with the cyclopropanation of styrene and EDA. Once again, the best catalytic system in terms of reproducibility of the results on the reuse corresponds to the Merrified one. For the first use they were quite equivalents.

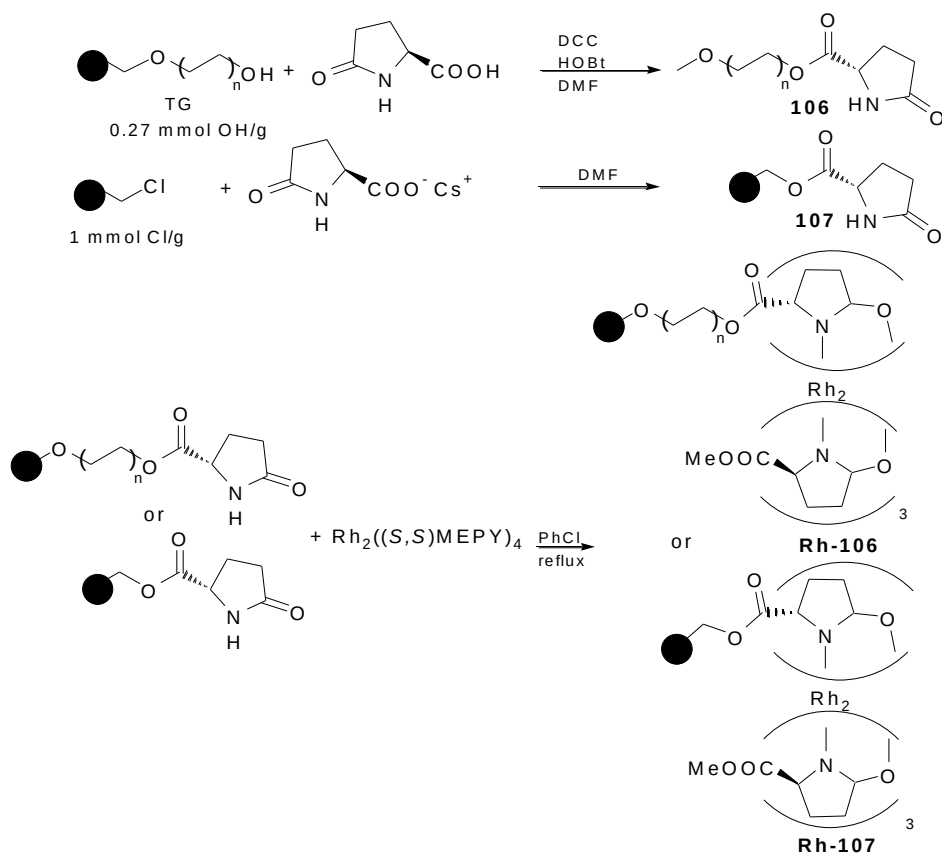


Scheme 49.

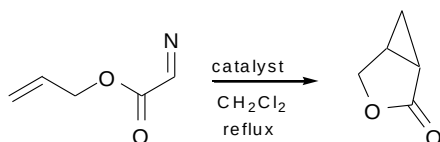
In 2003, Xia [100] has reported the cyclopropanation of styrene with alkyl diazoacetates by copper complexes of Schiff bases, derived from chitosan and substituted salicylaldehydes as the catalyst (Scheme 52). This natural polymer is an environmental friendly natural material: biocompatible, biodegradable, non toxic...

The influence of several parameters: nature of the solvent, temperature, the molar ratio styrene/EDA and the copper content [100] has been studied. Better yields were obtained with high temperature but better ee were found at 60°C, temperature for which the nature of the solvent had a great influence. From all the solvent tested, 1,2-dichloroethane, ethylacetate, acetonitrile and toluene, the best yield (91.5%) was obtained with 1,2-dichloroethane; toluene led only to 41.5% yield. Better ee were also found in 1,2-dichloroethane. When the molar ratio styrene/EDA was about 17/1 the results of this reaction were fairly good; as this ratio diminished, the yield and ee decreased and for a ratio of 2/1, the yield reached only 45.3%. Taking into account of all these parameters, it has been shown that to obtain the best compromise between the yield (81.5%), the best *cis/trans* ratio (35.3/64.7) and the best ee (*cis*: 20.7% ee, *trans*: 10%ee) for the cyclopropanation of styrene, a copper content

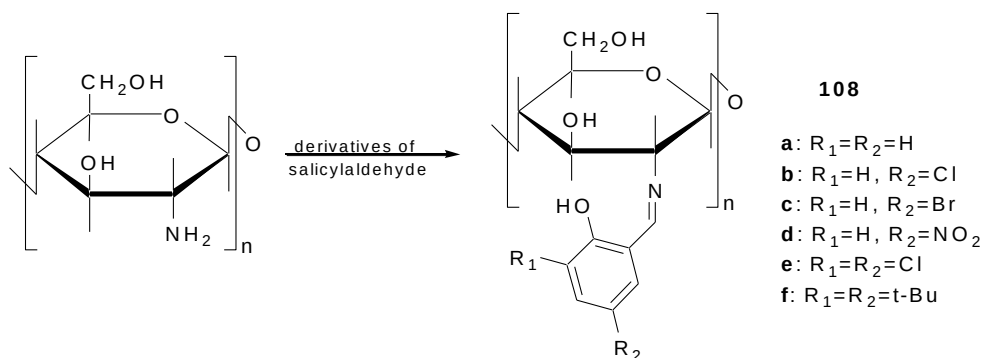
$(\text{Cu}(\text{OAc})_2)$ of 4.4 mol% was necessary with ligand 108a. More or less amount of the copper content led to a decrease of all these reaction results. It is noteworthy that neither the electron-withdrawing nor the bulky substituents on the salicylaldehyde of the catalysts had much influence on the yield, the ee of the *cis* and *trans* isomers but the nature of the diazoacetate had a great influence. Using *t*-Bu diazoacetate instead of the Et one resulted in a important increase of the ee for both the *cis* and *trans* isomers but with a dramatic drop of the yield. This behaviour could be a result of the steric hindrance of the *t*-Bu groups which provoked a difficulty to form metal carbene species by the reaction of *t*-Bu diazoacetate with the Schiff base copper complexes. These catalytic systems have also been use to transform other alkenes into cyclopropyl derivatives. In some cases, compared to the styrene reaction the cyclopropanation of 1-hepten or 1-octene gave better ee.



Scheme 50.



Scheme 51.



Scheme 52.

To conclude, for the cyclopropanation reaction, the difficulties consist in the achievement of high enantioselectivity close to a good stereoselectivity. To be useful in organic synthesis, the last requirement is preponderant and depends on the nature and the number of the substituents of the cyclopropane ring. It is the reason why, most of the catalytic systems used in heterogeneous supported catalysis cyclopropanation are formed by bis oxazolines complexes which have shown a excellent efficiency in non supported conditions.

In most of the cases, this reaction seems to be very sensitive to the polymer morphology controlled by crosslinking and the nature of the porogen agent which determine the performance of the immobilized catalyst.

5. CYCLOADDITIONS AND HETEROCYCLOADDITIONS

Discovered in 1928, the Diels-Alder reaction is one of the powerful synthetic methods for the construction of substituted cyclohexene that fits the modern concept of atom economy [4]. For this reason, in the last two decades, the asymmetric Diels-Alder reaction, leading to carbon-carbon bond formation, has received considerable attention and enantioselectivities greater than 90% have been reported [101]. In homogeneous conditions, a wide range of metal, ligands and dienophiles have been studied. Because of their high stabilities, most of the studies are focused on the use of *N*-containing complexes.

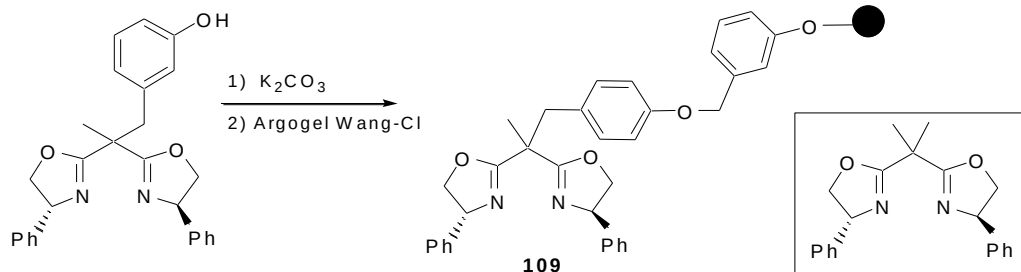
Concerning the Diels-Alder reaction, polymeric supports were mostly involved in solid phase synthesis where the diene and the dienophile are grafted onto the polymer. Compared to these procedures, only few examples involving supported catalysts were reported in the literature.

Most of these supported catalysts contain nitrogen as ligands such as Box, aminoalcohol, *N*-sulfonylamino acid and salen.

5.1. Supported Box Ligands

Moberg [102] developed a polymer bound bis(oxazoline) 109 (Scheme 53) as a zinc complex catalyst for the Diels-Alder reaction of cyclopentene with 3-(2-propenoyl)-2-oxazolidinone

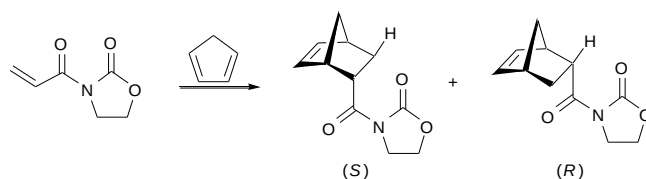
(Scheme 54). This supported catalyst was formed by grafting a phenolic bis(oxazoline) derivative onto an ArgoGel Wang-Cl resin and presented 0.071 mmol of ligand/g polymer.



Scheme 53.

Compared to the monomer (conversion 100%, *exo/endo* ratio: 94/6, ee: 85% for the *exo* adduct), the polymer supported catalyst gave no selectivity (racemic compounds are formed) and lower reactivity (13% at -40°C). This behaviour is probably due to the low swelling and the rigidity of the polymer at low temperature.

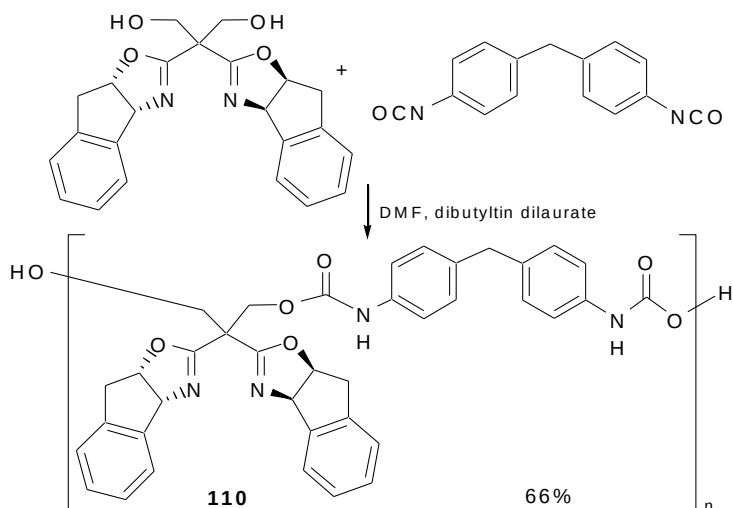
At the same time, Cozzi described the immobilization of Box ligands on PEG polymer (polymer 99, Scheme 49), and the corresponding copper catalyst used for the cyclopropanation reaction was also involved in Diels–Alder cycloaddition between cyclopentadiene and *N*-acryloyloxazolidinone (Scheme 54) [95]. This reaction was performed with 15 mol% each of Box ligand and $\text{Cu}(\text{OTf})_2$ in DMF in order to obtain homogeneous conditions. The reaction occurred in good yield (up to 83%) and excellent diastereoselectivity in favour of the *endo* stereoisomer (ratio *endo/exo* >98/2). However, the maximum of enantioselectivity was only 45% contrary to the non-supported Box equivalent catalyst which led to complete end at 95% ee and 88% yield.



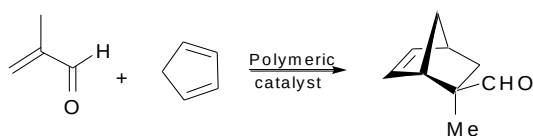
Scheme 54.

In 2002, Lemaire chose to immobilize indaBox, not only for its rigidity but also for its good enantioselectivities for the Diels-Alder cycloadditions [103]. The heterogeneization was carried out by polymerization as part of the main chain of a polymer backbone (Scheme 55). Mixed with $\text{Cu}(\text{OTf})_2$, polymer 110 (8 mol% relative to the oxazolidinone) was allowed to react with methacrolein and cyclopentadiene at -78°C (Scheme 56). The reaction was quantitative and led to the major *endo* diastereoisomer with 51-56% ee with 87-90% yields for the first three reaction cycles.

Itsuno synthesized supported aminoalcohols 111-113 (Scheme 57) [104] and *N*-sulfonylamino acid 114 [105-107] (Scheme 58) by radical suspension copolymerization of the corresponding monomer chiral styryl aminoalcohols and styryl sulfonylamino acid derivatives with styrene and eventually with a crosslinker.



Scheme 55.



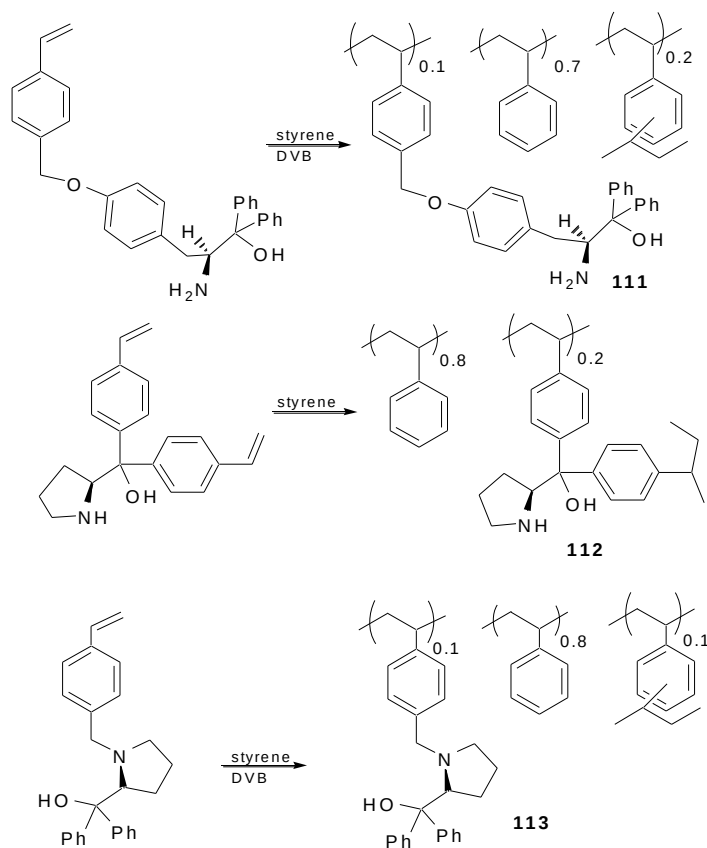
Scheme 56.

5.2. Supported Aminoalcohol and *N*-Sulfonylamino Acid-Derived Oxazaborolidine or Oxazaborolidinone

The styryl chiral sulfonylamino acid derived from L-valine 114a, L-isoleucine 114b, L-threonine 114c or D-2-phenylglycin 114d (Scheme 58). The loading of aminoacid residue was about 0.78-0.88 mmol/g for a polymer formed with 10% of the styryl chiral sulfonylamino acid, 80% styrene and 10% of DVB with a yield range of 85-96%. In the case of valine, for a polymer formed with 50% of the styryl chiral sulfonylamino acid, 40% styrene and 10% of DVB, it could be up to 2.55 mmol/g and 73% yield [105].

The Diels-Alder reaction was performed with cyclopentadiene and methacrolein (Scheme 56) in presence of 15 mol% of the oxazaborolidine and oxazaborolidinone catalysts derived respectively from supported aminoalcohols and from *N*-sulfonylamino acid polymers. The oxazaborolidine and oxazaborolidinone catalysts were formed in situ by action of BH_3 , BH_2Br , BHBr_2 or BBr_3 . The diastereoselectivity was excellent in favour of the *exo* adduct and yields from 65 to 99%. It is noteworthy that higher loading of chiral catalyst site in the polymer, lower *exo* selectivity and enantioselectivity. The diastereoselection depended not only on the nature of the supported ligand, the crosslinker but also on the borane and the solvent. Results are summarized in Table 6.

From all the oxazaborolidine catalyst, the L-valine derived catalyst 115a gave the highest enantioselectivity and an excellent ratio *endo/exo*. Moreover oxazaborolidinone polymeric catalysts having oxyethylene crosslinkages (116) present better performance.



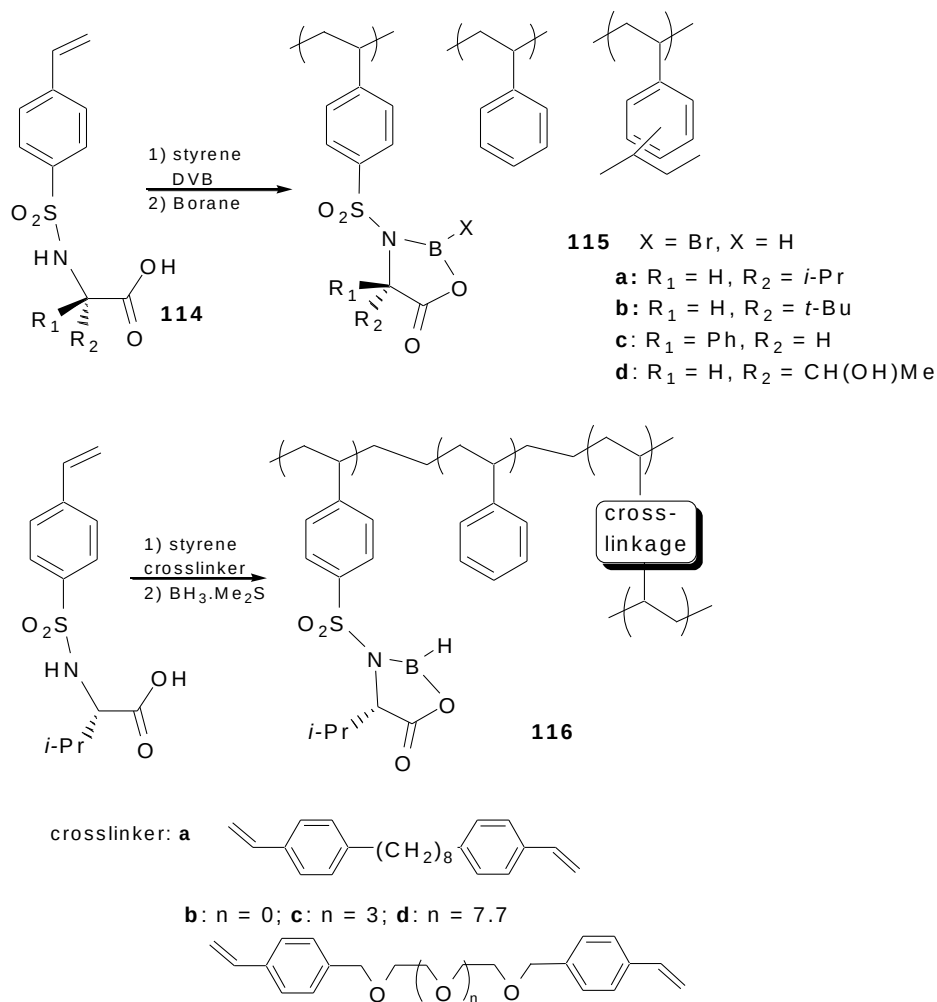
Scheme 57.

5.3. Supported Salen as Ligand

Seebach [108] prepared non-dendritic 117 and dendritic 118 and 119 styryl-substituted salen, monomers for crosslinking suspension copolymerization with styrene (Schemes 59 and 60). Complexed with Cr, these resulting copolymers were involved in Diels-Alder reaction of Danishefsky's diene with several aldehydes (Scheme 61). In all cases, these new Cr-salen catalysts led to slightly lower enantioselectivities than those observed with their homogeneous analogs under the same conditions. Surprisingly, upon reuse, enantioselectivities generally increased around 5% from the first to the fifth catalytic cycle. With caproaldehyde and with benzaldehyde enantioselectivities are respectively higher than 85% and 75%.

Recently, Schulz was carried out electropolymerization, an original methodology to prepare polymer supported salen 113 [109][110]. It consisted in the introduction of a thiophene moiety, an electropolymerizable functionality, on the salen backbone (Scheme 62) followed by electropolymerization under cyclic voltammetry conditions on a platinum grid. These polymeric catalyst 120a and 120b were then evaluated in hetero Diels-Alder reaction (HTR) between several aldehydes and 1-methoxy-3-[(methylsilyl)oxy]-1,3-butadiene

(Scheme 61) using 4 mol% 120a or 6 mol% 120b. It has been shown that the counter ion has quite no influence on the selectivity but the activity is lower with 120b containing BF_4 .



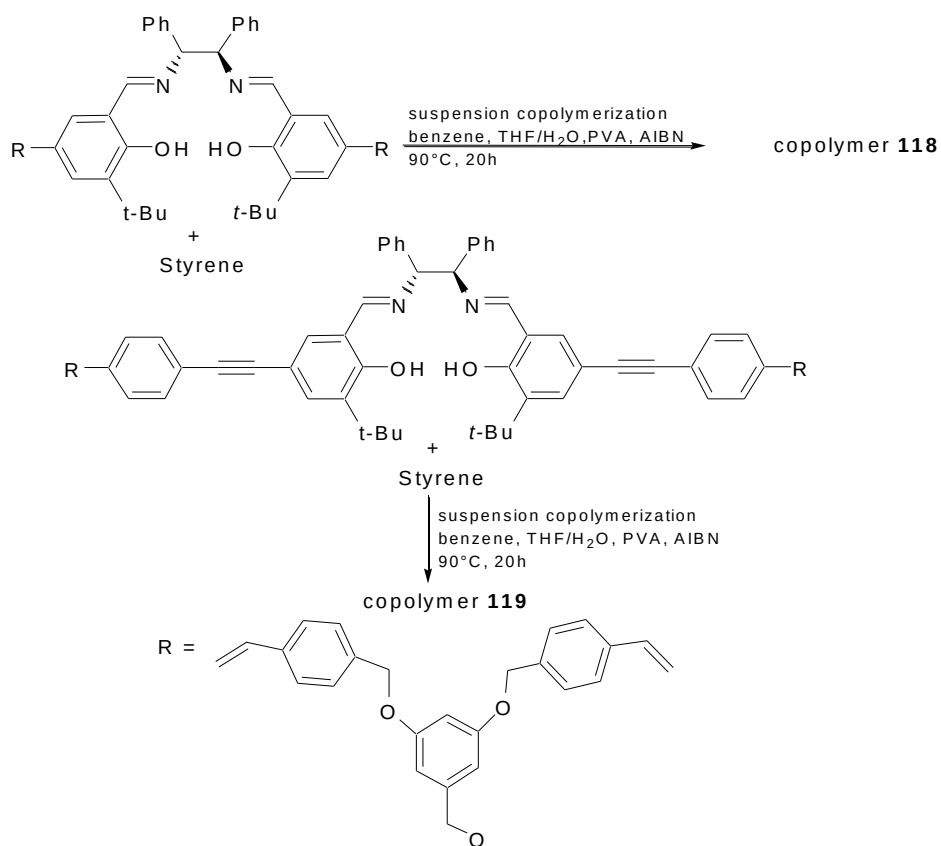
Scheme 58

Table 6. Asymmetric cycloaddition reaction of cyclopentadiene and methacroleine in presence of 15 mol% polymeric boron catalyst, at -78°C

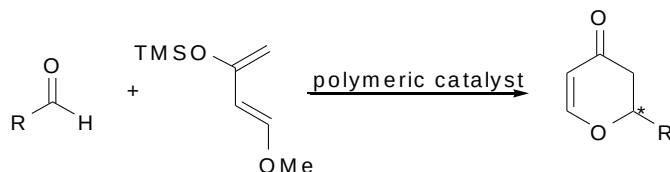
Polymer	Borane	Solvent	Yield (%)	Endo/exo	Ee (%)	Ref.
111	BH_2Br	CH_2Cl_2	96	8/92	16	[104]
112	BH_2Br	CH_2Cl_2	98	4/96	25	[104]
113	BH_2Br	CH_2Cl_2	99	< 1/99	44	[105]
113	BH_3	CH_2Cl_2	95	< 1/99	57	[104]
113	BH_3	$\text{CH}_2\text{Cl}_2/\text{THF}$	89	< 1/99	65	[104]
113	BBr_3	$\text{CH}_2\text{Cl}_2/\text{THF}$	96	5/95	54	[105]

Among the ligands used, chiral ligands bearing nitrogen chelating donor atom have been extensively studied due certainly to their easy preparation and availability. Furthermore, a lot of chiral ligands have proved to be highly efficient for the asymmetric alkylation of carbonyl or imine compounds in homogeneous phase. But, for the reasons explained in introduction, the use of homogeneous supported or heterogeneous ligand is preferable.

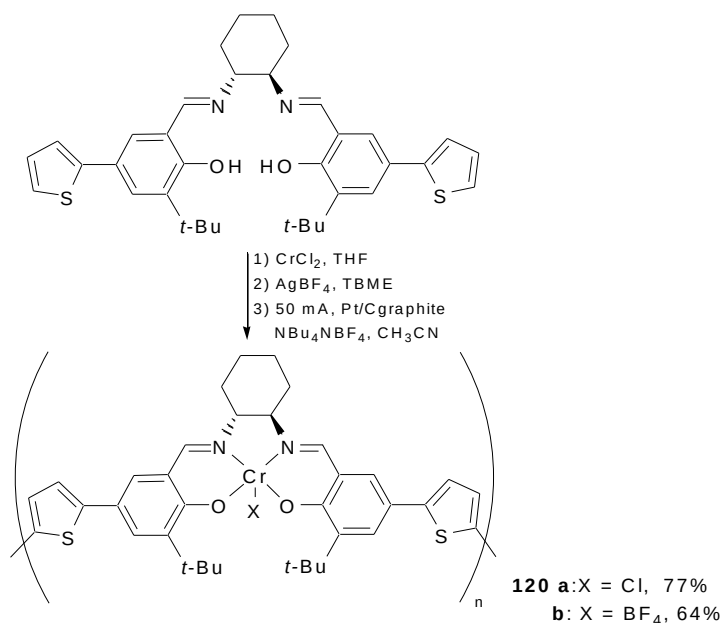
Among the polymer-supported ligands, derived-aminoalcohol ones have been largely used in this reaction but few are derived either from *N*-sulfonamideoalcohols, or oxazoline or salen.



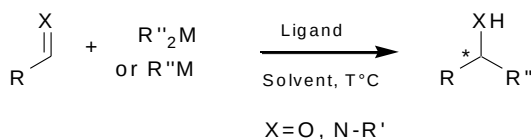
Scheme 60.



Scheme 61.



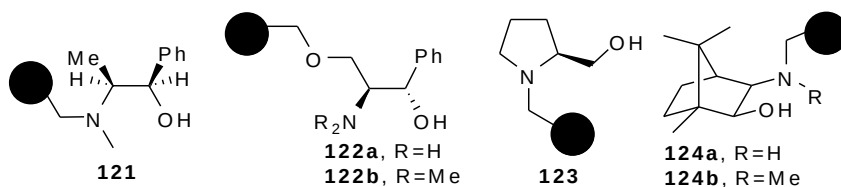
Scheme 62.



Scheme 63.

6.1. Supported Aminoalcohols as Ligands

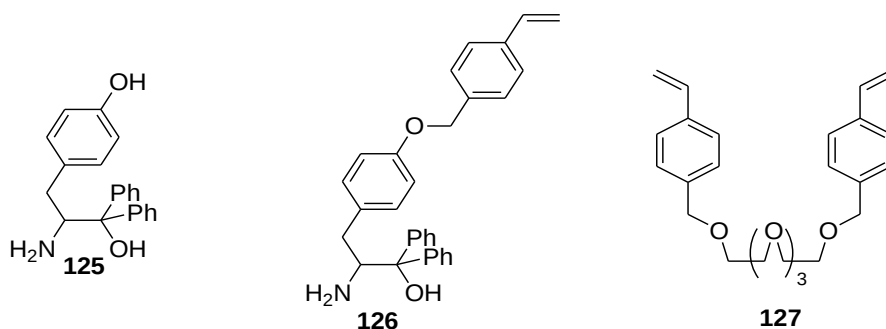
The first work about polymer-supported β -aminoalcohol used in the asymmetric nucleophilic addition to aldehydes was reported by Fréchet [113]. The best result (95% ee) was obtained by using a polymeric catalyst derived from *N,N*-dialkylated (-)-3-*exo*-aminoisoborneol **124b** for the asymmetric addition of diethylzinc to *o*-methoxybenzaldehyde in toluene at 0°C (Scheme 64). This catalyst was prepared through reaction of aminoalcohols with 1-2% crosslinked chloromethylated polystyrene. The chiral polymeric catalyst of the reaction could be used several times in further asymmetric reactions.



Scheme 64.

Soai has described the enantioselective addition of dialkylzinc reagent to aromatic and aliphatic aldehydes by using the supported-ligand 121 [114]. This latter was also prepared from (1*R*,2*S*)-(-)-ephedrine and chloromethylated polystyrene (1% divinylbenzene, 0.8 mmol Cl/g, 100-200 Mesh). In the case of benzaldehyde, the enantioselectivity was better than those reported with 124a (89% vs 80%) and with the *N*-alkylephedrine-based homogeneous catalyst. The authors mentioned that the catalyst could be easily recovered and reused. They also studied the reaction with norephedrine homolog and reported enhanced enantioselectivity in the case of aliphatic aldehydes [115]. Polymer-supported ephedrine 121 was also employed in the first heterogeneous enantioselective alkylation of *N*-diphenylphosphinoylimines and the best results (80% yield and 80 % ee) were obtained when the reaction was carried out in toluene at room temperature for 2 days [116].

Itsuno has reported interesting work about the effect of the difference of the structure of the polymeric part on the enantioselectivity of the reaction and the stability of the support [117]. They first prepared the chiral aminoalcohols 125 which could react with a crosslinked chloromethylated polystyrene or 126 which could be copolymerised with styrene and some styrene-derived crosslinking compound (Scheme 65).



Scheme 65.

Five different chiral polymers containing the same aminoalcohol moiety were synthesized (Scheme 66). Reaction of aminoalcohol 125 with a chloromethylated polystyrene crosslinked with 2% of divinylbenzene led to chiral polymer 128. When the highly crosslinked polystyrene containing 20% of DVB 129 was used, no reaction between 125 and this resin because of the lack of the swellability of the resin in organic solvents occurred. To avoid this problem, the crosslinking agent containing an oxyethylene chain 127 and the corresponding crosslinked chloromethylated polystyrene 131 were prepared. This latter swelled very well in organic solvents such as toluene and THF, even in the case of a highly crosslinked resin. Phenoxide anion of 125 could react with the chloromethyl group of polymer 131 to give the chiral supported ligand 132.

Three other chiral polymers have been synthesised by copolymerization of the chiral monomer 126 with styrene in the presence or not of crosslinking agent (Scheme 66). Chiral polymer 133 was prepared by suspension copolymerization of aminoalcohol 125 with styrene and DVB in a 1/7/2 molar ratio. Polymer 133 swelled well in organic solvents such as toluene, benzene and THF and that unusual swellability could be due to the bulkyness and polarity of the chiral monomer 125. The replacement of DVB by 127 as the crosslinking agent afforded chiral polymer 134 after copolymerization. This one also swelled well in

organic solvents and presented interesting mechanical stability. The solution polymerization of 127 and styrene led to the soluble linear chiral polymer 135.

The main problem of polymers containing a high degree of crosslinking is their stability with stirring over a long period of time. Indeed, their spherical beads are not enough stable and their breakdown during stirring lead to formation of a fine powder of the insoluble polymer. So the filtration at the end of the reaction is difficult and the reuse of the chiral polymer was not possible. The authors studied the effect of the magnetic stirring on the three highly cross-linked polymer beads and found that chiral 20% 127-crosslinked polymers 132 and 134 were more stable than polymer 133 prepared by using 20% DVB. For example, when stirring at 350 rpm for 4 days in toluene, 50% of polymer 133 was transformed into a fine powder contrary to 132 and 134 which kept their original bead form.

The five chiral polymers 128 and 132-135 were then tested in asymmetric addition of diethylzinc to benzaldehyde. Good enantioselectivities were obtained with chiral polymers 133-135 in opposite to the two others polymers 128 and 132. In the case of *p*-chlorobenzaldehyde, an excellent ee of 99% was obtained with polymer 134 in opposite to *o*-alkoxybenzaldehydes (21-54%) and longer reaction times were necessary to have satisfactory conversions with aliphatic aldehydes.

The recyclability of the chiral polymers was studied in a batch system using a simple loading of polymeric ligand 134 and both yield and ee were highly reproducible. Large scale of a chiral product could be obtained by using a continuous flow system. This technique have been tested with chiral polymer 133 and showed that a column containing 5 mmol of the polymer could produce about 90 mmol of (*S*)-1-(*p*-chlorophenyl)propanol with 94% ee. The main advantage of this technique is that it avoids the stirring which destroy the polymer during repeated reactions.

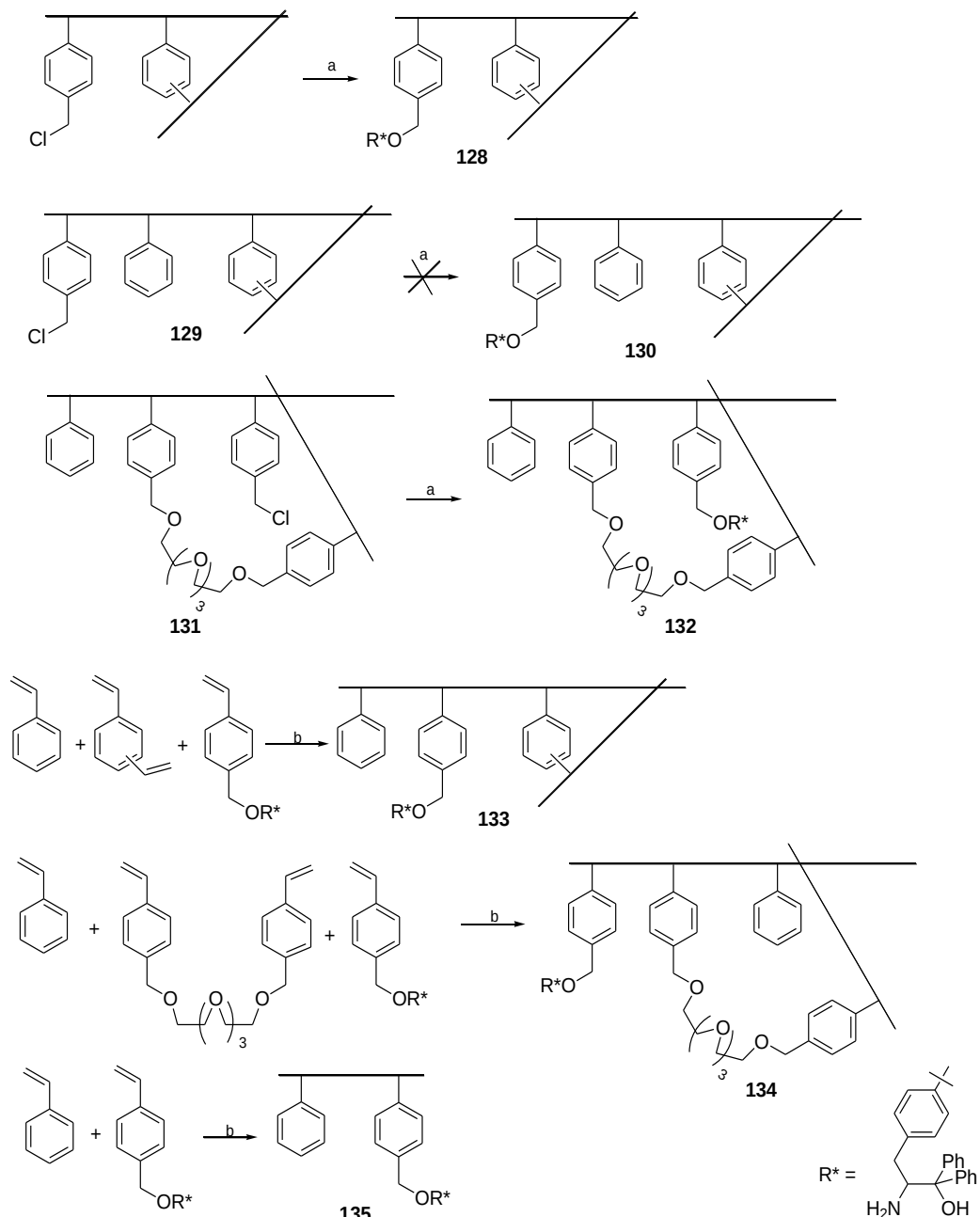
Soai and Watanabe have studied the effect of the introduction of a spacer between the ligand and the polymeric support [118]. In fact, when the polymer is directly connected to the nitrogen atom of the aminoalcohol, the polymer part could have an influence on the enantioselectivity since it is known that nitrogen atom is strongly involved in the formation of intermediate chiral zinc complex.

The two chiral polymers 137 (content of aminoalcohol moiety is up to 0.085 mmol/g) and 138 (content of aminoalcohol moiety up to 0.25 mmol/g) were prepared from polymer 136 (1% DVB; Cl: 0.8 mmol/g; 100-200 mesh) and the corresponding chiral aminoalcohols (Scheme 67).

The enantioselective addition of diethylzinc to aldehyde at 0°C with chiral polymers 137-140 was examined. With aromatic and aliphatic aldehydes, higher enantioselectivities were obtained with chiral polymers 137 and 138 containing a six-methylene spacer compared to the two chiral polymers 139 and 140. The same level of enantioselectivity was found with recycled chiral polymers. The authors assumed that the spacer has here two effects. The steric repulsion between the aminoalcohol part and the polystyrene is reduced and the spacer acts as a substituent of the nitrogen atom which assists the stereochemical control of the reaction.

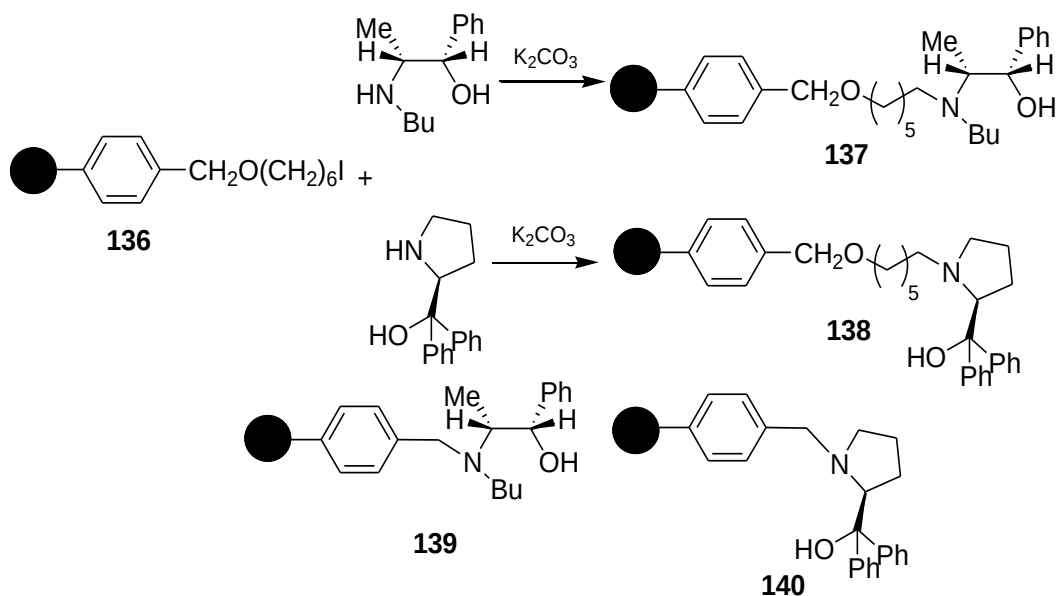
The four-methylene chain analog of chiral polymer 137 and chiral polymer 139 were also tested in the asymmetric alkylation of *N*-diphenylphosphonylbenzaldimines [119]. Contrary to aldehydes, both yield and enantioselectivity were lower with chiral polymer containing a spacer between the polymeric moiety and the catalytic part. The authors then examined the reaction conditions with 139. The result of their screening was that the best yields and ee's

were obtained when the reaction was carried out in toluene at room temperature in presence of 1 equivalent of the polymeric ligand.



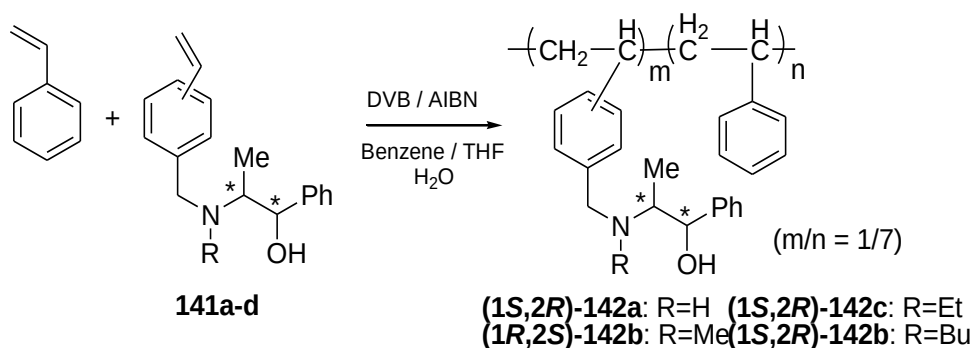
Scheme 66. (a) R^*OH , NaH , DMF . (b) $AIBN$, THF

Ephedrine or norephedrine-derived copolymers 142a-d have also been used in the same reaction [120]. These chiral polymers were prepared by copolymerization of monomer 141a-d with styrene and DVB in a molar ratio 141a-d/styrene/DVB of 1/7/2 (Scheme 68).



Scheme 67.

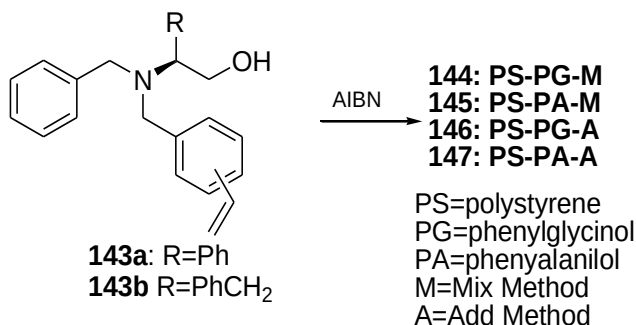
The asymmetric addition of diethylzinc to *N*-diphenylphosphinylbenzaldimine was carried out in toluene at room temperature in presence of the chiral copolymerized ligands 142a-d. Although the yields were low to moderate, the enantioselectivity was moderate to high (64%-88% ee) particularly with the chiral ligands 142b and 142c. The enantioselectivities with these two polymers were comparable with those observed with the corresponding monomer 141b and 141c. The recyclability of polymer 142b was also tested and this one could be reused without loss of enantioselectivity.



Scheme 68.

Hosoya has reported the preparation of polymer-supported ligand which has only moderate enantioselectivity because the aim of the work was to show the effect of the type of immobilization [121]. The polymeric ligands were prepared by two different techniques, the Mix Method and the Add Method. The Mix Method was a classical polymerization: the ligand-containing monomer was dissolved in the mixture of monomers and porogenic solvent was used for the second-step swelling. After completion of this step, the polymerization step was carried out at 70°C with slow stirring for 24h to lead to the resulting polymers 144 and

145. The Add Method consisted in adding the same amount of monomers 143 in the aqueous polymerization medium 4h after the initiation of the polymerization to give the polymers 146 and 147 (Scheme 69). The two monomers were quantitatively incorporated in the beads produced by the Mix Method and only 44% of monomers for the Add Method.

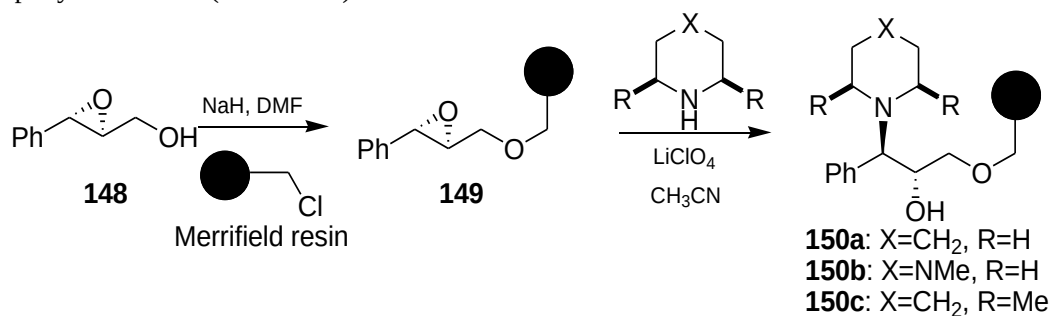


Scheme 69.

The catalytic activity of the different polymeric ligands was evaluated in the asymmetric ethylation of aldehyde in hexane. The polymers derived from the Mix Method gave better results in terms of activity and enantioselectivity than those from the Add Method. However, both yields and ee were slightly lower than those obtained with the monomeric ligands 137.

When a mixture of toluene/hexane (1/1) was used as solvent, chemical yield dropped significantly.

The effect of the level of functionalization and crosslinkage of different Merrifield resins was also tested [122]. Chiral polymers 150 were prepared in two steps from enantiopure epoxyalcohol 148 (Scheme 70).



Scheme 70.

These chiral polymers 150 with different levels of crosslinking and ligand functionalization were evaluated in the asymmetric addition reaction of diethylzinc to benzaldehyde and the results are summarized in Table 7. Although the conversions were higher than 95%, the enantioselectivities were low to moderate and significantly lower than those observed with the corresponding homogeneous ligand [123]. In all cases, the best results were obtained with both lower level of cross-linking (1%) and level of chlorine per gram of resin (1.2 mmol) of the chloromethylated polystyrene. Higher the level of aminoalcohol residue is, more important the formation of dimeric zinc alkoxide is. These

dimeric species are suspected to be inactive in catalysis, requiring a preliminary dissociation before the catalysis step.

Table 7. Enantioselectivity for the ethylation of benzaldehyde with chiral polymers 150

Ligand (%DVB ; fa)	Amount (%) ^b	ee (%)
150a (1; 0.8)	5	36
150a (2; 1.6)	4	22
150a (2; 1.8)	3	20
150b (1; 0.9)	5	39
150b (2; 1.6)	4	20
150b (2; 1.7)	3	19
150c (1; 1.0)	3	69
150c (2; 1.6)	4	57
150c (2; 1.7)	3	57

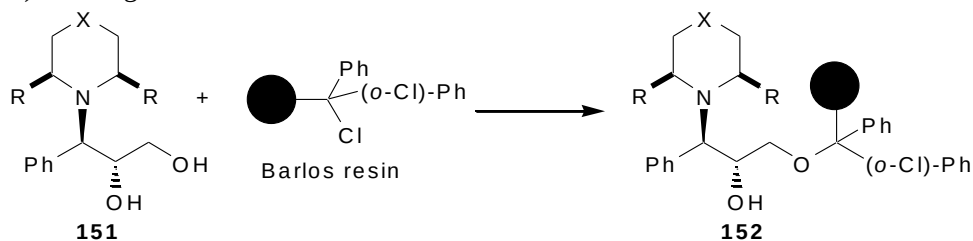
^a f=mmol of ligand/g resin (calculated by elemental analysis of nitrogen).

^b amount of catalyst (% molar with respect to benzaldehyde)

. It was assumed that the low enantioselectivity was probably due to a lack of bulky substituents on the primary hydroxy group of the chiral aminodiol. The *cis* 2,6-dimethylpiperidine-derived aminoalcohol 151 was anchored to 2-chlorotrityl chloride resin (Barlos resin) leading to polymeric ligand 152 (Scheme 71, Table 8).

The use of an amount of 5 mol% of functionalized Barlos resin 152 in the asymmetric addition of Et₂Zn to benzaldehyde in toluene was highly efficient and (S)-1-phenylpropanol could be isolated with an excellent ee (entry 2, Table 8. When the reaction was carried out at 0°C, the enantioselectivity was slightly improved (entry 3, Table 8).

The asymmetric addition of Et₂Zn to different aromatic and aliphatic aldehydes using the functionalized Barlos resin 146 was also studied and both conversions (> 82%) and ee's (>86 %) were high.

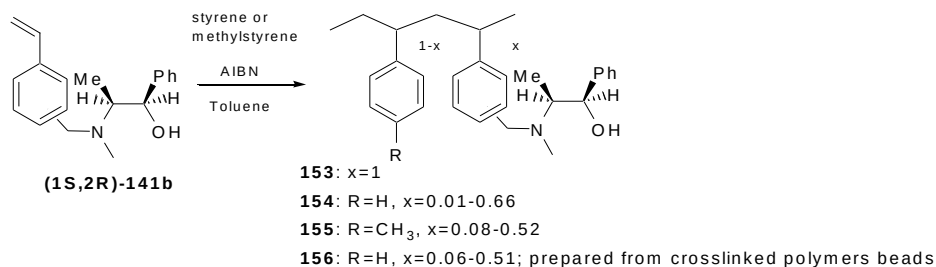


Scheme 71.

Table 8. Asymmetric addition of diethylzinc to benzaldehyde using 152

Entry	f (mmol ligand/ g of resin)	% molar ligand	T (°C)	Ee (%)
1	0.9	4	rt	79
2	1.1	5	rt	92
3	1.1	5	0	93
4	1.2	5	0	94

Hodge has also studied the reaction by using chiral polymers from ephedrine-derived monomer 141b [124]. Homopolymerization of monomer 141b in presence of AIBN in toluene and copolymerisation with styrene or 4-methylstyrene in various proportions led respectively to chiral polymers 153, 154 and 155 (Scheme 72).



Scheme 72.

Chiral polymers 153-155 were used for the asymmetric addition reaction of diethylzinc to benzaldehyde. The reactions were carried out in toluene at room temperature for 24 hours. The results are summarized in Table 9. Although the major product was the 1-phenylpropanol, benzyl alcohol was detected as a minor product with each polymer 153 (9%), 154 (0-6%) and 155 (6-7%). As we can noticed in Table 9, the higher the loading of catalyst is, the lower the yield and the ee are. It can be explained for highly loading polymers by the presence of dimeric zinc alkoxide species which drop the catalytic activity of the catalyst. Higher yield and ee were obtained with Zn-complex derived from 154f and 154g which were soluble in toluene (entries 7-8, Table 9). In the case of polymers 155 (entries 9-13, Table 9), the reaction was heterogeneous and yield and ees increased as the loading decreased. The enantioselectivities obtained with polymers 154d-154g (loading $\leq 1.32 \text{ mmol.g}^{-1}$) and 154d-155e (loading $\leq 1.32 \text{ mmol.g}^{-1}$) were similar or better than those obtained with the model ligand, (1R,2S)-N-benzylephedrine.

Table 9. Effect of the ligand loading of polymers 153-155 on the catalytic activity

Entry	Polymer	Fraction of monomer 135b (x)	Loading (mmol.g^{-1})	Yield (%)	ee (%)
1	153	1	3.52	47	44
2	154a	0.66	2.98	56	56
3	154b	0.52	2.65	66	67
4	154c	0.28	1.81	80	79
5	154d	0.18	1.32	95	81
6	154e	0.05	0.44	98	82
7	154f	0.03	0.27	100	83
8	154g	0.01	0.09	100	83
9	155a	0.52	2.56	65	69
10	155b	0.46	2.38	67	74
11	155c	0.36	2.03	74	76
12	155d	0.17	1.16	92	81
13	155e	0.08	0.61	92	86

The authors then turned their attention to the preparation of crosslinked polymer beads which are more insoluble and are more convenient to use than the linear polymers 153-155. Different chiral crosslinked polystyrene beads 156 were prepared by reaction of various crosslinked polystyrene beads with (1*R*,2*S*)-*N*-benzylephedrine in presence of potassium carbonate.

The catalytic properties of these various crosslinked polymer-supported ephedrine have been tested in the asymmetric addition reaction of diethylzinc to benzaldehyde and the results are summarized in Table 10. The reactions were carried out either in toluene or hexane at 0°C or 20-23°C. As it can be noticed in Table 10, the enantioselectivities were higher in toluene. Compared to linear polymers 153-155, lightly crosslinked chiral polymers led to the best results in terms of yield and ee. The use of Amberlite XAD-4 and Polyhipe™ as support proved to be not efficient. It was assumed that probably for both supports the catalytic sites are more in the inner surfaces of the pores and that result in a high local concentration of aminoalcohol residue which lead to a significant site-site interaction. Chiral polymer 156a was also used in the asymmetric ethylation of 2-methoxybenzaldehyde and 4-chlorobenzaldehyde under similar conditions and ees reached 90-93% when the reaction was performed at 0°C.

Three other polymers 158 were prepared by homopolymerisation and copolymerisation of aminoalcohols 157 and by grafting of the corresponding aminoalcohol onto 1% crosslinked polystyrene beads containing 0.70 mmol.g⁻¹ of chloromethyl group leading to a polymer containing 0.64 mmol.g⁻¹ of ligand residue (Scheme 73) [124].

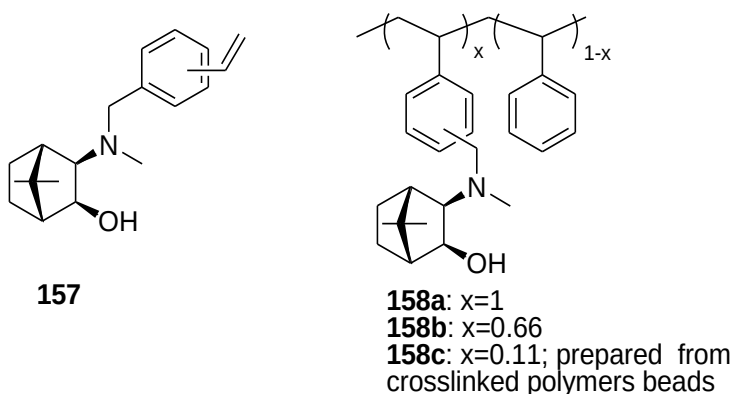
Table 10. Asymmetric diethylzinc addition to benzaldehyde using crosslinked polymer beads 156.

Entry	Polymer	Starting polymer	Catalyst loading	Degree of substitution	Yield (%) (yield) ^a	ee (%) (ee) ^a
1 ^b	156a	1% crosslinked gel	0.93	0.12	81 (81)	81 (64)
2 ^c	156a	1% crosslinked gel	0.93	0.12	85 (-)	78 (-)
3 ^b	156b	1% crosslinked gel	1.13	0.15	77 (83)	77 (62)
4 ^c	156b	1% crosslinked gel	1.13	0.15	85 (81)	74 (65)
5 ^b	156c	1% crosslinked gel	2.30	0.40	80 (82)	74 (62)
6 ^c	156d	1% crosslinked gel	2.30	0.40	86 (97)	73 (65)
7 ^b	156d	2% crosslinked gel	1.06	0.14	70 (-)	72 (-)
8 ^b	156e	2% crosslinked gel	2.62	0.51	71 (76)	69 (62)
9 ^b	156f	Amberlite XAD-4	0.90	0.11	59 (62)	28 (39)
10 ^c	156g	Amberlite XAD-4	0.50	0.06	75 (70)	28 (39)
11 ^b	156h	Polyhipe™	1.51	0.21	59 (57)	42 (23)

^a Under brackets, reaction was carried out in hexane. ^b Reaction was carried out at 0°C for 70h. ^c Reaction was carried out at 20-23°C for 20h.

Contrary to ephedrine-derived polymers 153-156, the use of a high loading of the catalytic residue (≥ 2.48 mmol.g⁻¹) for chiral polymers 158a and 158b gave excellent enantioselectivities for the ethylation of benzaldehyde and similar to those obtained with the corresponding non-polymeric chiral aminoalcohol. This surprising excellent result with a high loading of aminoalcohol unit polymer is probably due to their high solubility in toluene. The

enantioselectivity obtained with the crosslinked polymer beads 158c with a ligand loading of 0.64 mmol.g^{-1} was also high (97% ee).



Scheme 73.

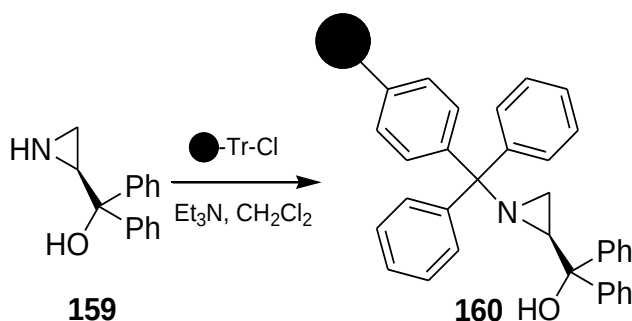
The authors were then interested to use the two enantiomers of ephedrine- and camphor-derived polymeric ligands 153-156 and 158 in a flow system [125]. When polymeric ligand 156a and its enantiomer analog (1% crosslinking, 1.11 mmol/g of aminoalcohol residue) were employed with a flow rate of 2 mmol.h^{-1} of benzaldehyde and a diethylzinc/benzaldehyde ratio of 2.5/1, the ee were respectively 81% and 72%. Lightly crosslinked beads 156 (0.2% crosslinking, 1.78 mmol/g loading) produced the (*R*)-alcohol in a yield of 98% and in 98% ee. With a flow rate of 2.5 mmol.h^{-1} of benzaldehyde, the ee dropped slightly (91% vs 98%).

Supported-ligand 158c (with a ligand loading of 0.64 mmol/g) was also tested in a flow system because this polymer-supported catalyst gave better results than ephedrine one 156. A loss of catalyst performance was noticed here; indeed, the chemical yields and enantioselectivity dropped significantly after approximately twelve runs (run 1: 95% yield and 97% ee; run 12: 59% yield and 87% ee). It was suggested that the deterioration in performance could be due to the oxidation of the hydroxyl group of the aminoalcohol unit.

(*S*)-aziridinyldiphenylmethanol 159 was immobilized to polymer-bound triphenylchloromethane (1.1 mequiv/g) to lead to the new chiral polymer 160 (Scheme 74) [126]. This latter was employed in the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes. For example, (*S*)-1-phenylpropanol was isolated in a yield of 92% and an ee of 96% when the reaction was performed in a 1/1 mixture of toluene and dichloromethane. The presence of dichloromethane proved to be essential for swelling of the polymer and making the catalytic sites accessible to substrates. With other aromatic aldehydes and cyclohexane carboxaldehyde, the same range of chemical yield and ee was obtained. But with acyclic aliphatic aldehydes the chemical yield and ee dropped significantly. The recyclability of the chiral polymer 160 has been investigated and it was noticed a slightly decrease of the enantioselectivity of 1% per run.

Styrenic L-prolinol-derived ligand *N*-Boc-60 was immobilized on chemical inert, mechanically stable polyethylene fibers by electron beam induced preirradiation grafting using styrene as a co-monomer to lead to polymer fiber 161 with a loading of 0.2 mmol/g [127]. Carbamate function was then removed under classical conditions to produce polymer 162 (Scheme 75). Chiral polymer 162 was used as ligand in the diethylzinc addition to

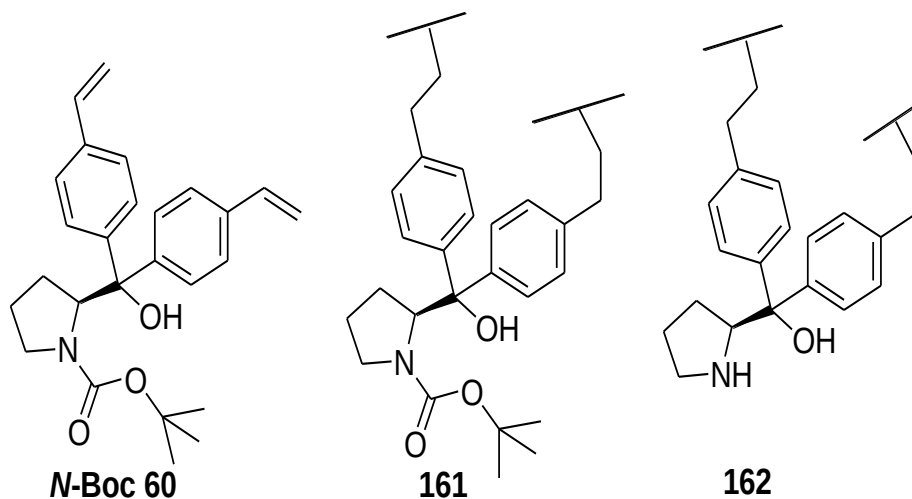
benzaldehyde and yield and ee were very low (36% and 24% respectively). A higher yield of 55% could be obtained in a titanium-mediated addition of diethylzinc to benzaldehyde by using the protected chiral polymer 161 with the same enantioselectivity.



Scheme 74.

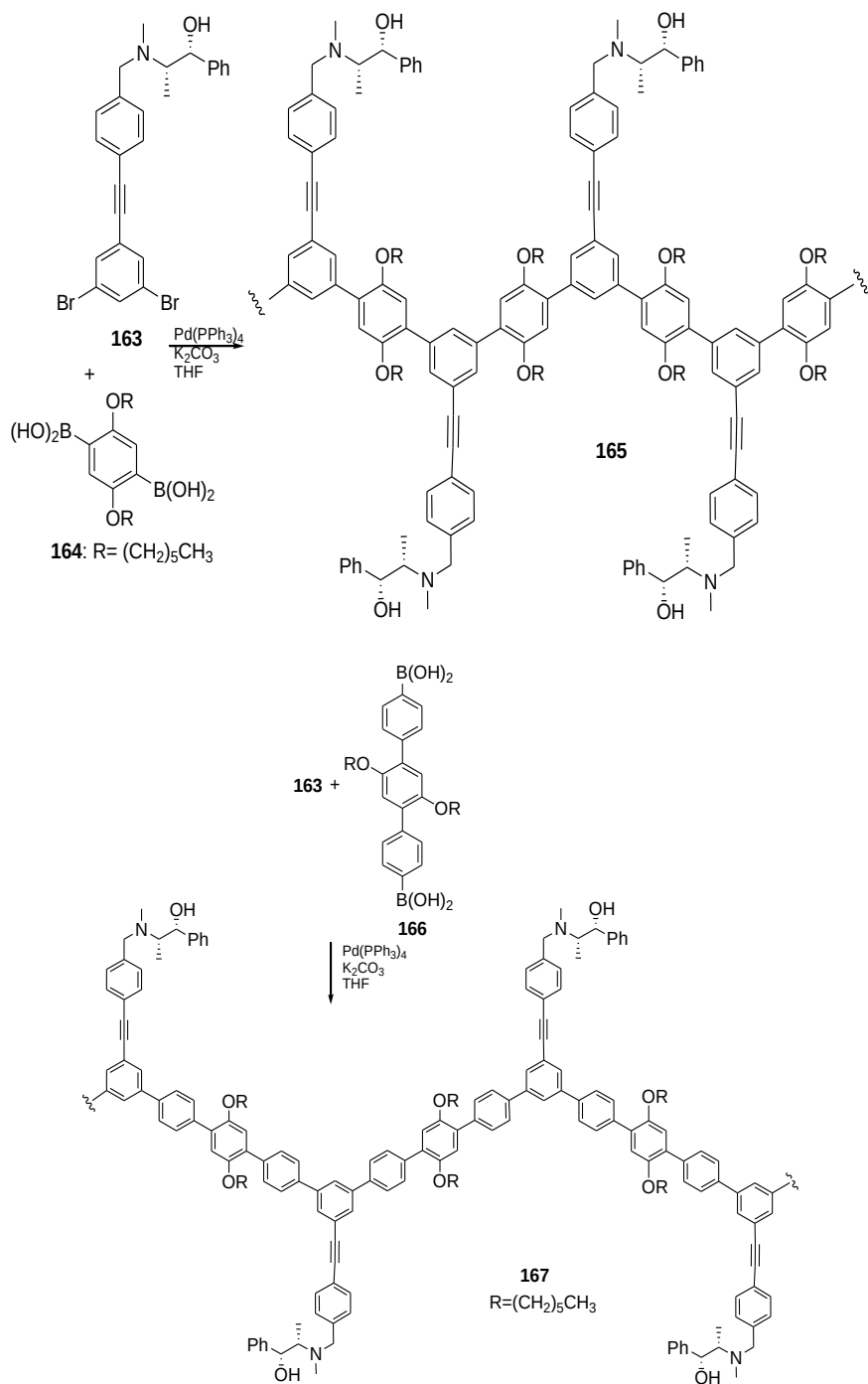
In order to improve the catalytic properties of this supported- α,α -diphenylprolinol polymer fibers, Degni has tested the immobilized ligand 67 with a loading of 0.4 mmol/g (Scheme 30) [128] in the diethylzinc addition to benzaldehyde.

The chemical yields were largely superior to those obtained with polymer 162 (95-98% vs 30-36%) and the enantioselectivities were also higher and reached 40% which was comparable to the corresponding non-polymeric ligand.



Scheme 75.

Chiral polymer 67 was also tested in another enantioselective reaction, the Carreira reaction. The phenylacetylene addition to benzaldehyde in presence of zinc triflate using 67 as polymeric ligand was carried out. The corresponding propargyl alcohol was isolated in a moderate yield but with an excellent enantioselectivity of 91%. This supported ligand was also recycled for this reaction without loss of catalytic activity.



Scheme 76.

A new strategy for optically active chiral polymers was envisaged and based on a Suzuki coupling polymerisation of (1*R*,2*S*)-ephedrine unit-bearing monomer with rigid linkers [129]. The Suzuki coupling of ephedrine-derived dibromide **163** (which was prepared in four steps from (1*R*,2*S*)-ephedrine) with the diboronic acid **164** in presence of Pd(PPh₃)₄ afforded chiral

polymers 165 (Scheme 76). Synthesis of chiral polymer 167 containing a longer linker between two chiral units has been performed by using diboronic acid 166. Both polymers were soluble in common solvents such as CH_2Cl_2 , THF, CHCl_3 ...

The chiral polymeric ligands 165 and 167 were then employed in the diethylzinc addition to benzaldehyde and anisaldehyde. The enantioselectivities obtained with both polymers were between 74 and 76% for the two aldehydes. The polymers could be recovered by precipitation from methanol and the recycled polymeric ligand showed the same catalytic properties.

Chiral bicyclic aminoalcohol-containing polymers 170 and 173 were produced from the industrial waste material 168a generated in the industrial process of synthesizing the ACE inhibitor Ramipril at Aventis. Supported ligand 170 was obtained by grafting of compound 168b (obtained in two steps from 168a) onto a Merrifield resin (1.1 mmol Cl/g) and after reaction of the resulting polymer with phenyl Grignard (Scheme 77) [130]. Excellent yields and ee (83 and 89 % respectively) were observed for the diethylzinc addition to benzaldehyde for the heterogeneous ligand 170 and were similar to those obtained for the homogeneous reaction.

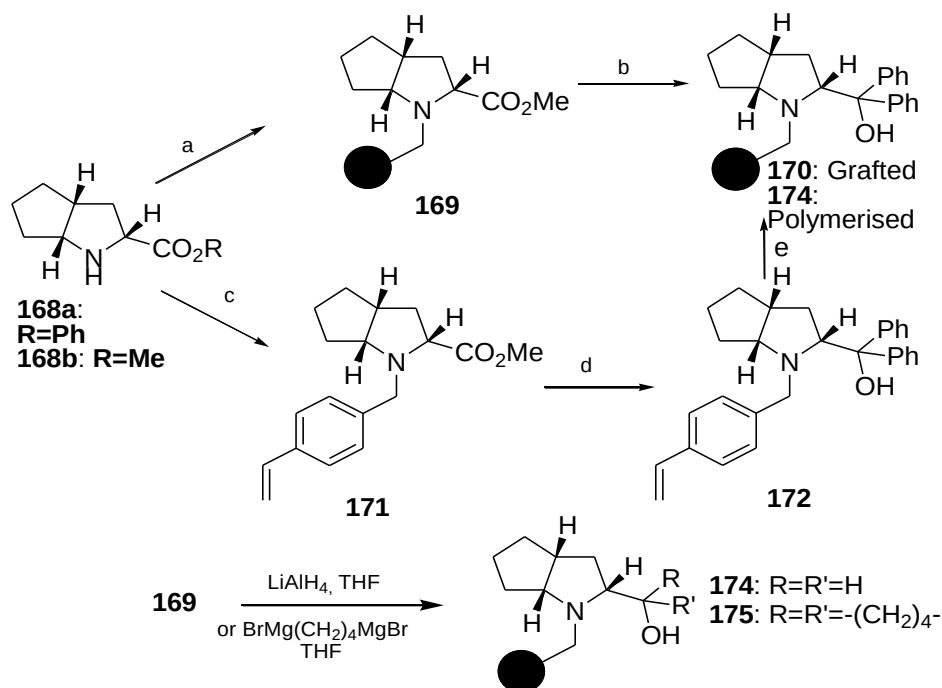
In a second time, the authors turned their attention on the preparation of flow systems. They considered that in some cases the chiral supported ligands isolated by polymerisation led to higher enantioselectivity. The monolithic column was selected as polymerisation technique because the resulting material is more suitable for the preparation of flow systems because of its better porosity properties. Monoliths 173 with the desired morphology and properties were obtained by mixing 40 wt% of monomers (10 mol% of 172/90 mol% of DVB; no styrene) and 60 wt% of toluene/1-dodecanol as the porogenic mixture (10 wt% of toluene). A flow system was performed and after 24 h, (*R*)-1-phenylethanol was isolated with an excellent ee of 99%. This enantioselectivity is better than those obtained with the corresponding homogeneous ligand and with the grafted ligand 170 and is one of the best ee observed with a polymeric ligand. The authors assumed that this efficiency could be due to the formation of more appropriated chiral cavities because of the polymerization process or to the high level of crosslinking agent used which isolates the aminoalcohol residue. Chiral polymer 173 could be reused for four successive runs without loss of enantioselectivity.

Reduction of the ester function of polymer 169 or treatment with a dimagnesium bromide reagent led to the two immobilized aminoalcohols 174 and 175 (Scheme 77). Chiral polymer 174 proved to be not efficient for the diethylzinc addition to benzaldehyde (11% yield and no ee) and with chiral polymeric ligand 175, for the same reaction, the yield was excellent but the enantioselectivity was low (40%) [131].

The same group has developed a small library of supported chiral aminoalcohols from different amino acid [132]. The hydrochloride salt of different amino acid methyl esters 176 reacted with a chloromethylated polystyrene-divinylbenzene (1 mmol Cl/g, 1% DVB) under basic conditions to afford the polymeric amino acid ester 177.

Reduction of the ester function or addition of Grignard reagents led to supported-amino alcohols 178-181 (Scheme 78). The nitrogen atom of these polymers was then methylated to afford the *N*-methylated polymeric aminoalcohols 182-185.

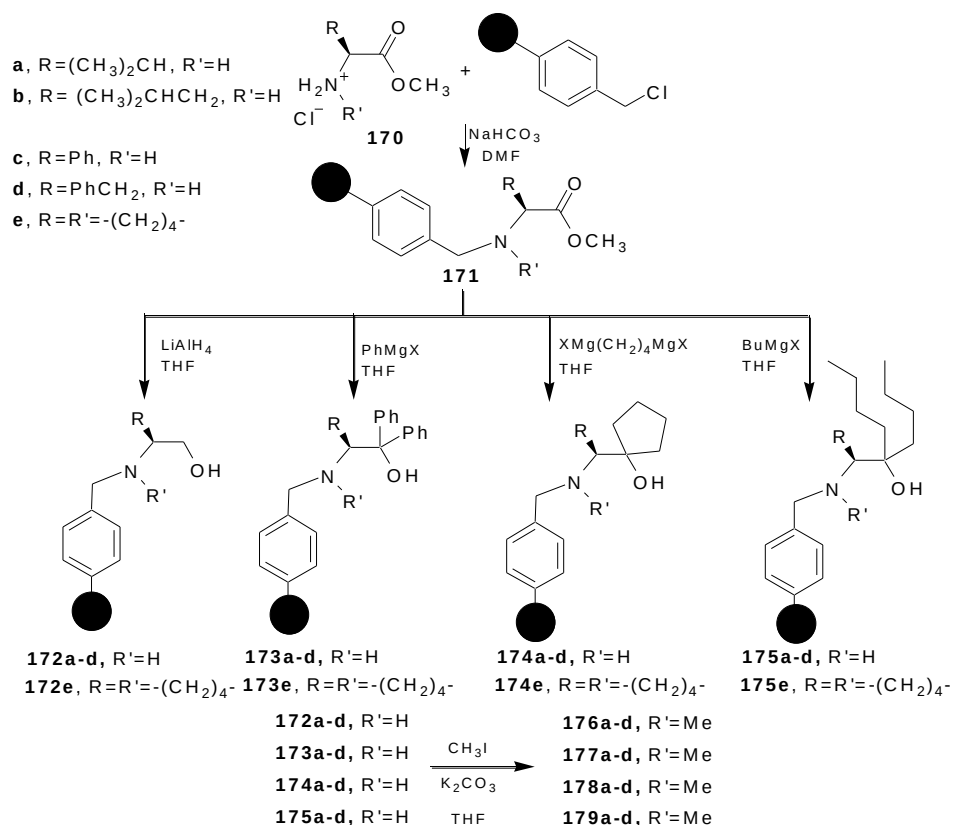
Chiral polymers 178-181 were first tested for the diethylzinc addition to benzaldehyde using 10 mol% of the supported catalyst. In all cases, the chemical yield and the selectivity (based on the 1-phenylethanol/benzyl alcohol ratio) were moderate and the ee were around 10 % except for the (*S*)-proline-derived polymer 180e (45% ee). The low catalytic activity could be due to the presence of the NH group in polymers 178a-d – 181a-d.



Scheme 77. Reagents and conditions: (a) Merrifield resin (1.1mequiv/g, 1%cross-linking), NaHCO_3 , THF. (b) PhMgX , THF. (c) 4-vinylbenzyl chloride, NaHCO_3 . (d) PhMgCl , THF. (e) A49/DVB/Toluene/1-dodecanol, AIBN.

In order to improve the catalytic activity of these supported ligands, the nitrogen atom of these polymers was then methylated to afford the *N*-methylated polymeric aminoalcohols 182-185. The catalytic activity of these heterogeneous ligands was evaluated and the results are summarized in Table 11. The analysis of the results showed that an increase in selectivity is accompanied by an increase in the enantioselectivity. Polymers 182 were poor catalysts and that is probably due to the non-presence of substituent in α position. The most surprising results are those obtained with polymers 183 bearing two phenyl groups in α position since this type of aminoalcohols give generally high enantioselectivity. The best results were obtained with immobilized aminoalcohols 184a and 185b which are derived from respectively valine and leucine. This last one gave a higher selectivity (91 vs 86 % for 184a) but a lower enantioselectivity (74 vs 80 % for 184a) (entries 9 and 14, Table 11).

Supported chiral bispidine-derived aminoalcohols were screened in the addition of diethylzinc to benzaldehyde [133]. These immobilized ligands were obtained in three steps from compound 186 isolated from *N*-Boc-piperidin-4-one (Scheme 79). The hydroxyl function of 186 was first linked onto chloromethylated polystyrene to afford polymer 187. The carbamate was then removed under classical conditions and reaction of the resulting polymer with chiral epoxides led to chiral polymeric bispidine-derived aminoalcohols 188.

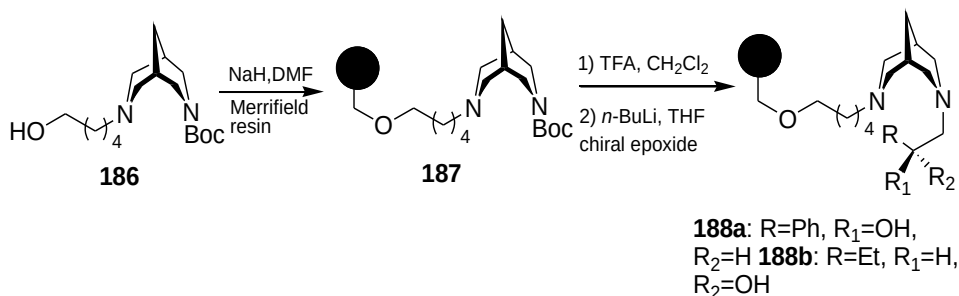


Scheme 78.

Table 11. Enantioselective diethylzinc addition to benzaldehyde using 182-185.

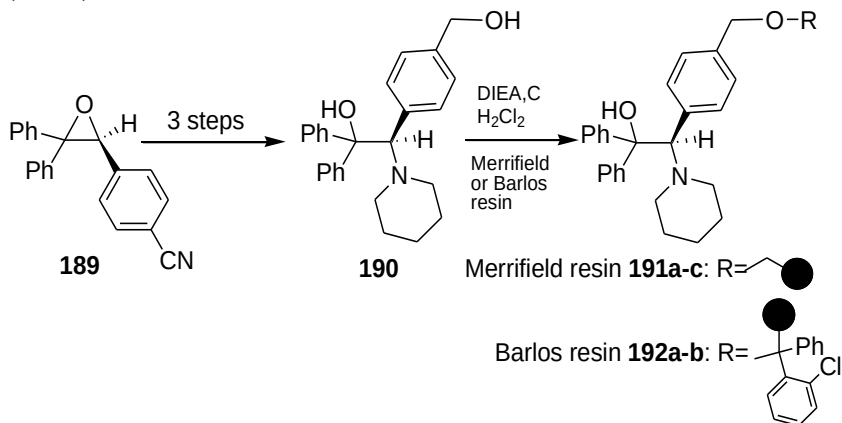
Entry	Polymer	Yield (%)	Selectivity (%)	ee (%)
1	182a	89	55	10
2	182b	94	65	15
3	182c	93	56	7
4	182d	82	48	2
5	183a	89	63	15
6	183b	90	70	24
7	183c	83	58	11
8	183d	97	70	24
9	184a	99	86	80
10	184b	81	53	22
11	184c	90	68	23
12	184d	92	70	20
13	185a	92	73	34
14	185b	98	91	74
15	185c	94	86	17
16	185d	95	85	45

Catalytic activity of both chiral polymers **188** was then evaluated in addition of diethylzinc to benzaldehyde. Although yield reached 95%, the enantioselectivity was poor (25% ee for **188a** and 5% ee for **188b**) contrary to the corresponding non-polymeric ligand homolog of **188a** (96% ee).



Scheme 79.

Pericas has reported the immobilization of (2*R*)-2-piperidino-1,1,2-triphenylethanol analog **190** onto several resins with different levels of crosslinking and functionalization [134]. These different chiral supported aminoalcohols **191** and **192** were prepared by attaching the aminoalcohol **190** via the benzylic hydroxyl group to different Merrifield resin (0.63-1.49 mmol Cl/g; 1 or 2 % DVB) and to two Barlos resin (1.24-1.6 mmol Cl /g) (Scheme 80). These functionalized resins were then tested in the enantioselective diethylzinc addition to benzaldehyde and the results are summarized in Table 12. The five polymer-supported aminoalcohols exhibited high enantioselectivities (>92 %) and except **192b**, they presented a similar profile of catalytic activity. After six consecutive runs, the recovered **191c** showed no loss of performance. This supported-ligand **191c** was also used with other aldehydes including aromatic and aliphatic aldehydes and both conversion and enantioselectivities were excellent (>95%).



Scheme 80.

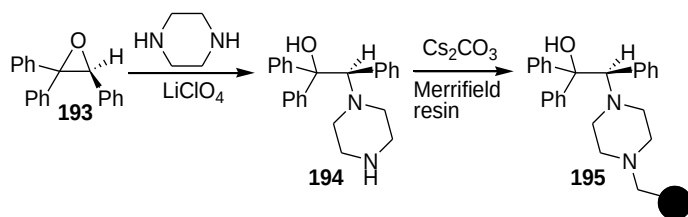
Table 12. Effect of functionnalized resins 191 and 192 on the enantioselectivity

Entry	Starting resin	Functionalized resin (f^b)	Ee
1	Merrifield (1% DVB; $f_0^a = 0.63$)	191a (0.375)	95
2	Merrifield (1% DVB; $f_0 = 1.49$)	191b (0.850)	93
3	Merrifield (1% DVB; $f_0 = 0.63$)	191c (0.389)	95
4	Barlos ($f_0 = 1.6$)	192a (0.925)	93
5	Barlos ($f_0 = 1.24$)	192b (0.689)	92

^a f_0 =mmol Cl/g. f =mmol/g (calculated by elemental analysis of nitrogen with the following formula: $f=0.714\%$ N).

The asymmetric phenylation of different aldehydes was performed with chiral supported ligand 191 and the corresponding diarylmethanols were isolated in good to excellent yields (74-99%) and high enantioselectivities (85-91%) were observed but were slightly lower to those recorded with the homogeneous ligand [135].

Although the enantioselectivity obtained previously were among the best for supported ligands, the preparation of the aminoalcohol unit just before anchoring required up to five steps from commercial precursors. The supported-ligand 195 was prepared in only two steps from (*S*)-triphenylethylene oxide 193 (Scheme 81) [136]. The aminoalcohol 194 was anchored to a Merrifield resin (2% DVB, $f_0 = 0.84$) with an anchoring yield of 97 %.



Scheme 81.

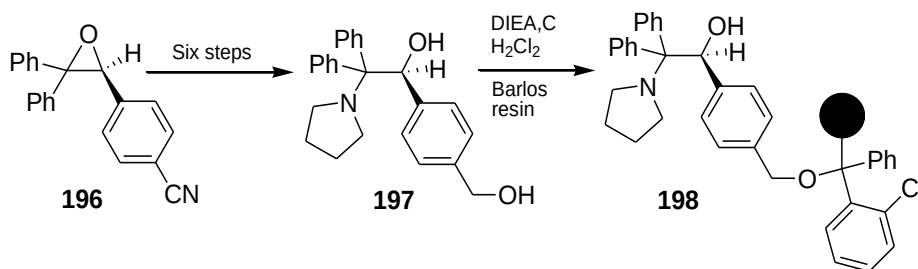
The catalytic activity of the polymer-supported aminoalcohol 195 was then evaluated for the diethylzinc addition of aldehydes. After optimization of the reaction (temperature, amount of catalyst), two types of reaction conditions (2 mol% of 195, 0°C, 8h and 4 mol% of 195, 0°C, 6h) were tested with 15 different aldehydes. With the first reaction condition type, the conversion and the enantioselectivity were already high ($\geq 95\%$) for most aromatic aldehydes, the second one permit a complete conversion for all aromatic and aliphatic aldehydes and a better one for the α -substituted aldehydes.

In order to evaluate the effect of the polymer part on the catalytic activity, two parallel kinetic measurements on the diethylzinc addition to benzaldehyde using either 195 or the *N*-benzyl non-polymeric ligand were performed. The profiles for both ligands are practically similar and at short reaction times, the polymer-supported ligand 195 showed a slightly better activity than its homogeneous analog (83% conversion vs 80% after 30 min).

This supported ligand proved to be highly recyclable in five consecutive runs without any loss of catalytic activity ($> 99\%$ conversion) and enantioselectivity (average of 95.1 %).

The enantioselective phenyl transfer to different aldehydes was also carried out using the chiral polymer 195 with 5 mol % of catalyst amount and the enantioselectivities were also high ($\geq 82\%$) for aromatic aldehydes and moderate for aliphatic ones (68-79 %) [135].

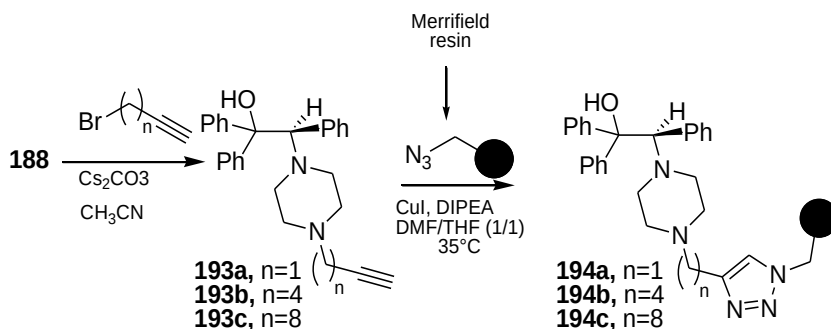
Polymeric regioisomer of 191 and 195 was also synthesized and evaluated in the ethylation of aldehydes since the homogeneous analog was a highly active ligand [135]. Aminoalcohol 197 which was synthesised in six steps from epoxide 196 was anchored to Barlos resin with $f_0 = 1.6$ to lead to polymeric ligand 198 ($f = 0.90$) (Scheme 82).



Scheme 82.

The ethylation of aromatic and aliphatic aldehydes in toluene at 0°C in presence of an amount of 8 mol% of the supported-ligand 198 was performed. Except for α -substituted aldehydes (around 50% conversion), both conversion and ee were high. The phenylation of aromatic aldehydes was also tested with polymeric ligand 198. Although conversions were excellent, the enantioselectivities were moderate (38-48% ee) and lower than those obtained with functionalized resin 191 and 195.

In order to avoid the limitation of the use of the anchoring step as a source of diversity to prepare libraries of supported ligands containing the same type of aminoalcohol as 195, click chemistry was employed. This more convenient and efficient technique is a copper(I)-catalyzed cycloaddition between an alkyne and an azide [137]. Aminoalcohol-derived alkynes 199 were prepared by reaction of 194 with different bromine reagent. The reaction between these alkynes and a variety of azido resins with different degree of functionalization ($f = 0.74 - 2.25\text{ mmol N}_3/\text{g}$) was performed to afford the supported-ligands 200 (Scheme 83).



Scheme 83.

The new functionalized resin 200a was first tested in the phenylation of *p*-tolualdehyde and *p*-anisaldehyde in toluene at 10°C using 5 mol% of the catalyst and the dependance of enantioselectivity on the level of functionalisation was studied (entries 1-6, Table 13). The

first analysis of the results was that the enantioselectivity depended strongly on the level of functionalisation of the resin. For the phenylation of *p*-tolualdehyde (entries 1-4), the higher the degree of functionalization, the lower the enantioselectivity. When a high ligand-loaded polymer was employed, the diarylcarbinols were isolated in their racemic form (entry 4). In this case, the triazole ring could interfere with the catalytic site involving a drop of the enantioselectivity. In order to avoid that, catalytic activity of resins 200b and 200c bearing a spacer were evaluated in the phenylation of *p*-tolualdehyde and *p*-anisaldehyde (entries 7-14, Table 13). It can be noticed that the two polymeric ligands 200a and 200b gave the best results in terms of conversion and ee. Resin 200b with a level of functionalization of 0.72 mmol/g exhibited the best catalytic activity (entries 9 and 13). This last one was chosen for phenylation of other aromatic and aliphatic aldehydes and the same range of conversion and enantioselectivity was obtained. The recyclability of this supported-ligand was studied on *p*-anisaldehyde and no decrease of the conversion was observed after three consecutive runs while a slightly drop in the enantioselectivity was recorded.

The enantioselectivities were around 20% lower than those obtained with similar supported-ligand 195 with no triazole ring and for that reason the idea that the triazole ring could interact with zinc reagent is reinforced.

Until now, supported diphenylprolinol were build either by copolymerisation with a vinylbenzyl group on nitrogen atom or a vinyl group on phenyl or by anchoring the ligand onto a Merrified resin via its nitrogen atom. Chen has reported a strategy to support this type of ligands using 4-hydroxydiphenylprolinol 201 [138]. Basic treatment of 201 with polymers 202 prepared in two steps from Merrifield resin (1% DVB, 100-200 mesh, 1 mmol Cl /g) led to supported-aminoalcohols 203a and 203b with a loading of aminoalcohol residue of 0.66 and 0.42 mmol/g respectively (Scheme 84).

Table 13. Effect of the level of functionalisation of polymer 200 on activity and selectivity.

Entry	Polymeric ligand	<i>F</i> (mmol L/g)	Conversion (%)	ee (%)
1	200a	0.59	95	74
2	200a	0.74	>97	68
3 ^a	200a	0.71	89	63
4	200a	1.16	>99	0
5	200a	0.59	64	77
6 ^b	200a	0.71	92	71
7	200b	0.66	100	66
8 ^c	200b	0.66	68	66
9	200b	0.72	95	76
10 ^b	200b	0.72	99	78
11	200c	0.67	79	75
12	200b	0.66	68	77
13	200b	0.72	97	82
14	200c	0.67	54	76

^a3.6 % of catalyst. ^b10% of catalyst. ^cHigher crosslinked polymer (2% DVB).

These two immobilized ligands were tested in the diethylzinc addition to benzaldehyde and the best results were obtained when the reaction was performed in hexane at rt using an

amount of 10 mol% of catalyst. Polymeric ligand 203a showed a slightly better activity than 203b (91 % yield and 63% ee vs 85% yield and 57% ee). The optimized reaction conditions in the presence of 203a as ligand were used with different aldehydes. Except for salicylic aldehyde, *p*-nitrobenzaldehyde and cyclohexanecarboxaldehyde, the same range of yield and ee were observed. Five consecutive diethylzinc addition to benzaldehyde reactions using the same batch of polymer 203a were carried out without loss of the catalytic activity for the three first ones while a slight decrease of the catalytic was detected for the fourth and fifth run. The replacement of the ether bond between the 4-hydroxyprolinol and the spacer by an ester link has been performed [139]. Wang has prepared the polystyrene-supported diphenyl prolinol 205 and the soluble polymer-supported analog 206 in two steps from aminoalcohol 201 (Scheme 84). The loading of aminoalcohol was evaluated to be at 0.76 mmol/g for supported ligand 205 and 0.42 mmol/g for the soluble one. With polystyrene-supported ligand 205 for the enantioselective diethylzinc addition to aldehyde, the best result (92 % yield, 68% ee) was obtained when the reaction was carried out in toluene at 25°C using 15 mol% of the catalyst.

Both yield and ee were similar to those obtained with the ether-linked polymeric ligand 203 but the reaction time was shorter. The optimized conditions were also used with other aromatic aldehydes and the enantioselectivities were moderate to good (34-71%).

Soluble polymer-supported ligand 206 was also tested and for all the aldehydes used both yield and enantioselectivity were higher than those using the polystyrene-supported 205. This latter could be reused at least 3 times without significant loss of performance contrary to its soluble analog.

The first immobilization of a pyridine-based tridentate ligand has also been investigated since the tridentate can stabilize the zinc complex and reduce the effect of the polymer backbone [140]. The aminoalcohol 207 was prepared in six steps from 2,5-dibromopyridine and was anchored onto a 2% DVB crosslinked Merrifield resin to afford the supported-tridentate ligand 208 (Scheme 85). This immobilized ligand was then employed in the diethylzinc addition to benzaldehyde and the excellent catalytic activity was recorded when the reaction was carried out in toluene at rt using 5 mol% of catalyst and a low benzaldehyde/Et₂Zn ratio of 1/1.1 (>99% conversion and 93% ee).

The best reaction conditions were used with other aromatic aldehydes and yields and ees were similar to those observed with benzaldehyde except for pyridine carboxaldehyde. In this case, nitrogen atom of pyridine ring was suspected to be too chelating. Excellent enantioselectivity (93%) was also obtained with an enolizable aldehyde, *n*-octanal. Furthermore the catalyst could be recovered by simple filtration and could be reused five times without loss of catalytic activity.

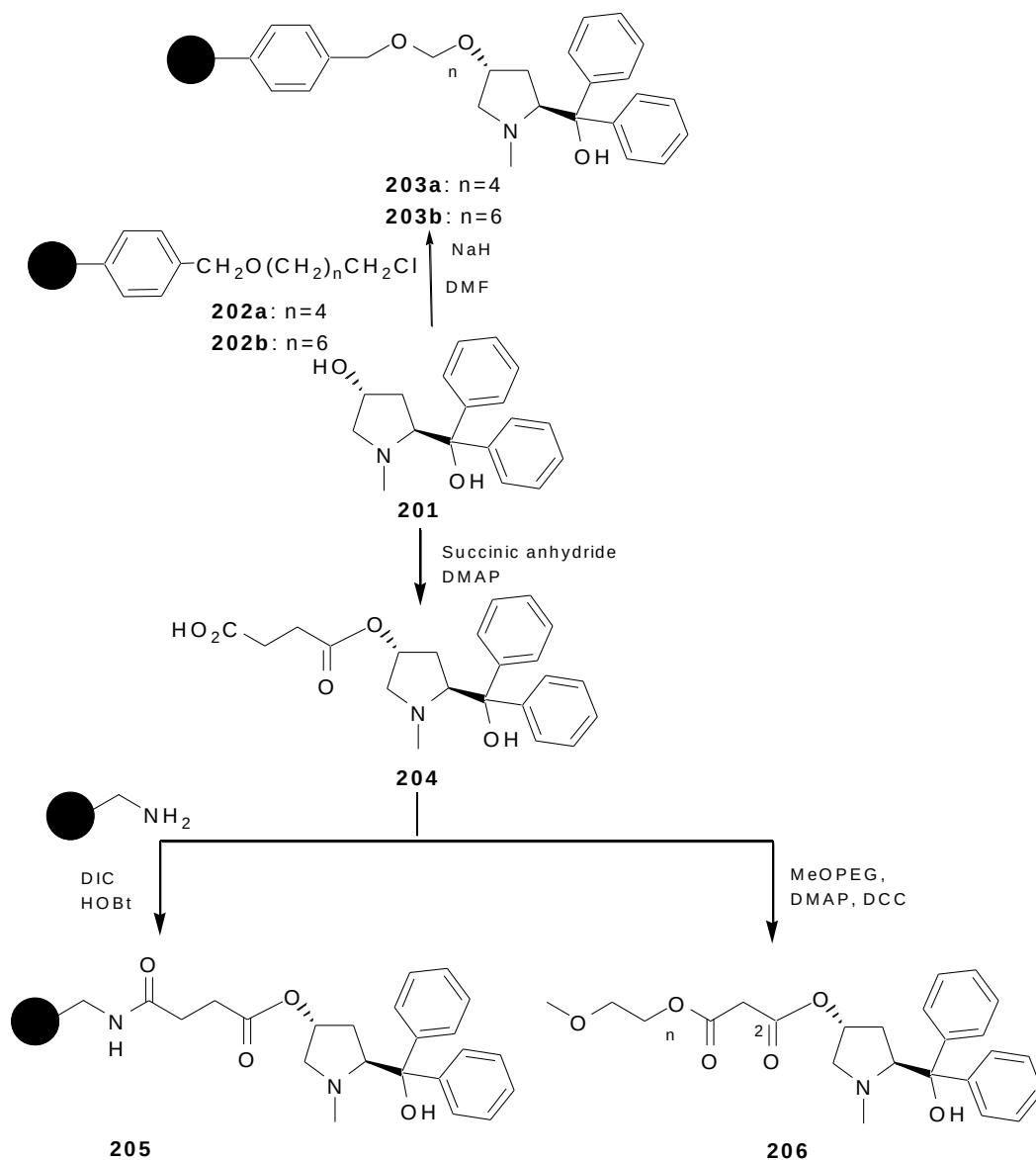
The results obtained are interesting since the supported-ligands containing a NH group gave generally poor to moderate enantioselectivities.

El-Shehawy studied the effect of the loading of the ephedrine moiety and the degree of crosslinking of polymer-supported ephedrine for the diethylzinc addition to benzaldimine [141].

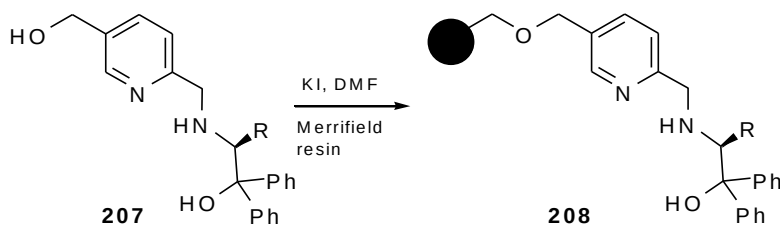
Different chiral polymers were prepared by copolymerisation of monomers 141 with styrene and DVB. The compositions of these polymers are summarized in Table 14.

These chiral polymers 209-213 were then tested in the asymmetric addition of diethylzinc to benzaldimines. First, the catalytic activity of the copolymers 209, 210a, 211 and 213 having a molar ratio of copolymerization of 1/7/2 were evaluated and the best result was obtained with polymer 210a (92% yield and 82% ee) when the reaction was carried out in

toluene at $-10\text{ }^{\circ}\text{C}$. The enantioselectivity of the reaction with polymeric ligand 210a was highly temperature-dependant and surprisingly a significant decrease of the chemical yield when the reaction was performed at 0°C or rt was observed.



Scheme 84.



Scheme 85.

Table 14. Compositions of polymers 209-213.

Chiral Polymer	Chiral Monomer	Molar Ratio ^a	Loading of ligand (mmol/g) (DF) ^b
209	(1 <i>S</i> ,2 <i>R</i>)-141a	1:7:2	0.764 (0.10)
210a	(1 <i>S</i> ,2 <i>R</i>)-141b	1:7:2	0.771 (0.10)
210b	(1 <i>S</i> ,2 <i>R</i>)-141b	1:8:1	0.750 (0.10)
210c	(1 <i>S</i> ,2 <i>R</i>)-141b	1:6:3	0.821 (0.10)
210d	(1 <i>S</i> ,2 <i>R</i>)-141b	1:5:4	0.735 (0.10)
210e	(1 <i>S</i> ,2 <i>R</i>)-141b	2:6:2	1.292 (0.20)
210f	(1 <i>S</i> ,2 <i>R</i>)-141b	3:5:2	1.863 (0.30)
210g	(1 <i>S</i> ,2 <i>R</i>)-141b	4:4:2	2.127 (0.40)
210h	(1 <i>S</i> ,2 <i>R</i>)-141b	5:3:2	2.449 (0.50)
211	(1 <i>S</i> ,2 <i>R</i>)-141c	1:7:2	0.792 (0.10)
212	(1 <i>S</i> ,2 <i>R</i>)-141d	1:7:2	0.721 (0.10)
213	(1 <i>R</i> ,2 <i>S</i>)-141b	1:7:2	0.807 (0.10)

^a Molar ratio of copolymerization: chiral monomer:styrene:DVB. ^b Degree of functionalization

The increase of the crosslinking reagent (DVB) involved a significant decrease of both yield and ee. The same effect was observed when the loading degree of the aminoalcohol unit increased.

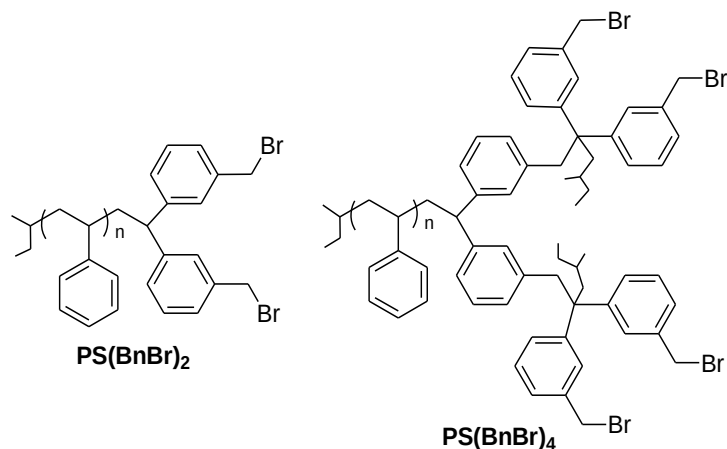
The optimized procedure with chiral polymer 210a was employed with other aromatic aldimines and the same range of enantioselectivity was recorded.

El-Shehawy has reported the synthesis of original polystyrene-supported dendritic chiral ephedrine [142]. Chain end-functionalized polystyrenes bearing a number of 2, 4, 8 or 16 BnBr residues at their chain-ends, PS(BnBr)₂-PS(BnBr)₁₆ were first isolated (Scheme 86).

Reaction of polymers of PS(BnBr)₂-PS(BnBr)₁₆ having two-sixteen BnBr moieties with ephedrine led to the corresponding polymers PS(Ephed)₂-PS(Ephed)₁₆ bearing the same numbers of ephedrine at their chain-ends (Scheme 87).

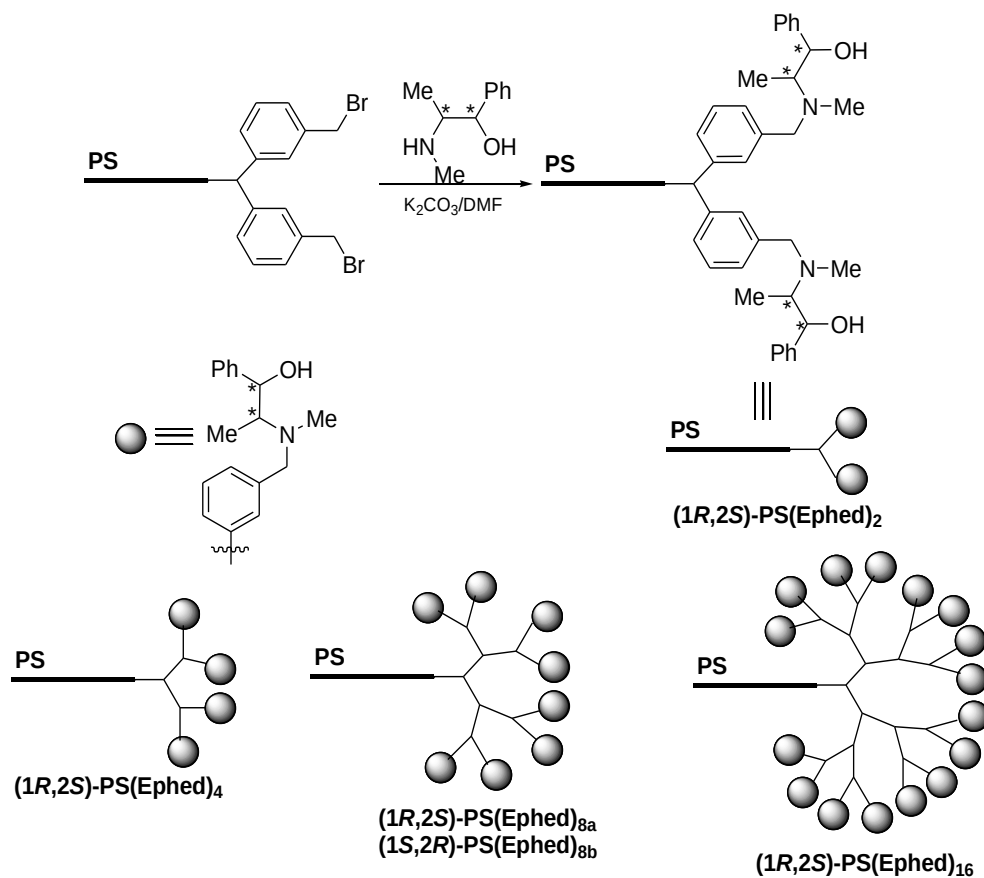
The catalytic activity of these four chiral polymer-supported dendritic aminoalcohols was evaluated in the enantioselective diethylzinc addition to *N*-diphenylphosphinoylbenzalimine. The reaction was first carried out in toluene at rt for 48 h using an equimolar amount of supported-ligand (based on the total numbers of ligand unit).

The best chiral polymer, PS(Ephed)₈a, was also tested with other *N*-diphenylphosphinoylarylimine under the same reaction conditions and similar level of yield and enantioselectivity were observed.



Scheme 86.

The same trend as with imine was observed for the enantioselective diethylzinc addition to benzaldehyde and the best results (94% yield and 90% ee) were also obtained with PS(Ephed)₈ [143].



Scheme 87.

Table 15. Enantioselective diethylzinc addition to *N*-diphenylphosphinoylbenzalimine using polymer-supported dendritic aminoalcohols.

Entry	Supported-ligand	Reaction time (h)	Yield (%)	ee (%)
1	PS(Ephed) ₂	48	53	81 (R)
2	PS(Ephed) ₂	90	85	83 (R)
3	PS(Ephed) ₄	48	71	84 (R)
4	PS(Ephed) ₄	72	90	85 (R)
5	PS(Ephed) _{8a}	48	92 ^{a,b}	90 ^{a,b} (R)
6	PS(Ephed) ₁₆	48	78	79 (R)
7 ^c	PS(Ephed) ₁₆	48	93	80 (R)
8	PS(Ephed) _{8b}	48	91	90 (S)

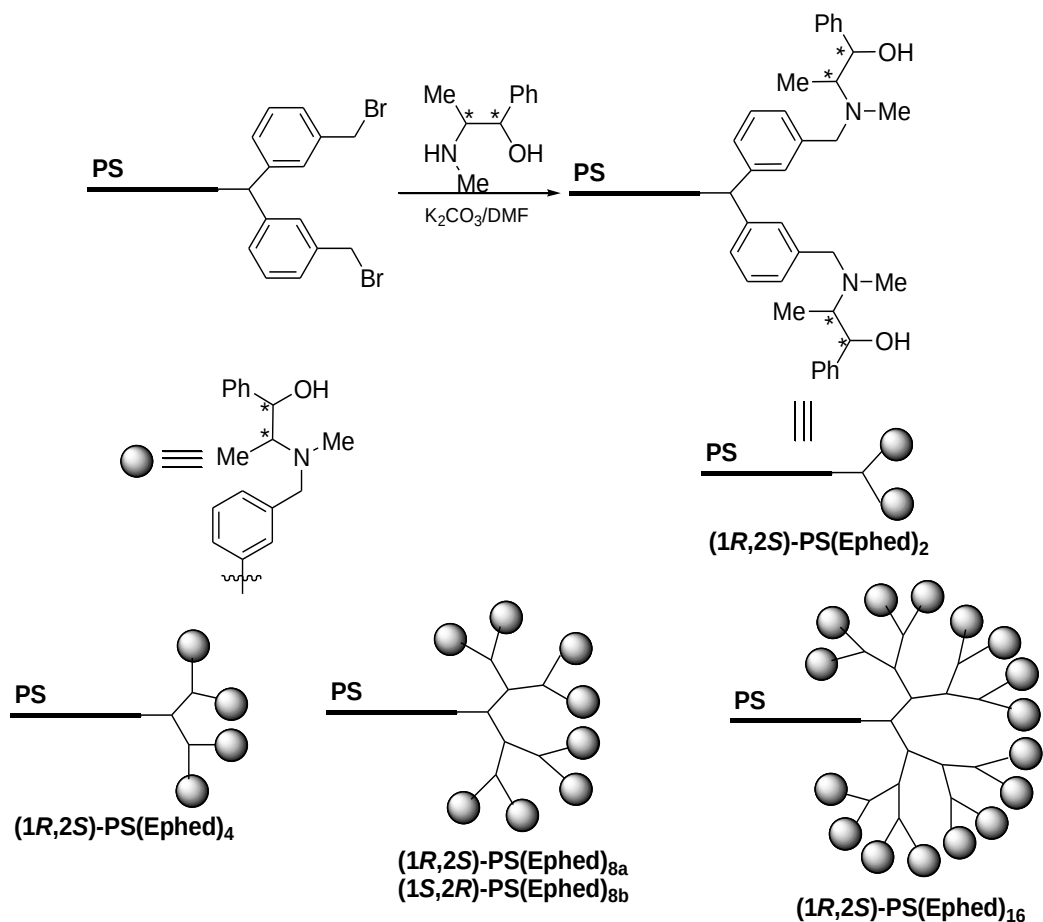
^a91% yield and 92% ee when using 1.0 molar of (1R,2S)-*N*-benzylephedrine as chiral ligand. ^b74% yield and 89% ee when using 1.0 molar of (1R,2S)-*N*-vinylbenzylephedrine copolymerized with styrene and DVB as chiral ligand. ^c1.5 molar equivalent of chiral polymer.

Although high catalytic activity was observed with polymer-supported aziridine-derived ligand 160, the attachment on this type of chiral ligand through the phenyl group was studied [144]. The protected monomers 214 were prepared and copolymerized with styrene and DVB to afford the chiral aminoalcohol-containing copolymers 215 with a loading of 0.1 mmol/g (Scheme 88).

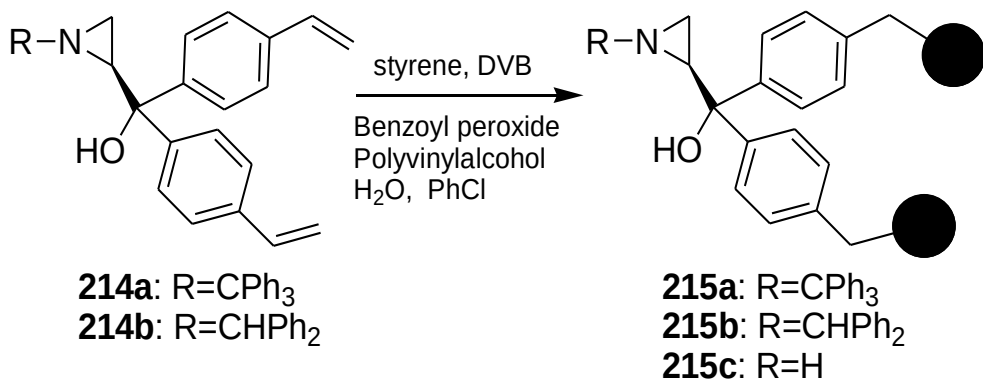
The three polymeric ligands were then examined in the diethylzinc addition to benzaldehyde. Protected polymer-supported ligand 215a and 215b were slightly less active than the Zwannenburg's polymeric ligand 160. The trityl-protected supported-ligand 215a was also recycled and showed a complete loss of catalytic activity (3%) and enantioselectivity (0%).

It is important to pointed out the high enantioselectivity (84% ee) obtained with the unprotected polymer-supported ligand 215c while the conversion was moderate (52 %) after 24h of reaction.

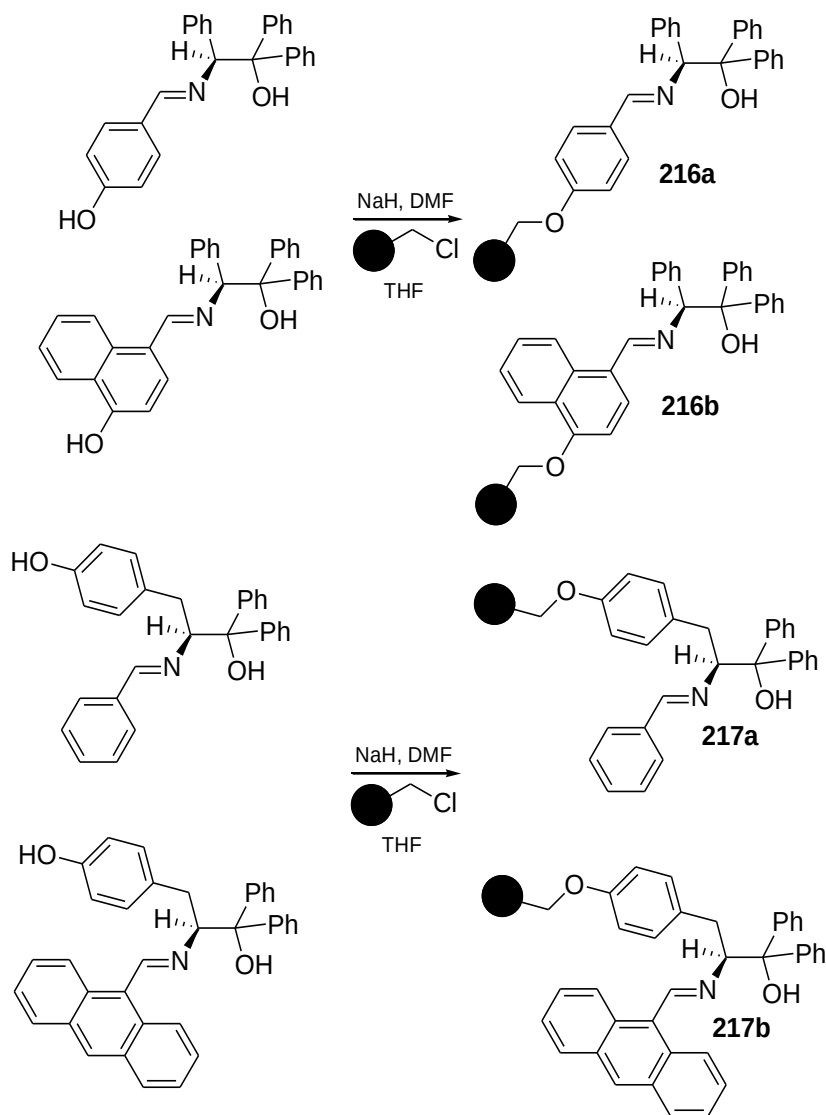
Polymer-supported chiral Schiff-base amino alcohols have also been used as chiral ligands. The four polymeric Schiff-base ligands 216a, 216b, 217a and 217b have been anchored onto Merrifield resin (1 mmol Cl/g, 1% DVB, 200 mesh) using the corresponding chiral ligands (Scheme 89) [145]. These chiral polymers have been first tested as chiral ligand in the phenylacetylene addition to acetophenone and chiral polymer 217a induced the best enantioselectivity (63%) when the reaction was performed in toluene at rt using 10 mol% of the catalyst. When the reaction temperature decreased to – 18 °C, a significant increase of the enantioselectivity (75%) was observed. The optimized reaction conditions with chiral supported-ligand 217a were then applied to different functionalized acetophenone and enantioselectivities were comprised between 62 and 89%. The polymeric ligand 217a could be reused in five successive reactions with an average loss of enantioselectivity of 1% per run.



Scheme 87.



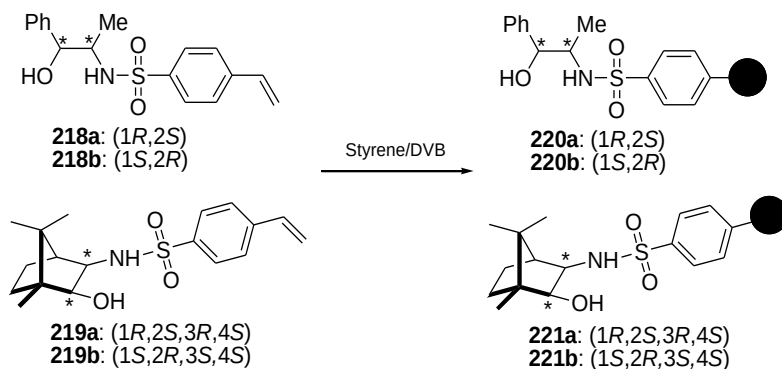
Scheme 88.



Scheme 89.

6.2. Supported Sulfonamide and *N*-Sulfonylated Amino Alcohols

Itsuno has described the first enantioselective allylation of aldehydes using crosslinked polymer-supported *N*-sulfonylated aminoalcohols as chiral ligands [146]. Polymer-supported ligands 220 and 221 were prepared by copolymerisation of the norephedrine-derived monomer 218 or D-camphor-derived 219 with styrene and divinylbenzene (DVB) in a [chiral monomer]/[styrene]/[DVB] molar ratio of 1/8/1 (Scheme 90).



Scheme 90.

Reaction of these chiral polymer-supported ligands with triallylborane led to the corresponding allyboron reagents which were allowed to react with aldehydes. When the norephedrine-derived ligands **220** were employed in the asymmetric allylation of benzaldehyde, homoallylic alcohol (*S*) was isolated in a 93% yield and in 75% ee. The enantioselectivity was slightly higher with the camphor-derived analog **221a** (85% ee). The polymer-supported ligands induced better enantioselectivities than the non-polymeric analogs. High enantioselectivities were also observed in the allylation of aliphatic aldehydes (92% for acetaldehyde and 84% for pivalaldehyde).

Liskamp has reported the synthesis and the screening in asymmetric catalysis of a library of polymer-supported peptidosulfonamide [147]. (*R,R*) or (*S,S*)-pyrrolidines **222** prepared in six steps from *D* or *L*-tartaric acid were anchored onto Argonaut resin (0.41 mmol/g) to afford the corresponding supported pyrrolidines **223** (Scheme 91). The polymeric peptidosulfonamides **224** and **225** were then synthesized in four steps from the immobilized pyrrolidines **223**. The different chiral polymers were tested in the titanium-mediated diethylzinc addition to benzaldehyde, *p*-chlorobenzaldehyde, cyclohexanecarboxaldehyde and phenylacetaldehyde. Both yield and ee were very low with all these supported-ligands for the enantioselective reaction with the two aliphatic aldehydes. With aromatic aldehydes, the best results were observed with both leucine-derived supported peptidosulfonamides **224d** and **225d**.

Isoborneolsulfonamide-containing *trans* 1,2-diaminocyclohexane have been immobilized on solid support [148]. The four polymer-supported ligands **227** were synthesized by suspension copolymerization in polyvinyl alcohol (average M_w =85,000-146,000) of chiral monomer **226** with styrene and DVB (Scheme 92). These four chiral polymers **227** were then employed as chiral ligands in the enantioselective titanium-mediated diethylzinc addition to acetophenone. Although enantioselectivities were excellent (99%) with these four polymer-supported ligands, the chemical yields were low (16 (**227a**), 23 (**227b**) and 36% (**227d**)) to moderate (56% (**227c**)) even after a very long reaction time (17 days).

A more reactive zinc reagent, the ethyl phenyl zinc reagent prepared by transmetalation of diethylzinc with triphenylboron was the employed. This reagent was used with *p*-bromoacetophenone in the presence of 5 mol% of polymeric ligand **227** and an excess of titanium tetraisopropoxide and the corresponding tertiary alcohol was isolated with good enantioselectivities (71-86%). The amount of the crosslinking agent had a strong influence on

(R,R) or (S,S)-**216**

BOP
DIPEA

(R,R) or (S,S)-**217**

1) TFA, Et₃N
 2) ClO₂S-CH₂-CH(R)-NH-Fmoc
 NMM, CH₂Cl₂
 3) Piperidine, DMF
 4) Boc₂O, NMM, CH₂Cl₂

a, R=H
 b, R=Me
 c, R=ⁱPr
 d, R=ⁱBu
 e, R=Bn

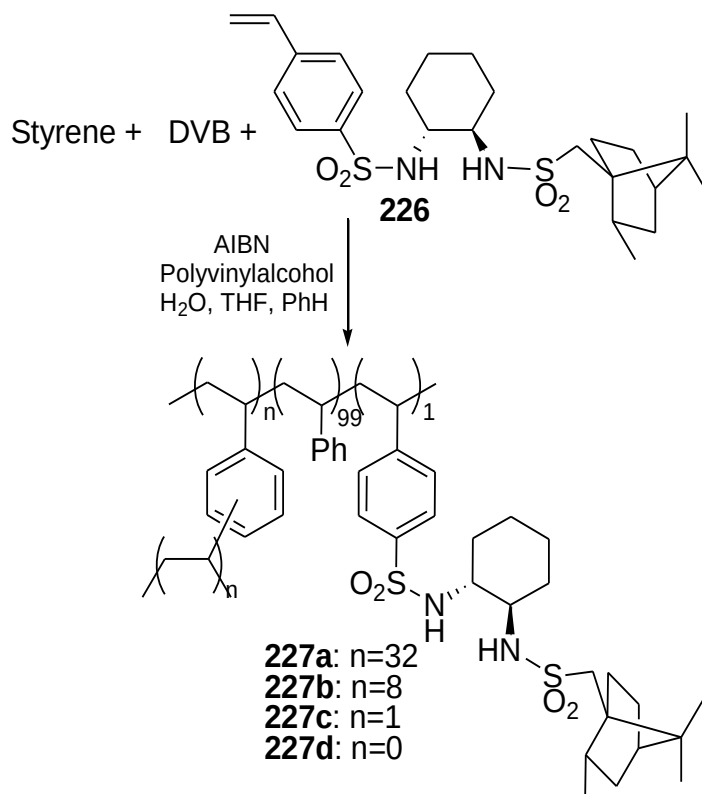
218a-e (R,R)
219a-e (S,S)

This ligand was employed in the enantioselective phenyl addition to different ketones, and the same level of chemical yield and enantioselectivity was observed for aromatic ketones while the enantioselectivity dropped significantly with hexan-2-one (38% ee).

Gau has prepared three different types of polymer-supported *N*-sulfonylated aminoalcohols. The first one 230 was produced by anchoring the aminoalcohol 229 through the nitrogen atom to a chlorosulfonated resin (1 mmol Cl/g; 2% DVB) with a ligand loading of 2.30 mmol/g (Scheme 93) [149]. In order to decrease the ligand unit loading, the authors have also synthesized chiral monomer 231 which was allowed to copolymerize with DVB and styrene to lead to polymeric ligands 232a and 232b with a ligand loading of 1.28 mmol 1.76 mmol, respectively.

It was not surprising to observe moderate yield (62%) and enantioselectivity (44%) for the titanium-mediated diethylzinc addition to benzaldehyde with the polymeric ligand 230 since a high ligand-loaded polymer is generally less active because of the proximity of the catalytic sites. The best result (100% yield and 92% ee) was obtained when 10 mol% of the low ligand-loaded 232a in the presence of 10 equivalents of titanium tetrakisopropoxide

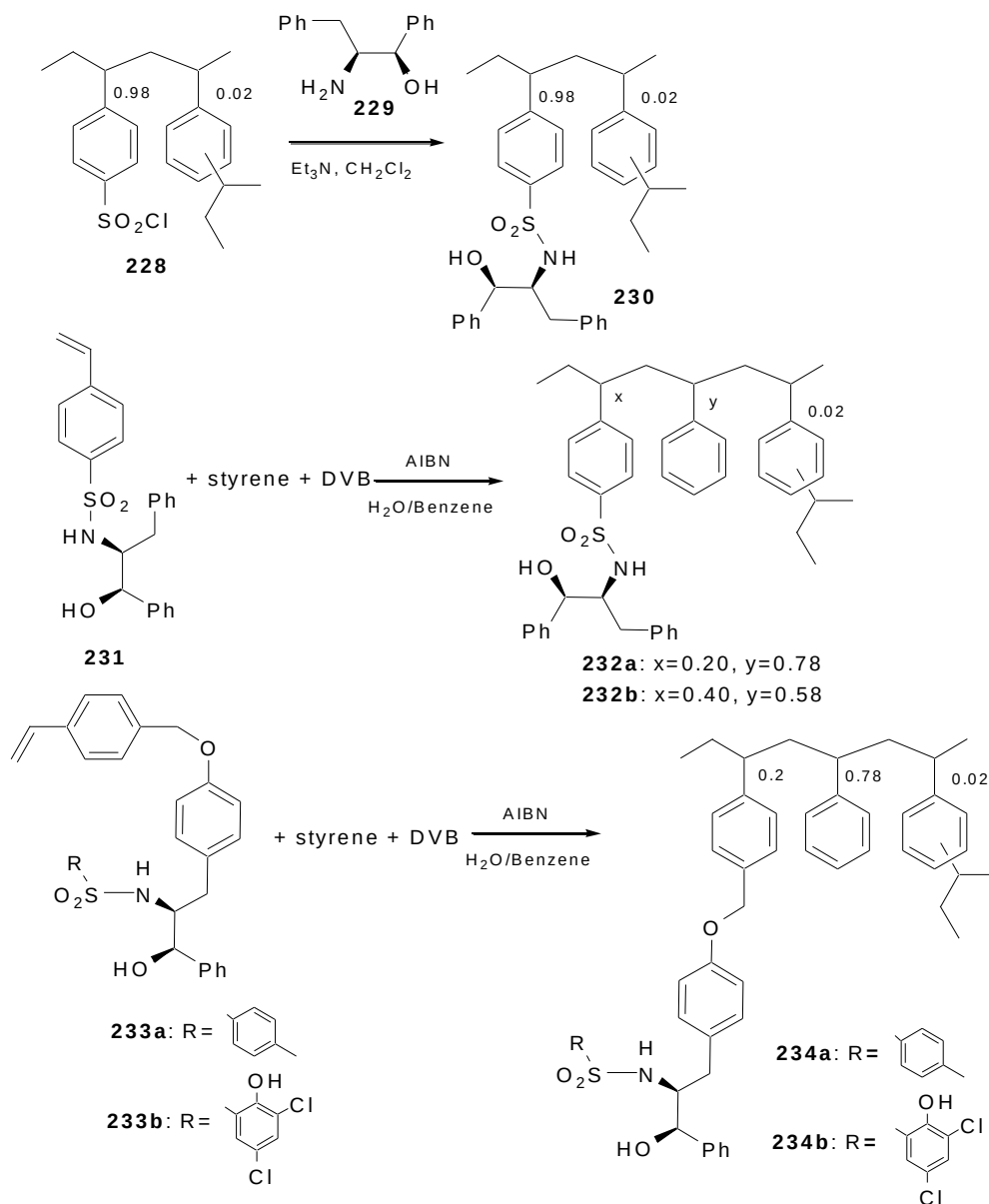
(relative to the ligand). This polymer-supported ligand was also employed with different aldehydes and both yield and ee were high in all cases. This latter could be also reused five times and the enantioselectivity decrease from 92 to 86%.



Scheme 92.

In the aim to discover other polymer-supported catalysts having a better activity and reusability, chiral polymers **234a** and **234b** were prepared by copolymerization with styrene and DVB with respectively a ligand loading of 0.93 mmol/g and 0.95 mmol/g [150]. The heterogeneous **234a**/Ti(OiPr)₄ system proved to be better than the **232**/Ti(OiPr)₄ systems for the enantioselective diethylzinc to aldehydes and a highly recoverable catalyst. Indeed, this polymeric ligand/Ti(OiPr)₄ catalyst could be reused 9 times with enantioselectivities $\geq 87\%$ ee.

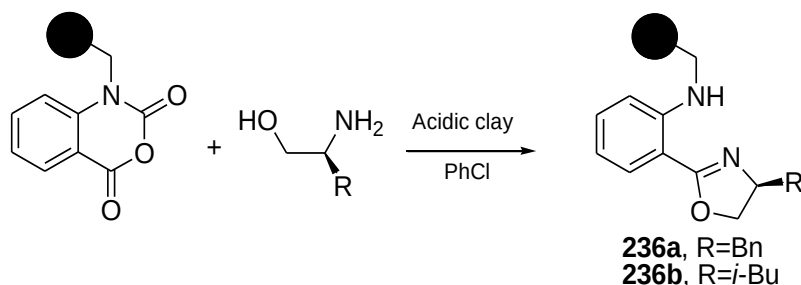
The polymer-supported tridentate ligand **234b** was employed in the enantioselective triethylaluminium addition to aldehydes. To obtain the same level of enantioselectivity as precedent system, 28 equivalents of Ti(OiPr)₄ relative to the chiral ligand was necessary. With most aldehydes used, the enantioselectivities were slightly lower than those obtained with the heterogeneous **234a**/Ti(OiPr)₄ system.



Scheme 93.

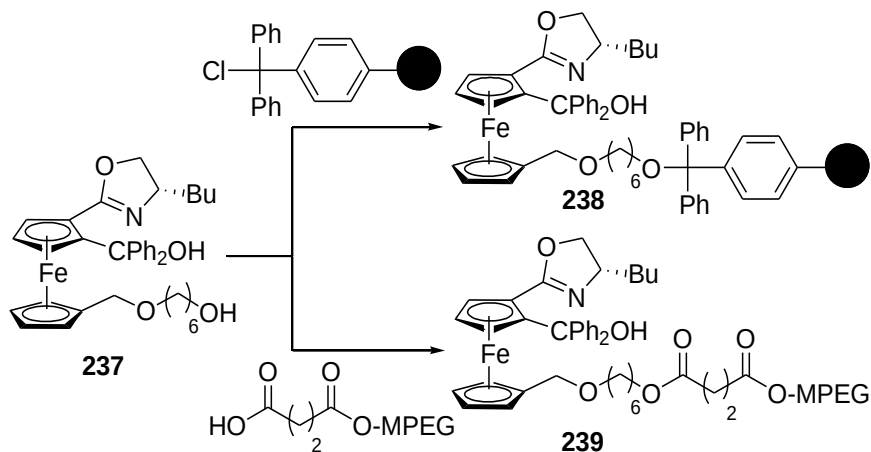
6.3. Supported Oxazoline or Oxazolidine as Ligands

Two polymer-supported chiral aminooxazoline **236** have been prepared because of better chelating properties of this type of ligand due to the higher nucleophilicity of the amino group [151]. Polymers **236** were produced after reaction of polymer-supported isatoic anhydride **235** (isolated from chloromethylated styrene-DVB polymer (4.8 eq. Cl/g)) and the corresponding amino alcohol under acidic conditions (Scheme 94).



Scheme 94.

The catalytic activity of these polymeric oxazolines was examined in the enantioselective diethylzinc addition to benzaldehyde. Chiral supported-oxazoline **236b** exhibited slightly better enantioselectivity (89%) and yield (90%) than its analog **236a** when the reaction was carried out in a 20% CH₂Cl₂/toluene mixture at 0°C. This chiral supported-ligand has been recycled three times without a significant loss of performance.



Scheme 95.

Chiral ferrocenyl oxazoline-based ligand which is often used in asymmetric catalysis have been immobilized onto two different supports, an insoluble trityl chloride polystyrene and a soluble polymer, a polyethylene glycol monomethyl ether [152]. The linker-containing compound **237** has been anchored to both polymers to produce respectively chiral insoluble polymer **238** and chiral soluble polymer **239** (Scheme 95). These polymer-supported ligands were then tested in the enantioselective phenyl and ethyl addition to *p*-chlorobenzaldehyde and benzaldehyde respectively. Polystyrene-supported oxazoline **238** was totally inefficient for the asymmetric phenyl transfer to *p*-chlorobenzaldehyde while a high enantioselectivity (87%) was observed for the ethyl addition to benzaldehyde. Contrary to the insoluble one, the soluble polymer **239** exhibited high enantioselectivity for both reactions (97 and 86% respectively). In general, the enantioselectivities were slightly lower than those obtained with the non-polymeric ligand. Furthermore, no significant loss of enantioselectivity was detected after five consecutive phenyl additions to *p*-chlorobenzaldehyde with the recovered polymer.

Portnoy focused his attention on the immobilization of PyBox ligands [153]. The polymer-supported PyBox 240 were prepared in five steps from the Wang trichloroacetamide resin (Scheme 96). The supported-ligands 240 were allowed to react with copper (I) triflate for 24h to afford the corresponding catalysts 241. These catalysts were then used in the first heterogeneous catalyzed addition of phenylacetylene to imine. The best enantioselectivity (83%) was obtained when the reaction was performed in dichloromethane at 40°C for 24h using 10 mol% of the catalyst 241f which possesses a steric group on the oxazoline ring. When a recovered catalyst was employed for a second run, a drop of the catalytic was observed which is probably due to the oxidation of the metal. The use of other solvents such as THF in order to improve the recyclability was attempted but a decrease of the catalytic activity (80 to 56%) was detected during three consecutive reactions while the enantioselectivity increased (54 to 60%). To reduce the oxidation, ascorbic acid was added to the reaction mixture and proved to preserve the catalytic activity but the enantioselectivity was totally lost.

Another strategy to immobilize a PyBox ligand has been described by Moberg and Levacher [154]. Supported PyBox 243 has been prepared using click-chemistry reaction between alkyne 241 and polystyrene-supported azide (1.2 mmol N₃/g) (Scheme 97). The PyBox loading was estimated at 0.8 mmol/g. This polymer-supported PyBox/Cu(I) catalyst was then tested in the phenylacetylene to *N*-benzylideneaniline. The enantioselectivity was lower than that observed with the non-polymeric but slightly better than those with Portnoy's immobilized PyBox 240. Compared to catalyst 241 similar trend was observed concerning the recyclability. When the immobilized PyBox-Cu(I) catalyst was only filtered, a drop of both catalytic activity and enantioselectivity were detected after five consecutive runs. When the supported-ligand was washed several times and reloaded with copper triflate, catalytic activity and enantioselectivity were recovered. The same level of conversion and ee were observed with other aromatic imines.

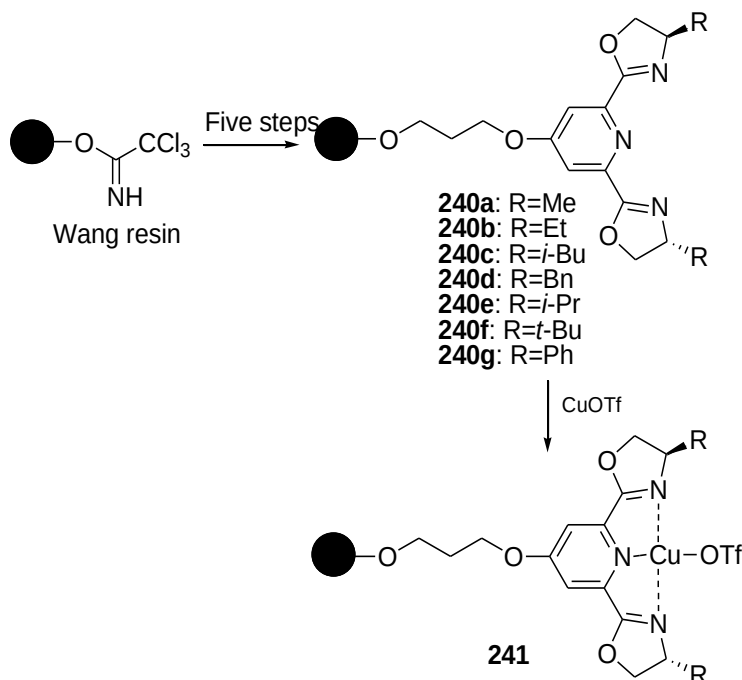
The use of polymer-supported oxazolidine derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol for the asymmetric alkynylation of aldehyde has been reported [155]. Three chiral supported-oxazolidines 244 were prepared in two steps from Merrifield resin (2.5 mmol Cl/g) (Scheme 98).

The optimization of the enantioselective addition of phenylacetylene to benzaldehyde has been done with the polymeric ligand 244a. The best result (82% yield and 79% ee) was obtained when the reaction was performed in THF at room temperature for 24 h in the presence of Et₂Zn, Ti(OiPr)₄ and 10 mol% of the ligand. The two other polymeric ligands 244b and 244c induced higher enantioselectivity (83% and 90% respectively) under the optimized reaction conditions. The same level of catalytic activity and enantioselectivity was observed with a variety of aromatic and heteroaromatic aldehydes when the polymer-supported oxazolidine 244c was employed. This supported ligand could be reused three times without significant loss of performance.

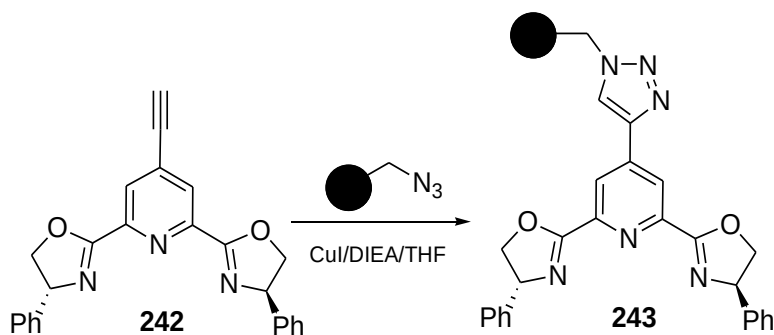
6.4. Supported Salen as Chiral Ligands

The catalytic activity of polymer-supported chiral salen has been also studied in the enantioselective diethylzinc addition to aldehydes since the importance of this type of ligand in asymmetric catalysis. Soluble polymer-supported salens have been synthesized by Venkataraman

[156]. Salen 245 was prepared and was then anchored on MeO-PEG changing only the spacer between the PEG matrix and the salen to lead to the polymer-supported salens 246-248 (Scheme 99).



Scheme 96.

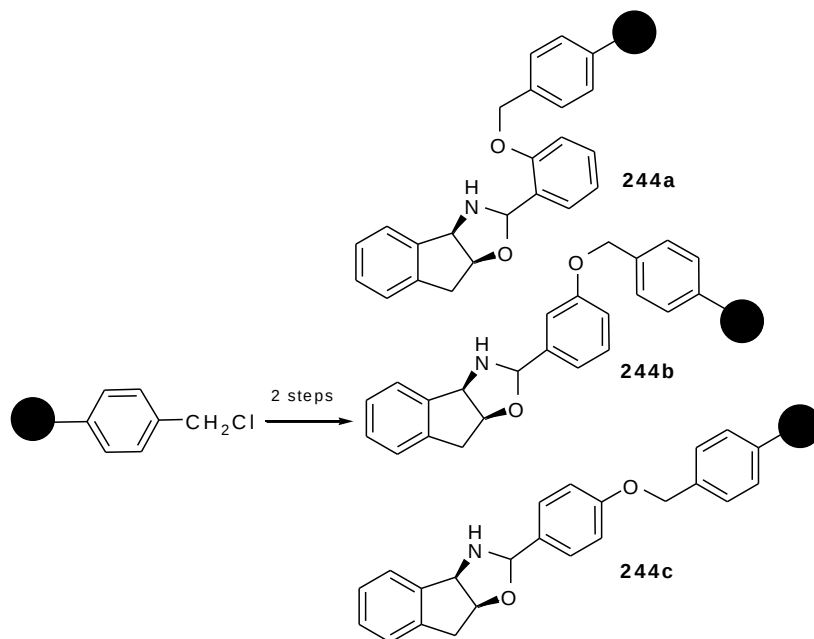


Scheme 97.

The enantioselective diethylzinc addition to benzaldehyde was then carried out using 10 mol% of polymeric salens 246-248 and the best result (90% yield and 82% ee) was obtained when the chiral polymer was used. With other functionalized aromatic aldehydes, both yield and ee were lower. Furthermore the soluble polymers could be recovered and reused without significant loss in selectivity or reactivity.

Chiral salen-type linear polymers have been prepared and tested in the diethylzinc addition to aldehydes [157]. The symmetrical dialdehyde-containing compound **249** was first synthesized in five steps from 2-tertbutylphenol and allowed to react with 1,2-diaminocyclohexane and DPEN to afford the linear polymers **250** (Scheme 100). The catalytic activity of these chiral

linear polymers was evaluated in the diethylzinc addition to *m*-nitrobenzaldehyde using 1 mol% of 250 (with respect to the monomeric unit). Although yields were satisfactory the ee were moderate and chiral linear polymer 250b proved to be more efficient for the reaction. The recovered polymer has been reused without loss of performance.



Scheme 98.

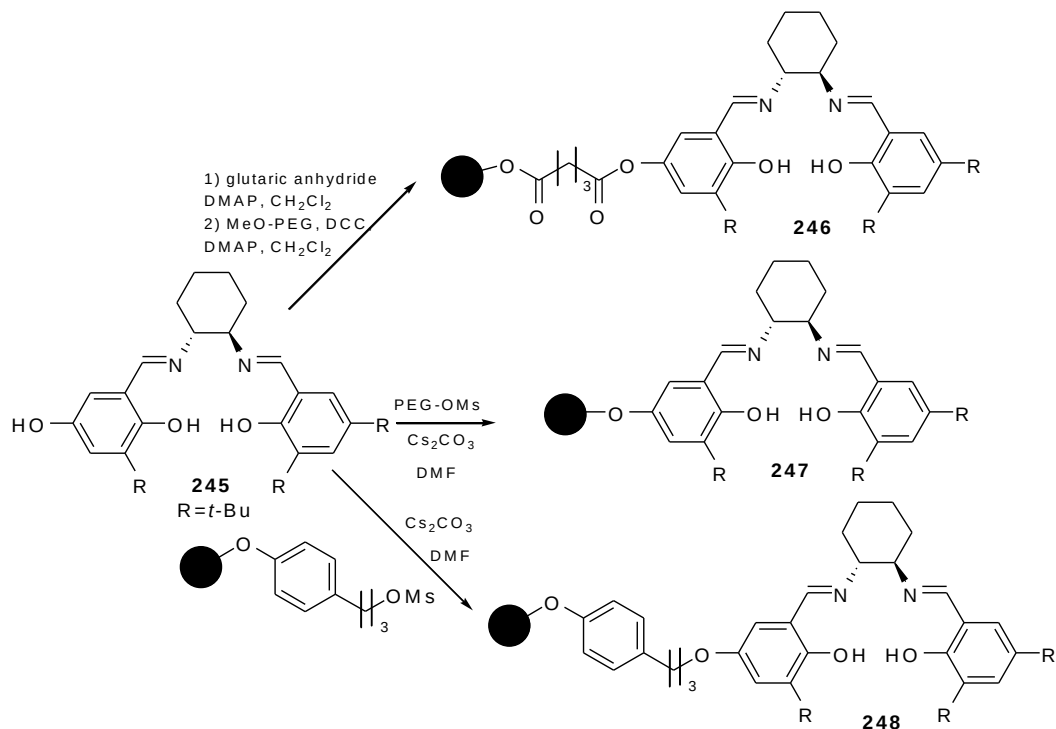
7. ASYMMETRIC π -ALLYLIC SUBSTITUTION

Another largely studied asymmetric reaction to form new carbon-carbon bond is the palladium-catalyzed allylic substitution using particularly homogenous ligand (Scheme 101) [158]. Among the ligands employed, numerous phosphine-containing ones have been reported and we report here only the phosphorus-free nitrogen-containing ligands. The use of heterogeneous ligands has not been studied extensively and the use of some immobilized nitrogen-containing ligands has been published.

To the best of our knowledge, the first polymeric ligand for this reaction was those of Lemaire's group [20]. Their chiral poly(amide) 23 and poly(urea) 24 (Scheme 13) was employed for the catalytic allylic alkylation. Using 23 the conversion was low (38%) and the ee reached 80% while with 24, the conversion was better (72%) and enantioselectivity was lower (38%). In both cases, conversion and ee were lower than those obtained with the corresponding monomeric diamine.

Moberg focused her attention on the immobilization of oxazoline-derived ligands for the enantioselective allylic alkylation [159]. Pyridine-containing oxazolines 251 were first prepared and were supported on TentaGel resin to afford the corresponding polymeric oxazolines 252 (Scheme 102). These polymer-supported ligands were then tested in the

palladium-catalyzed allylic substitution and the sterically bulky ones 252b and 252c proved not to be active (< 5% yield).



Scheme 99.

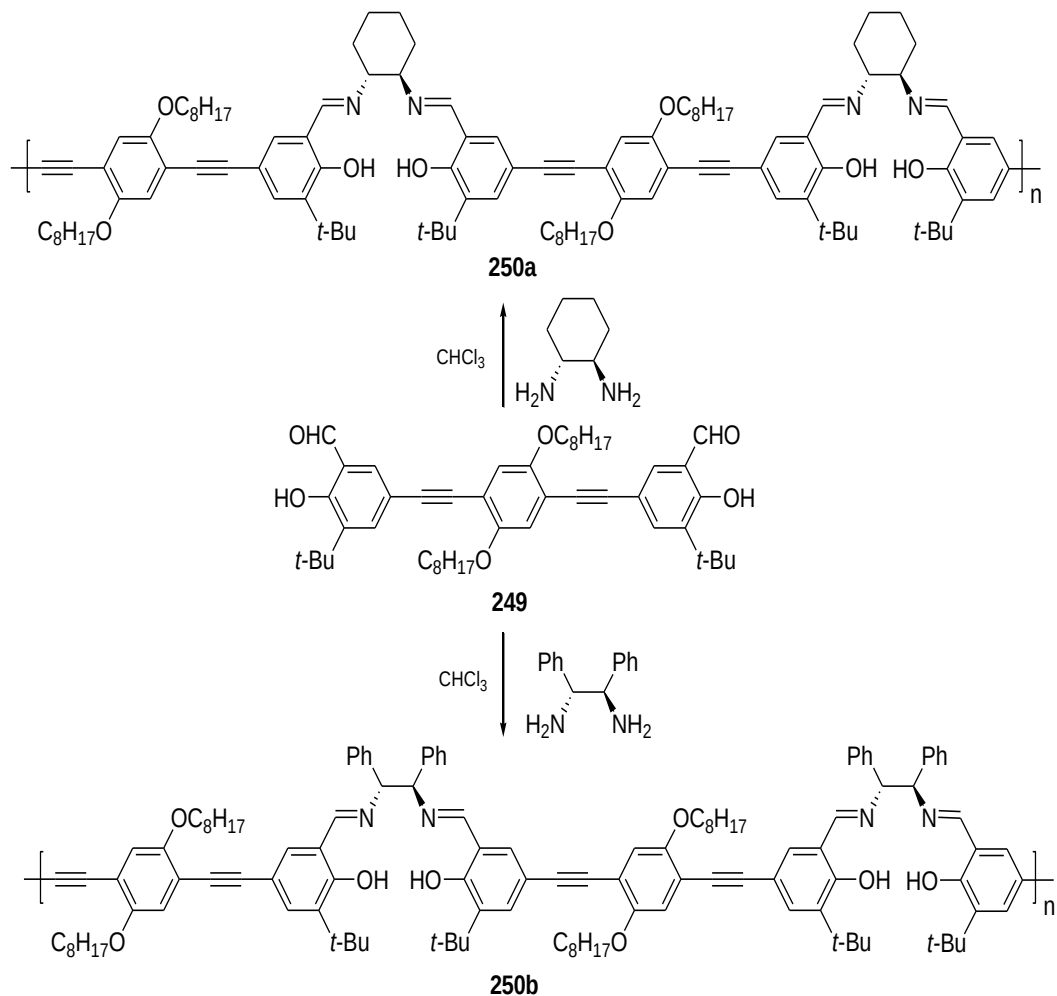
When the chiral polymer 252a was used as chiral ligand, the product was isolated in a yield comprised between 60 and 100% and in 80% ee; this result was closed to that obtained with the monomeric ligand.

Polymer-supported bis(oxazoline) 109 having a degree of functionalization of 0.071 mmol/g have been tested in the same reaction [102]. This polymeric ligand exhibited better enantioselectivity (94-95%) than the previous chiral polymers 252.

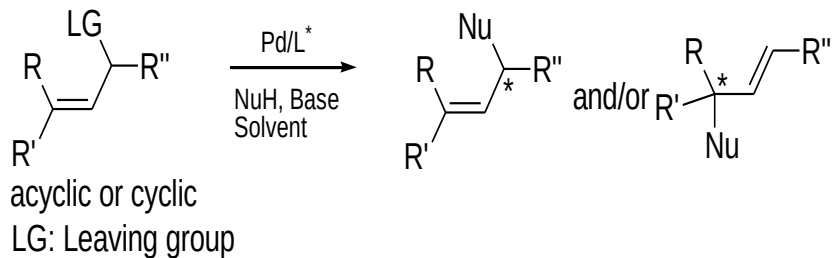
The asymmetric π -allylic alkylation using a polymer-supported pyridyldiamide as chiral ligand was applied to the synthesis of the (*R*)-baclofen which is an agonist of the GABA_B receptor [160]. The unsymmetrical cyclohexanediamine 253 was anchored onto a TentaGel HL-COOH resin using a classical coupling reaction to give the polymer-supported ligand 254 (Scheme 103). This one was then tested in the molybdenum-catalyzed allylation reaction of dimethylmalonate with 3-phenylprop-2-enyl methyl carbonate. A high branched-to-linear ratio (35/1) and enantioselectivity were obtained with the polymeric ligand and this result was quite similar to those observed with the non-supported ligands. The ligand could be recovered by filtration and could be reused for seven consecutive cycles without loss of catalytic activity and enantioselectivity.

Bandini has described the grafting of diamino-oligothiophene compounds onto the monomethyl ether of PEG5000 to give the soluble polymer 256 (Scheme 104) [161]. High yield (98%) and ee (99%) were observed with soluble polymer 256a when the allylic alkylation reaction between 1,3-diphenylallyl and dimethyl malonate was performed in THF

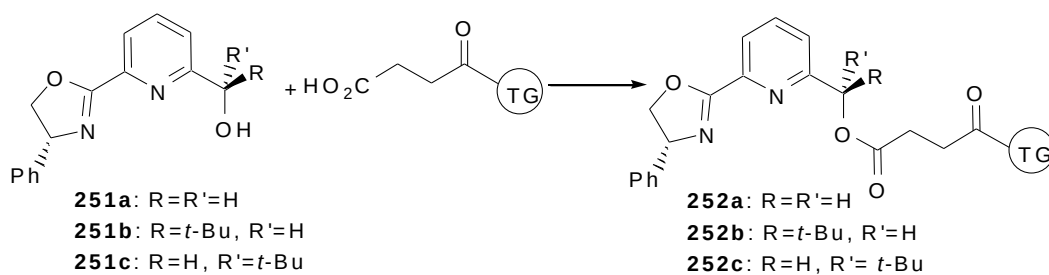
at room temperature using cesium carbonate as the base. This result is comparable to that obtained with the non-polymeric ligand. Polymer-supported ligand 256b proved to be less efficient than 256a. The recyclability of the supported-ligand/Pd catalyst was also evaluated and loss of performance was detected only after three cycles.



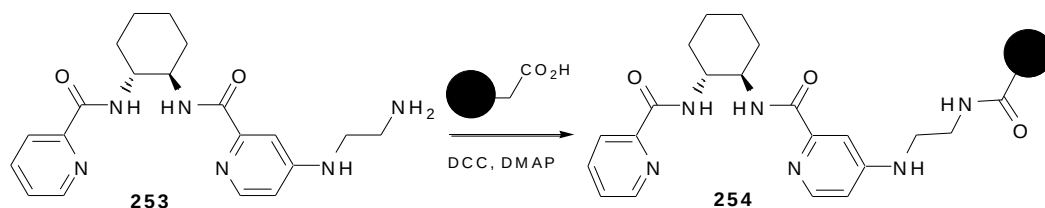
Scheme 100.



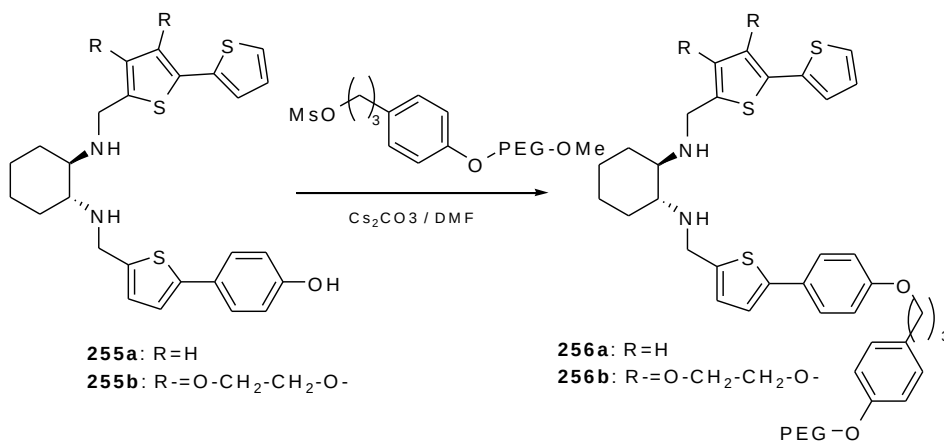
Scheme 101.



Scheme 102.



Scheme 103.

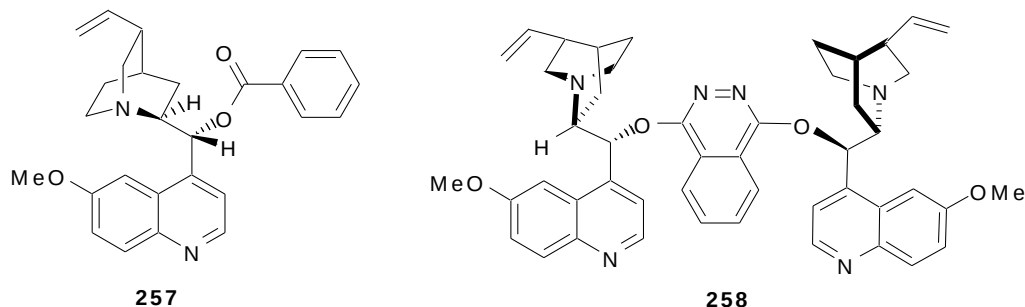


Scheme 104.

8. DIHYDROXYLATION AND AMINOHYDROXYLATION

The osmium-catalyzed asymmetric dihydroxylation (AD) is an excellent method to prepare chiral vicinal diols [162]. Most of the ligands employed are cinchona alkaloids and are derived from quinine or quinidine like ligand 257 for example. In 1992, Sharpless has described the improvement of the osmium-catalyzed asymmetric dihydroxylation by using bis cinchona alkaloids such as 1,4-bis(9-*O*-dihydroquinyl)phthalazine (258) as chiral ligand (Scheme 105) [163]. This type of ligand has then received much attention since high enantioselectivities were observed. Although the amount of OsO₄ has been reduced with the possibility to use cooxidants, the high cost of osmium and chiral ligands, the toxicity, the possible contamination of the chiral products by osmium avoid the use of this process in

industry. The possibility to support and to recycle the osmium/ligand catalyst and particularly the use of soluble or insoluble supported ligands has been explored. In order to recycle the catalyst, number of research groups has investigated the immobilization on soluble and insoluble polymers of this type of alkaloids.



Scheme 105.

8.1. Insoluble Supported Alkaloid as Ligand

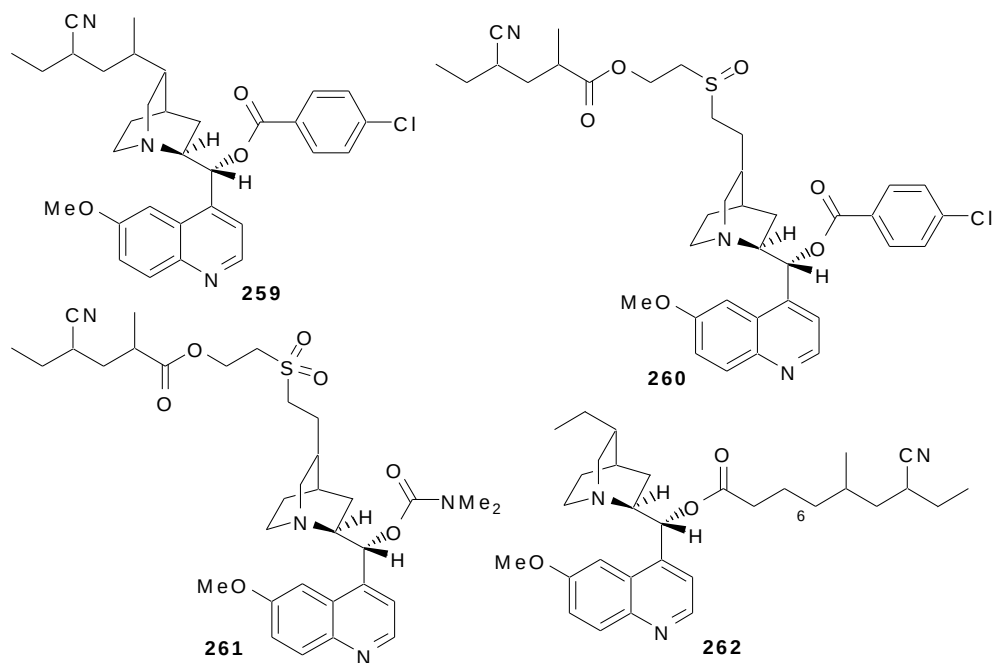
The first work about AD using heterogeneous ligand has been reported by Sharpless [164]. The polymeric alkaloids 259-262 (Scheme 106) were prepared by copolymerisation of the corresponding monomer with acrylonitrile in presence of the radical initiator AIBN. The performance of these polymer-supported cinchona were evaluated in the asymmetric dihydroxylation of *trans* stilbene using OsO_4 and NMO or $\text{K}_3\text{Fe}(\text{CN})_6$ as secondary oxidant. The reaction rate was slow and no ee was detected using the polymeric ligand 259 probably because of the proximity of the active site to the polymer matrix. The best results (81-87% yield and 85-93% ee) were observed when the supported alkaloid 260 was used as chiral ligand in presence of only 1 mol% of OsO_4 and NMO in acetone/water at 10°C. It is interesting to note that when the OsO_4 /supported ligand complex was reused a second time without further addition of OsO_4 , the yield and enantioselectivity dropped slightly. Both yield and ee were improved when $\text{K}_3\text{Fe}(\text{CN})_6$ was used as cooxidant with polymers 261 and 262.

When the same reaction was tested with different olefins using the acetate analog of polymer 259, the polymer-supported alkaloid 263, low enantioselectivities were observed (Scheme 107) [165]. High chemical yields could be obtained when low alkaloid-loaded copolymers were used (< 15 mol%). Moreover high degree of alkaloid incorporation seemed to inhibit the reaction. Use of chiral polymers 264 and 265 did not improve the enantioselectivity of the dihydroxylation of *trans* stilbenes and ee were very low with polymer 264 compared to those obtained with polymers 259-260.

Dihydroquinidine 266 containing a *p*-vinylbenzoate was prepared and was copolymerized either with styrene or with 4-phenylstyrene (Scheme 108) [166]. The effect of the loading of the alkaloid monomer on the activity of the corresponding polymer for the AD of *trans* stilbenes was examined and the results are summarized in Table 16. As already observed with different supported ligands, higher the loading of the alkaloid monomer, more important drop of chemical yield, reaction rate and enantioselectivity were. Polymer 267a proved to be more

efficient than its homolog 267b and the complex 267a/OsO₄ could also be reused without significant loss of performance. This system was employed for the asymmetric dihydroxylation of other olefins including non-aromatic and α,β -unsaturated alkenes and moderate enantioselectivities were obtained while chemical yields were high.

In order to improve the enantioselectivity obtained with their supported alkaloid for the AD, Salvadori has prepared polymer 269 which contained a spacer between the alkaloid and the polymer backbone [167]. This one was isolated after copolymerization of quinine-based monomer 268 with styrene and DVB in a 1/7/2 molar ratio (Scheme 109). This polymer-supported quinine was then tested in the AD of *trans* stilbene, styrene and (*E*)- β -methylstyrene. The enantioselectivities were higher than those obtained with polymers 263-264 with a shorter reaction time at rt (4-6h) or 0°C (7h). At 0°C, the enantioselectivity reached 87% for the dihydroxylation of *trans* stilbene. This polymer was also reused after recovering without significant loss of the activity.



Scheme 106.

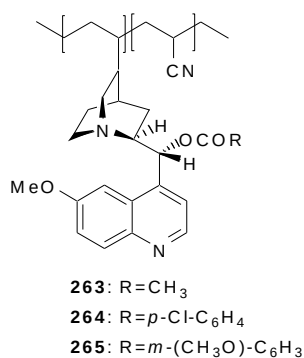
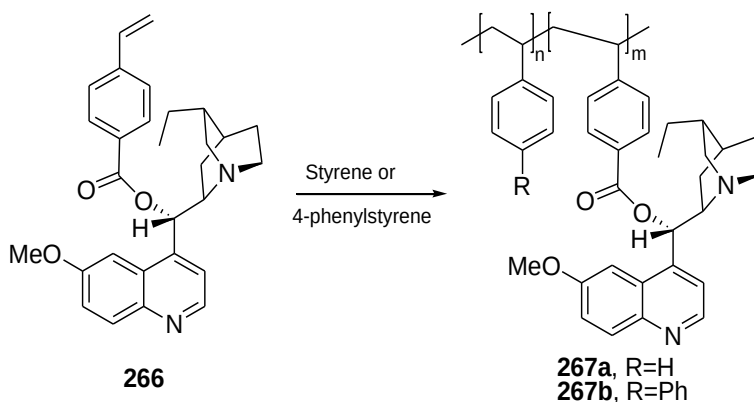


Table 16. AD of *trans* stilbene using polymer 267.

Entry	Polymer 267a (267b) n m	Reaction Time	Yield (%)	ee (%)
1	9.0 1.0	24 h	86 (68) ^a	82 (71) ^a
2	9.0 1.0	24 h	79 ^b	78 ^b
3	8.0 2.0	24 h	72 (65)	78 (68)
4	5.0 5.0	2 d	50 (50)	45 (40)
5	0.0 1.0	2-3 d	20	-

^aUnder brackets, yields and ee obtained with 267b. ^b Polymer containing dihydroquinine was used.

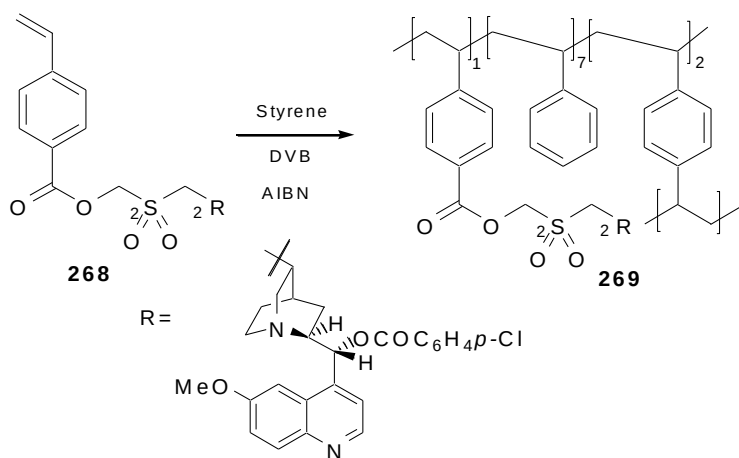


Lohray has reported the first example of immobilized bisdihydroquinyldipyridazine [168]. The monomer 270 has been prepared and was allowed to react with ethylene glycol methacrylate in a 1/9 ratio to afford the chiral polymer 271 (Scheme 110). When *trans* stilbene and styrenic olefins were dihydroxylated using supported ligand 271, OsO₄ as oxidant and K₃Fe(CN)₆-K₂CO₃ as cooxidant, both yields and ee were high, ees being slightly lower than those observed with the homogeneous ligand. In opposite, the enantioselectivities dropped significantly with aliphatic alkenes. The excellent results could be due to larger pore size and hydrophilicity of this type of polymer which facilitate the approach of the reactants to the catalytic site.

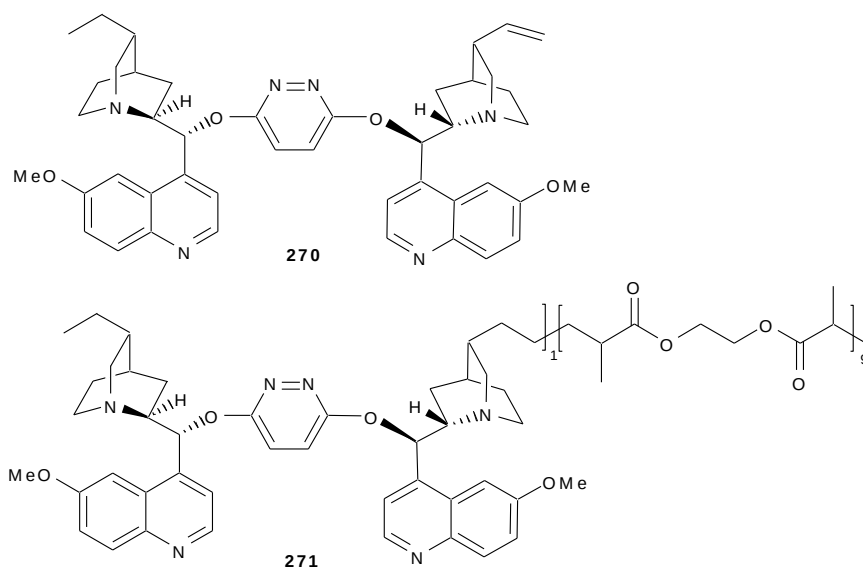
Since excellent results were obtained in the asymmetric aminohydroxylation in homogeneous phase by Sharpless [169], heterogeneous systems appeared to be of great interest. Nandanar has reported the first heterogeneous osmium tetroxide-catalyzed asymmetric aminohydroxylation of various olefins using polymer-supported bisdehydroquinine ligand 273 (Scheme 111) [170]. When chloramine T was used as nitrogen source, yields and ee were moderate with all olefins.

Monomer 268 was also copolymerized with hydroxyethyl methacrylate and ethylene glycol dimethacrylate as crosslinking agent in a 1/7/2 ratio to lead to the new polymer-supported alkaloid 274 (Scheme 112) [171]. This one was insoluble in all solvents and swelled very well in protic polar solvents. The catalytic activity of chiral polymer 274 was

tested in the AD of various aliphatic or aromatic olefins using two different reaction conditions (NMO or $K_3Fe(CN)_6$ as cooxidant in respectively acetone/ H_2O or t -BuOH/ H_2O). With all alkenes used, the enantioselectivities were higher when $K_3Fe(CN)_6$ was employed as secondary oxidant and comparable to those obtained with the non-polymeric alkaloid. Concerning the aliphatic olefins, the enantioselectivities remained low to moderate.



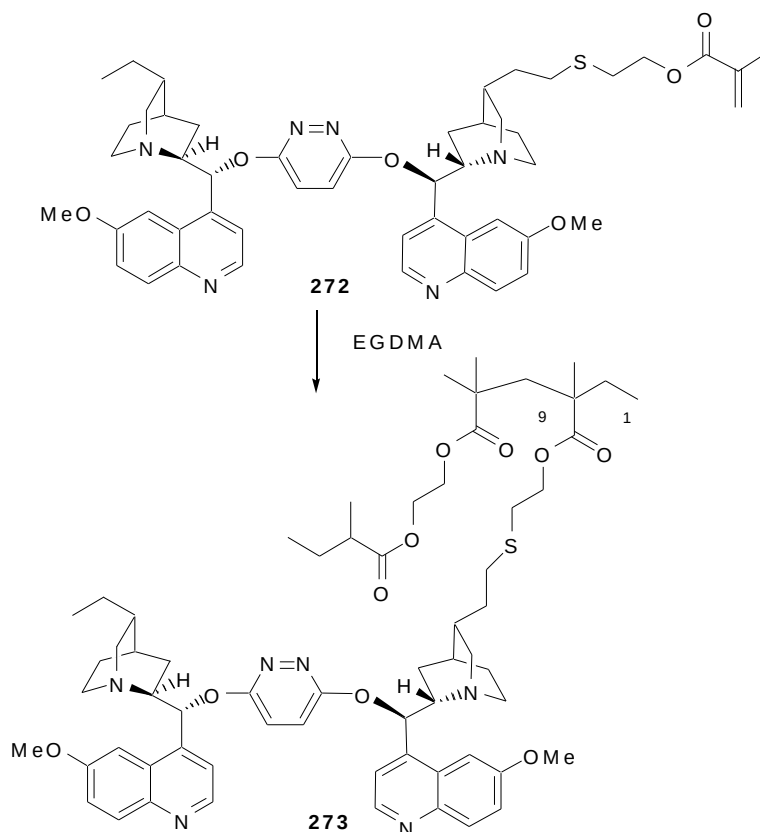
Scheme 109.



Scheme 110.

In order to improve the enantioselectivity in the AD of aliphatic alkenes, the two dihydroquinidine-derived polymers **275** and **276** were prepared by radical copolymerization of the corresponding monomers with hydroxyethyl methacrylate and ethylene glycol dimethacrylate as crosslinking agent (Scheme 112) [172]. These two polymers **275** and **276** exhibited enhanced enantioselectivities (88 and 86% vs 75% with polymer **274**) for the dihydroxylation of two aliphatic alkenes, 1-decene and 5-decene compared to those observed

with 274. Furthermore, when polymer 276 was used as chiral ligand in the dihydroxylation of aromatic alkenes, ee were higher than 91% in all cases and close to those observed with the non-polymeric analog [173].



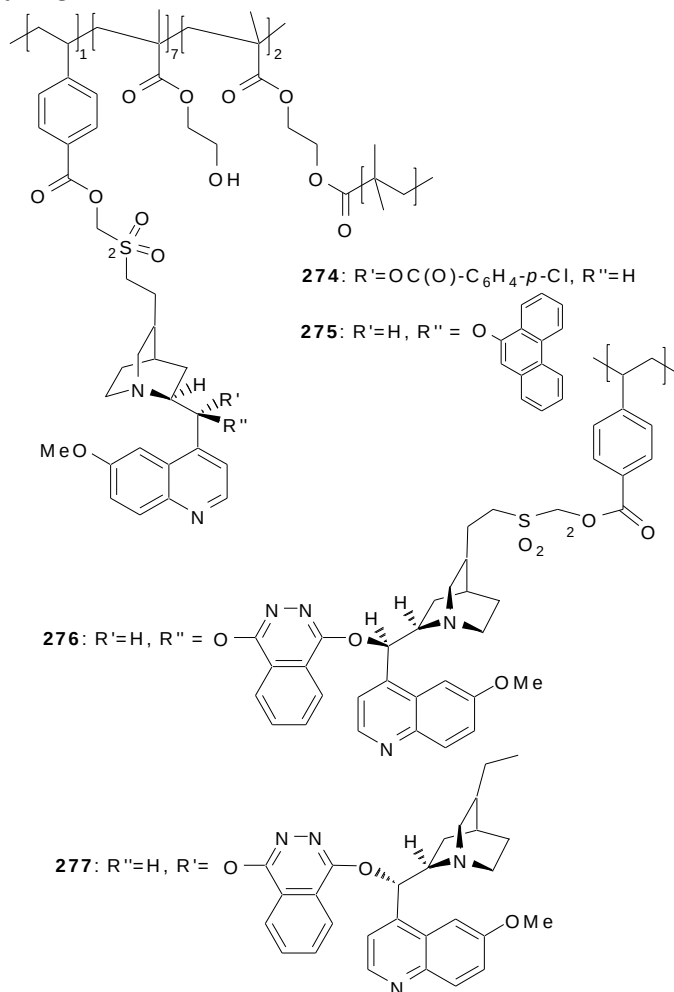
Scheme 111.

Salvadori has employed the polymer-supported bis(quinidyl)phthalazine 277 in the asymmetric aminohydroxylation of isopropyl cinnamate 278 in presence of *N*-chloromethanesulfonamide sodium salt and K_2OsO_4 in *n*-propanol/ H_2O (Scheme 113) [174]. The chemoselectivity, regioselectivity and ee are summarized in Table 17. Polymer 277 proved to be as efficient as homogeneous ligand in terms of activity, chemoselectivity and regioselectivity. Furthermore, the enantioselectivity was higher (87%) than those obtained with 273.

Table 17. Asymmetric aminohydroxylation with polymer 277.

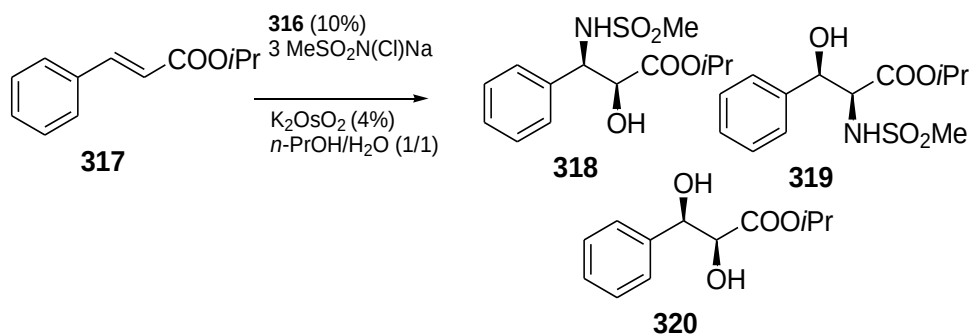
Entry	Conversion ^a (%)	Chemoselectivity ^b (%)	Regioselectivity ^c (%)	Ee of 279 (%)
1	98	94	91	87
2 ^d	73	91	89	83
3 ^d	58	84	89	81
4 ^e	59	79	88	78

^a279+280+281. ^b(279+280)/(279+280+281). ^c279/(279+280). ^dRecycling run without addition of K₂OsO₄. ^eRecycling run with addition of 10 mol% of K₂OsO₄.



Scheme 112.

When the osmium/ligand complex was recycled, both activity and chemoselectivity dropped significantly while chemoselectivity was remained. The enantioselectivity decreased slightly even when an initial amount of K₂OsO₄ was added to the mixture.



Scheme 113.

The polymer backbone polarity could influence the outcome of the reaction since the catalytic activity is strongly dependent on the solvent system. For this reason, the catalytic activity of homopolymers 284 and 285 and the copolymers 286 and 287 having a polar group on polymer backbone were compared [175]. Homopolymers 284, 285a and 285b were prepared by polymerization of dihydroquinidine acrylate 282a, dihydroquinidine 4-vinylbenzoate 283a and dihydroquinidine 4-vinylbenzoate 283b respectively using AIBN as radical initiator (Scheme 114). These supported cinchona were tested in AD of *trans* methyl cinnamate and *trans* stilbenes using either NMO in acetone/H₂O or K₃Fe(CN)₆ in *t*-BuOH/H₂O. Analysis of the results showed that better enantioselectivities were observed with alkaloid 4-vinylbenzoate-derived homopolymers 285. When the K₃Fe(CN)₆/*t*-BuOH/H₂O system was used with homopolymers, enantioselectivities were excellent with both alkenes.

Song assumed that in the acetone/H₂O solvent system, the homopolymers 285 formed a viscous lump which did not allow a high concentration of the substrate near the active site while in the *t*-BuOH/H₂O system these polymers swelled well. The accessibility of the active site is highly dependent on the compatibility between the polymer support and the liquid reaction medium.

For this reason, copolymers 286 and 287 having a polar polymer structure were prepared by radical copolymerization of monomer 283 with methylmethacrylate or 2-hydroxyethyl methacrylate in presence of AIBN (Scheme 114). Indeed, these polymers seemed to be more compatible with the liquid reaction medium because both yield and enantioselectivity were higher with the two NMO/acetone/H₂O and K₃Fe(CN)₆/*t*-BuOH/H₂O systems in the AD of *trans* methyl cinnamate.

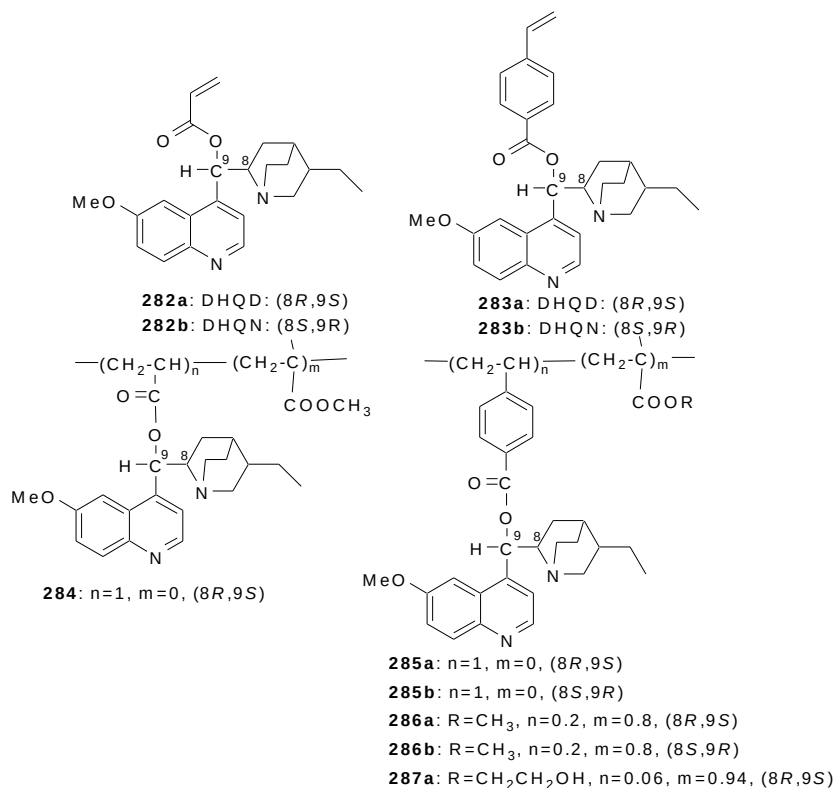
The polymer 286 and 287/OsO₄ complexes could be easily filtered from the reaction mixture and could be reused without significant loss of performance.

Since 1,4-bis(9-O-dihydroquininyl)phthalazine ((DHQ)₂-PHAL) 258 gave better results than the benzoate analog 257 (Scheme 105) in homogeneous catalysis, the heterogeneous ones were designed in order to check if the same trend was observed [176]. The copolymers 289a and 289b were prepared by copolymerisation of the monomer 288 with methylmethacrylate or 2-hydroxyethyl methacrylate respectively (Scheme 115). These two polymer-supported alkaloids were employed in the AD of *trans* methyl cinnamate and *trans* stilbene using OsO₄ as oxidant and K₃Fe(CN)₆-K₂CO₃ in *t*-BuOH/H₂O (1/1) at 10°C. Excellent enantioselectivities (>98%) were observed in all cases. The OsO₄/289a complex was easily filtered off from the reaction mixture and reused a second time in the dihydroxylation of *trans* stilbene. Although the enantioselectivity remained excellent (99%), the reaction rate was slower (65% yield after 32h vs 93% yield after 15h). In opposite, the polymer 289b was difficult to filter because of its high swellability.

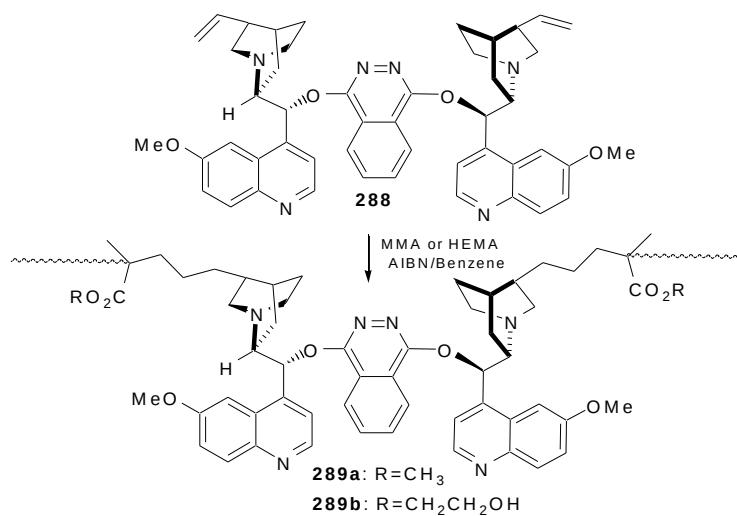
An analog of monomer 288 has been prepared replacing the phthalazine by a 2,5-diphenylpyrimidine and the corresponding monomer 290 was copolymerized with methyl methacrylate or ethylene glycol dimethacrylate to lead to the copolymers 291a and 291b respectively (Scheme 116) [177]. Unfortunately, the enantioselectivities were around 15-45% lower than those observed with the phthalazine-derived supported dihydroquinidine 289.

Another type of insoluble polymer-bound cinchona alkaloid was tested in the AD of olefins. Salvadori has prepared copolymers 294 by solution or suspension copolymerization of chiral monomers 292 with the two styrenic compound 293 and 294 with different monomer ratio (Scheme 117) [178]. Both yield and ee were very high and copolymer 295a proved to be more efficient than 295b and 295c. The better swellability due to the lower

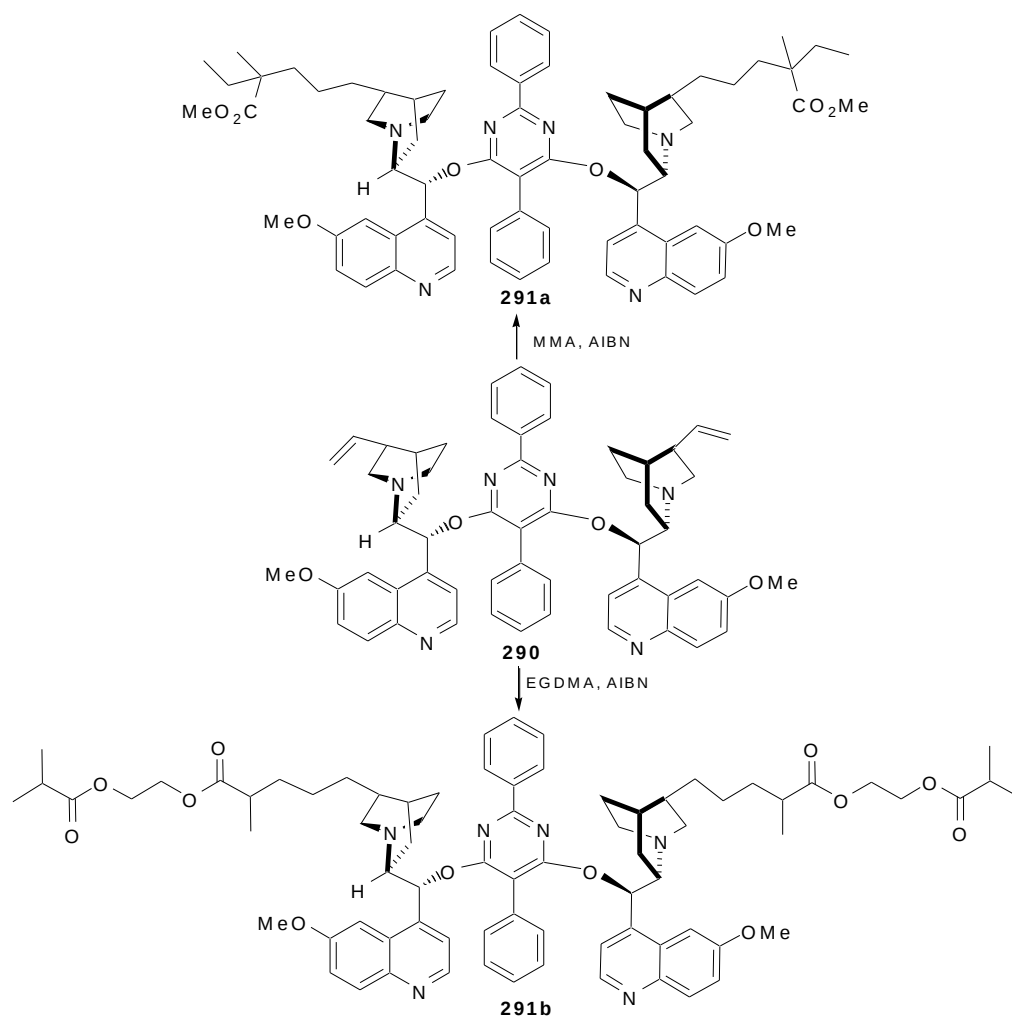
crosslinking degree has certainly more influence on the catalytic properties and the enantioselectivity than the solvent or the technique polymerisation. The supported alkaloid could be recovered and reused several times without significant loss of the enantioselectivity.



Scheme 114.



Scheme 115.



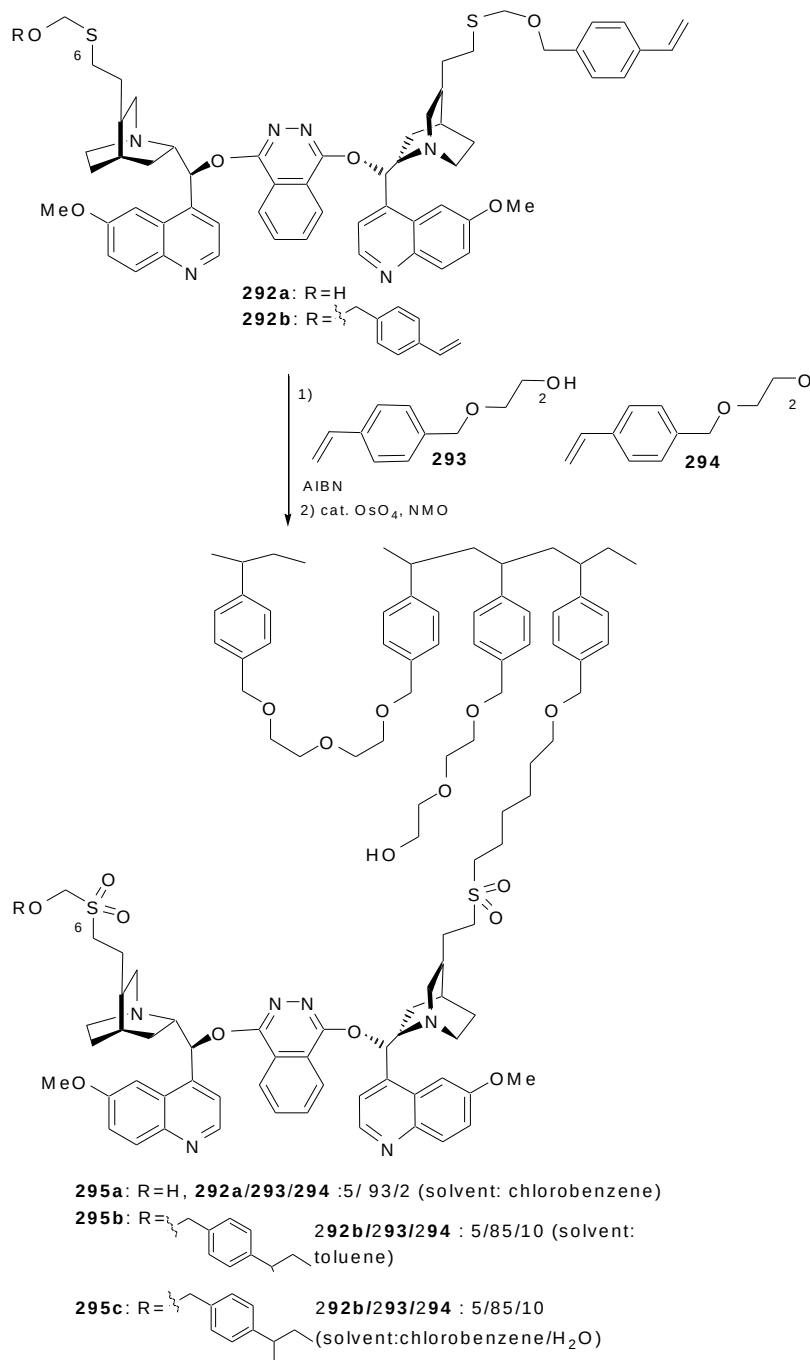
Scheme 116.

8.2. Soluble Supported Alkaloid as Ligand

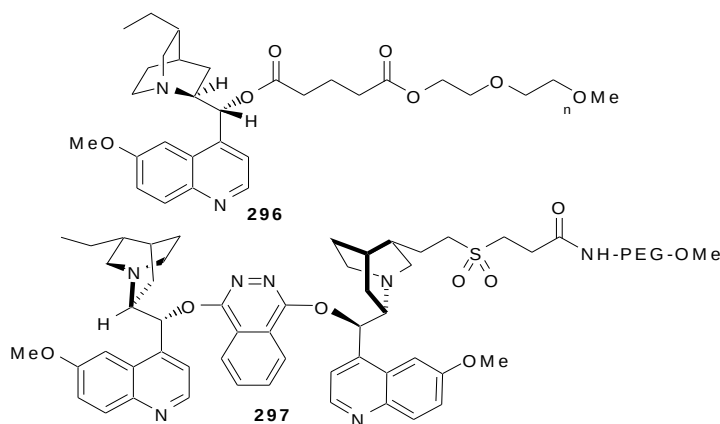
The immobilization of a ligand on a MeO-PEG leads to the corresponding soluble polymer and it is known that the solubility could have an influence on the outcome of the reaction.

For this reason, soluble polymer 296 was prepared and employed in the AD of olefins (Scheme 118) [179]. Similar yield and ee were observed for the reaction with *trans* stilbene than those obtained with the insoluble polymer-supported alkaloid 262 but with this soluble polymer the reaction time was very short (5h vs 48h). With other olefins used, the yield and ee were less satisfactory. The addition of diethylether allowed the precipitation of the supported alkaloid which could be reused without decrease of the catalytic activity and enantioselectivity.

The soluble polymer containing the highly active ((DHQD)₂-PHAL) **297** was also prepared and employed in the dihydroxylation of olefins (Scheme 118) [180]. The same level of enantioselectivity (> 97% for all alkenes) than that obtained with the insoluble analog **289a** was observed.

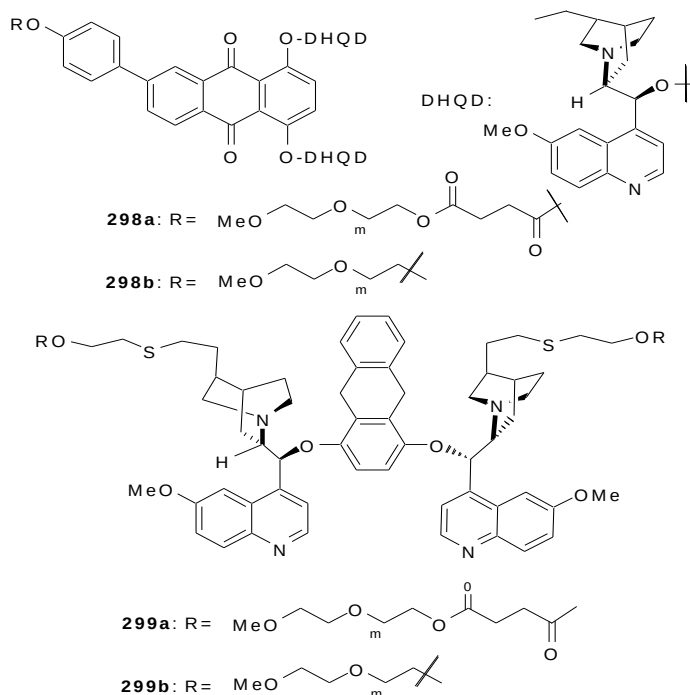


Scheme 117.



Scheme 118.

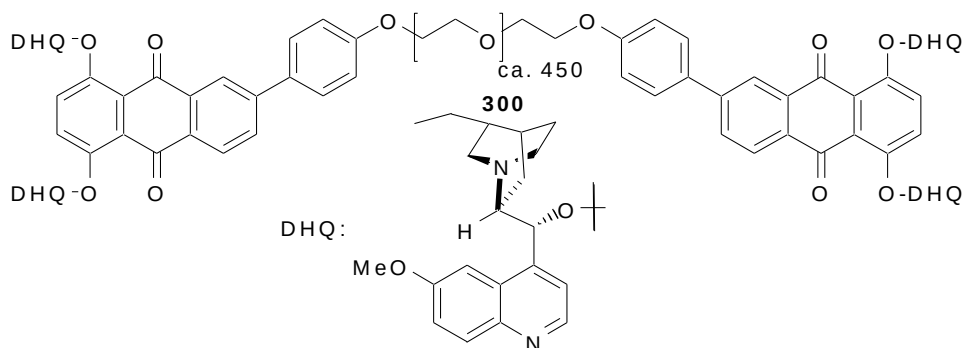
Bolm has reported the first anthraquinone-derived supported dihydroquinidine for the dihydroxylation reaction [181]. Two different ways about attaching the anthraquinone ligand were studied: either via the anthraquinone part or via the double bond of the natural quinidine (Scheme 119). The two families of soluble supported bisdihydroquinidine 298 and 299 were prepared and tested in the AD of allyl iodide and indene using 0.4 mol% of $K_2[OsO_2(OH)_4]$ as oxidant and $K_3Fe(CN)_6 \cdot K_2CO_3$ as cooxidant in *t*-BuOH/H₂O (1/1). In the case of allyl iodide, the soluble supported ligands gave the same enantioselectivities than the non-polymeric ligand. Although the yields were better for the AD of indene, the ee were slightly lower for all the supported ligands employed. The anchoring or the binding site had absolutely no influence on the enantioselectivity.



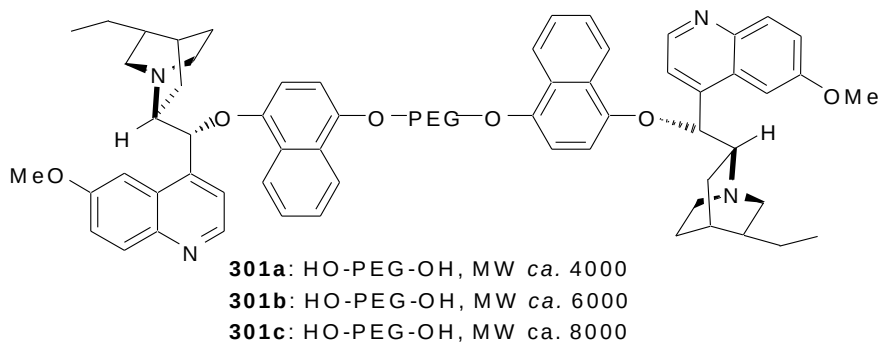
Scheme 119.

After addition of MTBE, the supported alkaloid 298a and 299a could be recovered and reused in another dihydroxylation reaction and no loss of performance was detected. This type of supported anthraquinone-derived alkaloid has been also applied in a continuous flow Sharpless dihydroxylation using the continuously run chemzyme membrane reactor (CMR) in which the catalyst attached to the soluble polymeric ligand **300** is retained by a membrane (Scheme 120) [182]. The two cooxidant systems have been tested and although the NMO one gave lower ee, this system was more compatible with the CMR. The different solutions were delivered in the reactor and after a residence time of 85 minutes, fractions from the reaction mixture were collected. At the beginning, both conversion and ee were around 80% and after only six residence times the conversion dropped to 18% suggesting that a leaching of osmate occurred.

Excellent results were obtained for the asymmetric aminohydroxylation using the soluble polymer-bound bisdehydroquinine **301**, prepared in two steps from dehydroquinine (Scheme 121) [183]. When analogs of *trans* cinnamate **278** were used using $K_2[OsO_2(OH)_4]$ as oxidant, AcNHBr as nitrogen source in presence of LiOH in *t*-BuOH/H₂O (1/1), regioselectivity (>20/1) and ee (> 95%) were excellent particularly with **301b** and **301c**. Results were less satisfactory when the acetone/water was used as solvent. After precipitation and filtration, the PEG-bound ligand **301c** could be reused in five consecutive runs with an average decrease of 0.8% per run for the enantioselectivity.

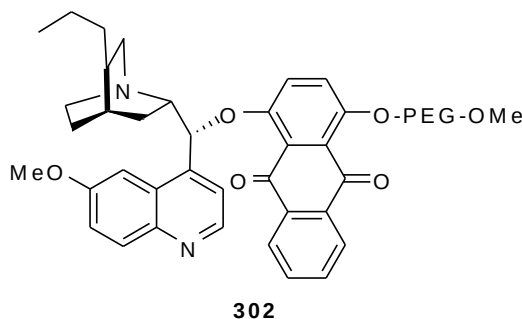


Scheme 120.



Scheme 121.

Anthraquinone-derived quinine has also been anchored onto PEG-OMe to produce soluble polymeric alkaloid 302 (Scheme 122) [184]. Good to excellent yields (80-94%) and ee (80-99%) were observed with different olefins using $K_2[OsO_2(OH)_4]$ as oxidant, $K_3Fe(CN)_6 \cdot K_2CO_3$ as cooxidant in *t*-BuOH/H₂O (1/1).

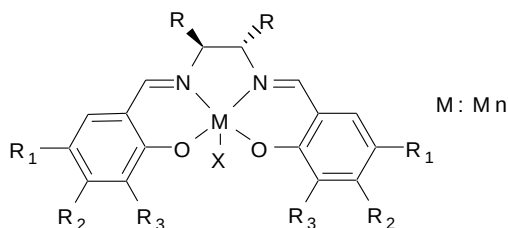


Scheme 122.

9. EPOXIDATION

Epoxides constitute a class of versatile intermediates, as they can be easily transformed into a wide variety of functional groups involving regioselective ring opening reactions [185]. Thus, asymmetric epoxidation (AE) of olefins is a key reaction for the synthesis of enantiomerically enriched compounds.

Complexed with Mn, Cr or Co, *N,N*-ethylenebis(salicylidene aminato) derivatives known as salen compounds, first described in 1990 by Jacobsen, are widely used as catalysts. From them, manganese complexes have been reported as highly active and enantioselective catalysts in the epoxidation of unfunctionalized alkenes in homogeneous phase using a wide range of oxidants [186]. Number of structure presenting the same backbone have been synthesized and involved in these oxidation reactions (Scheme 123). Easy to handle and to obtain, rather cheap, uses of Jacobsen type catalysts represent one of the most relevant methods of building chiral epoxides. Immobilization of such a compound was extensively studied because it restrains the formation of μ -oxoMn(IV) dimers by isolation of the catalytic sites.



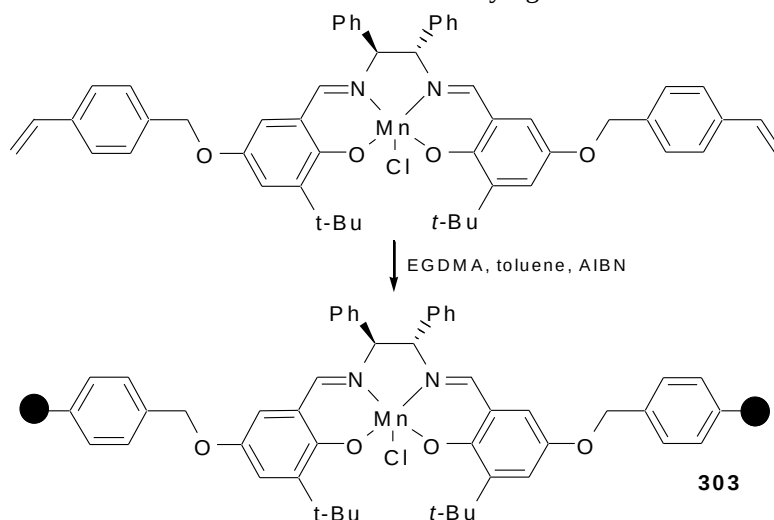
Scheme 123.

The immobilization of salen onto an organic polymer was achieved according to two strategies: a copolymerization of a salen monomer or by grafting onto a polymer followed by

subsequent solid phase synthesis of the salen. In the latter case, only unsymmetrical salen are formed.

9.1. Supported Salen as Ligand

The first example of a polymer-supported Jacobsen catalyst was reported by Dhal [187]. It involved the radical copolymerization of the corresponding distyryl monomer with EGDMA in a ratio of 10/90 to give the macroporous polymer 303 (Scheme 124). The epoxidation of unfunctionalized olefins led to moderate yields (55-72%) and low ee (up to 30%). Moreover, this catalytic system could be used at least five times without any significant loss of its catalytic activity.

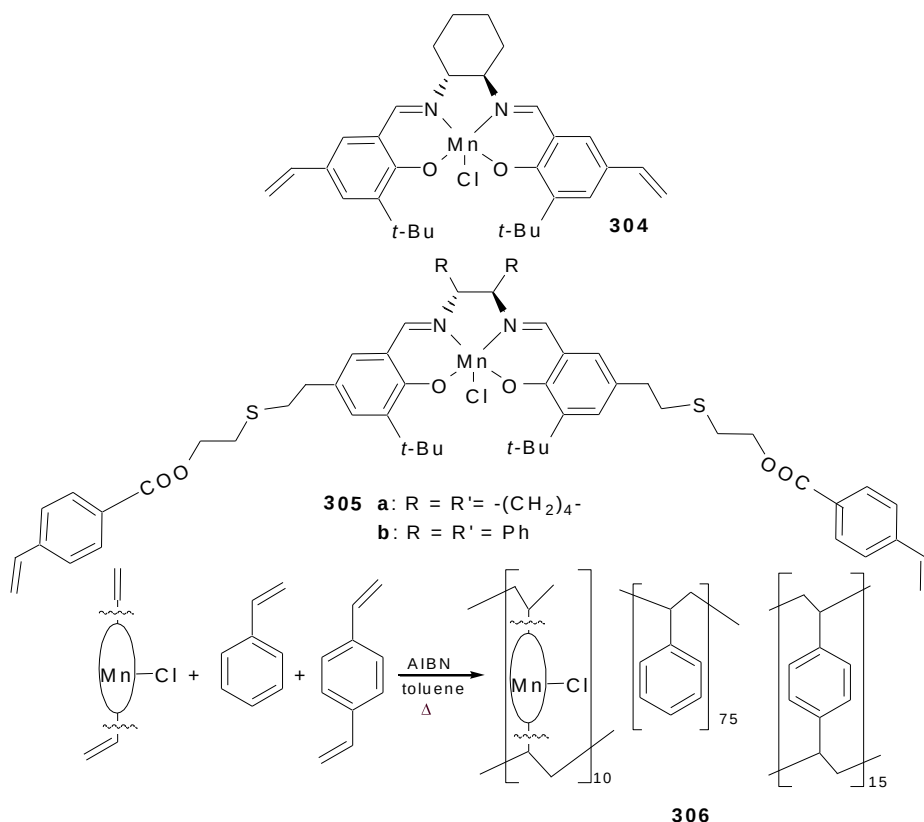


Scheme 124.

A similar approach permitted to prepare a macroporous polystyrene-based polymer 306 via a radical copolymerization of a divinylsalen 304 or of a “distyryl spaced” salen 305 with styrene and DVB (ratio 10/75/15) (Scheme 125) [188].

The oxidation was performed with *m*-CPBA/NMO instead of PhIO as oxidant because this latter was transformed into PhIO₂ its disproportionation product which was insoluble in the medium. The catalytic reaction was performed with 10 mol% of the catalyst at 0°C. After 30 minutes, modest to excellent conversions (67-99%) with low to moderate ee (10-62%) were observed. Moreover, the catalytic system could be recycled 5 times, the activity and the selectivity remained identical. Compared to homogeneous systems, enantioselectivity was still low. The epoxide of styrene, *cis*-β-methylstyrene and indene were formed in 16%, 62% and 60% ee respectively with conversions up to 99% in each case with polymer 305a as ligand.

First it was considered that as the salen ligand was localized at the crosslink it may induced a steric hindrance and a conformational rigidity responsible of the low ee. Therefore, Laibinis [189-190] and Sherrington [191] synthesized non symmetrical immobilized salen attached specifically to the polymer in a pendent fashion. The polymer was a styrene base resin.



Scheme 125.

Laibinis used a three steps synthesis for the polystyrene-supported salen **307** (Scheme 126) [189-190]. Asymmetric epoxidation was carried out in biphasic conditions with NaOCl as the oxidant in presence of 307_{Mn} as catalyst. The enantiomeric excesses and the yields of AE with styrene (9% ee, 7% yield), *cis*- β -methylstyrene (79% ee, 2% yield) or dihydronaphtalene (42% ee, 46% yield) were low to modest.

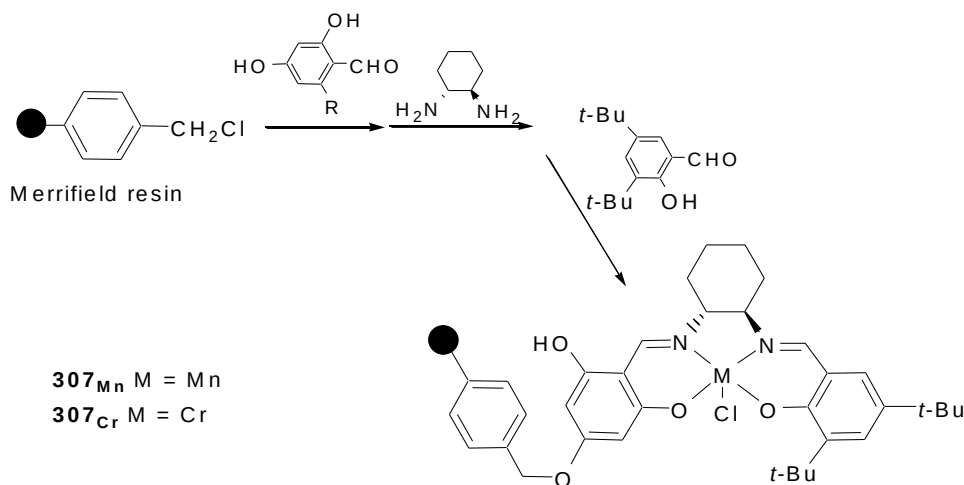
Sherrington [191] synthesized gel type and macroporous resins from 4-(4-vinylbenzyloxy)salicylaldehyde (Scheme 126). The gel type catalyst was rather inactive due to the formation of the oxo-bridged dimer of the catalytic center contrary to the macroporous one with an effective site isolation of the catalytic center. With the macroporous catalyst **310** (Scheme 127) although yields were good, ee were always low (up to 20% ee).

With an EGDMA polymer matrix (Scheme 128), polymer **311** afforded the epoxidation of 1-phenylcyclohex-1-ene with a high ee (91%) at 49% conversion. With the soluble Jacobsen catalyst, 92% ee and 72% conversion were observed [192-193].

The key factors for this result could be the low loading of Mn sites (0.08 mmol/g) and the high surface area.

From all these results a highly active and selective immobilized salen ligands should result in a molecular structure close to those of Jacobsen's catalyst. Sherrington [193] thought also that to provide good catalytic performance of the polymer-supported catalyst the following design criteria could be met. The complex could be attached to a single flexible linkage to the polymer support in order to minimize the steric hindrance. Moreover, a low

loading of the catalyst linked to the polymer was required to maximize site isolation of catalytic centres and hence to minimize the formation of the inactive oxo bridge dimer. The polarity of the resin should be such as to provide the optimum microenvironment for the catalyst and finally, the morphology of the resin must permit a high level of mass transfer to the active sites.



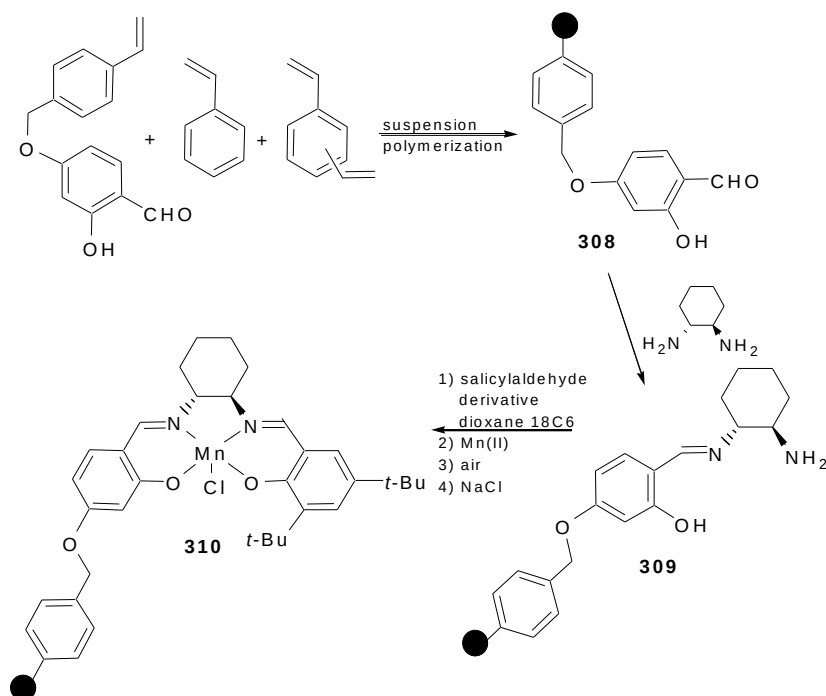
Scheme 126.

In 2000, taking into account the criteria edicted by Sherrington, Janda [194] described a convergent strategy to attach a salen ligand containing an appropriate linker to a low loading preformed polymer. A glutarate spacer (5 carbon atoms) was then used and the polymer 312 was prepared from styrene and polyTHF-derived crosslinker to form beads (Scheme 129). The AE in presence of *m*-CPBA as oxidant was effective. Goods yields were obtain in the AE of styrene and *cis*- β -methylstyrene with 51% ee and 88% ee respectively. These results were similar to those achieved with the homogeneous Jacobsen catalyst. The supported catalyst could be reused 3 times without loss of activity and selectivity.

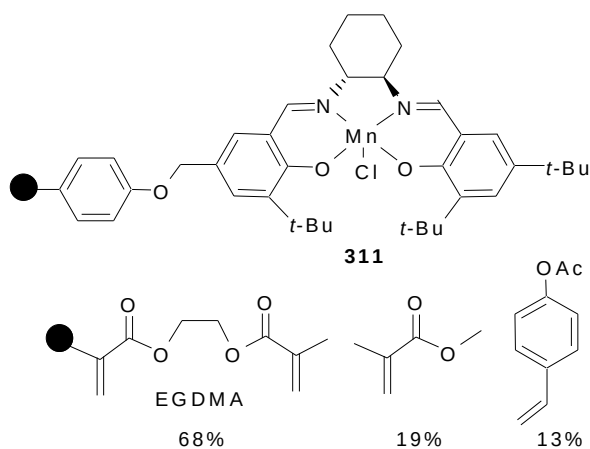
Another approach, keeping the C₂ symmetry, consisted in the immobilization of the catalyst on a TentaGel amine resin via the pyrrolidine part of a pyrrolidine-salen instead of the aromatic rings (Scheme 130) [195]. In presence of NaOCl or *m*-CPBA, with 4 mol% of catalyst 313 all underwent AE of 2,2-dimethylchromene, 6-cyano-2,2-dimethylchromene and 1-phenylcyclohex-1-ene in high yields, more than 70% and with enantioselectivities of 82%, 86% and 68% respectively. In these conditions, decomposition of this catalyst was observed.

To conserve the C₂ symmetry, Zhen [196-197] formed poly-salen complexes by condensation of a slight excess of chiral diamino cyclohexane with subsequent insertion of Mn ion (Scheme 131). These catalysts were soluble in CH₂Cl₂ but almost insoluble in ether. The oxidation reaction was performed in dichloromethane. To avoid any degradation of the polymer NaOCl was used in the presence of 4-phenylpyridine-*N*-oxide (4-PPNO) or *m*-CPBA in the presence of NMO as cooxidants. With *m*-CPBA/NMO, enantioselectivities and activities are higher than those obtained with NaOCl/4-PPNO. With salen 314a or 315 (Scheme 131), the catalytic system was similar to Jacobsen's one; at 0°C, up to 45% ee were observed for the AE of styrene. The lower temperature, the higher catalytic efficiency. For

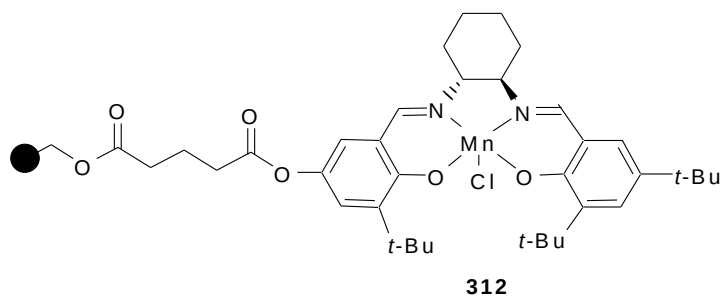
styrene epoxide formation, at room temperature and at -78°C the yields were 61% and 91% respectively with no significant improvement of the enantioselectivity of about 40%. Recovery and reuse of the catalytic system by precipitation was possible with only slight loss in enantioselectivity. The behaviour of catalyst 314b (Scheme 131) was a little different [197]. At -78°C , it presented much lower activity but at -22°C , 83% yield and 51% ee were observed which was represented the best ee for the epoxidation of styrene. This catalytic system unstable in the reaction conditions was not reused.



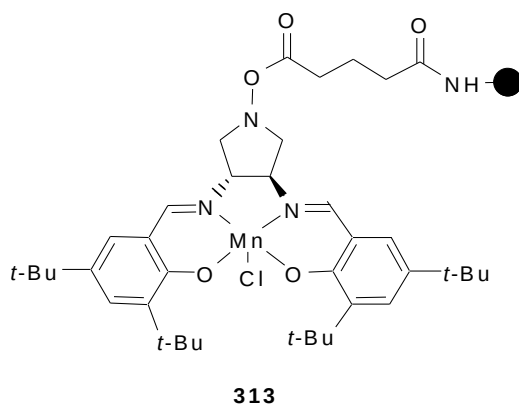
Scheme 127.



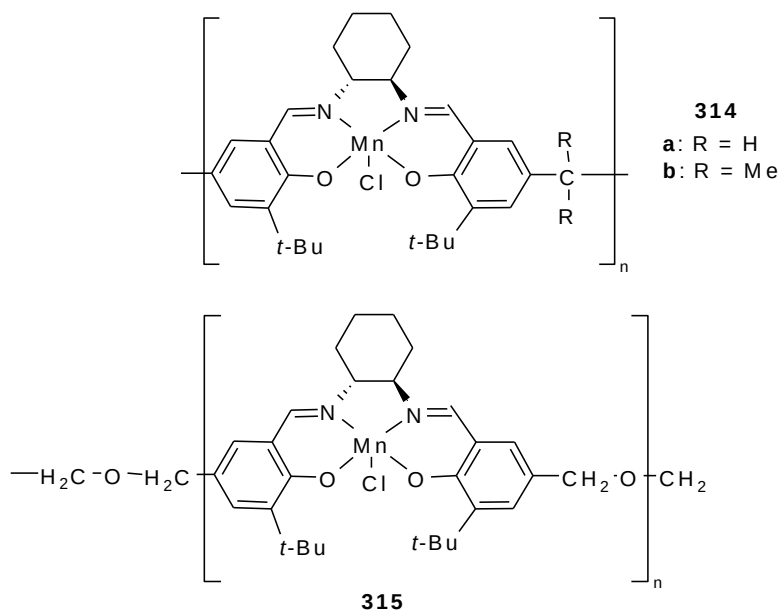
Scheme 128.



Scheme 129.

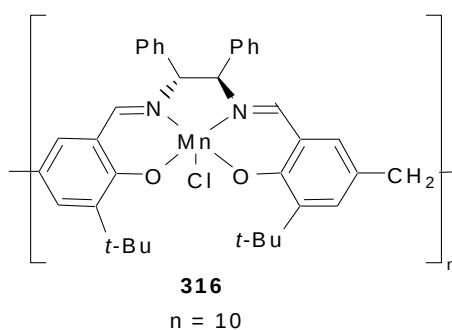


Scheme 130.

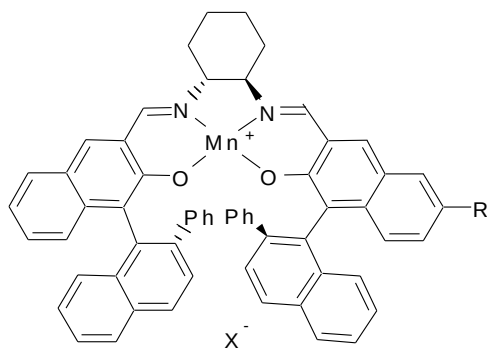


Scheme 131.

Kureshy [198] had also carried AE with a poly-salen. The poly-salen 316 derived from chiral diphenylethylenediamine (2 mol%) (Scheme 132) and NaOCl in the presence of cooxidant (NMO, 4-PPNO, PyNO, DMSO) forming the oxidative reagent were used for the epoxidation of styrene, indene and 6-cyano-2,2-dimethylchromene. In all cases, the best results in term of activity (yields up to 99%) and enantioselectivity were obtained with PyNo as cooxidant. The epoxide of styrene, indene and 6-cyano-2,2-dimethylchromene were formed in 32%, 78% and 100% ee respectively. Comparatively, Poly-salen 314a ($n = 12$, Scheme 131) led to 55% ee for epoxystyrene but for epoxyindene and epoxy 6-cyano-2,2-dimethylchromene 69% and 100% ee were observed. The turn over frequency (TOF) was higher with poly-salen 314a (Scheme 131). The activity of the recycled catalyst gradually decreased upon successive use possibly due to minor degradation under epoxidation conditions and/or weight loss during recovery process of the chiral catalyst, but the ee remained constant.



Scheme 132.



317: $R = CH_2CH_2CH_2OH$

318: $R = H$

319: $R = CH_2CH_2CH_2OCOC_6H_4$

a: $X^- = PF_6^-$

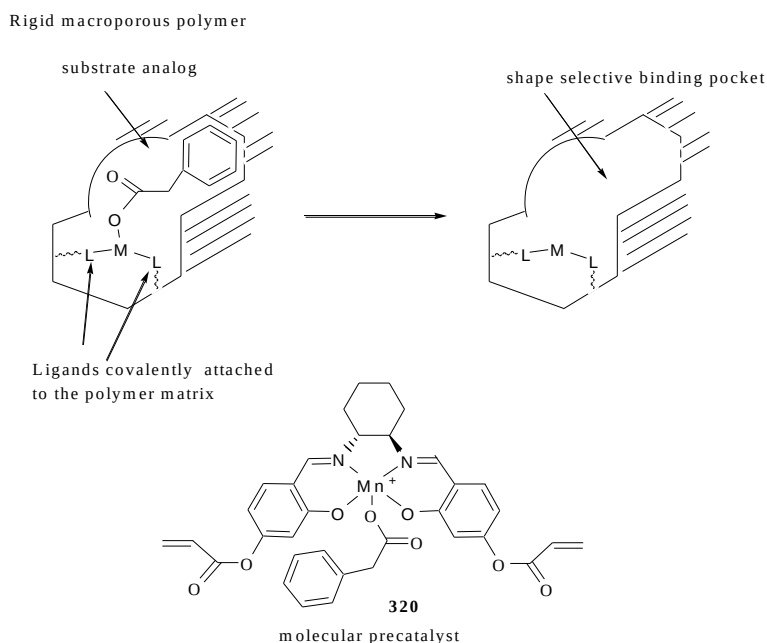
b: $X^- = AcO^-$

c: $X^- = CF_3SO_3^-$

Scheme 133.

Smith [199] involved immobilized Katsuki-type (salen)Mn complex 318 ($R = H$, Scheme 133) for the AE of 1,2-dihydronaphthalene with NaOCl/4-PPNO. The Katsuki-type (salen) 317 presenting an hydroxyalkyl group ($R = CH_2CH_2CH_2OH$ Scheme 133) on the 6-position was grafted onto a polystyrene resin via an ester link by means of polystyrene carboxyl chloride (1% crosslinked, 200-400 mesh, 1.17 mg/mol of chloride) (salen 319, Scheme 133). The counter ion seemed to have no influence on the catalytic efficiency and selectivity. For all of them, yields were about 40% with excellent ee (upper than 90%). Each catalytic system was reused after filtration, ee and yields remained quite unchanged. To increase the yield upon the recycle (up to 70%), concentration of the reaction mixture was required.

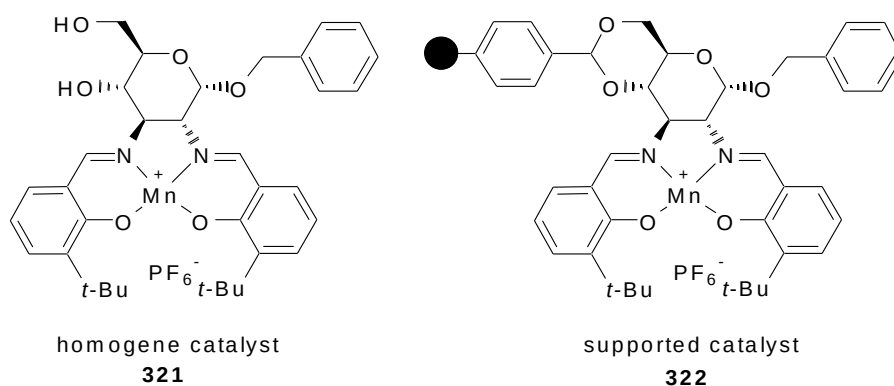
The molecular imprinting polymer (MIP) was tested by Gohdes [200]. The manganese salen precatalyst 320 (Scheme 134) having two polymerizable acryloyl groups could be covalently embedded in the crosslinked polymer network. In order to mimic the bound styrene substrate, phenylacetate ligand was fixed on the Mn atom which after its removal will leave behind the substrate-binding cavity. The MIP synthesis was performed with the precatalyst 320 in presence of EGDMA as the crosslinking agent, styrene as a non linking polymer and dichloroethane as a porogen. Exploration of porosity and crosslinking effects on activity on epoxidation of the styrene in presence of PhIO or *m*-CPBA was carried out. In the optimum conditions 40-50% porogen and 70% crosslinking and *m*-CPBA as oxidant, the ee was up to 14%. This imprinted polymer could be reuse at least 3 times without loss of ee.



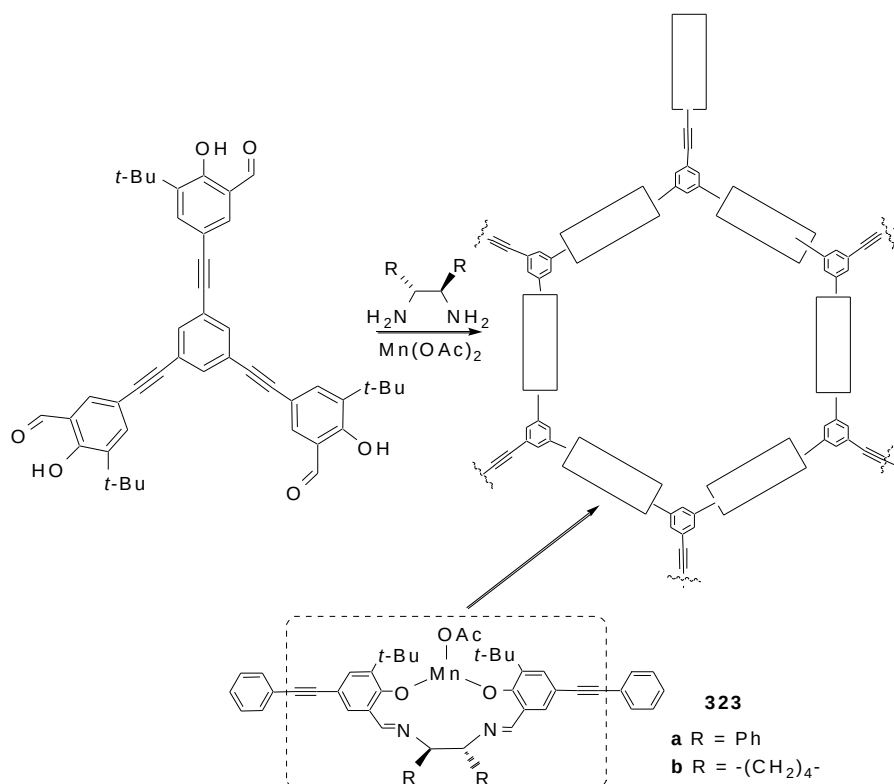
Scheme 134.

Another way to immobilize the salen catalyst was to use glucose as a linker and to graft it on CHO modified Wang resin (Scheme 135) [201]. The activity of the catalyst 322 in the AE of styrenes has been investigated with four oxidants: H_2O_2 , NaOCl, $(n-Bu_4N)HSO_5$ and *m*-CPBA. The best results in terms of activity (99%) have been achieved with *m*-CPBA/NMO;

the respective ee were 30% and 80% for styrene and *cis* β -methylstyrene. As the reaction was accompanied by extensive lack of metal from the solid, no recycle has been considered.



Scheme 135.

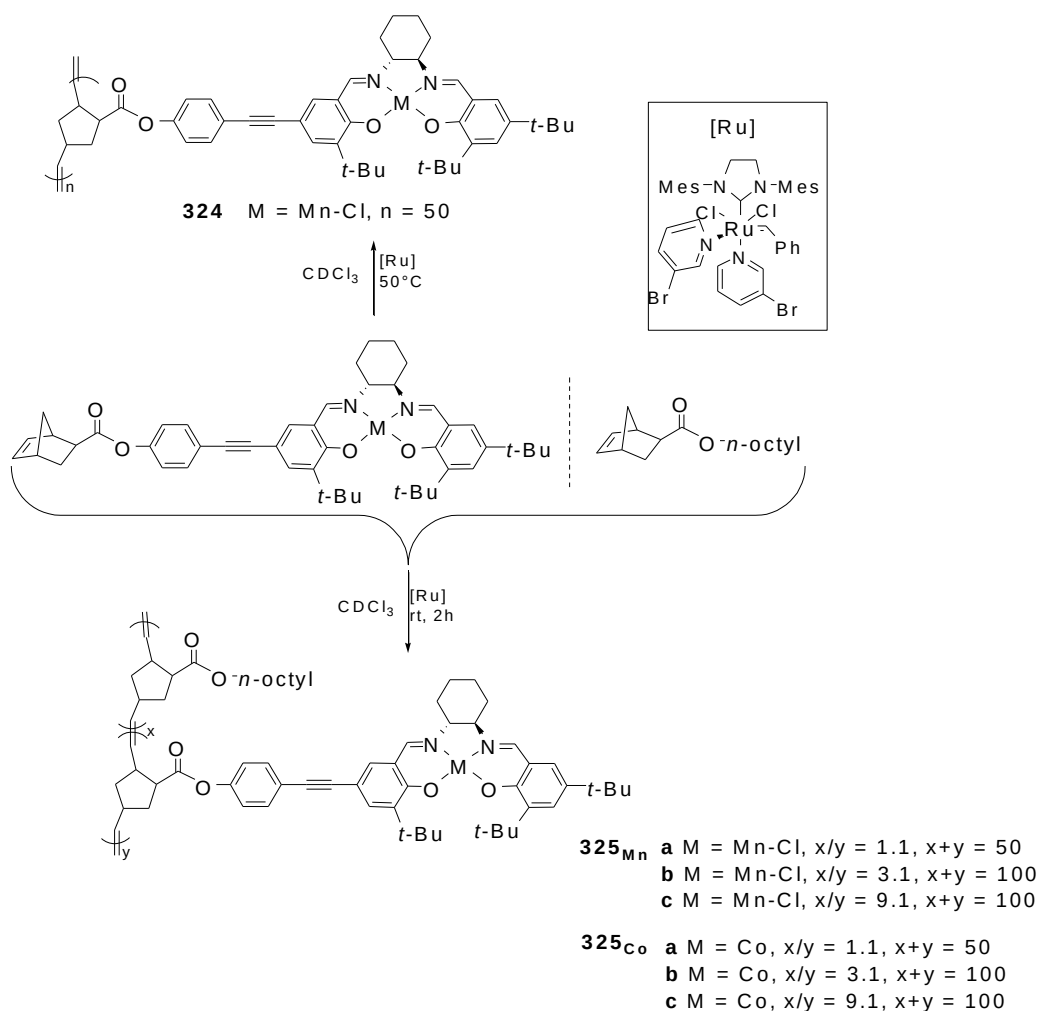


Scheme 136.

A new approach consisting in the formation of rigid and amorphe salen-polymer (323, Scheme 136) was reported by Gothelf [202]. It involved a condensation of a rigid tris(4-hydroxy-3-tert-butylphenyl)methyne with substituted ethylene diamines (Scheme 136). The AE of *cis* β -methylstyrene at 0°C, with *m*-CPBA in presence of NMO and polymer 323a led to 78% conversion with a *cis/trans* epoxide ratio of 17.0, with a catalyst loading of 15 mol%. Up to

67% ee for the *cis* stereoisomer and 23% ee for the *trans* diastereoisomer are obtained. After isolation from the reaction mixture, the catalyst was reused at least 6 times without significant drop in reactivity and selectivity.

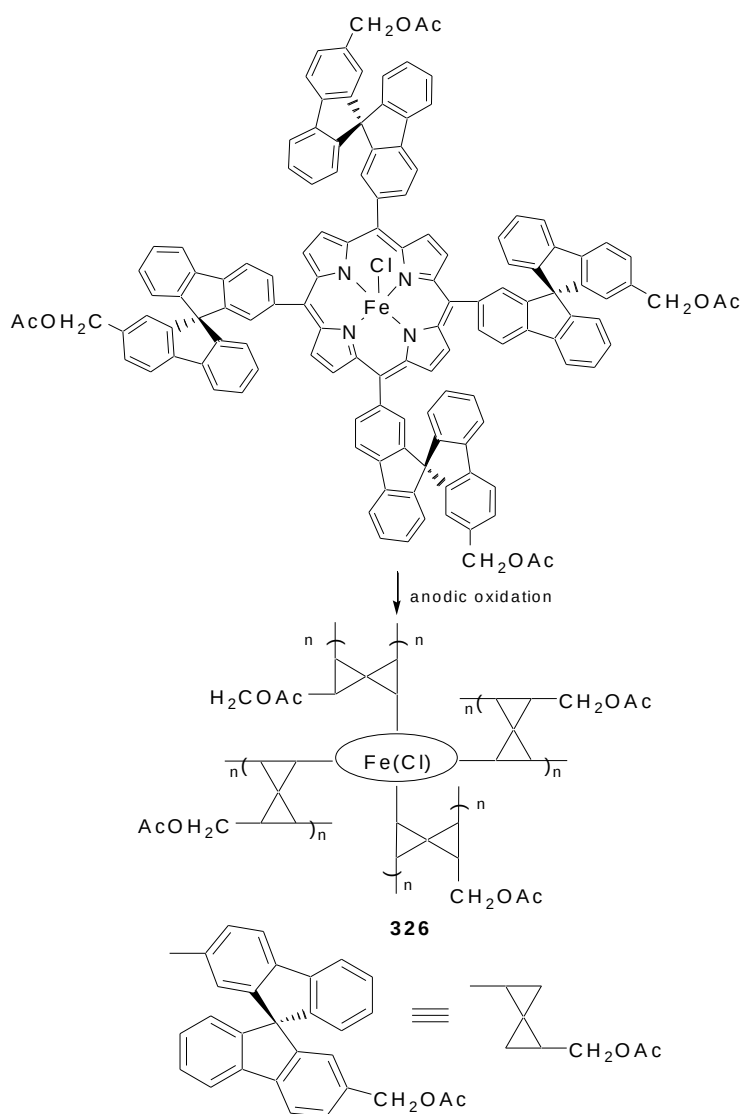
Weck [203] developed a monomer salen complex linked to a norbornene via a stable phenylene-acetylene linker and its subsequent polymerization by means of the controlled ROMP method using 3rd generation Grubb's catalyst (Scheme 137). This polymerization methodology led to fully functionalized immobilized metal-salen catalyst. By this way, the supported catalyst showed catalytic activities and stereoselectivities similar to the non-supported Jacobsen catalyst. Moreover, activities and selectivities seemed to depend on the density of the catalytic moieties: homopolymer **324** were less selective than their copolymer analogs **325**. For example, AE of 1,2-dihydronaphthalene led in both cases to total conversion and 76% ee for the homopolymer **324** vs 81% ee for copolymer **325a**. Recycle was possible and after 3 recycles a drastic decrease in ee was observed. AE of dihydronaphthalene led to 81% ee for the first cycle vs 6% ee for the third one.



Scheme 137.

9.2. Porphyrins

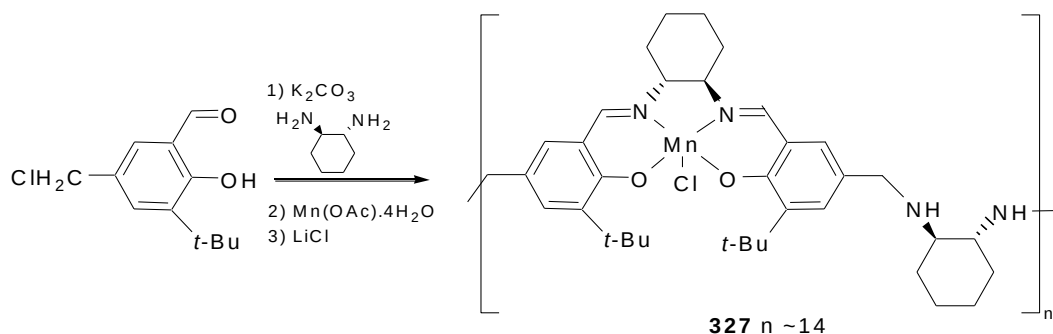
Polymer RuCO-porphyrins 102 and 103 (Scheme 48) were used for the cyclopropanation reaction of styrenes but they were also tested in the epoxidation reaction. Contrary to cyclopropanation for which moderate enantioselectivities and low activities were observed, these Ru porphyrin complexes gave good ee (up to 76%) and activity (up to 89%) for AE of unfunctionalized olefines [204]. Recently, Simoneaux showed that iron catalyst 326 derived from electropolymerized tetraspirofluorenyl porphyrin (Scheme 138) led to moderate yields without chiral induction [205].



Scheme 138.

9.3. Soluble Polymers

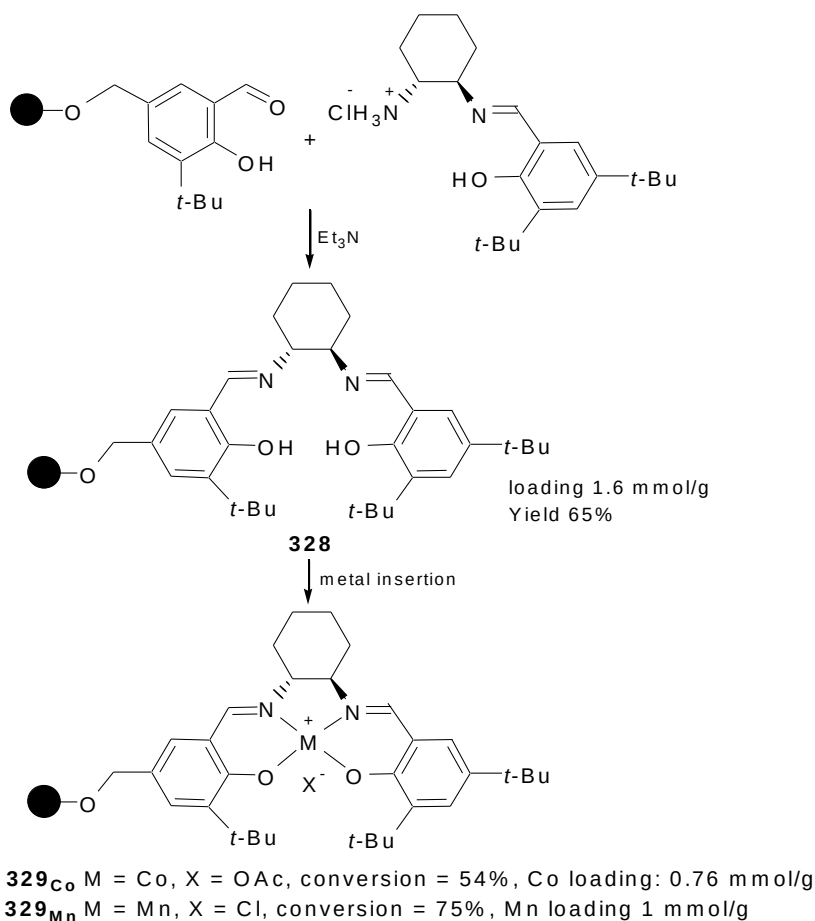
In 2006, Yu [206] prepared a polymeric chiral salen Mn(III) complex containing chiral diamine spacer, acting as a solvent regulated phase transfer catalyst (scheme 139). This catalyst presented a Mn ion content of 1.49 mmol/g and a molecular weight of 9100. Evaluation of its catalytic behaviour in AE of styrene was performed in the presence of the oxidative system *m*-CPBA/PyNO, *m*-CPBA/4-PPNO, *m*-CPBA/4-PPPyNO or *m*-CPBA/NMO. Enantiomeric excesses up to 35% were found similar to those observed in the same reaction conditions with Jacobsen catalyst. This was probably due to the solubility of the polymeric catalytic system in the reaction mixture acting thus as an homogeneous catalyst by minimizing the diffusion of the reactants to the active sites of the catalysts. The nature and the amount of the *N*-oxide cocatalyst showed some impact on both yield and ee. Without this additive, the yield was rather low and no ee was detected; and its presence led to an increase of both yield and ee. The optimum yield and ee were obtained when 2 equivalents of each additive were used. But NMO was the best one leading to 98% yield and 43% ee. Recycle was possible but after the third one, poor yields and ee were observed.



Scheme 139.

Recently, Liese [207-208] used a hyperbranched polyglycerol support as high loading Mn-salen complex (chemzyme) as a catalyst for AE 6-cyano-2,2-dimethylchromene for a continuous application in a membrane reactor. This polymer supported catalyst was performed using a polyglycerol which molecular weight is 8000 g/mol and OH group loading 13.5 mmol/g. The polymer purification was carried out by ultrafiltration leading to 65% of the desired polymer 328 (Scheme 140). The following metal insertion led to polymer-supported catalyst 329.

The oxidative reagent was formed by *m*-CPBA and NMO. Upon recycling it was observed an enhancement of the stability of the catalyst, the total turnover number increasing from 23.5 for a single batch to 80 in four repetitive batches. Moreover, some metal leaching occurred because the maximum conversion decreased from 98 to 75%, but enantioselectivities were less affected; they decreased from 95 to 88% ee from the first to the fourth batch. Nevertheless, in a continuously operated chemical membrane reactor, the TTN reached up to 240 after 20 residence times with conversions up to 70% and ee up to 92%.



Scheme 140.

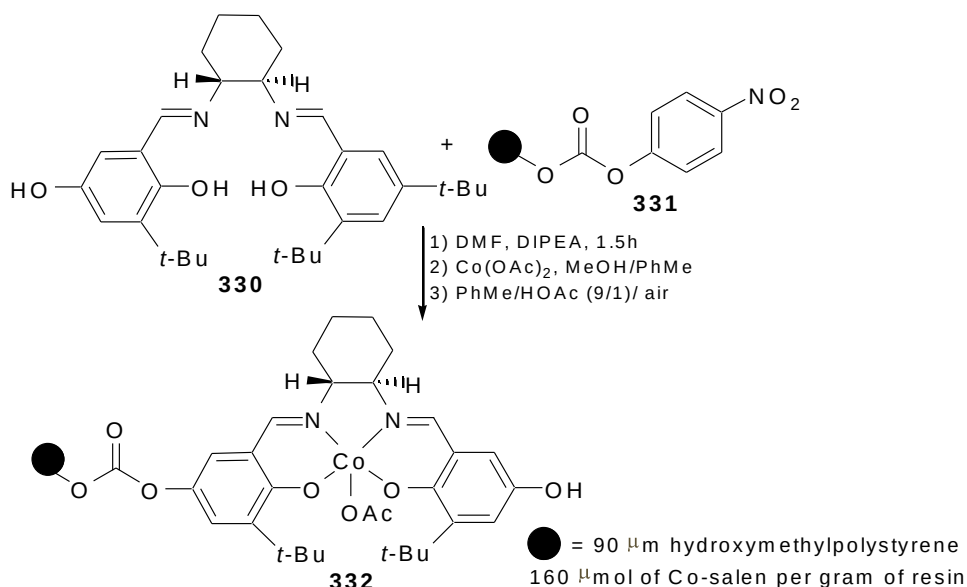
10. KINETIC RESOLUTION OF TERMINAL EPOXIDES

Close to Mn-salen complexed which were effective in the epoxidation of unfunctionalized alkenes Co or Cr-salen complexes have shown their ability in asymmetric ring opening such as hydrolytic kinetic resolution (HKR) of racemic epoxides. This reaction, performed in homogeneous conditions was able to furnish chiral epoxides and diols with high enantioselectivities. Numbers of inorganic supports have been used however some organic supports have also been studied. Other kinetic resolution could be performed such as ring opening epoxide with other nucleophiles and dynamic resolution.

Contrary to the catalytic systems employed for the epoxidation, mechanistic studies of asymmetric ring opening have shown that cooperative interactions between catalyst units are needed [209]. Thus, high local concentration of catalyst was necessary and high-loading support should increase the catalytic reactivity.

In 1999, Jacobsen [210] prepared a polystyrene-supported Co-salen complex 332 by grafting a monophenol derivative 330 of an highly efficient chiral salen onto hydroxymethyl polystyrene beads (90 μm) derivatized as their *p*-nitrophenyl carbonate 331 (Scheme 140).

The same polystyrene complex 332 could be synthesized by resin capture of the salen 330. The preparation of salen 330 was carried out using an excess of di-*tert*-butyl salicylaldehyde relative to 2,5-dihydroxy-3-*tert*-butylbenzyldehyde and enantiopure cyclohexane diamine (ratio: 3/1/2) yielding a 9/6/1 ratio of ditertibutyl, monophenolic (330) and diphenolic ligands. Then, addition of the carbonate derived polystyrene resin to the mixture allowed the selective capture of the two phenolic ligands. After washing, the polymeric mixture is formed by the incorporation of the diphenolic ligand in the resin bound ligand close to ligand 332. Complexed with Co, this small amount of the incorporated diphenolic ligand in the resin catalyst did not affect the rate and the enantioselectivity; compared to material prepared with pure ligand 332, similar results were observed.

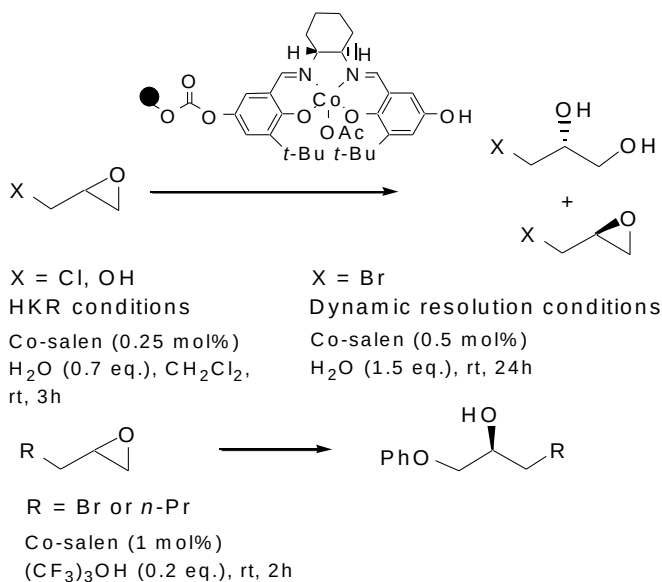


Scheme 140.

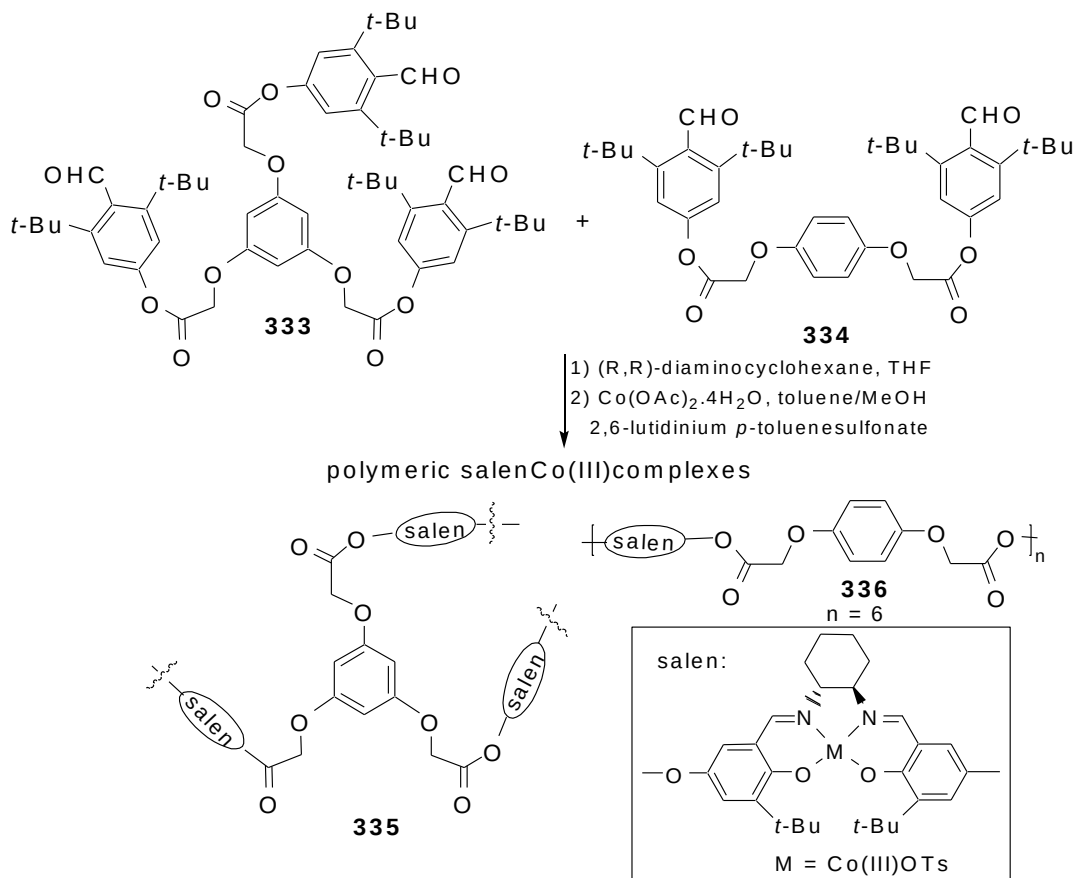
The HKR of epichlorhydrine (X = Cl, Scheme 141) and 4-hydroxy-1-butene oxide (X = OH, Scheme 141), the dynamic kinetic resolution of epibromhydrin and the enantioselective ring opening of epoxides by phenol were examined. In the first experiment, combination of the crude organic soluble products of the five recycle reactions and concentration led to the (*S*)-epichlorhydrine in 41% overall yield and > 99% ee and the (*R*)-chlorodiol in 93% ee. In the second one, the sum of five experiments provided (*S*)-triol in 36% overall yield and 94.4% ee while the enantioselectivity of the epoxide was only 59% ee.

The dynamic resolution of epibromohydrine provided only the bromodiol in 94% overall yield and 96% ee (sum of the five experiments). Excellent results were also obtained for the ring opening epoxides with phenol, ee could reach more than 99% and yield 98%.

The kinetic resolution of other epoxides with phenol was also studied in enantioselective parallel synthesis with the same catalyst, providing efficient access to important precursors of pharmacologically active compounds [211]. For all the studied substrates, the catalytic system was proved to be very efficient. β -aryloxyalcohols were formed in high yield (90-100%), purity (93-100) and ee (81->99%).

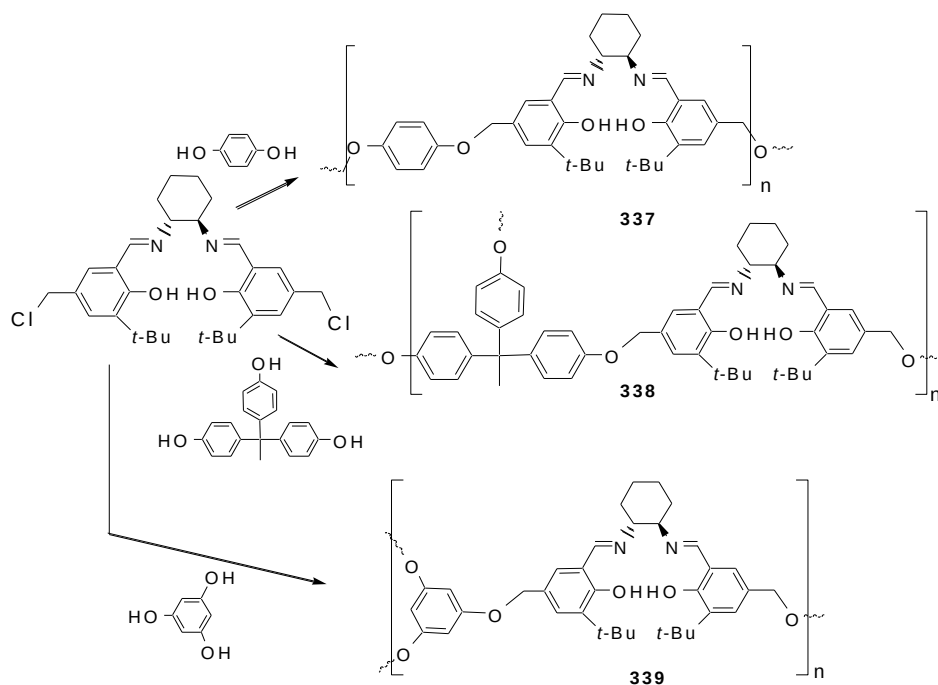


Scheme 141.



Scheme 142.

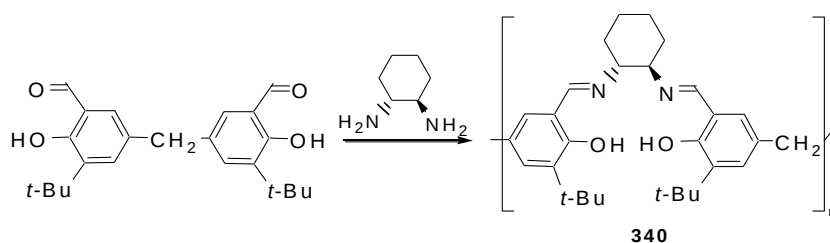
Zheng [212] prepared crosslinked polymeric Co(III)-salen complexes in order to induce cooperative effect. Trialdehyde 333 and dialdehyde 334 are formed via condensation of 2,5-dihydroxy-3-*tert*-butylbenzaldehyde with diacid and triacid derived from hydroquinone and chloroglycinol. Different proportions of tri and di aldehydes (tri/di) were subsequently condensed with enantiopure cyclohexane diamine to afford polymeric ligands 335 (Scheme 142). An average molecular weight between 4000 and 10000 were observed for these polymers. For the HKR of epichlorohydrine, styrene oxide, and phenylglycidyl ester, in a wide range of tri/di proportion, similar behaviour of the catalytic system was observed in the same reaction conditions. For example, with epichlorohydrine conversion based on racemic mixture varied from 50-52%, epoxide ee from 98-99% and diol ee from 91-97% using 0.02 mol% of the catalyst, at 10°C. Most of the crosslinked polymeric catalyst presented better activities than those of the oligomer 336, showing a positive effect on the cooperation on catalytic centers with the crosslinked polymer. But with the complete crosslinked polymeric catalyst 335 activities and enantioselectivities are slightly lower, behaviour probably due to the poor solubility of the catalyst. Moreover, attempts to recycle the catalytic system were unsuccessful. This fact was ascribed to the sensitive ester linkage to the reaction medium.



Scheme 143.

Kim [213] studied the effect of the counter ion on the HKR of epichlorohydrine, 1,2-epoxybutane, 1,2-epoxyhexane and epoxystyrene. The salen polymer catalyst was synthesized by copolymerization of salen bearing chloromethyl groups with sodium phenoxide derivatives of hydroquinone, 1,3,5-trihydroxybenzene or 1,1,1-tris(*p*-hydroxyphenyl)ethane in presence of *N*-methylpyrrolidine and NaH in THF (Schemes 143 and 144). Co(II) type polymeric chiral salen ligands were formed by reaction of the corresponding salen ligand with hydrous Co(II) acetate. To obtain Co(III) polymeric chiral

salen catalysts, the Co(II) polymer salen was treated with ferrocenium hexafluorophosphate or ferrocenium tetrafluoroborate noted respectively Co(III).(PF₆), Co(III).(BF₄). The HKR of epichlorhydrine, 1,2-epoxybutane, 1,2-epoxyhexane and epoxystyrene was performed. With all these substrates, excellent enantioselectivities (up to 99.8%) were observed with 337-, 338-, 339-, 340-Co(III).(PF₆), -Co(III).(BF₄) catalysts. Both type of catalysts exhibited almost the same ee as monomeric salen catalyst. These catalytic systems were stables; they could be recovered and reused at least seven times without further treatment without loss of activity and selectivity and without regeneration of the catalyst. However, it is noteworthy that 340-Co(III)OAc catalyst, the regeneration with AcOH/air is necessary to avoid an ee decreased to 20% in the second hydrolysis. Moreover with 340-Co(III)OAc catalyst a racemization during the reaction and the product isolation by distillation could occurred The ee decreased slowly via racemization which is not the case with 340-Co(III).(PF₆).



Scheme 144.

Other 340-Co-salen complexes containing Lewis acid were studied [214](Scheme144).

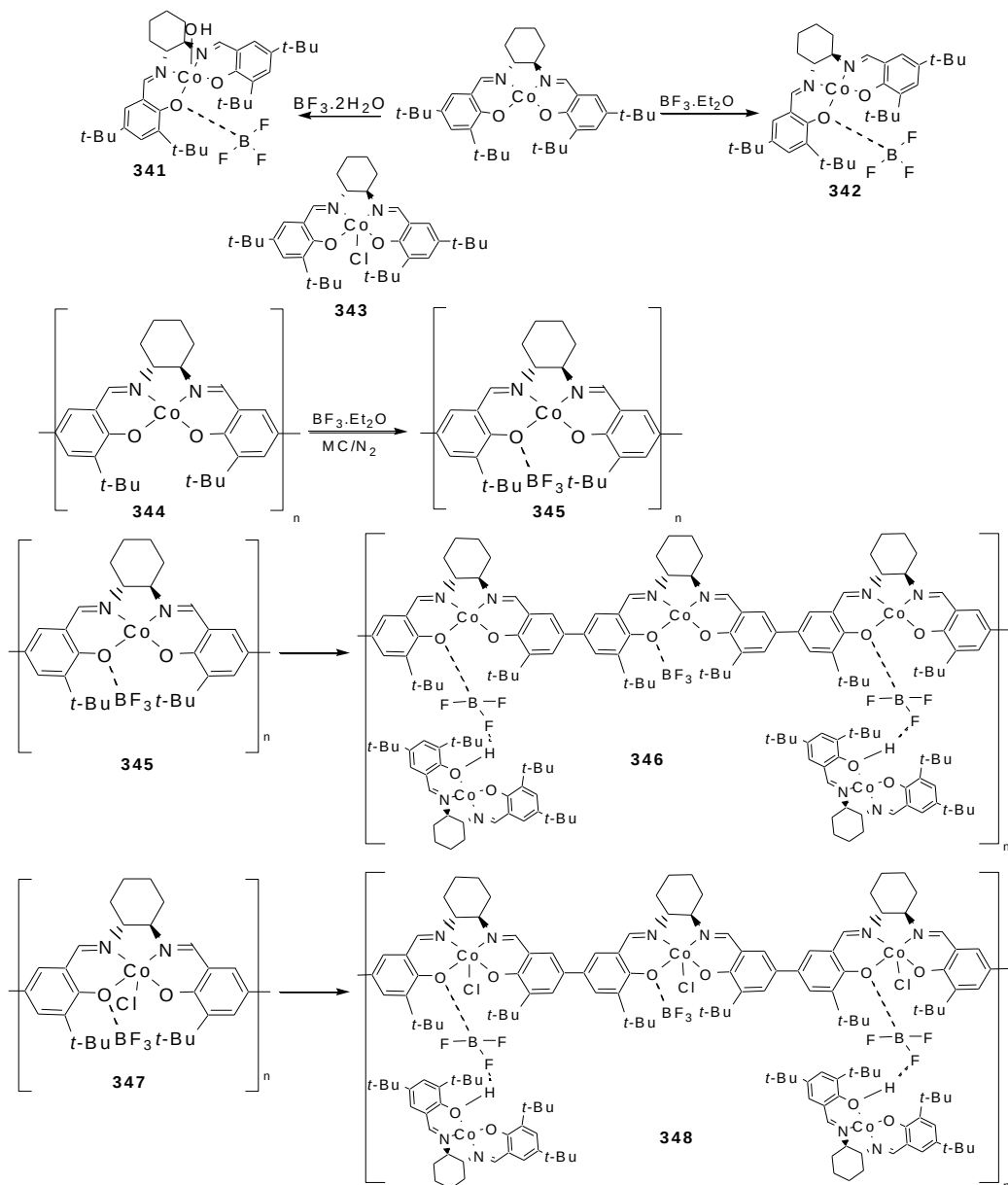
Monomeric salen Co(II) or Co(III) unit are supposed to be attached to the polymer salen catalyst by means of the Lewis acid. Thus, salen units were linked together as a dimeric form (polysalen 346 and 348, Scheme 145). It was observed a great increase of the catalytic activity for the HKR reaction of various epoxides. For example, in presence of 0.4 mol% polysalen catalysts 346 and 348 the HKR reaction of epichlorhydrine led to about 98% ee, after 6h whereas with complex 345 ee was up to 55%. As dissociation of monomeric salens from the polymer backbone partially occurred after their first use, the polymeric salen 346 and 348 lost their catalytic activity. It is noteworthy that the activity of the salen catalyst could be recovered upon treatment with monomeric salen.

Contrary to Mn salen 256_{Mn} (Scheme 126), which is used for the AE, Laibinis used the heterogeneous Cr salen 256_{Cr} catalyzed ring epoxide opening in the presence of TMSN₃ [190]. In the conditions of ring opening epoxide, ee reach 36% and yield 47% for the propylene oxide. But the catalytic system is stable and could be reused 3 times without loss of activity and enantioselectivity.

Weck [203] has performed the HKR of several epoxides by means of polymer-supported cobalt salen catalysts containing different counterions (325/Co-OAc, 325/Co-I, 325/Co-OTs, 325/Co Scheme 137). 325/Co-I and 325/Co-OTs catalysts have shown higher activities than 325/Co-OAc and ee could be up to > 99% with a conversion of 55% after 1h with 325/Co-I for the HKR of epichlorhydrine. These catalysts can only be recycled once as a result of their decreased solubility after the reoxidation step.

Weck [215] has also described polystyrene-supported chiral salen ligands 349 and 350 synthesized respectively by radical homopolymerization or copolymerization of an

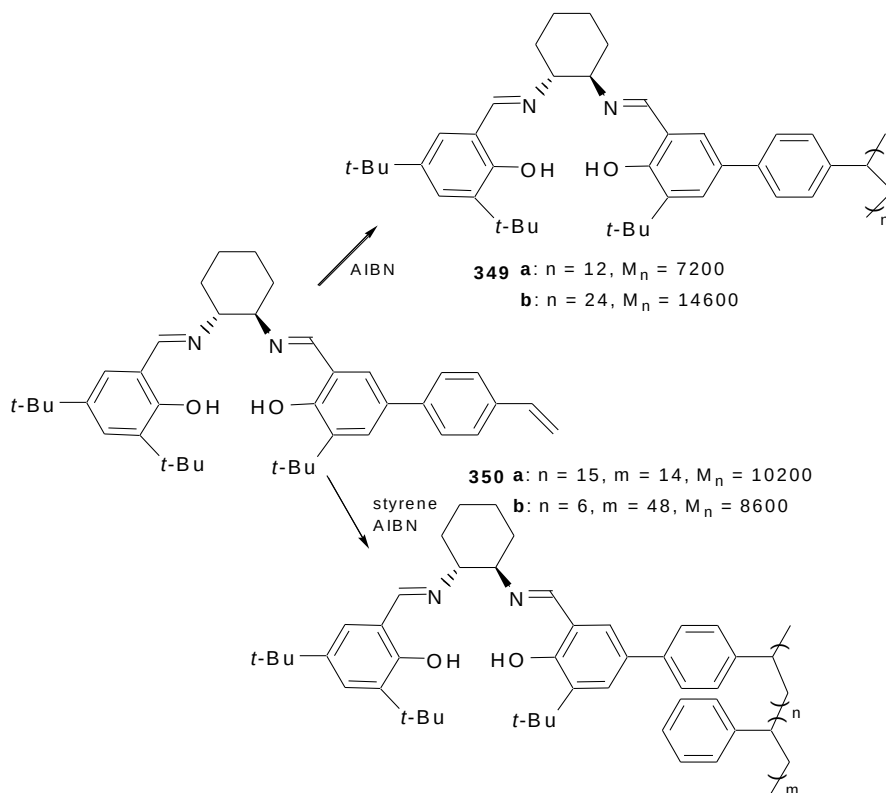
unsymmetrical styryl-substituted salen monomer (Scheme 146). They were easily converted into their Co(III) acetate complexes and then tested in the HKR of epichlorohydrin at room temperature. The reaction was carried out with 0.5 mol% of the catalyst and after 1h, conversion is about 55% and ee >98% even after four recycling (catalyst 350b).



Scheme 145.

Polyethylene glycol-salen-Co-OAc (Scheme 140) were applied in the HKR of several terminal epoxides with a catalyst loading of 0.5 mol% using 0.55 equiv. of water in THF. A positive dendritic effect was observed; the dendritic backbone was supposed to increase the intramolecular cooperation between Co active site by bringing the reactive site of the reactant

adjacent to each other (cooperative bimetallic catalysis) [208]. This reason was evoked to explain that better results were obtained with the polymeric catalyst contrary to the non polymeric one. With epichlorohydrine, the conversion reached 52.5% and the enantioselectivity 90.5%.

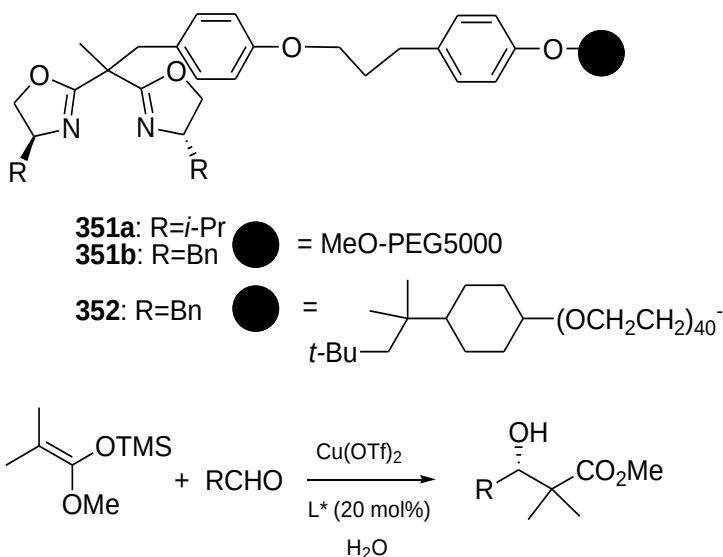


Scheme 146.

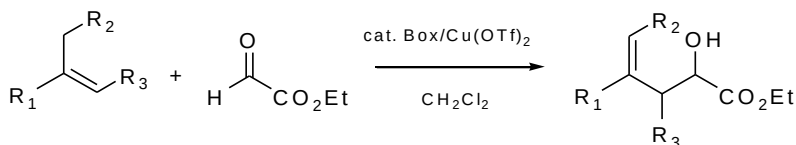
11. MISCELLANEOUS

Few other asymmetric reactions have been performed using insoluble or soluble polymer-supported ligands. The first example is a Mukaiyama-aldol condensation between silyl ketene acetal and different aldehydes using polymeric Box analog of 99 as chiral ligands and $\text{Cu}(\text{OTf})_2$ as metal source in water (Scheme 147) [216]. When using benzaldehyde as substrate, yields were very low (12-34%) and ee were moderate (40-62%) whatever the polymer-supported Box. The same level of enantioselectivity was observed with other aldehydes while the yield was better with all the ligand/Cu complexes used.

Insoluble polymer-supported Box 82 ($n=1$) (Scheme 40) was also used in an enantioselective glyoxylate-ene reaction (Scheme 148) [217]. In most cases, although the yields and the ee were satisfactory, they were slightly slower than those observed with the corresponding non-polymeric Box.



Scheme 147.



Scheme 148.

The possibility to recycle the catalyst was examined in the ene reaction of α -methylstyrene and ethyl glyoxylate. The conversion dropped from 90 to 60% after the fourth recycle (conversion was evaluated after six hours for each run) while the enantioselectivity remained constant.

Furthermore, a continuous flow-system has been developed using the polymer 82 and overall 23 mmol of α -methylstyrene have been transformed into the corresponding product after 5 consecutive batches. The enantioselectivity did not change between the successive runs (close to 90% ee). The TTN was estimated at 44 or 51 versus the supported Box and copper salt respectively.

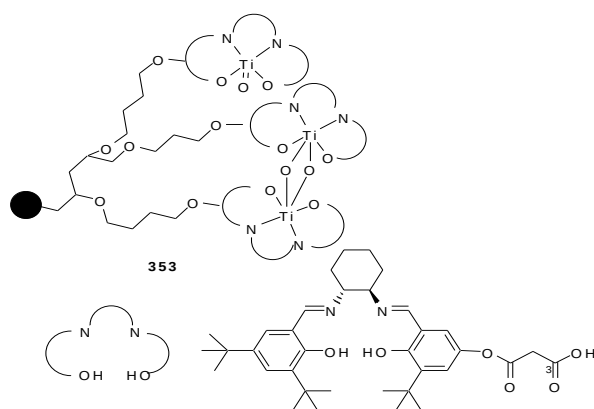
The complexes of polymer 243 (Scheme 97) with YbCl_3 and LuCl_3 have been used for the ring opening of cyclohexene oxide by trimethylsilylcyanide [154]. Although the conversions were excellent, the ee were low to moderate. Furthermore a significant drop of the enantioselectivity was observed when the recovered supported Yb-complex was reused.

The same complexes were then evaluated for the enantioselective TMSCN addition to benzaldehyde. For this reaction, both yield and ee were better with the Lu-complex.

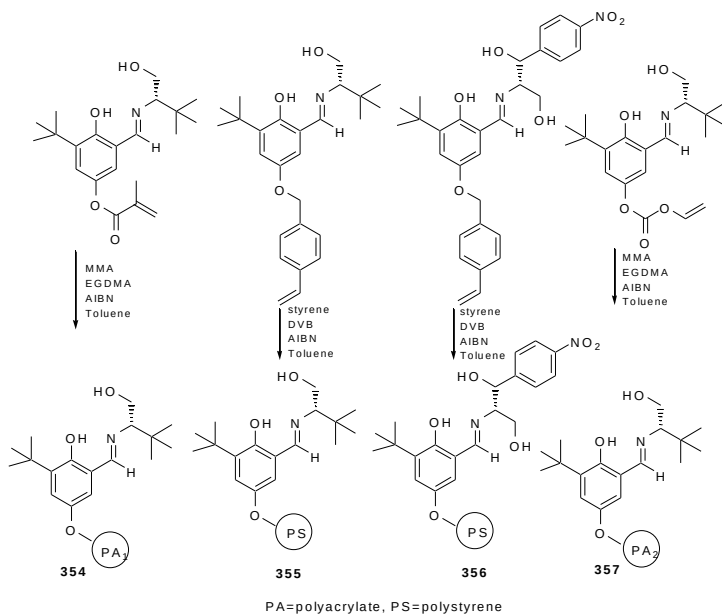
The asymmetric TMSCN addition to benzaldehyde was also performed in a microreactor using the polymeric catalyst 353 (Scheme 149) [218]. A normal batch procedure was first carried out and the protected cyanohydrin was obtained with 91% conversion and 73% ee.

When a microreactor using this catalyst 353 was employed, same result was observed with a flow rate of 0.8 μL .

Enantioselective sulfoxidation has been also studied using polymeric aminoalcohol-derived Schiff bases. Polymers 354-357 have been prepared by copolymerisation of the corresponding monomer with either MMA and EGDMA or styrene and DVB (Scheme 150) [219]. These four polymers were then stirred with $\text{VO}(\text{acac})_2$ for 4h at rt to lead to the vanadium complexes. For the enantioselective oxidation of thioanisole, although the yields were similar to those obtained with the homogeneous analogs, the enantioselectivity were lower. The best selectivity was obtained with the catalyst derived from 355.



Scheme 149.



Scheme 150.

12. CONCLUSION

The performance of the soluble catalysts supported on a polymer or of the heterogeneous catalysts is highly dependant on the polymer morphology which is, in the last case, mainly controlled by the degree of crosslinking, the nature of the crosslinker and nature of the porogen.

For soluble polymer catalysts, the catalytic performances are generally close to that observed with homogeneous non-supported catalysts. This behaviour is mainly inherent to high mobility of the bound catalyst and a good mass transport. However, the stability of the catalyst depends on the reaction conditions, some catalytic systems being not stable in some solvents. Their recovery needs filtrations or precipitation, sometimes under inert atmosphere. But, their use could be interesting for an industrial point of view, particularly in continuous flow systems involving membranes where important conversions of the substrate with good selectivity could be involved.

As for insoluble catalysts they could be separated into two series. The ligand could be anchored onto swellable or unswellable polymers.

In the first case, the support is formed by a crosslinked polymer, mostly a polystyrene crosslinked with 0.5 to 3% DVB.

In the second case, practically unswellable polymers formed the support. This latter is a highly crosslinked polymer. A large variety of solvent could be used without changing the texture of the catalyst. In order to obtain a good mass transport, it is generally necessary to obtain immobilized catalysts with a pore size enough larger to include the size of the metal complex catalyst and the substrate. This parameter depends on the nature of the porogen. These immobilized catalysts must present a large surface area

For the specific molecular imprinting polymer, the catalyst is efficient if a good mass transport is possible and particularly if the chiral cavity fits perfectly with the size and the structure of the substrate. It is the reason why in most of the cases the shape of the polymer is specific to a single substrate.

Reaction performed with monolithic polymer-supported catalysts, lead generally to good to excellent behaviour in terms of catalytic activity and enantioselectivity and as the reaction is performed without stirring, the catalytic system is generally very stable.

The catalyst ability for recycling and reuse is in correlation to the stability of the catalytic system itself. A simple change of the nature of the polymer support could increase the stabilization and thus the recyclability of the catalytic system.

Concerning the nature of the nitrogen-containing ligand itself, immobilized derivatives of DPEN revealed to be the most efficient in the reduction of prochiral ketones by catalytic hydrogenation in the presence of BINAP or by HTR and CBS-supported ligands for the enantioselective hydride reduction.

As for C-C bond formation via an addition of organometallic reagent to aldehyde, ketone or imine or allylation, supported-complexes of prolinol, ephedrine and oxazoline derived constitute the best catalytic systems.

Most of the polymeric-catalytic systems used for the dihydroxylation or aminohydroxylation of C=C bond is issued from alkaloid, mainly cinchona which has been proved to be the best ligand for this type of reaction.

For the epoxidation or kinetic resolution of terminal epoxide, polymer-supported salens have shown to be either as efficient as or more efficient than their non-supported homologs.

It is noteworthy that concerning the loading, low loading in ligand and metal are required to achieve asymmetric hydrogenation, C-C bond formation or dihydroxylation or aminohydroxylation. But, high loading is necessary for epoxidation or resolution of terminal epoxides if salen derivatives ligands are employed.

To conclude, the nitrogen-containing ligands are easy to handle, to synthesize and to support them on polymers, thus this constitutes a crucial advantage for using them in various separation systems (precipitation, ultrafiltration, membrane reactor, biphasic solid/liquid or liquid/liquid).

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Chapter 4

SMALL MOLECULE STABILIZATION: A NOVEL CONCEPT FOR THE STABILIZATION OF SMALL INORGANIC NANOPARTICLES

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ABSTRACT

In the last 20 years, the synthesis of nanoparticles with defined size and shape has been studied with strongly growing interest, leading to a multitude of synthetic approaches and strategies. Whereas the synthesis of the nanocrystals has been studied in great detail, far less effort has been directed towards the stabilization of the obtained materials against agglomeration. This is surprising as the stabilization determines their dispersibility in various solvents, which is a crucial parameter for most applications. For conventional colloids, the classical theories of electrostatic, steric and electrosteric stabilization are well established, but application of these theories to the stabilization of small nanomaterials leads to some peculiarities and at the same time has some limitations, which is known from experimental experience but has not been studied in a systematic fashion yet.

One important conclusion from the theories is that short organic molecules sufficiently serve to provide steric stabilization of nanoparticles less than about 50 nm in size, without a need for long-chain polymeric stabilizers. This concept has been successfully applied using commercial metal oxide nanoparticles in the 50 nm size range, and it is even possible to tailor nanoparticle dispersions with respect to their rheological properties by adjustment of the stabilizer size. Through proper choice of the stabilizer, nanoparticle slurries with high solids content but at the same time low viscosity can be realized, which is highly advantageous for applications especially in the field of ceramic processing.

For ultrasmall nanoparticles in the sub-10-nm regime, the picture is somewhat different. On the one hand, the dispersions of such particles in a stabilized state show

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very special properties on the verge to molecular solutions, rendering them highly relevant for applications and thus their preparation highly important. On the other hand, due to the lack of suitable model materials, the fundamentals of interaction and stabilization of such small nanoparticles remains largely in the dark. Only a small number of reports were specifically directed to address these problems and systematically investigate the effects of stabilizer chemistry and structure as well as solvent influence. A brief overview of these studies is provided to show that first concepts have been presented, but the general applicability of these concepts still remains to be seen, and to demonstrate the substantial need for further research in this field in order to develop concepts for the rational stabilization and preparation of dispersions with tailored nanoparticle interactions and thus tailored properties.

INTRODUCTION

The strong tendency of nanoparticles and nanomaterials to agglomerate and aggregate constitutes probably the most important challenge for their synthesis and application [1, 2]. Already since the work of Graham and Ostwald [3] it is known that dispersions of particles in aqueous (but also gaseous) media are thermodynamically unstable. The agglomeration of particles, which is termed coagulation in the field of colloids chemistry, results in a reduction of the surface free energy, and therefore occurs instantly [4]. In the case of nanoparticles, which by common definition are colloidal particles less than 100 nm in size, the formation of agglomerates usually is observed already during the particle synthesis [5, 6]. The agglomerates, also termed secondary particles, in many cases exceed the size of the individual nanocrystals, or primary particles, by orders of magnitude [1].

For many applications, such agglomerates are undesired as they corrupt the materials' performance and complicate processing and storage, especially if the nanoparticles are to be processed or applied as dispersions. In these cases, agglomerates usually lead to an increase in viscosity of the system, are prone to sedimentation (as the sedimentation velocity increases with the square of the particle diameter), and strongly increase the turbidity. Another important application of nanoparticles where the agglomeration state has a crucial importance is the field of nanocomposites. Commonly, nanocomposites are fabricated by incorporation of inorganic nanoparticles into a polymer matrix, resulting in a material that can be processed and shaped like a polymer but possesses strongly enhanced mechanical or optical properties. The mechanical properties of nanocomposites on the one hand were reported to be strongly dependent on the secondary particle size of the nanomaterial filler [2], and on the other hand of course also the optical properties, especially transparency, are greatly influenced by aggregation of the nanoparticles [7].

Since the beginning of colloids science, however it is also known that the agglomeration of colloids and dispersed particles can be prevented or controlled by stabilization [8]. The attractive interactions between the colloidal particles, caused by van-der-Waals forces, need to be compensated by repulsive interactions. The latter can be based either on electrostatic repulsion due to same-sign surface charges (electrostatic stabilization), or on repulsion via a polymer shell formed through adsorption of polymers to the particle surface (steric stabilization, in presence of polyelectrolytes termed electrosteric stabilization due to additional charged-induced repulsion) [9, 10]. The stabilization by control of the interaction forces between colloidal particles has been in the focus of extensive research efforts. Already

in the early days of colloid science, the forces between particles were studied theoretically [11], and for electrostatic stabilization the so-called DLVO theory was proposed [12, 13] and its validity for a broad range of systems and conditions is accepted until today [14].

A special focus of research has been the steric stabilization of colloidal particles by adsorption of organic polymers to the particle surface [15-17]. Typically used polymer stabilizers possess a molecular weight ranging between 5,000 Da and 15,000 Da. These polymers are targeted to adsorb to the particle surface and form an organic layer around the particles (often termed adlayer), of about 3-10 nm thickness. The general understanding of steric stabilization is that when two particles approach each other, the polymer layers interpenetrate, creating an osmotic pressure that counteracts the attractive interparticle force, thereby efficiently preventing close contact of the particles that would result in agglomeration [17].

The stabilization of colloidal particles can be achieved by addition of the stabilizer in a distinct stabilization step following the synthesis (*post-synthesis* method) [18], or by addition to the reaction system already prior to the particle formation (*in-situ* method) [19-22]. The latter strategy has the potential benefit of a perfect stabilization as the forming particles are instantly capped with the stabilizer, but in many cases possesses the disadvantage of a modification of the particle formation process, as strongly binding stabilizers may lead to altered particle sizes, different morphologies or even completely prevent the particle formation [23-25]. In the *post-synthesis* method, particle fabrication and stabilization are carried out independently, thus rendering this strategy suitable also for solventless high-temperature particle synthesis methods that would prevent the use of a stabilizer during the formation process. During their synthesis in the absence of stabilizers, however, the nanoparticles may strongly agglomerate or aggregate, which in many cases necessitates the use of mechanical dispersion methods such as ultrasonic treatment additionally to a chemical process to achieve a successful stabilization. For many applications, steric stabilization is the strategy of choice due to the higher stability, its suitability also for hydrophobic media and matrices, and the lower sensitivity towards pH and additives. Besides the stabilization effect, the adsorbed organic layer around inorganic particles can additionally be used for functionalization, which is a more encompassing concept that is based on achieving chemical functionality of the particles, resulting in functions such as selective binding to biological molecules, affinity to certain media or surfaces, environmentally responsive behavior, etc. [26-28].

STERIC STABILIZATION OF NANOPARTICLES

Whilst a great deal of research has been carried out to study the interactions of particles featuring adsorbed polymer chains, especially with respect to the chemistry and conformation of the polymer chains, the dependence of these interactions on the size of the involved particles is an aspect that has not so much been in the focus of research activities. Whereas the particle interaction is relatively independent of the particle size for larger colloids, for particles smaller than 100 nm in size, this is no longer true [29]. The thickness of the adlayer formed by common polymer stabilizers for such particles starts to become considerable

compared to the particle size, and for small nanoparticles can even exceed the size of the core particle, which has severe, and mainly undesired, consequences [20].

On the other hand, it is generally known that the stabilization of particles with sizes below the critical range of 100 nm also follows some special principles. Already from Hamaker's theory of the attraction between particles, it can be inferred that for very small particles, the range of attractive potential decreases, and already for 50 nm sized particles only amounts to a few nm. This has severe consequence on electrostatic interaction, as is described by the DLVO theory, as well as for steric stabilization [13, 30]. It needs to be stated, however, that the attractive potential strongly depends on the nature of the material, as is illustrated in Figure 1, presenting calculations by Sigmund et al. of the attractive potential between two 100 nm sized particles of SiO_2 and Al_2O_3 [31]. It is clearly visible that the attraction between Al_2O_3 particles is much more long-ranged than between silica spheres, which would imply that alumina particles need a stabilizing layer with substantially larger thickness to prevent them from reaching an interparticle distance small enough to result in a high attractive potential. The horizontal line in Figure 1 indicates the stabilization range, as the thermal energy is sufficient to easily overcome an attractive interaction of $2 k \cdot T$. Hence, the critical separation distance for the SiO_2 spheres amounts to about 3.5 nm, whereas for the Al_2O_3 spheres it is increased to 12 nm [31].

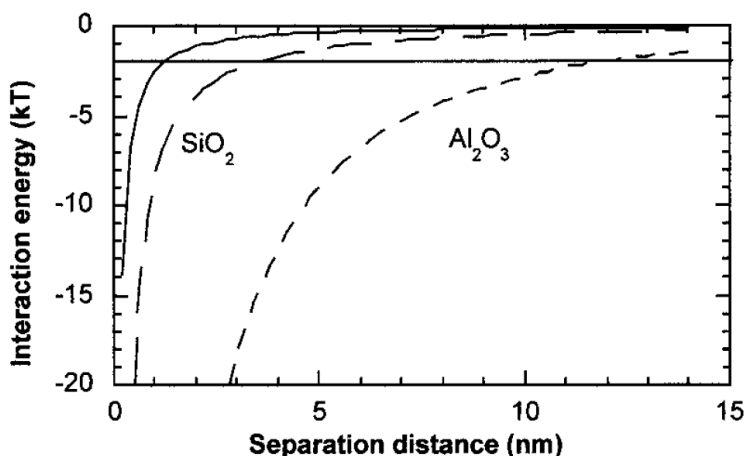


Figure 1. Comparison of van der Waals interaction energies for SiO_2 (—) and Al_2O_3 (- · -) spheres of 100 nm radius in water, and of SiO_2 spheres in *n*-dodecane (—). Reproduced from Ref. [31] with kind permission of Wiley-VCH.

These results imply that for the steric stabilization of SiO_2 particles, polymers with substantially lower molecular weight, corresponding to a thinner stabilizing layer, are required than for Al_2O_3 . The molecular weight M_w of an adsorbed homopolymer can be approximately related to the adlayer thickness by [17]

$$L \text{ [nm]} = 0.06 \cdot (M_w)^{0.5} \quad (\text{Eq. 1}),$$

indicating that the polymer used for the formation of an adlayer of sufficient thickness would require a minimum molecular weight of 40,000 Da for the alumina particles, but only of about 3,000 Da for the silica.

For smaller particles, the minimum required stabilizing layer thickness decreases substantially. Lu performed theoretical calculations of the particle-particle interaction energies of aqueous dispersions of Al_2O_3 nanoparticles with a particle size of 20–45 nm stabilized by a protective adlayer of an adsorbed polymer [32]. The distance-dependent steric interaction energy, which was calculated based on the work of Vincent and Edwards [33] assuming a uniform polymer segment density at small interparticle distances, as well as the total interaction energy are presented for various protective layer thicknesses in Figure 2. For this system, a protective layer of 5 nm in thickness was found to be more than sufficient to achieve stabilization of the particles, with repulsion steadily increasing as the particles approach each other, whilst for a layer thickness of 2.5 nm and less, the interparticle forces become dominantly attractive at low separation distance. The system with a stabilizing layer thickness of 2.5 nm however still shows an energy barrier of several kT in total interaction energy at intermediate separation (Fig. 2, b). Consequently, a layer thickness of 2.5 nm should be sufficient to prevent coagulation of the particles, and these findings nicely correspond to experimental results of successful stabilization when using a polymer with a molecular weight of 1,800 g mol^{-1} [32].

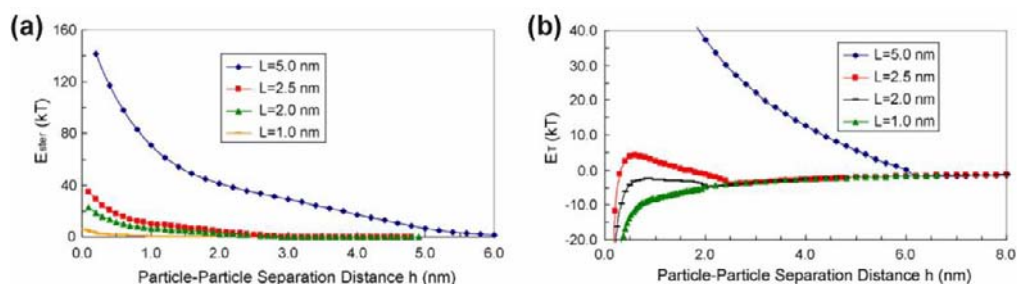


Figure 2. Theoretical calculation of the dependence of the steric interaction energy E_{ster} (a) and the total interaction energy E_T (b) on interparticle distance for different values of polymer layer thickness. Reproduced from Ref. [32] with kind permission of Elsevier.

As the particle size is further reduced, successful stabilization is achieved with even smaller stabilizers. Here, an adlayer of sufficient thickness may even be formed by adsorption of oligomers or even of common organic molecules [34]. Experimentally, the stabilization of such small nanoparticles by adsorption of simple organic molecules such as surfactants or complexing agents is indeed broadly applied. Many well-known and successful strategies to nanoparticle dispersions involve the use of surfactants as stabilizers, such as fatty acids or alkylammonium salts, for the preparation of dispersions of small nanoparticles, especially for metal nanoparticles [35–37]. In many cases, e. g. for the famous citrate stabilization technique for gold nanoparticles [38], it has been shown that in fact the binding of the utilized surface modifier results in the immobilization of charges to the particle surface, leading to stabilization via an essentially electrostatic rather than steric mechanism [39–41]. The preparation of magnetic fluids and other nanoparticle dispersions in hydrophobic media on the other hand prove the feasibility of steric stabilization *via* molecular species, as in these cases an electrostatic mechanism can be excluded due to the absence of charges. In order to

distinguish the mechanisms of steric stabilization by adsorption of low-molecular weight species from polymer-based stabilization concepts, the term “small molecule stabilization” has been coined and shall also be used in this Chapter.

UTILIZATION OF SMALL MOLECULE STABILIZATION CONCEPTS FOR TAILORING THE PROPERTIES OF NANODISPERSIONS

Even though the concepts of small molecule stabilization are hence in broad use for many applications, knowledge about the underlying fundamentals and mechanisms is by no means complete. Often the stabilization is applied in a trial-and-error fashion, without any general rational concept for a directed stabilization that would be optimized for a specific system. Additionally, the usual goal of a perfect stabilization in fact does not always represent the optimum case with respect to handling, processing and application issues. For example, in ceramic processing, but also in many other fields, weakly flocculated dispersions are highly advantageous [42, 43]. Such dispersions are easy to purify, due to the presence of larger structures that can be centrifuged or filtered, and afterwards can be restabilized via simple processes [44]. Therefore, concepts need to be developed that reach beyond the usual black-and-white image of stabilization or agglomeration, rather targeting improved control and even tunability of the particle interactions [45]. This offers the possibility of tailoring dispersions with respect to their rheological properties [46, 47], and it has been shown that also processes such as the fractionation and size selection of particles are greatly facilitated or even only made possible through customization of the particle interactions [48]. One of the most straightforward strategies to tailor the particle interactions for a given material and particle size is an adjustment of the thickness of the stabilizing steric layer. It is generally known that a thinner stabilizing layer, equivalent to smaller chain length or lower molecular weight of the stabilizer, results in increased attractive interaction between the particles, whereas a thicker layer vice versa leads to better shielding of the core particles and thus to lower attractive particle interaction, although it needs to be stated that this rule-of-thumb implies analogous chemistry of the stabilizers which does not apply in all cases. However, it becomes clear that tailoring of the stabilizer and its size is an essential means to control and optimize the properties of nanoparticle dispersions [31, 44].

One important case illustrating the practical relevance of controlled stabilization is found in dispersions with high solid content, as used in ceramic processing. Here, solid bodies are formed from particle slurries via various shaping methods, followed by drying and calcination to result in a dense and dry rigid body. A high solid content of the slurry is generally desired to facilitate the drying process, leading to a lower risk of cracks and lower shrinkage. In the recent years, exact control of the size of the utilized particles and of their surface interactions has become more and more important for the fabrication of advanced ceramics with enhanced properties [49, 50]. One particular focus has been the emerging field of nanoceramic processing, where nanostructured ceramic bodies are obtained through special processing strategies [51, 52]. For the fabrication of such ceramics, two important requirements are a high solid content to allow fast and facile drying, and on the other hand a relatively low viscosity in order to enable processing of the slurry. Both of these requirements strongly depend on the stabilizing layer thickness. The maximum solid content that can be achieved in

stable slurry is realized when the particles are packed in an optimized fashion. As illustrated in Figure 3, the packing of small particles is however strongly influenced by the adlayer thickness Δ . For a large Δ in the range of the particle radius, within a given volume less particles can be packed (solid lines) as compared to small Δ (dashed lines). This can also be expressed as the effective volume fraction Φ_{eff} which is based on the entire particle including the adlayer and is related to the true volume fraction Φ of the core particles by

$$\Phi_{\text{eff}} = \Phi \left(1 + \frac{\Delta}{r} \right)^3 \quad (\text{Eq. 2}),$$

where r refers to the particle radius [53]. Hence, the maximum achievable solids volume fraction based on the core particles increases as Δ is decreased. Vice versa, the maximum allowable layer thickness for reaching a random close packing state ($\Phi_{\text{rcp}}=0.64$) at a given volume fraction Φ can be calculated from [54]

$$\Delta_{\text{max}} = r \left[\sqrt[3]{\frac{\Phi_{\text{rcp}}}{\Phi}} - 1 \right] \quad (\text{Eq. 3}).$$

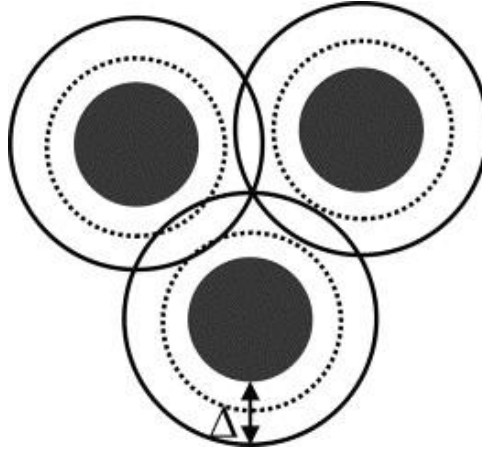


Figure 3. Illustration of the packing of spherical particles dependent on the thickness Δ of a stabilizing layer [54]. Image reprinted with kind permission of Elsevier.

On the other hand, the adlayer thickness has also an influence on the viscosity of the dispersion. It is generally known that the viscosity η of a particle dispersion depends on its solids volume fraction Φ . The particles start to form a network as Φ is increased, which leads to an increase in relative viscosity η_r as described in the modified Krieger-Dougherty equation

$$\eta_r = \frac{\eta}{\eta_l} = \left[1 - \frac{\Phi}{\Phi_{\text{max}}} \right]^{-n} \quad (\text{Eq. 4}),$$

where η_l is the viscosity of the liquid medium, $\Phi_{\max}$ is the maximum filling level at which any shearing is blocked, and n is a fitting parameter [55, 56]. The combined effect of a decrease in dispersion viscosity together with higher maximum loading levels creates a strong impetus for investigations on the influence of stabilizer size on the dispersion properties [43].

Due to the high practical relevance of the rheological properties of suspensions and slurries, it is thus no surprise that the tailoring of interparticle properties by variation of adlayer thickness has been increasingly studied. Most studies were directed towards ceramic processing and utilized metal oxide nanoparticles in the 50 nm size range that by now are also commercially easily available. As an example, the validity of the modified Krieger-Dougherty equation (Eq. 4) for highly concentrated suspensions of nanoscale ZrO_2 particles about 40-50 nm in size was investigated by Renger et al. [54]. The authors used different stabilizers, including triammonium citrate (TAC) and 2-(2-(2-methoxyethoxy)ethoxy)acetic acid (TODA). The relative viscosity η_r of suspensions stabilized with each stabilizer was thereby determined for various high solid contents, as shown in Figure 4. It is clearly visible that TODA is capable of stabilizing dispersions with much higher volume fraction of solids than TAC. The authors applied fittings to the obtained data points utilizing the modified Krieger-Dougherty equation, and it is clearly visible that the TODA-stabilized system follows this equation ($\Phi_{\max} = 0.43$, $n = 8.24$). For the TAC stabilizer, the fit is rather bad, indicating that the particles in this case probably were not well-dispersed, which agrees with the observed higher viscosity of dispersions of TAC-stabilized zirconia nanoparticles as compared to TODA-stabilized dispersions at the same solids content. Moreover, due to the smaller thickness of the repulsive barrier layer, the maximum achievable filling level for TODA is much higher as compared to TAC, both experimentally and in theory [54]. This example illustrates that the suitability of a stabilizer cannot only be judged on the size of the repulsive layer that is formed upon its adsorption, but also other factors such as the adsorption strength and affinity play a key role.

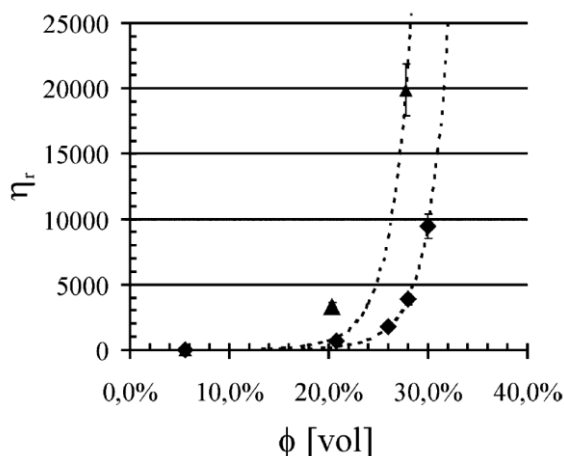


Figure 4. Relative viscosity of suspensions of ZrO_2 nanoparticles stabilized with TODA ($\blacklozenge$) and TAC ($\blacktriangle$) vs. solid content. The experimental data were fitted using Eq. 4 (---) [54]. Image reprinted with kind permission of Elsevier.

Studart and Gauckler performed extensive studies on the stabilization of 65 nm-sized Al_2O_3 nanoparticles, and first investigated the minimum adlayer thickness sufficient for stabilization to then be able to prepare dispersions with highest solids concentrations [57, 58]. They stabilized the alumina particles with alkyl chains as well as polyether chains that were linked to the particle surface in a very stable and controlled fashion via a gallol linker. The minimum thickness of the stabilizing shell was determined to 3.6 nm, corresponding to a molar weight of about 500 g mol^{-1} ; smaller stabilizers resulted in agglomeration of the nanoparticles and a significantly higher viscosity of the medium [57]. Optimization of the stabilizing shell allowed the authors to prepare suspensions with volume concentrations above 40 % [58]. However, it was also demonstrated that the nature of binding to the nanoparticles is of crucial importance to stability: besides the gallol linker, also poly(methacrylic acid) was used as linker, and additionally purely electrostatic stabilization was employed (Figure 5). Whereas under certain conditions, the poly(methacrylic acid)-coupled polymer provided good stabilization, and also the electrostatic stabilization mechanism was efficient at low salt concentrations, only the strongly binding gallol-coupled polymer stabilizers provided high stability at all tested conditions. These results by Gauckler et al. show that only a strong, in the best case covalent linkage of the stabilizer can ensure stability in a broad range of salt concentrations, pH levels, temperatures, etc.

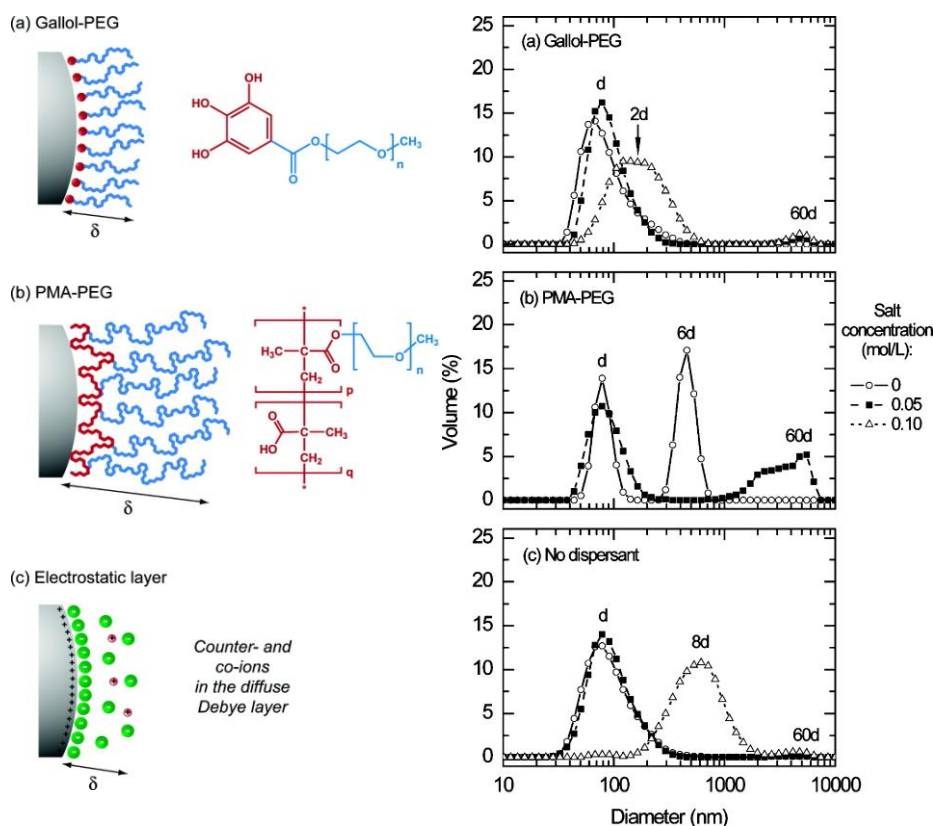


Figure 5. Stabilization of alumina nanoparticles with PEG chains via gallol linkers (a), with block copolymer chains (b), or electrostatic stabilization (c); left: schematic, right: obtained particle size distributions at various salt concentrations. Reprinted from Ref. [58] copyright 2007 American Chemical Society.

Aside from aqueous and hydrophilic systems, also the rheology of suspensions of alumina nanoparticles in hydrophobic organic solvents has been of high interest [53, 59, 60]. Again, slurries with high solid contents but low viscosity are desired, which also sparked investigations as to the optimization of the utilized stabilizers. Bell et al. performed extensive tests of the rheology of suspensions of alumina nanoparticles in decalin (*cis/trans*-decahydronaphthalene). Various fatty acids were employed as stabilizers, and the authors clearly observed a dependence of the stability on the chain length of the used stabilizer (Figure 6). Propionic up to heptanoic acid were found not to create sufficiently thick layers, leading to strongly flocculated systems with elastic properties, whereas the use of oleic acid resulted in only a very weak overall attraction between the particles, thus creating stable fluid-like dispersions [53].

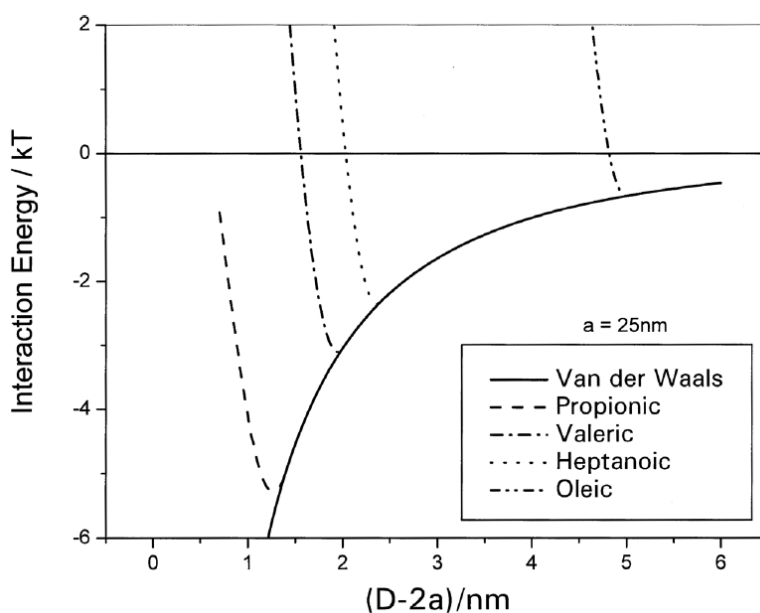


Figure 6. Interparticle total energy potential for alumina nanoparticles stabilized with various fatty acids in decaline (a ...particle radius). Reprinted from ref. [53] with kind permission of Elsevier.

An interesting schematic by Studart et al. illustrating the general correlation between adlayer thickness and the maximum achievable volume fraction is depicted in Figure 7. At small stabilizing layer thickness, the particles can be regarded as attractive spheres, with strong attraction between the particles. As the adlayer thickness increases, the attraction is diminished, leading to higher volume fractions that can be realized for a given viscosity. As the adlayer thickness reaches and then exceeds a critical value, full stabilization is realized, and the particles can be considered as hard spheres. However, the increasing exclusion volume results in a decrease in maximum volume fraction. This nicely illustrates that indeed, an optimum adlayer thickness needs to be found if one wants to realize concentrated ceramic suspensions with low viscosity.

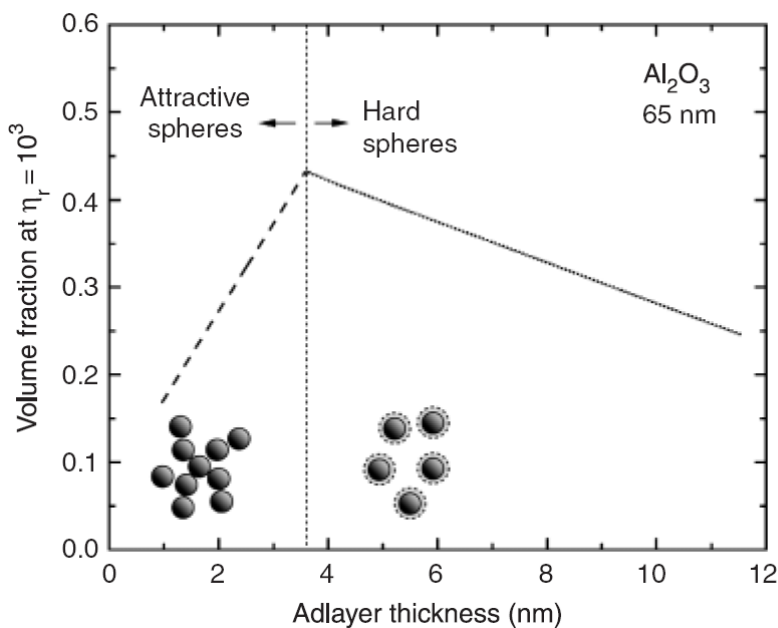


Figure 7. Volume fraction of Al_2O_3 nanoparticles resulting in a relative viscosity η_r of 1000 in dependence of adlayer thickness. Image reproduced from Ref. [58] copyright 2007 American Chemical Society.

SMALL MOLECULE STABILIZATION OF ULTRASMALL NANOPARTICLES: PROBING THE LIMITS

Within the world of nanoscale objects, smallest nanoparticles in the size regime below 10 nm play a special role [61]. In this size range, a significant amount of atoms is located at the particle surface, resulting in extreme surface energies, and additionally quantum effects start to emerge [62, 63]. Also dispersions of such ultrasmall nanoparticles are unique, in that they have the appearance of molecular solutions even at high solid concentrations due to the small dimensions of the particles, bringing about very low light scattering and low viscosity. This renders the dispersions of ultrasmall nanoparticles difficult to characterize with regard to the nanoparticle properties, but on the other hand leads to exceptional and fascinating properties that enable numerous new applications.

Therefore, the preparation of such dispersions by stabilization of ultrasmall nanoparticles is of special importance. Again, the elaboration of rational concepts for the stabilization, ideally being able to specifically tailor the particle interactions to realize desired properties, is an ambitious but highly important goal. For many applications, especially in the optical field, agglomeration of the nanoparticles is practically not tolerable, whereas for others, weakly flocculated systems are advantageous also in this case. The stabilization of nanoparticles in the size range below 10 nm on the other hand is still also of fundamental interest. As stated before, all calculations based on the colloidal models of particle interaction predict that the thickness of any stabilizing adlayers would now lie in the Ångström regime and could in principle be reached already by the adsorption of organic solvent molecules. The colloidal

models are, however, based on assumptions that reach their limitations when the particle size approaches the lower nanometer regime, such as treatment of the solvent as continuum [64] or approximating the surfaces of polymer-coated particles as planes [34]. Recent theoretical work by Roan and Kawakatsu on the interaction of nanoparticles with end-grafted homopolymers challenges the results of earlier models of steric stabilization such as the Edwards model [16], suggesting attractive forces between particles at large interparticle distance, repulsive forces at intermediate distance, and again attractive forces at small separation [65-69].

Even though the stabilization of ultrasmall metal nanoparticles with small organic species has already been applied since the early days of colloids chemistry, the stabilization of metal oxide nanoparticles at the frontier to the molecular scale is still only partially explored. Although numerous reports deal with the preparation of dispersions from nanoparticles, the specific study of the interactions between stabilizer and the nanoparticle surface, as well as of their precise effect on the particle agglomeration and disagglomeration and the general influence of stabilizer size and geometry, has not been a strong focus of research, much in contrast to the particle synthesis itself. Moreover, due to the general lack of suitable materials with required homogeneity, the systematic and reliable study of size effects on the particle stabilization and the elucidation of fundamentals have proven difficult. To the knowledge of the author, no studies exist so far as to the effects of a systematic variation of stabilizer size and chemistry on the properties of small nanoparticle dispersions. Only a small number of studies have been explicitly devoted toward the investigation of specific aspects of the stabilization of ultrasmall nanoparticles, and some examples are presented below to highlight recent findings in this area.

Most of these investigations were performed on metal oxide nanostructures due to their high application relevance. Of these systems, titania nanoparticles certainly represent one of the most explored systems, due to their high application potential especially in photocatalysis. Numerous synthesis approaches have been reported, ranging from gas-phase pyrolysis to solvent-based approaches, especially aqueous and nonaqueous sol-gel chemistry, and mainly lead to ultrasmall nanoparticles only a few nm in diameter. The further processing of these nanoparticles requires the preparation of particle dispersions, and therefore it is no surprise that also the stabilization of these particles against agglomeration has been a focus of research. TiO_2 nanoparticles used for the preparation of aqueous dispersions are usually charge-stabilized, whilst diverse strategies are pursued for their stabilization in organic media. In the latter case, most often organic polymers or surfactants are added to adsorb to the nanoparticles, for example fatty acids [70, 71]. In basically all cases, this results in substantial deagglomeration of the nanoparticles, however in the most cases no full stabilization, equivalent to the exclusive presence of individual nanoparticles, is observed. The reason for this might in fact be an only partial suitability of the stabilizer, which forms an insufficiently thick shell to be able to prevent attraction between the particles, or even induces these interactions, or shows insufficient binding, thereby not forming a compact and uniform shell. Not many studies are dedicated to a detailed investigation on these mechanisms, whilst generally a still very empirical approach is pursued here, often solely being based on trial-and-error principles [72].

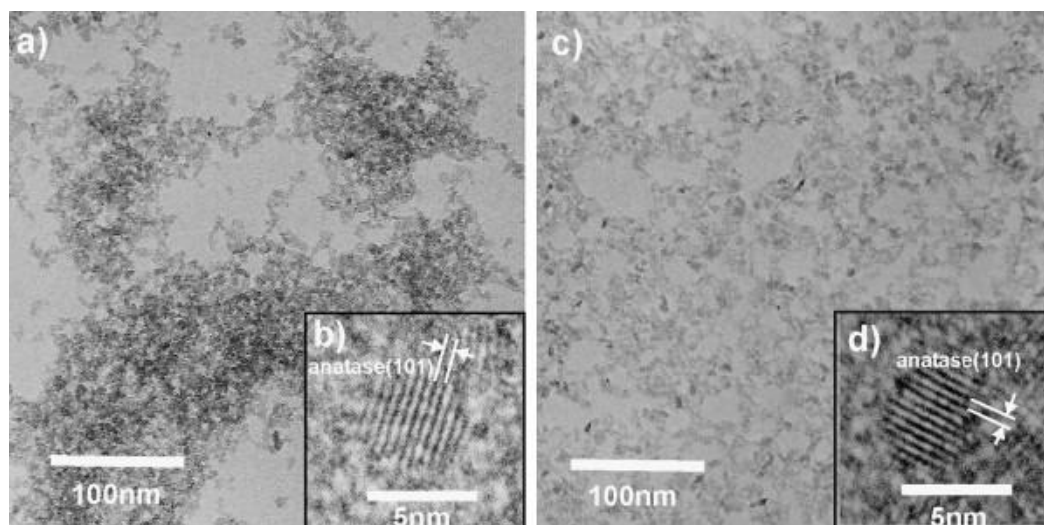


Figure 8. TEM images of TiO_2 nanoparticles without stabilizer (a) and stabilized with both propionic acid and *n*-hexylamine (c); the inset images (b) and (d) present the corresponding high-resolution images of one particle [73]. Reproduced with kind permission of Elsevier.

Further insight into the stabilization of small nanoparticles can be gained by looking at a very interesting study by Nakayama and Hayashi, who investigated the stabilization of TiO_2 nanoparticles prepared via a chemical method. Their aim was to realize good stability of the nanoparticles using organic surfactants of the smallest possible quantity in weight by reducing the chain length of alkyl surfactants [73]. Thereby, the binding of the surfactants to the nanoparticle surface turned out to be a crucial aspect: the authors identified the surface of titania to show different acid sites, both Lewis acid sites (Ti^+) and Brønsted acid sites ($\text{Ti}-\text{OH}$). Therefore, a combination of two stabilizers, both a carboxylic acid and an alkyl amine, was used in order to have binding and saturation of both sites. Indeed, when applying a two-step approach with both classes of stabilizers, much better stabilization was achieved as compared to the individual agents. Figure 8 shows images of transmission electron microscopy (TEM) indicating that the individual nanoparticles, about 5 nm in size and highly crystalline, are strongly agglomerated after the synthesis, whereas after the treatment they are much more evenly distributed on the TEM grid after drying, indicating their lower agglomeration state and lower attractive interaction. This is also evident in photographs of dispersions of the stabilized nanoparticles in various solvents (Figure 9). Due to the formation of hydrochloric acid as side product of the synthesis, a good dispersion of the nanoparticles in water is achieved even in the absence of stabilizers (a). In this case, the mechanism of stabilization is clearly of electrostatic nature. Such “bare” TiO_2 nanoparticles however cannot be stabilized at all in organic solvents, necessitating the use of a stabilizer. Whereas the sole use of hexanoic acid (b, c) and *n*-hexylamine (d) however resulted in significant turbidity, the two-step strategy employing a mixed stabilization led to a completely transparent dispersion (e), proving that the utilized combination of stabilizers strongly reduces or even fully prevents the agglomeration. An important conclusion from this work therefore must be a careful study of the various surface sites of the particles, as the use of a stabilizer only binding to one particular type of site may result in an insufficiently dense stabilizing layer.

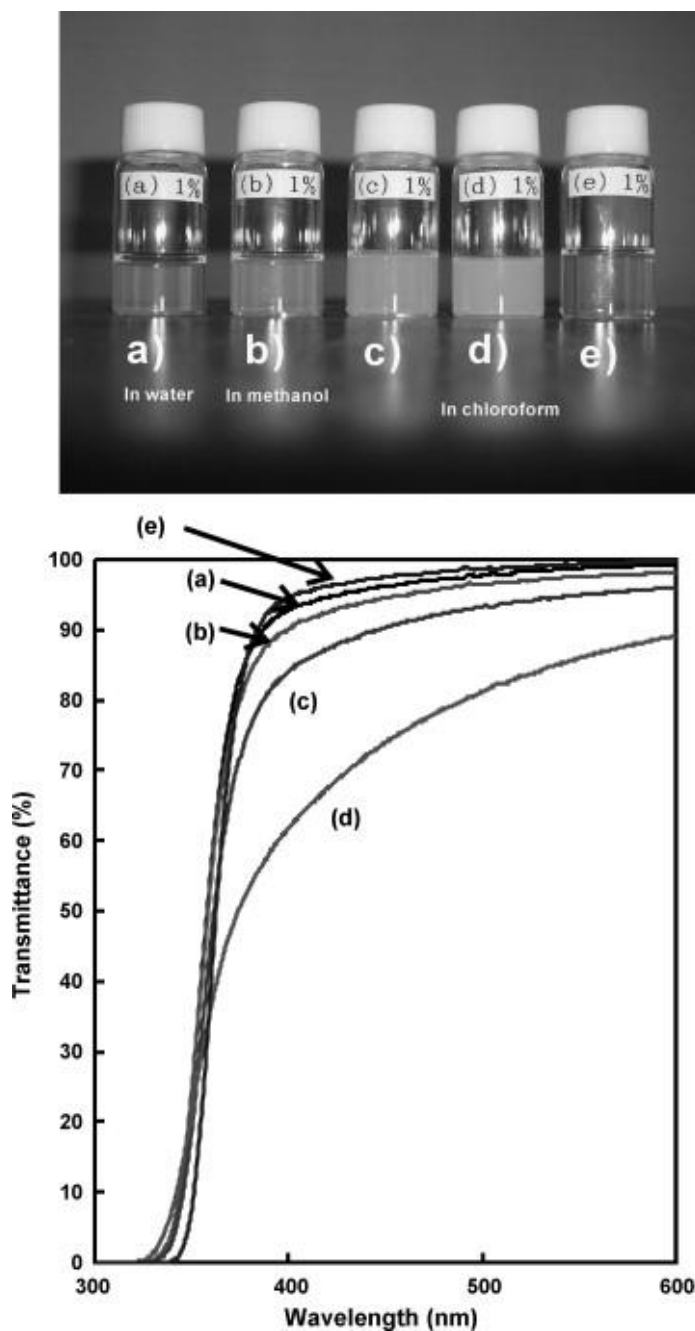


Figure 9. Photograph (top) and UV-vis spectra (bottom) of bare TiO₂ nanoparticles in water (a) and of TiO₂ nanoparticles stabilized with alkyl carboxylic acid in methanol and chloroform (b, c) and with an *n*-alkylamine (d) as well as the mixed stabilizers in chloroform (e). Reproduced from Ref. [73] with kind permission of Elsevier.

As mentioned in the Introduction section, the adsorption of stabilizers to achieve stabilization of particle dispersions can not only be carried out in a separate step, but also already during the particle synthesis (*in-situ* modification or *in-situ* functionalization), which

can be especially beneficial for small nanoparticles with their extremely high specific surface area. For titania nanoparticles, thorough studies on the *in-situ* modification with organic adsorbands were pursued, not only with the goal of optimizing the particle stabilization, but also as this is a means to alter and enhance the photocatalytic properties [74-76]. It has been shown that special ligands can form charge-transfer complexes with titania surface species, which results in a shift of the absorption edge towards the visible range and thus, a change in color of the material [77]. In these studies, *ortho*-catechols were identified as an especially suitable class of ligands, because they bind to the titania surface in a very stable fashion due to the confined geometry of the two hydroxyl groups [77]. Usually, they cannot be replaced by other ligands and thus can be considered as covalently bound [78]. This brings about a great advantage, as the stabilization of titania nanoparticles modified with such ligands can be studied independently of the effect of ligand affinity or exchange. Niederberger and the author utilized this concept to perform studies of the dependence of stabilization on the chemical structure of the stabilizer [78]. It was shown that via modification of the side chain of catechol ligands, the stabilization of the nanoparticles could be optimized for a specific solvent. By using an aminoethyl sidechain, the nanoparticles were tailored to form highly stable aqueous dispersions, being redispersible even after full drying; when employing more hydrophobic side groups, transparent dispersions were formed in various organic solvents [78]. Figure 10 shows a photograph depicting dispersions of nanoparticles capped with two kinds of catechol species in the respectively suitable solvent. It however also needs to be stated that due to the employed synthesis conditions, also a high quantity of charges (protons) was located on the nanoparticle surface, allowing the preparation of aqueous dispersions also in the absence of ligands under certain pH conditions [79, 80].

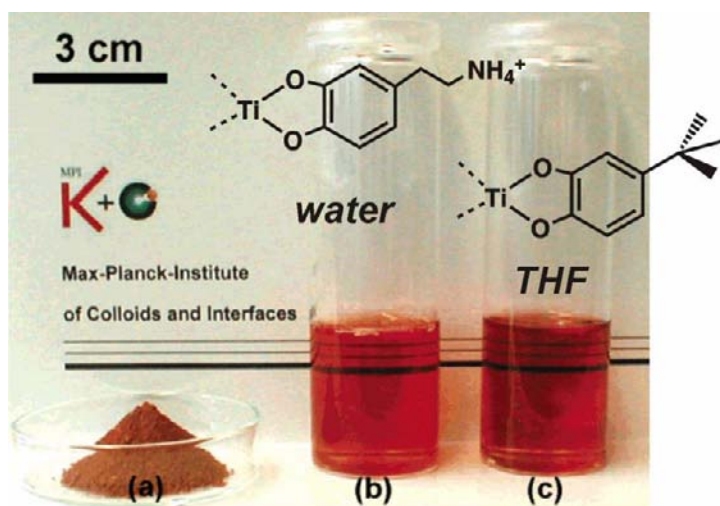


Figure 10. Titania nanoparticles modified with various catechol ligands as stabilizers in the dry state (a) and dispersed in water (b) and tetrahydrofuran (c). Reproduced with alterations from Ref. [78] copyright 2004 American Chemical Society.

Stabilization studies have also been carried out with other metal oxide nanoparticles. Due to the demanding requirements as to transparency and homogeneity of nanocomposites for optical applications, which are greatly determined by the agglomeration state of the

nanoparticles, the stabilization of nanoparticles of high-refractive index materials such as zirconia is of high practical relevance. The author has recently performed an extensive study of the stabilization of ultra-small zirconia nanoparticles about 3 nm in size that were utilized for the fabrication of holographically structured optical devices [81]. The particles were pre-fabricated via the benzyl alcohol-based nonaqueous synthesis strategy, which represents one convenient route to highly crystalline, well defined and homogeneous metal oxide nanoparticles and nanostructures [82, 83]. The synthesis was performed in the absence of stabilizers; however the used solvent was detected to bind to the particle surface to a considerable extent. As the solvent has insufficient stabilizing properties, the particles were initially obtained as weak agglomerates, but could easily be stabilized via the addition of a suitable stabilizer. Stabilization experiments in polar organic solvents such as THF revealed that silanes are highly suitable for particle stabilization due to their stable linkage to the particle surface, and the results suggested that the stability of the formed dispersion can be correlated to the amount of stabilizer adsorbed to the particle surface [84]. Investigations in hydrophobic organic solvents on the other hand mainly were focused on long-chain fatty acids, the addition of which resulted in instant stabilization and even disintegration of previously formed agglomerates without any need for additional mechanical treatment, as is illustrated in the photograph and the TEM micrographs presented in Figure 11. The nanoparticles could be redispersed in very small volumes of solvent, which resulted in concentrated dispersions reaching up to 200 mg mL^{-1} solids content whilst being completely transparent. The TEM image of a dried dispersion (Figure 11, b) proves that the particles are completely free-standing in the dispersions, and the repulsive forces even prevent their reagglomeration on the sample grid upon drying [81].

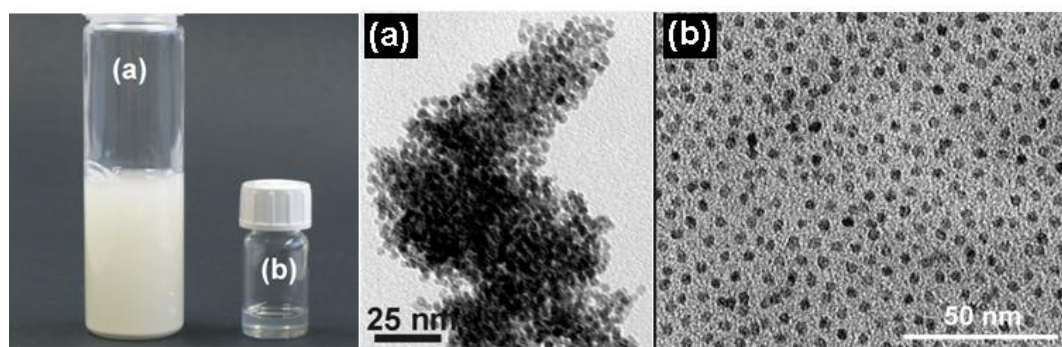


Figure 11. Photograph (left) and TEM images (right) of ZrO_2 nanoparticles before (a) and after (b) stabilization with oleic acid. Images taken from Ref. [81] with kind permission of Wiley-VCH.

In this system, the adsorption of the stabilizer was characterized thoroughly employing various spectroscopic techniques. Especially, ^1H and ^{13}C liquid state NMR spectroscopy proved as a useful probe for the surface chemistry of nanoparticles in concentrated dispersions, as species adsorbed to the surface can be identified, however the functional groups directly adjacent to the surface are motionally hindered, which results in spectral broadening [85]. It is hence possible to assess the amount of surface-bound species, determine the functional groups binding to the particle surface, and qualitatively investigate the chemistry of both particle surface and bulk solution. In the zirconia case, it was detected that indeed only partially the initially bound benzyl alcohol solvent is replaced by the stabilizer

arachidic acid (Figure 12, a). The stabilizer is bound via a deprotonated carboxylic acid functional group, and no free arachidic acid was detected. A quantitative evaluation of the adsorbed species was possible via complementary TGA measurements (Figure 12, b), and revealed further interesting details of the stabilization process. For example, it turned out that the addition of higher amounts of stabilizer did not increase the total amount of organics on the particle surface but merely led to an increased exchange of the arachidic acid stabilizer with previously adsorbed benzyl alcohol, indicating that after the initial synthesis, the particle surface is saturated with benzyl alcohol [81].

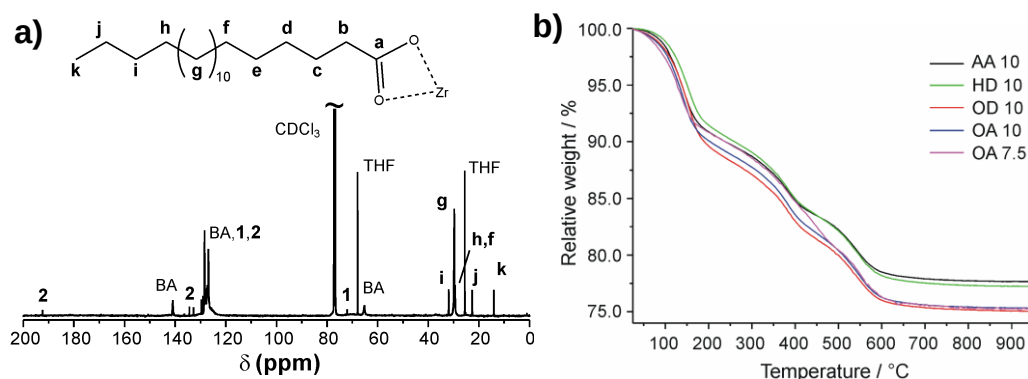


Figure 12. Characterization of the binding mode of fatty acid stabilizers to the surface of ZrO_2 nanoparticles can be carried out via ^{13}C NMR spectroscopy (a; BA=benzyl alcohol) and thermogravimetric analysis (b; AA=arachidic acid, HD=hexadecanoic acid, OD=octadecanoic acid, OA=oleic acid). Image (a) reproduced from Ref. [81] with kind permission of Wiley-VCH; image (b) is courtesy of the author.

CONCLUSION

In this Chapter, the concept of small molecule stabilization of inorganic nanoparticles has been introduced. It has been shown that whilst the steric stabilization of colloids by adsorption of polymers has been intensively studied both experimentally and in theory, the stabilization of nanoparticles is a much less understood process. The established theories of colloidal stabilization, based on electrostatic or steric stabilization mechanisms, can also be applied for nanoparticles, revealing that already small adsorption layers created by small molecules rather than polymers can suffice to achieve stabilization, which has also been confirmed by experimental results. Indeed, practical experience even in the early days of colloids chemistry has already shown that the small molecule stabilization of nanoparticles is a feasible and highly advantageous strategy. Despite this long-time utilization, only selective aspects of the precise influence of the stabilizer on the microscopic (particle size and agglomeration) and macroscopic (rheology) properties of nanoparticle dispersions have however been studied in more detail. For larger nanoparticles in the 50 nm size range, investigations have been performed by several groups in the last years, showing the applicability of concepts that utilize a specific tailoring of stabilizer length and chemistry to achieve particle dispersions with tunable rheological properties.

For small nanoparticles in the 10 nm size range that are of key interest for novel applications, only some aspects of small molecule stabilization have been explored so far, such as the advantage of using mixed stabilizers that can provide a true, dense particle adlayer via the specific saturation of several different surface sites, or the applicability of a “two-face” concept where double-functional stabilizers are used, featuring a head group that selectively and in a stable manner can bind to the particle surface, and a tail that is specifically adapted to be compatible with the solvent. Many other fundamental aspects still remain unclear, as it is known that the colloidal theories reach their limitations precisely in the low nanometer size regime, with novel studies predicting severe deviations and a higher interaction complexity when applying more elaborate and realistic models. Moreover, smallest nanoparticles are on the limit to the molecular scale, and the general question arises as to the validity of the conventional concepts of stabilization for such structures. It remains to be seen whether it will be possible to bridge the gap between theoretical explanation and practical experience in this field, whilst in view of the high relevance of particle stabilization for almost all areas of applications, the development of rational concepts for tailoring the particle interactions would be highly desirable and will certainly create a strong research impetus in the future as small nanoparticles in high quality and homogeneity will become increasingly available.

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Chapter 5

MOLECULAR IMPLICATIONS IN THE SOLUBILIZATION OF THE ANTIBACTERIAL AGENT TRICLOCARBAN BY MEANS OF BRANCHED POLY (ETHYLENE OXIDE)-POLY(PROPYLENE OXIDE) POLYMERIC MICELLES

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ABSTRACT

Aiming to gain further insight into the complexity of drug/polymeric micelle interaction phenomena, the present chapter investigated the incorporation of the poorly water-soluble topical antibacterial agent triclocarban (TCC) into polymeric micelles of the branched pH/temperature-responsive poly(ethylene oxide)-poly(propylene oxide) block copolymers Tetronic® 1107 (MW = 15 kDa, 70 wt% PEO) and 1307 (MW = 15 kDa, 70 wt% PEO). Solubility extents showed a sharp increase of up to 4 orders of magnitude. Due to the pH-

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dependent character of both the carrier and the drug, studies were performed under different pH conditions. Due to a more efficient poloxamine aggregation at higher pH-values, a clear increase in the solubilization capacity was apparent under these conditions. However, ionization of TCC at pH 12.7 constrained the formation of hydrogen bonds between the urea moieties and the polyether chain, leading to a decrease in solubility above this pH. The size and size distribution of drug-loaded micelles was evaluated by Dynamic Light Scattering (DLS). Findings indicated the increase in the size of the aggregates with the incorporation of the drug. The morphology of the nanostructures was visualized by transmission electron microscopy (TEM). The stability of the systems over time was also evaluated. Finally, the antibacterial activity of different TCC/poloxamine complexes was assayed on different bacteria collections. For example, while a poloxamine-free TCC aqueous solution (pH 7.4) was not effective on *Staphylococcus aureus*, a 10% drug-containing T1307 system inhibited the bacterial growth to some extent. These results supported the release of the drug from the polymeric reservoir. However, as opposed to previous reports, overall findings indicated the limited intrinsic activity of TCC against the investigated pathogens.

1. INTRODUCTION

Adhesion of bacteria to the surface of biomedical devices, tissues and working areas and the later progression of the colonization process involves a first stage (phase one) of physical and reversible surface/pathogen interactions [1]. Then, a second stage (phase two), entails a permanent time-dependent adhesion and the secretion of a slimy extracellular matrix known as biofilm [2,3]. Microorganisms embedded in a biofilm frequently display higher minimal inhibitory concentrations (MIC) and resist common antibiotic chemotherapy [4,5]. This phenomenon would stem from a modified metabolism. Biomaterial-centered infections (BCIs) originate in the colonization of biomaterial-made devices by bacteria and the generation of a biofilm [3,6]. Among the microorganisms, *Staphylococcus epidermidis* and other *staphylococci* were indicated as highly prevalent actors in the development of BCIs [4,7,8]. Generation of biofilm by antibiotic-resistant clinical strains (e.g. methicillin-resistant *staphylococci* or MRS and vancomycin-resistant *enterococci* or VRE) plays also a central role in the spreading of hospital-acquired infections [9,10].

The low aqueous solubility displayed by more than 50% of the FDA-approved drugs constitutes a main obstacle towards the development of formulations for oral, parenteral and topical administration [11,12].

Triclocarban (TCC, 3,4,4'-trichlorocarbanilide, see structure in Table 1) is a synthetic antibacterial agent used as antiseptic in cosmetic and health-consumer products [13,14]. It presents low acute and chronic toxicity. Due to its molecular nature, TCC remains unionized in a broad range of pH-values ($pK_a = 12.7$). Contrary to triclosan (TS), another well-known topical and broadly used biocide, reports indicated that TCC displays a more limited activity (essentially against Gram positive microorganisms) [15,16]. The extremely low solubility of TCC in water (~ 50 ng/mL) constrains the development of water-based antibacterial TCC-containing formulations [17]. In order to enhance the solubility of TCC, different approaches have been investigated [18]. For example, complexation of the drug with different cyclodextrins (CDs) led to good solubility improvements [19,20]. In this context, whether the

low antibacterial activity stems from the intrinsic resistance to the drug or, by the contrary, from the extremely low concentrations attainable in aqueous media remains unclear.

Polymeric micelles are nanostructures generated by the self-assembly of polymer amphiphiles in water [21]. Micelles are conformed by two zones: (A) an inner and hydrophobic core and (B) an outer and hydrophilic shell. The hydrophobicity of the core enables the inclusion and solubilization of poorly water-soluble molecules [22]. Solubilization is governed by two main parameters, namely the micellization ability of the polymer and the drug/micelle interaction. Poly(ethylene oxide)-poly(propylene oxide) block copolymers (PEO-PPO) are one of the most extensively investigated groups of micelle-forming biomaterials [23,24]. A number of advantageous features support their application: (A) a broad range of commercially available molecular weights and EO/PO ratios, (B) a proven cell and tissue-compatibility and (C) the approval of several derivatives by different regulatory agencies (e.g., FDA, EMEA) as additives in pharmaceutical and cosmetic products [25-27]. The most thorough work was performed on micelles of the linear PEO-PPO-PEO poloxamers (Pluronic®) [24]. On the other hand, the 4-arm poloxamines (Tetronic®) present a central ethylenediamine segment that renders the molecule two tertiary amine moieties. Thus, molecules are both temperature and pH sensitive [28]. Also, amine groups enable further chemical modification to produce more cell-adhesive substrates [29].

Our research group dedicates efforts to investigate the application of polymeric micelles as nanocarriers for poorly-water soluble biocides in the context of hospital biofilm prevention and treatment. In a recently published work, we investigated the inclusion of TS into polymeric micelles of the poloxamine Tetronic® 1107 at different pH-values [30]. Solubility levels increased up to 4 orders of magnitude. Microbiological assays demonstrated that TS-loaded micelles were active against a broad spectrum of pathogens, including MRS and VRE. Moreover, TS/poloxamine systems were effective against *Staphylococcus epidermidis* biofilm.

Aiming to gain further insight on the molecular aspects controlling the solubilization process of TCC the present chapter reports on the inclusion of the drug into polymeric micelles of two branched PEO-PPO block copolymers, Tetronic® 1107 and 1307. The size and size distribution of drug-loaded micelles were studied by Dynamic Light Scattering (DLS) and the morphology of the aggregates visualized by Transmission Electron Microscopy (TEM). Finally, the antibacterial activity of TCC-containing systems was investigated on different collections and clinical pathogens.

2. MATERIALS AND METHODS

Materials. Tetronic® T1107 (MW = 15 000 Da, 70 wt% PEO, HLB 18-23) and 1307 (MW = 18 000 Da, 70 wt% PEO, HLB > 24) were a kind gift of BASF (NJ, USA). Triclocarban (TCC, Sigma, St. Louis, MO), KH_2PO_4 (Carlo Erba, Italy), KCl (Merck, Germany), NaOH (Merck, Germany) and concentrated HCl (Anedra, Argentina) were used as received. Buffers of pH 2.0, 5.8 and 7.4 were prepared in distilled water according to the USP 24 edition. Buffer pH 12.7 was prepared using Na_2HPO_4 (Merck, Germany) and the pH adjusted with NaOH 0.2M.

Thermal analysis. In order to establish the enthalpy of fusion of TCC (ΔH_f) a sample (~ 5 mg) of the drug was sealed in a 40 μ L Al-crucible pan and analyzed by Differential Scanning Calorimetry (DSC, Mettler TA-400 differential scanning calorimeter) in a single heating ramp (25 to 300°C, 10°C/min.). The value of enthalpy was normalized to the weight of the sample and expressed in kJ/mol.

Preparation of poloxamine micelles. Poloxamine micellar systems (1 to 10%) were prepared by dissolving the required amount of polymer in the different media at 4°C. Systems were equilibrated at 23°C, 24 hours prior to use in order to allow the formation of the micelles. Concentrations are expressed in % w/v.

Preparation of TCC-loaded micelles. TCC (in excess, ~ 20 mg/mL poloxamine solution) was added to T1107 or T1307 micellar systems (3 mL, 1 to 10% w/v) in dark glass vials (10 mL) and sealed appropriately with Parafilm®. Specimens were vigorously shaken (48 h) in a temperature-controlled horizontal shaker at 23°C (Minitherm-Shaker; Adolf Kuhner AG, Switzerland). Suspensions were filtered through clarifying filters (0.45 μ m, cellulose nitrate membrane, Microclar, Argentina) and dried in a vacuum oven at room temperature. Dry samples were re-dissolved in ethanol and the concentration adjusted as required. Drug concentrations were determined by measuring the absorbance in a UV spectrophotometer (265 nm, CARY [1E] UV-Visible Spectrophotometer Varian, USA) at 23°C using a calibration curve of TCC solutions in ethanol covering the range between 2.7 to 13.7 μ g/mL (correlation factor was 0.9985). Mean concentrations are expressed in μ g/mL $\pm$ S.D. (n = 3). Ethanol was used as blank. Molar solubilization ratios (MSR) were calculated by ratioing the molar concentration of the drug by the molar concentration of the polymer, at every condition.

Measurement of the micellar size by Dynamic Light Scattering (DLS). The average hydrodynamic diameter of drug-loaded poloxamine micelles was measured in a Zetasizer Nano Series (Zetasizer Nano-Zs, Malvern Instruments, UK) provided with a He-Ne (633 nm) laser and a digital correlator ZEN3600. Measurements were performed in PMMA disposable cuvettes at 23°C. Samples were filtered by clarifying filters (0.45 μ m) prior to the assay. Results are expressed as the average of five measurements.

Visualization of the drug-containing micelles. In order to investigate the morphology of drug-containing micelles, samples were visualized by Transmission Electron Microscopy (TEM, EM 109T Zeiss Transmission Electron Microscope, Karl Zeiss, Berlin, Germany). Briefly, TCC-containing poloxamine systems were placed on grids covered with Formvar film and stained with 2% w/v phosphotungstic acid solution in water. Then, samples were dried in a closed container with silicagel and observed under the microscope.

Stability of the TCC-loaded micelles upon storage. In order to study the stability of the drug-containing micelles along the time, specimens previously prepared were stored at room temperature for 1 month and the concentration of TCC in the different samples determined by UV (see above). Samples were worked up as previously described. Results of % of remaining TCC (% TCC) are expressed as Mean $\pm$ S.D. (n = 3).

Antibacterial activity of TCC/poloxamine systems. Antibacterial evaluation of different TCC-containing T1107 and T1307 micelles (pH 7.4) was evaluated in plate experiments. Bacteria were cultured on Tryptone Soy Agar (TSA, Britannia, Argentina) plates and were incubated at 35°C for 24 h. Then, microorganisms were removed from the isolation medium, suspended in 0.9% NaCl to a final concentration equivalent to an optical density of 0.6 (at 600 nm) and diluted 1/10 (0.9% NaCl). Suspensions (0.1 mL) were diluted in cold molten TSA (10 mL) containing 2,3,5-triphenyltetrazolium hydrochloride (TTC, 0.007% final concentration, Sigma, USA), plated in sterile Petri dishes and allowed to solidify. Paper discs (6 mm diameter) were embedded in the corresponding samples, namely, poloxamine-free saturated TCC solution in buffer (pH 7.4, control), drug-free poloxamine T1107 and T1307 micelles (blank) and TCC/poloxamine systems, incubated (35°C, 24 h) and the inhibition zone in disc diffusion tests was measured. Results are expressed in diameter. Inhibition zones of <6 mm indicate no antibacterial activity.

Table 1. Physicochemical properties of triclocarban (TCC).

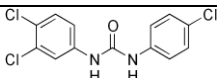
Molecular structure	M / g·mol ⁻¹	ΔH_{fus} / kJ·mol ⁻¹	T_{fus} / K	X_2^{id} / x 10 ⁻³	S_{water} / μg/mL	X_2 / x 10 ⁻⁹	$\Delta G_{\text{soln}}^0 - \text{ideal}$ / kJ mol ⁻¹	ΔG_{Exc}^0 / kJ mol ⁻¹
	315.6	41.94	528	4.25	0.049	2.86	13.54	35.22

Table 2. Estimation of solubility parameters of triclocarban by means of Fedors and van Krevelen methods ^(a)

TCC					
Group	Quant	Fedors	Van Krevelen		
		V / cm ³ mol ⁻¹	F_d / J ^{1/2} cm ^{3/2} mol ⁻¹	F_p^2 / J cm ³ mol ⁻²	U_h / J mol ⁻¹
Disubstituted phenylene group	1	1 × 52.4	1 × 1270	1 × (110) ²	-
Trisubstituted phenylene group	1	1 × 33.4	1 × 1110	1 × (110) ²	-
-Cl	3	3 × 24.0	3 × 450	3 × (550) ²	3 × 400
>=O	1	1 × 10.8	1 × 290	1 × (770) ²	1 × 2000
-NH-	2	2 × 4.5	2 × 160	2 × (210) ²	2 × 3100
		177.6	4340	1612800	9400
			$\delta_d =$ (4340/177.6) = 24.44 MPa ^{1/2}	$\delta_p = ((1612800)^{1/2}/177.6)$ = 7.15 MPa ^{1/2}	$\delta_h =$ (9400/177.6) ^{1/2} = 7.28 MPa ^{1/2}
			$\delta = (24.44^2 + 7.15^2 + 7.28^2)^{1/2}$ = 26.48 MPa ^{1/2}		

^(a)Calculated according procedures described by Barton [31].

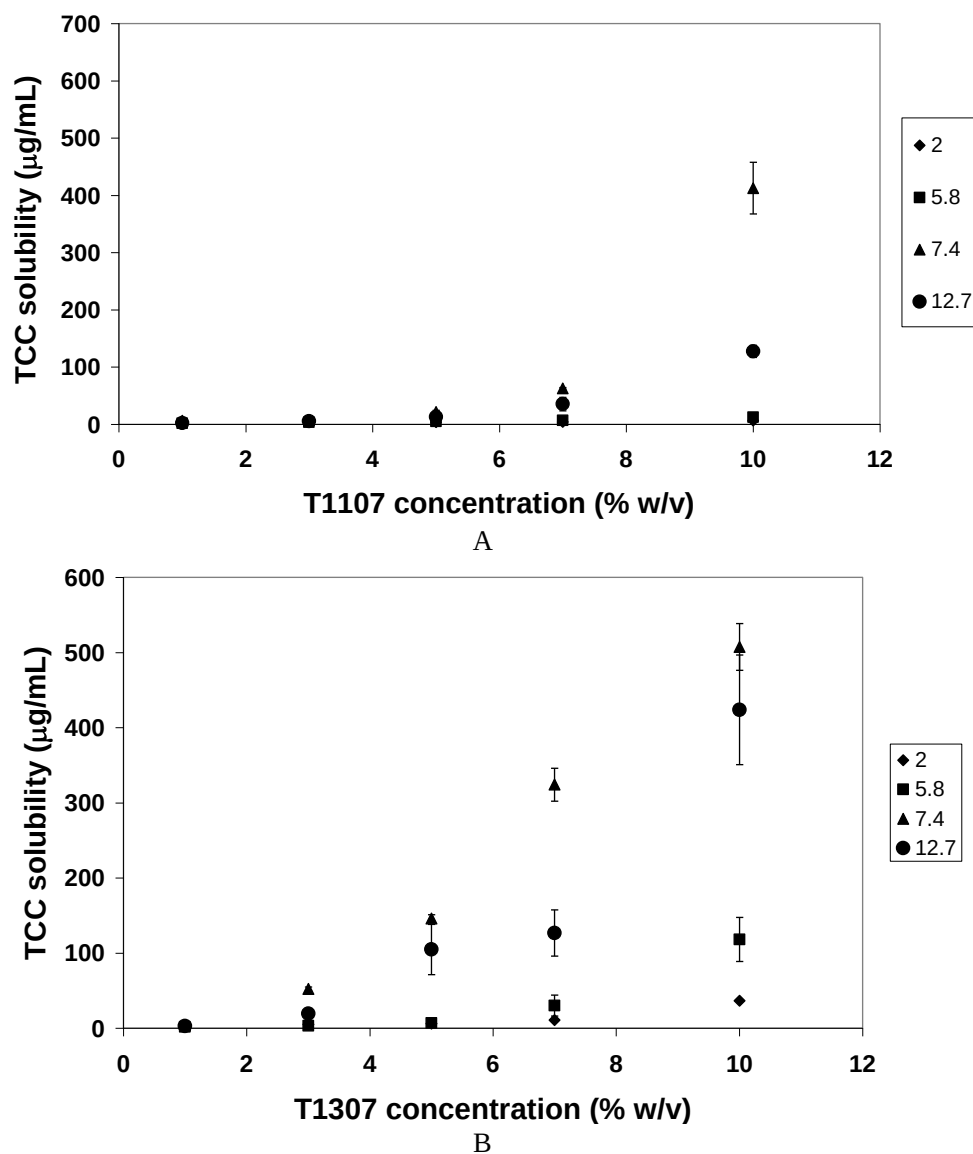


Figure 1. S_a of TCC versus poloxamine concentration at four different pHs. A) T1107 and B) T1307.

3. RESULTS AND DISCUSSION

3.1. Water-Solubilization of Triclocarban

The goal of the present work was to investigate the molecular implications governing the solubilization process of TCC into the core of poloxamine polymeric micelles and the further understanding of the phenomena associated with the limited antibacterial performance of the drug.

Table 3. Triclocarban/poloxamine molar ratios (MSR) in poloxamine systems between 1 and 10% at four different pH-values.

Poloxamine	Polymer concentration (%)	pH			
		2.0	5.8	7.4	12.7
T1107	1	13.88	7.76	30.18	11.74
	3	5.55	5.69	11.49	8.75
	5	3.55	4.63	20.42	12.27
	7	2.74	4.84	42.60	24.03
	10	3.09	6.02	196.08	60.66
T1307	1	21.16	10.04	20.22	17.17
	3	9.32	6.03	99.54	36.90
	5	6.89	7.63	166.46	119.50
	7	8.62	24.44	264.07	103.24
	10	20.90	67.39	289.39	241.57

The ideal solubility of a solute is controlled by the melting point and the enthalpy of fusion [32]. The molecular form of TCC could interact with solvents and among itself by hydrogen bonding, namely, as hydrogen-donor through the N-H groups present in the urea moiety, whereas it could act as hydrogen-acceptor through the carbonyl-oxygen in the same functional group. In addition it could interact through weak interactions, such as London dispersion forces due to the presence of highly hydrophobic aromatic rings. The ideal solubility of a crystalline solute in a liquid solvent can be calculated by Eq. 1:

$$\ln X_2^{\text{id}} = -\frac{\Delta H_{\text{fus}} (T_{\text{fus}} - T)}{RT_{\text{fus}} T} + \left(\frac{\Delta C_p}{R} \right) \left[\frac{(T_{\text{fus}} - T)}{T} + \ln \left(\frac{T}{T_{\text{fus}}} \right) \right] \quad (1)$$

Where, X_2^{id} is the ideal solubility of the solute as mole fraction, ΔH_{fus} is the molar enthalpy of fusion of the pure solute (at the melting point), T_{fus} is the absolute melting point, T is the absolute solution temperature, R is the universal gas constant ($8.314 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$), and ΔC_p is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical super-cooled liquid form, both at the solution temperature. Since ΔC_p cannot be easily determined, in this investigation it is assumed that ΔC_p may be approximated to the entropy of fusion ($\Delta S_{\text{fus}} = 79.4 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$). Values of ideal and aqueous solubility are presented in Table 1. Since the thermal behavior is a function of the solute-solute interactions in the crystalline lattice, the stronger these forces are, the more insoluble the solute is. As opposed to triclosan that melts around 56°C (and shows an enthalpy of fusion of 17.75 kJ/mol) [33], TCC displays an extremely high melting point around 255°C , supporting the presence of strong solute-solute forces. In order to characterize the ideal solubility of crystalline TCC, the enthalpy of fusion was determined by DSC. The high value observed (41.94 kJ/mol) supported the very poor solubility of the drug observed in water ($\sim 50 \text{ ng/mL}$) (Table 1). The low solubility of TCC was also supported by calculations according to the group contribution methods of Fedors and van Krevelen (Table 2). Based on the analogy

that ‘like dissolves like’, the gap between the value of the parameter of solubility (δ) of TCC ($\delta = 26.5 \text{ MPa}^{1/2}$) and the one of water ($\delta = 48.0 \text{ MPa}^{1/2}$) supported the limited drug solubility in aqueous medium.

Even though some minimal solubilization improvement could be theoretically attained below the critical micellar concentration (by means of the interaction between isolated amphiphile molecules known as unimers and drug molecules), maximization of the inclusion phenomenon relies on the presence of the micelles. Due to their structure, poloxamines are both temperature and pH-responsive. In general, pK_a values are between 4 and 6 for the first amine group and around 6-8 for the second [34]. Thus, depending on the pH of the medium, from diprotonated to unprotonated forms (going through a monoprotated one) are available. When positively-charged ($\text{pH} < \text{pK}_a$), central ethylenediamine groups repel each other and hinder micellization, leading to an increase in the CMC; repulsion is stronger for diprotonated than for monoprotated forms. Once the molecule displays an uncharged form (at $\text{pH} > 8$), the CMC usually decreases sharply. Consequently, the efficiency of the solubilization usually increases at higher pH-values. On the other hand, the affinity of TCC/poloxamine affinity also plays a fundamental role. Thus, the present study focused on polymer concentrations above the CMC for both T1107 and T1307, in the whole range of pH-values [30,34]. Two main factors influencing the aggregation phenomenon and the solubilization were evaluated: (A) the concentration of the polymer and (B) the pH. Due the high enthalpy of fusion shown by TCC and the tremendously low solubility in water, a more limited solubilization of the drug in the hydrophobic polymeric core in comparison to triclosan (a previously investigated biocide) was predicted. The apparent solubility (S_a) of TCC in T1107 and T1307 micellar systems (1 to 10%) saturated with the drug was determined at pH-values between 2.0 and 12.7 (Figure 1). Findings indicated a sharp increase as the concentration of both amphiphiles rose. For example, for T1107 at pH 7.4, S_a increased from $\sim 50 \text{ ng/mL}$ in poloxamine-free medium to 6.4, 21.48 and $412.6 \text{ }\mu\text{g/mL}$ for 1, 5 and 10% systems, respectively. It is worth stressing that these results meant an increase in solubility of up to more than 3 orders of magnitude. A decrease in the pH (see pH-values between 2.0 and 7.4) hindered the micellization due to the repulsion between the positively-charged ethylenediamine blocks and rendered lower S_a levels. These findings were in agreement with previous reports that indicated the concomitant decrease in solubility as the pH decreased [35]. Due to the unprotonated character of poloxamine molecules at pH 12.7, an even higher solubility was a priori envisioned. However, TCC contains a ureide moiety in the structure that displays the ability to form hydrogen bonds with the polyether chain. Ionization of this functional group at pH-values above the pK_a (~ 12) is supported by the increase in the intrinsic solubility of the drug above this pH from 50 to 300 ng/mL . Thus, even if micellization was favored under these conditions, a more limited interaction between the drug and the polymer resulted in lower solubilization extents between 2.5 and $127.6 \text{ }\mu\text{g/mL}$ for 1 and 10% systems, respectively. T1307 displays a higher molecular weight and a consequent enlargement of the micellar core (from about 4500 to 5400 Da) that could favor a more efficient solubilization. On the other hand, HLB data indicate that T1307 presents, overall, a more hydrophilic structure. Results with T1307 followed a similar trend for similar polymer concentrations and pH conditions; solubility gradually increased from pH 2.0 to 7.4 and then decreased at pH 12.7. It is worth remarking that in this case values increased utmost 4 orders of magnitude. The sharp increase in the apparent solubility of TCC as the pH rose can be

further evaluated in Table 3, where calculations of MSR are presented. In general, values steadily increased in the pH range between 2.0 and 7.4 due to the higher aggregation tendency of the amphiphiles. Then, under more basic conditions (pH 12.7), where the drug was ionized, a sharp decrease was apparent. A similar trend was observed as a function of the polymer concentration in the range 3-10% and pH-values between 5.8 and 12.7. The analysis of (A) 1% systems and (B) specimens at pH 2.0 (at every concentration) was less straightforward. In both conditions, the apparent solubility (expressed in $\mu\text{g/mL}$) was relatively low. However, MSR values were, often, higher than those calculated for 3 and 5%, indicating a higher number of solubilized TCC molecules per poloxamine molecule. An interesting phenomenon is also the one observed for T1107 at pH 2.0 where MSR values gradually decreased between 1 and 7% and then showed a slight recovery for a 10% sample. T1307 (pH 2.0) showed a similar tendency though the recovery was apparent at a lower concentration: 7%. These results were particularly observed under conditions where micellization was strongly hindered due to (A) very low polymer concentrations slightly above the CMC ($\sim 0.5\text{-}1\%$) and (B) repulsion of poloxamine molecules derived from diprotonation. Previous investigations showed that the lower the pH the smaller the size of poloxamine aggregates is [35,36]. In the proximity of the CMC (1% systems) at pH 2.0, the presence of very small aggregates (including a high incidence of unimers in the composition) probably led to higher MSR values. This, even with very low S_a levels. Then, as a consequence of the increase in the polymer concentration, more micelles were generated and a sudden decrease in the molar ratio was found (even if higher TCC amounts were solubilized). Finally, additional increase in the poloxamine concentration led to a substantial recovery in MSR. These findings also suggested the presence of a phenomenon where larger micelles are formed, enabling the inclusion of a higher number of TCC molecules per polymer molecule. On the other hand, the solubilization ability of poloxamines for TCC was lower than the one found for TS [30]. These findings expectedly emerged from the stronger solute-solute forces showed by the former and a more limited tendency to interact with the liquid-like hydrophobic micellar core.

3.2. Effect of TCC on the Aggregation of Poloxamine

Inclusion of TCC into the polymeric micelles was expected to affect the size and size distribution of the aggregates [37]. TCC-loaded micelles of 3, 5 and 7% poloxamine systems (at pH 7.4) were evaluated by means of DLS (Figure 2). An increase in the micellar size due to the enlargement of the core associated with the incorporation of the solute molecules could be anticipated [37,38]. Findings of T1107 and T1307 indicated the presence of two main populations (Table 2). Small size aggregates ($\sim 6\text{-}8$ nm) were mainly consistent with the presence of regular drug-loaded micelles. However, this population decreased in intensity as the polymer concentration rose (and consequently the drug loading); the area of the small-size peaks was 82.9 to 56.5% for 3 and 7% samples, respectively, for T1107 micelles. By the contrary, for the same amphiphile, the presence of larger aggregates ($\sim 65\text{-}110$ nm) suggested the enlargement of the micelles due to the incorporation of TCC into the core. In addition, the higher the polymer concentration was, the higher the incidence of this large-size fraction. Results for T1307 followed a similar trend as the recurrence of the large-size micelles increased for high polymer concentrations from 46.3 to 63.0% for 3 and 7% T1307 systems, respectively. On the other hand, these aggregates displayed a smaller size than those

generated by T1107 and a slight decrease in the size of the aggregates was found as the polymer concentration rose. This behavior was probably associated with both the higher hydrophilicity and the larger shell of T1307 micelles that rendered more stable aggregates. It is worth mentioning that TCC/poloxamine systems were completely transparent and supported the fact that micellar fusion was not involved in the aggregates enlargement process [30]. Visualization of TCC-loaded systems by means of TEM is exemplified for 10% T1107 micelles in Figure 3. Findings showed the presence of spherical aggregates of different sizes and supported the DLS data. Also here, no evidence of secondary aggregation was found [30]. It is noteworthy that size determination by TEM was unreliable due to the non-representative character of the sample.

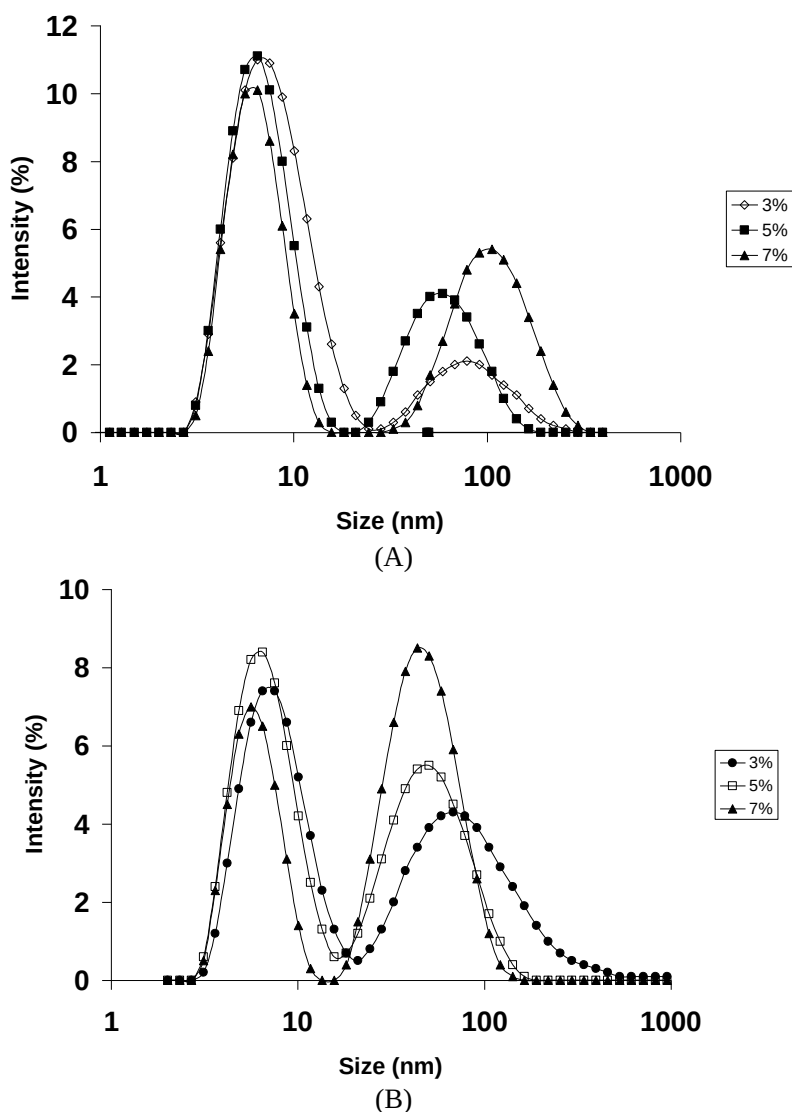


Figure 2. Micellar size and size distribution (% intensity) of TCC-loaded 3, 5 and 7% T1107 (A) and T1307 (B) systems.

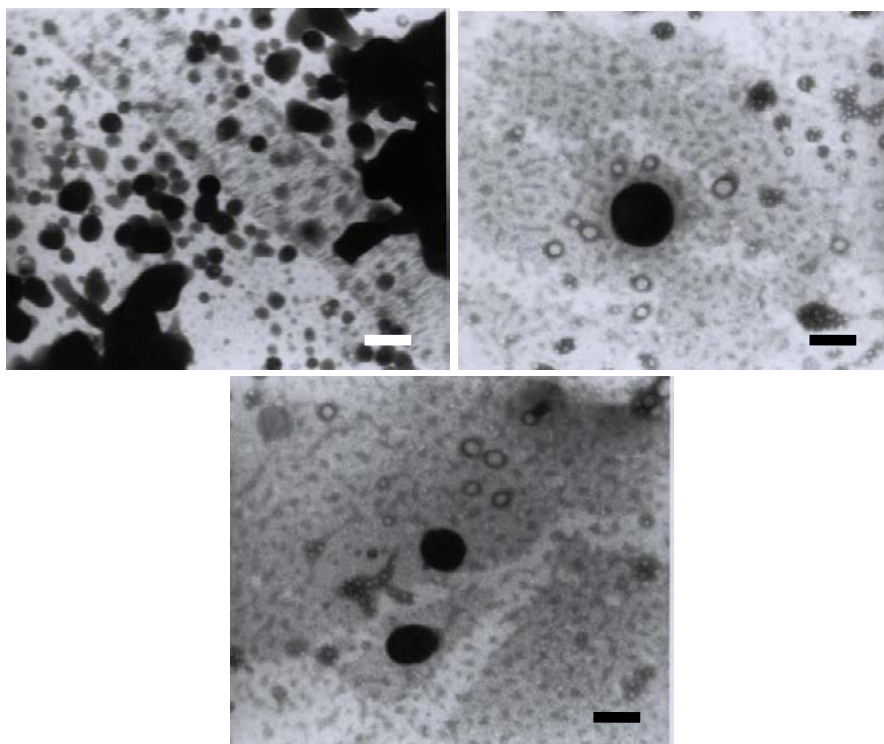


Figure 3. TEM micrographs of TCC-saturated 10% T1107 micelles negatively stained with 2% phosphotungstic acid at pH 7.4. Different sizes are apparent. Scale bar = 100 nm (microscope mag. = 100,000x).

Table 4. Micellar size and size distribution (% intensity) of TCC-loaded 3, 5 and 7% T1107 and T1307 systems

Poloxamine	Poloxamine concentration (%)	Peak 1		Peak 2	
		Size (nm)	%	Size (nm)	%
T1107	3	8.03	82.9	89.81	17.1
	5	6.89	68.8	64.11	31.2
	7	6.51	56.5	112.7	43.5
T1307	3	8.05	52.2	76.4	47.8
	5	6.97	53.3	54.3	46.7
	7	6.05	37.0	50.3	63.0

3.3. Stability of the TCC-Loaded Micelles upon Storage

Solubilization encompasses the inclusion of TCC molecules into the hydrophobic core of the aggregates. Usually, under regular storing conditions, temperature can fluctuate, affecting the micellization of the thermo-responsive poloxamines. In this context, a decrease in temperature would lead to the disassembly of the micelles and a decrease in the micellar concentration, often to concentration levels close or below the CMC. Moreover, according to

the thermodynamic calculations (strong solute-solute interactions), TCC displays a high tendency to aggregate. Consequently, in the case of TCC/poloxamine complexes, a precipitation phenomenon and a titer loss over time was envisioned. Different drug-containing specimens (1-10% of pH 7.4) were maintained at room temperature and the concentration of the drug determined after 1 month. A T1107 1% system displayed a sharp drug-load loss of about 64% and the appearance of insoluble drug crystals. Then, higher polymer concentrations improved the stability upon storage. For example 10% systems of T1107 and T1307 lost only 16.6 and 15.6% of the initial TCC loading, respectively. Also, a slight increase in stability was observed for T1307, consistent with its more stable structure in water due to a higher hydrophilicity [24]. It is remarkable that TCC/poloxamine complexes presented a more limited stability than the highly stable TS/poloxamine ones that remained almost unchanged for at least 3 months [30]. Solubilization relies on the generation of strong solute-solvent interactions in order to overcome solute-solute and solvent-solvent ones. The ΔH_f displayed by TCC was substantially higher than the reported for TS and indicated much stronger solute-solute forces. Thus, as expected, weaker drug/core and stronger drug/drug interactions resulted in a higher sensitivity of the complex to small changes in temperature and a higher tendency of the drug to precipitate.

3.4. Antibacterial Activity of TCC/Poloxamine Systems

According to previous reports, TCC displays a relatively limited antibacterial spectrum and effectiveness. Studies of the antibacterial activity of the complex aimed to explore if the low activity of the drug was an intrinsic limitation or, otherwise, it stemmed from the poor solubility attainable under regular conditions (e.g., in water). In contrast to a previously published study on TS where 5% polymer were used, herein, due to the more limited solubility of TCC and its lower antibacterial activity, more concentrated poloxamine solutions (10%) were tested. Plate assays indicated a slightly broadening of the inhibition area when Gram positive *Staphylococcus aureus* and methicilin-resistant *Staphylococcus aureus* (clinical strain) were exposed to the substantially higher biocide concentrations attained in micellar systems. On the other hand, findings stressed the substantially lower activity of this agent compared to the previously investigated TS and suggested that the poor antibacterial activity relied on the intrinsic resistance of the different pathogens to the antibacterial agent. These results contrasted with previous reports indicating minimal inhibitory concentrations of TCC in the 0.5-5 $\mu\text{g/mL}$ range. In addition, inhibition for drug-loaded T1107 specimens was more limited probably due to the lower concentration attained.

4. CONCLUSION

Inclusion of the poorly water-soluble drug triclocarban into poloxamine polymeric micelles enhanced the aqueous solubility in up to 4 orders of magnitude. In agreement with previous reports, higher solubilization extents were found at higher pH values in the range between 2.0 and 7.4. In contrast, a pronounced decrease in solubility was found at pH 12.7, regardless the more efficient micellization of the polymers under these conditions. This

phenomenon could be explained by the pH-sensitive ionization of the -NH-CO-NH- moiety of TCC under this pH. At a lower pH (e.g., 7.4) where aggregation was less favored, unionized ureide groups formed H bonds with the poly(ether) chain and solubilization was enhanced. By the contrary, once unprotonated, TCC molecules displayed a weaker interaction with the polymer and a lower solubility was found. Finally, the activity of the complexes was assayed on a number of bacteria. Even though complexation slightly increased the effectiveness of the antibacterial agent under study, activity was dramatically lower than that demonstrated by TS. Overall findings supported the relatively limited activity of TCC even at concentrations significantly higher than those attainable in poloxamine-free media.

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Chapter 6

SILOXANE-CONTAINING COMPOUNDS AS POLYMER STABILIZERS

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ABSTRACT

Generally, surfactants are used as stabilizers of interfaces or particles and their applications are very wide, from foams or adhesion modifiers to the orientation of chemical reactions.

Siloxane surfactants are known for their ability to decrease the surface tension of liquids in such extent that is comparable only with some fluorinated compounds, which are thought to exhibit potential toxicological problems. On the other hand, polysiloxanes are unique by their set of properties, like for example low glass transition temperature, hydrophobic behavior, transparency to visible and UV light, high permeability to various gases (especially oxygen), physiological inertness, excellent blood compatibility (low interaction with plasma proteins). In addition, their chemistry is very versatile, and as a result, a very broad range of siloxane-organic compounds can be synthesized, including amphiphilic macromers or polymers.

The most commonly known siloxane surfactants are the so called „silicone polyethers”, but other nonionic, as well as ionic surface active agents have been prepared and used over the years in cosmetics, textile conditioning, foam stabilization, coatings or agriculture.

Recent developments in this research field and especially our experimental results on the synthesis, properties and applications of siloxane-containing surfactants will be reviewed. Our main interest is to propose new surfactants or alternative synthetic procedures, and new stabilization systems for polymeric nanoparticles. Carbohydrate modified (poly)siloxanes with different architectures have particularly been studied and tested, due to their biocompatibility and bioavailability.

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INTRODUCTION

Surfactants are crucial for certain applications in the modern technique, from laundry and heavy washing to personal care or medicine. The most recent applications of surfactants are related to nanotechnologies; they are used as templates for nano-patterning, as well as for the stabilization of nanoparticles -the „new wave” in science- [1].

Various surface active agents have been synthesized and investigated, as well as their interaction with polymers [2]. New surfactants continue to appear, and even slight modifications of the molecular structure are very useful for understanding of their properties [3].

In the domain of polymer stabilization (polymerization in dispersed media as well as using physico chemical procedures), it becomes of first importance to anchor the surfactant onto the surface of the particles not only to avoid flocculation, but also to limit water pollution. In the case of emulsion polymerization, a good way to overcome these drawbacks is to use polymerizable surfactants (also called "surfmers") [4-6].

Polymeric surfactants, and particularly block and grafted copolymers, offer another quite versatile way to stabilize nanoparticles [7], with enhanced properties with respect to the molecular emulsifiers. The consequence is excellent surface properties at low concentrations, which allows using lower amounts of emulsifier for the stabilization of emulsions [8]. This is an obvious economical benefit, and the fact that the residual concentration of emulsifier in the aqueous phase is lower, brings another advantage limiting secondary effects such as air entrapment and foaming, or adsorption at various interfaces. Among polymeric surfactants, polyethylene oxide - polypropylene oxide (PEO-PPO) diblock and triblock copolymers (Pluronics® or Poloxamers®) are well-known and their properties and uses are broadly documented [9, 10]. The hydrophobic PPO block can advantageously be replaced by a biodegradable block polyester such as polycaprolactone or polylactide [11-16].

In the field of surface active compounds, one cannot disregard the unique properties of siloxanes as hydrophobic components in connection with such applications. Siloxane surfactants are used since the 1960s in textile conditioning, polyurethane foams, as adjuvants in agriculture, paint additives, cosmetic formulations and so on. Their uniqueness is their solubility both in water and in organic solvents, reducing the surface tension of all these media and exhibiting hydrophobic as well as oleophobic properties. The reasons for this unique behavior are the high flexibility and low cohesive energy of the siloxane bond. The siloxane backbone can adapt to the interface geometry very easily, without creating steric hindrance due to this flexibility [17, 18].

On the other hand, there are some additional properties that make siloxane compounds very attractive. For example, polydimethylsiloxanes (PDMS) have a very low glass transition temperature, transparency to visible and UV light, high permeability to various gases (especially oxygen), physiological inertness, excellent blood compatibility (low interaction with plasma proteins) [19]. The very low surface tension of the polysiloxanes, along with their versatile chemistry and biocompatibility increased the interest for siloxane-containing surfactants. Thus, amphiphilic compounds of all kinds of molecular architectures and variable chemical structures have been synthesized and studied as surface active materials. A wide range of organic moieties, namely nonionic, anionic, cationic and zwitterionic organic groups, have been linked to polysiloxane backbones in order to get soluble products [20].

Siloxane surfactants are usually required in small amounts and often provide better performances than their purely organic counterparts. For example, it was calculated that one

$\text{Si}(\text{CH}_3)_2$ unit can be compared to 4 CH_2 units, while a $\text{C}(\text{CH}_3)_2$ unit is equivalent to 2 CH_2 groups in terms of surface activity [21].

Many of these surfactants are largely used and commercially available. The first and thus the most studied were those having polyethyleneoxide as hydrophilic part, either as block copolymers or as trisiloxanes (Schemes 1-3). Only some of the most recent developments in this class of surfactants will be reviewed here, since the subject is quite vast and other comprehensive references are available.

In various domains, the choice of surfactants is not dictated only by their surface properties, but is limited by many other constraints. This is particularly true for applications that concern living organisms, environment and humans. That is why a more and more important topic is that of biocompatibility and / or biodegradability.

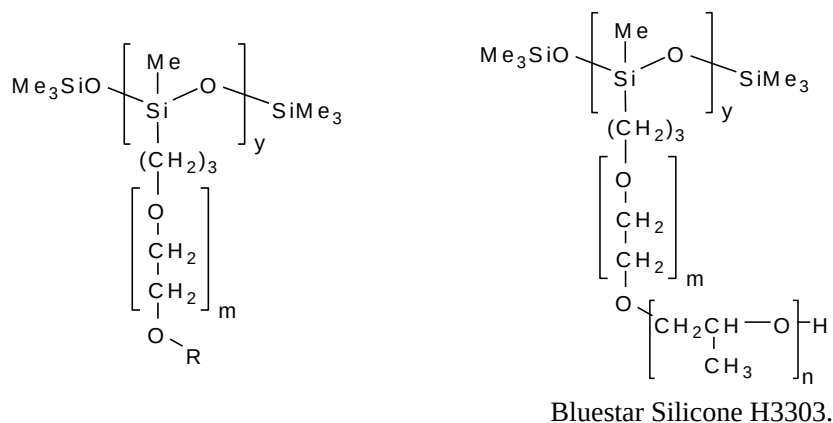
Carbohydrate-containing siloxane surfactants have attracted much attention, since they can be obtained from a natural resource and thus be more eco-friendly. The reports on this particular class of siloxane surfactants will be summarized, including our own contribution.

1. SILICONE POLYETHERS (SPE)

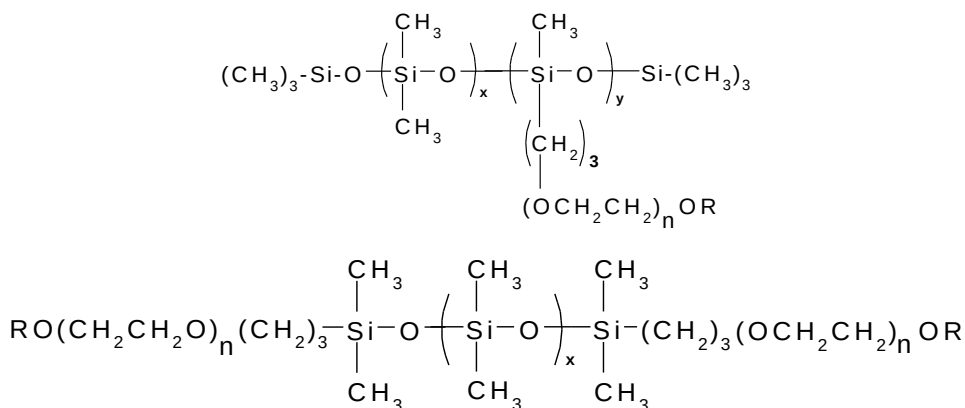
The most commonly known siloxane surfactants contain polyoxyalkylenes (polyethers) as hydrophilic parts. They have been investigated since the 1960s and silicone polyethers have practically become the definition itself of siloxane surfactants.

Their effectiveness in organic systems as well as in water and their use in cosmetics, textile conditioning, foam stabilization, coatings and agriculture has been reported [22-28].

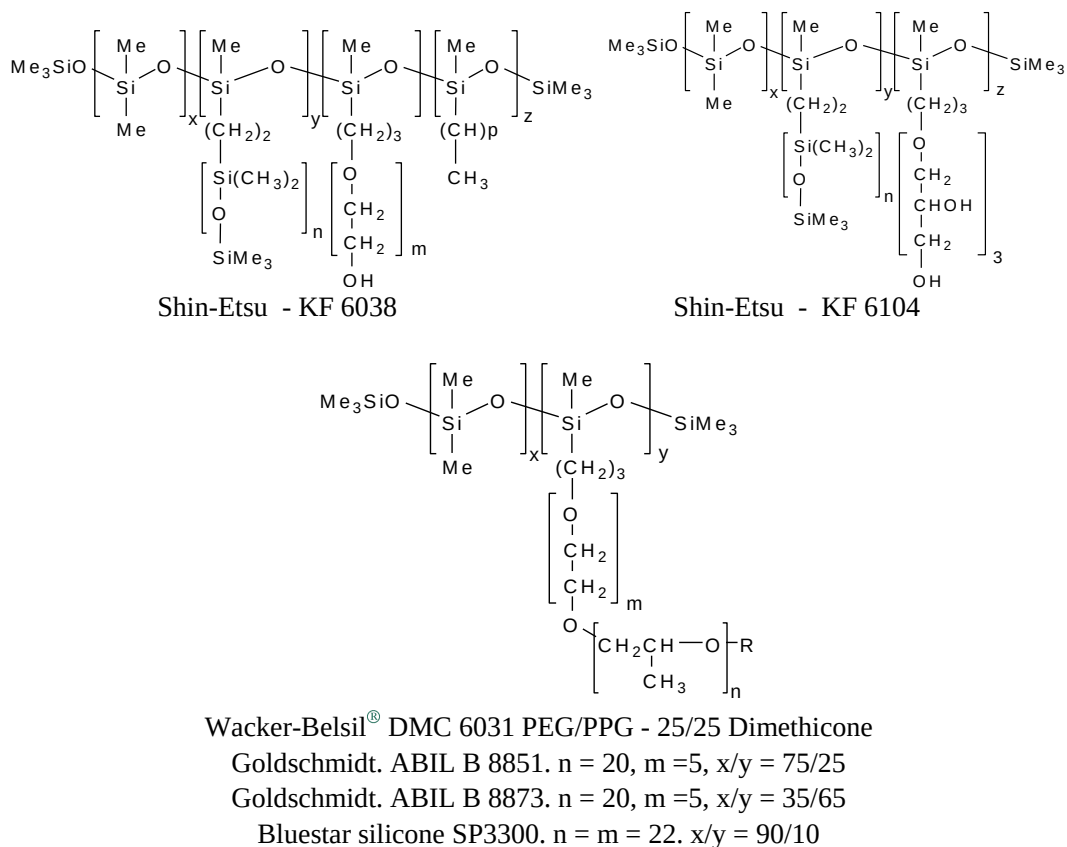
The polyether groups are polyethylene oxide (PEO) and/or polypropylene oxide (PPO), and are attached as side chains to the siloxane backbone through a hydrosilylation or condensation process. They can have a linear or grafted (comb) architecture and a great diversity of structures are available (Schemes 1-4), since molecular weight and composition of the polyether chain (PEO/PPO) as well as the functionality of the end group and the ratio of siloxane to polyether can also be varied. Siloxanes with a very high molecular weight are more suitable for forming water/oil emulsions [29]. Depending on their solubility parameters, silicone polyethers can stabilize foams or act as antifoaming agents [30].



Scheme 1. Polyether trisiloxane surfactants



Scheme 2. General structures of the main types of SPE copolymers



Scheme 3. Examples of commercial surfactants

Extensively studied nonionic surfactants are PDMS / polyether block copolymers [31] and poly(ethylene oxide) substituted trisiloxanes [32-35]. They are able to achieve a maximum surface tension depression to about 21 mN/m and a low critical micelle concentration (CMC) [36]. These siloxane surfactants can self-assemble into a variety of

ordered morphologies in the melt as well as in solution, depending on the volume fractions of the hydrophilic units [37].

1. A. RECENT DEVELOPMENTS IN THE SYNTHESIS AND INVESTIGATION OF SPEs

The preparation, uses, and physical chemistry of silicone surfactants have been described in a well-known reference [38], focusing on silicone polyoxyalkylene copolymers. This book explores many aspects of SPEs as surfactants, like interfacial processes, surface viscoelasticity, and aggregation, explains the unusual wetting behavior of the trisiloxane surfactants and the ternary phase behavior of mixtures of silicone surfactants with water and silicone oils. That is why we only try to emphasize some newer insights into the subject, reported mainly after year 2000.

From the chemical point of view, some improvements in the structure and synthesis of SPEs have been made. In order to avoid Si-O-C linkages, which are susceptible to hydrolytic instability, hydrosilylation reactions are used to prepare these compounds, starting from unsaturated precursors [21, 39-41].

Triblock PEO-PDMS-PEO copolymers have been obtained by anionic polymerization of ethylene oxide using a PDMS diol as transfer agent. These copolymers have been fully characterized by NMR and Maldi-Tof mass spectrometry. As expected, the solubility depends on the PEO/PDMS ratio [42].

It was found that, when the hydrophilic functional groups are linear or when the end-capped units of the hydrophilic groups are of hydroxy type, the hydrolytic stability decreases and chemical attack of silicone surfactants backbone occurs easily in the aqueous solution. A way to avoid this is to synthesize grafted copolymers or to use PEO blocks having methoxy end groups [43].

Although such siloxane surfactants were extensively exploited, their surface active properties are still investigated [21, 27, 44]. All types of aggregates known for hydrocarbon surfactants comprising micelles, lyotropic liquid crystalline phases from lamellar to the inverse hexagonal phase, vesicles, and "sponge" (L3) phases have been found in aqueous solution [37, 45].

It was found that the minimum ratio which insures water solubility in siloxane surfactants is 9 PEG units to 29 siloxane groups. The critical aggregation concentration decreases systematically with the decrease in the hydrophilic PEG substitutions. The surface and self-assembling properties have been investigated with surface tension, viscosity, fluorescence, and contact angle measurements [21].

Recent investigations still approach different aspects of this complex subject, like self-assembling behavior, adsorption on different substrates, rheology. Many studies have been undertaken for siloxane surfactants in dilute aqueous solutions, but their potential applications in organic solvents or as nanoreactors are not yet fully investigated.

The CMC, micelle hydrodynamic diameter, microviscosity in the micelle core in water and in mixtures of water with polar solvents have been investigated for a polyoxyalkylene siloxane surfactant, by means of fluorescence [46].

The self-aggregation in long PEO-PDMS surfactants showed their ability to form inverse micelles and liquid crystals in nonpolar oils, including octamethylcyclotetrasiloxane (D4). These structures, which are not found in conventional hydrocarbon surfactant systems, were explained by the segregation tendency of the PEO chains and the flexibility of the siloxane chains [27].

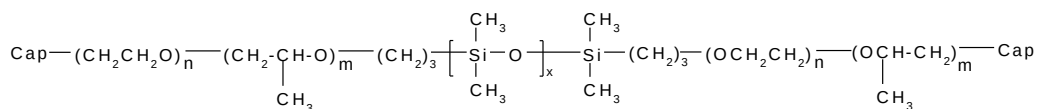
A polyethyleneoxide-*b*-polydimethylsiloxane-polyethyleneoxide surfactant, (EO)₁₅-(DMS)₁₅-(EO)₁₅, was studied with freeze-fracture transmission electron microscopy and pulsed-field gradient nuclear magnetic resonance spectroscopy, in order to establish the effect of glycerol on the permeability of vesicle membranes. Small vesicles with diameters of less than 25 nm and multilamellar vesicles with diameters larger than 250 nm were observed in pure water, which were modified when water was gradually replaced with glycerol [47].

Polydisperse (PPO-*b*-PEO) allyl ether siloxane surfactants were synthesized by the hydrosilylation reaction of 1,1,1,3,5,7,7,7 octamethyltetrasiloxane (MD₂'M) with oligo(PO-*b*-EO) allyl ethers. In this series, the surface tension increased with increasing the EO chain length and it decreased with increasing the PO ratio, while the sedimentation time of the aqueous solution showed opposite trend. The cloud point temperatures tended to increase with the increase in the EO chain length and decrease of the PO ratio [48].

Recently, a series of well defined amphiphilic poly[methyl(3,3,3-trifluoropropyl)siloxane]-*b*-poly(ethylene oxide) (PMTFPS-*b*-PEO) diblock copolymers with different block lengths have been prepared by hydrosilylation [49].

Trisiloxane surfactants containing polyethyleneoxide chains of different lengths, known as superwetters, have been studied by soft-contact AFM imaging and direct force measurements at the solid-liquid interface, using different substrates [50]. The surface aggregate structures for these siloxane surfactants correlate with those of their hydrocarbon-based equivalents and resemble bulk structures.

Surface force measurements of ABA type SPEs (Scheme 4), compared to hydrocarbon-based Pluronic surfactants, at the solid/liquid interface in water/ethanol mixtures showed that SPEs are capable of providing steric stabilization at a hydrophobic surface up to 80% and even up to 95% ethanol level (depending on structure), while in the case of hydrocarbon-based surfactants this barrier was 40% [51].



Cap: OH or OAc

Scheme 4. General formula of triblock SPE surfactants [51]

Although the nature of superwetting remains enigmatic, the surface aggregate structures are studied in order to better understand colloidal phenomena and to approach nanotechnologies by self-assembly of hierarchical structures [50].

1.B. SPEs as Polymer Stabilizers: Applications of SPEs

Oil-in-water emulsions obtained with certain SPEs are stable in the presence of alcohol, which is an important advantage for many emulsion and dispersion formulations, where alcohols are common co-solvents or additives. At the same content of ethanol, hydrocarbon-based Pluronic surfactants do not emulsify oil-in-water [51].

Silicones give a unique dry-lubricity feel to surfaces such as textiles, hair, and skin [38]. That is why graft polysiloxane-poly(oxyalkylene) copolymers are used for making water-in-silicone oil (w/o) emulsions for personal care products [52]. The question of how to solubilize polymeric silicone oils, preferentially in microemulsions, is of high technological importance [53] and has received special attention. Silicone surfactants alone or in combination with short-chain alkanols are efficient emulsifiers for short chain siloxanes. It was found that organic surfactants are not as suitable as silicone surfactants for stabilizing silicone/water emulsions [54]. The chemical affinity of the hydrophobic part of the surfactant to the silicone oil is a benefic factor, helping the solubilization process [53].

Silicone oil in water (o/w) emulsions are more difficult to stabilize. To prepare such dispersions, nonionic PDMS-polyoxyalkylene copolymers with high degree of polyoxyalkylene substituents are generally used, in order to render the surfactant more hydrophilic. Thus, the resulting emulsions are sterically stabilized by the polyether chains [54].

Viscoelastic and viscosimetic measurements have been performed on model systems and on commercial products [29]. Water-in-silicone emulsions have been prepared, in which the oil phase consisted of decamethylcyclotrisiloxane (cyclomethicone, D5) and the surfactant used was a branched type silicone copolymer. The interfacial rheology study of such surfactants revealed that the ability of these copolymers to effectively stabilize water-in-D5 emulsions is a result of a process involving the nucleation, growth, and accumulation of surfactant-rich particulates at the D5/water interface [55].

The w/o/w or o/w/o emulsions are important, in particular when the protection of sensitive ingredients or controlled release of active substances is required [54]. Silicone-based emulsifiers are suited for these applications. They are strongly adsorbed at the oil interface, and do not migrate from one interface to the other, thus preventing the destabilization. Two emulsifiers have to be used to stabilize these multiphase emulsions. The hydrophilic-lipophilic balance (HLB) values of the emulsifiers should be above 10 for the hydrophilic emulsifier and below 6 for the hydrophobic emulsifier [54].

The ability of SPEs to form vesicles, which are structurally comparable to liposomes, has opened a wide range of possibilities for the incorporation of active ingredients. Silicone vesicles can have a diameter from about 0.05 to 1 micron and an internal volume of $10^{-6} \mu\text{m}^3$. The membrane thickness of these vesicles is about 3 to 4 nm [56]. The main application of siloxane-based surfactants vesicles is in cosmetics. For example, using silicone vesicles, hydrophilic and hydrophobic active substances can be separated and protected from each other, thus reducing for example skin irritancy. Active delivery systems include non-aqueous emulsions of polyols in silicone fluids, multiple-phase emulsions, and polar solvent-in-oil emulsions.

Silicone-based surfactants offer many benefits in waterborne coatings. The coating surface tension can be modified to improve substrate wetting, in particular when trisiloxane polyethers are used, since these structures provide excellent wetting to low-energy substrates,

like plastics. Copolymers with linear or grafted structures give moderate wetting, but can provide mar resistance, slip and de-aeration [30]. For waterborne coatings and ink formulations, polymeric surfactants are used in conjunction with polar organic solvents. The numerous patents covering this area of research are discussed in a review [57].

In view of such applications, the adsorption of a grafted (rake-type) polymeric siloxane surfactant containing 48% PDMS, 39% PEO, and 13% PPO on carbon black particles dispersed in mixtures of water with polar organic solvents has been investigated [58]. The adsorption was found to obey the Langmuir isotherm below the critical micelle concentration and a sharp increase in the adsorbed amount was observed at higher surfactant concentrations. DLS and SANS data indicate that the structure of the adsorbed layer is similar to that of micelles.

An aqueous laundry stain pretreater composition which would provide outstanding cleaning performance on both oil and water based stains on a variety of fabrics has been developed using polyalkylene oxide modified trisiloxanes [59].

Trisiloxane surfactants have been used as adjuvants in agriculture. They increase the foliar uptake of pesticides, due to reduction of surface tension and superspreading. A method for improving the performance of agricultural compositions under conditions of low humidity has been developed, by using silicone surfactants that reduce the surface tension to less than 30 mN/m in 0.10% (w/w) aqueous solution, without concomitant spreading of the spray solution [60].

SPEs can act as stabilizers in chemical reactions. For example, silver nanoparticles with an average diameter of about 3 nm have been obtained inside the aggregates of a PDMS-*g*-PEO copolymer, without adding a reducing agent [61]. Polymerization of halogen-containing monomers in aqueous medium using siloxane surfactants instead of potentially toxic fluoroalkyl surfactants has been described [62].

2. SILOXANE SURFACTANTS WITH CARBOHYDRATE MOITIES

Siloxane-polyethers usually have a poor emulsification activity at the siloxane-water interface, which has been explained by the weak intermolecular interactions between the surfactant molecules [63]. This is one reason for seeking surfactants with stronger intermolecular interactions.

Carbohydrates are bioavailable, biocompatible, biodegradable, biologically active and suitable for molecular recognition. They are hydrophilic and capable of self-association. So, there are a lot of reasons for using them as partners for siloxane compounds, in order to produce more environmentally friendly surfactants with superior properties.

Glycopolymers are often defined as synthetic polymers bearing sugar moieties [64-68]. This definition can also be enlarged to any macromolecular structure resulting from chemical modification of natural polymers (cellulose, dextran ...). They are used in a lot of biomedical application fields including drugs and drug delivery devices because of the ability of sugar moieties to interact with protein receptors (the so-called cluster glycoside effect). In most cases, glycopolymers are amphiphilic polymers because of the presence of hydrophilic and hydrophobic units and they can act as polymer surfactants. These glycopolymers can therefore offer a unique combination of macromolecular recognition and colloidal

stabilisation of nanoparticles in dispersed media to get opportunities for the production of novel targeted drug delivery systems.

For instance, maleic copolymers with different contents of galactose moieties and dodecyl chains were synthesized and used as both a stabilizer and a surface coating for the preparation of poly(ϵ -caprolactone) nanoparticles by the emulsification-diffusion technique. The surface modification of nanoparticles was confirmed by ζ -potential measurements. Nanoparticles were also shown to be recognized by a galactose-specific lectin, demonstrating the presence of galactose units on the particle surface [69].

More recently, 8-amino-3,6-dioxaoctyl α -D-mannopyranoside and 8-amino-3,6-dioxaoctyl β -D-galacto-pyranoside were prepared for coupling with a copolymer made from ϵ -caprolactone macromonomers and maleic anhydride. The glycopolymers thus obtained were used in conjunction with Pluronic® F-68 for the stabilization of PCL nanoparticles prepared by the emulsification-diffusion technique [70].

The combination of carbohydrates and silicones has received a great attention in both scientific and economic media [71]. Hybrid materials, from small molecules, to polymers, oligomers and nanostructured composites have been prepared and their applicability especially in biomedical fields has been proved.

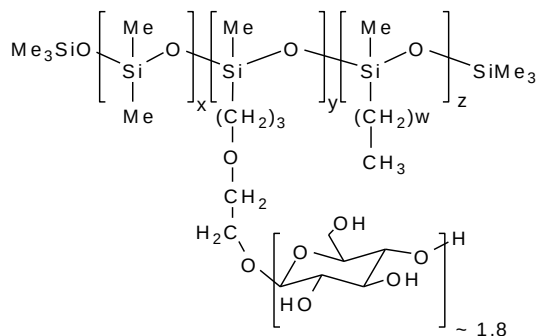
2.A. Synthetic Methods for Carbohydrate – Modified Siloxane Surfactants

A broad variety of carbohydrate-modified siloxane surfactants have been synthesized and tested as surfactants [72-75] or in cosmetic formulations [76-79]. Such compounds are currently produced on an industrial scale (see for example Scheme 5) and their use has gradually increased due to their excellent biodegradability, good dermatological compatibility, and the absence of toxic effects.

The chemistry of carbohydrate modified polysiloxanes is not easy, starting from the totally different solubility of the reagents and continuing with the instability of the siloxane and glycosidic bonds in certain conditions. Nevertheless, various structures have been obtained, sometimes applying very ingenious solutions to overcome such problems. Different carbohydrate moieties have been used, as well as various HO-protecting procedures (mainly using acetyl or trimethylsilyl derivatives) and subsequent deprotection methods. The most common method for linking carbohydrate derivatives with siloxanes is the hydrosilylation. An alternative is the ring-opening reaction between an amino-functional siloxane and a carbohydrate lactone [79, 81-83], but other methods have also been described and are still developed.

Allyl glycosides, allyl ethers and allyl amides of glucose, gluconic acid and glucuronic acid- γ -lactone with protected hydroxyl groups have been used to obtain silane precursors for modified polysiloxanes [84].

A great variety of carbohydrate-modified siloxane surfactants have been prepared by Wagner and coll. [72-75, 78, 79]. They described a synthetic path yielding to straight-chained glycosides-functionalized siloxanes with amide linkages, via allyl-glycidyl ether –modified intermediates [78]. Similar compounds have been prepared from silanes, carbosilanes, polysilanes and non-permethyated siloxanes [73] and the role of the key intermediates for the surface properties of the surfactants has been thoroughly investigated.

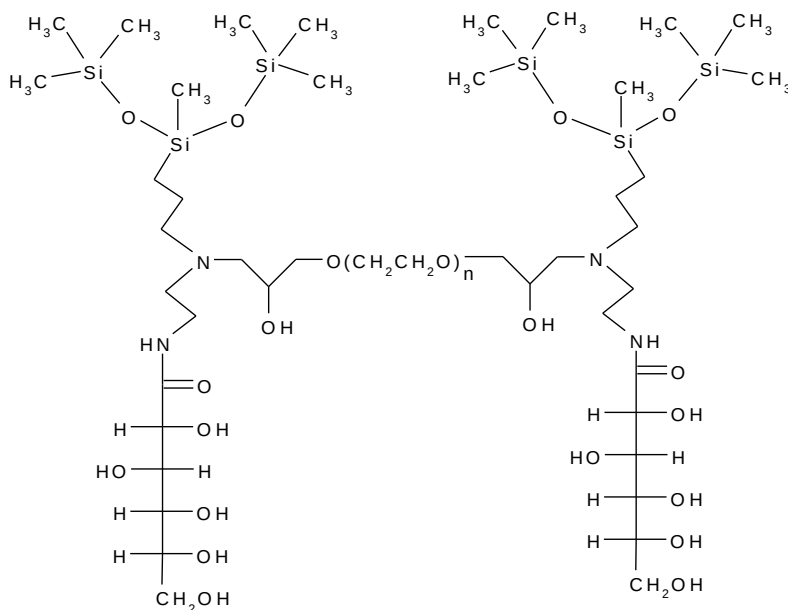


Scheme 5. A commercially available carbohydrate-modified polysiloxane (Wacker Belsil SPG-128VP): Caprylyl Dimethicone Ethoxy Glucoside, 20% in cyclopentasiloxane (D5)) [80]

Different approaches have been used for the hydrosilylation of allylglycosides with various H-functional polysiloxanes [71, 78, 85-87]. Glucopyranosyl- and cellobiosyl-terminated oligodimethylsiloxanes with thioether or ether linkages have been prepared and tested as transdermal penetration enhancers [87]. The monosaccharide-modified compounds exhibited a pronounced permeation acceleration for antipyrine, while the disaccharide ether siloxane had no enhancing activity.

High molecular weight polysiloxanes modified with mono-, di- or oligosaccharides showed different aggregation behavior in solution, depending on the detailed chemical structure of the carbohydrate moiety and its stereochemistry [88].

Gemini surfactants have been obtained from a trisiloxane amine, D-gluconic acid δ -lactone and oligoethylene glycol diglycidyl ethers [89] (Scheme 6). These surfactants reduced the surface tension of water to approximately 21 mN/m at a concentration of around 10^{-5} mol/L and showed two critical aggregation concentration values.

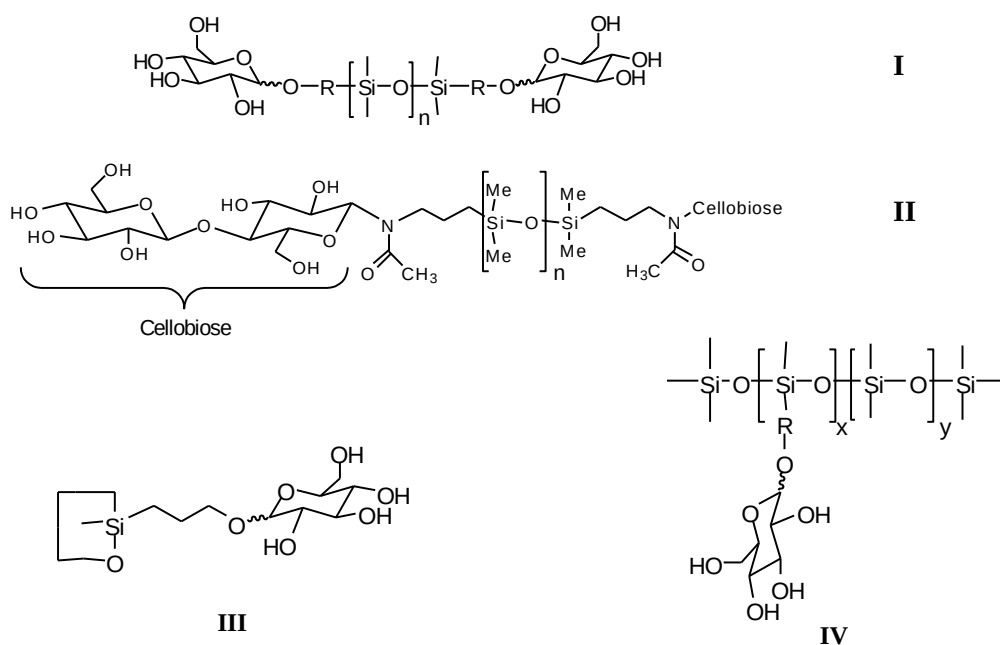


Scheme 6. Gemini surfactants [89]

Amphiphilic polysiloxanes have been recently obtained by reacting a water-soluble poly(3-aminopropyl)siloxane with fatty acid chlorides to attach hydrophobic moieties and subsequently with gluconolactone which provided the hydrophilic groups. The regularity of the nanoaggregates in water formed from the amphiphilic polysiloxanes was relatively controlled by the chain lengths and functionalities of the hydrophobic parts [90].

Glucose functionalized polysiloxanes have been obtained by transacetalation [63]. Different acidic catalysts have been tested and activated clay was found to be the best, due to the great advantage of avoiding the contamination of the final product.

We have described the synthesis of mannose, glucose, galactose or cellobiose modified siloxanes: telechelic difunctional oligosiloxanes, siloxane copolymers with pendant monosaccharide groups and cyclic oligosiloxanes (Scheme 7) by a method involving hydrosilylation and cation exchangers as deprotecting catalysts [91-93].



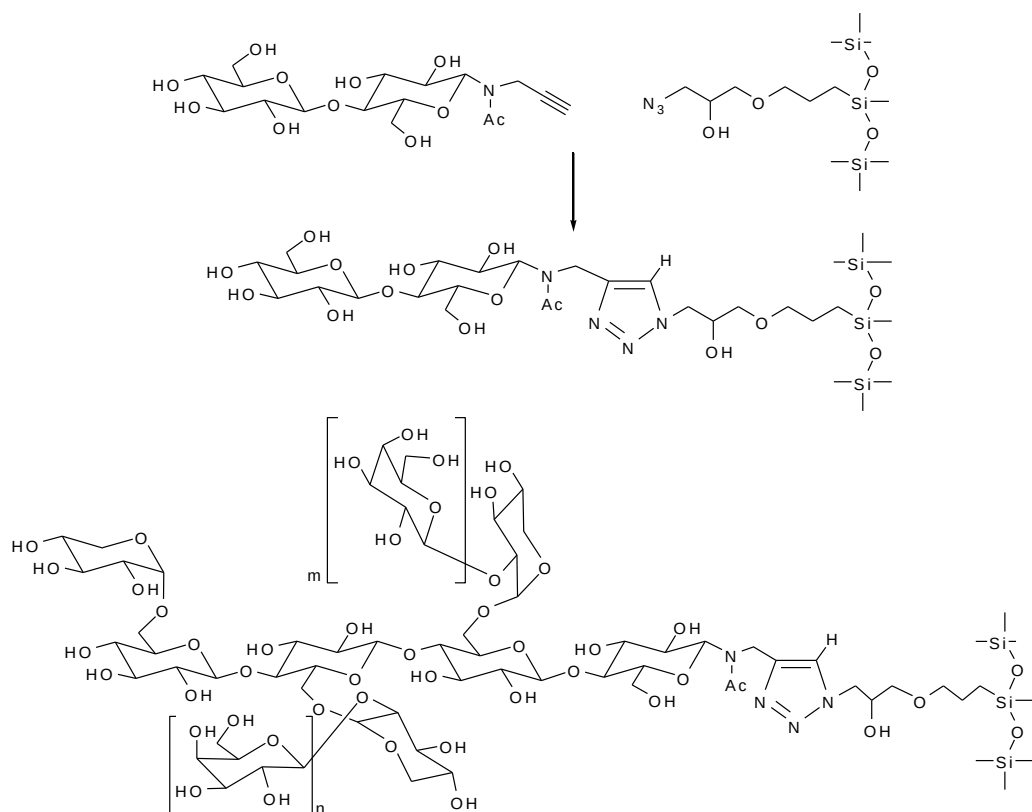
Scheme 7. Carbohydrate modified siloxanes [91-93]

In this approach, the protection-deprotection method was based on the fragile solubility equilibrium. In a first version [91, 92], the trimethylsiloxy groups were removed in the presence of a cation exchange resin which was used in wet state (gel form), in order to prevent the cleavage of the Si-O bonds. Indeed, cation exchangers with similar exchange capacity are largely used for the polymerization of cyclosiloxanes, in laboratory and in industry [94-97]. The only difference is that these polymerization catalysts are thoroughly dried before use, by azeotropic distillation of toluene, and only traces of water remain in their structure. Thus, the highly hydrophobic siloxanes have access to the active sites. For the deprotection of the saccharide OH groups, the catalyst that we used had a high content of water (50%) and in this situation the active sites are not available for the hydrophobic part of

the molecules: in other words, the water has a screening effect between the siloxane backbone and the catalytic sites and therefore prevents the breakage. On the other hand, the protected compounds were dissolved in a mixture of THF and methanol. The deprotection occurs gradually and the solubility of the deprotected compounds shifts towards methanol. The higher the content in hydrophilic groups the better the methanol and water solubility. In this case, cleavage of the siloxane bonds may occur, but the phenomenon is limited, especially if the reaction time is strictly controlled. The polymer conformation and self-assembling in solution have probably a great importance in preserving the integrity of the siloxane chains.

On the contrary, when the same cation exchanger was used, but after drying to constant weight, the siloxane chain break became more important [93]. The reaction time was significantly reduced, but the chain length control was not possible anymore. However, the glycosidic bonds in cellobiose moieties were not affected by the deprotection catalyst.

This deprotection method proved to be as „tricky” as effective, but the overall advantages of ion exchangers have to be considered, and especially the easy removal from the reaction mixture, without significant contamination of the final product.



Scheme 8. Cellobiose and xyloglucan modified heptamethyltrisiloxane (MD'M) obtained by click chemistry [98]

Although the procedure based on Fischer glycosidation and deprotection of HO- groups using a cation exchanger may be adjusted to produce as less damage to the siloxane chain as possible, it remains dangerous for the integrity of oligosaccharide segments, since those are also cleaved and reformed according to an equilibrium process. Oligosaccharide modified

polysiloxanes can be obtained, but the precise control of their structure remains uncertain with this procedure. An alternative may be the „click chemistry” applied to silicon-based materials. This reaction is quite versatile and appropriate to be used with compounds with different solubilities. Thus, the application of click chemistry to generate surfactants appears to be promising and particularly valuable.

Well-defined glyco-polyorganosiloxanes with cellobiose and xyloglucan oligosaccharide have been synthesized by „click” chemistry (Scheme 8) [98]. The method is based on Huisgen 1,3-dipolar cycloaddition from azido-containing PDMS with plant polysaccharide xyloglucan and cellobiose bearing a terminal alkyne functionality. It involves non-protected sugar derivatives, easy purification steps and it allows regioselective introduction of the alkyne function onto the carbohydrate moiety.

2.B. Applications of Carbohydrate Modified Siloxanes in Polymer Stabilization

Attempts have been made to prepare microemulsions of hexamethyldisiloxane or longer PDMS, using carbohydrate modified siloxane surfactants [78, 79], but the approach was not successful due to the siloxane insolubility of the amphiphile [53]. The addition of ethanol was helpful, but only in certain cases.

The surface active properties of a xyloglucan modified trisiloxane (Scheme 8) at the dodecane/water interface, as well as at the silicone/water interface, were studied and compared with those obtained with other surfactants usually involved in cosmetic formulations. The tests indicated that this glyco-organosiloxane was a poor emulsifier, but its foaming behavior is promising for detergent and cosmetic applications [98].

Glycopolysiloxanes with cellobiose moieties have been used for the steric stabilization of vinyl acetate miniemulsion polymerization [93]. The first attempts to get stable PVAc nanoparticles by using only the glycosiloxane derivatives as polymer surfactants failed, but stable nanoparticles were obtained using a mixture of glycosiloxane and a non-ionic triblock PEO-*b*-PPO-*b*-PEO copolymer.

The observation that glycosiloxanes employed alone are unable to stabilize miniemulsion polymerizations is in good agreement with the fact that mannose derivatives grafted onto vinylic polymer backbones are ineffective in assuring the colloidal stability of polycaprolactone nanoparticles [70]. This may tentatively be interpreted in terms of the layer thickness of the polymer surfactant adsorbed onto the particles. The siloxane chain is highly hydrophobic and forms a flattened alignment with the interface. The sugar moieties grafted either onto the backbone or at the chain ends are solvated by the aqueous phase but their small molecular size does not allow a sufficient extension into the solution to give a thick enough polymer layer to ensure a good steric stabilisation, contrary to silicone polyethers. Adding a triblock copolymer such as Pluronic is therefore needed to provide a good colloidal stability since the PEO segments extend further into water.

Polymer nanoparticles are more and more investigated and one of their most spectacular applications is in the medical field, where they are largely used for encapsulation of drugs [10]. For such a purpose, the polymers have to be biodegradable, biocompatible or bioresorbable [10, 99, 100]. Siloxane surfactants containing monosaccharides, as well as

potassium salts of siloxane-aliphatic carboxylic acids, have been used for the stabilization of polymer nanoparticles by nanoprecipitation [91, 92].

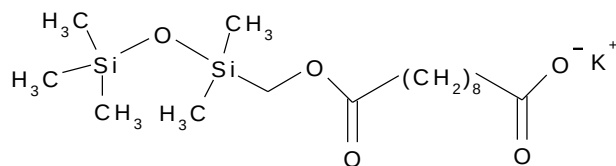
In the emulsification process, it was assumed that the chemical affinity of the hydrophobic part of the surfactant to the silicone oil promotes solubilization [53]. Nevertheless, this compatibility seems to be insufficient and other factors also intervene. For the same surfactant and experimental parameters, we observed differences in the size and size distribution from one polymer to another, and especially the stability after drying was greatly influenced by the thermo-mechanical properties of the polymer core. Well-defined spherical nanoparticles were obtained with polysulfone (PSF), a rigid polymer with high T_g . Polycaprolactone, PCL (negative T_g , but positive T_m) formed stable monodisperse particles in water, which exhibit a tendency of aggregation after drying. The nanoparticles obtained by nanoprecipitation of high molecular weight PDMS (both negative T_g and T_m collapsed) [91, 92].

In our attempt to obtain stable silicone nanoparticles, we have tested the possibility of crosslinking polysiloxane chains in the presence of siloxane surfactants [101]. The crosslinking reactions occur in the formed particles and improve their colloidal and dry-state stability. However, the average diameter and size distribution of the particles measured by DLS were not very good, which may be due to the insufficient hydrophilic content, or insufficient sterical repulsion.

Other chemical reactions can be performed in the presence of carbohydrate modified siloxane surfactants. For example, a glucose substituted cyclosiloxane has been successfully used to stabilize silver nanoparticles (Figure 2) [102].

3. OTHER SYSTEMS

Alkali metal salts of siloxane-aliphatic acids can play the role of anionic surfactants. Such compounds have been described in a pattern long time ago and their possible use as anti-corrosion agents and emulsifiers has been claimed [103]. We studied potassium salts of mono- and di-substituted sebacomethyl disiloxane (Scheme 9) as surface active compounds and we used them as stabilizers for polymeric nanoparticles [92, 101].



Scheme 9. Example of anionic siloxane surfactant

For example, polymer nanoparticles have been obtained combining nanoprecipitation with polycondensation. We have prepared poly(siloxane-azomethine) nanoparticles in a one step procedure, using a siloxane surfactant [101]. These particles were small and monodisperse (Figure 1d), as in the case of polysulfone. The core polymer has a positive T_g , as well, and this seems to be an important criterion for obtaining small and stable polymeric nanoparticles.

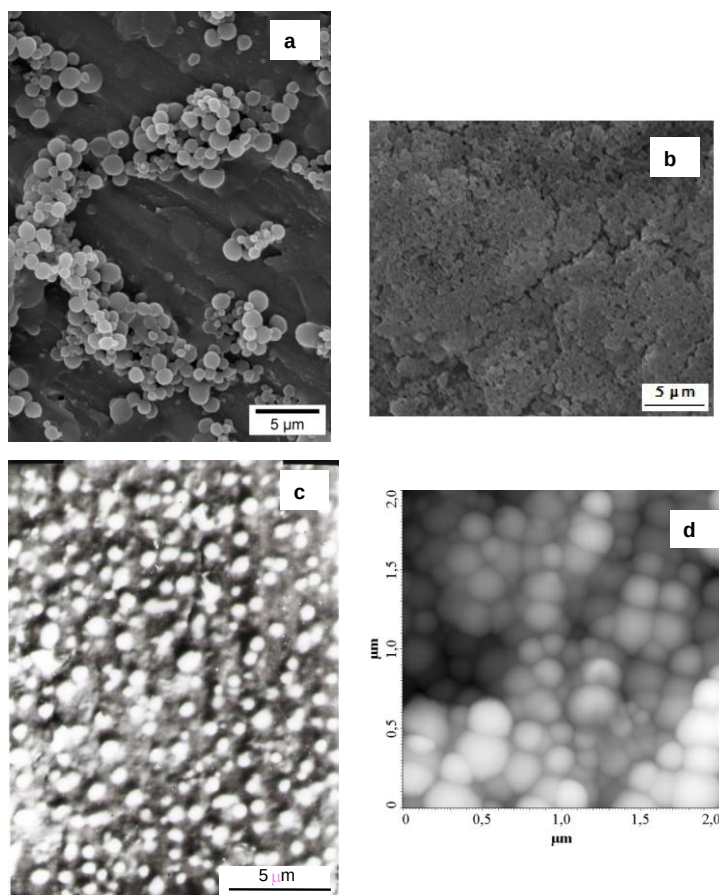


Figure 1. SEM and AFM images of nanoparticles stabilized with nonionic or anionic siloxane surfactants: (a) polycaprolactone, (b) polysulfone, (c) crosslinked PDMS, and (d) poly(siloxane-azomethine)

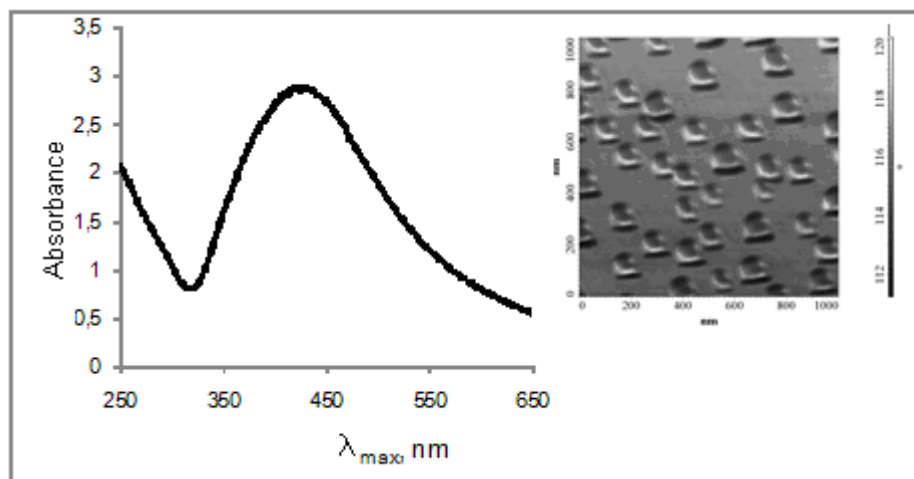


Figure 2. UV-Vis spectrum and AFM (phase) image of Ag nanoparticles obtained with a glucose-modified cyclosiloxane

The ability of siloxane surfactants to stabilize different chemical reactions allows the preparation of different nano-materials. For example, gemini surfactants containing a siloxane moiety have been used as templates for the preparation of mesoporous metal oxides such as zirconium, titanium, and vanadium oxides. The siloxane segment seems to play an important nano-propping role during the surfactant removal by direct calcination [105].

Amphiphilic ABA-type triblock copolymers containing PDMS, two poly(2-methyl-oxazoline) –PMOXA- side blocks and methacrylate terminal groups have a complex self-assembling behavior, which allows for the synthesis of covalently cross-linked hydrogels, with applications as contact lenses [106]. Cross-linked vesicles of such polymers are nano- and microcapsules which act as stable nanoreactors with controlled permeability [107-109].

Siloxane copolymers with polar groups may form aggregates in nonaqueous media, too. Their behavior is similar to that of surfactants in water. The relationship between nanostructure and rheological properties of such systems, and their potential use as nanoreactors are still under investigation [61, 110, 111]. For example, the micellization of a siloxane- ketimine in organic media may lead to metal complex nanoparticles [112].

CONCLUSION

Although siloxane surfactants and especially silicone polyethers are known and produced for some decades, they continue to incite the interest of the scientific world. New structures are emerging, new methods are used for their investigation and new applications are discovered. In particular, biocompatible surfactants are of great importance nowadays, as well as those obtained from renewable sources. Nano-materials may be prepared with siloxane-containing surfactants, which are active both in water and in organic media.

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Chapter 7

AMPHIPHILIC BLOCK COPOLYMERS: POTENT EFFLUX PUMP INHIBITORS FOR DRUG DELIVERY AND CANCER THERAPY

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ABSTRACT

The ability of amphiphilic block copolymers to modulate multi drug resistance related processes has been demonstrated the first time more than 10 years ago. Nowadays, the efflux pump inhibitory activity of amphiphilic block copolymers is used in two main areas. First, to improve the transport of efflux pump substrates across the blood brain barrier (BBB) and second, in cancer therapy. It has been shown that in the presence of amphiphilic block copolymers higher concentrations of certain anticancer drugs, which are known as efflux pump substrates, can be found in the brain. Within the current chapter, recent developments in the field of amphiphilic block copolymer mediated efflux pump inhibition are discussed. Besides presenting data from in vitro and vivo studies, also the mechanisms involved in efflux pump inhibition are addressed. In addition, the influence of hydrophilicity/lipophilicity of various amphiphilic block copolymers as well as factors such as micelle formation on the efflux pump inhibitory activity are explained.

1. INTRODUCTION

Efflux pumps are transmembrane located transporter proteins which are expressed in various tissues including liver, placenta, the proximal tubule in the kidney, capillary endothelial cells of brain and testis, and epithelial cells of the intestine [1,2]. In addition, they are over-expressed in cancer cells and are involved in the multi drug resistance (MDR) mechanisms of tumors. Besides other mechanisms such as CYP3A, efflux pumps constitute an integral part of the body's natural detoxification system. Due to their localisation in various tissue they affect absorption, distribution, metabolism and elimination [3]. They are

known to actively transport a wide range of structurally diverse compounds out of the cells; including anticancer agents [4], immunosuppressants [5], steroid hormones [6], calcium channel blockers [7], beta-adrenoreceptor blockers [8] and cardiac glycosides [9]. The most prominent representative of the group of efflux transporters is P-glycoprotein (P-gp)[10], but also other efflux pumps such as the multidrug resistant proteins (MRP) 1 and 2 as well as the breast cancer resistant protein (BCRP) [11] gain increasing attention. Efflux pumps are ATP-dependent proteins which are encoded by the ATP Binding Cassette (ABC) gene family.

It has been demonstrated that a broad variety of substances are capable of inhibiting efflux pumps. As MDR can be regarded as a main problem in cancer therapy, an inhibition of efflux pumps can contribute to the development of improved cancer therapeutics by increasing the transport of efflux-pump substrates into MDR cells. Another promising approach of efflux pump inhibition is to improve the transport of efflux pump substrates through physiological barriers, such as the blood-brain barrier (BBB) or the small intestine. Various therapeutic and already marketed drugs were identified to exhibit efflux pump inhibitory properties, in addition to their main pharmacological activity. Representatives of these so called “first generation” inhibitors are for example Verapamil or Tamoxifen [7,12]. In the following years, effort has been put in the development of inhibitors that lack therapeutic effects but still retain their efflux pump inhibitory properties. Therefore, “second generation inhibitors” were synthesised by chemically modifying first generation efflux pump inhibitors. Examples of second generation efflux pump inhibitors, which are based on the lead structure of first generation inhibitors are KR30031, a verapamil analogue, and PSC833 (Valspodar[®]), which is based on cyclosporine D [13,14]. Finally, “third generation inhibitors” which often lack CYP3A4 interactions and which are capable of inhibiting P-gp in a non-competitive manner were developed. Representatives which entered clinical trials are Elacridar (GF120918; GlaxoSmithKline), XR9576 (Tariquidar; Xenova), LY335979 (Zosuquidar; Eli Lilly), R101933 (Laniquidar) and ONT-093 (Ontogen).

Recently, it has been discovered that some widely used polymeric auxiliary agents can interact with efflux pumps. Many of these polymeric efflux pump inhibitors have been used for decades because of their proposed lack of pharmacological activity. The use of polymeric efflux pump inhibitors in pharmaceutical applications has been comprehensively reviewed previously [15,16]. Representatives of polymeric or polymer based efflux pump inhibitors are anionic gums and sodium alginate [17], polyethylene glycol (PEG)[18,19], PEG based detergents [20-23], thiolated polymers [24-26] and poloxamers such as pluronics [27]. Among the amphiphilic copolymers which are capable of inhibiting efflux pumps, pluronics have been evaluated in most detail so far. By modifying the length of the ethylene oxide (EO) and propylene oxide (PO) segments which are arranged in the basic A – B - A structure, polymers with various hydrophilicity/lipophilicity ratios can be synthesized. These “functional excipients” are known to affect immune response [28] and wound healing [29]. In addition, it was discovered already 10 years ago, that pluronics can modulate MDR related processes.

2. EFFLUX PUMP INHIBITION MECHANISMS OF PLURONICS

Various mechanisms which are responsible for the efflux-pump inhibitory properties of pluronics have been identified and discussed in detail previously [30]. Among them are inhibition mediated by ATP depletion, membrane fluidization and ATPase inhibition. As

already mentioned, efflux pumps are ATP dependent, which means that ATP is required in order to sustain the function of efflux pumps. It was demonstrated that the intracellular ATP level of cancer cells was depleted following a 2 hour incubation period with pluronic P85 [31]. Additional studies by Batrakova et al. using various MDR and non-MDR cell lines showed that the pluronic mediated ATP depletion is reversible and that MDR cells are much more responsive to pluronic than non-MDR cells [32,33]. Another mechanism which appears to be responsible for the efflux pump inhibitory activity of pluronics is mediated by the ability of pluronics to be absorbed on cell membranes. This effect leads to changes in the microviscosity of cell membranes, due to alterations in the structure of the lipid bilayers [34]. In particular, the presence of pluronic P85 leads to fluidization of membranes of healthy and cancer cells [35]. It has been suggested that non-specific changes in lipid and protein conformation and mobility can lead to ATPase inhibition, which would consequently lead to decreased efflux pump activity [36]. Studies showed that exposure of cells to pluronic P85 led to dramatically decreased ATPase activity in comparison to the control which contained no polymer [35].

3. FACTORS INFLUENCING THE EFFLUX-PUMP INHIBITORY ACTIVITY OF PLURONICS

The hydrophilicity/lipophilicity ratio was identified to have a direct impact on the efflux-pump inhibitory activity of pluronics [37]. In a study focussing on this topic, the efficacy of 20 pluronics with different hydrophilic (EO) / lipophilic (PO) ratios on the accumulation of rhodamine 123 into MDR cell lines (KBv) was investigated. Based on their efficacy, pluronics were divided into three groups. Group 1 comprised of hydrophilic pluronics with a hydrophilic/lipophilic balance (HLB) between 20 and 29. Representatives of this group are F68, F88, F108 or F127. Group 1 pluronics showed no or only minor effects on P-gp. The most effective P-gp inhibitors belonged to group 2 and were identified to be hydrophobic pluronics with a HLB below 19 and with 30 – 60 repeating PO units in the PO block. In this group, P85, L81 and L61 can be found. Group 3 pluronics, which are less effective than group 2 pluronics, are also hydrophobic copolymers with a HLB below 19, but the number of PO units is either lower than 30 or higher than 60. Representatives of group 3 pluronics are L35, L44 or L121 [37]. It was shown that only the group 2 pluronics were transported to the inside of the cells, and that group 2 pluronics showed the strongest effect on ATP depletion as well as on ATPase inhibition. The properties of the 3 groups are summarized in Table 1.

Another important factor which is not directly related to the hydrophilicity/lipophilicity ratio of various pluronics but which strongly influences the efflux pump inhibitory activity of pluronics is micelle formation. Above a certain concentration, the so called “critical micelle concentration” (CMC), amphiphilic block copolymers self assemble into micelles. It has been demonstrated, that the efflux pump inhibitory activity of pluronics increases with increasing pluronic concentrations, but only until the CMC is reached. Above the CMC, substrate accumulation in cancer cells could not be further increased or was found to even decrease [37]. Therefore, the occurrence of pluronic unimers can be regarded as the crucial prerequisite for the efflux pump inhibitory activity of pluronics [37]. As one mechanism for efflux pump inhibition has been identified to be ATP depletion, it seems necessary that the pluronic unimers are transported into the cells in order to exert this action.

Table 1. Properties of the three groups of pluronics

	Group 1	Group 2	Group 3
Representatives	F68, F88, F108, F127	P85, L81, L61	L35, L44, L121
Character	hydrophilic	hydrophobic	hydrophobic
HLB	20 - 29	< 19	< 19
Number of PO units per PO Block	29 - 65	30 - 60	30 < or > 60
Cell accumulation behaviour	No cell accumulation	Accumulation in the cytoplasm	Accumulation in the intracellular endosomal compartments, not released in the cytoplasm
Inhibitory activity	-	+++	+

4. APPLICATION IN CANCER THERAPY AND DRUG DELIVERY

Based on their ability to inhibit efflux pump transporters, pluronics have been utilized in cancer therapy as well as in order to overcome the blood brain barrier (BBB). The BBB is known to prevent the transport of certain drugs to the brain. Brain microvessel endothelial cells which form tight extracellular junctions and display low pinocytic activity as well as efflux pumps that remove drugs from the epithelial cells have been identified to be responsible for the limited transport [38]. As pluronics are capable of inhibiting efflux pumps, an improved transport of efflux pump substrates through the blood brain barrier in presence of pluronics was anticipated [39]. The potential of pluronics for BBB delivery has been reviewed in detail previously [30]. Miller et al. [27] were maybe the first who demonstrated a concentration dependent inhibitory activity of pluronic P85 by monitoring the accumulation of rhodamine 123 in brain microvessel endothelial cell (BMVEC) monolayers. Extensive data of *in vitro* permeation studies using bovine brain microvessel endothelial cells (BBMEC) and a broad variety of efflux pump substrates including e.g.: etoposide, doxorubicin and paclitaxel that show an improved apical to basolateral drug transport are available [40]. In addition, *in vivo* studies that demonstrate the efficacy of pluronics to improve the transport of efflux pump substrates through the BBB have been performed. As way of example, the brain accumulation of digoxin in wild type mice, *mdr1a* knockout mice and wild type mice treated with pluronic P85 was investigated and it was reported that in the presence of pluronic a prolonged residence time and an increased concentration of digoxin in the brain was observed [39]. Another physiological barrier besides the BBB which displays efflux pump expression and which can limit drug transport is the intestinal mucosa. Drug transporters located in the intestine have been identified to be responsible for the low oral bioavailability of a number of efflux pump substrates. Moreover, it has already been demonstrated in various studies, that the oral bioavailability of efflux pump substrates can be improved by co-administrating efflux pump inhibitors [20,26].

A review article focussing on the applications of pluronics in cancer therapy has been published previously [41]. Apart from their efflux pump inhibitory activity, pluronics are promising agents in cancer therapy because they affect drug sequestration and the GSH/GST detoxification system, which is also discussed in the mentioned review article [41]. The *in vivo* efficacy of pluronic formulated doxorubicin for the treatment of various different kinds of cancer has been demonstrated [42]. It was concluded that the enhanced cytotoxicity of

anticancer agents in the presence of pluronics can at least partly be assigned to P-gp inhibition. An enhanced doxorubicin accumulation in P-gp expressing cells was observed in the presence of pluronics, whereas such an effect was not observed when using non P-gp expressing cell lines [37,43]. These findings were supported by studies in which it was shown that the accumulation and permeation of various P-gp substrates was enhanced in the presence of pluronics when using MDR1 transfected cell lines. In contrast, no or only minor effects were observed in non-transfected cells [39,44]. In addition, no enhanced accumulation of non-P-gp substrates in neither resistant nor sensitive cell lines was observed [27,39,45]. Besides the capability of pluronics to inhibit P-gp, there is evidence that pluronics can also inhibit other efflux pumps including MRP1 and MRP2. However, a comparison of the effect of pluronics on P-gp ATPase activity and MRP1/MRP2 ATPase activity revealed that the effect on P-gp ATPase activity was more pronounced than that on MRP1/MRP2 ATPases [46].

5. CONCLUSION

The potential of pluronics to inhibit efflux pumps and their efficacy in cancer therapy as well as drug delivery has been demonstrated in numerous studies. Especially an intended use of pluronics for cancer therapy is very promising and a plethora of data is already available. In conclusion, the ability of pluronics to inhibit efflux pumps is believed to play an important role in the development of novel drug formulations in the near future.

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Chapter 8

THE ABSENCE OF PHYSICAL AGING EFFECTS IN THE SURFACE REGION OF GLASSY POLYMERS

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ABSTRACT

The effects of physical aging near the surface region of glassy polymers are studied via the relaxations of (1) surface topographic features created by rubbing, and (2) the rubbing induced birefringence (RIB). Extensive experimental results are presented to show that physical aging processes that would have drastic effects on the relaxations of bulk polymers have little effects on the relaxations of rubbed surfaces. We also found that surface topographic features, such as ditches and ridges created by rubbing, relax at temperatures at about 20 °C below the bulk glass transition temperature of the polystyrene for the molecular weight of 442 kg/mol, even though the Laplace Pressure driving the relaxation is 1/500 of the yield limit. The relaxation of RIB in polystyrene (PS), its derivatives with modified side group, and polycarbonate (PC), involves only the length scale of the order of an individual segment. A phenomenological model based on individual birefringence elements is proposed for the RIB relaxation. The relaxation times (RT's) of the elements are found to be independent of the thermal or stress history of the samples, either before or after the formation of the birefringence. The RT's are also independent of the molecular weight, rubbing conditions, and film thickness, while the RT's distribution function does depend on the molecular weight and rubbing conditions. The model provides quantitative interpretations that agree very well with all the reported experimental results, and sheds important light to the novel behaviors of the RIB relaxation. The absence of physical aging effects is probably due to the combined effects of small length scale of the RIB relaxation, and the accelerated aging speed in the near surface region. This is consistent with the mobility enhancement in the surface layer previously reported in the literature.

PART I. INTRODUCTION

Upon cooling a polymer melt or rubber, its volume (enthalpy) begins to deviate from the equilibrium liquid value at glass transition temperature (T_g) that depends upon the cooling rate. When the cooling is stopped the glass spontaneously evolves towards its equilibrium thermodynamic state (volume or enthalpy) [1]. Associated with the changes in thermodynamic structure are the changes in the mechanical, dielectric, etc., responses of the material that have come to be referred to as physical aging [2]. In general, the behavior of the physical aging response for the linear viscoelastic properties of polymers is widely accepted to follow the broad outlines put forward by Struik [2] and often referred to as following a time-aging time superposition principle analogous to the time-temperature superposition found in viscoelasticity of polymer melts [3].

For creep compliance, typical value of the characteristic time τ_0 of polystyrene (PS) at 60 °C in thermodynamic equilibrium state is well beyond the realistic experimental time scale [3], but its value of a sample freshly quenched from above T_g (~ 100 °C) is many orders of magnitude smaller than the one in equilibrium state [1]. PS pre-strained below T_g also exhibits much shorter τ_0 at 40 °C [4]. The compliance curve then shifts to longer time along the logarithmic time axis as the aging time increases, following the time-aging time superposition principle. Compliance curves at different aging times can be shifted to form a master curve. If the evolution of the creep compliance is viewed as the relaxations of microscopic segmental units, then all the time constants of the relaxation elements are shifted by the same factor (thermorheologically simple) [1]. Thermal quench aging and stress aging behave qualitatively the same [1] [2] [4]. Quantitatively there are differences. The time-aging time exponential factor is smaller for increasing strain [4]. It is modeled in the strain dependent aging clock theory [5]. Recent constitutive theory based on Holmholtz free energy can fit a wide range of physical aging phenomenon quantitatively [6].

Aging in glassy polymer films were also investigated in the frame of solvent induced glass transition [7] [8]. Results are utterly different from those obtained with equivalent temperature cycles. Hysteresis at small activity as well as complex behavior of the melting time depending on the quench amplitude had been observed. This behavior was attributed to the possible coupled evolution of the free volume and the solvent fraction.

Physical aging also exists in thin films. The gas permeability of 400 nm thick polysulfone decreases when the films continued to densify [9]. Thin films age faster in gas permeability [10]. Kawana and Jones reported [11] thin supported films of PS aged below T_g exhibit clear overshooting in expansivity temperature curves when reheated for thicknesses of 18 nm or more, but not for a thickness of 10 nm, suggesting the existence of a surface layer of the order of 10 nm in which aging is complete within the time scale of 10^3 s, while the rest of the film essentially has thermal properties identical to bulk samples.

In this article we review the work on the effects of physical aging in the region near the surface of glassy polymers. In Part-II the relaxation of topographic features of PS surface is examined. In Part-III the relaxation of RIB in PS is examined. In Part-IV the relaxation of RIB in PS derivatives and polycarbonate (PC) is examined. In Part-V we conclude.

PART II. TOPOLOGICAL RELAXATION OF POLYSTYRENE SURFACE

1. Introduction

The dynamics of polymer surfaces is an intriguing subject in polymer physics, in addition of being of significant technological importance. There has been much experimental evidence that demonstrate the existence of a surface mobile layer [12 – 24]. Positron annihilation [12] and muon spin probes [13] indicated the presence of a surface mobile layer about 2 nm in thickness near the polystyrene (PS) surface. The T_g of PS thin films were found to decrease drastically with the reduction of thickness [14] [15], and later studies revealed the broadening of the glass transition in polymer thin films with depth [16] [17] [18]. These phenomena were attributed to the existence of a liquid-like surface layer that extended deeper with the rise of temperature and diverged at bulk T_g . Surface friction force microscopy also showed a significant decrease in T_g of the surface layers [19] [20] [21]. The higher mobility of the surface layer was attributed to the chain ends enrichment at the surface, which was confirmed by experiments [20]. Gold spheres of 10 nm and 20 nm in diameter placed on PS surfaces were found to sink into PS at temperatures well below bulk T_g [22] [23], and the phenomenon was interpreted as due to the presence of a liquid-like surface layer. Rough PS surfaces were found to turn mobile at temperatures well below T_g under the driving force of Laplace Pressure [24].

Despite of the rich evidence listed above, there are a few equally strong experimental evidence that seem to contradict the presence of such mobile layer [25] [26]. Using a vigorous viscoelastic mechanic contact analysis, Hutcheson and McKenna showed that the sinking of gold spheres on PS surface could actually take place without the decrease in surface T_g [25]. The creep compliance of 30 nm thick PS films was found to have a lower T_g but a much stiffened rubbery plateau than the bulk value [26]. A direct measurement of the local segmental mobility as a function of depth from surface is strongly desired. But such an experiment without disturbing the segmental motions near the surface would be a rather difficult challenge. However, if physical aging is fast in the near surface region and can come to completion within reasonably short time ($\sim 10^3$ s), the complication of physical aging effects on the dynamic properties of surface will no longer be present and the analysis of the properties of surface relaxation could be simplified.

Gentle rubbing with a velvet cloth on PS surfaces can create molecular segment alignment and distortion [27] [28], in addition to surface ridges and ditches with depths and heights of the order of nanometers. The relaxations of the rubbing induced optical birefringence [29] [30] [31] and the segmental alignments [27] [28] [32] were investigated. These relaxations, however, occurred at even lower temperature than the surface topography relaxations [31]. Preliminary experimental evidence showed that the birefringence relaxation is also independent of the aging effects [31].

We study the evolution of the topological features of rubbed surfaces of samples undergoing various aging processes. The approach is similar to creep experiments that are widely employed in the study of segmental relaxations in bulk polymers, but with two distinctions. One is that here the stress due to the Laplace Pressure (LP) from the surface topographic features, such as ditches and ridges created by rubbing, is present at all time until

the surface is mostly flattened. The other more important one is that the process to generate the initial roughness (by rubbing with a velvet cloth) introduces large mechanical deformation on the surface, and deformation is known to greatly accelerate the relaxations in bulk samples [4]. Extensive experimental results will be presented to reveal the relaxations of PS surfaces deformed by rubbing with velvet cloth. We found that the dominant driving force of the relaxations is the LP due to the surface topographic features. The surface layer turns to rubbery at about 20 °C below the bulk glass transition temperature for the molecular weight of 442 kg/mol, even though the LP is only about 1/500 of the yield limit. However, this is not due to the accelerated relaxations caused by large mechanical deformation often observed in bulk samples, because the relaxation is independent of the thermal aging before the rubbing process, and post rubbing aging below 55 °C. In other words, the effects of these physical aging processes that would have great influence on the relaxations of bulk polymers are completely absent in the relaxations of surface strain.

2. Experiments

Mono-dispersed PS with molecular weights 442 kg/mol ($M_w/M_n < 1.1$) in toluene solution was spin coated on silicon wafers with 20 nm of thermal SiO₂ to form 62 nm films. The samples were then annealed in vacuum at 150°C for several days to completely drive off the solvent before slowly cooled down (< 0.1 °C/min) to room temperature. These will be referred to as *fresh samples* from now on. Rubbing was done at normal pressure of 90 kg/m² and at a constant speed of 1.0×10^{-2} m/s at 23 °C. Each rubbing run consisted of 90 passes, with each pass covering 2.0 cm distance. All were done in ambient atmosphere so no solvent induced effects occurred [7]. The samples were thick enough that possible influence of the PS/substrate interface was avoided. This was confirmed by PS films on two types of substrates, namely the SiO₂ which is known to have weak interaction, and hydrogen terminated Si which is known to have strong interaction with the PS films [33]. No difference in surface strain relaxations was observed for the films on the two types of substrates.

For the sake of completeness, the samples investigated were divided into two series, namely the A-series and the B-series. Starting from *fresh samples*, the A-series samples underwent thermal aging processes *before* rubbing, while the B-series samples underwent thermal aging processes *after* rubbing. There are three possibilities of aging effects. The first is that the aging prior to rubbing affects the morphology of the rubbed surfaces and their subsequent relaxations. The second is that due to large mechanical deformation the previous thermal history is ‘erased’ by rubbing so the relaxation depends on post rubbing aging only. The third is that the aging has no effect on the surface relaxation. The study of the A-series samples will substantiate or rule out possibility-1. If possibility-1 is ruled out, the study of the B-series samples will then decide whether possibility-2 or -3 is true.

The surface topography was measured on a scanning probe microscope (SPM) in tapping mode. The lateral resolution is about 10 nm and the height resolution is about 0.1 nm. An on-stage heater provided the controlled thermal processes (aging and annealing). The measurement sequences were the same for both the A-series and the B-series samples. The samples were measured using either type-I or type-II measurement sequences. In the type-I measurement sequence, the sample was first raised quickly from 23 °C to the annealing

temperature (say 40 °C), kept there for 0.5 hours, then quickly cool down to 23 °C. SPM measurements were then carried out on a selected $5 \times 5 \mu\text{m}^2$ area and completed within 1 hour at 23 °C. The process was then repeated but with a higher annealing temperature, until the surface had flattened. In the type-II measurements, the sample temperature was quickly raised to a fixed value (say 85 °C) for a certain duration (say 0.5 hours), then quickly cooled down to 23 °C for SPM measurements. The process was then repeated except that the duration (annealing time) the sample temperature was maintained at the given value was progressively longer. In all, the annealing times were 0.5 hours, 1.0 hours, 3.0 hours, and 10 hours. This resulted in the accumulative annealing time of the samples as 0.5 hours, 1.5 hours, 4.5 hours, and 14.5 hours. In both measurement sequences the total time taken to measure the viscoelastic response of the samples (< 20 hours) was much shorter than the aging times (up to 7 days). Several images of nearly the same area were analyzed in both sequences. Using recognizable topological features, a smaller but identical area was selected from the set of micrographs for analysis. This enabled us to track the evolution of particular topological features such as ditches and ridges, as well as statistical averages such as the root mean square roughness $\sqrt{\langle h^2 \rangle - \langle h \rangle^2}$, over the whole area. The main reason SPM was carried out only at 23 °C was that the PS surfaces remained frozen at such low temperature, where no detectable change of the topographic features was found in any samples up to 7 days. The surfaces undergoing relaxation at elevated temperatures were frozen once they were quickly cooled to 23 °C, allowing ‘snap shots’ to be taken without the surfaces going through continuous changes.

3. Results and Discussions

3.1. Typical surface relaxation behavior

A reference sample (Sample-A1), which was a *fresh sample* rubbed and then measured within one hour, was studied first. Figure 1 shows a typical topographic image of the sample surface just after rubbing (Figure 1(a)), and after consecutive 30-minute annealing at 40 °C, 50°C, 60°C, 70°C, 80°C, 90°C, and 100°C (Figure 1(b)), following the type-I measurement sequence. The fresh surface contains ditches and ridges along the rubbing direction. A ‘roughness spectrum’ obtained from the Fourier transform of a line scan across the rubbing direction is shown in Figure 1(c). The dominant features are about a fraction of micrometer in width. Features less than 20 nm are nearly absent. However, it is possible that there are smaller features that cannot be resolved by the limited lateral resolution of the AFM tip. Our analysis is therefore limited to the features that can be resolved in our instrument, which is comparable to the study reported in Ref. [24]. The surface remained unchanged up to 80°C. The deep ditches that had survived the annealing at 100°C can be matched well with the original ones before annealing. The images taken after annealing above 80°C show that the general evolution pattern of the surface was a nearly uniform reduction of the height of the ridges and the depth of the ditches, so the shallow ditches and low ridges disappeared first. No lateral (horizontal and perpendicular to ditch/ridge) movement of the ditch/ridge walls was observed. The center positions of the ridges and ditches remained unchanged. At 100°C the reduction in height or depth across the entire area ranged between 2 – 3 nm, and the shallow ditches with original depth < 2 nm were smeared out. There was no irregular local

stress driven relaxation [34], indicating that the LP was the main driving force [24]. This is consistent with the statistical aspect ratio data in Ref. [24]. The average height differences $\langle \Delta h \rangle_{line}$ between several ditch/ridge pairs, a typical one being marked by a pair of small arrows at the bottom of Figure 1(a), are plotted as a function of annealing temperature in Figure 1(d). It is seen that the reduction of $\langle \Delta h \rangle_{line}$ with annealing temperature follows the same trend, regardless of the initial height differences of the pairs. In particular, the reduction from 23 °C to 100 °C is 3.4 ± 0.4 nm for all the pairs with initial height difference ranging from 5 nm to 11 nm. This is true for all other samples reported in this study. Figure 2 depicts the average roughness over the whole area $\langle \Delta h \rangle_{area}$ as a function of annealing temperature together with that of the other four samples underwent various aging processes to be described later. The behavior of the average roughness resembles that of the height differences of the ridge/ditch pairs shown in Figure 1(d). Noticeable changes of morphology features (≥ 0.1 nm) occurred only at ≥ 80 °C, and the decrease in roughness was rather rapid beyond this point. Because the average roughness $\langle \Delta h \rangle_{area}$ and the individual ridge/ditch $\langle \Delta h \rangle_{line}$ relaxations behaved the same, the average roughness $\langle \Delta h \rangle_{area}$ will be used as the indicator of the surface relaxations in the rest part of the article.

The main driving force to flatten a rough polymer surface is the Laplace Pressure $P = \gamma_0 / \rho$ [24], where $\gamma_0 = 0.035$ N/m is the surface energy of PS [25] [35], and ρ is the surface curvature along the direction normal to the surface. In the case of an indent of radius w and depth h , the effective radius is approximately given by $\rho = \frac{w^2}{4h}$, assuming that the arc passes through the middle point of the bottom and the edge of the indent. The same applies to a long ditch of width w and depth h . The LP becomes

$$P = 4\gamma_0 h / w^2 \quad (1)$$

Typical depth (height) and width of ditches (ridges) in Figure 1 ($h \approx 10$ nm, $w \approx 100$ nm) gives rise to $LP \approx 1.4 \times 10^5$ N/m², and varies by a factor of < 4 across the surface. This is about 1/500 of the yield stress of PS [4], so the relaxation was under a driving force well below the yielding limit [36].

The reduction of roughness on the surface is given by, in analogy to conventional creep theory,

$$C = PJ(T, t) \quad (2)$$

where C is the ‘relative deformation’ with the freshly rubbed surface as the reference, P is the Laplace Pressure, t is the time and $J(T, t)$ is the surface effective compliance (SEC), which is expected to be a sensitive function of temperature T . Its counterpart, the bulk creep compliance, also depends sensitively on the thermal history of the sample, i. e., the effects of physical aging [1]. As the width w remains unchanged the average LP of the area under investigation is proportional to the roughness, and the ‘relative deformation’ is proportional to the change of roughness.

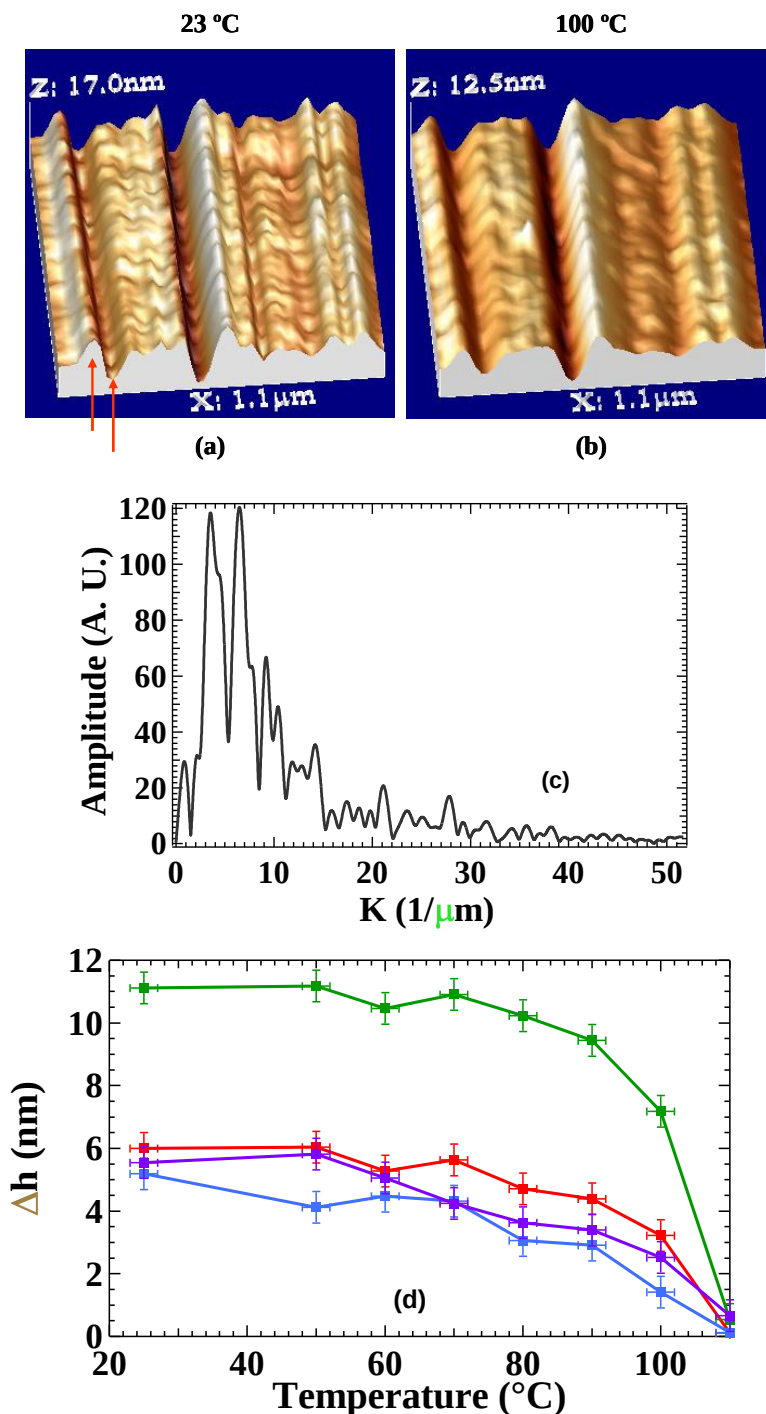


Figure 1. (a) SPM image of a rubbed PS surface; (b) SPM image of the same area as (a) after annealing at consecutive temperatures up to 100 °C described in the text; (c) A roughness spectrum obtained from the Fourier transform of a typical line scan across the ridges and ditches in Figure 1(a); (d) The height difference of selected ridge/ditch pairs as a function of annealing temperature. All the images were taken from a reference Sample-A1, i. e., it was in thermal equilibrium before rubbing and the measurements were taken right after rubbing.

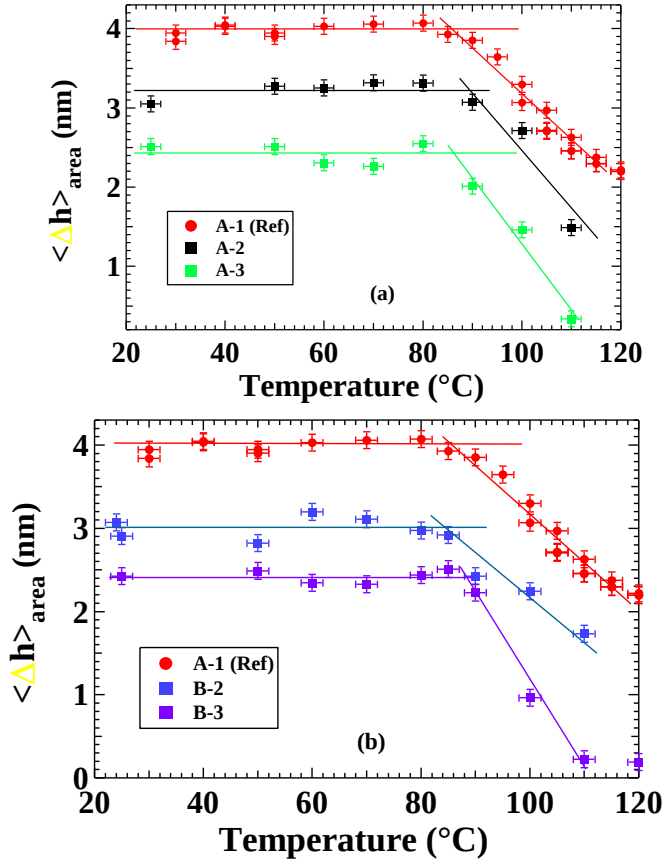
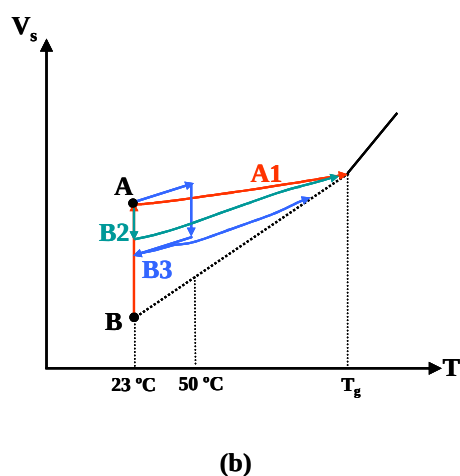
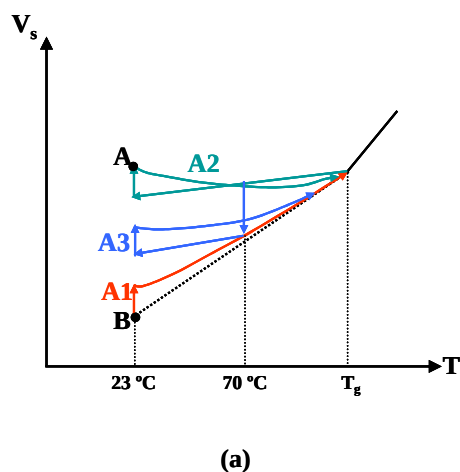


Figure 2. (a) The surface average roughness versus temperature curves of the reference sample and the A-series samples underwent various aging processes before rubbing. The points for A-1 have been shifted upwards by 1.0 nm, while that of the A-3 have been shifted down by 0.5 nm. (b) The surface average roughness versus temperature curves of the reference sample and the B-series samples underwent various aging processes after rubbing. The points for A-1 have been shifted upwards by 1.0 nm, while that of the B-3 have been shifted down by 0.5 nm.

Consider the red curve in Figure 1(d) as an example. At 90 °C the reduction of height difference $\langle \Delta h \rangle_{\text{line}}$ as compared to the fresh surface is about 1.5 nm from the initial 6.0 nm value. For the sake of discussions we take two extreme scenarios. If the entire 62 nm film is involved in the relaxation one obtains a relative change along the film depth of about 2.5 %. Since the LP is only 1.4×10^5 Pa, it results in an average compliance over the entire film depth of about 1.8×10^{-7} Pa⁻¹, much higher than the bulk compliance in glassy state ($J_G = 8.5 \times 10^{-10}$ Pa⁻¹). If only the initially deformed layer (~ 6.0 nm) is taken as reference the relative change is then 25 %, and the compliance is close to that of the bulk rubbery plateau ($J_R = 6.1 \times 10^{-6}$ Pa⁻¹). The actual situation is probably somewhere in between, but even in the extreme case the effective compliance is still much higher than J_G . In the meantime, as no lateral movement of ditches and ridges was observed, and considering the fact that the spacing between ditches is hundreds of nanometers as compared to the film thickness of 62 nm, the randomly distributed local stress [34], if ever present, must be at least 200 times smaller than the LP.



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Figure 3. (a) The schematics of the free volume evolution of A-series samples. (b) The schematics of the free volume evolution of B-series samples.

The change of surface topographic features in glassy state under the present LP is expected to be about $\sim 1.2 \times 10^{-4}$ in relative change and $\sim 8 \times 10^{-3}$ nm in actual displacement, which is well below the SPM detection limit. Therefore, only when the surface is near the rubbery state can the displacement be detected. For a ditch 10 nm deep, a height reduction of 3 nm due to the increase of temperature from 23 °C to 100 °C reduced the original LP by only 30 %, while the SEC changed by several orders of magnitude. It is therefore a good approximation to take LP as nearly constant when analyzing the drastic change of SEC with temperature, and the roughness (height difference) versus annealing temperature curves in Figure 1(d) and Figure 2 therefore represent a measure of the viscoelastic SEC as a function of temperature within a fixed time scale of 30 minutes. In the following, we examine the physical aging effects on the roughness versus temperature curves of samples undergone different thermal processes. In particular, we concentrate on the onset temperature of the glassy-to-rubbery transition, and examine the curves up to 110 °C when there was still considerable roughness left and the driving force, while somewhat weakened, was still present.

3.2. Aging before rubbing

In Figure 3(a) the bulk specific volume of the surface layers of the PS samples undergoing various physical aging processes is shown schematically. Following Struik [1] [2] we use the term ‘specific volume’ to describe the degree of deviation from thermodynamic equilibrium of the system and the enhancement of segmental mobility in general term, rather than the actual excessive volume, since mechanical deformation may not actually decrease the actual mass density but does increase the segmental mobility, or ‘free volume’ [4]. In the following discussions the speculation about the thermodynamic states of the samples is based upon the assumptions that (i) the aging behavior of the surface region of the rubbed PS follows the general trend of bulk PS undergoing the same processes; and (ii) the rubbing process places the samples away from thermodynamic equilibrium but not enough to ‘erase’ the effect of previous thermal history.

As shown in Figure 3(a), Sample-A1 was in thermodynamic equilibrium before rubbing, while after rubbing it was away from the thermodynamic equilibrium state as indicated by the dashed line below T_g . During the subsequent measurement sequence, its specific volume evolved close to the thermodynamic equilibrium line. It served as a reference sample and its surface relaxation has already been presented in sub-section 3.1.

Sample-A2 was quenched from 130 °C to 23 °C and rubbed within 10 minutes. Its specific volume is expected to be far away from the equilibrium line. During the subsequent measurement sequence, it might age slightly towards equilibrium, but it would evolve far away from the equilibrium line, and its segmental mobility is expected to be well above that of Sample-A1. As a result, its surface is expected to turn rubbery at lower temperature than Sample-A1.

Sample-A3 was quenched from 130 °C to 70 °C, aged there for 7 days, then quenched to 23 °C, and rubbed. Due to the 7 days aging its specific volume is expected to be closer to the equilibrium line than Sample-A2, but may not be as close as Sample-A1, in the subsequent SPM measurements.

Although the three samples had been under different thermal treatments before rubbing, their surface morphology characteristics after rubbing were the same. The typical ditches and ridges shown in Figure 1 were observed on all three surfaces, and the average roughness over some typical areas was about the same. This implies that before rubbing the surface of Sample-A2 was not much ‘softer’ than Sample-A1 in thermal equilibrium, which is in stark contrast with the bulk cases where a freshly quenched sample would have much higher creep compliance [1].

The subsequent relaxation behaviors of the three surfaces were the same. All the surfaces remained frozen below 80 °C, and started to turn rubbery above 80 °C. Figure 2(a) shows the $\langle \Delta h \rangle_{area}$ versus temperature curves of the three A-series samples. For clarity, the red points for the Sample-A1 are shifted up by 1 nm, and the green points for Sample-A3 are down shifted by 0.5 nm. As the LP was comparable in all three samples, their surface roughness evolution is a direct measure of the SEC as a function of temperature. Adopting the approach in determining T_g from thermal expansion curves, we use the cross point of two lines, one horizontal when the surface remains frozen and the other when the surface is relaxing, as the onset temperature of the glassy-to-rubbery transition T_R . The values of T_R are $(86 \pm 2)^\circ\text{C}$, $(88 \pm 2)^\circ\text{C}$, and $(86 \pm 2)^\circ\text{C}$ for samples A-1, A-2, and A-3, respectively. The results imply that the SEC remained unchanged by the thermal history before rubbing. Such results rule out

possibility-1 speculated in Figure 3, leaving possibility-2 and -3 for further investigations. One is that the rubbing process had effectively erased the effects of all the previous thermal history, and placed the surface layers of all three samples in nearly the same state far from thermodynamic equilibrium, such as in the neighborhood of point-A in Figure 3(a), which is well above all the volume curves due to various thermal quenches. The other possibility is that the surface layers of all samples were at point-B (in thermodynamic equilibrium) before the measurement sequence was started, due to the quick aging of the surface layer despite of the large mechanical deformation caused by rubbing. The original viscoelastic properties of the surface were therefore restored before the start of the SPM measurements.

3.3. Aging after rubbing

As discussed above, rubbing introduces large mechanical deformation to the surface, which may effectively ‘erase’ all the previous thermal history and place the surface in nearly the same non-equilibrium state. Here we study the effects of aging after rubbing. Since we found that surface features would change significantly at above 80 °C, all post rubbing aging processes reported below were done at < 60 °C.

Similar to the discussions in sub-section 3.2, in Figure 3(b) the bulk specific volume of PS samples undergoing various physical aging processes is shown schematically. We take the first scenarios as suggested at the end of sub-section 3.2, and assume that the rubbing processes placed the samples far away from thermal equilibrium, i. e, at point-A in Figure 3(b). Therefore, the reference Sample-A1 was at point-A after rubbing. Sample-B2 was aged at 23 °C for 4 days after rubbing, before being tested in the same way as the A-series samples. Assuming that the surface layer aged at a rate comparable to bulk, Sample-B2 should be closer to the thermodynamic equilibrium line than Sample-A1. Sample-B3 was aged at 50 °C for 2 days after rubbing, then quenched to 23 °C and tested. Right before testing the sample was probably closer to the equilibrium line than Sample-B2. Despite of the large differences in their thermal history after rubbing, the observed surface morphology evolution of the two samples is the same as the A-series samples. Their roughness at different annealing temperature as plotted in Figure 2(b). The transition temperature for the three samples are (86 ± 2) °C, (84 ± 2) °C, and (88 ± 2) °C for samples A-1, B-2, and B-3, respectively. These experimental results rule out the possibility that the surface layer of PS follows the aging behavior of bulk polymers.

Physical aging affects the temperature dependence of a number of dynamic responses of bulk polymers. It is well known that in differential scanning calorimetry there is a large enthalpy peak right below T_g for quenched samples, and the peak reduces as the samples age [37]. Physical aging of PS was investigated by dynamic viscoelasticity measurements [38]. The effect of physical aging was observed for samples aged at 60 and 80 °C after quenched from 190 °C. The temperature curves of the dynamic viscoelastic functions of the bulk samples right after quench and that of well aged were significantly different. The curves of the samples partially aged at 60 °C coincided with that of the quenched sample in the low temperature range. It then started to deviate from the curve at above 65 °C and gradually merged to the curve of the well aged sample at high temperature. The ‘merge temperature’ increased with the aging time. On the other hand, the curves of the samples aged at 80 °C differed from the curves of the well aged ones and the quenched samples in the entire temperature range. This is significantly different from the aging behavior of the surface viscoelastic response of our samples.

We now study the post rubbing aging using the type-II measurements, which according to the discussion in subsection 3.1, are effectively the measurements of the viscoelastic SEC versus time at a fixed temperature. The annealing temperature is 85 °C. Sample-C1 is a reference sample similar to Sample-A1 and tested within one hour after rubbing. Before the measurements Sample-C2 was aged at 50 °C for 2 days, and then quenched to 23 °C. Sample-C3 was aged at 23 °C for 7 days after rubbing. The speculation on their thermodynamic states follows the general arguments on the samples underwent similar processes.

Figure 4 shows the isothermal temporal evolution of the average roughness at 85 °C of the three samples. Individual surface topological features behaved the same as the average roughness. Following the same argument above, it is clear that at 85 °C the surface is near rubbery state. Furthermore, the temporal evolutions of the three samples are identical within experimental uncertainties. In particular, since the aging times of Sample-C1 and Sample-C3 differed by about 170 times, even at a shift rate of 0.6 [2], the bulk creep compliance curve of Sample-C3 should have shifted by a factor of 22 ($= 170^{0.6}$) relative to Sample-C1 along the time axis. Had the SEC followed the bulk creep compliance, it would have taken 22 hours for the roughness of Sample-C3 to decrease by the same amount as Sample-C1 in 1.0 hour. Similarly, the bulk shift factor at 50 °C is about unity, and the aging time of Sample-C2 was 48 times of that of Sample-C1, so the time shift factor between Sample-C2 and Sample-C1 is about 48, i. e., it would have taken more than 48 hours for the roughness of Sample-C2 to decrease by the same amount as Sample-C1 in 1.0 hour. No detectable drop in its roughness should have been observed within the experimental time span of 14.5 hours. The fact that the SEC of all three samples behaved the same is consistent with a surface layer in which aging effects are absent.

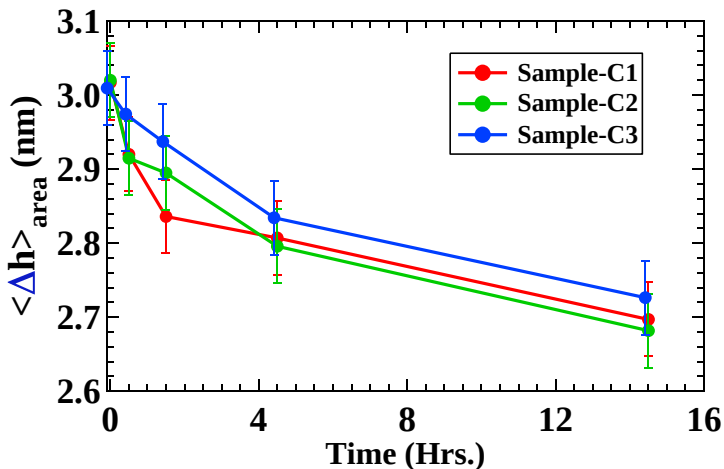


Figure 4. The isothermal temporal evolution at 85°C of the surface average roughness of three samples aged according to the description in the text.

3.4. Discussions

The experimental results in this paper show that the aging effects are absent in the relaxation of surface of PS. This implies that in the surface region either aging was complete within an hour at room temperature, or aging was extremely slow that even after 7 days no noticeable effects could be observed, a very unlikely scenario that is in stark contradiction to

the previous reports [9] [12 – 24]. As the surface ages quickly, the deformed surface recovers its thermodynamic properties within the 1 hour time scale. We therefore suggest that their viscoelastic properties determined from the evolution of surface topographic features at elevated temperatures are the intrinsic properties of PS surfaces. Indeed, relaxations of surfaces deformed in two different ways, namely by rubbing below T_g (like cold rolling), and by deformation above T_g (like hot drawing) [24], behaved much the same. It is consistent with the findings in Ref. [11] that physical aging effects were absent in PS films 10 nm thick, and is consistent with the general expectation of the enhanced mobility in the surface layer.

The observed surface relaxation behaviors, apart from their independence on physical aging, are themselves intriguing. For example, in bulk creep experiments, the deformation of the specimen creates internal stress that counter balances the external force until reaching the balance point before the rubbery plateau is reached over a long period. In the surface relaxation studied here, the only ‘counter balance’ is the reduction of LP due to the reduction of roughness. As seen in Figure 4, the roughness decrease in the first 4 hours is about 0.2 nm, which is twice the decrease (0.1 nm) in the following 10 hours. In other words, the relaxation rate became slower with increasing time. Such behavior cannot be accounted for by a film with uniform compliance that remains constant or *increases* with time as in the bulk, because it cannot explain why under nearly the same LP (reduced by only 10 %), the reduction of roughness becomes much slower at longer time. Instead, it hints a depth dependent compliance which is much enhanced at the surface. As the absence of aging effects has been established in this work, the stage is set for the detailed analysis of these surface relaxation behaviors, which will be reported in our subsequent publications.

4. Conclusion

Extensive experimental results have been presented to reveal the relaxations of polystyrene surface deformed by rubbing with velvet cloth. We found that the relaxations were mostly driven by the Laplace Pressure due to the surface topographic features, such as ditches and ridges created by rubbing. The relaxation at elevated temperatures was dominated by a nearly uniform reduction of the depth of the ditches and the height of the ridges across the surface, while the centers of these topological features remained fixed. There was no lateral movement (perpendicular to the ditches/ridges) of ditch/ridge walls. The randomly distributed stress, if present, was at least 200 times smaller than the Laplace Pressure. For PS with molecular weight of 442 kg/mol the surface layer turned to rubbery at about 20 °C below the bulk glass transition temperature, even though the Laplace Pressure was only about 1/500 of the yield limit. This, however, was not due to the accelerated relaxations due to mechanical deformation, a phenomenon well known in bulk polymer samples, because the relaxation was independent of the thermal history before the rubbing process, and post rubbing history below 50 °C. Physical aging processes at 23 °C for up to 7 days and at 50 °C for 2 days, which would have drastic effects on the relaxations of bulk polymers, have little effects on the relaxations of strained surfaces. This is consistent with the observed mobility enhancement in the surface layer. The observed enhanced mobility of the surface layer is most likely the intrinsic property of a polymer surface, which is consistent with many previous experimental results.

PART III. RELAXATION OF RUBBING INDUCED BIREFRINGENCE IN POLYSTYRENE

1. Introduction

The relaxations and related dynamic properties of glass forming polymers have been extensively studied in the past decades [39 - 48]. The birefringence of polystyrene (PS) uniaxially drawn at above the glass transition temperature (T_g) remains almost unchanged at temperatures below T_g . Above T_g there are three well separated relaxation steps with distinct time scales τ_1 , τ_2 , and τ_3 [40]. The relaxation of the segmental alignment dichroism of cold rolled PS at 60 °C can be fitted by two single exponential functions of time with relaxation times of 76 s and 3600 s [39]. Many other relaxation processes below T_g follow the Kohlrausch-Williams-Watts (KWW) stretched exponential function [41] [42] [43]:

$$\phi(t) = \phi(0)e^{-t/\tau_0^\beta} \quad (1)$$

These include creep compliance [41], density fluctuations [42], volume relaxation of quenched PS [43], etc..

Unlike the cold rolled or hot drawn PS where the polymer specimen is usually elongated by several times of its original length, rubbing with a velvet cloth on a PS surface at a modest pressure of ($\sim 9 \text{ g/cm}^2$) and speed ($\sim 1 \text{ cm/s}$) creates segmental alignment and segmental distortion, mostly within the top 20 nm layer near the surface [27] [31]. The surface layer is severely deformed, with ditches up to 5 nm deep, but the average thickness of the PS film, as measured by ellipsometry, remains unchanged, implying that little materials are removed by the rubbing cloth. The majority ($> 89 \%$) of the rubbing induced birefringence (RIB) in PS comes from the segmental distortion. Only less than 11 % comes from the segmental alignment [27]. For a 20 nm thick PS, the RIB can be as large as 20 % of the intrinsic value of undistorted PS segments. The RIB relaxations of a number of polymers were first studied by Kovacs and Hobbs [44], and more recently by a number of groups [27] [28] [30] [31] [45], but there is no consistent theoretical interpretation [30] [45] [46].

Upon cooling a polymer melt, its volume (enthalpy) begins to deviate from the equilibrium liquid value at T_g that depends upon the cooling rate. When the cooling is stopped the glass spontaneously evolves towards its equilibrium thermodynamic state (volume or enthalpy) [1]. Associated with the changes in thermodynamic structure are changes in the mechanical, dielectric, etc., responses of the material that have come to be referred to as physical aging [2]. In general, the behavior of the physical aging response for the linear viscoelastic properties of polymers is widely accepted to follow the broad outlines put forward by Struik [2] and often referred to as following the time-aging time superposition principle analogous to the time-temperature superposition in the viscoelasticity of polymer melts [3].

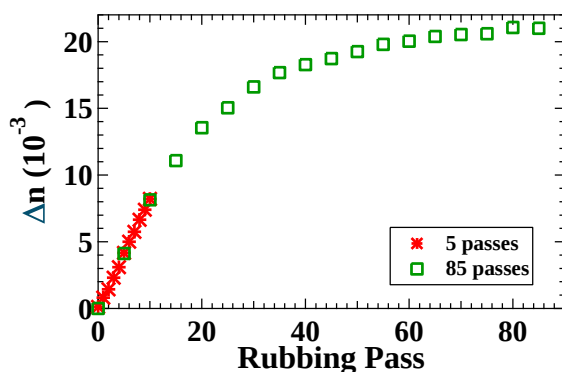


Figure 5. Rubbing induced birefringence versus rubbing pass of two *standard* samples.

The characteristic time τ_0 of the creep compliance of PS at 60 °C in thermodynamic equilibrium state is well beyond the realistic experimental time scale, but its value of a sample freshly quenched from above T_g (~ 100 °C) is many orders of magnitude smaller [1]. PS pre-strained below T_g also exhibits much shorter τ_0 at 40 °C [4]. The compliance curve then shifts to longer time along the logarithmic time axis as the aging time increases, following the time-aging time superposition principle. Compliance curves at different aging times can be shifted to form a master curve. If the evolution of the creep compliance is viewed as the relaxations of microscopic segmental units, then all the time constants of the relaxation elements are shifted by the same factor (thermorheologically simple) [1]. Thermal quench aging and stress aging behave qualitatively the same [5]. Quantitatively there are differences. The time-aging time exponential factor is smaller for increasing strain. It is modeled in the strain dependent aging clock theory [5]. Recent constitutive theory based on Holmholtz free energy can fit a wide range of physical aging phenomenon quantitatively [6]. This is the characteristics of the cooperative relaxation that it depends sensitively on global thermodynamic states.

As the RIB is due to segmental alignment and distortion, it is most relevant to examine the RIB relaxation in the context of segmental relaxations below T_g . And in such regime physical aging is expected to play an essential role. Our preliminary results indicated [31], however, that the RIB relaxes in a way that is characteristically different from any other known forms of relaxation in glass forming polymers. In this part, we explore further along this line. In particular, conventional segmental relaxation times (RT's), such as the parameter τ_0 in Eq. (1), strongly depend on the thermal and strain history, in addition to temperature [1] [4]. Extensive results will be presented to show that the RIB RT's are independent of the thermal and strain history, while having about the same temperature dependence as the conventional segmental relaxations.

This part is divided in the following way. After Introduction (Section-1) and Experiments (Section-2), experimental evidence to prove the absence of physical aging effects on the relaxation of RIB is presented in section-3. In section-4 a phenomenological model based on a generic energy barriers distribution is presented. In section-5 extensive experimental results are analyzed based on the model. The model provides quantitative interpretations that agree very well with all the reported experimental results, which in turn further confirms the absence of physical aging effects. And in section-VI we summarize the main conclusions.

2. Experiment

The details of the experiments can be found in Ref. [46]. Briefly stating, PS in toluene solutions was spin-coated on thermally grown SiO₂ on silicon substrates. The samples were then annealed at 130 °C in vacuum for at least 24 hours, and slowly cooled down (< 0.1 °C/min) and stored at room temperature before testing. The thickness of the resulting PS films ranged from 7 nm to 50 nm depending on the solution concentration and spin speed. These samples will be referred to as *fresh samples*. As many samples were used in the study, a *standard* film thickness of 30 nm is taken unless otherwise specified. Fresh samples rubbed to saturation but without going through any other rubbing and thermal processes will be referred to as *reference samples*. Rubbing was done on a home-made apparatus. Each rubbing pass covered 2 cm distance at a speed of 1 cm/s in one direction, with a normal pressure of 9 g/cm². The optical RIB of the PS films was measured using the reflectance difference spectroscopy at 633 nm in wavelength.

Various thermal and rubbing processes were imposed on the test samples, and their effects on the RIB relaxation behaviors of the samples were studied by using the following ‘standard’ tests. The first was to measure the normalize birefringence (*NB*) as a function of temperature when the sample temperature was raised continuously at 2 K/min. The results are referred to as the *Continuous Curves* $\Delta n(T)$. The second was the isothermal relaxation of *NB*, i. e., the *NB* of a sample was measured as a function of time at a fixed temperature. Note that the isothermal relaxation process also served as physical aging as both are expected to take place. The third was the combination of the two, i. e., a continuous temperature increase at 2 K/min after an isothermal process at a given temperature for a given period of time.

3. Physical Aging

In this section, we examine the effects of physical aging on the relaxation of RIB.

3.1. Rubbing induced birefringence

Figure 5 depicts a typical plot of RIB vs rubbing pass at 23 °C of two fresh PS samples with molecular weights (M_w) of 99 Kg/mol. For the first sample, the RIB was recorded after each rubbing pass up to 10 passes. For the second sample the birefringence was recorded at every 5 passes. The birefringence increased quickly with the first few rubbing passes, and then gradually approached the saturated value. More than 70 % of the total birefringence was generated by the first 20 passes, and the subsequent 65 passes created the remaining birefringence. Further rubbing after saturation resulted in destroying roughly the same amount of birefringence as creating it, and the net birefringence fluctuated around the saturation value with amplitude of about 1 % of the saturation value. There was also a birefringence transient, which is not shown in the figure, of $\Delta n \approx 1.0 \times 10^{-4}$ that relaxed within 30 s after each pass. The net birefringence value of each sample was measured within 100 s after the completion of the relaxation of the transient birefringence due to the last rubbing pass. It was then used as the normalization factor in determining the *NB* in the subsequent relaxation studies. After the completion of the transient, the birefringence relaxed slowly, decreasing by about $\Delta n = 1.0 \times 10^{-4}$ in the first hour after rubbing. The maximum

saturation birefringence was about 20 % of the intrinsic segmental alignment value [40]. However, since only about 10 % of the birefringence was from the segmental alignment and the rest from the segmental distortion [27], the degree of segmental alignment was around 2 % [40]. This could be highly non-uniform, however, with higher concentration close to the surface and decreasing with depth. The intrinsic maximum birefringence of segmental distortion is not known to the best of our knowledge, leaving the degree of segmental distortion still undetermined.

3.2. Typical relaxation behaviors of RIB and surface morphology

Besides the RIB, rubbing also creates grooves on the surface which flatten and finally disappear at elevated temperatures, as reported in Part-II. One issue of significance is whether the relaxations of RIB and surface morphology are related. A typical *Continuous Curve* of RIB of a reference sample with $M_w = 99$ Kg/mol is shown in Figure 6(a), along with the evolution of surface morphology roughness (points) measured by atomic force microscope (AFM) in tapping mode. The RIB had completely relaxed near 114 °C. If a freshly rubbed sample is heated to 130 °C within seconds, all its RIB will disappear within 30 s. A portion of the AFM images are shown in Figures 6(b) and 6(c). The micrographs of nearly the same $5 \times 5 \mu\text{m}^2$ area were recorded at 23 °C after each annealing at the given temperature for 30 minutes. Using recognizable topological features, such as the crossing of two ditches as markers, a smaller but identical area was selected from the set of micrographs for analysis. The surface Laplace Pressure is estimated as 1.4×10^5 N/m², and varies by a factor of < 4 across the surface. This is about 1/500 of the yield stress of PS [4]. Careful tracking of the individual topographic features showed that noticeable relaxation of morphology features (≥ 0.1 nm) occurred only at ≥ 85 °C, and the decrease in roughness was rather rapid beyond this point. On the other hand, at 80 °C about 30 % of the RIB had already relaxed, while no noticeable change ≥ 0.1 nm in any morphology features occurred. Also, no change in morphology could be detected if the sample was left at 23 °C for up to 7 days, but during the same period there was significant RIB relaxation (See subsection 3.4 below). It is seen that significant RIB relaxation occurred at much lower temperatures than surface morphology relaxations, a first sign that the two are not directly related. The relaxations of RIB can take place without any collective segmental movement beyond 0.1 nm in length, which is an indication of their very small length scale.

The possibility that the morphology birefringence (MB) is or contributes significantly to the observed RIB has been ruled out in our previous works [31] [46]. For the sake of completeness in the discussion, we revisit the main findings. First, the amplitude of MB can be estimated from the surface morphology, and the result showed that the amplitude is too small to account for the observed birefringence [46]. Second, we performed the following experiments [31]. Poly(vinyl alcohol) (PVA) dissolved in water was spin coated on top of some PS samples of different molecular weights after rubbing to saturation. The samples were then dried at 20 °C in dry air for two weeks, together with the reference samples rubbed under the same condition but without PVA cover. This resulted in a flat surface PVA cover of about 15 nm with a refractive index ($= 1.5$) almost the same as PS. The MB will be completely masked even though the PS/PVA interface still preserves the original PS surface morphology. However, the observed birefringence of the PS samples after PVA coating remained the same as before, varying by no more than 1 % of the original Δn , indicating that the observed birefringence was not due to surface morphology, and little birefringence was disturbed by the PVA cover. Third, if the RIB of PS was concentrated only within the very top layer, the PVA coating would certainly alter its relaxation behavior at elevated

temperature. However, no noticeable difference in relaxation behavior at elevated temperatures was observed for samples covered with PVA as compared to the reference samples. For example, the *Continuous Curves* for both the PVA covered and the reference samples were essentially the same. This has two implications. First, the relaxations of PS surface grooves are expected to be hindered by the PVA, due to the reduction of Laplace Pressure and the presence of PVA that impedes the movements. But this has no effects on the RIB relaxations. Second, the RIB relaxation is mainly from the segments below the very top PS surface layer, away from the influence of the PVA cover. Combining all the evidence, we conclude that the RIB is not due to the MB of surface, and the relaxations of surface morphology and RIB are not directly related.

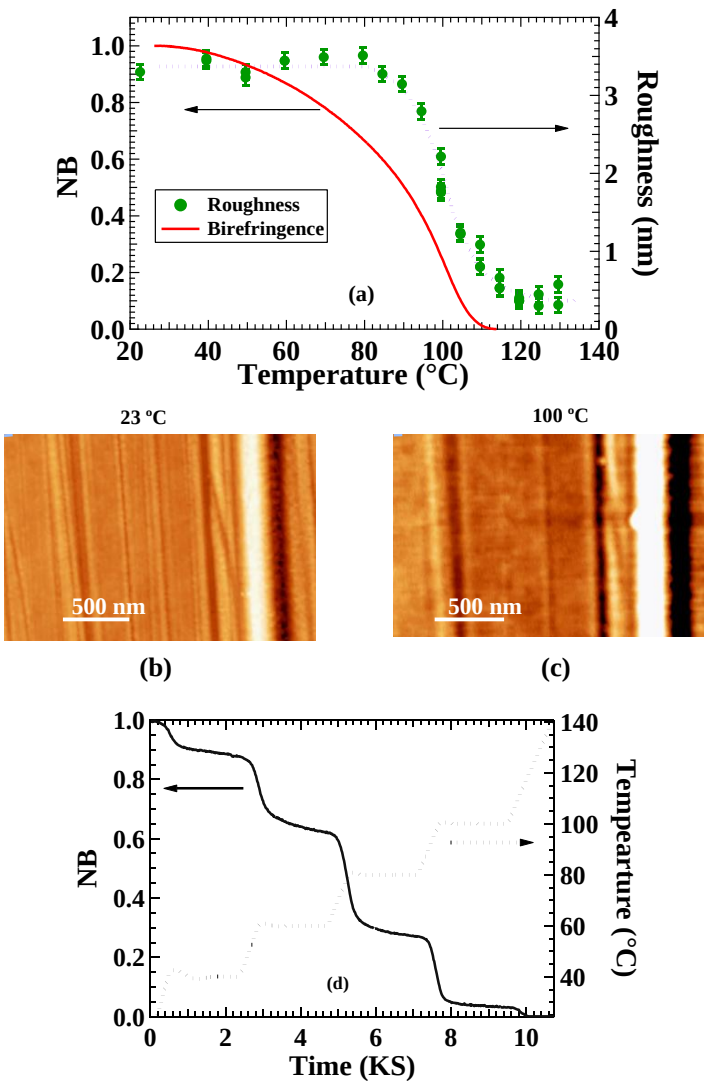


Figure 6. (a) The surface average roughness (points, right axis) versus annealing temperature, together with a typical *Continuous Curve* (solid curve, left axis) of a $M_w = 99$ Kg/mol reference sample. The dashed curve is for guide of eyes only. (b) AFM image of a fresh rubbed surface of PS; (c) AFM image of the same surface area of (b) after annealing at 100 °C for 30 minutes. (d) Normalized birefringence as a function of time (solid curve), with the temperature shown as the dashed curve.

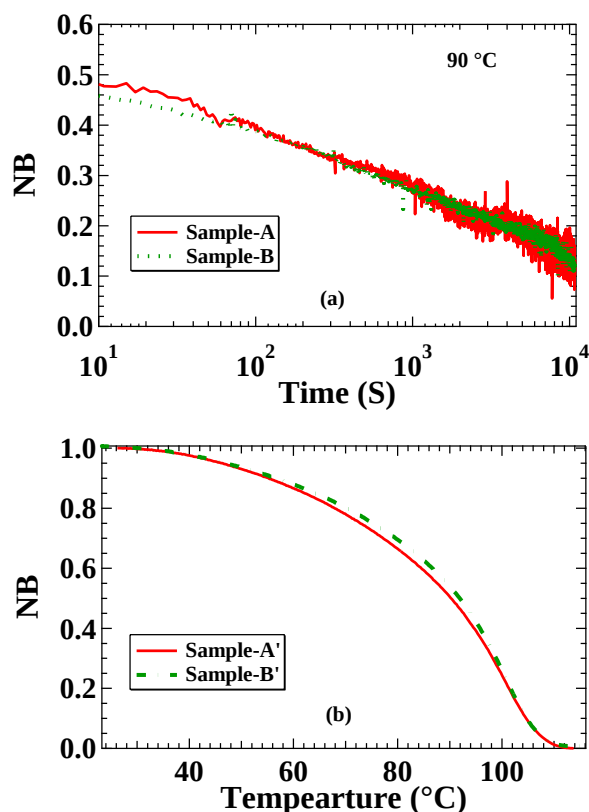


Figure 7. (a) The isothermal relaxation curves at 90 °C of a reference sample and a sample which underwent repeated rubbing process as described in the text. (b) The *Continuous Curves* of two PS samples. The solid curve is for a reference sample, while the dashed curve is for a sample which underwent repeated rubbing process.

Figure 6(d) shows the *NB* of a reference sample under a step-like temperature rise sequence. The solid curve is the *NB* as a function of time as its temperature underwent the sequence shown as the dashed curve in the figure. When the sample was subjected to a fast rise in temperature from 45 °C to 60 °C, a sizable portion of its *NB* disappeared along with it, followed by a slower and smaller decay as the sample temperature was maintained at 60 °C. After 30 minutes at 60 °C, subsequent rise-then-hold in temperature from 60 °C to 80 °C and from 80 °C to 100 °C brought about similar responses of the *NB*, until all RIB disappeared.

An isothermal relaxation curve of a reference Sample-A is shown in Figure 7(a). The temperature was raised at $t = 0$ from 23 °C to 90 °C in less than 3 seconds, and then was maintained there for 10 hours. Within the first 10 s about 52 % of the original birefringence had relaxed. The *NB* then decayed slowly, approaching logarithm in time. Simple isothermal relaxations of reference samples at other elevated temperatures behaved in similar way in that there was always an initial quick drop in *NB* followed by a slow decay [31].

3.3. Thermal quench before rubbing

Several fresh samples were first heated up to 130 °C and quenched to 23 °C in less than 300 s, and then rubbed to saturation. Their saturation RIB and *Continuous Curves* show no

noticeable difference from the typical ones presented in Figure 5 and Figure 6. This is inconsistent with the established physical aging theory, according to which the samples quenched to 23 °C should have preserved the majority of the segmental RT's at 130 °C. If a reference sample is quickly heated to 130 °C, all its RIB will disappear within 30 s, implying that at 130 °C the RIB RT's are all shorter than 30 s. Therefore, had the RIB RT's followed the segmental RT's, all of them in the quenched sample would have been short (≤ 30 s). All RIB in the sample would have relaxed quickly even at 23 °C, and no net RIB should have even been obtained. This is in clear contradiction to the experimental results.

3.4. Repeated rubbing

Conventional segmental relaxations are greatly sped up by high strain/stress [4]. In rubbed PS the RIB is due to the segmental alignments and distortion, so it is taken as a measure of the degree of distortion in the discussion here. More experimental results are presented in Figure 7. Here sample-A was one of the reference samples. Sample-B was from group-B where the samples were first rubbed to saturation (> 80 passes), heated up at 2K/min till 90 °C, then quenched to 23 °C and rubbed again until the RIB was back to its original saturation value at the end of the first rubbing run. The entire quenching and rubbing process was completed within 30 minutes. The molecular weight of the samples in both groups was 99 Kg/mol. The isothermal relaxation curves, the dashed curve for sample-B from group-B and the solid curve for a reference sample-A, are depicted in Figure 7(a). The *Continuous Curves* of a reference sample-A' and a sample-B' from group-B are depicted in Figure 7(b). The two curves coincide well in both cases. No significant difference is seen. All these again show that once the RIB is created, its RT's are not affected by further deformation, in clear contradiction with the behavior of the conventional segmental relaxations.

3.5. Disrupted continuous curve

The experimental results presented so far demonstrate that the RIB relaxation does not depend on the rubbing and thermal history before the final rubbing process and the start of the subsequent relaxation measurements. There could be a small possibility that somehow the final rubbing process 'resets the clock' and puts the PS all to a state that relax in a very similar way, i. e., similar to mechanical 'rejuvenation' in segmental relaxations even though the term itself is not exact [5] [47]. To clarify, we studied the effects of thermal processes conducted after rubbing. The *NB* curves as a function of temperature of two originally identical samples are shown in Figure 8. For a reference sample-A, the temperature was raised at 2 K/min from 23 °C to 130 °C without interruption. The result is a typical *Continuous Curve*. The second sample, sample-C, underwent more complicated temperature sequence. First the temperature was raised continuously from 23 °C to 90 °C at 2 K/min. Its *NB* decreased in almost the same way as sample-A up to 90 °C. Upon reaching 90 °C the temperature was lowered at 2 K/min till 44 °C (when ambient cooling could no longer maintain the 2 K/min rate). The *NB* continued to decrease by a small amount until the temperature reached about 80 °C, then maintained its value from 80 °C to 44 °C. Upon reaching 44 °C the temperature was raised again to 90 °C at 2 K/min. The *NB* remained unchanged during the second temperature rise to 80 °C. Upon reaching 90 °C again, the sample was dropped into liquid nitrogen, and then let to warm up in a dry air ambient environment (~ 23 °C) for 16 hours. During the period no RIB change was observed. Finally the temperature was raised continuously from 23 °C to 130 °C at 2 K/min. The *NB* again

traced the curve where the temperature was raised from 44 °C to 90 °C, and joined the *NB* of sample-A after 94 °C.

Several points are noted in the above temperature sequence. First, the relaxation of *NB* of sample-C was identical to that of sample-A for $T > 94$ °C, i. e., the relaxation above 94 °C was not affected by the thermal history below 90 °C, within the time scale of ~20 hours. Second, no relaxation of *NB* was observed below 80 °C after the first temperature rise, indicating that by the first time the temperature reached 90 °C the relaxation of *NB* below 80 °C was already complete. That is also the reason why the *NB* curves of the second (before liquid nitrogen quench) and the last temperature rise (after quench and annealing at 20 °C for 16 hours) are identical. Third, above 80 °C the relaxation was still active, and the relaxation of *NB* was again activated when 80 °C was reached from below in both the second and the last temperature rises. Fourth, unlike in the case of physical aging where further non-equilibrium can be introduced by additional thermal process, quenching or other thermal process below 90 °C on rubbed PS brought no increase to the remaining RIB.

According to the conventional physical aging theory, the quench in the above case will freeze the thermodynamic state and the segmental RT's at 90 °C. If the linear compliance of the sample is tested at 20 °C, its characteristic time will be close to that at 90 °C, and many orders of magnitude shorter than the one in thermodynamic equilibrium [1]. If the RIB RT's had followed the trend of the conventional segmental RT's in the quench process, then the measured *NB* would have decreased during the 16 hours at 20 °C and when the temperature was raised again from 20 °C, because the RT's should have been close to those at 90 °C. The portion of curve-C above 94 °C should have shifted horizontally to the left (lower temperature), and the amount of shift would have depended on the elapse time at 20 °C, as is indicated by the imaginative curve labeled 'Following PA' (PA stands for physical aging) in the figure. When the temperature reached 90 °C for the third time the thermodynamic state of sample-C was certainly different from that of sample-A at the same temperature. The fact that the RIB in sample-C relaxed in the same way as sample-A at above 94 °C indicates that although the thermodynamic state of sample-C was different from sample-A, the portion of RIB that would relax at above 94 °C was still the same as before, unaffected by the quenching and reheating.

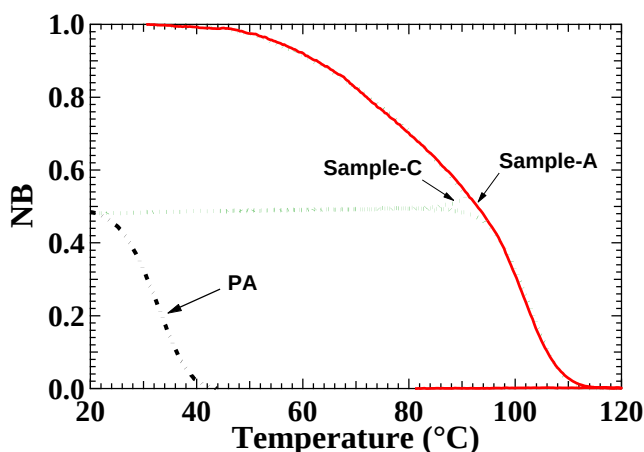


Figure 8. Normalized birefringence versus temperature of two PS samples. The solid curve is for a reference sample-A, while the dashed curve is for sample-C which underwent several temperature rise and fall sequences as described in the text.

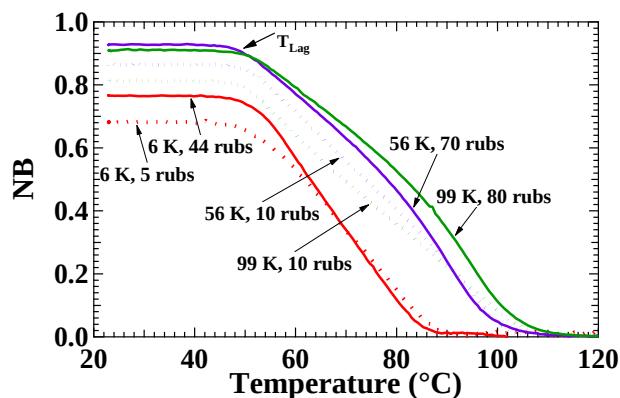


Figure 9. Normalized birefringence of three pairs of samples versus temperature at a heating rate of 2 K/min after annealing at 23 °C for 7 days. The sample parameters are given in the text.

3.6. The temperature lag phenomenon

The *Continuous Curve* of any rubbed sample following a period of isothermal annealing differs from the ones without the annealing. This is the temperature lag phenomenon first reported in Ref. [31]. Three pairs of samples were studied here. The molecular weights of the pairs were 6.4 Kg/mol, 56 Kg/mol, and 99 Kg/mol, respectively. For each pair of samples, one was rubbed for only a few passes (5 for the $M_w = 6.4$ Kg/mol sample and 10 for the other two samples) and the other one till saturation (44 passes for the 6.4 Kg/mol sample, 70 passes for the 56 Kg/mol sample, and 80 passes for the 99 Kg/mol sample). The net RIB of the lightly rubbed samples was about 40 % of the saturation values ($\Delta n = 0.012$ for the 6.4 Kg/mol sample, $\Delta n = 0.017$ for the 56 Kg/mol sample, and $\Delta n = 0.021$ for the 99 Kg/mol sample).

The rubbed samples were then left at 23 °C for 7 days, during which they aged and the RIB relaxed but no surface morphology change could be detected by AFM. Figure 9 shows the *Continuous Curves* of the samples after the aging. Several features are noted.

The temperature at which the NB vanished was around 90 °C for the $M_w = 6.4$ Kg/mol samples, 104 °C for the $M_w = 56$ Kg/mol samples, and 110 °C for the $M_w = 99$ Kg/mol samples. These temperatures are close to but do not strictly follow the T_g 's of PS at these molecular weights. Also, they are almost rubbing condition independent. This effectively rules out the possibility of significant chain scissions by rubbing, as shorter chains are equivalent to smaller molecular weights which would lower the T_g and the temperature at which RIB disappears. The same were observed for the reference samples without aging.

Within the 7 days, for samples of the same molecular weight, the decrease in NB for lightly rubbed sample was larger than the saturated one. For example, for the 99 Kg/mol samples, the RIB of the lightly rubbed one reduced to 81 % of its original value right after the rubbing, a drop of 19 %, while that of the saturated one reduced to 91 % of its original value, a drop of 9 %. This is in contradiction with the strain accelerated relaxation mechanism [4].

The NB's did not immediately decrease as the temperature was raised above the aging temperature T_A until it reached a higher temperature T_D . Above T_D the *Continuous Curves* resembled those reference samples rubbed in the same ways but without the 7-day aging at 23 °C. Despite the large difference in molecular weights and in the number of rubbing passes, the temperature lag, defined as $T_{Lag} = T_D - T_A$, of the six samples were the same within the experimental uncertainty of $\pm 1^\circ\text{C}$.

More results measured under similar conditions on other samples are summarized in Table 1. The aging/annealing times t_A ranged from 1 hour to 7 days. The molecular weights ranged from 6.4 Kg/mol to 550 Kg/mol. The film thicknesses ranged from 7 nm to 30 nm. The annealing temperatures were 23 °C and 60 °C. At a given annealing temperature, T_{Lag} increased with the logarithm of annealing time, in a similar way as reported earlier [31]. At a given annealing temperature and for a given annealing duration t_A , the T_{Lag} 's of all the samples were the same within the experimental uncertainty of $\pm 1^\circ\text{C}$, regardless of the molecular weight, the film thickness, and the rubbing passes. In a similar experiment as in subsection 3.4, several group-B samples, after repeated rubbing and heating, were tested for their T_{Lag} at 60 °C, and the outcome showed no discrepancy to the normal values shown in Table-1 and in Figure 10. Therefore, the T_{Lag} is also independent of the thermal and rubbing history.

Table 1. The temperature lags of the PS samples investigated.

Film Thickness (nm)	T_A (°C)	Duration t_A (s)	Molecular Weight (kg/mol)	T_{Lag} (°C)
22	23	3600	6.4	15.3
			6.4	15.7
			12	15.4
			12	15.7
			56	15.8
			56	16.1
			99	15.8
			99	15.6
		36,000	6.4	24.2
			6.4	25.1
			34	25.9
			34	24.6
		6.05×10^5	6.4	29.1
			6.4	28.8
			56	28.4
			56	29.6
			99	27.1
			99	29.1
30	60	36,000	6.4	20.0
			22	20.8
			99	18.9
			550	19.0
			99	20.1
7			99	20.1
10			99	20.1

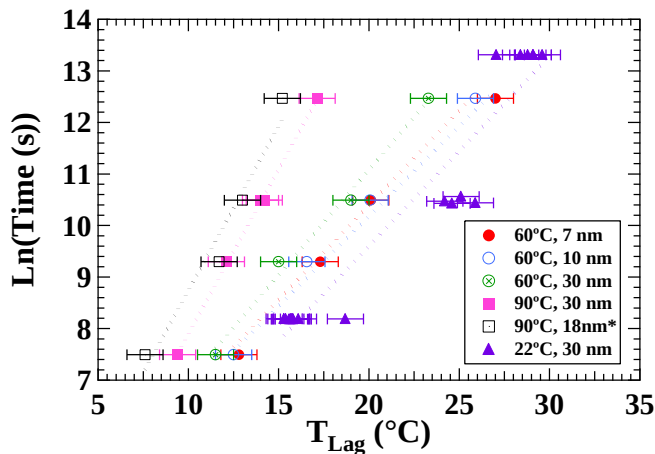


Figure 10. Logarithm of annealing time t_A versus temperature lag T_{Lag} at several annealing temperatures. The 18* nm sample was quenched from 130 °C to 23 °C several minutes before it was rubbed at 23 °C.

The logarithm of annealing time t_A as a function of T_{Lag} is plotted in Figure 10 at several annealing temperatures. A nearly linear relation between the two quantities can be confirmed. More quantitative analysis will be present in later sections. Here we concentrate the discussions on its implication on the effects of physical aging. The temperature lag phenomenon is one of the most important characteristics of RIB relaxation, and plays a critical role in the quantitative analysis of its relaxation behaviors. The RIB remains unchanged when the temperature is still in the range of T_{Lag} , while above the range the RIB decreases with the increasing temperature in exactly the same way as a sample without going through the annealing and aging. For example, for a sample annealed (and aged) at 23 °C for 7 days, there was no change in RIB in the temperature range of the subsequent *Continuous Curve* from 23 °C to 50 °C, while the portion of the *Continuous Curve* above 60 °C was the same as the one in Figure 5. In other words, the annealing at 23 °C for 7 days eliminated all the low temperature RIB relaxation up to about 50 °C, but left the one well above 50 °C unchanged. This is in stark contradiction with the effects of physical aging, where the segmental relaxations at *all temperatures* sufficiently below T_g , regardless whether they are above or below the aging temperature, are affected by the aging process [1].

4. Model

We have conducted many similar experiments on many other samples. The outcome, together with the experimental results presented in Section-3, can be summarized in the following.

- (i) The relaxation of RIB does not depend on thermal history before rubbing. Representative experimental evidence is presented in subsection 3.3.
- (ii) The relaxation of RIB does not depend on the thermal and rubbing history prior to the *last rubbing run*. Representative experimental evidence is presented in subsection 3.4.

- (iii) The dependence of the RIB relaxation on the thermal history after the last rubbing run is governed by the temperature lag effect. If a rubbed sample is aged at temperature T_A for a duration of t_A , then a 'lag temperature' T_{Lag} can be found experimentally from its subsequent *Continuous Curve* such that below $T_A + T_{Lag}$ the *Continuous Curve* is flat, and the portion of *Continuous Curve* above $T_A + T_{Lag}$ resembles the one obtained from reference samples without aging. Furthermore, T_{Lag} is proportional to the logarithm of t_A . Representative experimental evidence is presented in subsections 3.5 and 3.6.

Optical probes have been used to study the relaxations of PS and other polymers, and substantial physical aging effects were observed. Thureau and Ediger reported photobleaching studies on the segmental relaxations of PS [48]. The rotational probe relaxation followed the KWW function, while the translational probe decayed in a simple exponential form. After quenching from above T_g , the RT's at 33 °C were much shorter than the equilibrium values. The aging effect was much less drastic than the typical ones seen in creep compliance experiments [1]. Aging from 10^3 s to 10^5 s, a change of time scale of 100 folds, brought RT increase by only three times. The fluorescence intensity of chromophore-doped/labeled PS thin films studied by Ellison *et al.* [49] was insensitive to aging, changing by only 6 % in total intensity over 5 hours of aging. These results indicate that the relaxations involving smaller length scales are not as sensitive to aging as the ones involving larger scales in creep experiments.

Besides the small length scale, the absence of physical aging effects in the RIB relaxation could also be due to the accelerated aging speed in the near surface region. In fact, the aging speed could be depth dependent, similar to the speculated depth dependent T_g [50]. Kawana and Jones reported [11] thin supported PS films aged below T_g that exhibited clear overshooting in expansivity temperature curves when reheated for thicknesses of 18 nm or more, but not for a thickness of 10 nm, suggesting the existence of a surface layer of the order of 10 nm in which aging was complete within $\sim 10^3$ s, while the rest of the film essentially had thermal properties identical to bulk samples. The absence of the physical aging effects in the RIB relaxations could therefore be due to the combined effects of accelerated aging of the near surface region and the small length scales involved in the relaxation process.

As was pointed out earlier [31], the RIB relaxation does not follow the KWW function. One essential element for the KWW function to be applicable is that the start and end values of the relaxation observable must be well defined, as in the case of photobleaching where the values are 1 and 0, or in the glass to rubbery transition of creep compliance where the end values are the well established J_G and J_R values. In isothermal RIB relaxation, the only well defined values are 0 and 1 for NB and there is no 'level off' in between. Taking the short time ($\sim$ a few hours) end value as 'level off' is mistaking [31]. Since KWW function does not apply here, we must start with the generic distribution function and proceed to determine it using experimental results.

One of the characteristics of the relaxation processes in glass forming polymers is the heterogeneity. A monotonic relaxation process can in general be expressed as

$$\alpha(t) = \int_0^{\infty} g(\tau) e^{-t/\tau} d\tau \quad (2)$$

where α is the relaxation function of an observable, such as the segmental alignment dichroism, the optical birefringence, etc., τ is the relaxation time (RT), and $g(\tau)$ is the RT density distribution. In thermodynamically simple cases $g(\tau) = G(\kappa\tau)$ where the shift factor κ is temperature and thermal history dependent but the functional form of $G(x)$ remains fixed, following the well known time-temperature superposition law and the time-aging time superposition law. There is no general and systematic way to extract $G(\kappa\tau)$ from experimental results, but fortunately in many cases [41] [42] [43] $G(\kappa\tau)$ takes the simple form of KWW function in the time scale within which the change of κ can be ignored. The $G(\kappa\tau)$ after various length of aging times can then be determined and the shift factor κ extracted. The dominant effect of physical aging in the conventional cases is on the time shift factor κ , which leads to the well known time-aging time superposition principle [1].

Extensive experimental evidence in the last section has shown clearly that the RIB relaxation depends strongly on temperature but is insensitive to physical aging. The RIB relaxation can therefore be described by an RT distribution function $g(\tau)$ that *depends only on temperature but not on thermal or strain history*. This is the most significant difference between the conventional segmental relaxations and the RIB relaxation. As the RIB $g(\tau)$ depends on temperature only, the existing models that predict the physical aging effects [5] [6] are no longer applicable here. Instead, a new and systematic approach [31] can be devised to determine the distribution function from carefully designed experiments.

The phenomenological model we propose is based on the generic model for the relaxations in glass forming polymers that consists of individual relaxing units overcoming an energy barrier under thermal excitations. In the model, the total RIB of a PS sample is taken as the combined contribution of individual RIB elements. To remove its contribution to the total RIB each element must overcome an energy barrier E . The RT is expressed in the conventional Arrhenius form

$$\tau = Ae^{\frac{E}{(273+T)R}} \quad (3)$$

where $R = 8.315 \text{ J/(K} \cdot \text{mol)}$ is the gas constant, A is a pre-exponential factor, and T is the temperature in the unit of $^{\circ}\text{C}$. *Once an RIB element is created by rubbing, its RT will not be altered by further thermal process or strain*, until it has relaxed and disappeared. By expressing the energy barrier in the form

$$E = (273 + \xi)\eta_0 \quad (4)$$

where η_0 is the same for all RIB elements, and ξ (in the unit of $^{\circ}\text{C}$) is element specific, the RT becomes

$$\tau(T, \xi) = \tau_0 e^{\gamma(\xi-T)} \quad (5A)$$

with

$$\tau_0 \equiv Ae^{\eta_0/R} \quad (5B)$$

and

$$\gamma \equiv \eta_0 / R(273 + T) \quad (5C).$$

The parameters γ and τ_0 in Eq. (5A) are the same for all elements and depend weakly on temperature, while ξ is generally different for different RIB elements and is independent of temperature. At a given temperature T the parameter ξ alone determines the RT of the element. The prefactor A for all the RIB elements is the same at any given temperature, which means that all elements have the same ‘vibration frequency’ in their potential wells. This results in the RT’s in the ‘threshold temperature’ form as expressed in Eq. (5A), with the ‘threshold temperature’ proportional to the well depth, as is hinted by the step-like drop in NB following a step-like rise of temperature in Figure 6(d). At a given temperature T , the elements with $\xi \leq T$ will have short RT’s ($\sim$ seconds) and relax quickly, while those with $\xi > T$ will have RT’s that increase exponentially with ξ .

The rubbing process generates an initial density distribution $N(\xi, 0)$ of elements, where $\int_0^\infty N(\xi, 0) d\xi = 1$. After spending t_A at temperature T the distribution becomes

$$N(\xi, t_A) = N(\xi, 0) e^{-\frac{t_A}{\tau(T, \xi)}} \quad (6A)$$

The isothermal relaxation of the normalized RIB is then given by

$$NB(T, t) = \int_0^\infty N(\xi, 0) e^{-\frac{t}{\tau(T, \xi)}} d\xi \quad (6B)$$

The expression is equivalent to Eq. (2).

5. Analysis

We now proceed to the analysis of the experimental results presented in Section-III.

5.1. Range of ξ where $N(\xi, 0)$ is non-zero

According to Eq. (5A), any elements with $\xi < 23$ °C created by rubbing will have relaxed quickly before any subsequent measurements are carried out. The relaxation of these elements is the origin of the transient birefringence right after each rubbing pass reported in subsection 3.1. On the other hand, the RIB relaxation is complete when the temperature is near T_g (see Figure 6). Therefore, taking into account of the experimental *Continuous Curve* in Figure 6, we expect $N(\xi, 0)$ to be a smooth and continuous function of ξ in the range of 23 °C $\leq \xi \leq \sim T_g$. According to the experimental results in Figure 9, in the $M_w = 6.4$ Kg/mol samples there were no RIB elements with $\xi > 90$ °C, while in the $M_w = 99$ Kg/mol samples there were RIB elements with $\xi > 90$ °C but not the ones with $\xi > 114$ °C. When the temperature of a freshly rubbed sample is raised quickly from 23 °C to 90 °C there must be a quick drop of birefringence because the elements with barrier height 23 °C $\leq \xi \leq 90$ °C will relax within ~ 10 s. This quick drop of NB has indeed been observed if one keeps track of the original

birefringence before temperature rise, as is shown in Figure 7(a). Likewise, a step-like rise of temperature will bring a step-like drop in NB , which was indeed observed (See Figure 6(d)). More analysis on the distribution function will be presented in subsection 5.7.

Note that although ξ is in the unit of $^{\circ}\text{C}$, it describes the potential well depth and itself is independent of temperature.

5.2. Interpretation of temperature lag phenomenon

The RT of an RIB element increases exponentially with ξ at a given temperature T . Equation (6) then predicts the ‘temperature lag’ phenomenon reported in subsection 3.6. For a freshly rubbed sample, its initial density distribution is $N(\xi, 0)$. As its temperature $T(t)$ is raised at a constant rate, the elements with $\xi = T(t)$ will relax quickly as their RT’s become short enough. As a result, the NB decreases with temperature, leading to a typical *Continuous Curve* as shown in Figure 6(a). However, after a freshly rubbed sample has gone through an isothermal annealing process for certain duration t_A at temperature T_A , subsequent temperature rise at a constant rate will not bring immediate decrease in NB until a higher temperature T_D is reached. This is because the elements with $\xi_0 \geq \xi$, where $\tau(T_A, \xi_0) = t_A$, have already relaxed. Subsequent rise in temperature will not bring any significant decrease in NB until it reaches $T_D \geq \xi_0$. By measuring the temperature lag $T_{\text{Lag}} (\equiv T_D - T_A)$ at different annealing time t_A , the relation between $\tau(T_A, \xi)$ and ξ can be obtained, namely $t_A = \tau(T_A, \xi = T_A + T_{\text{Lag}})$. According to Eq. (5A), T_{Lag} is linearly dependent on the logarithm of t_A . Using linear fit we obtained the parameters [31] for $\tau(T_A, \xi)$ at $T_A = 60^{\circ}\text{C}$, namely $\gamma = 0.42 \pm 0.05 \text{ K}^{-1}$ and $\tau_0 = 14 \pm 8 \text{ s}$, which lead to $\eta_0 / R = 140$, and E ranging from 340.4 kJ/mol to 445.7 kJ/mol. Similarly, in the subsequent part of the paper the parameters at other temperatures from 23°C to 90°C and their possible dependence on PS properties will be extracted from the experimental results presented in Section-3. We found that Eq. (5) is followed, and the parameters γ and τ_0 can be extracted in all the cases studied.

5.3. Molecular weights, film thickness, and rubbing distance dependence

As presented in subsection 3.6, at a given temperature the T_{Lag} of samples with different thermal histories, thicknesses, molecular weights, and prepared by different rubbing distances were all the same. This implies that the dependence of $\tau(T, \xi)$ on ξ , the energy barriers the RIB elements must overcome, is the same regardless of the molecular weight, the film thickness, thermal history, and the rubbing conditions. This indicates that only the local environment immediately surrounding an individual element determines its energy barrier, rather than the global parameters such as the chain length, the net RIB, or the film thickness.

5.4. Temperature dependence of γ and τ_0

For a fixed annealing time t_A , T_{Lag} is smaller at higher temperatures. The NB curves of four samples are plotted against $(T - T_A)$ in Figure 11, where T was the temperature at a constant heating rate of 2 K/min and T_A was the annealing temperature prior to the temperature rise. The annealing time was $t_A = 10 \text{ hours}$ for all the samples. The $(T - T_A)$ at which NB started to drop was the largest for $T_A = 45^{\circ}\text{C}$ and smallest for $T_A = 90^{\circ}\text{C}$. The T_{Lag} data extracted from the curves are plotted against T_A in the insert of Figure 11. A linear relation is seen between T_{Lag} and T_A .

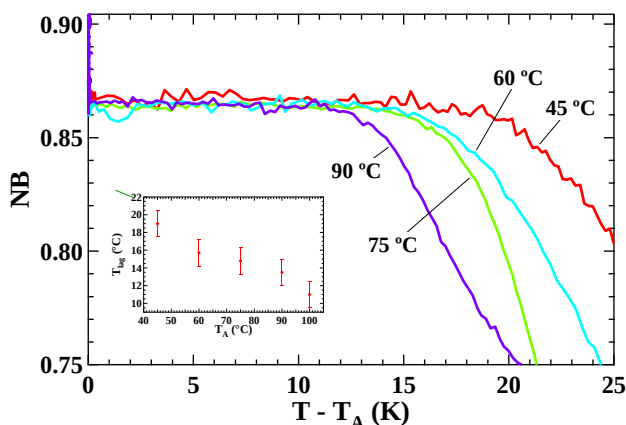


Figure 11. The NB curves of four PS samples vs $(T - T_A)$, where T is the temperature at a constant heating rate of 2 K/min and T_A is the annealing temperature prior to the temperature rise. The insert shows the T_{Lag} obtained from the curves as a function of T_A . The molecular weight of the samples is 550 Kg/mol.

Table 2. The parameters of the relaxation times obtained from the linear fitting in Figure 6. The 18* nm sample was quenched from 130 °C to 23 °C several minutes before it was rubbed at 23 °C.

Film Thickness (nm)	T_A (°C)	τ_0 (s)	γ (K ⁻¹)	η_0/R
7	60	15 ~ 44	0.35 ± 0.05	116 ± 17
10	60	15 ~ 33	0.37 ± 0.04	123 ± 13
30	60	11 ~ 24	0.41 ± 0.03	136 ± 10
30	90	4.5 ~ 5.5	0.64 ± 0.02	232 ± 7
18*	90	3.3 ~ 33	0.64 ± 0.09	232 ± 32
30	23	5.5 ~ 45	0.37 ± 0.04	110 ± 12

According to Eq. (5), the above results indicate that either or both the parameters γ and τ_0 increases with temperature. To quantitatively determine the two parameters, T_{Lag} 's at fixed annealing temperatures were measured at different annealing time t_A , and the results are shown in Figure 10. Straight lines of $\ln(t_A)$ vs. T_{Lag} are found. The linear fitting results of the data in Figure 10 are summarized in Table 2. The value of τ_0 in all the cases are of the order of 5 ~ 50 s, although at 90 °C the parameter τ_0 does seem to be smaller than at lower temperatures. The data at 60 °C hint some weak thickness dependence of γ , but the difference is still within the experimental error. The value of γ increases by about 50 % from 60 °C to 90 °C. Also to be noted is the 18* nm sample, which was quenched from 130 °C to 23 °C several minutes before it was rubbed at 23 °C. The entire quenching and rubbing process was completed in 30 minutes. Compared to conventional physical aging, such drastic thermal quench had surprisingly little, if any, effects on the RIB RT's.

Summarizing the results presented so far, we conclude that the RT's of the RIB elements follow Eq. (5A) in the temperature range investigated. The parameter τ_0 is at most weakly dependent on temperature, changing by no more than a factor of 10 over the temperature range from 23 °C to 90 °C. As a comparison, the actual RT's change by about 10^{11} times in

the same temperature range. The RT's are independent of the molecular weights, the number of rubbing passes, the film thickness down to 7 nm, and the thermal history. The parameter γ increases linearly with temperature at a rate of $7 \times 10^{-3} \text{ K}^{-2}$, and its value at 90 °C is 0.64 K^{-1} . According to Eq. (5C) an increase of γ leads to η_0 to increase with temperature, indicating that the well depth of the RIB elements not yet relaxed increases with temperature. But since the pre-factor A , according to Eq. (5B), decreases exponentially with η_0 , an RIB element with $\xi = 100 \text{ °C}$, for example, will still relax quickly only when the temperature reaches 100 °C.

5.5. Disrupted Continuous Curve

If the temperature is lowered shortly after T_1 is reached, the RIB elements with $\xi \leq T_1$ will have relaxed and those above T_1 will simply go 'hibernation' until the temperature is raised back to the neighborhood of T_1 . This explains the relaxation behavior of sample-C in subsection-3.5. By the first time the temperature reached 90 °C, all elements with $\xi \leq 90 \text{ °C}$ in sample-C had already relaxed while most of those with $\xi \geq 90 \text{ °C}$ were still intact. During the first and the second temperature drop and rise, the NB remained constant because there were no $\xi \leq 90 \text{ °C}$ RIB elements left, and the RT's of the remaining elements with $\xi \geq 90 \text{ °C}$ were very long. Therefore there were few elements that would relax in that temperature range within the time scale of the experiment. The small decrease in NB above 80 °C was due to the slow relaxations of the elements with ξ slightly above 90 °C. Once the temperature was finally raised above 90 °C, the elements with $\xi \geq 90 \text{ °C}$ then relaxed in earnest in the same manner as the reference sample, because their RT's remained unaltered by the thermal processes.

5.6. Density distribution $N(\xi, 0)$

The analysis so far shows that the dependence of the RT of an RIB element $\tau(T, \xi)$ follows Eq. (5A), and the parameters γ and τ_0 are the same for all the PS samples investigated so far. As shown in Eq. (6B), $\tau(T, \xi)$ and $N(\xi, 0)$ together determines the relaxation of RIB in a sample. The difference in the relaxations of samples with different molecular weights or rubbing conditions lies in the difference between their density distributions. For example, the reduction of NB at a fixed temperature is faster if there are more elements with lower barrier heights and therefore shorter RT's. As $N(\xi, 0)$ approaches zero when ξ is near T_g , the upper bound of ξ , above which $N(\xi, 0)$ is zero, of a lower molecular weight sample is lower than that of a higher molecular weight sample. In this part, we concentrate on the extraction of the density distribution $N(\xi, 0)$ from the experimental data, using the relaxation times obtained in subsection 5.5.

In our early work [31], a qualitative argument was given to show how to extract the density distribution from the experimental *Continuous Curve* $\mathcal{Q}(T)$. Here we present a quantitative derivation. It is noted that $\mathcal{Q}(T)$ is a special form of $NB(T, t)$ with

$$T(t) = T_0 + \alpha t \quad (7)$$

At 2 K/min, $\alpha = \frac{1}{30}$ K/s, and T_0 is the starting temperature at $t = 0$. For $\Omega(T)$ after annealing at temperature T_A for a certain duration, $T_0 = T_A$. To obtain the initial density distribution $N(\xi, 0)$, the measurement of $\Omega(T)$ must start from the rubbing temperature within 100 s after rubbing.

The general expression for the relaxation of NB with given temperature $T(t)$ is

$$NB(T(t), t) = \int_0^{\infty} N(\xi, 0) e^{-f(\xi, t)} d\xi \quad (8A)$$

with

$$f(\xi, t) = \int_0^t \frac{dt'}{\tau(T(t'), \xi)} \quad (8B)$$

The relaxation time $\tau(T, \xi)$ is given by Eq. 5(A). We take $\tau_0 = 15$ s, and $\gamma = 0.64$ K⁻¹ at 90 °C and increases linearly with temperature at a rate of 7×10^{-3} K⁻², and proceed to show how to extract the density distribution from the measurements of $\Omega(T)$. We define the relaxation function as

$$K(t, \xi) \equiv e^{-f(\xi, t)} \quad (9)$$

where $T(t)$ is given by Eq. (7). From the numerical results with $\alpha = \frac{1}{30}$ K/s shown in Figure 12(a), it is seen that $K(t, \xi)$ is nearly a step function of ξ , the rise being at the point where $\xi = T(t)$. The dashed curve is the negative derivative $-\frac{\partial K}{\partial T} = -\frac{\partial K}{\alpha \partial t}$. It is a narrow peak function with half width at half height proportional to $1/\gamma$ and a total area of unity. It then follows that

$$\frac{d\Omega}{dT} = \frac{d\left(\int_0^{\infty} N(\xi, 0) K(t, \xi) d\xi\right)}{\alpha dt} = \int_0^{\infty} N(\xi, 0) \frac{\partial K}{\partial T} d\xi \approx -N(\xi, 0) \Big|_{\xi=T} \quad (10)$$

i. e., the density distribution $N(\xi, 0)$ can be extracted from the experimentally measured *Continuous Curve* by taking its derivative with respect to temperature. The same conclusion was reached in the qualitative argument [31]. A typical density distribution $N(\xi, 0)$ of a reference sample is shown in Figure 12(b), extracted from the experimental *Continuous Curve* in the same figure. The density distribution was then put back to Eq. (8), and by using Eq. (5A) for the relaxation times, to generate a calculated *Continuous Curve* at the heating rate of 2 K/min. It is seen that the calculated one coincides with the experimental one very well. It should be noted that the relaxation times used in the calculation were extracted from the T_{Lag} measurements from other samples. The fact that the two curves agree well with one another provides a strong evidence to support the theoretical model.

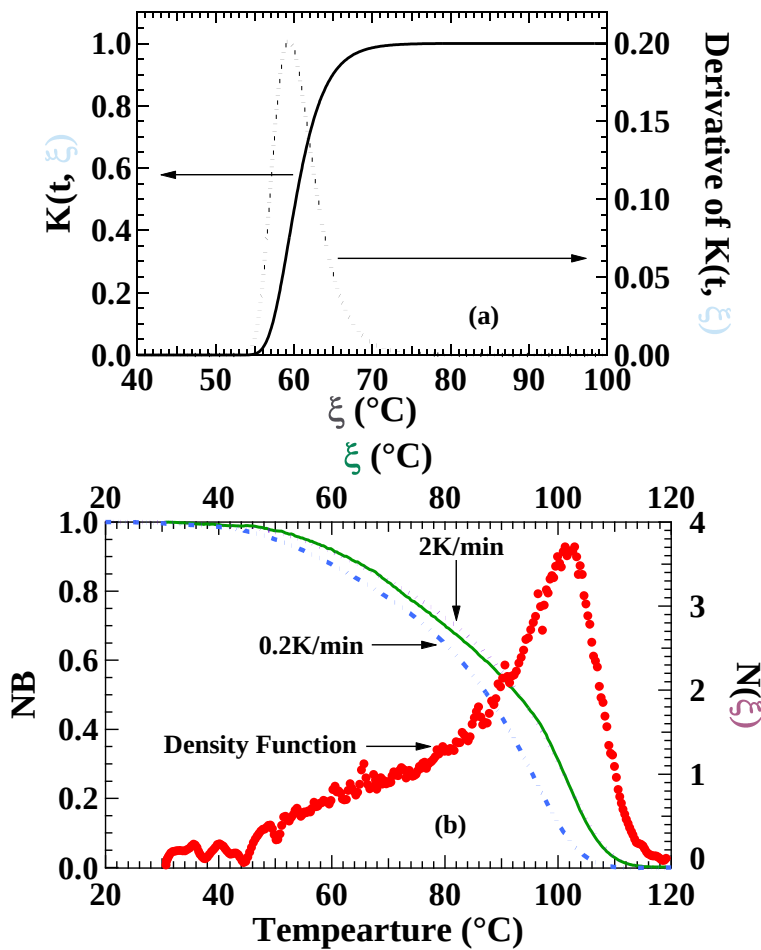


Figure 12. (a) The calculated decay function at a constant heating rate of 2 K/min (solid curve) along with its derivative (dashed curve) as a function of the energy barrier parameter ξ at the time when the corresponding temperature is 60 °C. (b) The experimental *Continuous Curve* and the density distribution $N(\xi)$ together with the numerical simulation results. The solid curve is the experimental curve (left and bottom axes). The circular points are the density distribution $N(\xi)$ obtained from the experimental *Continuous Curve* by taking derivative versus temperature (right and top axes). The two dashed curves are numerical simulations of the *Continuous Curve* at two heating rates. The molecular weight of the sample is 550 Kg/mol.

Using the same data, we also simulated the *Continuous Curve* for heating rate at 0.2 K/min, 10 times slower than the one used in the measurements. It is seen that because the elements now have more time to relax, the amount of remaining elements at any temperature is smaller than at a faster heating rate. Extracting the density distribution from such *Continuous Curve* therefore requires more complicated numerical work than simple derivative operations.

5.7. Rubbing dependence of $N(\xi, 0)$

In the sections above we have shown that the RT's are independent of the rubbing conditions. In this section, we explore the effects of rubbing on the density

distribution $N(\xi, 0)$. Shown in Figure 13 are the density distributions of the six samples obtained from the *Continuous Curves* in Figure 9. It is seen that below $\xi \approx 45$ °C the density is zero for all the samples, due to the relaxation for 7 days at 23 °C. The ‘temperature lag’ phenomenon is clearly manifested. For the two $M_w = 6.4$ Kg/mol samples, the density distributions are about the same, and are nearly uniform between $\xi \approx 60$ °C and $\xi \approx 80$ °C. Both drop to zero at $\xi \approx 90$ °C. For the $M_w = 56$ Kg/mol and $M_w = 99$ Kg/mol samples, the density distribution of the lightly rubbed ones are nearly constant between $\xi \approx 50$ °C and $\xi \approx 100$ °C, but the distribution of the ones rubbed to saturation have a hump above $\xi \approx 90$ °C. The results indicate that in relatively high molecular weight PS, the rubbing process first creates birefringence elements with a nearly uniform distribution of energy barriers, and further rubbing creates elements with barriers more concentrated between $\xi \approx 90$ and 100 °C. For light molecular weight PS, the rubbing process creates a uniform density distribution all the way to the saturation birefringence. This could be due to the entanglements of the PS molecules, as 6.4 Kg/mol is below the entanglement limit of $M_w \approx 20$ Kg/mol [51] while 56 Kg/mol is above it. Further study is being carried out to understand the microscopic mechanism of the rubbing process.

5.8. Repeated rubbing

As has already been shown above, the RT’s of the RIB elements, once created, are independent of the subsequent thermal or rubbing processes until the elements have relaxed. Repeated rubbing processes were attempted in the hope to generate higher concentration of deeper barriers in the samples. As presented in subsection 3.4, a rubbed sample was first raised to 90 °C and quenched to 23 °C to eliminate all the RIB elements except for the ones with the barriers $\xi \geq 90$ °C. It was rubbed again, in the hope that if the chance of generating barriers of all depths had been the same, then there would have been more barriers with $\xi \geq 90$ °C after the second rubbing run than the first run. The experimental results presented in Figure 7, however, imply that the distribution density function $N(\xi, 0)$ at the end of the second rubbing run was nearly the same as the first run. This is somewhat surprising. A likely scenario is that the second rubbing run destroyed and created about the same amount of elements with $\xi \geq 90$ °C. As a result, the relaxations of the repeatedly rubbed samples were the same as the reference ones.

5.9. Discussions

The major findings presented so far seem to contradict the cooperative motion characteristics of segmental relaxations. For example, the RT’s of creep compliance can change by many orders of magnitude during aging. Yet such change has little effects on the local environment of the remaining RIB elements, such as their energy barrier heights and/or well width, either before or after they are formed. Such finding, however, is consistent with the very small length scale involved in the RIB relaxations. The change in thermodynamic state changes the large scale cooperative motions, but has diminishing effects on the smaller length scale RIB relaxations.

The small length scale of RIB relaxation could imply that it is of the nature of β -relaxation due to side group motions. However, the β -relaxation relaxation times are much shorter than 1 s at 20 °C and above, while the RIB relaxation times can exceed 10^{10} s, comparable to that of the cooperative segmental relaxations (α -relaxation). This effectively

rules out the possibility that the RIB relaxation is of the nature of β -relaxation. The microscopic picture of RIB is still largely unknown other than that most of it is due to the segmental distortions, a subject that is still poorly understood.

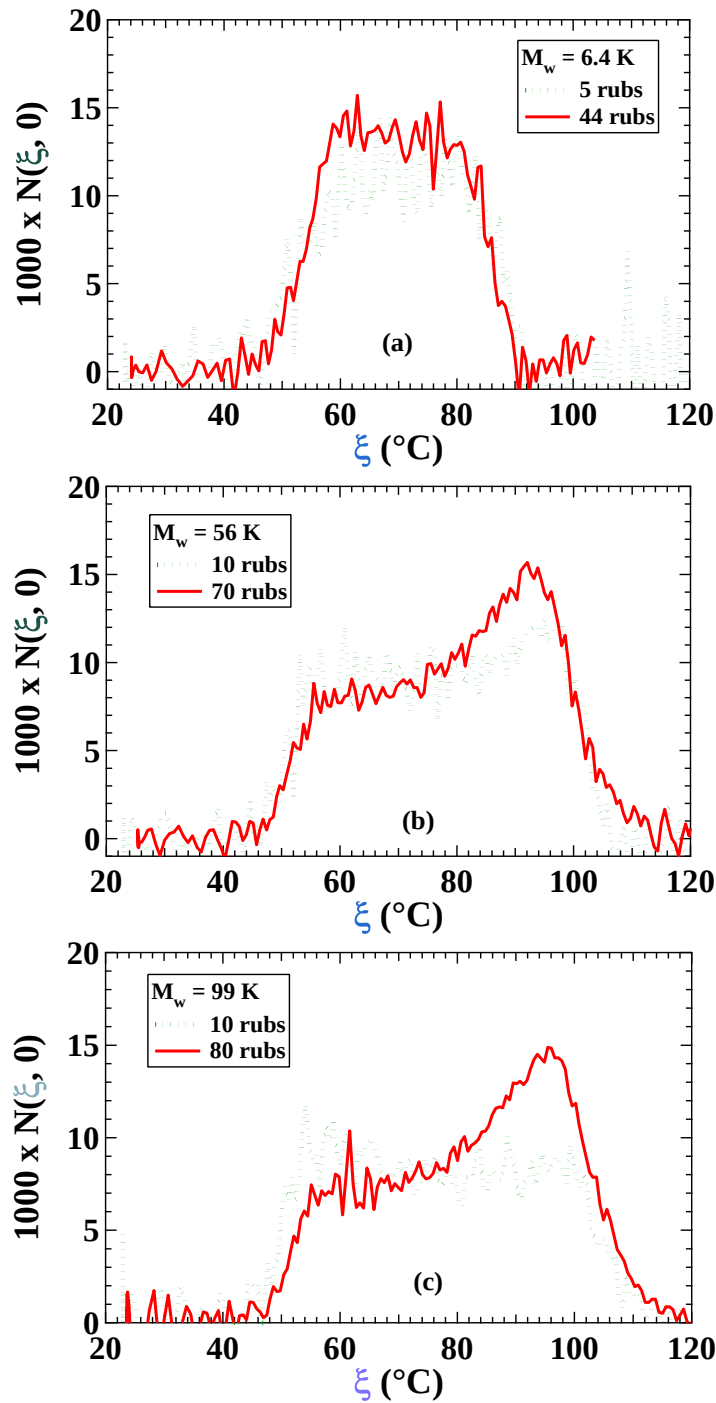


Figure 13. The density distributions of the three pairs of samples extracted from the *Continuous Curves* in Figure 8.

6. Summary

A systematic study of the relaxation of rubbing induced birefringence in PS has been conducted. Extensive and clear experimental evidence have been found that show the absence of the physical aging effects in the relaxation of RIB, and the relaxation of RIB involves very small length scales. The RIB relaxation is then modeled by a relaxation times distribution function that depends only on temperature but not on thermal or strain history. An individual birefringence elements model has been proposed and a systematic way has been devised to extract the parameters in the model from specifically designed experiments, namely the *Temperature Lag* measurements and the *Continuous Curve* measurements. The results predicted by the model agree well with experiments.

The absence of physical aging effects in RIB relaxation is in stark contrast to the conventional segmental relaxations, where the relaxation times can be changed by many orders of magnitude by thermal processes or stress, a phenomenon that has been extensively studied in the last four decades. This is probably due to the much accelerated aging process in the near surface region, and the very small length scale of the RIB relaxation. A model for the RIB relaxation and for the absence of the physical aging effects based on microscopic first principles is still lacking. The results presented here provide a concrete test ground for the development of future theoretical models.

PART IV. RIB IN OTHER GLASSY POLYMERS

1. Introduction

The viscoelastic properties and segmental relaxations of glass forming polymers above the glass transition temperature (T_g) are generally well understood. The viscoelasticity follows the time-temperature superposition principle [52]. In the segmental alignment relaxation of polystyrene (PS) drawn at above T_g there are three well separated relaxation steps with distinct time scales τ_1 , τ_2 , and τ_3 [40]. The relaxation time constants in these cases all follow the so-called Vogel–Fulcher temperature law [3] [52] [53]. Below T_g the relaxation phenomena are much more diversified and without a unified picture as in the cases above T_g . The segmental relaxation of polycarbonate (PC) still follows the time-temperature superposition, and the relaxation time follows the *Arrhenius* form with activation energy of $958 \text{ KJ}/(\text{mol}\cdot\text{K})$. The relaxation becomes much slower at temperatures below $T_g - 20^\circ\text{C}$ [52]. Additional α -relaxation besides the normal α -relaxation peak was observed in dielectric relaxations [54] [55]. The relaxation times follow the *Arrhenius* form with activation energies in the range of $17 - 55 \text{ KJ}/(\text{mol}\cdot\text{K})$. Dielectric probe molecules were mixed with PS and their size dependence of dielectric relaxations was investigated [56] [57]. Below a particular size-1, no coupling between the probe and host PS was found. Above size-1 but below size-2, both α -relaxation and β -relaxation coupled to the probes occurred. Above size-2 no β -relaxation coupling was observed [56]. In Ref. [57], the shortest probes revealed β^* -relaxation in addition to the normal α -relaxation and β -relaxation. Reorientation of detrapped molecules dissolved in PS revealed by electron parametric resonance is much faster even at low temperatures (190 GHz at 200 K) and encounters much lower barriers ($\sim 600 \text{ J}/(\text{mol}\cdot\text{K})$) [58].

Non-linear optics probe molecules dispersed in PS [59] revealed that below T_g the relaxation time τ follows the *Arrhenius* form with activation energies of 45 – 50 $\text{kcal}/(\text{mol}\cdot\text{K})$, or 188 – 209 $\text{kJ}/(\text{mol}\cdot\text{K})$. Similar relaxation has been found in labeled PS [60]. Other non-linear optical probe molecules have much longer decay time ($\sim$ days) [61]. Relaxation of poled order in dye doped PS was probed by isothermal and non-isothermal current measurements [62]. Neutron scattering revealed that the fast process of phenyl rings starts at 200 K, and main chain starts at 250 K [63]. The relaxation of the segmental alignment dichroism of cold rolled PS at 60 °C can be fitted by two single exponential functions of time with RT's of 76 s and 3600 s [39].

The rubbing induced birefringence (RIB) relaxations of a number of polymers were first studied by Kovacs and Hobbs [44]. Significant relaxations were observed below T_g . In Part-III, we found that the physical aging effects are absent in the relaxation of RIB in PS, and the relaxation involves very small length scale. A phenomenological model based on individual birefringence elements was proposed for the RIB relaxations. The relaxation times (RT's) of the elements were found to be independent of the thermal or stress history of the samples, either before or after the formation of the birefringence. The RT's were also independent of the molecular weight, rubbing conditions, and film thickness, while the initial RT's distribution function did depend on the molecular weight and rubbing conditions. The model provided quantitative interpretations that agreed very well with all the reported experimental results, and shed important light to the novel behaviors of the RIB relaxation in polymers below T_g .

In this part, we report on the RIB relaxations of other glass forming polymers, including PC and PS derivatives with various modifications to the phenyl ring side group. It is found that the RIB relaxations follow qualitatively the same way as PS, but there is quantitative difference in minor details among them. On the other hand, they are qualitatively different from any of the other reported relaxations mentioned above [39, 57 – 68]. No physical aging effects in the relaxations of RIB are found. The relaxations are then analyzed under the same theoretical framework as in Part-III. The energy barrier height decreases with decreasing temperature in all the cases, leading to a sub-*Arrhenius* form of RT dependence on temperature at temperatures below T_g .

2. Experiments

Polymers in toluene solutions were spin-coated on thermally grown SiO_2 on silicon substrates. The samples were then annealed at 20 °C above T_g in vacuum for at least 24 hours, and slowly cooled down (< 0.1 °C/min) and stored at room temperature before testing. The thickness of the resulting polymer films ranged from 38 nm to 70 nm. Rubbing was done on a home-made apparatus. Each rubbing pass covered 2 cm distance at a speed of 1 cm/s in one direction, with a normal pressure of 9 g/cm^2 , except for the B5 samples which required 25 g/cm^2 . The optical RIB of the PS films was measured using the reflectance difference spectroscopy at 633 nm in wavelength.

The RIB vs rubbing pass at 23 °C of the polymers behaved in a similar way as PS. The birefringence increased quickly with the first few rubbing passes, and then gradually approached the saturated value. For PC about 10 % of the total birefringence was created in the first 5 rubbing passes, and the subsequent 75 passes created the remaining birefringence.

Further rubbing after saturation resulted in eliminating roughly the same amount of birefringence as creating it, and the net birefringence fluctuated around the saturation value with amplitude of about 1 % of the saturation value. Other polymers behaved almost the same. The RIB approached saturation at about 80 rubbing passes, except for B2 samples, the saturation pass of which being 60 due to its low molecular weight. The net birefringence value of each sample was measured within 100 s after the last rubbing pass. It was then used as the normalization factor in determining the normalized birefringence (NB) in the subsequent relaxation experiments. Details about the samples parameters and the maximum birefringence are listed in Table 3. The maximum birefringence ranges from 8.0×10^{-3} for B2 samples (poly(4-methylstyrene), $M_w = 2.7$ kg/mol) to nearly 6.0×10^{-2} for B3 samples (poly(4-methoxystyrene), $M_w = 10.5$ kg/mol), as compared to the maximum birefringence of 2.5×10^{-2} for PS. This indicates that the side groups contribute significantly to the RIB.

The RIB relaxation behaviors of the samples were studied by using the following ‘standard’ methods. The first was to measure the NB as a function of temperature when the sample temperature was raised continuously at 2 K/min. The results are referred to as the *Continuous Curves* $\alpha(T)$. The second was the isothermal relaxation of NB , i. e., the NB of a sample was measured as a function of time at a fixed temperature. The third was the combination of the two, i. e., continuous temperature rise at 2 K/min immediately following an isothermal process at a given temperature for a given period of time.

3. Results and Discussions

3.1. Disrupted continuous curve

Rubbing deforms the surface region of the sample and puts the sample in non-equilibrium. To verify the absence of physical aging effects, we studied the effects of thermal processes conducted after rubbing, namely the disrupted *Continuous Curve* experiment, in the same approach as in Part-III. The NB curves as a function of temperature of two originally identical PC samples are shown in Figure 14. For a reference sample-A, the temperature was raised at 2 K/min from 23 °C to 180 °C without interruption. The result is a typical *Continuous Curve*. The second sample, sample-B, underwent more complicated temperature sequence. First the temperature was raised continuously from 23 °C to 100 °C at 2 K/min. Its NB decreased in almost the same way as sample-A up to 100 °C. Upon reaching 100 °C the temperature was lowered at 2 K/min till 30 °C. The NB increased slightly and linearly with the lowering of temperature due to thermal expansion. Upon reaching 30 °C the temperature was raised again to 100 °C at 2 K/min. The NB traces back the nearly flat line formed during the lowering of temperature. Upon reaching 100 °C again, the sample was dropped into liquid nitrogen, and then let to warm up in a dry air ambient environment (~ 23 °C) for 16 hours. During the period no RIB change was observed. Finally the temperature was raised continuously from 30 °C to 180 °C at 2 K/min. The NB again traced the straight line where the temperature was raised from 30 °C to 100 °C for the second time, and joint the NB of sample-A after 104 °C.

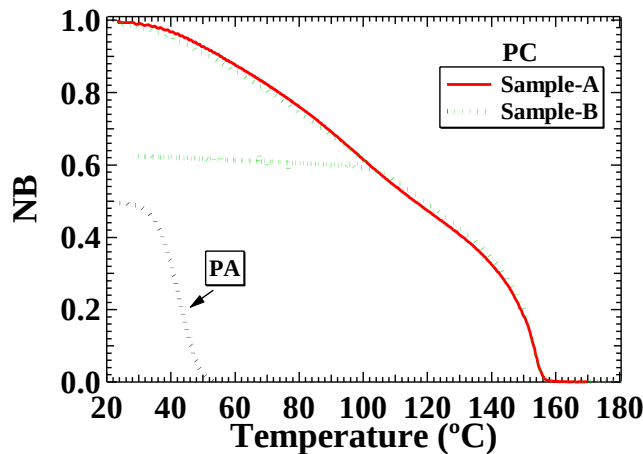


Figure 14. Normalized birefringence versus temperature (*Continuous Curve*) of two PC samples. The solid curve is for a reference sample-A, while the dashed curve is for sample-B which underwent several temperature rise and fall sequences as described in the text.

Table 3. Physical parameters of the samples used in the study.

Sample Name	Polymer	M_w (kg/mol)	Thickness (nm)	RIB (10^{-3})	T_A (°C)	τ_0 (s)	$\eta(C^{-1})$
B2	poly(4-methyl styrene)	2.7 K	58	8.0	45	30 ~ 90	0.36 ± 0.04
B3	poly(4-methoxy styrene)	10.5 K	40	47.4 ~ 59.3	85	16 ~ 25	0.54 ± 0.02
B4	poly(4-methyl styrene)	90 K	49	23.6 ~ 27.4	95	22 ~ 33	0.45 ± 0.02
B5	poly(α -methyl styrene)	112 K	38	16.4 ~ 19.6	140	37 ~ 180	0.32 ± 0.04
B6	poly(4-methyl styrene)	50 K	45	11.6	N/A	N/A	N/A
B7	poly(4-tert-butylstyrene)	3.2 M	40	42.0	130	1.7 ~ 3.7	0.59 ± 0.02
T3	Poly(4-hydroxyl styrene)	69.5 K	50	13.0 ~ 16.8	60	0.33 ~ 2.5	0.38 ± 0.04
PC	Polycarbonate	Poly-dispersed	70	11.4 ~ 15.2	60	74 ~ 134	0.24 ± 0.01
					80	90 ~ 245	0.25 ± 0.02
					100	15 ~ 40	0.41 ± 0.03
					120	5.5 ~ 15	0.49 ± 0.03

Several points are noted in the above temperature sequence. First, the relaxation of *NB* of sample-B was identical to that of sample-A for $T > 104^\circ\text{C}$, i. e., the relaxation above 104°C was not affected by the thermal history below 100°C , within the time scale of ~ 20 hours. Second, no relaxation of *NB* was observed below 95°C after the first temperature rise, indicating that by the first time the temperature reached 100°C the relaxation of *NB* below 95°C had already completed. That is also the reason why the *NB* curves of the second (before

liquid nitrogen quench) and the last temperature rise (after quench and annealing at 23 °C for 16 hours) are identical. Third, above 95 °C the relaxation was still active, and the relaxation of NB was again activated when 95 °C was reached from below in both the second and the last temperature rises. Fourth, unlike in the case of physical aging where further non-equilibrium can be introduced by additional thermal process, quenching or other thermal process below 100 °C brought no increase to the remaining RIB.

According to the conventional physical aging theory, the quench in the above case will freeze the thermodynamic state and the segmental RT's at 100 °C. If the linear compliance of the sample is tested at 30 °C, its characteristic time will be close to that at 100 °C, and many orders of magnitude shorter than the one in thermodynamic equilibrium [1]. If the RIB RT's had followed the trend of the conventional segmental RT's in the quench process, then the measured NB would have decreased during the 16 hours at 23 °C and when the temperature was raised again from 30 °C, because the RT's should have been close to those at 100 °C. The portion of curve-B above 104 °C should have shifted horizontally to the left (lower temperature), and the amount of shift would have depended on the elapse time at 23 °C, as is indicated by the imaginative curve labeled 'PA' (PA stands for physical aging) in the figure. When the temperature reached 100 °C for the third time the thermodynamic state of sample-B was certainly different from that of sample-A at the same temperature. The fact that sample-B relaxed in the same way as sample-A at above 104 °C indicates that although the thermodynamic state of sample-B was different from sample-A, the portion of RIB that would relax at above 104 °C was still the same as before, unaffected by the quenching and reheating.

3.2. Continuous Curves

The two solid curves in Figure 15 are the *Continuous Curves* of two PC samples, one rubbed for 5 passes and the other rubbed till saturation. The curves are smooth and monotonic, without step-like features which could be caused by possible discrete RIB domain relaxations. The temperature T_0 at which RIB reaches zero is 156 °C, which is close to the glass transition temperature T_g of PC. The curve for the lightly rubbed sample is lower than that of the one rubbed to saturation. The density distribution functions $N(\xi, 0)$ of the two samples (dashed curves in Figure 15) obtained by using Eq. (10) in Part-III are depicted as well. Unlike low molecular weight PS or lightly rubbed high molecular weight PS, where the density function is nearly flat between $\xi \sim 23$ °C and $\xi \sim T_g$, the density function of even the lightly rubbed PC sample has a peak right below T_0 , and the rest of the density is nearly flat. For the rubbed to saturation sample, the peak is even higher. This indicates that unlike in PS, initial rubbing on PC already creates more favorably the high energy barrier birefringence elements. Like high molecular weight PS, further rubbing creates even more high-barrier elements and relatively less low-barrier elements. The width of the peak of PC, however, is narrower than that of PS.

More *Continuous Curves* for other polymers rubbed till saturation are shown in Figure 16(a). All curves behave qualitatively the same. The RIB approaches zero near the T_g of the corresponding polymers, except for poly(4-tert-butylstyrene) (B7) which has a tail extending well above its T_g . Again, all curves are without step-like features, which rules out domain-like relaxation behavior. The density functions of the polymers obtained from the curves in Figure 16(a) are depicted in Figure 16(b). It is seen that except for poly(α -methyl styrene) (B5), all the others show a peak in their density functions. The shape of the density function of the

poly(4-methyl styrene) (B4) sample is close to that of high molecular weight PS, with a peak near $\xi = 90$ °C. For the same type of polymer (B2) with lower molecular weight ($M_w = 2.7$ kg/mol) the peak of the density is near the barrier value of $\xi = 50$ °C. The density functions of poly(4-methoxy styrene) (B3) and poly(4-tert-butylstyrene) (B7) have high peaks below their T_g 's but with somewhat different shapes. The detailed differences between these polymers indicate different microscopic details of the birefringence elements in different polymers, which remain to be further explored.

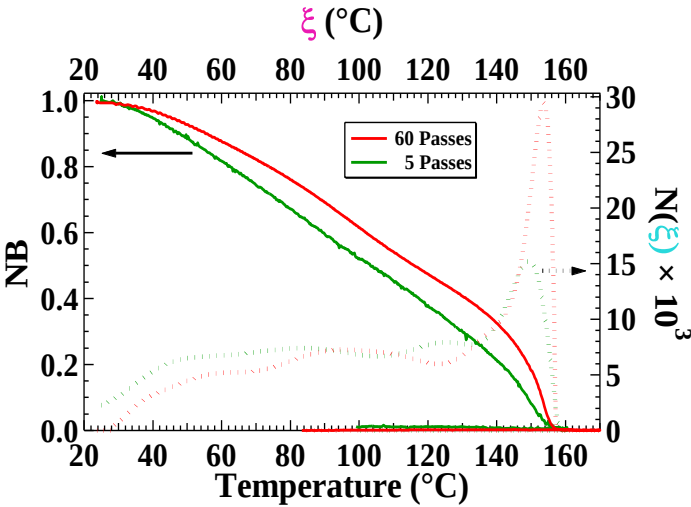
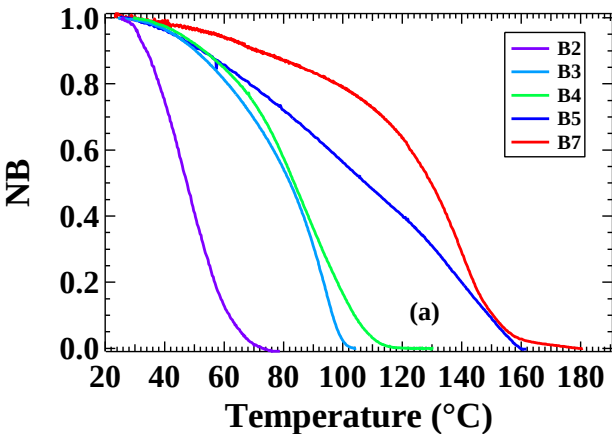


Figure 15. *Continuous Curve* (left and lower axes) and *distribution of barriers* (right and upper axes) of two PC samples, one lightly rubbed and the other rubbed till saturation.



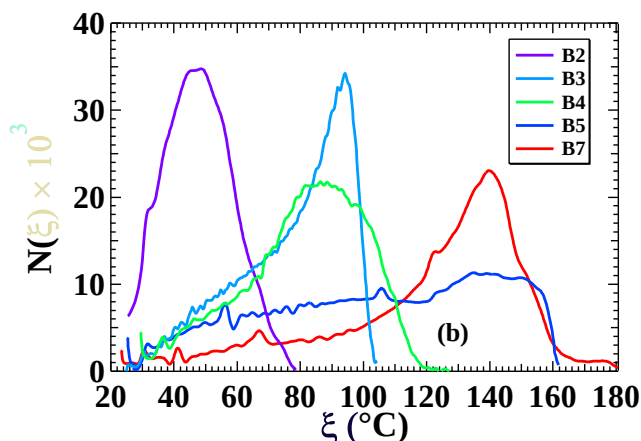


Figure 16. (a) *Continuous Curves* and (b) Density distribution of barriers of several polymers.

The surface layer of PS-like polymers is expected to have a gradient of mobility enhancement, with the top layer at the surface being much more mobile than the one deep in the bulk. The density function of the polymers presented here might be related to such depth dependent mobility, with the birefringence elements with higher barriers being in the deeper region from the surface, and the elements with lower barriers closer to the surface. Further investigations are required to verify the hypothesis.

3.3. Isothermal relaxation curves

Figure 17 shows the RIB isothermal relaxations of several samples as a function of time, together with a PS sample for comparison. The $NB(t)$ curve for B2 has been shifted upward by 0.3 for clarity. All curves behave qualitatively the same. For example, when the temperature is raised quickly from 23 °C to the isothermal relaxation temperature T_A (60 °C for PC, PS and T3, 45 °C for B2), there is a quick drop of NB within ~ 10 s, because the elements with barrier height $23\text{ °C} \leq \xi \leq T_A$ will readily relax. The NB then decayed slowly, approaching logarithm in time. The RT's of the polymers span a wide range. Some are shorter than 10 s, while others are longer than 10^4 s. For example, for PC, 17 % of the elements have RT's shorter than 10 s, while over 70 % of the elements have RT's exceeding 10^4 s. At such rate, it would probably take a time in the geological time scale for the remaining RIB elements of PC to relax completely. Similar conclusions can be drawn for the other polymers.

3.4. Temperature lag

The temperature lag phenomenon has been observed in the RIB relaxations of all the polymers we have investigated in this study. Figure 18 shows a typical set of experimental temperature lag *Continuous Curves*. Notice that after the samples had stayed at a certain temperature T_A for certain duration t_A , subsequent temperature rise above T_A did not bring the RIB to decrease immediately. Instead, the RIB remained unchanged until a higher temperature $T_A + T_{Lag}$ was reached. Beyond $T_A + T_{Lag}$ the RIB started to decrease again, in much the same way as the sample without having spent time t_A at T_A . The temperature lag T_{Lag} was larger for longer annealing time t_A . According to the discussion in Part-III, the dependence of RT of the birefringence elements on the barrier height parameter ξ , in the form

of Eq. (5A), can readily be obtained from the measured T_{Lag} and t_A , namely $t_A = \tau_0 e^{\gamma T_{Lag}}$. The experimental t_A vs T_{Lag} data are presented in Figure 18 together with the least square fittings. The obtained parameters τ_0 and γ are listed in Table 3. It is seen that the value of τ_0 differs by up to a factor of 10 for all the polymers except for T3, its τ_0 being about 100 times smaller than the rest of the polymers. The exponential parameter γ varies by a factor less than 3, ranging from 0.23 for PC at 60 °C to 0.59 for B7 at 130 °C. The variation is within that of the temperature dependent γ of PS. There is no correlation between γ and T_0 of the corresponding polymer, even though their T_0 varies from about 80 °C (B2) to nearly 180 °C (B7), indicating that the relaxation of RIB is influenced only by a very small scale local environment. Taking into account the fact that in PS nearly 90 % of the RIB is due to segmental distortion and the fact that the RIB relaxations of all the polymers studied here behave in much the same way, we speculate that the majority of RIB in these polymers is due to the segmental distortion in the polymers.

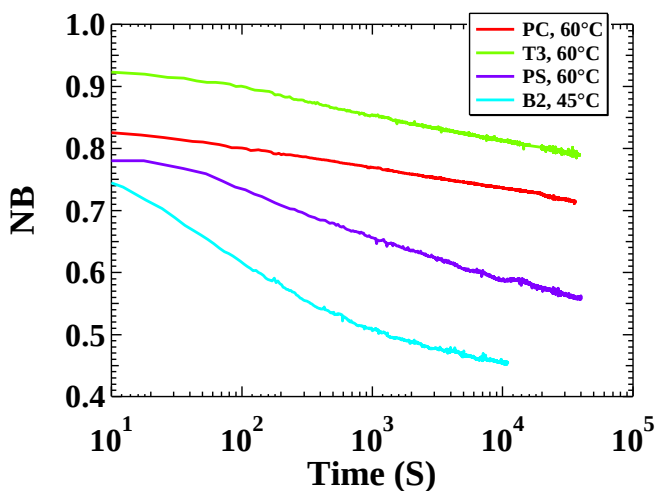


Figure 17. Isothermal relaxation curves of RIB of several polymers.

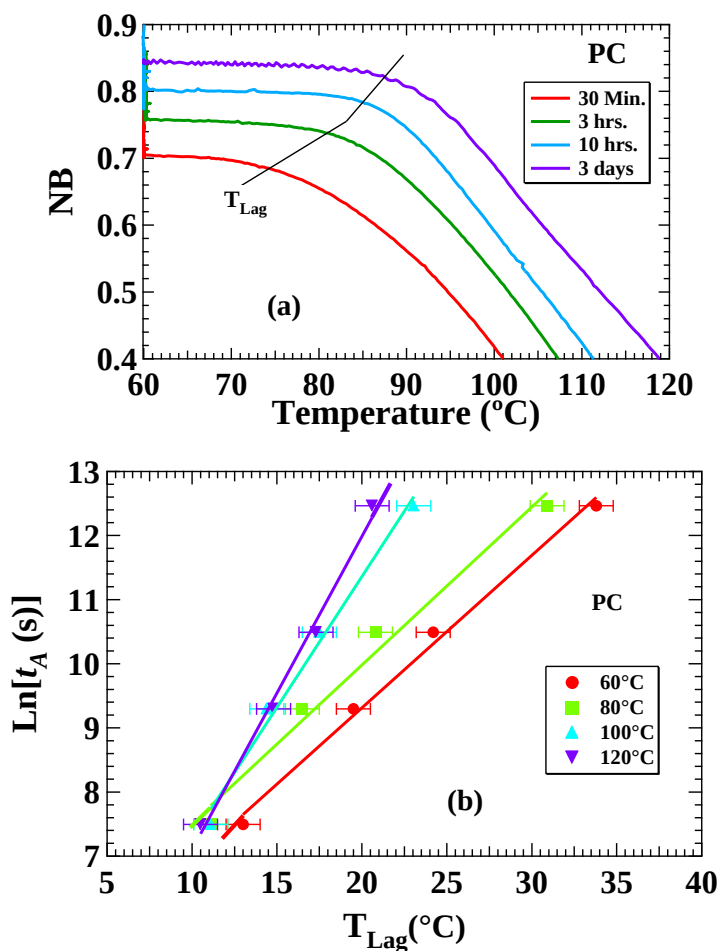
The samples listed in Table 3 are all thick enough that the finite thickness effects are avoided. This can be verified by the fact that none of their T_0 is substantially lower than their T_g . In Part-III, we have shown that the amount of temperature lag of PS is independent of the film thickness. We expect the same for the polymers presented here.

We want to emphasize again that the temperature lag phenomenon is in contradiction with the effects of physical aging, proving once again that aging effects are absent in the relaxation of RIB. In the temperature lag phenomenon, the RIB remains unchanged when the temperature is still in the range of $T_A + T_{Lag}$, while above $T_A + T_{Lag}$ the RIB decreases with the increasing temperature in the same way as a sample without going through the annealing (aging) at T_A . The annealing at T_A eliminated all the RIB elements up to about $\xi \leq T_A + T_{Lag}$, but left the ones with ξ 's well above $T_A + T_{Lag}$ unchanged. This is in stark contrast with the effects of physical aging, where the segmental relaxations at *all* temperatures sufficiently

below T_g , regardless whether they are above or below the aging temperature, are affected by the aging process [1].

3.5. Temperature dependence of energy barriers

At fixed annealing times the temperature lag T_{Lag} is usually temperature dependent. A typical one is shown in Figure 19(a). The general trend is that T_{Lag} decreases with increase temperature. Figure 19(b) summarizes T_{Lag} at fixed annealing time of 10 hours at different temperatures for several polymers. It is consistent with the increase of parameter γ with temperature shown in Tab. 3. For PC, T_{Lag} is nearly temperature independent above 100 °C, and increase with decreasing temperature below 100 °C at about the same rate as PS. For B6, the T_{Lag} increases with decreasing temperature in the entire temperature range of investigation and at a rate faster than PS. For T3, T_{Lag} is nearly constant below 80 °C and then decreases with increasing temperature at a rate nearly the same as B6. These detailed differences among the polymers suggest the influence of detailed microscopic environment on the RT's of the RIB elements.



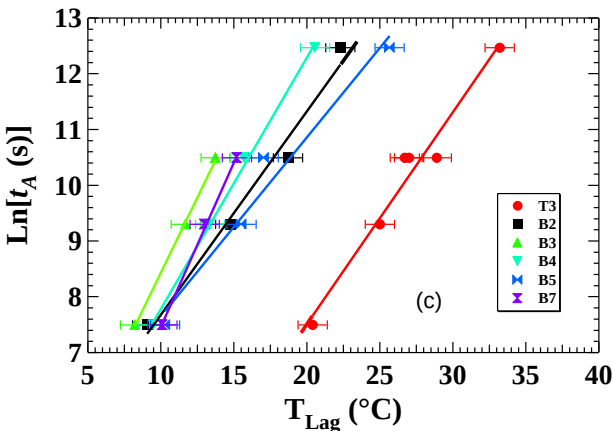


Figure 18. (a) The T_{lag} curves of PC at fixed temperature and different annealing times; least square fittings of logarithmic annealing time t_A vs T_{lag} for (b) PC at different temperatures, and (c) other polymers.

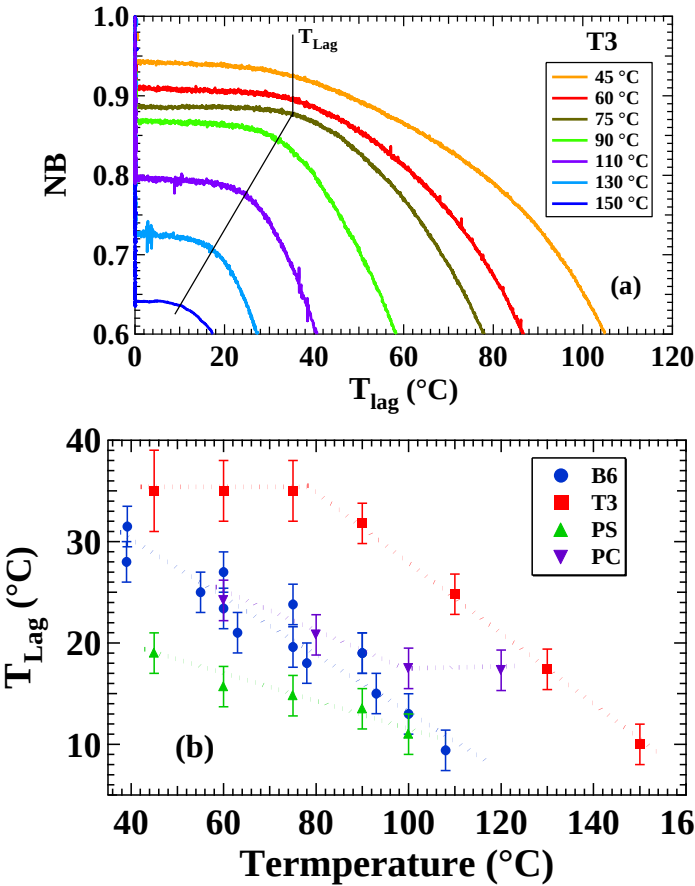


Figure 19. (a) Typical *Continuous Curves* of PC showing T_{lag} at fixed annealing time of 10 hours and at different temperatures; (b) T_{lag} vs temperature at fixed annealing time of 10 hours of several polymers.

The highest energy barrier for PC at $T = 120\text{ }^{\circ}\text{C}$ for the RIB elements with $\xi = 150\text{ }^{\circ}\text{C}$ is $E = 677\text{ kJ/mol}$, which is lower than the value for segmental relaxations of $958\text{ kJ/(mol}\cdot\text{K)}$ [52]. The energy barriers of the same elements at $60\text{ }^{\circ}\text{C}$ are $E = 273\text{ kJ/mol}$, which is less than half of the value at $120\text{ }^{\circ}\text{C}$, mainly due to the temperature dependence of γ . Similar results are obtained for other polymers. Such results have an interesting implication. It is well known that above T_g the segmental RT's follow the Vogel – Fulcher form [3] [52] [53], which increases faster than the *Arrhenius* form with decreasing temperature. It is equivalent to an *Arrhenius* form with an energy barrier that *increases* with *decreasing* temperature. Below T_g the relaxation times of other forms of relaxation reported so far are in *Arrhenius* form with a smaller but temperature independent barrier ranging from 50 kJ/mol to 209 kJ/mol [54] [55] [59] [60]. What we have observed here is an energy barrier that *decreases* with *decreasing* temperature. The RT still increases with decreasing temperature but at a rate that is slower than the *Arrhenius* form, because the energy barrier is also decreasing. We call it *sub-Arrhenius* form of relaxation times. Figure 20 shows the simulation RT in an *Arrhenius* form and that of PS RIB elements with $\xi = 100\text{ }^{\circ}\text{C}$, based on the temperature dependent RT's obtained in Part-III. The *Arrhenius* energy barrier E and the pre-factor are so chosen such that the two curves have the same slope and value at $T = 100\text{ }^{\circ}\text{C}$. It is clear that the increase of RT of RIB elements with $\xi = 100\text{ }^{\circ}\text{C}$ is indeed slower than the *Arrhenius* form at temperatures much lower than $100\text{ }^{\circ}\text{C}$. Above $T = 100\text{ }^{\circ}\text{C}$, however, the RT of RIB increases faster than *Arrhenius* with temperature.

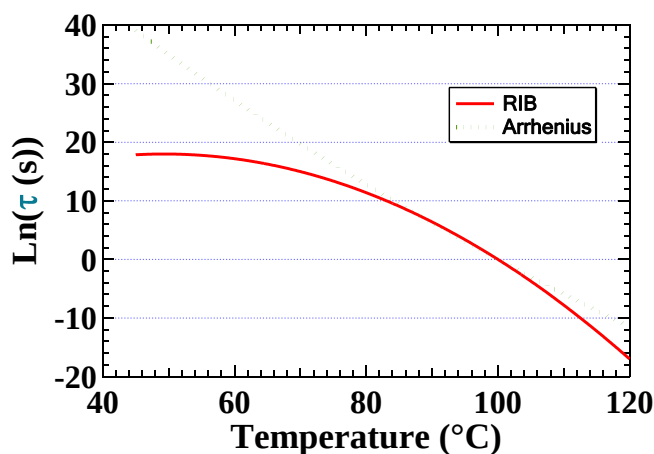


Figure 20. Simulation of RIB relaxation times of PS (solid curve) and an imaginative one following *Arrhenius* form as a function of temperature.

4. Summary

In summary, we have shown that RIB can be generated in many glass forming polymers. Significant relaxations of RIB can take place well below the glass transition temperature T_g , similar to what Kovacs and Hobbs have reported [44]. The relaxation times span a wide range from $\sim 10\text{ s}$ to probably geological time scale. Physical aging effects are absent in the RIB relaxations. The model proposed for the interpretation of RIB in PS works well for all the

polymers investigated here. The energy barriers are of the order of a few hundred kJ/mol and decrease with decreasing temperature. It is in opposite of the trend of Vogel – Fulcher form for polymer segmental relaxations above T_g , and is different from the barriers found in other relaxation processes below T_g , which are temperature independent [39, 57, 60 – 68]. The relaxation behaviors of different polymers are qualitatively similar but somewhat different in quantitative details, such as in the values of the saturated birefringence, the shape of the initial barrier density distribution functions, the rates of barrier decrease with decreasing temperature, and the dependence of relaxation times on temperature and parameter ζ , etc. They are different from any of the relaxations below T_g that have been reported in the literature [39, 57, 60 – 68]. In view of the substantial amount of experimental results, a microscopic model for the relaxations of RIB is much desired.

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Chapter 9

CURRENT DEVELOPMENTS IN DOUBLE HYDROPHILIC BLOCK COPOLYMERS

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ABSTRACT

Double hydrophilic block copolymers (DHBCs) constitute a novel class of water-soluble macromolecules with potential utilization in a wide range of applications. The exceptional combination of features, coming from their block copolymer structure and their ability to be stimuli responsive, establishes this class of copolymers as a core of intense research interest, aiming at elucidating aspects regarding their targeted synthesis, solution behavior and application possibilities. In this chapter, the current developments in the field of double hydrophilic block copolymers are discussed. In particular, synthetic strategies leading to the preparation of DHBCs are described. Moreover, their aqueous solution behavior is examined in respect to their ability to self assemble, due to changes in the solution temperature, and/or pH, as well as due to complexation. Additionally, the potential applications of DHBCs in mineralization processes, nanomedicine, nanotechnology and so on are mentioned. Finally, future perspectives in the field of DHBCs regarding general polymer science and nanotechnology issues, as well as open scientific questions, on synthesis and solution behavior of this class of materials, are also discussed.

1. INTRODUCTION

Double hydrophilic block copolymers (DHBCs) are a class of polymers that combine the self assembly ability of block copolymers with the water solubility of hydrophilic macromolecular chains. Numerous sophisticated works have been already described in the literature, indicating the potential of this class of copolymers in emerging technologies. The synthesis of novel DHBCs, using either new monomers or post polymerization functionalization schemes, is the subject of intense investigation during the current years.

Moreover their self-assembly in aqueous media has been also studied in considerable detail. Emphasis has been given to the stimuli responsive character of the DHBCs upon environmental changes, like solution pH, ionic strength or temperature. Moreover, the potential utilization of DHBCs in a wide range of applications has been demonstrated in a number of publications.

The synthesis of DHBCs has been realized by several synthetic strategies. Typically, controlled polymerization schemes are used in order to ensure the formation of block copolymers. A plethora of monomers have been polymerized following a number of polymerization mechanisms, involving, but not limited to, anionic polymerization, atom transfer radical polymerization (ATRP) or reversible addition-fragmentation chain transfer polymerization (RAFT). The formation of supramolecular structures, like core-shell micelles or vesicles, has been indentified for a numerous block copolymers upon changes in pH, salinity or temperature. The combination of blocks, able to respond at different stimuli, within the chemical structure of the copolymer chain has immersed as an appealing way for controlling and enriching the self assembly behavior of DHBCs. Finally, DHBCs have been established as a key component in a wide gamut of applications, related to drug and gene delivery, surface functionalization or creation of smart surfaces and mineralization of inorganic matter.

In this chapter recent developments in the field of DHBCs are described. Excellent review articles have already outlined the major features of DHBCs [1,2]. A number of excellent reviews summarize specific aspects of DHBCs in detail [3,4,5]. This chapter is focused on recent advances in the particular research area. The synthetic strategies followed for the preparation of DHBCs, important investigations on their aqueous solution behavior and a number of potential applications are presented. The field is growing rapidly. Therefore, the creation of a complete list of works, concerning DHBCs, is practically impossible and beyond the goal of this chapter. The works presented here have been selected in order to representatively describe the current developments in DHBC research.

2. SYNTHESIS OF LINEAR DIBLOCK DHBCS

The synthesis of a variety of linear diblock DHBCs structures has been realized by the vast majority of the so called controlled polymerization techniques. Herein, we describe recent achievements in the synthesis of DHBCs categorized according to the followed polymerization mechanism.

2.1. Synthesis via Anionic Polymerization Methodologies

Anionic polymerization is known to give model block copolymers with controlled molecular weights, narrow molecular weight distributions and versatile architecture. Anionic polymerization has been used for the synthesis of DHBCs in several cases although this type of polymerization technique is relatively intolerant to the presence of polar functionalities on the monomers utilized. A recent example has been described by Hadjichristidis and coworkers [6]. They have presented the synthesis of a series of poly (2-vinylpyridine-b-

ethylene oxide) (P2VP-PEO) block copolymers with different molecular weights and composition. The synthesis was performed by sequential polymerization of the vinyl pyridine monomer followed by the polymerization of the ethylene oxide, in a polar solvent, Figure 1. The high enough molecular weights, as well as the low polydispersity index of the obtained copolymers, indicate the successful utilization of anionic polymerization techniques for the synthesis of P2VP-PEO DHBCs. The synthesis of P2VP-PEO block copolymers has been reported several years ago [7,8] with rather poor results concerning the purity of the final block copolymers.

Combination of anionic polymerization and post polymerization reactions has been used for the synthesis of poly(acrylic acid-*b*-N,N-diethylacrylamide) (PAA-PDEA) copolymers [9]. Initially the synthesis of a precursor poly(*tert*-butylacrylate-*b*-N,N-diethylacrylamide) (PtBMA-PDEAAm) block copolymer was realized via sequential anionic polymerization of the *tert*-butyl acrylate and diethylacrylamide monomers. However, an amount of PtBMA homopolymer was detected in the crude reaction product. In order to remove the vast majority of the homopolymer, the authors proposed the precipitation of the crude product in hexane, where the homopolymer is highly soluble, in contrast to the block copolymer. The purified block copolymer was subjected to deprotection of the *tert*-butyl group in acidic media, leading to the desirable DHBC. The final block copolymer showed pH and thermosensitive solution aggregation.

DHBCs of the type poly(*p*-hydroxystyrene-*b*-methacrylic acid) (PHOS-PMAA) were also synthesized via anionic polymerization followed by acidic hydrolysis [10]. Both blocks of the precursor poly(*p*-*tert*-butoxystyrene-*b*-*tert*-butylmethacrylate) (PtBOS-PtBMA) copolymers, formed by sequential addition of the protected monomers, could be deprotected in a single step giving the desired pH-responsive block copolymers, Figure 2. Hydrolysis was found to be nearly quantitative and resulted in a series of copolymers with well defined molecular characteristics and of variable composition.

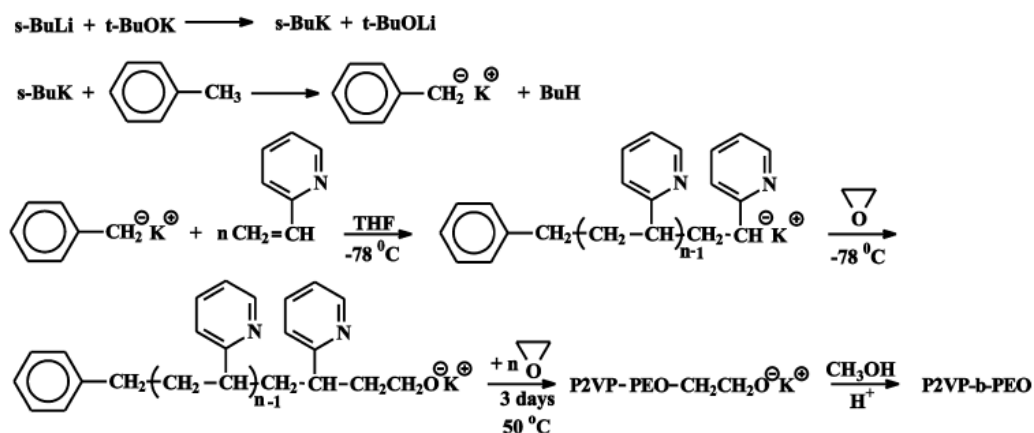


Figure 1. Synthesis of P2VP-PEO DHBCs by anionic polymerization. Reproduced from [6] by permission of Elsevier.

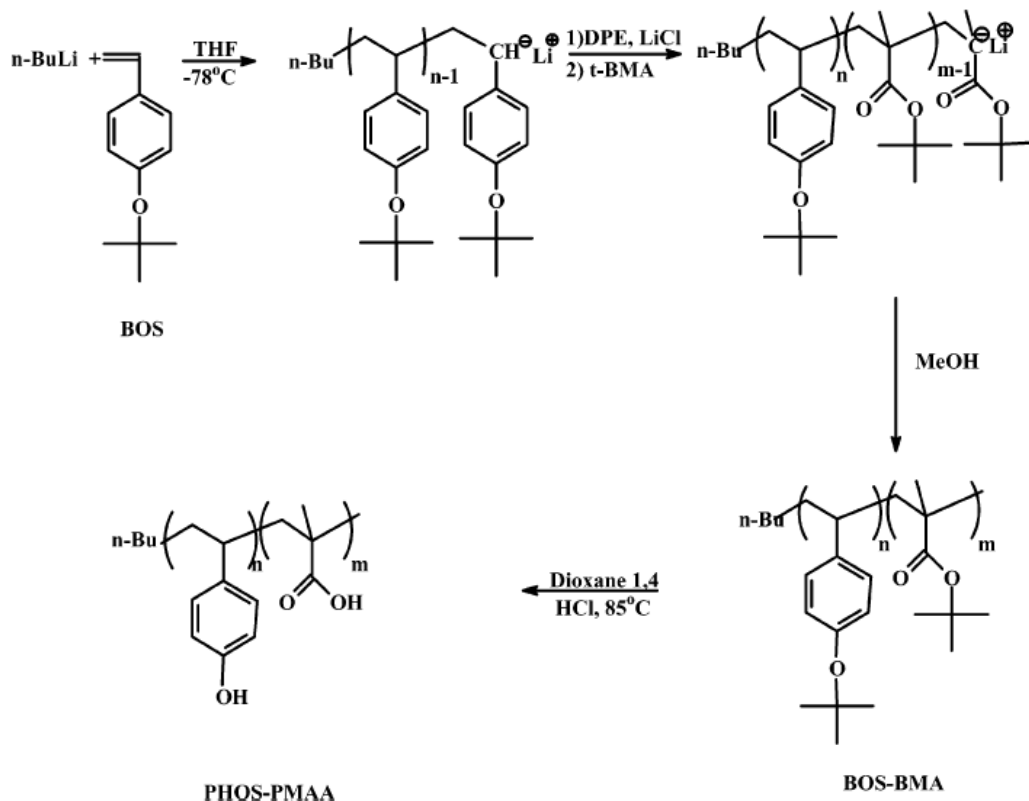


Figure 2. Synthesis of PHOS-PMAA by combination of anionic polymerization and post polymerization deprotection reaction. Reproduced from [10] by permission of the American Chemical Society.

A new family of neutral-ionic block copolymers were synthesized by post polymerization functionalization of anionically prepared poly(isoprene-*b*-ethylene oxide) amphiphilic diblock copolymers. Reaction of the double bonds of the polyisoprene block with excess chlorosulfonylisocyanate, followed by alkaline hydrolysis of the intermediate lactam functionalized copolymers, led to the synthesis of poly[sodium (sulfamate/carboxylate) isoprene-*b*-ethylene oxide] (PSCI-PEO) DHBCs [11]. Degrees of functionalization of the polyisoprene block were found in the range 0.70-0.78 molar. The PSCI block of the copolymers carries surfamate and carboxylate groups that can change the state of their ionization depending on the solution pH, giving to the copolymer variable degrees and type of charges.

Different series of DHBCs were prepared from anionically synthesized poly(*p*-tert-butoxystyrene-*b*-ethylene oxide) (PtBOS-PEO) precursors [12]. Post polymerization acidic hydrolysis of the PtBOS block resulted in poly(*p*-hydroxystyrene-*b*-ethylene oxide) (PHOS-PEO) copolymers. Further functionalization of the PHOS block via a Mannich type aminomethylation reaction gave the poly[3,5-bis(dimethylaminomethylene)hydroxystyrene-*b*-ethylene oxide] (PNHOS-PEO) copolymers, as testified by FT-IR and NMR experiments. In these copolymers the PNHOS block carries two dimethylamino groups per monomeric unit that can be protonated in acidic media and weakly acidic phenolic groups that have their own pH sensitivity. The PNHOS-PEO block copolymers were further quaternized with

methyliodide to give the corresponding cationic-neutral block copolymers that retain their cationic nature at all pH values.

2.2. Synthesis via Atom Transfer Radical Polymerization Methodologies

The synthesis of an interesting DHBC, namely poly (4-vinylbenzoic acid-block-2-(diethylamino)ethyl methacrylate) (PVBA-PDEAEMA), has been presented by Armes and Liu [13]. The synthesis was performed by ATRP using protecting group chemistry in three steps. Initially the polymerization of a tert-butyl protected PVBA macro-initiator was performed followed by the polymerization of the second monomer, DEAEMA. Finally the hydrolysis of the tert-butyl protected block was realized giving rather monodisperse block copolymers.

A similar procedure has been presented by the same group for the synthesis of another block copolymer, namely poly[4-vinylbenzoic acid-block-2-N-(morpholino)ethyl methacrylate] (PVBA-PMEMA). The protection of the VBA monomer with a tert-butyl group is essential for the synthesis of the desired copolymer, otherwise a mixture of PVBA-PMEMA diblock and PVBA homopolymer was obtained. The particular copolymer is expected to have interesting solution properties since the PVBA block is a weak polyacid, while PMEMA is a conjugated acid, soluble over a wide pH range at room temperature and in the absence of salt [14].

The synthesis of an ampholytic block copolymer, namely PMAA-PDEAEMA, carrying carboxylic and tertiary amino side groups, has been also realized by ATRP, as has been reported by Tam and coworkers [15]. Initially, the synthesis of the tert-butyl protected PMAA block was performed using p-toluenesulfonyl chloride as an initiator and CuCl complexed with N,N,N',N',N'',N''-hexamethyltriethylenetetraamine as a catalyst in 50 vol % anisole at 90 °C. The obtained polymer was used as the macroinitiator for the subsequent polymerization of the second monomer, DEAEMA, under similar reaction conditions, Figure 3. The resulted copolymer was subjected to selective hydrolysis, under acidic conditions, for removal of the tert-butyl protecting group.

In the works mentioned, protecting group chemistry has been utilized for the synthesis of ampholytic/zwitterionic block copolymers. However, Armes and coworkers have also presented the synthesis of zwitterionic block copolymers without using protecting groups. In particular, various tertiary amine methacrylate monomers were copolymerized with 2-hydroxyethyl methacrylate to produce diblock copolymers with a hydroxyl functionalized block. The synthesis of the amine containing block was realized in bulk, followed by the polymerization of the hydroxyl group containing monomer in methanol [16]. The obtained diblock precursor was then derivatized using succinic anhydride in order to introduce the desired carboxylic groups on the hydroxyl functional block. The procedure followed led to high monomer conversion and to copolymers having fairly low polydispersities. However, as has been revealed by the solution behavior of the synthesized polymers, the existence of some amine containing segments in the carboxylated block could not be excluded. In order to improve the synthetic procedure, the polymerization of the first block was performed in protic media under mild conditions [17]. Moreover, the order of monomer addition has been also inversed, because of the low blocking efficiency of the amine block, when it was polymerized in methanol. Finally, pure block copolymers, with polydispersities ca. 1.2, were obtained following the above synthetic procedure.

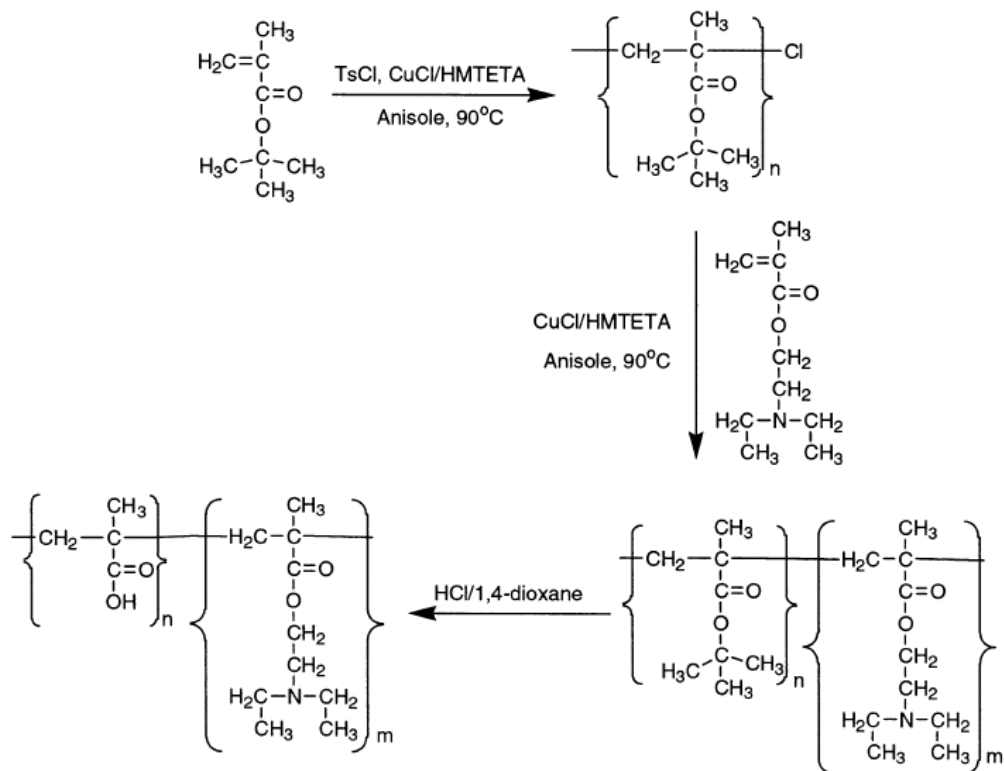


Figure 3. Synthesis of the amphoteric PMAA-PDEAEMA by ATRP. Reproduced from [15] by permission of the American Chemical Society.

The ATRP mediated synthesis of non-zwitterionic copolymers, without the use of protecting groups, has been also presented in the literature [18]. An interesting example is the case of the poly(N-isopropylacrylamide)-b-poly(4-vinylpyridine) (PNIPAM-P4VP) copolymers. The synthesis of the particular type of copolymer was achieved by using conventional ATRP techniques. The molecular characteristics and the data obtained by size exclusion chromatography (SEC) analysis indicate the successful synthesis of copolymers with polydispersity index values ca.1.2.

2.3. Synthesis via RAFT Polymerization

Laschewsky and coworkers have presented the synthesis of a series of DHBCs using RAFT polymerization methodologies, which is a “controlled” free radical polymerization. The system, that they have reported, is a temperature responsive block copolymer, namely poly(N-isopropylacrylamide)-b-3-[N-(3-methacrylamidopropyl)-N,N-dimethyl]ammonio propane sulfonate) (PNIPAM-PSPP) [19]. The synthesis was performed by sequential polymerization of NIPA and SPP monomers. The molecular weight was determined to be close enough to the theoretically calculated one. Interestingly, the followed polymerization procedure led to macromolecular chains with high enough molecular weight, up to about 60,000 g/mol. The same polymerization technique has been also utilized for the synthesis of other polyacrylamide containing DHBCs, like PNIPAM-PDEAEMA [20] or

poly(*N,N*-dimethylacrylamide-*b*-*N*-isopropylacrylamide) (PDMA-PNIPAM) [21]. In the last case, Liu and coworkers have presented the synthesis of a PDMA-PNIPAM, where some azide-containing monomers (AzPAM) have been copolymerized within the PNIPAM block [21]. The above azide-containing monomer seems to be polymerized quite easily in dioxane at elevated temperatures, while the azide groups are relatively inert and compatible with RAFT processes. The authors assumed that the structural similarity of AzPAM and PIPAM monomers has as a result the statistical copolymerization of the two monomers.

The RAFT process has been also used in the synthesis of novel ionic liquid containing DHBCs [22]. The polymerization of ionic liquid monomers was performed in methanolic solutions at elevated temperatures. The synthesis of copolymers with predictable molecular characteristics was described, indicating the living nature of the polymerization procedure. The synthesis of block copolymers of the type poly(ionic liquid-*b*-acrylamide) (PIL-PAm) and PMAA-PIL was successfully realized by using the as synthesized first block as a macro-chain transfer agent for the polymerization of the second block. The final copolymer could be molecularly dissolved in water. However, chemical modification, by either esterification of the carboxylic groups of the PMAA block or ion exchange in the PIL block, could be used for the introduction of hydrophobic character in one of the blocks, leading to the formation of supramolecular self-assembled structures in aqueous media.

The synthesis of a well defined block copolymer, containing a poly(*N*-vinylimidazole) block (PVim), has been demonstrated by Ge et al. [23]. The polymerization was realized via a RAFT procedure employing xanthates as chain transfer agents. Initially, the polymerization of NIPAM monomer, affording PNIPAM macro-CTA, was realized followed by the polymerization of Vim, Figure 4. The obtained block copolymers had controllable molecular characteristics with a M_w/M_n value ca. 1.2. The living nature of the Vim polymerization has been confirmed by kinetic experiments, for the first 150 min of the polymerization reaction. It has to be noted that the above procedure was the first example of the synthesis of PVim containing block copolymers.

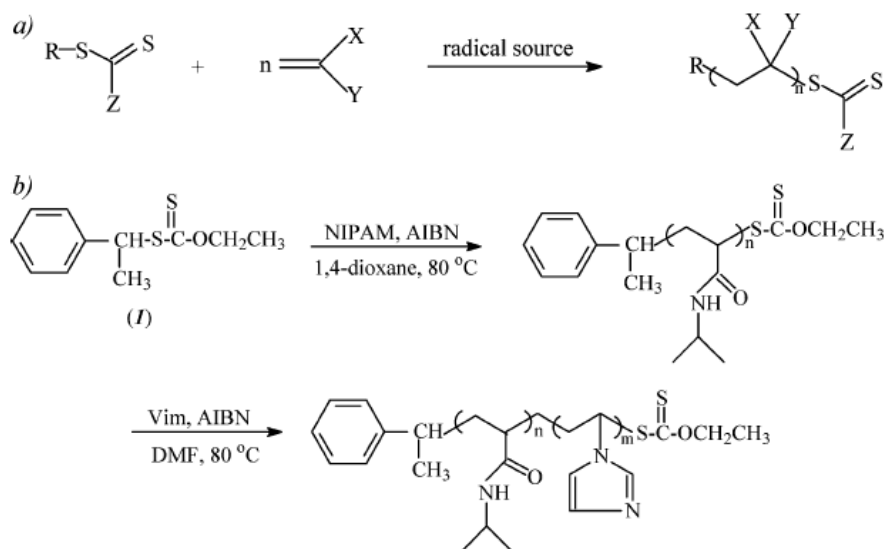


Figure 4. Synthesis of a PVim containing DHBC by RAFT. Reproduced from [23] by permission of the American Chemical Society.

2.4. Synthesis via Other Types of Polymerization Methodologies

Group transfer polymerization (GTP) has been recognized as a powerful alternative methodology, toward the synthesis of methacrylate containing copolymers, with well defined structure and narrow molecular weight distribution. Armes and coworkers have presented the synthesis of a diblock copolymer, namely poly[2-(dimethylamino)ethylmethacrylate-*b*-2-(diethylamino)ethylmethacrylate] (PDMAEMA–PDEAEMA), utilizing the GTP technique [24]. The particular synthesis was the first effort to synthesize a block copolymer in which both component blocks are polybases. The molecular weight of the synthesized polymers was up to about 20,000 g/mol with narrow molecular weight distributions (typically less than 1.15). The chemical modification of the copolymer by quaternization of the PDMAEMA block has been also presented by the same group [25]. Moreover, the synthesis of block copolymers consisting of DMAEMA and other tertiary methacrylate blocks has been also described [26,27]. Finally, Tsitsilianis and coworkers have presented the synthesis of an A-*b*-(B-*co*-C) DHBC where A is PDEAEMA and B-*co*-C is poly[(oligo(ethylene glycol) methacrylate)-*co*-methyl methacrylate] (P(EGMAco-MMA)) [28]. A series of copolymers with different content of MAA were synthesized in order to obtain macromolecules with different hydrophilicity.

An interesting class of DHBCs is the case of the polypeptide diblock copolymers. Lecommandoux and coworkers have presented the synthesis of such a type of copolymer, i.e. poly(γ -benzyl-L-glutamate-*b*-N-trifluoroacetyl-L-lysine) (PBLG-PTFALys). The synthesis was performed by sequential ring-opening polymerization of the corresponding R-amino acid N-carboxyanhydrides. The PTFALys block was synthesized first, followed by the polymerization of the second monomer. The polymerization took place in organic media and at room temperature. The final DHBC copolymer was obtained upon removing the benzyl (Bz) and trifluoroacetyl (TFA) protective groups of L-glutamic acid and L-lysine using KOH in THF. The copolymer is a zwitterionic diblock copolymer with only about 15 repeating units in each block [29].

The synthesis of a hybrid DHBC, containing both a polypeptide block and a polyacrylamide block, has been also presented [30]. The synthesis was realized by using an amine terminated PNIPAM as the macroinitiator in the ring-opening polymerization of γ -benzyl-L-glutamate, followed by deprotection of the benzyl groups of the polypeptide block, Figure 5. Interestingly, samples with high enough molecular weights were obtained following the aforementioned method; however, the polydispersity of the copolymers was also relatively high.

The synthesis of a novel, primary amine containing, DHBC has been described by Liu and coworkers [31]. The synthesis of the amine-containing monomer was performed by a two step click reaction. The preparation of the block copolymer, namely poly(N-isopropylacrylamide)-*b*-1-(3-aminopropyl)-4-acrylamido-1,2,3-triazole hydrochloride (PNIPAM-PAPAT), was realized by RAFT. In the first step, the polymerization of PNIPAM was achieved and the as synthesized polymer was used as the macroinitiator for the polymerization of APAT. However, in order to polymerize primary amine containing monomers, acidic media are needed in order to eliminate some side reactions (the primary amine moieties have to be protonated in order to suppress the side reactions).

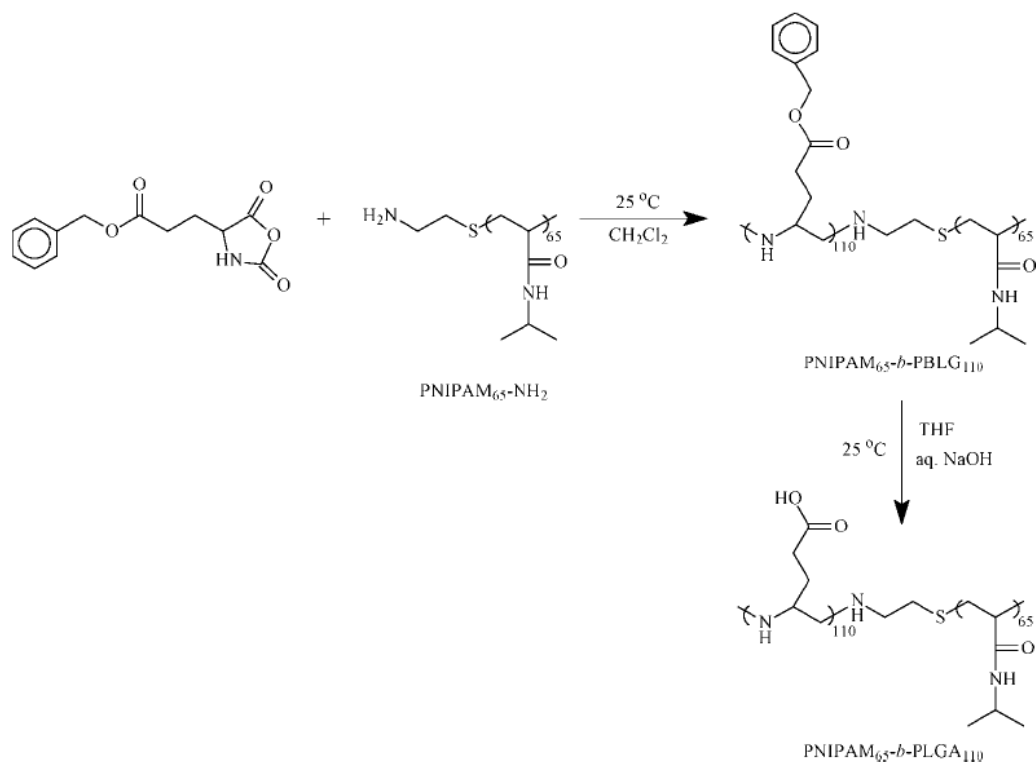


Figure 5. Synthesis of a polypeptide containing DHBC by ring opening polymerization. Reproduced from [30] by permission of the American Chemical Society.

The synthesis of a well defined poly(vinyl alcohol)-*b*-poly(acrylic acid) (PVA-PAA) DHBC has been recently reported in the literature [32] by a two step synthetic scheme. First the synthesis of a poly(acrylonitrile) (PAN) block was realized via cobalt-mediated radical polymerization, using a poly(vinyl acetate) (PVAc) macroinitiator, followed by hydrolysis of both blocks. The polymerization was performed in DMF, a very good solvent for PAN, and at low temperature, where block copolymers with low polydispersity were obtained. The polymerization procedure led to well defined macromolecules with relatively high molecular weights. The obtained copolymers were transformed to the desired DHBCs by hydrolysis, using large excess of potassium hydroxide in a water/ethanol mixture. The successful completion of the hydrolysis reaction was monitored by NMR and IR spectroscopy. An additional macroscopical indication of the DHBC formation was the aqueous solubility of the reaction product.

An interesting approach for the synthesis of DHBCs has been presented by Shi and coworkers [33]. In particular, end functionalized homopolymers, namely P4VP and PNIPAM, were synthesized by conventional RAFT polymerization, using the appropriate initiators. Mixing equimolar amounts of the above polymers led to the formation of well defined non-covalent bonded DHBCs through inclusion complexation between the β -cyclodextrin and the adamantyl end groups, Figure 6. The copolymer seems to behave as a typical diblock copolymer, i.e. forms supramolecular self-assembled structures under appropriate solution conditions. Furthermore, the synthesis of a “covalent analogous” polymer via ATRP methodologies has been also described in another work [34].



Figure 6. Schematic illustration of DHBCs formation through inclusion complexation. Reproduced from [33] by permission of The Royal Society of Chemistry.

A similar approach has been also used for the synthesis of “covalently linked” DHBCs. Polysaccharide based DHBCs were prepared by end-to-end coupling of two readily available biocompatible water-soluble homopolymers [35]. The synthesis was a two step reaction where a) a terminal aldehyde group of a dextran homopolymer was oxidized and b) a monoamine end functionalized PEG reacted with the oxidized dextran, via a lactone aminolysis reaction. Interestingly, the obtained polymer could be chemically modified, in a controlled way, in order to produce neutral-cationic or neutral-anionic DHBCs.

Finally, the controlled aqueous polymerization of various monomers, via nitroxide mediated polymerization has been recently demonstrated by Phan and coworkers [36]. The polymerization was realized by using a chemically modified nitroxide, which bears a carboxylic acid function. The introduction of carboxylic groups offers water solubility, when the groups are in the ionized form, allowing the controlled polymerization of water soluble monomers. The controlled (co)polymerization of nonionic, anionic and cationic monomers has been demonstrated under mild conditions. The polymerization scheme presents the characteristics of controlled polymerizations, such as first-order kinetics up to high conversions, linear increase of the molecular weight with monomer conversion and good agreement between experimentally obtained and theoretically expected molecular weights. However, the relatively high polydispersity index values of the products discourage the use of the above polymerization scheme for the preparation of well defined block copolymers for structure-properties relationship investigations. Additionally, the synthesis of block copolymers was accompanied by the presence of unreacted homopolymer, due to some termination reactions.

3. SYNTHESIS OF DHBCs WITH OTHER ARCHITECTURES

3.1. Linear Multiblock DHBCs

The synthesis of an ABA triblock copolymer, where A is a P2VP block and B is a PEO block, was described in the literature [6]. The synthesis of the copolymer was performed via anionic polymerization high vacuum techniques. Initially a diblock copolymer was synthesized by sequential polymerization of vinyl pyridine and ethylene oxide monomers. Subsequently, the as synthesized diblock copolymer was reacted with p-dibromoxylene. A portion of the diblock copolymer reacts with the difunctional reagent leading to the formation of a triblock, namely P2VP-PEO-P2VP, having double the molecular weight of the precursor

diblock. Fractionation of the crude reaction product took place at elevated temperature in order to remove the unreacted excess diblock.

Anionic polymerization has been also used for the synthesis of another ABA DHBC, where A is PAA and B is P2VP [37,38]. The synthesis of a precursor polymer was realized by using a bifunctional initiator and by sequential addition of 2VP and tert-butyl acrylate monomers (tBA). The obtained SEC data indicate the formation of well defined triblock chains, without the presence of neither P2VP homopolymer, nor P2VP-PtBA diblock copolymer. The formation of the desired DHBC triblock was finally achieved by acidic hydrolysis of the PtBA blocks in order to remove the tert-butyl protecting group. A similar procedure has been used by the same group for the preparation of another ABA block copolymer, namely PEO-P2VP-PEO. However, in this case the deprotection step is not necessary, since the PEO block is already hydrophilic [39].

The synthesis of an ABA triblock double hydrophilic copolymer, where A= PEO and B= PSCI has been also reported via the utilization of chlorosulfonylisocyanate functionalization reaction on an anionically synthesized poly(ethylene oxide-*b*-isoprene-*b*-ethylene oxide) triblock precursor [11].

Finally, the synthesis of a BAB triblock copolymer, where A is a PDMA block and B is a PNIPAM block, has been realized via RAFT polymerization using a symmetrical bistrithiocarbonate as the bifunctional chain transfer agent for the polymerization of the middle block [40]. The polydispersity indices for the synthesized triblocks, determined by SEC, were in the range 1.19-1.31. The high M_w/M_n values could be also correlated with the possible interaction of the copolymers with the column material, as well as to the association of block copolymer chains in the carrier solvent. A series of copolymers with an identical middle block and outer blocks with different molecular weight have been synthesized. However, the presence of diblocks or unreacted homopolymers in the final product could not be excluded.

An ABC triblock terpolymer was successfully synthesized by a sequential three-step RAFT polymerization process of N-*n*-propylacrylamide, N-isopropylacrylamide and N,N-ethylmethacrylamide monomers [41]. The different cloud points of the respective blocks, present in the terpolymer, are responsible for the rich temperature depended solution self-assembly of the sample in aqueous media.

In the concept of water soluble ABC block copolymers one has also to mention a huge amount of work that has been presented on the synthesis and solution behavior of copolymers with two hydrophilic blocks and one hydrophobic. However, the presence of a permanently hydrophobic block in this type of block polymers makes difficult their categorization as DHBCs. The synthesis of ABC triblock terpolymers with at least two hydrophilic blocks has been realized via a number of polymerization methodologies, like GTP and cationic polymerization, and has been studied in detail [42,43,44,45,46,47,48,49]. In most of the cases, the terpolymers were based on suitably functionalized methacrylate monomers and have been produced by the sequential monomer addition method.

Finally, the synthesis of multiblock DHBCs has been also reported. The desired multiblocks have been obtained via RAFT polymerization, using polytrithiocarbonate as the chain transfer agent [50]. The synthesis of two multiblocks with different molecular characteristics was achieved. Both block copolymers were consisted of PDMA and PNIPAM sequences. The molecular characteristics of the synthesized macromolecules were studied

both by NMR and SEC. Polymers with quite high molecular weight were obtained. However, it has to be noted that the polydispersity of the samples was about 1.5.

3.2. Non Linear Double Hydrophilic Block Copolymers

One of the first syntheses of non-linear DHBCs has been described by Armes and coworkers [51]. They have prepared a series of A₂B miktoarm star copolymers via ATRP of several hydrophilic methacrylate monomers by utilizing Jeffamine macroinitiators. The macroinitiators (which were the B blocks of the copolymers) were synthesized by reaction of the terminal amino group of the polyalkyleneoxide chain with two equivalents of 2-hydroxyethylmethacrylate, followed by esterification with 2-bromoisobutryl bromide. The A blocks carried pH responsive substituted amine groups (water soluble and positively charged at low pH) or zwitterionic phosphatidylamine groups. The expected chemical structures for the macroinitiators and the resulting star copolymer were confirmed by NMR, MALDI-TOF-MS and SEC techniques.

Liu and coworkers [52] have described the synthesis of two different types of branched block copolymers, namely A₂BA₂ and A₄BA₄. In both cases, the B block was poly(propylene oxide) (PPO) while the A block was PDEAEMA. The synthesis was realized via ATRP using a commercially available diamine terminated PPO as the backbone of the copolymer. The initial PPO central block was functionalized in order to introduce multi-ATRP initiator functionalities at both free ends of the polymer. Subsequently the polymerization of DEAEMA monomer was performed following typical ATRP procedures. The followed synthesis scheme is shown in Figure 7.

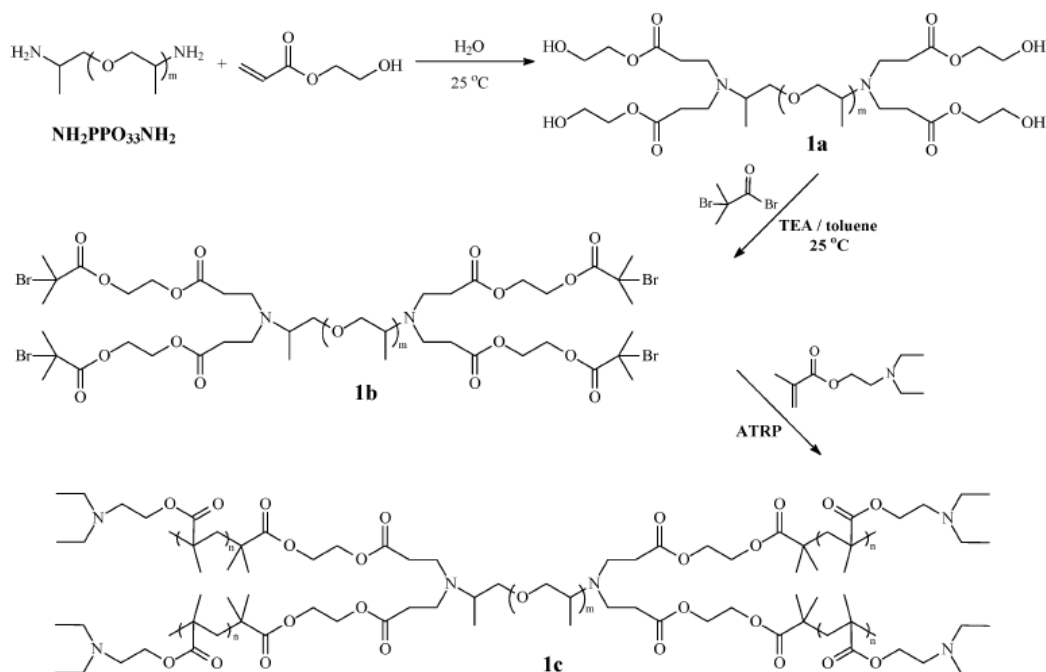


Figure 7. Synthesis of an A₂BA₂ DHBC by ATRP. Reproduced from [52] by permission of the American Chemical Society.

ATRP has been also utilized for the synthesis of an AB₄ miktoarm star copolymer, where A is a PNIPAM block and B is a PDEAEMA block [53]. At first, a mono-amino terminated PNIPAM homopolymer was synthesized. Subsequently, an addition reaction on the amino group using glycidol was realized, followed by esterification with excess 2-bromoisobutyryl bromide. The end functionalized PNIPAM formed in this way could be used as a tetrafunctional macroinitiator for the polymerization of DEAEMA monomers via ATRP. The formation of pure AB₄ miktoarm star copolymer was assumed by the authors based on results from size exclusion chromatography. However, the polydispersity index was quite high ($M_w/M_n = 1.23$), therefore, SEC alone could not unambiguously confirm the level of purity of the miktoarm stars.

The synthesis of a miktoarm star copolymer of the type A_nB_n has been also demonstrated. The synthesis was performed via ATRP using divinylbenzene, as the core cross-linking agent. PEO macroinitiator chains were utilized for the polymerization of divinylbenzene forming a star polymer, with a random number of branches. The above star polymer was used as a multi-functional initiator for the polymerization of methacrylate monomers. Therefore, the synthesis of an amphiphilic miktoarm star copolymer was realized [54]. Finally, the hydrolysis of the protected methacrylate block led to the preparation of the desired DHBCs, namely the PEO_n-PMAA_n stars. SEC analysis of the precursor PEO_n-PMMA_n copolymer revealed a relatively broad molecular weight distribution. Nevertheless, this is a good example for the synthesis of A_nB_n double hydrophilic star copolymers.

The synthesis of a series of star copolymers using GTP has been described by Patrickios and coworkers [55]. The general route for the synthesis of the copolymers was the combination of the conventional polymerization of the desired monomer by GTP and the use of a bi-functional coupling agent, as has been described before. The synthesis of four different types of star copolymers, composed of DMAEMA and methoxy hexa(ethylene glycol) methacrylate (HEGMA) was presented. In particular, isomeric star copolymer, heteroarm, star block and statistical star copolymers were realized by varying the sequences of the monomers and coupling agent additions. In all cases a constant ratio of the two monomers (DMAEMA / HEGMA = 9/1) was utilized. The presence of linear (co)polymer precursors was evident by SEC analysis of the samples, indicating the incomplete formation of star copolymers.

Finally, the synthesis of a double hydrophilic linear-hyperbranched block copolymer has been realized by a four step reaction [56]. Initially a polyethylene oxide macroinitiator was synthesized either by anionic polymerization of ethylene oxide using Cs as the counterion or by deprotonation of a commercially available monohydroxyl terminated PEO via interaction with cesium hydroxide. Subsequently, the anionic polymerization of ethoxyethyl glycidyl ether monomer (EEGE) was performed under argon and at elevated temperature. The obtained diblock copolymer was subjected to acidic hydrolysis in order to recover the hydroxyl groups, by removing the acetal protecting groups on the PEEGE block. Finally, the desired linear-hyperbranched copolymer was synthesized by initiating the polymerization of glycidol from the hydroxyl groups of the diblock, using cesium hydroxide as the activating agent. The resulting copolymers exhibited low polydispersities, while the molecular weight was up to almost 1.6×10^4 g/mL. It has to be noted that the presented methodology allows for variation of the molecular weight in both the linear PEO block and of the hyperbranched block.

4. SOLUTION SELF-ASSEMBLY OF DHBCs

Several intriguing and interesting self-assembled nanostructures can be produced in aqueous solutions of DHBC, due to the stimuli responsive character of the blocks comprising the copolymer that in turn determines the amphiphilicity of the system. The solution properties of DHBCs can be tuned via the chemical structure of the copolymer and external parameters including solution pH, ionic strength, temperature, as well as the addition of oppositively charged chemical entities. These features open possibilities for understanding the self-assembly motifs in natural occurring systems and facilitates the utilization of DHBCs in a number of advanced nano(bio)technological applications. In the following sections we focus on selective studies concerning the aqueous solution behavior of this type of copolymers.

4.1. Temperature Responsive Self-Assembly

One of the most interesting examples of DHBCs which form self-assembled structures upon changes of solution temperature has been presented by Laschewsky and coworkers [19]. They have developed a system where one of the blocks presents a LCST and the other a UCST. Therefore the copolymer, namely PNIPAM-PSPP, could either be molecularly soluble or associate into aggregates at low and high temperature, Figure 8. The nature of the hydrophobic core of the formed aggregates depends on the solution temperature. In particular the PSPP block is soluble for temperatures higher than 20°C (depending on the molecular weight), while the PNIPAM block is soluble for temperatures lower than 32-34°C (almost independent of the chain molecular weight). In this way, by controlling the molecular characteristics of the copolymer, the desired aggregation/disaggregation profile could be achieved. The studied copolymer is soluble in the whole temperature range under investigation. However, at the low temperature aggregation limit, the insoluble microdomains are relatively polar and probably they have low solubilization efficiency for hydrophobic molecules, a property that would have been useful in the field of nanosized drug carriers.

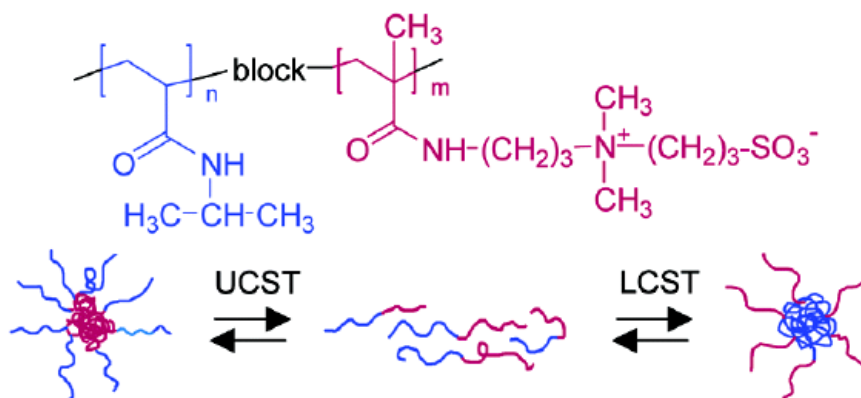


Figure 8. Micellization behavior of PNIPAM-PSPP upon changes in the solution temperature. Reproduced from [19] by permission of the American Chemical Society.

An interesting work on the temperature induced self-assembly of DHBCs has been presented by Pasparakis and Alexander. They have proposed the formation of vesicles by copolymers consisting of a highly hydrophilic poly(2-glucosyloxyethyl methacrylate) block and a water-soluble poly(diethyleneglycol methacrylate) block [57]. The above copolymer is molecularly dissolved at 15°C but forms aggregates at higher temperatures. The size of the aggregates depends on the solution temperature, due to the increased hydrophobicity of poly(2-glucosyloxyethyl methacrylate) upon increasing the temperature of the solution. Interestingly, the aforementioned aggregates were found to be vesicles, as has been demonstrated by transmission electron microscopy.

Schubert and coworkers observed a temperature induced cylinder-to-vesicles transition in aqueous solutions of P2VP-PEO copolymers [58]. By cooling the polymer solution down to 4°C the initial vesicles are transformed into wormlike micelles, through intermediate formation of basket-like aggregates. A subsequent increase in solution temperature allows for the appearance of vesicles through intermediate discoid and octopus-like structures. The preparation of unilamellar and nearly monodisperse vesicles with controlled sizes, in the range 60 to 500 nm, is possible in these systems by appropriate variation of heating rates, polymer concentration, ionic strength, as well as the incubation time at the limits of the transition temperatures. The authors also demonstrated that several model drugs could be encapsulated in the nanostructures formed in each case.

The formation of core-crosslinked, temperature responsive DHBCs micelles have been presented in the literature. The micelles have been prepared by the self assembly of PDMA-*b*-P(NIPAM-co-AzPAM) chains followed by crosslinking, utilizing a difunctional propargyl ether. The formation of the crosslinked micelles can be performed by following two different pathways. In the first one, the micelles were formed upon increasing the solution temperature, since the PNIPAM block becomes hydrophobic at temperatures higher than 32°C, and the rich PNIPAM cores were subsequently crosslinked via click chemistry. In the second approach, the copolymer was molecularly dissolved in DMF, a good solvent for both blocks, and the crosslinking reagent was added leading to the formation of supramolecular structures. After dialysis, of the DMF solution against water, stable polymeric micelles were observed. Both of the above methods had as a result the formation of polymeric micelles, which were not destroyed even at room temperature where both blocks are soluble, Figure 9. In contrast, the micellar core tends to swell at low temperature, leading to relatively larger micelles, indicating the possible use of core-crosslinked DHBCs micelles in drug delivery applications [21].

An insightful work on the temperature induced micellization kinetics has been presented by Zhang et al. [20]. The study was performed by utilizing a PNIPAM-*b*-PDEAEMA copolymer upon jumps of the solution temperature from 20 to 45 °C, where micelles with a PNIPAM core were formed. The solution pH was set at 4, a pH value where the PDEAEMA block is soluble in the whole experimental temperature range. The experimental results indicate the existence of two relaxation processes. The first, fast process was attributed to association of unimers into a large amount of small micelles and the formation of quasi-equilibrium micelles. The second, slow process was almost independent of the polymer concentration, indicating that unimer insertion/expulsion is the main mechanism for the slow process. The authors attribute the above unimer insertion/expulsion mechanism to electrostatic interactions, due to the charged PDEAEMA block. However, the influence of copolymer molecular weight has to be taken into account, as has been demonstrated by the same group later on [59].

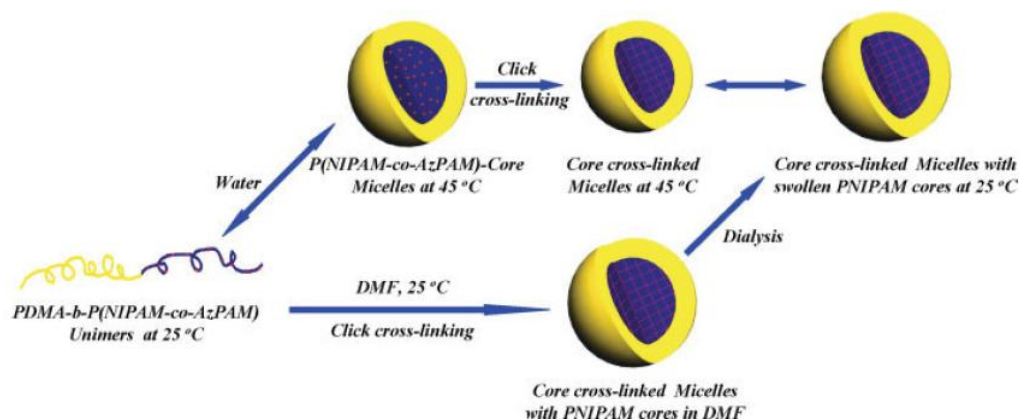


Figure 9. Formation of thermoresponsive crosslinked micelles following two different pathways. Reproduced from [21] by permission of Wiley.

The temperature induced micellization has been also studied for a linear triblock BAB, where A= PDMA and B= PNIPAM [40]. It is well known that the PNIPAM block is temperature responsive, i.e. is soluble for temperatures lower than the LCST. Therefore, the formation of supramolecular structures was observed at elevated temperatures. Interestingly, the aggregation process was not confined to a small temperature interval, but stretches over a range of 10 to 20°C, or even more. Moreover, the micellization temperature was strongly dependent on the molecular characteristics of the copolymer chains, like the composition and the molecular weight of the B block. Strong kinetic effects have been recorded during the micellization process, since larger aggregates and broader size distributions were observed for slower heating rates.

Finally, the solution behavior of thermoresponsive multiblock copolymers has been reported [50]. Multiblocks of PDMA and PNIPAM with sequences of different molecular weights were studied upon increasing the solution temperature. At elevated temperatures the PDMA block is water soluble, while the PNIPAM block becomes insoluble. Depending on the molecular weight of the sequences, the multiblock copolymer can adopt unimolecular flower-like micelle conformation or can aggregate through intermolecular interactions.

4.2. pH Responsive Self-Assembly

One of the first and more characteristic examples of pH responsive DHBCs is the solution behavior of P2VP-PEO [8]. The above copolymer is molecularly dissolved at low pH values due to the protonation of the P2VP block, considering that the PEO block is a neutral, water soluble polymer in the whole pH range. However, upon increasing the solution pH, deprotonation of the P2VP block leads to the formation of micelles at pH higher than 4. This behavior, i.e. the formation of micelles upon changes in the solution pH, is characteristic for a number of polymers, as it will be demonstrated below.

The micellization of a similar system, namely PHEGMA-PDEAEMA, upon changes in the protonation degree of the amine containing block has been studied in detail by light scattering and NMR [60]. The above polymer was molecularly dissolved when the degree of

protonation was higher than 30%, although a small fraction of aggregates was also observed, even at protonation degrees higher than 30%. However, the tendency for aggregation of the copolymer chains was increased by decreasing the percentage of the ionized amine groups to 20%. A further decrease of the protonation degree led to the formation of precursor micelles, while the equilibrium micelles were formed only upon complete deprotonation of the PDEAEMA block. The above, step-by-step investigation of the micelle formation reveals a detailed picture of the copolymer solution properties.

Changes of solution pH can induce micellization not only because of a decrease in the ionization degree of one block, but also because of the development of secondary interactions, like hydrogen bonds. An example of the above situation is the solution behavior of the PVA-PAA block copolymer [32]. The particular copolymer was almost molecularly dissolved in aqueous media at neutral or alkaline environments. However, the formation of aggregates was observed at low pH values, not only because of deprotonation of the PAA block but also due to the development of intermolecular hydrogen bonds between the PAA and PVA blocks.

In a similar context the aggregation behavior of PHOS-PMAA block copolymers was found to be pH dependent [10]. In this particular system both blocks can be considered as acidic, but the pK_a values of PHOS and PMAA differ substantially. Loose polydisperse aggregates were observed at $pH > 9$ where phenolate and carboxylate groups are dissociated. At $4 < pH < 9$ micellar like aggregates were formed having a more compact structure with PHOS cores and PMAA coronas. The copolymers precipitated at $pH < 4$ due to the protonation of the PMAA and possibly hydrogen bond formation. The micellization pathway is shown schematically in Figure 10.

A pH dependent self-assembly behavior was also observed for PNHOS-PEO diblock copolymers [12]. The presence of basic and acidic groups on the same segment of the PNHOS block allows for variation of the solubility and the internal structure of the aggregates formed at different pH values, as it was confirmed by dynamic light scattering and fluorescence spectroscopy.

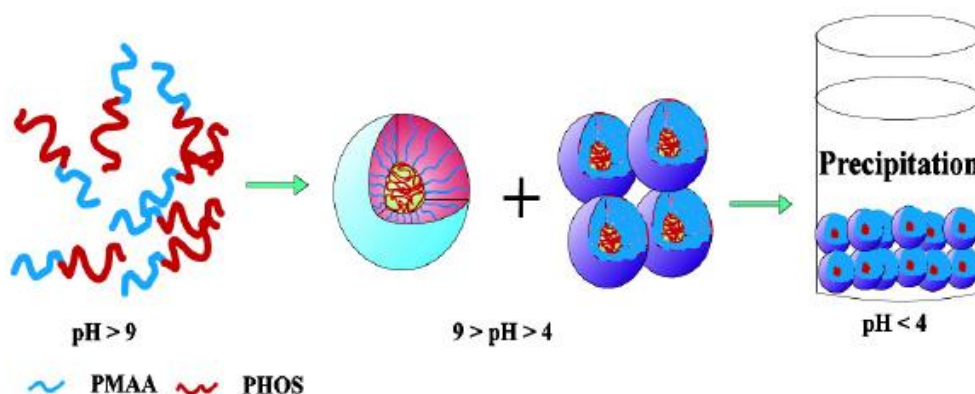


Figure 10. Micellization behavior of the PHOS-PMAA pH-responsive DHBC. Reproduced from [10] by permission of the American Chemical Society.

The first example of micelle formation by a so called “schizophrenic” block copolymer has been given by Armes and coworkers [13]. The term “schizophrenic polymer” was proposed by the authors in order to describe macromolecules that can form micelles or inverse micelles upon changes of the environmental conditions. In particular, the copolymer PVBA-PDEAEMA was observed to form well defined micelles both in acidic and basic environments, while it precipitated at pH values between 6.6 and 8.3. In acidic environment, the micellar core was formed by the PVBA blocks, while the inverse micelle was observed for alkaline solutions, Figure 11. Interestingly, well defined micelles were observed only in the case of very low and very high pH values, i.e. $\text{pH} < 2$ and $\text{pH} > 10$. At all the other pH ranges, where the polymer was still water soluble, non-micellar aggregates were formed, with hydrodynamic diameters up to 150nm.

Schizophrenic solution behavior has been also observed in a PMAA-PDEAEMA DHBC. The particular copolymer formed core-shell micelles at extreme pH ranges, i.e. $\text{pH} < 5.5$ or $\text{pH} > 9.2$, while it was phase separated at intermediate pH values. Micelles having PMAA cores were formed in acidic solutions, while micelles with PDEAEMA cores were formed in alkaline solutions [15].

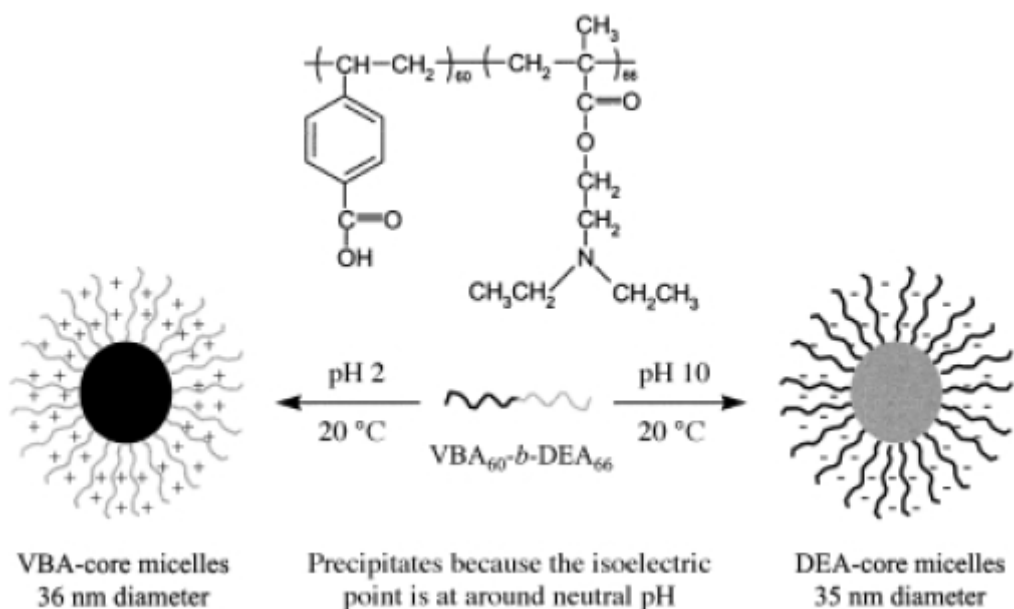


Figure 11. Schizophrenic micellization behavior of a PVBA-*b*-PDEAEMA DHBC. Reproduced from [13] by permission of Wiley.

The micellization behavior of a series of zwitterionic DHBCs with an amine group containing block and a carboxylic group containing block has been also studied. The copolymers formed supramolecular aggregates in acidic and alkaline solutions, while an isoelectric point (IP) was observed at intermediate pH values. The well defined structure of these aggregates strongly depends on the purity of the samples used [17]. Therefore, the formation of large aggregates at low pH values, which could not be explained by the formation of simple core-shell micelles, indicates the existence of amine containing monomers in the carboxylic block, due to inefficiencies in the synthetic procedure utilized [16].

The micellization behavior of a triblock DHBC, namely PAA-P2VP-PAA, has been studied upon changes in solution pH [37]. At low pH values the polymer can be either molecularly dissolved or can form transient networks, depending on the polymer concentration. The formation of a network was possible because of the development of physical cross-links, which arise from electrostatic interactions among the oppositely charged PAA and P2VP blocks. By increasing the solution pH the isoelectric point (IP) was reached. Close to the IP, i.e. $4 < \text{pH} < 7$, precipitation of the copolymer chains was observed. However, further increase of the pH had as a result the redissolution of the macromolecule and the formation of compact micelles with a P2VP core. The aforementioned phase transformation upon pH changes was found to be reversible.

A comprehensive study of the micellization kinetics has been performed by Liu and coworkers on an ABC double hydrophilic triblock terpolymer upon alteration of the solution pH [62]. The studies have been performed by applying the stopped-flow light scattering technique on a poly(glycerol monomethacrylate-*b*-2-(dimethylamino)ethyl methacrylate-*b*-2-(diethylamino)ethyl methacrylate) (PGMA-PDMAEMA-PDEAEMA) terpolymer, which has a block soluble at all pH values (PGMA) and two others blocks (PDMAEMA and PDEAEMA) with pK_a 's of 7.0 and 7.3 respectively. The particular terpolymer formed micelles upon changing the solution pH from 4 to values higher than 7. When the pH of the final copolymer solution was between 7 and 7.5, two relaxation processes were observed, one with positive and one with negative amplitude. This suggests that the micelle size and/or the micelle number density were initially increased, whereas the opposite occurred during the second relaxation mode, which is associated with micellar formation-breakup. In contrast, for a final pH value higher than 8, two processes with positive amplitude were recorded. The fast process was attributed to the aggregation of unimers, forming some transient micelles, and to intermicelle fusion, forming quasi-equilibrium micelles. The second, slower, process was related to micelle formation-break up because of unimer insertion/expulsion and seems to be concentration independent. The situation was different in the presence of salt. In that case, the two processes were much slower or leveled off, depending on the salt concentration. The authors concluded that the micellar fusion/fission mechanism is favored instead of the unimer insertion/expulsion mechanism [63].

Recently, the same group has presented also the micellization kinetics of a diblock copolymer, namely PEO-PDEAEMA [59]. Several samples of this type of copolymers have been synthesized having identical PEO blocks and PDEAEMA block with varying degrees of polymerization. The block copolymers tend to create micelles with PDEAEMA cores in basic conditions. Therefore, the micellization kinetics studies were performed using a stop flow technique in order to introduce micelles upon a pH-jump from 3 to 12. The observation of two processes, i.e. a fast one attributed to the formation of quasi-equilibrium micelles and a slow one attributed to the relaxation into final equilibrium micelles, were observed, as

expected. Interestingly, the authors concluded that the reorganization mechanism followed, during the slow process, was connected to the degree of polymerization. In particular, the unimer insertion/expulsion mechanism mainly dominated the relaxation from quasi-equilibrium micelles into stable micelles, in the case of copolymers with low degree of polymerization. In contrast, the same process was dominated by micelle fusion/fission in the case of copolymers with high enough molecular weight.

Finally, interesting results have been also obtained by the study of a diblock polypeptide [29]. The copolymer, poly(L-glutamic acid)-b-poly(L-lysine) (PGA-PLys), self-assembled spontaneously in aqueous basic (pH 12) and acidic (pH 3) solutions. At pH 3, the PGA block was neutralized adopting a compact R-helical structure, instead of the charged coil conformation at pH >4. In contrast, under basic conditions (pH >9), the PGA block was charged, while the PLys block was transformed into a neutral and insoluble block. Therefore aggregates with either the one or the other block as the core forming block could be obtained depending on the solution pH. The formed aggregates were determined to be vesicles. This was the first time that this schizophrenic behavior was observed in vesicle forming block copolymers, Figure 12. The vesicle formation was tentatively explained, according to the authors, by the systematic presence of a polypeptide in a rodlike conformation, in the hydrophobic part of the membrane, which induces a low interfacial curvature and as a result a hollow supramolecular structure.

4.3. Self-Assembly via Complexation with Other Building Blocks

The complexation of two DHBCs has been recently described in the literature. The complex formation between a miktoarm star copolymer $\text{PEO}_n\text{-PMAA}_n$ and a quaternized PEO-PDMA diblock was studied upon changes in solution pH [54]. At elevated pH values, where PMAA blocks were ionized, the formation of electrostatic complexes was recorded between the oppositely charged PMAA and quaternized PDMAEMA blocks. However, the aggregates were soluble due to the presence of the PEO uncomplexed blocks originating from both of the copolymers. The situation was dramatically different at low pH values, where the PMAA block was not ionized. At the aforementioned pH values the development of hydrogen bonds between the PMAA and PEO blocks took place. In the later case, the aggregates were electrostatically stabilized by the quaternized PDMAEMA polyelectrolyte block. The micellization/complexation behavior is schematically illustrated in Figure 13.

Complexation induced micellization can occur not only by using an oppositely charged polyelectrolyte but also by using a salt with divalent ions. Tam and coworkers have described in detail the mechanism of salt induced micellization [64] of a PEO-PAA diblock upon addition of CaCl_2 . The formation of supramolecular aggregates was strongly dependent on the $\text{Ca}^{2+}/\text{COO}^-$ ratio. When the ratio was 0.5, the formation of coil-like globules was observed due to charge neutralization. An increase of the above ratio to values higher than 2.5, led to the creation of aggregates with a mean diameter of ca. 50 nm. Interestingly, the data reveal that the aggregate formation was not caused by electrostatic interaction between the ions but it was the disruption of the water structure, due to the solvation of CaCl_2 excess. It was concluded that the copolymer chains formed clusters in order to compensate the entropic changes, caused by changes in the structure of water.

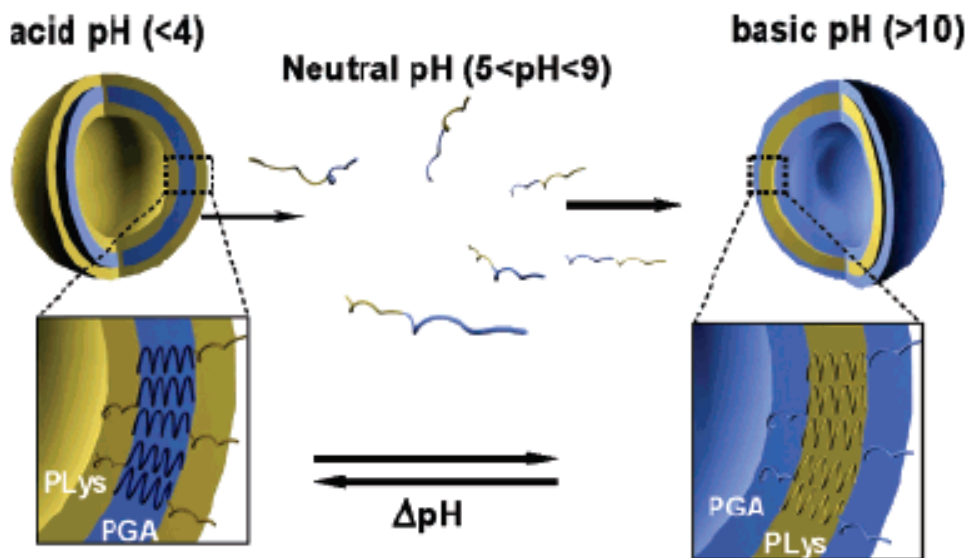


Figure 12. Schizophrenic behavior in the formation of vesicles by a polypeptide containing DHBC. Reproduced from [29] by permission of the American Chemical Society.

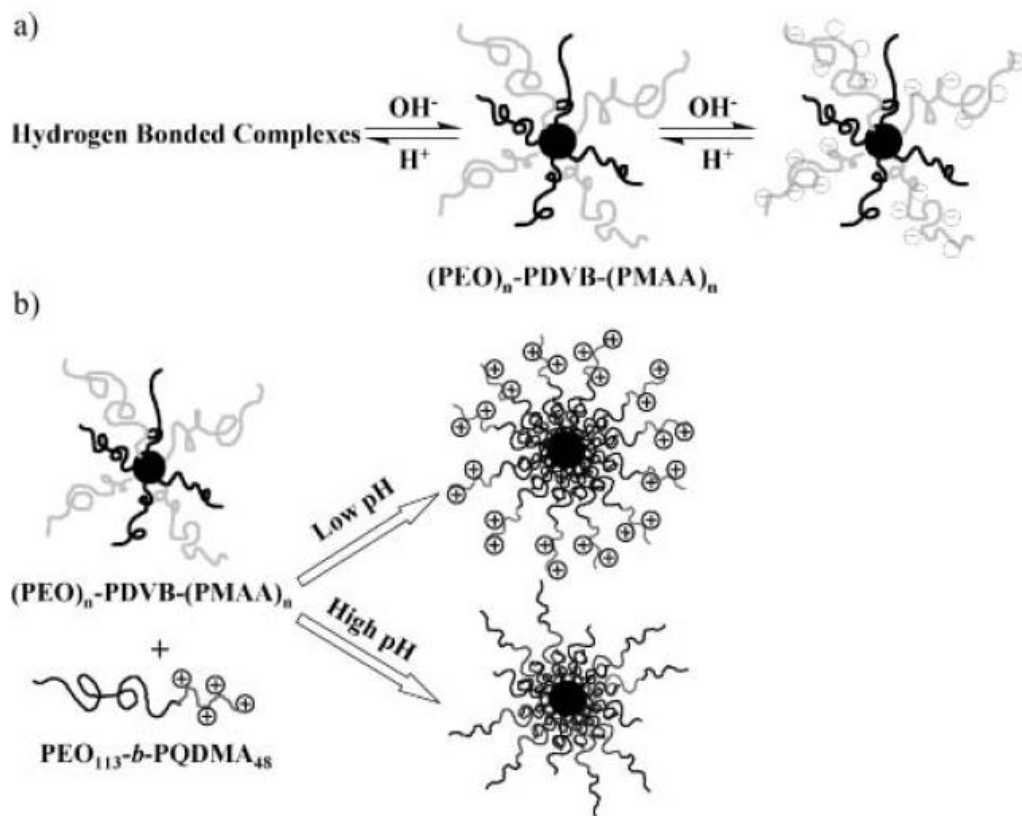


Figure 13. Complexation induced micellization of a star DHBC. Reproduced from [54] by permission of Wiley.

An example of electrostatically assembled complexes formed between a PEO-PMAA DHBC and poly(amidoamine) dendrimers of different generations was presented very recently [65]. An increase in the size of the complexes was observed by increasing the amount of G4 dendrimer present in the solutions. The structure of the core of the aggregates was dependent on the dendrimer concentration, while the overall structure of the assemblies could not be described as a micellar-like structure. At low dendrimer concentration a close aggregation of the PMAA chains and G4 dendrimer was evident, while at higher G4 concentration the PMAA chains efficiently fill the aggregate core. The behavior was the opposite for the G0 dendrimer. The size distribution of the aggregates was narrow and the structure of the assemblies was dependent on the solution pH as a result of the different ionization degree of the components.

A large amount of work, concerning the interaction and nanostructure formation in DHBC/surfactant and DHBC/polyelectrolytes mixed solutions has been published [66,67,68,69,70,71,72,73,74,75,76,77,78,79, 80,81]. The structural characteristics of the aggregates in such systems can be tuned and controlled by the chemical structure of the block copolymer, the surfactant and the polyelectrolyte utilized. A very important parameter that determines the structure of the nanosystems is the charge ratio between the two components. Electrostatic interactions are the main reason for structure formation, but secondary interactions, like hydrophobic interactions and hydrogen bonding, play also a decisive role. Various morphologies including micellar core-shell like aggregates, cylindrical superstructures and vesicles have been observed. The mixed structures can be also influenced or be responsive to changes in the physicochemical parameters of the system (pH, salinity, temperature). The great versatility of DHBC/surfactant and DHBC/polyelectrolytes systems, concerning structural diversity and properties, makes them a very active field of current research with great potential towards nanoapplications, including drug and gene delivery and surface modification.

A special and very interesting class of complexes containing suitably designed and synthesized DHBCs, especially in terms of potential biotechnological applications, are the complexes formed in the presence of oppositely charged proteins and nucleotides [82,83,84,85,86,87,88,89,90,91]. The use of such complexes for delivery of protein drugs, separation and purification of proteins and for gene delivery has been proposed. Several mixed systems have been reported and the fundamental properties of the superstructures in aqueous solutions have been elucidated. Structural characteristics are depending on the structure of the DHBC and a number of physicochemical parameters. Responsiveness of the created nanostructures to stimuli that are primarily encountered under physiological conditions in living organisms, is of primary interest due to the desired functionality of the ensembles. Hydrophobic interactions in conjunction to electrostatic ones are determining the stability and structural and functional tunability of the nanoaggregates.

4.4. Self-Assembly via Combination of Stimuli

An interesting example of a DHBC system that can self assemble under the influence of two different stimuli is the PVBA-PMEMA copolymer, presented by Liu and Armes [14]. The particular system formed small well defined micelles with a PVBA core at pH values lower than 5.5 at room temperature and in the absence of salt. No precipitation was observed at the isoelectric

point. However, in the presence of a sufficient amount of Na_2SO_4 (0.80 M) or at elevated temperatures (more than 80 °C), well defined micelles with PMEMA cores were formed in alkaline media, because of salting out of the PMEMA block. By choosing the appropriate values of pH, salinity and temperature the observation of micelles with PVBA cores, PMEMA cores micelles or precipitation (at the isoelectric point) was possible. Moreover, the micellization temperature of the system was altered upon changes in the salinity. The micellization kinetics, of the above rather complicated system, has been also studied [92].

A system analogous to the PVBA-PMEMA copolymer, where a PDEAEMA block has been used instead of the PVBA block, has been also presented by the same group [26]. The particular copolymer could form micelles with either PDEAEMA or PMEMA cores depending on the solution pH and salinity. At low ionic strength the PMEMA block was soluble in the whole pH range, in contrast to the PDEAEMA block which is not soluble at pH higher than 7-8. Therefore, at zero salt concentration and pH=8, PDEAEMA core micelles were observed. However, when the solution pH was carefully adjusted to 6.7 and the salinity was increased by addition of NaSO_4 , then the PMEMA block was no longer soluble in water and PMEMA-core micelles were observed, Figure 14. The temperature of the solution plays a crucial role on the stability and polydispersity of the formed micelles.

Another example of a DHBC, which responds to two different stimuli, is the PNIPA-PSPP copolymer [93]. This copolymer presents both UCST (PSPP block) and LCST (PNIPAM block) in aqueous solutions. However, the addition of salt increases the hydrophilicity of the PSPP block leading to a disappearance of the UCST. In contrast, the hydrophilicity of the PNIPAM block, is decreased upon addition of salt. Therefore, the size of the supramolecular aggregates formed is altered not only upon changes in solution temperature but also upon changes in the salinity. Copolymer concentration was also found to play a crucial role on the dimensions of the self-assembled structures.

The micellization of a polypeptide containing DHBC has been also studied under variable solution pH and temperature [30]. A schizophrenic solution behavior was observed for a PNIPAM-PGA block copolymer. At room temperature and low pH values micelles having polypeptide cores were formed, while at elevated temperatures and increased pH values micelles with PNIPAM cores were observed. It has to be noted that the formation of PGA core micelles was accompanied by a coil-to-helix transition of the polypeptide sequence. The above transition had as a result a different micellization kinetic profile for the system in comparison with other conventional pH responsive systems.

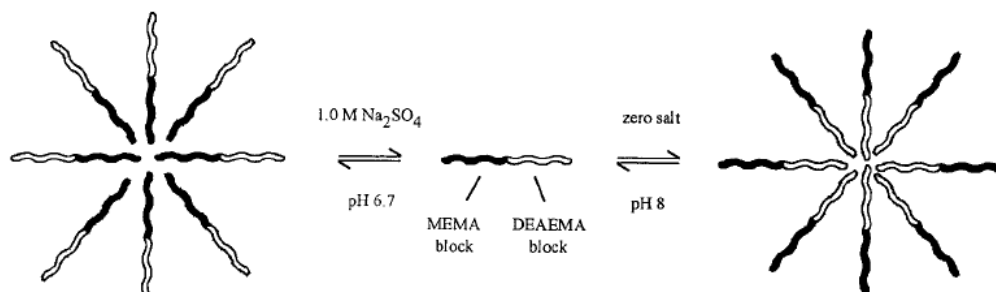


Figure 14. Micellization of MEMA-DEAEMA DHBC upon changes of more than one stimulus. Reproduced from [26] by permission of the American Chemical Society.

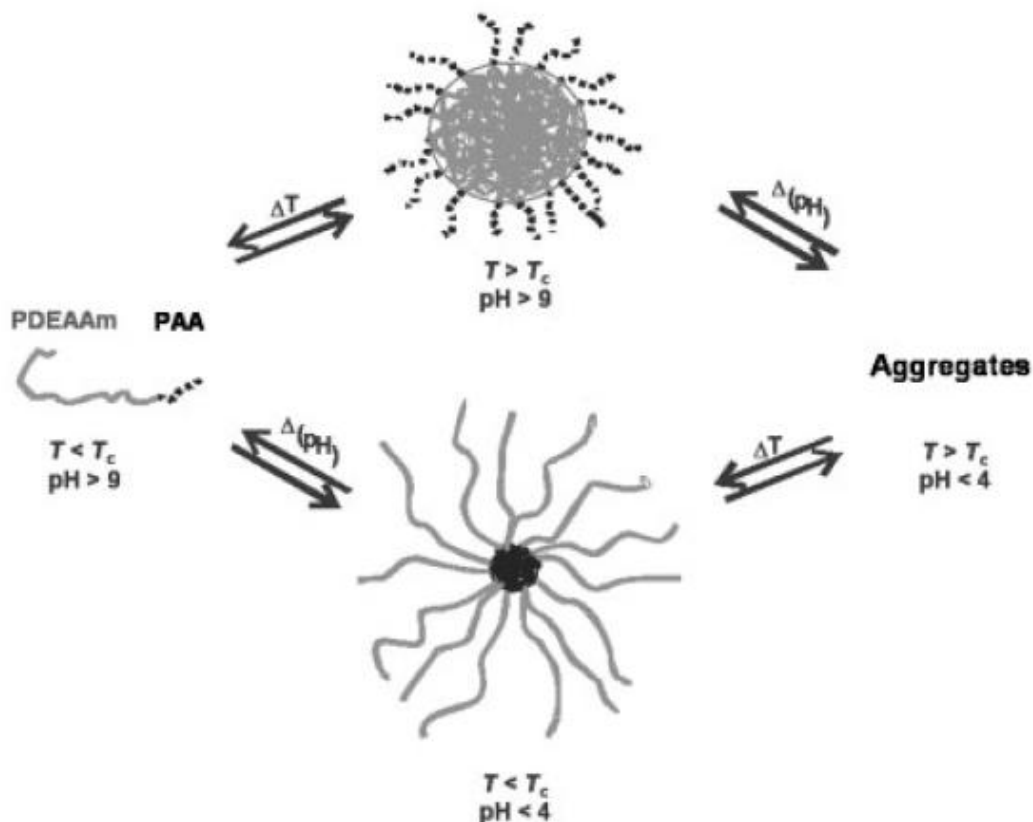


Figure 15. Schematic illustration of the combination of stimuli for producing different types of DHBC aggregates. Reproduced from [9] by permission of Wiley.

Another example of schizophrenic behavior has been observed in the case of A-b-(B-co-C) DHBCs. The copolymers P(EGMA-co-MMA)-PDEA (with various contents of MAA) associated in water either at elevated temperature and low pH values or at low temperature and increased pH values [28]. Inverse micelles were observed in each case. Moreover, both the solution salinity and the content of MAA had a great influence on the critical micellization temperature, as was revealed by the experimental observations.

The PAA-PDEA block copolymer has a pH responsive block (PAA) and a temperature responsive block (PDEA) [9]. The particular copolymer could be molecularly dissolved in alkaline aqueous solutions at room temperatures. However, upon increasing the solution temperature the formation of crew-cut micelles with a PDEA core were formed, mainly due to the high asymmetry in the lengths of the blocks. This rather effective strategy allows the formation of crew-cut micelles in water without using a cosolvent. Moreover, the formation of inverse micelles can be also achieved at room temperature and at low pH values. In the latter case, star-like core shell micelles are observed, Figure 15.

Temperature and pH responsiveness has been also recorded for a non covalently bonded DHBC inclusion complex, namely P4VP-PNIPAM [33]. The non-covalently connected copolymer tends to create micelles with PNIPAM cores at low pH values and at elevated temperatures. However, at room temperature and high pH values, the polymer formed vesicles instead of core-shell micelles. The formation of vesicles was confirmed by a number

of complementary techniques, including TEM and light scattering. The pH induced vesicle formation by a non-covalently connected DHBC is an attractive approach for the facile synthesis of drug and gene delivery systems. Moreover, the solution behavior of the analogous covalently connected PNIPAM-P4VP copolymer has been also reported [34]. This copolymer was molecularly dissolved at low temperature and low pH. However, increasing of either the temperature or the pH led to the formation of core-shell micelles with PNIPAM or P4VP cores respectively. The formation of core-shell micelles instead of vesicles is probably caused by the differences in the molecular characteristics of the two polymers. Additionally, the nature of the non-covalent connection between the constituting blocks may allow for a more efficient reorganization of the polymer chains under appropriate conditions.

The solution behavior of an ABA block copolymer, namely PEO-P2VP-PEO, has been also studied under variable pH, temperature and salinity conditions [39]. In the present case, the polymer tended to form star like micelles with P2VP core at high pH values and room temperature. However, the situation was different at low pH values, increased salinity and elevated temperature. Under those conditions the formation of flower like micelles was observed, since the outer blocks became hydrophobic.

Block copolymers with non-linear structure have been also studied under the concept of formation of multi-stimuli responsive DHBCs supramolecular structures [52]. The solution behavior of A_4BA_4 and A_2BA_2 copolymers, where A is the pH responsive PDEAEMA block and B the temperature responsive PPO block, has been studied upon changes in solution pH and temperature. According to the authors, the experimental results indicate that the copolymers tend to form large, flower-like aggregates at low temperature and in a basic environment, where the water soluble PPO block forms loops surrounding the PDEAEMA cores of the aggregates. In contrast, unimolecular micelles are formed at higher temperatures and at pH 6.4, where the PPO is insoluble.

Finally, the solution behavior of another schizophrenic non linear DHBC has been also investigated. An AB_4 miktoarm star copolymer, where A is a temperature responsive PNIPAM block and B is a pH responsive PDEAEMA block, has been studied under varying solution pH and temperature [53]. The copolymer forms PNIPAM core micelles at high temperatures and at low pH values, and the reverse PDEAEMA core micelles at room temperature and high pH values. The micelles with a PDEAEMA core have a much smaller size in comparison with the micelles formed by a linear diblock copolymer with similar composition and molecular weight. Finally, different micellization kinetics has been recorded for the miktoarm star and the linear block copolymer upon pH jumps from 4 to 10, using a stop flow light scattering technique.

5. CURRENT AND POTENTIAL APPLICATIONS

The versatile synthetic procedures for the preparation of a wide variety of DHBCs, as well as their intriguing solution properties have promoted and suggested the utilization of such polymers in several demanding and “smart” technological applications. Some of them are discussed in the following sections.

5.1. Mineralization of Inorganic Compounds

The use of double hydrophilic block copolymers in biomimetic mineralization processes has been investigated in recent years. In contrast to rigid templates (like carbon nanotubes and porous aluminum templates which predefine the final structure) water soluble polymers could be used as soluble species at various hierarchy levels. Usually, in the case of DHBCs, one of the block acts as scaffold for the development of the crystal, while the other acts as a soluble-stabilizing matrix. Therefore, both of the blocks play a crucial role on the development of the crystals. There is a plethora of reports on the emerging bio-inspired mineralization field. Various crystal structures have been presented during the last years, following versatile synthetic routes. A very detailed and illustrious review has been recently given by Colfen [3]. The above review describes in detail all aspects of the specific field. Herein, we present just a few selected examples.

Antonietti and coworkers have demonstrated the designed synthesis of barium sulfate crystallites using a large gamut of DHBCs with different functional groups [94]. In particular, the growth of BaSO_4 into novel morphologies has been achieved by using block copolymers with varying binding and solvating blocks. Morphologies like rods, peanuts, peaches, nanofibers and flowers have been observed using different polymeric stabilizers and morphology promoters/modifiers.

The development of CaCO_3 tablet-like arrays was achieved at the air/water interface through the cooperative mineralization regulated by a polypeptide and a DHBC, namely PEO-PMAA [95]. The experimental data indicate that the role of the block copolymer is focused on the regulation of the arrangement and orientation of the CaCO_3 tablets. The cooperative action of a polypeptide is essential for the formation of CaCO_3 tablet at the air/water interface. In the absence of the polypeptide, the formation of calcite CaCO_3 particles in the water phase was observed.

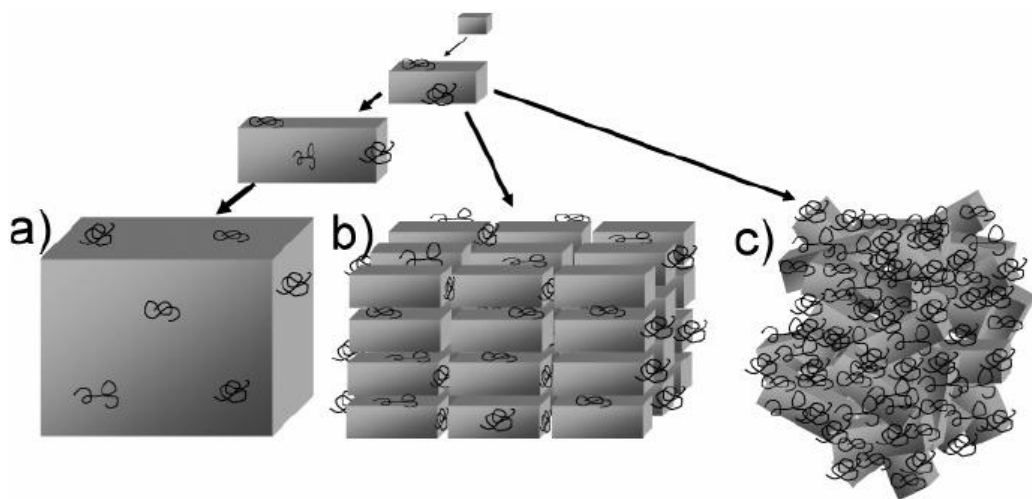


Figure 16. Schematic demonstration of the formation of single crystals, mesocrystals, and polycrystalline aggregates in the presence of DHBCs. Reproduced from [96] by permission of the American Chemical Society.

Experimental evidence for a unifying model of copolymer-directed crystallization has been recently presented by Colfen and coworkers [96]. According to the proposed model a continuous transition in particle structures and crystallization mechanisms occurs between polycrystalline aggregates, mesocrystals, and single crystals, Figure 16. Particularly, a number of crystals with different shapes could be obtained by aggregation, and the observed aggregation (with low or high degree of orientation) depends on the solution supersaturation. Therefore, a single crystal, a mesocrystal or a polycrystal could be obtained by changing the solution conditions.

5.2. Nanomedicine

The utilization of DHBCs as key-playing component in potential nanomedicinal applications has been demonstrated by Kataoka and coworkers [4, 82-90]. An interesting example of using DHBCs for encapsulation and targeted release of oligonucleotides has been demonstrated some years ago [97]. Partially thiolated PEO-PLys block copolymer has been used for the formation of polyion complex (PIC) micelles with a specific oligonucleotide. The formed micelles are stabilized in aqueous media because of the presence of the polyethylene oxide block, while the nucleotide is located at the micellar core in the form of a complex with PLys. After the formation of the PIC micelles, crosslinking of the core took place, by creation of disulfide bonds due to the oxidation of thiol groups preattached on the PLys chain. The resulting core-crosslinked PIC micelles are an effective carrier for the transportation and delivery of the oligonucleotide, since the stability against nuclease was appreciably increased, compared to that of free oligonucleotide and that in the micelles without crosslinking. Selective release of the oligonucleotide in the intracellular environment could be achieved. The increased concentrations of glutathione, an agent that could cleave the disulfide bonds, inside the cells leads to the located release of the oligonucleotide. The present example is featuring the potential of thiolated block copolymers in nucleotide delivery systems.

The formation of a model system for targeted drug delivery and smart release has been proposed by Liu and coworkers [98]. The model system is a shell crosslinked micelle formed by a triblock copolymer, namely Ald-PEGMA-PDMAEMA-PDEAEMA where Ald is an aldehyde end-group. The above polymer forms micelles in acidic solutions with a PDEAEMA core, a PDMAEMA inner shell and a Ald-PEGMA outer corona. The PDMAEMA block can be crosslinked, leading to stable structures. In parallel, the core is pH responsive, thus a tunable swelling/shrinkage, for controlled release of encapsulated guest molecules, can be achieved. The formed micelles are biocompatible due to the PEGMA outer corona. Finally, the micelles are surface functionalized with aldehyde groups, which can be used for the controlled conjugation with a number of biomolecules. The authors have already demonstrated the conjugation of the above micelles with the model protein lysozyme, Figure 17.

An outstanding approach for the development of drug delivery systems has been recently presented by Zhang and Ma [99]. In this work, the use of a β -cyclodextrin (β -CD) containing DHBC has been proposed for the inclusion of many hydrophobic substances. In their work, the synthesis of a block copolymer with a PEO block and a polyaspartamide block carrying some β -CD units has been described. The β -CD units are used as host sites for a plethora of hydrophobic small molecules, like pyrene and coumarine, as well as for hydrophobic polymers. However, the formation of inclusion complexes leads to the creation of located hydrophobic areas within the copolymer domain, which, in turn, has as a result the formation

of multi-chain, core-shell supramolecular structures. Moreover, the inclusion of charged molecules has been also achieved leading to the formation of micelles after complexation with oppositely charged polymers. The novelty in the use of CD containing block copolymers is the versatility in choosing various guest molecules, since the solubilization effect of CD toward a wide range of hydrophobic compounds has been well documented.

Another approach for the stabilization, transport and delivery of the hydrophobic nonsteroidal anti-inflammatory drug indomethacin (IND) has been presented by Giacomelli et al [100]. They have utilized the covalent attachment of the drug on DHBCs by an esterification reaction. The above reaction leads to an amphiphilic block copolymer/drug conjugate. The block copolymer/drug conjugate forms supramolecular structures in water with variable size and morphology (micelles or vesicles) depending on the molecular characteristics of the DHBCs and the content of IND in the conjugate. Moreover, unbounded IND moieties can be also encapsulated in the polymer aggregates, leading to a further increase of the drug load in the conjugate (up to 58% w/w), Figure 18. However, it has been found that high drug loading has as a result the formation of vesicles with an accompanying undesired increase of the aggregate size. It has been also observed that the drug release is a pH-dependent process. At neutral pH the release of charged unbounded IND is favored, while at acidic conditions, where the ester bond between drug and polymer is no longer stable, the slow release of both free and chemically attached IND was possible.

The interaction of aggregates of DHBCs with bacteria has been also recently demonstrated [57]. The interaction of a glucose containing copolymer, which forms vesicles at temperatures higher than 15°C, with *E. coli* has been studied in detail. The obtained data demonstrate that specific interactions between synthetic vesicles and cells can be developed. However, the most interesting finding was the controllable nature of the interactions according to the size of the polymeric vesicle. The authors assumed that by changing the vesicles' size it is possible to change the interactions, from bulk aggregation to individual associations.

The incorporation of ether phospholipid drugs, used for the treatment of leishmania, into supramolecular structures, formed by chemically modified DHBCs has been also studied [101]. A PEO-PDMAEMA block copolymer, where a portion of the tertiary amine groups of the PDMAEMA block was transformed into phosphorozwitterions, was used for the incorporation of the drug. The above copolymer can form both micelles and/or vesicles in aqueous solutions, depending on solution pH, temperature and the molecular characteristics of the copolymer chains. The phospholipid drug could be encapsulated in both micelles and vesicles. However, the introduction of an increased amount of drug favors the formation of vesicles. Moreover, the vesicles formed have a reduced size, probably due to the better organization of the aggregates in the presence of the drug.

A series of star DHBCs were evaluated for their ability to transfect human cervical HeLa cancer cells with the modified plasmid pRLSV40, bearing the enhanced green fluorescent protein as the reporter gene [55]. The copolymers utilized were composed of PDMAEMA and PHEGMA blocks (where PDMAEMA is an ionizable block, while PHEGMA is a non-ionic water soluble block). The experimental data indicate a decreased toxicity for the star copolymer, compared to a reference PDMAEMA star homopolymer, for the same amounts of star polymer tested. Moreover, it has been found that the architecture of the star copolymer, i.e. star block, miktoarm star etc, plays a decisive role on the transfection efficiency. The best performance, for all star copolymers tested, was observed for a star block copolymer with

PDMAEMA as the outer block. Interestingly, the transfection efficiency of the particular copolymer is comparable with that of the commercially available transfection reagent SuperFect.

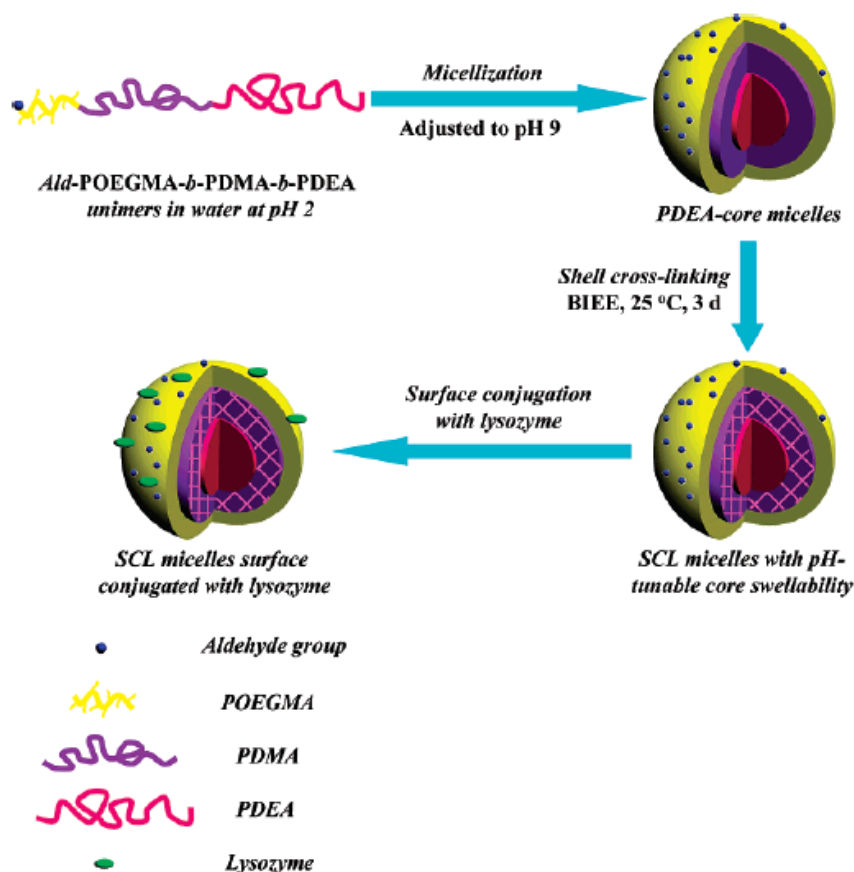


Figure 17. Schematic demonstration of the micelle formation by an Ald-PEGMA-PDMAEMA-PDEAEMA DHBC and interaction of the micelles with lysozyme. Reproduced from [98] by permission of the American Chemical Society.

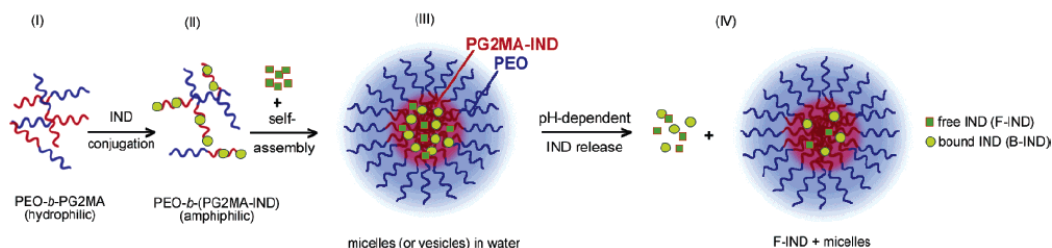


Figure 18. Inclusion and release of a drug in a micelle formed by a PEO-(PG2MA-IND) DHBC. Reproduced from [100] by permission of the American Chemical Society.

5.3. Other Nanotechnological Applications

Liu and coworkers have presented the synthesis of gold nanoparticles in crosslinked micelles. They have succeeded in selectively crosslinking either the core or the shell of the micelles, formed by a primary amine containing block copolymer, namely PNIPAM-PAPAT [31]. The gold nanoparticles have been synthesized by addition of HAuCl_4 , which is selectively located at the crosslinked, primary amine containing block. Subsequently, reduction of the gold ions leads directly to the formation of gold nanoparticles at either the core or the shell of the polymeric aggregate.

The synthesis of Pt nanoparticles has been also reported in the literature [102]. Three different types of DHBCs, namely PEO-PV2P, PHEGMA-*b*-PDEAEMA, and PEO-*b*-PDEAEMA, have been used as templates for the development of Pt nanoparticles. All the copolymers tend to self-assemble in solution at high pH values due to the deprotonation of the P2VP or PDEAEMA blocks. Therefore, in both cases, micelles with cores containing amine moieties were formed. The amine groups could be used as coordination sites for Pt ions leading to the preferential location of the ions in the micellar core. In another approach, Pt ions could be used in order to induce micellization in solutions containing molecularly dissolved block copolymers. Pt ions could electrostatically interact with the positively charged block copolymer at acidic solutions. The electrostatic attractions lead to the formation of supramolecular structures. In both cases, addition of Pt ions in polymeric micelles or molecularly dissolved copolymers, leads to core-shell micelles with Pt ions preferentially located in the cores. In these micellar nanoreactors, metal nanoparticles nucleate and grow, upon reduction, with sizes in the range of a few nanometers.

5.4. Miscellaneous Properties and Applications of DHBC Systems

The adsorption of DHBCs on solid surfaces has attracted considerable scientific interest due to the possibilities that offers for the construction of smart/responsive surfaces with tunable properties.

Biggs and coworkers have studied the behavior of PDMAEMA-PDEAEMA micelles, adsorbed onto mica surfaces, upon changes in solution pH using an in situ AFM instrumentation set-up [103]. In aqueous solutions, the copolymers tend to be molecularly dissolved in acidic environment and to form micelles at elevated pH values [103]. The adsorbed polymer chains were found also to respond to changes of the solution pH. However, unlike micelles in bulk solution, the adsorbed copolymer micelles do not dissociate at low pH, but remain attached to the solid/solution interface. Furthermore, the micellar core can open or close upon changes in the solution pH – due to this behavior the term “nanoanemones” was coined in order to describe the specific nanosystem. The above behavior leads to smart surfaces with tunable lubricity, which can be used in a number of emerging technologies. However, the situation is dramatically different in the case where the PDMAEMA block has been quaternized. Increasing the number of permanent charges, in the copolymer, leads to the formation of random surface structures which are irreversibly damaged at low pH values [25].

Gohy and coworkers have studied the adsorption of PMAA-PDMAEMA copolymers on silicon surfaces under varying solution pH [104]. A series of copolymers with different

molecular weights and composition have been utilized in order to elucidate the influence of polymer molecular characteristics on the adsorbed amount. The experimental results indicate that all the parameters (copolymer molecular weight, composition and pH) play their role on the final adsorbed amount and other characteristics of the adsorbed polymer layer. The investigation of another system, namely P2VP-PDMAEMA, by the same group has led to similar results [105]. The latter copolymer formed micelles at pH higher than 5, while it precipitated at pH higher than 8. The adsorption profile upon changes in the solution pH indicates two adsorption maxima: at the beginning of the micelle formation and at the precipitation regime. The great influence of pH on the adsorption was correlated with the ionization degree of the polyelectrolyte chains.

Preliminary results have been also presented by Armes and coworkers on the adsorption of zwitterionic block copolymers, both on silica and mica surfaces [17]. The copolymer forms negatively and positively charged micelles depending on the solution pH. Positively charged micelles can easily be adsorbed on oppositely charged silica particles and also on planar mica surfaces. However, the adsorption of even negatively charged micelles on mica has been also observed. The later observation was assigned to the relatively weak hydrophobic interactions between the micelle cores and the mica surface, rather than to strong electrostatic interactions. Nevertheless, the ability of pH responsive zwitterionic micelles to be adsorbed on surfaces has been demonstrated.

In a detailed study of the adsorbed DHBCs chain conformation, Hamley et al. have presented experimental results on adsorbed Pluronic triblock copolymers onto both silica and mica substrates [106]. The experimental data were obtained for a wide range of bulk polymer concentrations, even below the critical micelle concentration. The results indicate that, depending on the hydrophilicity of the substrate, the copolymer chains are adsorbed in a completely different way. Moreover, it was concluded that the polymer concentration plays a significant role on the conformation of the adsorbed polymeric layer.

The catalytic activity of PVim containing DHBCs has been also demonstrated [23]. A PNIPAM-PVim copolymer was found to form micelles with PNIPAM cores at elevated temperatures. The above micelles showed catalytic activity toward the hydrolysis of p-nitrophenyl acetate. Interestingly, molecular dissolved copolymer chains do not show the same catalytic activity. The Arrhenius plot for the PVim-based DHBCs exhibited a pronounced upward curvature above the critical micellization temperature.

The ability of DHBCs to encapsulate metalloporphyrins under different pH environments has been recently studied [107]. The polymer utilized was a PAA-P4VP block copolymer which forms micelles both in acidic (PAA core) and alkaline (P4VP core) solutions. The encapsulation of porphyrin molecules in both types of micelles has been observed. However, interactions between the P4VP block and metalloporphyrins leads to higher encapsulation ability for the P4VP core micelles. Depending on the initial micellar type, release of the metalloporphyrins can occur either by increasing or decreasing the solution pH. A similar system, more specifically designed for bioapplications, has been reported by Kataoka and coworkers some years earlier. The formation of core-shell micelles of dendrimer metalloporphyrin with DHBCs has been reported by these authors [108]. The micelle formation took place due to electrostatic interaction of charges at the periphery of the dendrimeric metalloporphyrins with opposite charged block copolymers. Depending on the porphyrin/DHBC system, the formed micelles were stable against NaCl solutions (due to the formation of hydrogen bonds) or dissociated at increased salt concentration. Such kind of

systems could be used in the battle against cancer, as photosensitizers in photodynamic therapies. Kataoka and coworkers have illustrated the potential of mixed porphyrin/DHBCs systems on this kind of therapies [109]. Particularly, the formation of PIC between dendrimer metalloporphyrins and DHBCs can effectively deliver the porphyrin moieties into cancer cells. Importantly, no toxicity effects were recorded, at least for the concentration range utilized.

6. SOME REMARKS ON FUTURE PERSPECTIVES ON DHBC RESEARCH

The existing capabilities on sophisticated synthetic procedures for the designed preparation of DHBCs are enormous and they are expanding rapidly. The knowledge on DHBC self-assembly behavior under varying conditions is continuously enriched with new behavioral motifs, tuned by the chemistry of the systems. However, novel and demanding technological applications require the further development of new DHBC systems. The synthesis of new DHBCs has to be realized by utilizing novel monomers, efficient polymerization schemes or/and post polymerization functionalization methodologies. A future goal could be the synthesis of multicomponent DHBCs with linear and non-linear macromolecular architectures. Surely the development of novel polymers will help to establish more precise structure-properties relationships that will aid the application potential of such systems. A number of aspects have to be elucidated in more detail, in order to improve the design and properties of the block copolymers. Theoretical calculations may help substantially and to some extent orient the experimental work.

The application spectrum of DHBCs is extended into a wide range of nanomedicine and nanotechnology oriented fields. Considering, the increasing interest for water compatible systems, further increase of DHBCs utilization in emerging technological applications is expected. The outstanding aqueous solution properties of DHBCs have already started to be utilized in a number of applications and these trends will be enhanced in the future.

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Chapter 10

THERMO-OXIDATION STABILITY OF POLY(BUTYLENE TEREPHTHALATE) AND CATALYST COMPOSITION

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1. SYNTHESIS AND THE STABILIZATION OF POLYESTERS

Polyesters are heterochain macromolecular substances characterized by the presence of carboxylate ester groups in the repeating units of their chains. Predominant in terms of volume and products value are those based on poly(ethylene terephthalate) (PET), long established as basis of fibers, films, molding plastics and containers for liquids, and poly(butylene terephthalate) (PBT) largely used to produce fibers as well as for special applications in motor and electric industry.[1-3]

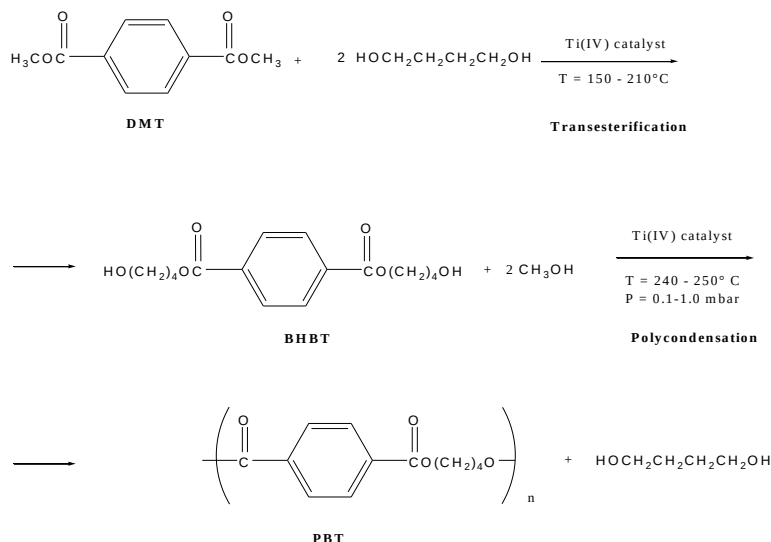
PET and PBT can be conveniently synthesized, both at laboratory and industrial scale, in the presence of metal catalysts in a two-step-polyesterification of the diols, ethylene glycol or 1,4-butanediol respectively, and dimethyl terephthalate (DMT) or terephthalic acid (TPA). The first step is basically a transesterification or esterification process depending on the use of DMT or TPA respectively, while the second step is the polycondensation of the resulting oligomers. The polycondensation step occurs at higher temperature and at reduced pressure to facilitate the distillation of the diols and consequently the polymerisation of the oligomers.

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There are important differences in the synthesis of these two polymers, depending also on the choice of dimethyl terephthalate (DMT) or terephthalic acid (TPA) as starting materials. A single catalyst, usually a titanium(IV) alcolate, is used in the synthesis of PBT for both ester-interchange and polycondensation steps. Two different catalytic systems are necessary in PET synthesis if DMT is used as starting material: Mn(II), Co(II), Mg(II) as acetate salts are the common catalysts for the transesterification step and Sb(III), usually Sb_2O_3 , is the catalyst for the polycondensation step. Titanium (IV) alcolates are also good polycondensation catalysts for PET synthesis but they are not often used because of the yellowing of the obtained polymer. One of the most accredited hypothesis for the explanation of this phenomenon is the formation of coloured titanium-based complexes during the high temperature polycondensation stage. For these reasons only small amounts of a titanium(IV) alcolates are usually used as co-catalyst in addition to Sb(III) catalyst. However the exploitation of Ti(IV) based compounds for PET synthesis is a hot subject and several questions are still open in order to solve these problems.[4]

Direct esterification of TPA is catalysed by COOH terminal groups and ester-interchange metal-catalysts are not necessary. The synthesis from TPA is particularly convenient for the production of PET because the use of the metals is limited only to polycondensation catalytic system. For PBT synthesis, TPA is less convenient because the presence of acidic groups leads to the decomposition of 1,4-butanediol to the formation of tetrahydrofuran.

A typical example of the two-step synthesis of PBT is reported in Scheme 1.



Scheme 1.

Since the early application of polyesters, great importance was attributed to the stability and shelf-life of these materials.[5-19] The stabilization for poly(ethylene terephthalate) (PET) is mostly related to the stabilization of ester-interchange catalysts. When these metals are not stabilized, a strong degradation and yellowing of the PET occurs at higher temperature in the following polycondensation stage. In this case the addition of phosphates or phosphonates at the end of transesterification stage suppresses the undesired processes and

increases the stability of the PET. These additives probably form inert complexes or salts with the ester-interchange catalysts.[12-19]

Even if several studies demonstrate that PBT is less stable than PET, less attention has been paid to the improvement of the stability of poly(butylene terephthalate).[7,8] The usual strategy to increase PBT stability is the addition, during the synthesis or the manufacturing, of anti-oxidizers, like Ultrinox and Irganox the typical phenol-type radical scavengers.[20] However, during the last years, a good number of new catalytic systems are claimed to catalyse efficiently PBT synthesis, but in these studies very few information are available about possible relationships between catalyst composition and polymer stability.[21-23]

Only recently Colonna et al. reported that in PBT synthesis, the use of mixtures of titanium(IV) tetrabutoxide and Hafnium(IV) acetylacetonate as catalysts in the presence of metal phosphates as co-catalysts improved the thermal stability of the polymers.[24] Unfortunately these interesting results have not received significant attention and no hypothesis has been formulated about the relationships between the improved stability and the catalyst composition.

It is worthy to note that at the end of the typical synthesis of polyesters, the catalytic system is a residual dispersed in the polymer matrix. But what are the effects of these metal impurities? Is this metal residual still active? Can these metal impurities catalyse the degradation processes and reduce the life of the material?

For example, solid state polycondensation (SSP), a way to increase the molecular weight directly on pellets of solid PET, is the evidence that Sb(III) residual is still active in solid polymer.[25-28] On the contrary less information are available about the effect of Ti(IV) residual on SSP for PBT. It is a matter of fact that in all the studies about thermal and thermo-oxidation degradation, the effects of the catalytic system are usually ignored because the catalyst is always present as residual in every PBT sample. It is simply a background effect.

2. RELATIONSHIPS BETWEEN CATALYST COMPOSITION AND PBT STABILITY: THE CASE OF $\text{Ti}(\text{acac})_2(\text{O-}i\text{Pr})_2$

Following the idea that the decomposition processes in PBT can be related to catalyst residual and that degradation can be inhibited by “metal deactivators”, we started to test a series of new potential catalytic systems and additives with specific characteristics for polyester synthesis. A “metal deactivator” can be defined like a kind of chelating agent which forms inactive complexes with residuals of metal catalysts or impurities.[20,29] In our investigations the chelating agents, the additives are introduced in the synthesis as complexes with the metal catalysts. For this reason the catalysts must be effective in the synthesis of the polymer and at the same time should reduce the degradation reactions.

As a result of these considerations and after a wide screening of several chelating agents and Ti(IV) complexes, we found that commercially available $\text{Ti}(\text{acac})_2(\text{O-}i\text{Pr})_2$ (titanium bisacetylacetonate diisopropylate) can be conveniently used in the synthesis of poly(butylene terephthalate) (PBT 1) both at pilot plant and industrial scale.[30] This new catalyst showed higher activity than standard $\text{Ti}(\text{O-}n\text{Bu})_4$ and very interestingly the obtained polymers showed higher thermo-oxidation stability than PBT 2 synthesized in the presence of $\text{Ti}(\text{O-}n\text{Bu})_4$. Furthermore, PBT 3 stabilized with Ultrinox 626 and synthesised with $\text{Ti}(\text{O-}n\text{Bu})_4$ was less stable than new PBT 1, but more stable than that synthesized only in the presence of $\text{Ti}(\text{O-}n\text{Bu})_4$ (PBT 2).[30]

Even the mixture of acetylacetone and $\text{Ti}(\text{O}-n\text{Bu})_4$ was effective in PBT synthesis and the obtained polymer 4 showed again improved thermo-oxidation stability, similar to PBT 1.[31]

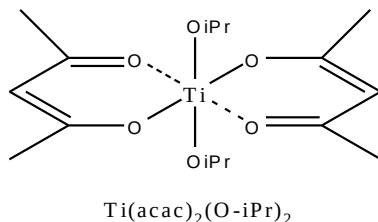


Figure 1.

Table 1. characteristics of different PBTs

PBT polymer	Catalyst	EI stage Time(min.)	PC Stage Time(min.)	I.V. (dl/g) ^a
1	$\text{Ti}(\text{acac})_2(\text{O}-i\text{Pr})_2^b$	72	78	0.889
2	$\text{Ti}(\text{O}-n\text{Bu})_4^b$	86	87	0.851
3 ^c	$\text{Ti}(\text{O}-n\text{Bu})_4 + \text{U626}$	85	85	0.829
4	$\text{Ti}(\text{O}-n\text{Bu})_4 + \text{acetylacetone}^d$	67	83	0.851

^aDetermined on a solution of PBT in *o*-chlorophenol with an auto viscosimeter Shotte-Gerate

^bThe complex was supplied from Aldrich.

^cThe stabilizer U626 was added to the reaction mixture at the end of the transesterification step at a concentration of 0.1% w/w.

^dThe catalytic system was prepared according to the procedure reported in the experimental section.

Regarding the experimental details, these four different types of PBTs were synthesized in a 20 L pilot plant under standardized conditions and they were submitted to standard oven testing for the evaluation of thermo-oxidation stability.

In particular, experimental data about reaction time for ester-interchange and polycondensation steps and the values of the intrinsic viscosity (I.V.) of the PBTs are summarized in table 1. It is worthy to note that both $\text{Ti}(\text{acac})_2(\text{O}-i\text{Pr})_2$ and the mixture acetylacetone/ $\text{Ti}(\text{O}-n\text{Bu})_4$ were more effective for both EI and PC stages and the resulting polymers were obtained with a higher I.V. and consequently with a higher molecular weight. This is very important from economical point of view because in the presence of a more active catalyst there is a significant reduction of the manufacturing costs of the materials. Moreover a shorter reaction time involves a reduced permanence of the polymer at high temperature with the consequent reduction of the thermal decomposition processes.

The effects of thermo-oxidation were evaluated by means of the standard method of ageing a large quantity of pellets of the four PBTs in forced circulating air oven at 160°C.[32] This is considered the most reliable method for ageing acceleration tests.[33] Then at different time, we measured colour-L (Figure 2), colour-b (Figure 3), intrinsic viscosity (I.V.; Figure 4) and carboxyl end groups (C.E.G.; Figure 5) for the treated samples. All these parameters are reasonably related to the “level” of degradation of macromolecules. Degradation causes the cleavage of the polymer chains and consequently the decrease of molecular weight, the decrease of the related I.V. and the increase of C.E.G. The colour, the

appearance is also important and in the practical experience of everyone the yellowing is commonly related to the ageing. The colour of polymers can be numerically measured in terms of L-value and b-value directly on the pellets, according to Cielab scale. L-Value is related to the degree of whiteness with a greater numerical value showing a higher (desirable) whiteness. The whiteness and consequently colour L is usually related to the level of crystallinity. The b-value is related to the degree of yellowness, and a higher numerical value shows a higher (undesirable) degree of yellowness. A particular importance is attributed to colour b for the relationship with the level of degradation and oxidation of macromolecules.[13]

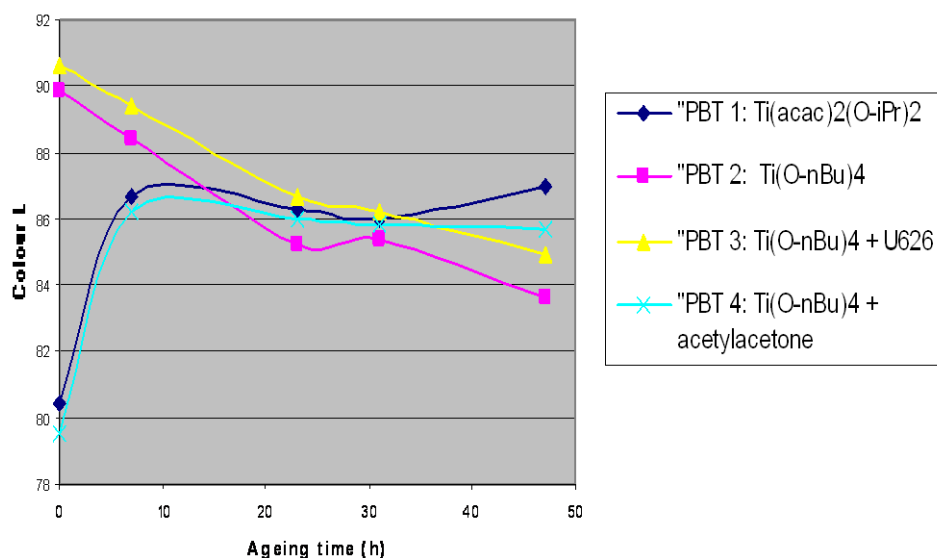


Figure 2. Colour L of PBTs aged at 160°C

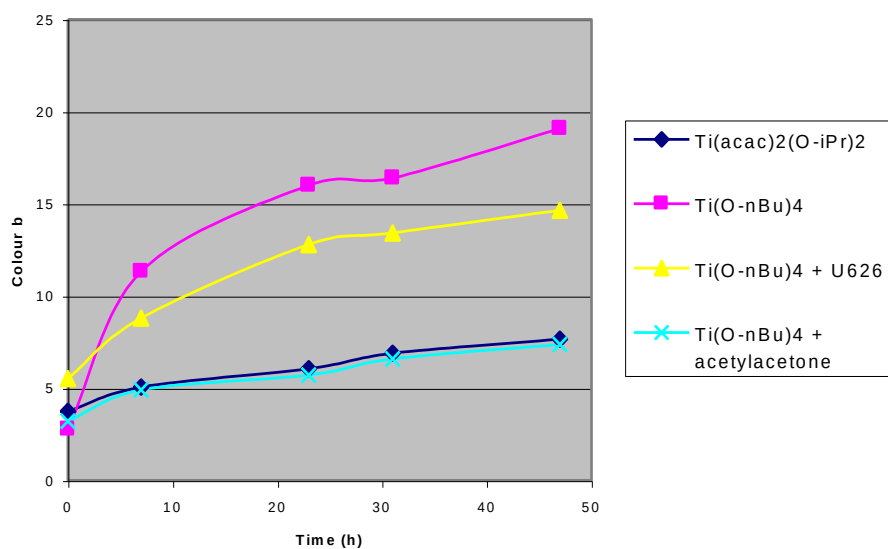


Figure 3. Colour b of PBTs aged at 160°C

The comparison of the obtained data shows that, after prolonged ageing time, PBTs 1 and 4 keep their properties practically intact. PBTs 1 and 4 suffer a very slight discolouring with a constant degree of whiteness (Colour-L, Figure 2), and a very reduced increase of yellowness (colour-b, Figure 3); a constant value of C.E.G. (carboxyl end groups, Figure 4) and a slight increase of I.V. (Figure 5). However PBT 3, stabilised with U626, is more stable than 2 and less stable than 1 and 4. In this case both the discolouring, the decrease of the intrinsic viscosity (I.V.) and the increase of C.E.G. are not as strong as in 2. Therefore the use of the stabilizer has a positive effect on the stability of the polymer obtained in the presence of $\text{Ti}(\text{O}-n\text{Bu})_4$, but it is useless when $\text{Ti}(\text{acac})_2(\text{O}-i\text{Pr})_2$ is employed as catalyst.

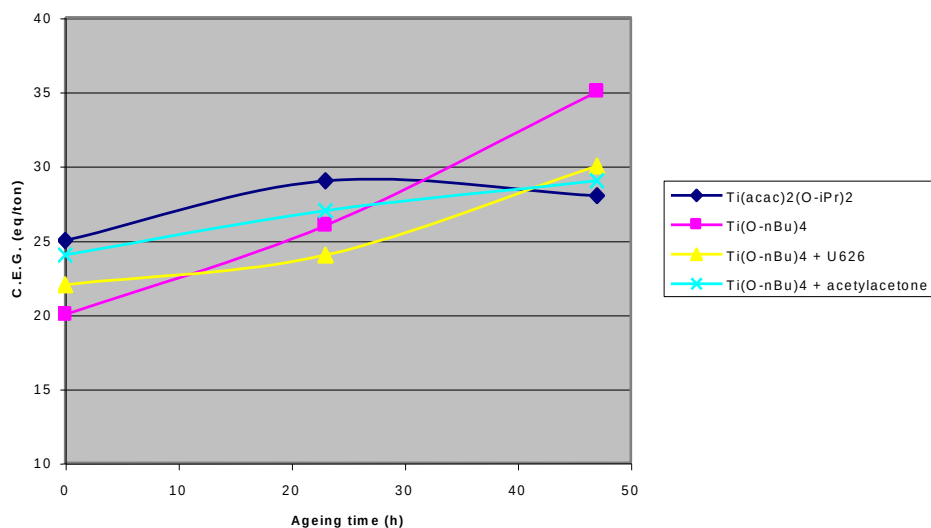


Figure 4. C.E.G. of PBTs aged at 160°C.

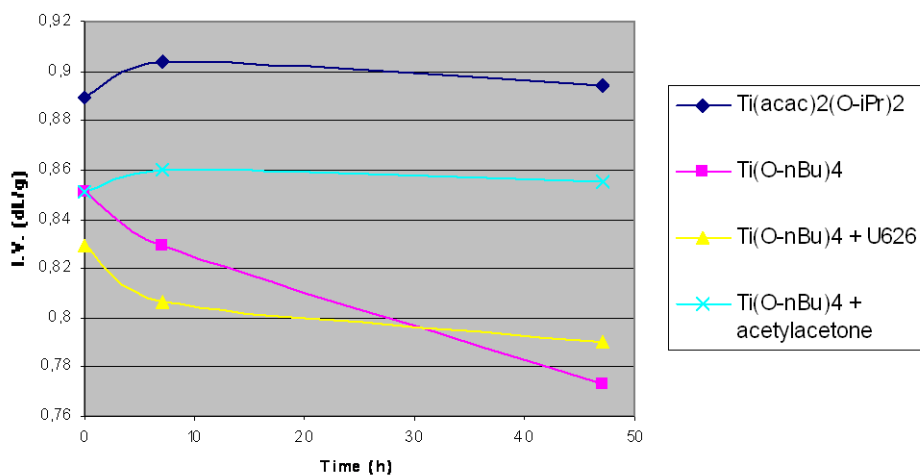


Figure 5. I.V. of PBTs aged at 160°C.

Moreover the analysis of the data shows some peculiar features for PBTs 1 and 4 that have to be noted. The significant improvement of colour L (and of the related level of whiteness), after the first 7 h of heating, can be related to the annealing that crystallizes the otherwise crystallinity-retarded polymer (Figure 1). This behaviour as well as the lower value of colour L at $t=0$ of freshly synthesised PBT 1 and 4, can be explained through the formation and incorporation of a small amount of an additional co-monomer as di(butanediol).

The trend of I.V. in PBT 1 and 4, since it cannot be related to the accuracy of the method (0.002 dL/g), is very interesting. If on one hand the slight decrease from 7 to 47 h can be attributed to a slight degradation, the increase after the first 7 h can be related to a small increase of molecular weight. This effect is very intriguing and can be related both to the possibility of a solid state polycondensation on PBT (SSP) and reticulation processes.

In addition to acetylacetone other additives and well-known complexing molecules, like those depicted in Figure 6, were tested in the synthesis of PBT. The new potential catalytic systems were obtained as a reaction mixture of the additives with $\text{Ti}(\text{O}-n\text{Bu})_4$ in 1,4-butanediol. This mixtures were used in PBT synthesis without any modification or purification.[31,32] In particular, among the tested additives, it is worthy to note that commercially available titanium complexes are reported for ethylacetoacetate:[34] EDTA is one of the most universally employed chelating agent. A different approach was considered in the choice of TEPF and TEPA. TEPA as a phosphonate based compound, can be used as stabilizer for transesterification catalysts in PET synthesis.[35-37] In this case the aim was to verify if this type of compounds have the same effect on the stability of PBT as widely described for PET.

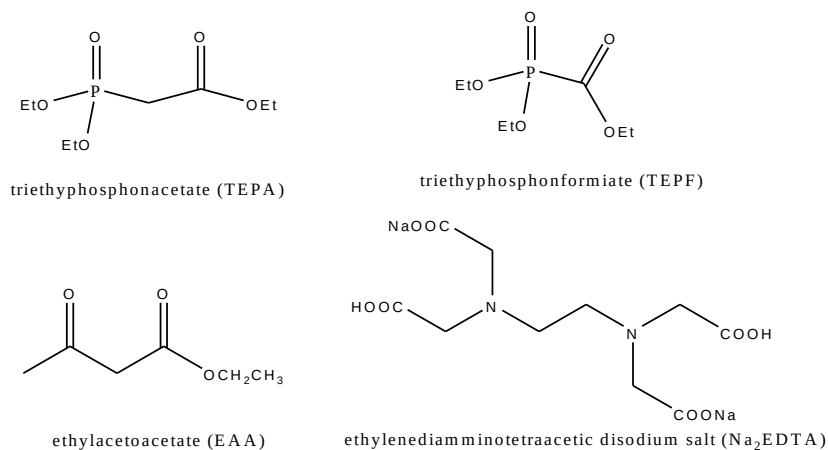


Figure 6.

Comparing the experimental data about reaction time and the intrinsic viscosity (I.V.) of these new PBTs (Table 2), the $\text{Ti}(\text{O}-n\text{Bu})_4$ /acetylacetone catalyst showed again a significant higher activity than the other systems both for ester-interchange and polycondensation steps (Table 2). Only in the case of $\text{Ti}(\text{O}-n\text{Bu})_4$ /TEPF the polymer was obtained with a higher I.V., even if in longer reaction time.

Then thermo-oxidation stability of the PBTs was tested in the usual way by oven ageing, and the results are summarized in the following figures 7-9.

Table 2. characteristics of different PBT

Entry	Catalyst	EI stage Time(min.)	PC Stage Time(min.)	I.V. (dl/g) ^a
2	Ti(O- <i>n</i> Bu) ₄	86	87	0.855
4	Ti(O- <i>n</i> Bu) ₄ + acetylacetone	67	83	0.851
5	Ti(O- <i>n</i> Bu) ₄ + EDTA	75	90	0.843
6	Ti(O- <i>n</i> Bu) ₄ + EAA	84	91	0.828
7	Ti(O- <i>n</i> Bu) ₄ + TEPF	85	91	0.875
8	Ti(O- <i>n</i> Bu) ₄ TEPA	81	89	0.849

^aI.V.s were measured on a solution of PBT in *o*-chlorophenol employing an auto viscosimeter Shotte-Gerate.

^bAccording to Cielab scale, colours were determined employing a colorimeter BYK Gardner.

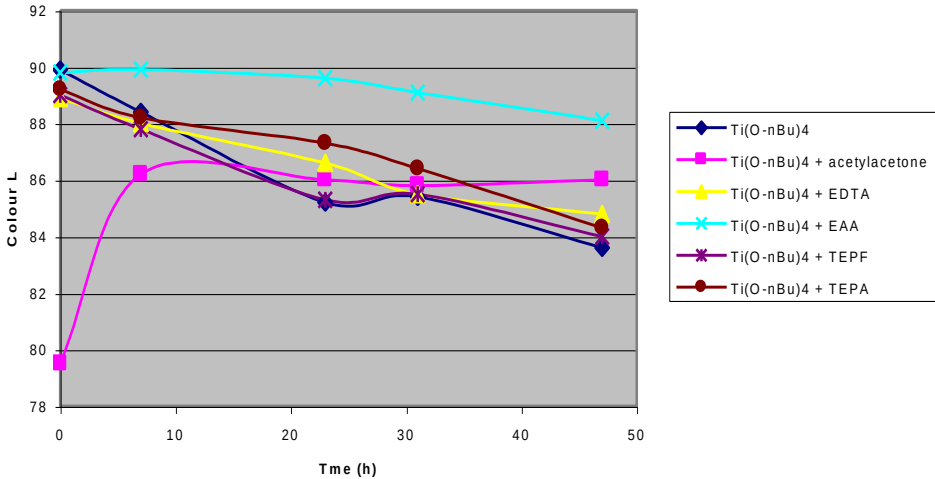


Figure 7. Colour L of PBTs aged at 160°C.

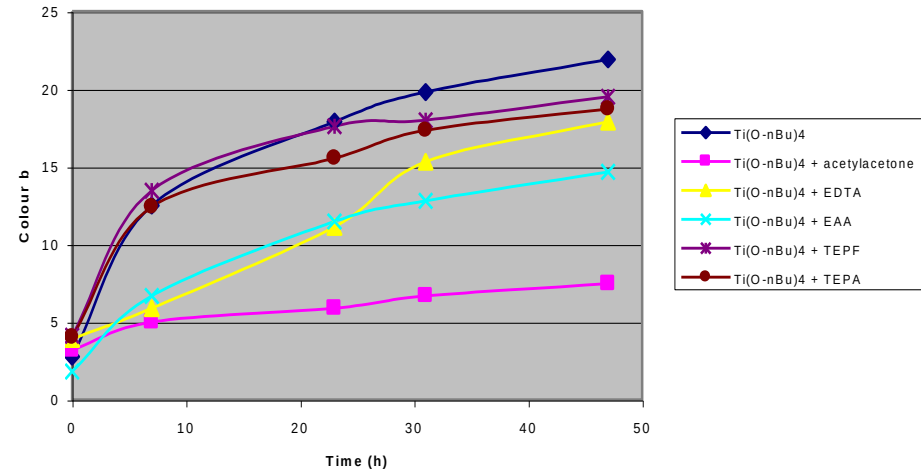


Figure 8. colour b of PBTs aged at 160°C.

The comparison of the reported data for colour L, colour b and I.V. shows again that PBT 4, synthesized in the presence of $\text{Ti}(\text{O}-n\text{Bu})_4$ / acetylacetone, is the most stable. All the other catalytic systems influenced negatively the stability of PBT even if $\text{Ti}(\text{O}-n\text{Bu})_4$ is the worse. However, there are significant differences among the several catalysts on PBT properties. These effects are probably related to the strength of the complexes formed between $\text{Ti}(\text{IV})$ and the complexing agents. In particular it should be noted that $\text{Ti}(\text{O}-n\text{Bu})_4$ / ethylacetoacetate is less deleterious: in this case we noted a constant level of colour L, and the decrease of I.V. and color b was less pronounced than in the other cases.

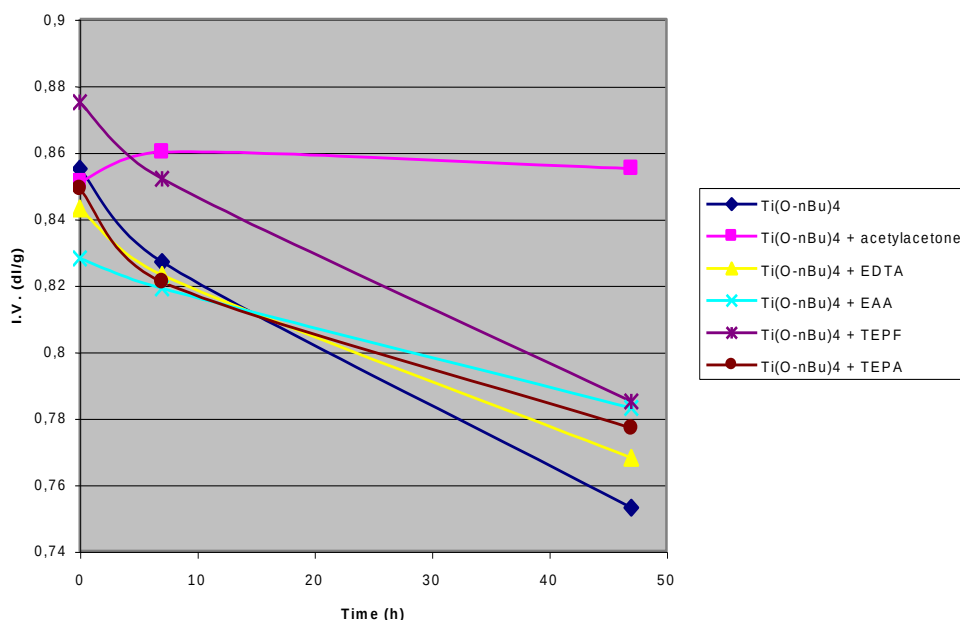


Figure 9. I.V. of PBTs aged at 160°C.

However, it is very difficult to propose a mechanistic explanation of the obtained results, but a look to the general features of the accepted thermo-oxidation mechanism of organic materials and polymers can be helpful to have an idea about the processes involved during the degradation. This subject will be explored in the next sections.

In conclusion it is important to say that the use of $\text{Ti}(\text{acac})_2(\text{O}-i\text{Pr})_2$ at industrial scale led to a higher quality and cheaper PBT. This polymer has been commercialised for several years until the bankruptcy of our old company. The main characteristic of this product was of course the high stability, achieved without the use of any stabilizer.

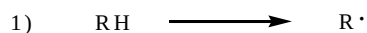
3. THERMO-OXIDATION OF ORGANIC MATERIALS AND POLYMERS

The study of degradation processes of polymers and organic materials is a fundamental topic both from academic and industrial point of view and it can be expected that thermal and thermo-oxidative decomposition mechanisms are reasonably well established.[20,38] These complex reactions proceed via a typical free-radical chain as outlined in scheme 2.

However the details of the initiating process (step 1), the very early formation of radicals, are not yet fully understood. Usually it is assumed that the oxidation initiating radical $R^\cdot$ is formed by heat, light, by mechanical stress or by reactions with radicals originating from foreign sources. Then, in the presence of oxygen the radicals lead to the formation of hydroperoxides (step 3). These are the key intermediates of the thermo-oxidation process because the thermally induced homolytic decomposition of -OOH groups into different radicals renews oxidation chains (stage 4).[39]

Since homolytic decomposition of hydroperoxides into free radicals (stage 4) requires relatively high activation energies, this process is rather slow and becomes effective only at temperature of about 120°C or higher.[20] However, in the presence of catalytic amounts of certain metal ions, hydroperoxides decompose at a lower temperature and/or at higher rate. This degradation mechanism involves a series of redox processes in which the most active catalysts are those derived by metals easy to oxidize or to reduce by one-electron, such as a series of transition metals like Fe, Co, Mn, Cu, Ce, V. Then several competitive termination couplings between different radicals (step 5) or the decompositions of peroxy radicals (step 6) lead to radical destruction.

INITIATION



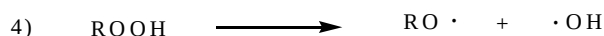
PROPAGATION



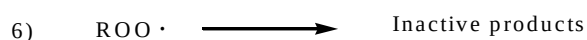
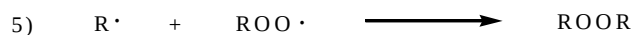
HYDROPEROXIDE FORMATION



CHAIN BRANCHING



TERMINATION

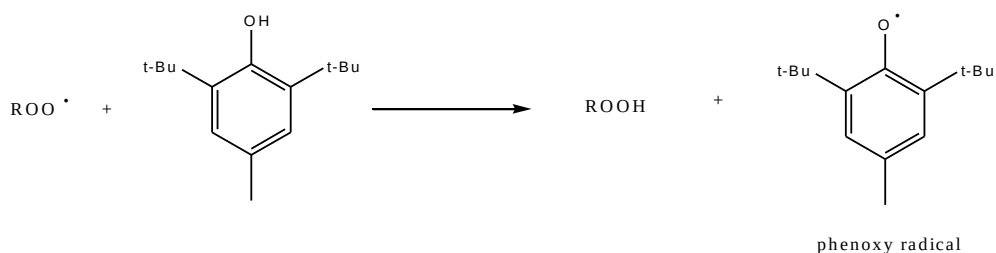


Scheme 2.

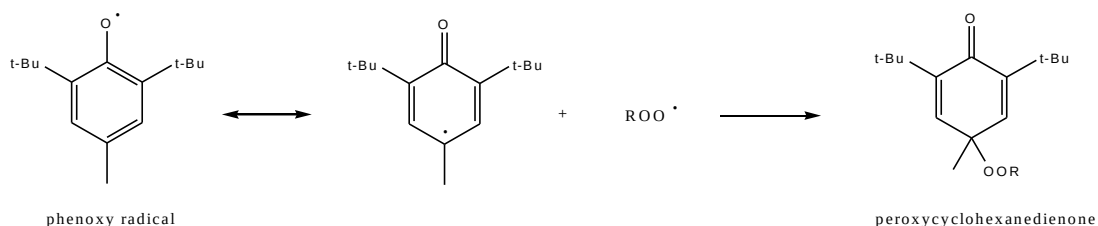
The best way to contrast these degradation reactions is the use of an antioxidant. The effectiveness of antioxidants is based on the fact that they are able to stop the reactions described in scheme 2. The majority of antioxidants belong to the class of sterically hindered phenols like those known with the trade names Ultrinox or Irganox. These compounds are peroxy-radicals decomposers, according to the reaction reported in scheme 3. The

stabilization is achieved by the fact that the reaction of scheme 3 competes with reaction 3 of scheme 2, transforming the reactive peroxy radical into the much less reactive phenoxy radical. In this way the chain branching in scheme 2 is inhibited and the radical chain process is terminated.

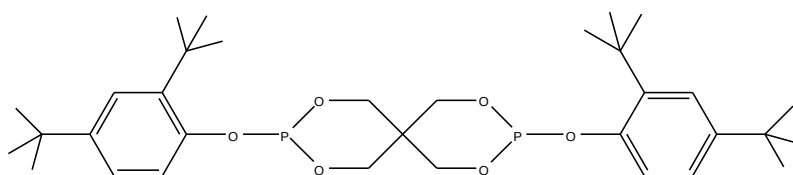
The phenoxy radical is also capable to react with another peroxy radical to give a peroxycyclohexanedione as widely established in literature (Scheme 4).[33, 40, 41].



Scheme 3.



Scheme 4.



U 626: bis-(2,4-di-tertbutylphenyl)-pentaerythryl-diphosphite

Figure 10.



Scheme 5.

The thermal stability of peroxycyclohexanedienones is limited. Their decomposition leads to new reaction chains at temperatures below 150°C. Also phenoxy radicals can initiate new radical chains at high temperature. Of course these features do not affect the performances of stabilizers during the normal life of stabilized materials, but these effects should be taken into account especially in high temperature application and testing of antioxidants-added materials. Otherwise this means that the effectiveness of sterically

hindered phenols decreases with increasing the temperature of application and manufacturing of the stabilized materials.

Even within the limits of the testing conditions, the positive effect of a typical antioxidant, Ultrinox U626, for the stabilization of PBT synthesised in the presence of $\text{Ti}(\text{O}-n\text{Bu})_4$ was previously highlighted in section 2. The structure of U626 is reported in Figure 10.

U626 is a rather complex molecule. Very interestingly the phosphite moieties in U626 can have also an important role in the stabilization. Phosphites are well-known stabilizers and they are called secondary antioxidants, while hindered phenol-based stabilizers are known as primary antioxidants. Phosphites have the ability to react with hydroperoxides to yield phosphates according to scheme 5.[20,38] U626 combines primary and secondary stabilizers in the same molecule.

4. THERMO-OXIDATIVE DEGRADATION OF PBT: THE ROLE OF TITANIUM (IV) RESIDUAL

An experimental investigation directly on polymers in order to find out the degradation products is difficult to realize. However, both the study of degradation of model compounds like butylene dibenzoate [5-7], and the general mechanism of thermo-oxidation of organic molecules (scheme 2), can be very helpful to propose a specific mechanism for the thermo-oxidative degradation of PBT (scheme 6). In order to simplify the discussion, the contribution of thermal degradation has not been considered.

The first step of thermo-oxidative degradation is believed to be the homolytic cleavage of α -CH bonds, a process that leads to the formation of α -radicals (step 1).[5-7] Then in the presence of oxygen the α -radicals react to form hydroperoxides that are the key intermediates of the degradation mechanism (step 2). In effect the decomposition of the hydroperoxides (step 4) is the beginning of complicated radical chains that lead to the formation of a great number of products and functionalities that are difficult to isolate and characterize (step 5).[5-11,42,43] However the results of these degradation reactions are mainly C-C and C-O cleavages of the bonds adjacent to radical moieties. One of the consequences of these cleavages is the decrease of the molecular weight and the increase of both aliphatic and aromatic carboxyl end groups.

As emphasized in section 3, the decomposition of hydroperoxides, the key step of the degradation mechanism, is rather slow and becomes effective only at temperature of about 120°C or higher. However in the presence of catalytic amounts of certain metal ions, such as a series of transition metals like Fe, Co, Mn, Cu, Ce, V, hydroperoxides decompose at a lower temperature and/or at higher rate.

According to this concept, the catalyst residual in PBT can have an important role to catalyze the degradation of hydroperoxides (step 4 of scheme 6). In fact it is well-known the capability of titanium(IV) to catalyze important oxidation reactions, such as epoxidation of allylic alcohols and sulfoxidation, in which hydroperoxides are involved as oxidants.[44,45] The role of titanium center in these reactions is the coordination and activation of the hydroperoxides to favor oxygen atom transfer.

Ti(IV) compounds are also able to catalyze hydroperoxides decomposition into ketone-alcohol mixtures, a well-known industrial process for acetone and phenol production.[46-48] In particular, a kinetic study reported by Sukin et al. showed that, in titanium(IV) catalysed

radical decomposition of peroxides, the decomposition increases in the order diacyl peroxides $\leq$ peroxy esters $<$ peroxy ketones = hydroperoxides. In these reactions, sterically hindered and chelated titanium(IV) compounds catalyse hydroperoxide decomposition only very slowly.[46]

Moreover, even Ti(III) based compounds play an important role in the radical decomposition of *t*-butyl hydroperoxide.[48] Therefore the possibility of the different redox species, Ti(IV)/Ti(III), can also affect radicals formation and polymer decomposition.

On the basis of these considerations we can confidently assume a relationship between titanium residual and PBT degradation. The different effect of $\text{Ti}(\text{O-}n\text{Bu})_4$ and the chelated $\text{Ti}(\text{acac})_2(\text{O-}i\text{Pr})_2$ on PBT stability could be explained with a different capability of the two metal residuals to coordinate the OOH groups and/or a different ability to catalyse hydroperoxides decomposition. Therefore $\text{Ti}(\text{O-}n\text{Bu})_4$ and the chelated $\text{Ti}(\text{acac})_2(\text{O-}i\text{Pr})_2$ should affect in a different way the key step 4 of the degradation mechanism (scheme 6) and consequently the rates of the entire degradation process are very different in the two cases.

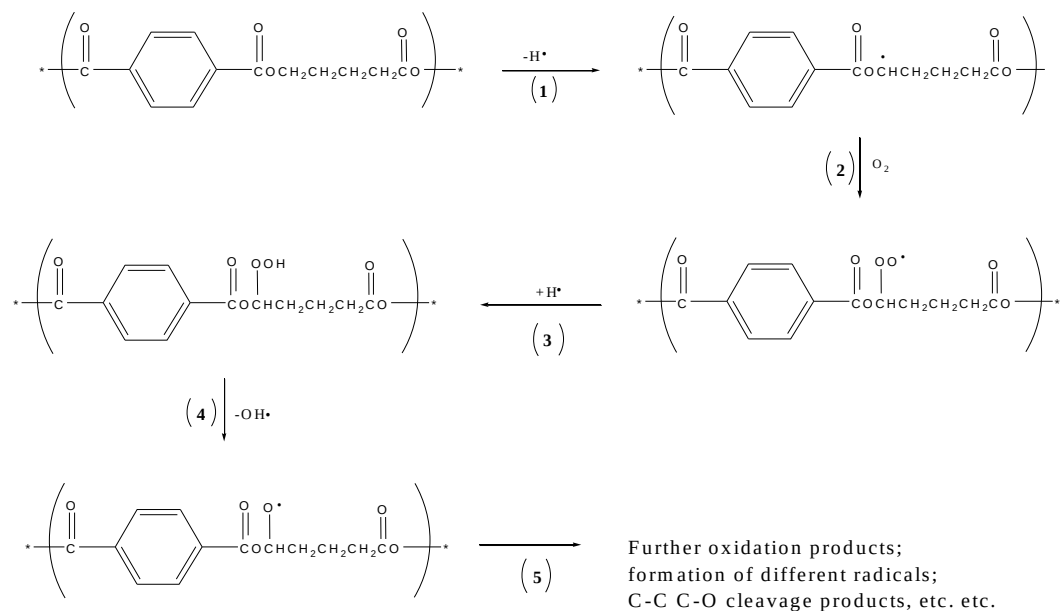
Then, the decrease of I.V., the increase of CEG and the yellowing of standard PBT 1 (see section 2) are related of the further decomposition the alkoxyl radicals (step 5). The observed yellowing could be correlated both to the formation of products with conjugated functional groups and to new coloured titanium species formed during high temperature oven testing. Of course it is difficult to determine experimentally the catalytic species and to establish the role of different Ti(IV) compounds on the degradation process in solid PBT. Probably the thermo-oxidation of the model compounds in the presence of different titanium based complexes can be useful.

In conclusion, even if a specific mechanistic model is not available yet for the obtained results, the improved stability of PBT in the presence of $\text{Ti}(\text{acac})_2(\text{O-}i\text{Pr})_2$ can be attributed to the inhibition of the degradation of hydroperoxides by means of metal deactivation using a chelating agent.

5. CONCLUSION AND OUTLOOK

Excellent progresses have been made over past decades in the development of new efficient catalysts for polyesters synthesis, and in the understanding of the properties of these materials. Even if an impressive quantity of information are available, several challenges are still open. One of the most important purpose in PET research is, without no doubt, the substitution of the toxic Sb(III) based catalyst with more friendly compounds. One of these possibilities, as described in section 1, is related to titanium (IV) based compounds. In effect $\text{Ti}(\text{O-}n\text{Bu})_4$ is an active catalyst in PET synthesis but it is not often used because of the yellowing of the obtained polymers. However, many studies are evaluating the use of different additives and/or several Ti(IV) based complexes in PET synthesis in order to solve these problems and to understand the reasons of the discoloration.

The different effect of titanium catalysts on PET and PBT colour could be related to the thermal degradation. Polycondensation temperature for PET is significantly higher than that of PBT, and titanium(IV) can affect their thermal decomposition in different ways. However, the role of titanium catalysts on PET properties is not clear yet, but, all these problems, the stability, the discoloration, are correlated directly or indirectly to the catalyst composition.



Scheme 6.

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Chapter 11

HINDERED AMINE STABILIZERS AS SOURCES OF MARKERS OF THE HETEROGENEOUS PHOTOOXIDATION / PHOTOSTABILIZATION OF CARBON CHAIN POLYMERS

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ABSTRACT

Application of Hindered Amine Stabilizers (HAS) is the state-of-the-art approach to protection of carbon-chain polymers such as polyolefins and polystyrene or blends containing these against weathering. During outdoor exposure, the polymers lose their material properties due to solar radiation-triggered photooxidation. The complex mechanism of the stabilization involving cyclic oxidation-triggered transformation of HAS is outlined. Monitoring of the formation of the HAS-developed key transformation products, HAS-related nitroxides, responsible within the regenerative mechanism for the effective stabilization was used to confirm the heterogeneous character of photooxidation of two carbon-chain polymers, polypropylene and a specific polyethylene copolymer. Depth profiles of nitroxides were monitored in a long-term photooxidation regime using Electron Spin Resonance Imaging (ESRI) technique. The shape of concentration profiles of the nitroxides accumulated in the equilibrium state upon filtered Xenon lamp-equipped Weather-Ometer exposure was interpreted in terms of the oxygen diffusion limited oxidation and radiation penetration in oxidation-stressed polymer surfaces. The data indicate differences in the character of the heterogeneous process in dependence on the polymer matrix and on the used stabilizer system based on secondary HAS and *O*-alkylhydroxylamine HAS and/or HAS combination with UV absorbers. Imaging of nitroxides is a precise tool for marking heterogeneous oxidation of polyolefins.

INTRODUCTION AND BASIC CONSIDERATION

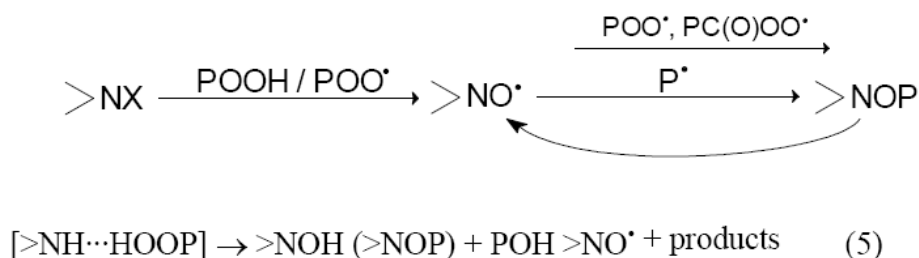
Carbon-chain commodity and engineering polymers (PH) suffer during all phases of their lifetime in the earth atmosphere from oxidative degradation, either thermal or phototriggered. Mechanism of oxidation was studied in detail [1, 2]. The oversimplified free radical oxidation scheme involves initiation (1), propagation (2 and 3) and termination steps (4) followed by reactions of primary intermediates and products.



The last two steps are rather well understood. There exist some uncertainties encountering initiation steps due to the character and distribution of initiation centers in the polymer mass such as sensitizing impurities, charge transfer complexes (CTC) and/or participation of active environmental pollutants [3-5]. Generally this does not affect however the structure of the oxidation products having oxidation properties formed in the consecutive steps to initiation [alkylhydroperoxides POOH, peroxyacids PC(O)OOH] and their oxygen-centered free radical precursors [POO[•], PC(O)OO[•]] that play an important role in the fate of polymer additives, stabilizers in particular.

Phototriggered reactions such as photolysis and photooxidation play a decisive role in outdoor exposure (weathering) of polymers [1, 4-6]. Degradation of real polymer systems was shown to be a heterogeneous process strongly affected by the sample morphology and geometry. Analysis of the physical chemistry of polymer oxidation and stabilization confirmed [7] differences between oxidation of amorphous and crystalline parts of the material. This results in degradation heterogeneity due to the oxygen impermeability of the crystalline areas. The heterogeneity on molecular and supramolecular level is primarily affected by the random localization of initiation and chromophoric centers in the polymer mass followed by infectious oxidative spreading from the centers [8]. Concentration of activated centers depends on the intensity of UV radiation penetrating through the polymer that depends on polymer transparency. Moreover the oxidation rate and localization of oxidation products are dependent on the availability of oxygen within the system. Consequently rate of oxygen diffusion into the material, rate of oxygen consumption and the possibility to supplement the consumed oxygen by diffusion are decisive factors affecting the depth of oxidation of thick walled materials. Diffusion limited oxidation (DLO) results in differences in oxidative changes between the heavily damaged surface layers and central parts of the materials [5]. The differences are dependent on the thickness of the material and are observed as concentration gradients from the surface to the bulk of the material using step-by-step analyses [5, 9-11]. DLO is a process characteristic of both thermal and photooxidation of thick-walled materials and results mostly in U-shape formed spatial distribution of changes [5, 9, 11].

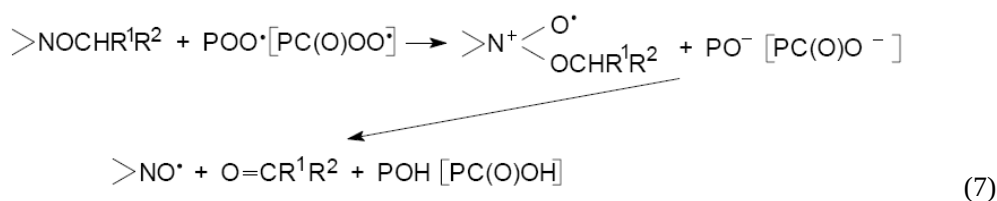
There is not a full consensus what everything is involved in the HAS mechanism because it is difficult to confirm some of the proposed mechanistic steps in the polymer matrix. Formation of HAS-derived nitroxides ($\text{>NO}^\bullet$) (5) is the assumed primary step of the stabilizing activity connected with the sacrificial transformation as shown for a secondary HAS (having active function >NH) [15, 16].



Identification of nitroxides in the oxidized hydrocarbon substrate doped with HAS is considered as a proof of the photoantioxidant activity of HAS. The latter involves unique mechanistic features in polymer stabilization differing thus from the activity of conventional chain-breaking antioxidants. The developed nitroxides are able to scavenge polymeric alkyls formed not only in the surface layers but also in areas of oxygen insufficiency in deeper polymer layers where they may be formed due to presence of residual oxygen. Participation of the polymeric alkyls in oxidative transformation into alkylperoxyls $\text{POO}^\bullet$ (2) is thus disabled. Resulting *O*-alkylhydroxylamines $>\text{NOP}$ are formed not only from $>\text{NH}$ but also from various *N*-substituted HAS ($>\text{NX}$, $\text{X}=\text{alkyl, aryl, alkoxy}$) and are considered as active reservoirs of HAS efficiency (6).

(6)

Nitroxide oxidative regeneration (Klemchuk-Gande mechanism) from $>\text{NOP}$ based on its interaction with oxygen-centered radical oxidation products of polyolefins (polymeric alkylperoxyls and acylperoxyls) was proposed (7) where symbol CHR^1R^2 represents “P” in $>\text{NOP}$ [18]. According to this scheme no peroxidic by-products with pro-oxidative character are formed within the resulting products.

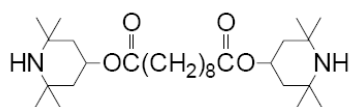


Formation and location of nitroxides, the key HAS-developed transformation products, was monitored using electron spin resonance imaging (ESRI) technique that confirms the heterogeneous character of photooxidation of polyolefins.

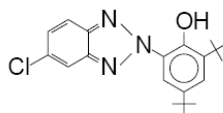
EXPERIMENTAL

Materials

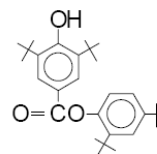
Polymer plaques containing stabilizers were prepared using additive-free polypropylene (PP) PH6 (Polymer Institute, Brno), $M_w = 308\,000$, $M_n = 62\,500$, of ca. 50 % crystallinity or recently developed amorphous polyolefin poly(ethylene-co-norbornene) Topas[®] 8007 (TP, TOPAS Advanced Polymers GmbH, Frankfurt am Main, Germany), volume flow index at 260 °C/2.16 kg: 30 ml/10 min, density 1.02 g/cm³, norbornene content ca 17 weight %. HASs Tinuvin[®] 770 and Tinuvin[®] 123, UVAbs Tinuvin[®] 327 as preventive light stabilizer acting by an excited state intramolecular proton transfer (ESIPT) mechanism and benzoate photoantioxidant Tinuvin[®] 120 were used as additives. All photostabilizers were supplied by Ciba Specialty Chemicals, Basel, Switzerland.



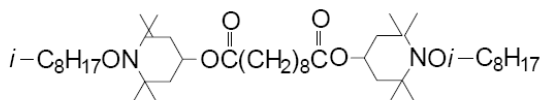
Tinuvin®770



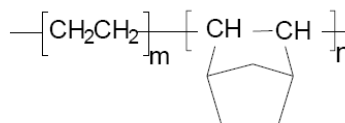
Tinuvin®327



Tinuvin®120



Tinuvin®123



Topas®

Polymer-stabilizer mixtures were homogenized in the W 50 EH chamber of a Brabender Plasti-Corder laboratory mixer at 190 °C and 60 rpm for 10 min. After removing the material from the chamber, 6 mm thick plaques 8 x 8 cm were molded in a laboratory hot press at 200 °C for 2 min under 50 kN for deairation plus another 2 min under 100 kN followed by water cooling to 70 °C for ca. 15 min under 150 kN.

Accelerated Photooxidation and Oven Test

The plaques were exposed to accelerated photooxidation in an Atlas Ci 3000+ Weather-Ometer under the following test conditions: filtered Xenon light wavelength bandpass 295-800 nm (inner and outer filtercombination Type S Boro/Type S Boro), irradiance 0.5 Wm⁻²nm⁻¹ at 340 nm, black panel temperature (bpt) 60 °C (used PP and TP were non-pigmented, accordingly the surface sample temperature was lower), dry bulb temperature (dbt) 30 °C, RH 20%. Oven tests were performed in a heating box at temperature 60 °C. Cylindrical samples (diameter 3 mm, length 6 mm) were bored out from the plaques after appropriate time periods of exposure. Between periods of exposure in Weather-Ometer or in oven the plaques were stored in the dark at room temperature. Tests proved a negligible change of concentration profiles in the samples bored out from the plaques during the storage.

Electron Spin Resonance Imaging

ESRI experiments were performed with a commercial Bruker ELEXSYS E540 X-band spectrometer equipped with a pair of eight-shaped Lewis gradient coils delivered by George Associates (Berkeley, USA) that are able to produce vertical gradient perpendicular to the external magnetic field $G_{\max} \sim 320$ G/cm. Concentration profiles of nitroxides in the samples along the axes of the cylinders coinciding with the direction of irradiation incident on the plaque in the Weather-Ometer were calculated using the 1D ESRI and deconvolution procedure described previously [19]. Matlab software tool was used for the data manipulation and programs targeting the deconvolution procedure in 1D experiment and filtered back projection procedure in 2D experiment based on the Matlab scripting language were developed. Spatial dependence of ESR spectral line shapes was excluded by checking spatial-

spectral images calculated using back projection algorithm from 2D ESRI data. Experimental scheme is given in Fig. 1. In order to obtain intensity of images in absolute units, usual spectrometer calibration for a given sample setup with the standard of known concentration was performed. In the 1D experiment we calibrated each sample spectrum (taken with gradient coils off) used for calculation of the particular one-dimensional profile using the spectrum of the standard taken under similar conditions. As the second integrals of the EPR spectra are directly proportional to the number of spins present in the measured sample, we were able to assess the total concentration of spins in the given sample and ascribe this number to the first integral of the resulting 1D profile. Anticipating axial symmetry of nitroxide distribution in the cylindrical sample we obtained the true concentration profile in number of spins per volume unit in particular depth of the sample after normalization of the calibrated 1D profile to the sample cross-section.

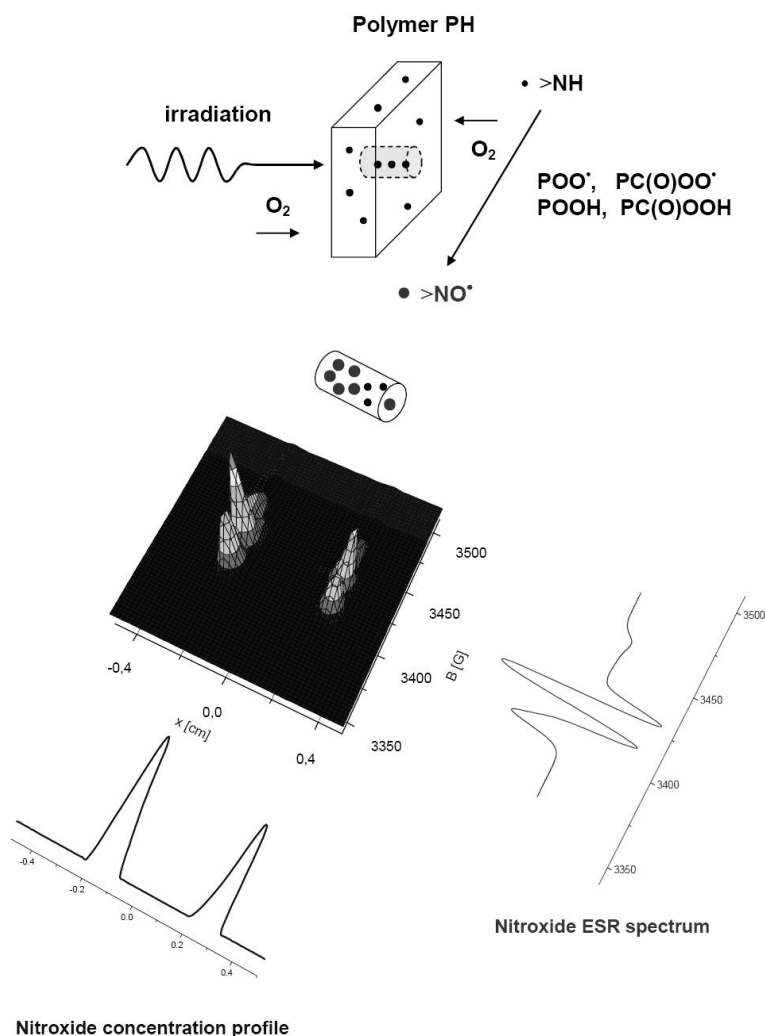


Figure 1. Experimental arrangement.

Nitroxide Formation and Location in Oxidized Polypropylene

In spite of some uncertainties in the individual steps of the HAS mechanism in polymer stabilization due to the specific effects of the polymer matrix and the environmental stress, the HAS-based nitroxides are considered the key intermediate in the HAS reactivity mechanism. Detection and quantification of the formed nitroxides using ESRI spectroscopic technique has been exploited for confirmation of the primary transformation step in HAS mechanism [15, 16, 20], as a consequence of interactions of HAS with oxygenated radical and molecular products of polyolefins (5). Monitoring of the nitroxide development enables tracing of the oxidation process within the polymer matrix. Consequently it is also a tool for marking the heterogeneity of the oxidative transformation of semicrystalline carbon chain polymers [polypropylene (PP), polyethylenes (PE)] or amorphous polymers [copolymers of ethylene with norbornene, polystyrene (PS), high impact polystyrene (HIPS), acrylonitrile-butadiene-styrene polymer (ABS)].

Most of the experimental studies dealing with tracing of nitroxide formation were performed using thin sectioned polymers, films of PP in particular [20, 21]. The determined nitroxide level is generally low [15]. Time-dependent ESR analysis of photooxidized and HAS-doped PP films revealed an increase in the amount of formed nitroxides from the beginning of the exposure [20, 21]. After reaching a maximum, a gradual decrease approaching slowly the steady state concentration characterizes the in-polymer behavior of nitroxides in consecutive steps, such as scavenging of polymeric alkyl radicals $P^{\bullet}$, formation of $>NOP$ (5) and nitroxide regeneration (7). The process is affected by the structure of the used HAS and by the external stress [4, 20]. Differences between accelerated and natural aging in PE doped with oligomeric HAS [22] or differences between thermal and photooxidation in ABS [23] were observed. Increase of the concentration of the HAS originally added to the polymer results in an increase of the concentration maximum of the nitroxide in the initial phase of the process [22] and prolongs the period of the effective material protection. The trend in the change of the nitroxide concentration indicating an approach to the equilibrium concentration is analogous at various in practice used concentrations between 0.5 and 3.0 % and confirms generally the overall cyclic HAS stabilization mechanism. Development trends in the nitroxide level analogous to that in plastics were found in HAS doped automotive clearcoats [24].

Determination of the heterogeneity of oxidative damages increases the insight into the material properties of aged polymers because the damaged regions influence seriously the overall properties of the material. For example the heavily degraded polymer surface layer deteriorates seriously tensile fracture properties of the whole material or infects components of polymer blends containing recyclates. Monitoring of nitroxides in thick materials (plates several mm thick) after oxidative stress is a sensitive method to localize the degradation within the material depth. Using HAS of various structures in different polymer materials provides moreover important information about specific mechanistic features of the process. In this paper we concentrate on secondary HAS Tinuvin[®] 770, *O*-alkylhydroxylamine-type HAS Tinuvin[®] 123, a combination of Tinuvin[®] 770 with UV absorber Tinuvin[®] 327 and photoantioxidant Tinuvin[®] 120 in semicrystalline additive-free PP. For matter of comparison, experiments with an amorphous polyethylene, poly(ethylene-co-norbornene) copolymer and a HAS-developed nitroxide additive were performed.

Several studies of the spatial resolution of oxidation processes in HAS stabilized polymer appeared since the pioneering paper [25] and deal with events in PP [26 - 28] or commercial poly(acrylonitrile-co-butadiene-co-styrene) (ABS) copolymer plaques with thickness from 2 to 6 mm [27, 29]. We preferred for our experiments plaques of 6 mm thickness providing more detailed information on the spatial distribution of nitroxides in both thermal and photooxidative stress situations [28].

Results of experiments performed with oxidized PP doped with secondary HAS Tinuvin® 770 show high concentration of nitroxides in the vicinity of both surfaces due to the DLO. This was observed after continuous exposure to radiation in the Weather-Ometer on the irradiated (front) and non-irradiated (back) surfaces as well as on the both surfaces of the samples exposed thermally in hot air oven. Very low concentration of nitroxides was present inside of the samples. The concentration profiles are of characteristic U-shape and indicate preferential surface oxidation of PP, with a specific response to thermal and photochemical stress (Fig. 2). The assumed complex HAS mechanism is thus more explicitly confirmed in thick samples than by monitoring nitroxide concentration in PP films. It is consistent with surface consumption of oxygen in thick plaques and lower availability of oxygenated products in the depth of the PP matrix necessary for a direct development of nitroxides from HAS as well as for nitroxide regeneration from *O*-alkylhydroxylamine >NOP within the regenerative cycle (7).

The comparison of the content of nitroxides generated in PP plaques containing 1 % of Tinuvin® 770 as a sole additive measured after 73 days exposure indicates faster degradation (monitored by nitroxide formation) during the phototriggered process (Fig. 2a) in comparison with oven aging (Fig. 2b). Generation of nitroxides in the oven aged samples confirms at the same time a heat stabilizing contribution of HAS in PP at used conditions (60 °C).

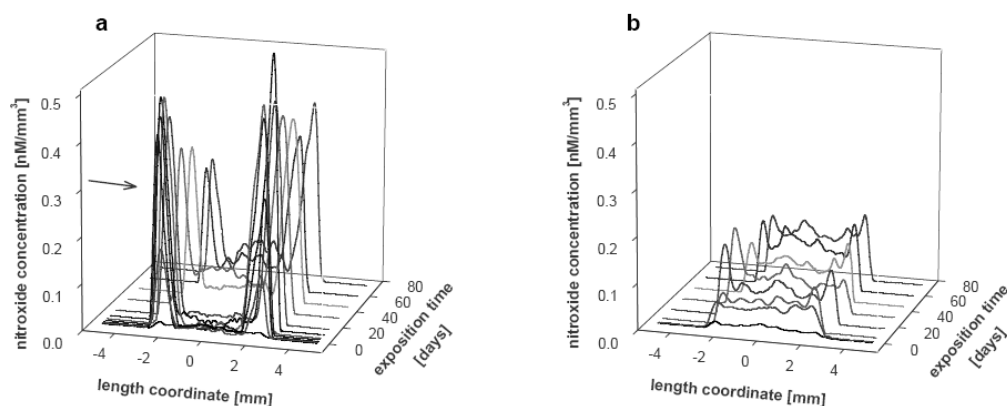


Figure 2. Dependence of nitroxide concentration profiles measured in PP plaques stabilized by 1 % of Tinuvin® 770 as a sole additive and exposed to accelerated photodegradation (a) or oven test (b) on the net exposure time. The arrow indicates direction of the incident light.

The nitroxide level in samples containing from 0.5 to 2.0 % of Tinuvin® 770 increased with increasing HAS concentration. Approximately symmetrical U-shape of the nitroxide concentration profile shown in Fig. 2a was confirmed by comparison of shapes of the nitroxide concentration profiles from the front and back surfaces of PP plaques oxidized for overall net exposure 87 days in the presence of different amounts of HAS (Fig. 3). A

significant decrease in the nitroxide concentration with exposure time in samples doped with the lowest concentration (0.5 %) of HAS was observed indicating consumption of considerable portion of the stabilizer during the degradation process.

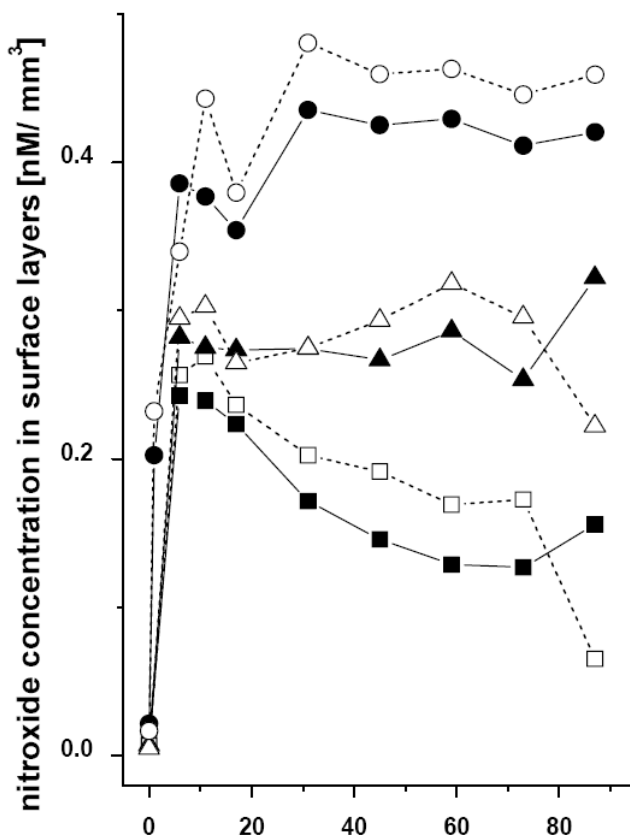


Figure 3. Dependence of concentration of nitroxides generated in the irradiated (full symbols and solid lines) and unexposed (empty symbols and dashed lines) surface layers of the PP plaques stabilized by 0.5 % (●, ▽), 1 % (■, X), and 2 % (○, –) of Tinuvin® 770 as a sole additive and exposed to accelerated photodegradation on the net exposure time.

A simplified model explains the observed shapes of nitroxide profiles in the thick polymer plates exposed to the environmental oxidative stress characteristic of DLO and radiation penetration. Oxygen is able to diffuse from both sides of the sample into the polymer mass and is consumed into radical and molecular oxygenated species. The latter are concentrated predominantly in the near surface areas as confirmed experimentally by formation of surface-centered concentration profiles of carbonyl species, accounting for transformations of the primary peroxidic species [2, 5, 12]. Within these areas the secondary HAS Tinuvin® 770 (>NH) is transformed into nitroxide (>NO[•]). Formation of *O*-alkylhydroxylamine (>NOP) after trapping polymeric alkyl radicals and regeneration within the cyclic mechanism (7) [18] follow in the next steps and result in equilibrium nitroxide concentration. The maximum equilibrium nitroxide concentration found in irradiated surface layer of the PP plaque stabilized by 1 % of Tinuvin® 770 equals approximately to 1 % of concentration of the stabilizer added. Intensity of the UV radiation penetrating through the

polymer and participating in formation of the polymeric alkyl radical depends on polymer transparency. Due to the high transparency of PP there is sufficient intensity of light to trigger oxidation also in the (rich in oxygen) back surface layer of the sample where the concentration of nitroxides similar as in the irradiated surface layer is generated. Due to the preferential surface oxygen consumption, the central part of the sample suffers from oxygen deficiency. The HAS developed >NOP, if present, has a limited possibility for nitroxide regeneration. The U-shape nitroxide concentration profile arises consequently in the PP plaque (Fig. 2a).

We found in an earlier study [28] and confirmed in new experiments that the shapes and time-dependent change of the nitroxide concentration profiles inside polymer plaques subjected to accelerated aging as measured by ESRI depend on the polymer matrix (comparison between PP and polystyrene) and on the responses of the HAS structure to oxidizing counterparts of the matrix. Nitroxide concentration profiles measured in TP plaque stabilized with 1.0 % of Tinuvin® 770 oxidized for overall net exposure 147 days shows slower increase of nitroxide concentration and lower concentration of nitroxides in the back surface layer when compared with PP plaque. Both observations are similar to the results obtained in polystyrene [28], but even more pronounced (Fig. 4). It indicates the lower transparency of TP in comparison with PP and even with PS which is confirmed by optical measurements.

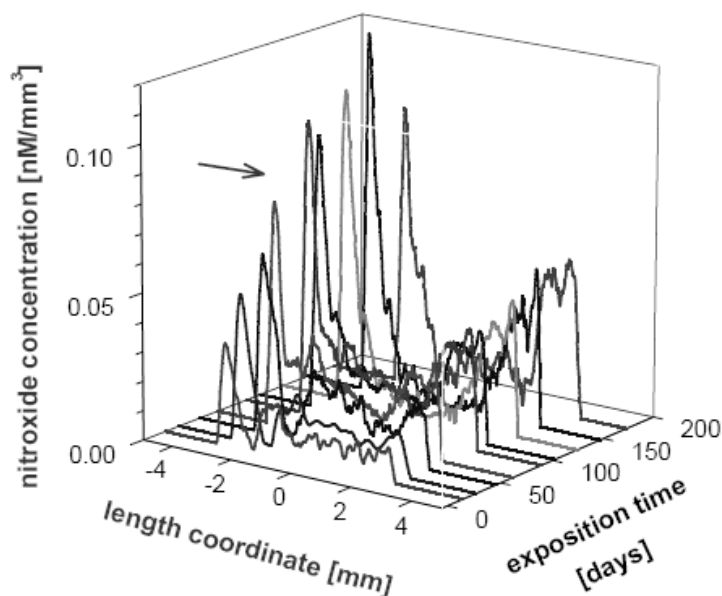


Figure 4. Dependence of nitroxide concentration profiles measured in TP plaques stabilized by 1 % of Tinuvin® 770 as a sole additive and exposed to accelerated photodegradation on the net exposure time. The arrow indicates direction of the incident light.

Generation of nitroxides in the PP matrix is dependent on the intensity of the incident UV radiation. By using effective UV absorbers (light stabilizers with preventive mechanism) in combination with HAS [4] the efficiency of the oxidative phototriggered process decreases with depth in the sample due to the light filtration effect. We studied two light stabilizers with

different activity mechanisms (Fig. 5), the benzotriazole-based UV absorber Tinuvin® 327 and the phenolic photoantioxidant Tinuvin® 120 for overall net exposure 73 days. Decrease of efficiency of the oxidative phototriggered process in the back sides of the exposed plaques is markedly shown by the changed shape of the nitroxide concentration profile. The gradually reduced penetration of the radiation through the sample results in reduced oxidation of the non-irradiated side of the sample shown by formation of lower concentration of nitroxides in the back side surface layer. The photostabilizing effect depends on the structure of the light stabilizer, i.e., on its activity mechanism and efficiency. The benzotriazole-based UV absorber Tinuvin® 327 is comparatively more effective (Fig. 5a) than the phenolic photoantioxidant Tinuvin® 120 (Fig. 5b) in decreasing nitroxide concentration in the irradiated surface layer.

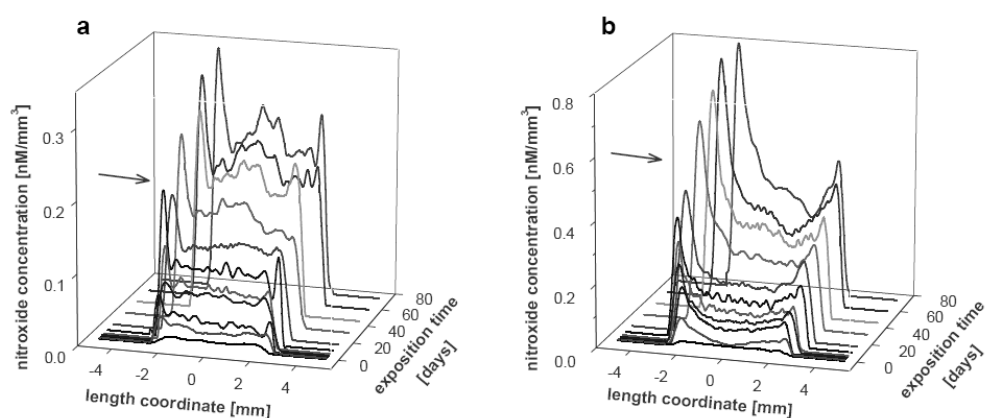


Figure 5. Dependence of nitroxide concentration profiles measured in the PP plaques stabilized by (a) 1 % of Tinuvin® 770 + 0.5 % of Tinuvin® 327 and (b) 1 % of Tinuvin® 770 + 0.5 % of Tinuvin® 120 and exposed to accelerated photodegradation on the net exposure time. The arrow indicates direction of the incident light.

Participation of the protective mechanism affected by the modified structure of HAS was evidenced by comparison of nitroxides developed in PP plaques doped with secondary HAS Tinuvin® 770 (Fig. 2) and NOR-HAS Tinuvin® 123 (Fig. 6). The latter was developed for polymer photostabilization in acid environment [15, 16]. Very high concentration of nitroxides was found in thermally pressed Tinuvin® 123 containing plaques prepared for oxidation experiments. Nitroxides were distributed almost homogeneously within the mass of the plaque. The high nitroxide concentration remained in thermally oxidized PP (Fig. 6b). A fully different progress in the development of the nitroxide distribution within the sample was observed in the phototriggered process (Fig. 6a, 7). The initial concentration decreased with increasing exposure time. At the same time the shape of the nitroxide profile changed from the nearly homogeneous distribution to the asymmetric U-shaped profile characterized by a lower amount of nitroxides in the irradiated front surface in comparison with the back surface and a low amount of nitroxides in the central part of the sample.

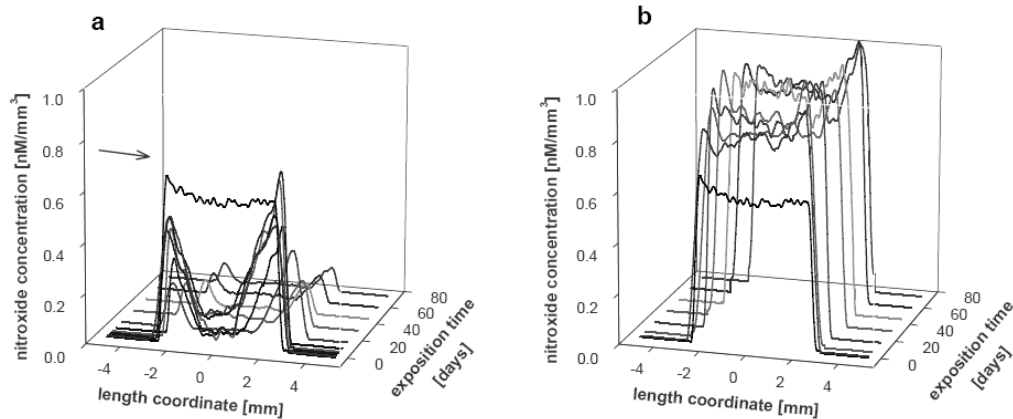


Figure 6. Dependence of nitroxide concentration profiles measured in the PP plaques stabilized by 1 % of Tinuvin®123 as a sole additive and exposed to accelerated photodegradation (a) or oven test (b) on the net exposure time. The arrow indicates direction of the incident light.

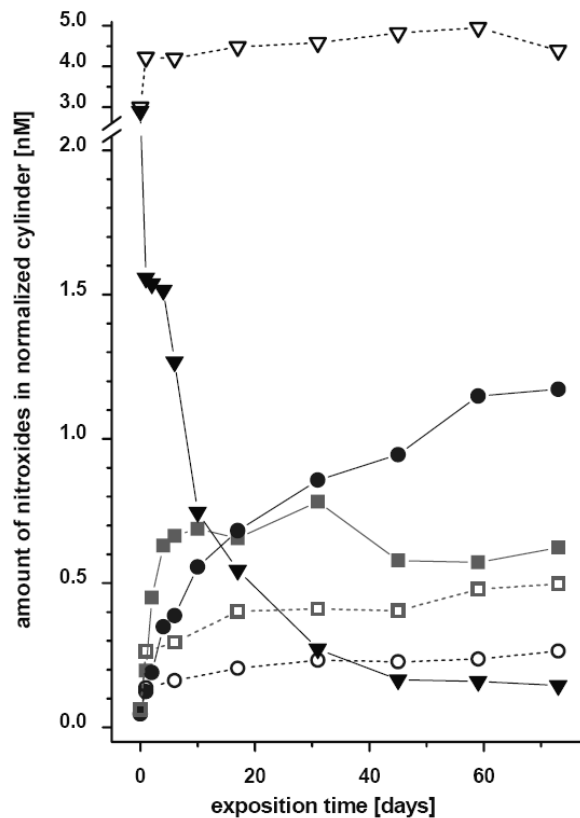


Figure 7. Dependence of the amount of nitroxides generated in normalized volume of the cylinder (1 mm² cross-section) bored out from the PP plaques stabilized by: 1 % of Tinuvin®770 (▲,▽), 1 % of Tinuvin®770 + 0.5 % of Tinuvin®327 (●,○), 1 % of Tinuvin®123 as a sole additive (■,□), and exposed to accelerated photodegradation (full symbols and solid lines) or to the oven test (empty symbols and dashed lines) on the net exposure time.

Development of the high nitroxide level generated from Tinuvin[®] 123 in the sample from the beginning of the experiment is explained by cooperation of thermochemical and photochemical degradation of NOR-HAS. The thermolysis participates even in the phase of the sample preparation and accounts for formation of nitroxides from the NOR-HAS according to (8) [15, 30].



Differences in the shape of nitroxide concentration profiles during photo and thermal degradation of the sample containing Tinuvin[®] 123 are most probably due to presence of polymer alkyl radicals generated during photodegradation proces in the whole volume of the PP sample. Nitroxide concentration in the central part of the sample subjected to photodegradation is reduced by the reaction of the nitroxides with polymer alkyl radicals (6) and cannot be renewed by reaction (5) due to the oxygen deficiency. Negligible concentration of polymer alkyl radicals are generated during thermodegradation process when practically no change of the nitroxide concentration profiles is observed.

CONCLUSION

In PP plaques, 6 mm thick, stabilized with secondary HAS Tinuvin[®] 770 as the sole additive, with the combination of Tinuvin[®] 770 with UV absorber Tinuvin[®] 327 or with photoantioxidant Tinuvin[®] 120, U-shaped concentration profiles of nitroxides were determined during exposure to accelerated photooxidation in a Weather-Ometer already after the first day of irradiation. This type of the nitroxide distribution results from the DLO and penetration of the incident radiation that initiates degradation of PP through the plaques and reaches the unexposed side of the plaque with sufficient intensity. Due to the DLO, radical and molecular oxidation products are formed from the alkyls predominantly near to the front and back surfaces of the PP plaques indicating the depth of oxygen diffusion. These oxidation products participate in transformation of the added HAS marking thus clearly the heterogeneous character of oxidation. Oxygen insufficiency in the central part of the plaques (accounting not only for limited oxygen diffusion but also for the effective and preferential oxygen consumption in the surface layers) allows polymeric alkyls to survive. Consequently, oxidation of the originally added HAS or oxidative regeneration of its transformation product $>\text{NOP}$ into nitroxide are practically hindered. Moreover, small amounts of nitroxides are effectively scavenged by the alkyls. Low concentration of nitroxides confirms unequivocally limited degradation in the central part of the plaques. Application of a combination of HAS with UV absorber indicates efficient cooperation between the two types of light stabilizers acting by different stabilization mechanisms as well as the heterogeneity of the degradation process. The latter is affected in the presence of UV absorbers by the lower radiation intensity of the UV light penetrating into the back (not directly irradiated) side of the plaque in comparison with the intensity of the incident light.

A lower level of nitroxides than in photooxidized PP plaques characterized by the concentration profile confirming slightly heterogeneous oxidation was detected in plaques

doped with Tinuvin[®] 770 and thermally treated in oven. This is a proof of the long term heating stabilization influence of HAS at experimental conditions.

Monitoring concentration of nitroxides in PP stabilized with the NOR-HAS Tinuvin[®] 123 reveals their high concentration already from the beginning of the oxidative stress. This is due to the nitroxides generated during thermal pressing of the plaques. Concentration of nitroxides decreased during the photooxidative stress. Scavenging of nitroxides by polymeric alkyls generated by the phototriggered degradation is assumed.

Performed experiments proved the heterogeneous character of oxidation of the PP plaques containing HAS by profiling nitroxide formation using ESRI method.

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