

Synthesis of Arborescent Amphiphilic Copolymers

by
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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Living anionic polymerization techniques were applied to the synthesis of arborescent (dendritic) well-defined graft polymers having core-shell morphologies, with a hydrophobic core and a hydrophilic shell. Cycles of polystyrene substrate acetylation and anionic grafting yielded successive generations of arborescent polystyrenes. The anionic polymerization of styrene with *sec*-butyllithium provided polystyryllithium serving as side chains. These were coupled with a linear acetylated polystyrene substrate to obtain a generation zero (G0) arborescent polymer. An analogous G0 hydroxyl-functionalized polystyrene substrate with hydroxyl end groups was also obtained by a variation of the same technique, using a bifunctional organolithium initiator containing a hydroxyl functionality protected by a silyl ether group to generate the polystyrene side chains. These were coupled with the linear acetylated polystyrene substrate and subjected to a deprotection reaction to give the G0 polymer functionalized with hydroxyl groups at the chain ends. A similar procedure was used to generate a hydroxyl-functionalized arborescent G1 polymer from the corresponding G0 acetylated polystyrene substrate. The growth of polyglycidol chain segments was attempted from the hydroxyl-functionalized cores, to form a hydrophilic shell around the hydrophobic cores, but led to extensive degradation. A click reaction was also developed to synthesize the amphiphilic copolymers and was much more successful. In this case alkyne-functionalized arborescent polystyrene substrates, obtained by a modification of the hydroxyl-functionalized arborescent polystyrenes, were coupled with azide-functionalized polyglycidol side chains.

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List of Abbreviations and Symbols

ATRP	Atom transfer radical polymerization
AM	Activated monomer mechanism
ACE	Active chain end mechanism
EEGE	2,3-Epoxypropyl-1-ethoxyethyl ether
DB	Degree of branching
DPMK	Diphenylmethylpotassium
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
dn/dc	Refractive index increment
DPE	1,1-Diphenylethylene
DRI	Differential refractometer detector
f_n	Number-average branching functionality
G	Generation number
$^1\text{H NMR}$	Proton nuclear magnetic resonance
M_n	Number-average molecular weight
$M_n(G)$	Number-average molecular weight of a graft polymer of generation G
M_n^{br}	Number-average molecular weight of the side chains
M_w	Weight-average molecular weight

MWD	Molecular weight distribution
M_w/M_n	Polydispersity index (PDI)
PAMAM	Polyamidoamine
PS	Polystyrene
SMA	Slow monomer addition
SEC	Size exclusion chromatography
THF	Tetrahydrofuran
TBAF	Tetrabutylammonium fluoride
2VP	2-Vinylpyridine
v/v	Ratio by volume
δ	NMR chemical shift (ppm)

Chapter 1

Introduction

1.1 Opening Remarks

Branched polymers have attracted special attention due to their distinctive physical properties. Among branched macromolecules, arborescent polymers are particularly interesting because of their highly branched and well-defined structure. Amphiphilic arborescent core-shell polymers, incorporating a hydrophobic core and a hydrophilic shell, should be likewise interesting as micelle-like species.

Amphiphilic arborescent copolymers can be synthesized by the living anionic and ring opening polymerization techniques. Under appropriate conditions, the absence of termination and chain transfer in these reactions allows the preparation of polymers with predictable molecular weights, narrow molecular weight distributions, and a high degree of structural control. Living/controlled polymerization techniques can be used to synthesize a variety of well-defined copolymer structures. However, not all polymer backbones can be easily combined into one single copolymer architecture due to incompatibilities between the different polymerization methods available and the specific conditions required in each case.

Click chemistry is an established method for the preparation of well-defined macromolecular architectures. It can be combined with living/controlled polymerization methods, which allow the synthesis of well-defined polymers with alkyne or azide groups. It will be shown in this thesis that amphiphilic arborescent core-shell polymers, incorporating a hydrophobic core and a

hydrophilic shell, can be obtained by combining anionic polymerization and grafting with click grafting techniques.

1.2 Thesis outline

The research presented in this thesis explores the synthesis of arborescent amphiphilic polymers. It starts in Chapter 2 with a general overview of the synthesis of branched polymers derived from styrene and glycidol, amphiphilic copolymers, click reactions, and other background information relevant to the work being discussed. The project objectives are explained in Chapter 3, while the detailed experimental procedures used are provided in Chapter 4. In Chapter 5, the results and obtained and their analysis are provided to explain the trends observed. The conclusions drawn from the research are summarized in Chapter 6, as well as recommendations for future work.

Chapter 2

Background Information and Literature Review

The arborescent graft polymers and core-shell copolymers described in this thesis were synthesized from vinyl and epoxide monomers by the living anionic polymerization and ring-opening polymerization techniques, respectively. Consequently, background information on anionic and ring-opening polymerizations, as well as click reactions will be provided to facilitate the understanding of the material presented in the following chapters.

2.1 Living Anionic Polymerization and Living Polymers

In 1956, Szwarc et al.^{1,2} discovered that the polymer chains remained active after the monomer was consumed in the sodium naphthalide-initiated anionic polymerization of styrene in tetrahydrofuran (THF). Following the addition of a new aliquot of monomer the macromolecules grew further, thereby proving that they were still reactive. Furthermore, analysis of the product resulting from sequential additions of styrene and isoprene demonstrated the formation of polystyrene-polyisoprene block copolymers without contamination by residual styrene homopolymer. Thus, because both termination and chain transfer to the monomer or the solvent were absent, the reactivity of the polymer chains could be retained. These macromolecules were accordingly described as “living polymers”, and the reaction was described as “living anionic polymerization”. This discovery attracted the attention of polymer chemists involved in both industrial and academic research. Many combinations of monomers, initiators and solvents were

subsequently found to proceed by this living anionic polymerization mechanism.³⁻⁵ Living polymerization is useful for the synthesis of macromolecules with well-defined architectures. Various polymers with controlled compositional and structural parameters, including molecular weight, molecular weight distribution, stereochemistry, branching, polymers with chain end and in-chain functional groups, and copolymers with controlled compositions and microstructures have been synthesized by these techniques.^{3,6-8}

2.1.1 The Features and Advantages of Living Anionic Polymerization

A living anionic polymerization system only involves two main steps: initiation and propagation. Side reactions including chain transfer or termination must not take place, and a fast initiation rate as compared to the propagation reaction provides a controlled molecular weight.⁸ The number-average degree of polymerization is determined by the mole ratio of monomer to initiator and increases with monomer conversion p , as given by Eq. 2.1.⁷

$$X_n = \frac{[\text{monomer}]}{[\text{initiator}]} p \quad (2.1)$$

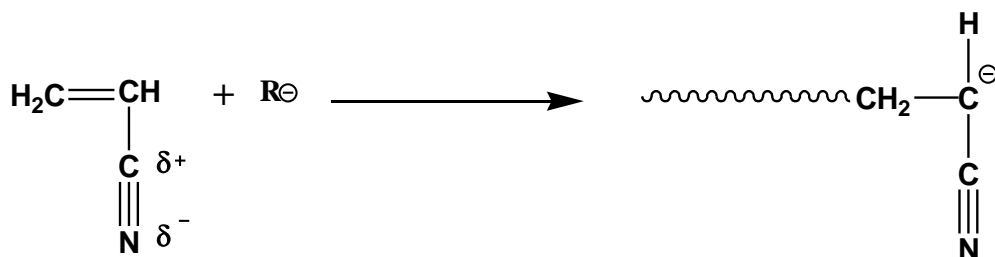
Furthermore the molecular weight distribution can be very narrow, with a theoretical polydispersity index given by Eq. 2.2, provided that a fast equilibrium exists between active and dormant propagating species.⁸

$$\frac{\bar{X}_w}{\bar{X}_n} = 1 + \frac{\bar{X}_n}{(\bar{X}_n + 1)^2} \simeq 1 + \frac{1}{\bar{X}_n} \quad (2.2)$$

Another advantage of the absence of side reactions is that the chain ends remain reactive; i.e., they are organometallic sites that can undergo further reactions. As a result, the preparation of block copolymers with controllable block sizes, graft polymers, as well as end-functionalized polymers can be achieved.^{3,6}

2.1.2 Monomers for Living Anionic Polymerization

Stability of the anionic propagating centres is required; consequently, a relatively small number of monomers are satisfactory for living anionic polymerization reactions. Generally, two types of monomers are suitable for these reactions: substituted vinyl monomers with one or more double bonds such as styrene, and heterocyclic monomers that can undergo ring opening by nucleophilic reactions such as glycidol and other epoxides.^{3,4,6} Vinyl monomers with electron-withdrawing or resonance-stabilized substituents can decrease the charge density at the propagating centre (i.e. make it less negative), as well as decrease the rate of propagation, which leads to fewer side reactions, as shown in Scheme 2.1.



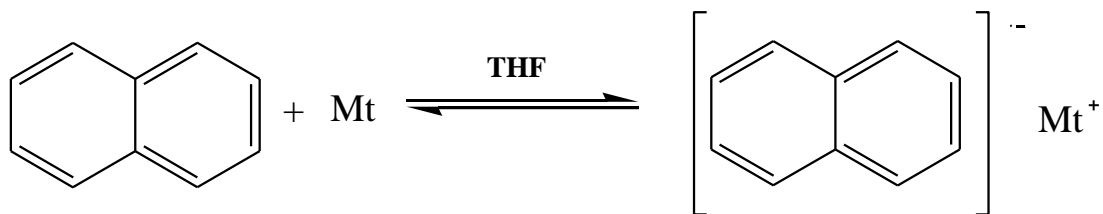
Scheme 2.1 Vinyl monomer with an electron-withdrawing substituent

Such substituents include aromatic rings, double bonds, carbonyl esters, nitriles, sulfoxides, and nitro groups. Heterocyclic monomers including epoxides, cyclic sulfides, lactones and lactides, cyclic carbonates, lactams, cyclosiloxanes, and cyclic phosphorus compounds can also be polymerized anionically.

In this thesis styrene and glycidol were used as monomers, and their polymerization was achieved, respectively, by anionic addition and ring opening polymerization without termination and transfer reactions. The mechanism of these reactions will be discussed in the following sections.

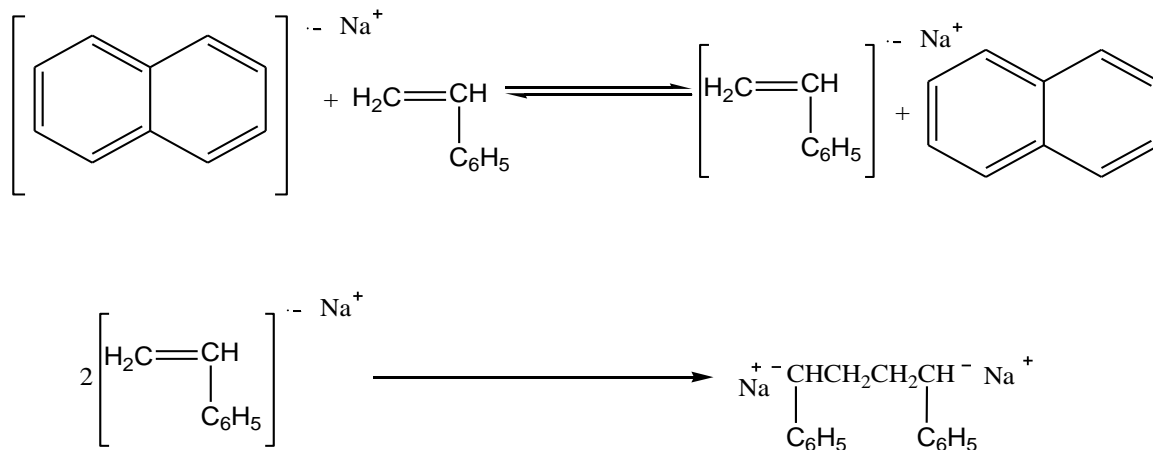
2.1.3 Initiators

Vinyl monomers can be polymerized using three types of initiators: alkali metals, radical anions, and organoalkali compounds such as the alkyllithiums.^{3,6,7} On the other hand, heterocyclic monomers can be polymerized using weaker bases such as hydroxides and alkoxides.^{3,6} The use of alkali metals as initiators for anionic polymerization is primarily of historical interest; currently, radical anions and alkyllithium compounds are most frequently used. Radical anions can be generated by reacting aromatic hydrocarbons (e.g., naphthalene) with alkali metals in polar aprotic solvents such as THF. Scheme 2.2 describes the formation of the radical anions.²



Scheme 2.2 The formation of radical anions from naphthalene and sodium metal

One electron is transferred from the metal to the lowest unoccupied orbital in the aromatic hydrocarbon molecule, leading to the formation of a delocalized radical anion. In a pre-initiation step, a monomer radical anion is formed via electron transfer when the aromatic radical anion reacts with the monomer. Rapid dimerization of the monomeric radical anion species thus formed takes place to yield a dianion initiator.² Scheme 2.3 gives an example of this:



Scheme 2.3 The formation of a dianion initiator in the polymerization of styrene

Among alkyllithium compounds, *n*-butyllithium and *sec*-butyllithium are the most frequently used initiators in anionic polymerization.⁶ These compounds are available commercially as solutions in hydrocarbon solvents such as hexane and cyclohexane. The main difference among the alkyllithium compounds is their degree of aggregation in solution, which determines their relative reactivity as initiators: the less associated alkyllithiums are more reactive in comparison to the highly associated species. The influence of polar and aromatic solvents on the reactivity of these initiators is also significant, as they tend to promote the dissociation of aggregates, thereby leading to initiation rates 10^2 - 10^3 times faster than in aliphatic solvents.⁸

2.1.4 Solvents and Reaction Temperature

The high reactivity (basicity and nucleophilicity) of the initiators and the propagating species requires aprotic solvents. Polar aprotic solvents such as THF, dimethoxyethane (DME), hexamethylphosphoramide (HMPA), and N,N-dimethylformamide (DMF) may be used in some cases but many are toxic, and may lead to degradation reactions with carbanions of high nucleophilicity.⁷ Furthermore, solvents such as dimethylsulfoxide (DMSO) can be deprotonated by highly basic active sites.⁷ Consequently, nonpolar solvents such as benzene, *n*-hexane, and cyclohexane are most commonly used, as they are essentially unreactive with respect to the propagating centers. Toluene, as a benzene derivative, may cause chain transfer reactions with nucleophilic sites such as living polystyrene at high temperatures. The rate of propagation is faster in polar solvents than in nonpolar solvents. For instance, styrene reaches full conversion in THF within a few minutes below -70 °C; in contrast, hours are required to obtain similar yields

in nonpolar media, even above 30 °C. To minimize side reactions as well as the effects of propagating center termination, the reaction temperature should be lowered in that case.

2.2 Branched Polymers

A branched polymer can be defined as a molecule with a non-linear chain architecture.⁹ Long-chain branching is characterized by the presence of at least three chain ends in the molecule, or by the presence of one or more branching points linking at least three chain segments.

2.2.1 Classification of Branched Polymers

Branched polymers can be classified into three main types: (1) star-branched polymers, with a central branching point linking a number of branches;¹⁰ (2) comb-branched polymers, with a main linear backbone and branches randomly distributed along it; and (3) dendritic polymers, with a multi-level (dendritic) branched architecture.⁷ The dendritic branched polymers can be further subdivided into three families based on the specific characteristics of the molecules, namely dendrimers,¹¹⁻¹⁴ hyperbranched polymers,^{9,15} and dendrigraft polymers,¹⁶ which are also called comb-burst or arborescent polymers.¹⁷ These branched polymer structures are represented schematically in Figure 2.1.

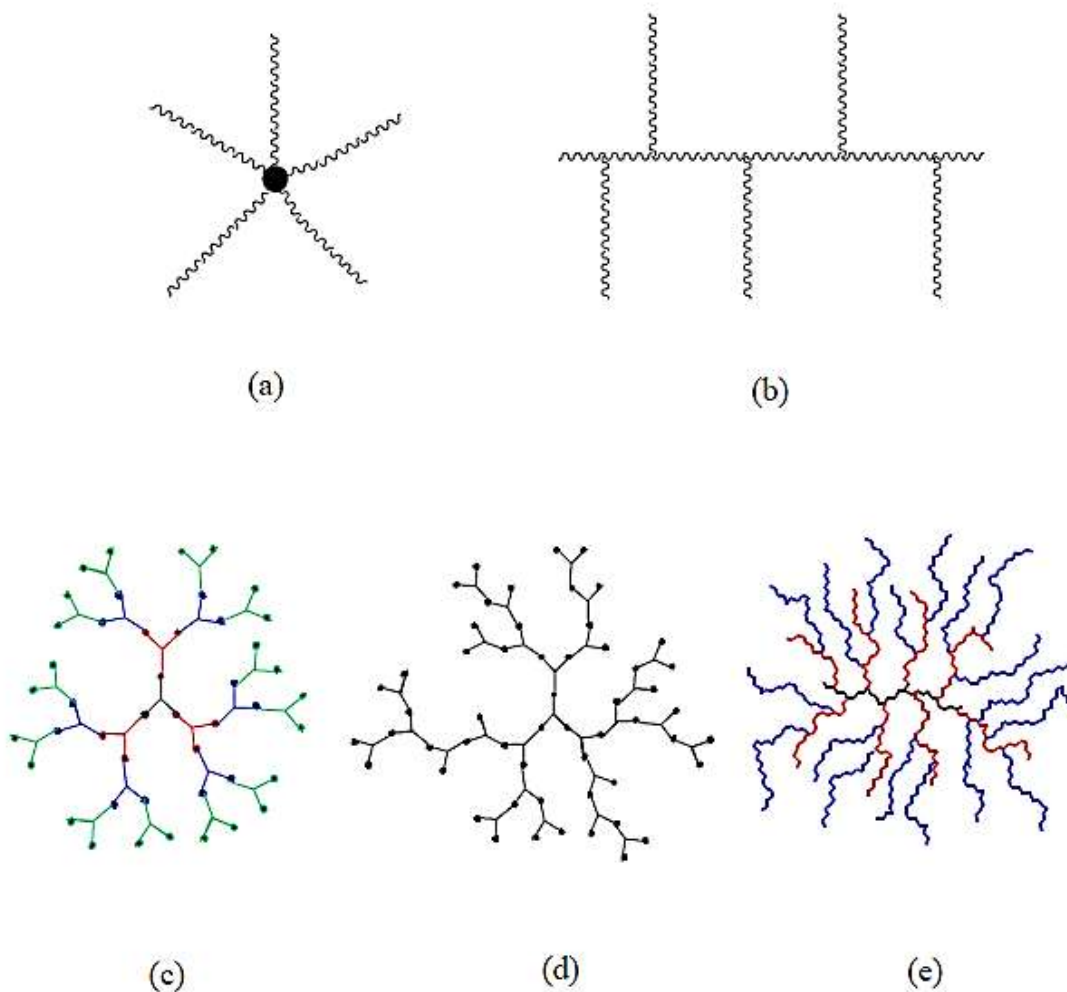


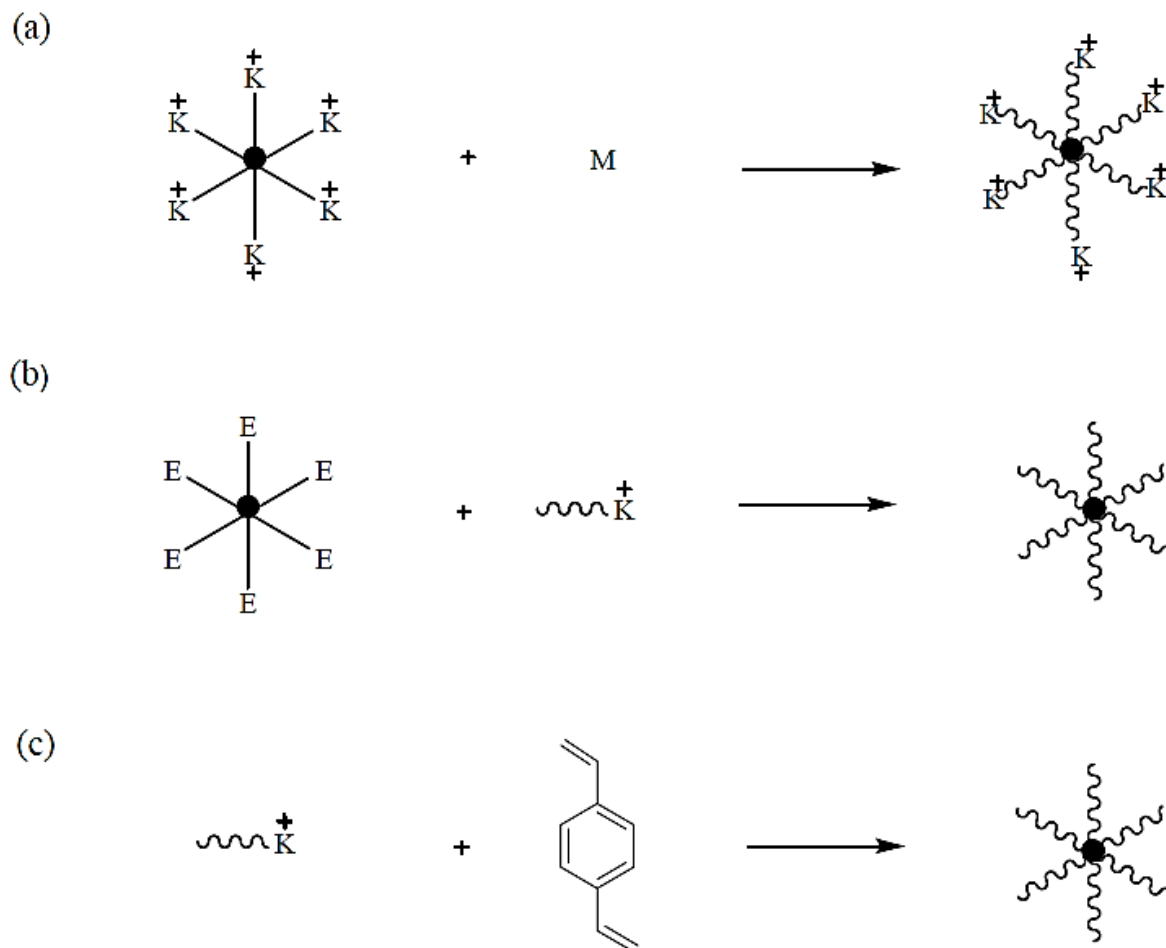
Figure 2.1 Schematic representation of branched polymers: (a) star-branched polymer, (b) comb-branched polymer, (c) dendrimer, (d) hyperbranched polymer, and (e) dendrigraft polymer⁹

2.2.2 Star-branched Polymers

Star polymers are the simplest branched polymer structures due to their single branching point linking a number of branches. The star molecules should be well-defined due to their uniform

number of chains of equal length among the molecules, and are therefore essentially monodispersed in size. However, in practice, star polymers are somewhat polydispersed due to variations in the size of the side chains or the number of chains linked together. Palm tree¹⁸ or umbrella polymers,⁹ with a single chain having a molecular weight different from the other arms, can also be synthesized and are described as asymmetric star polymers.¹⁹ Star-branched polymers are useful as model systems, to study the influence of branching on the properties of polymers in solution and in the molten state for comparison with their linear counterparts. They can also be used as viscosity modifiers in paints and coatings, and for their enhanced processability and desirable mechanical properties.

Star-branched homo- and copolymers are mostly synthesized via living anionic polymerization. The absence of termination and chain transfer in these reactions allows the preparation of chain segments with predictable molecular weights and narrow molecular weight distributions (MWD). Tailor-made star-branched polymers can be synthesized by three main methods, as shown in Scheme 2.4.



Scheme 2.4 Synthesis of star-branched polymers (a) using a multifunctional initiator, (b) by coupling with a multifunctional linking agent, and (c) by sequential copolymerization with a divinyl compound⁹

The first procedure, known as the “core-first” methodology (Scheme 2.4a), relies on a multifunctional initiator and the simultaneous growth of all the side chains from the central core. It is not widely used for the synthesis of star polymers, due to the difficulties in preparing pure multifunctional organometallic compounds and the poor solubility of these compounds in most

anionic polymerization solvents. Furthermore, it is impossible to characterize the size of the branches formed by this method. Eschwey and Burchard were the first to synthesize star polymers with very high molecular weights using polyfunctional organometallic nanoparticle initiators derived from divinylbenzene.⁹ Later, this method was extended to the synthesis of star-branched polymers with functional groups at the chain ends.^{20,21} More recently, this method was applied to the synthesis of star polymers using novel hydrocarbon-soluble organolithium initiators such as 1,3,5-tris(1-phenylethenyl)benzene.²² Series of 4-, 8-, and 16-arm star poly(ethylene oxide)s were also synthesized from multifunctional initiators derived from hydroxyl-terminated carbosilane dendrimers.²³

The second procedure, known as an “arms-first” methodology (Scheme 2.4b), is the most efficient way to synthesize well-defined star-branched polymers. This procedure begins with the synthesis of a living precursor by anionic polymerization, followed by the reaction of the living chains with a multifunctional electrophile acting as a linking agent (core or substrate).⁹ Multifunctional chlorosilanes (Si-Cl) have been used extensively as linking agents for the synthesis of regular stars.²⁴⁻²⁷ Series of 4- to 18-arm polystyrenes²⁸⁻³⁰ and polyisoprenes³¹⁻³³ were thus synthesized. Polybutadiene stars containing up to 128 arms,³⁴ and “miktoarm” stars, incorporating four different types of branches,³⁵ are other examples of star-branched polymers synthesized via an “arms first” coupling strategy.

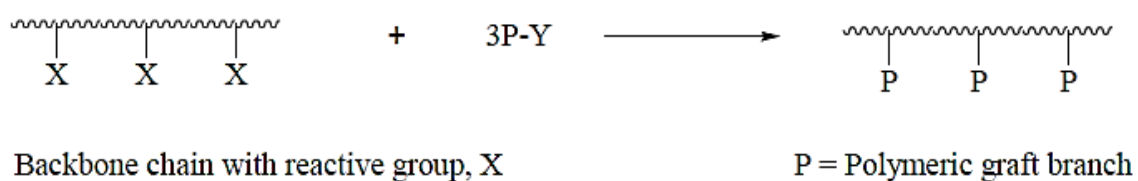
The third procedure (Scheme 2.4c) is also referred to as an “arms-first” methodology. However in the coupling procedure, the linking agent is a divinyl monomer such as divinylbenzene or ethylene glycol dimethacrylate. The addition of these monomers to the living anionic polymer precursor leads to the formation of small cross-linked nodules which link the

arms.³⁶ For instance, star polymers with polystyrene branches³⁷ were synthesized using the linking reaction of polystyryllithium with divinylbenzene (DVB). This procedure can be viewed as a block copolymerization of DVB, followed by coupling of the anionic propagating centers with the pendent vinyl groups within the DVB blocks.

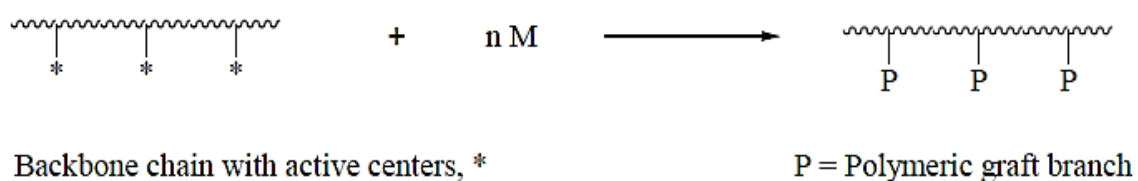
2.2.3 Comb-branched Polymers

Comb-branched polymers are graft polymers incorporating a linear chain as backbone, to which well-defined branches of identical or differing compositions are linked. These side chains are randomly distributed along the substrate.^{17,38} The synthesis of comb-branched polymers with side chains of uniform size can be achieved using anionic grafting. Two types of schemes for the synthesis of comb-branched polymers, known as the *grafting onto* and the *grafting from* methods,^{9,17,38} are shown in Scheme 2.5.

(1) "Grafting onto" approach



(2) "Grafting from" approach



Scheme 2.5 *Grafting onto* and *grafting from* schemes for the synthesis of comb-branched polymers⁹

2.2.4 Dendritic Polymers

Dendritic polymers are highly branched macromolecules characterized by a tree-like architecture, which integrates multiple branching levels.³⁸ These dendritic polymers can be synthesized with good control over their size, shape, branching functionality, and chemical functionality of the chain ends.³⁹ Most dendritic macromolecules have a compact globular shape, in contrast to linear chain polymers which adopt a flexible random coil conformation. Another

important difference between linear and dendritic polymers is that while linear chains can lead to entanglement formation, dendritic polymers are relatively free of entanglements.⁴⁰ Dendrimers (Figure 2.1c) can be synthesized according to either divergent (core first) or convergent (arms first) methods, using cycles of protection, condensation, and deprotection of AB_n-type monomers (n = 2 or 3). The structure of these macromolecules is strictly controlled, leading to very narrow MWD ($M_w/M_n < 1.01$) and precisely predictable molecular weights, in spite of a number of limitations. Due to the use of small molecules as building blocks, the increase in molecular weight per generation is relatively low. This means that many reaction cycles are required to reach high ($> 10^5$ g/mol) molecular weights. The growth of dendrimers is very sensitive to side reactions, causing structural defects which affect the topology of the molecules. In order to overcome these problems large excesses of reagents are required in their synthesis, thereby making dendrimers difficult to purify prior to subsequent reaction steps.

Dendritic polymers, such as the ones illustrated in Figure 2.2, have unusual physical properties due to their highly branched structure and three-dimensional architecture.⁴¹ There are two major distinctions between linear and dendritic polymers in terms of physical characteristics. First, most dendritic macromolecules have a compact globular shape, while linear polymers form a randomly coiled structure. Second, while linear chains of sufficient length lead to extensive entanglement formation, dendrimers are free of entanglements. This is because dendritic polymers are formed mainly by stepwise addition of small monomer units onto the central core.

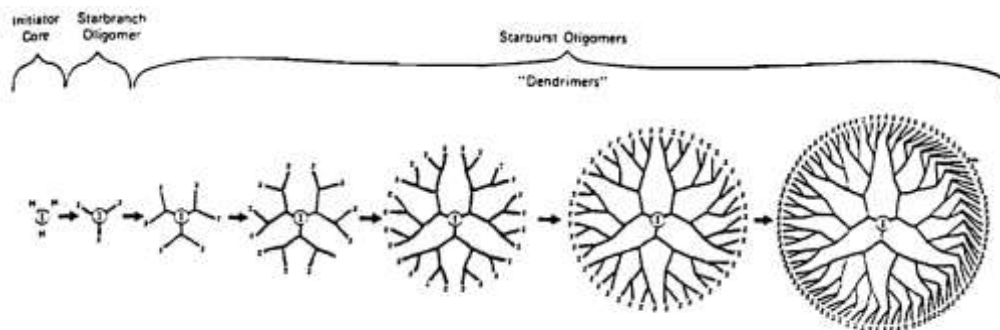


Figure 2.2 Schematic representation of dendrimer synthesis⁴¹

Typically, every generation of dendrimer produces the same type of terminal functional groups on the molecules, leading to the next generation. The number of terminal groups in one generation is usually twice as large as in the previous generation. Dendritic macromolecules have a well-defined structure, although a number of limitations are faced in their synthesis.

Because the monomers used as building blocks have a low molecular weight, their rate of increase in molecular weight per generation is relatively low. Thus, many steps are needed to produce high molecular weight materials. Another problem is that the molecular growth is sensitive to impurities, resulting in side reactions which lead to structural imperfections. In order to eliminate these side reactions, large excesses of reagents are necessary in the synthesis; unfortunately, it is difficult to eliminate excess reagents prior to subsequent reaction steps.⁴¹

The second family of dendritic polymers is hyperbranched polymers (Figure 2.1d), which are synthesized by one-pot self-condensation reactions of AB_n monomers.^{9,15} The third family of dendritic polymers is the dendrigraft polymers (Figure 2.1e), also called comb-burst® polymers by Tomalia et al.¹⁶ and arborescent polymers by Gauthier and Möller.⁴² The synthesis of these

polymers occurs in a generation-based scheme similar to dendrimers, but with cycles of ionic polymerization and grafting reactions. The use of polymeric chains rather than small molecules as building blocks can produce very rapid molecular weight growth in which high molecular weights are obtained in a few steps. The increase in molecular weight and branching functionality is typically 10- to 15-fold per generation for arborescent polymers, as compared to 2- to 3-fold for dendrimers. In contrast to dendrimers, the branches are distributed randomly on the grafting substrate rather than strictly at the chain ends. The random distribution of coupling sites over the substrate makes arborescent polymer growth less sensitive to side reactions. The architecture of dendrigraft polymers is not defined as strictly as in dendrimers, but the MWD achieved is usually fairly narrow ($M_w/M_n < 1.1$).

Dendritic macromolecules were first synthesized by Vögtle et al. in 1978,⁴³ but the study of cascade polymers has greatly expanded since then due to the special properties of these materials. Many applications are being developed for dendritic macromolecules, including microencapsulation and drug delivery, which are the primary concerns of the future work for this project.

2.2.5 Amphiphilic Dendritic Polymers

Amphiphilic copolymers, and in particular those with an A-B or A-B-A block architecture, are able to self-assemble into supramolecular structures such as micelles in solvents selective for one of the two components.^{44,45} Thus in polar solvents, micelles can be obtained with the nonpolar component forming the core while the polar component remains on the outside. This

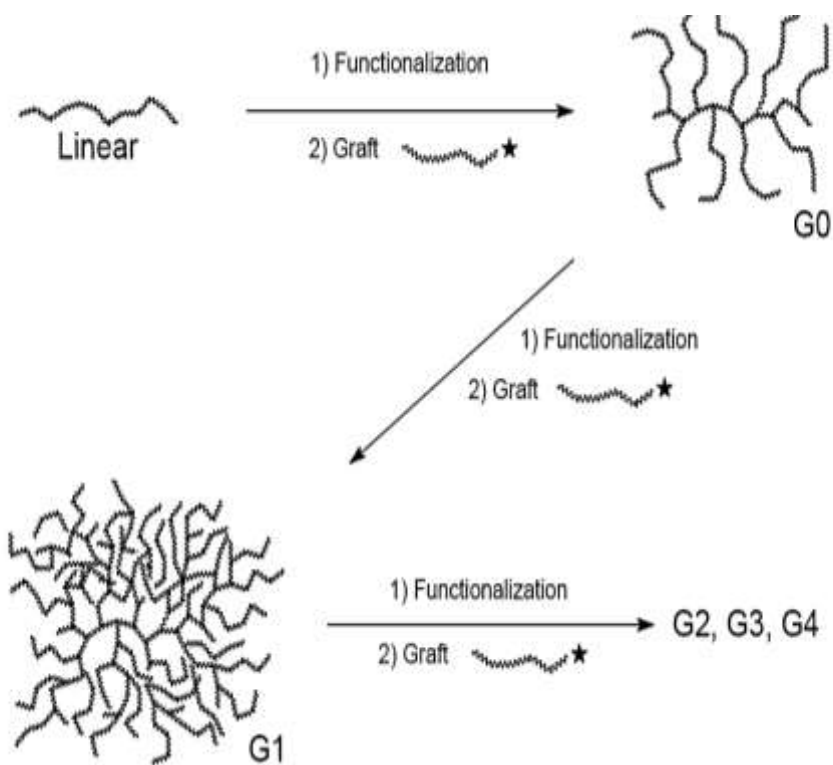
ability to form micelle-like aggregates can be useful in many applications such as in the preparation of dispersions and in controlled drug release systems. These micelles have a spherical shape and a core-shell morphology, and contain a core rich in one block and a shell rich in the other block. Polymeric micelles are generally more stable than surfactant molecule aggregates, but are still prone to rearrangements when solvency conditions are changed or when subjected to flow. Star-branched block copolymers can also be used for that purpose and are more stable than block copolymer micelles obtained by self-assembly. They can be prepared by coupling living block copolymers with difunctional vinyl monomers in anionic polymerization,^{46,47} or through successive monomer additions when using plurifunctional anionic initiators.⁴⁸ However, it is generally difficult to achieve well-defined structures and low polydispersities in these systems.

Some dendritic polymers such as polyamidoamine dendrimers (PAMAM) also display micellar properties, but these arise from the characteristics of the individual molecules rather than from multimolecular self-assembly. Dendritic micelles³⁸ are mostly obtained by the chemical modification of dendrimers, hyperbranched, or dendrigraft substrates. Because the structure of a dendrimer core is uniform and functional groups are present only at the periphery of the molecules, amphiphilic dendrimers should have a relatively sharp core-shell interface. On the other hand, the interface of amphiphilic hyperbranched and dendrigraft polymers should be more diffused because of fluctuations in the position of the branching points in these systems.³⁸ The ability of amphiphilic copolymers to assemble in solution and at interfaces is strongly dependent on the molecular architecture and the concentration of the polymers in solution. In general, branched amphiphilic polymers have a lower tendency to self-assemble into micelles

than linear polymers. This property is particularly interesting from the viewpoint of applications, since non-associated amphiphilic branched molecules still display solubilization properties typical of micelles. The covalent structure of these unimolecular micelles makes them much less sensitive to solvent quality changes since they cannot dissociate, in contrast to multimolecular micelles. A method commonly used to synthesize dendritic micelles from all dendritic polymer families is through the addition of hydrophilic *polymer segments* on a hydrophobic dendritic substrate.

2.2.6 Dendrigrraft or Arborescent Polymers

Dendrigrraft polymers are highly branched molecules synthesized from polymeric building blocks.^{16,42} These are assembled according to a generation-based scheme analogous to dendrimers, which relies on cycles of substrate functionalization and grafting. In dendrigrraft polymers the coupling sites are distributed randomly on the substrate, in contrast to dendrimers where the coupling sites are strictly located at the chain ends. The reaction of a functionalized linear substrate with linear side chains thus yields a generation zero (G0 or comb-branched) polymer. Subsequent functionalization and grafting cycles result in arborescent polymers of generations G1, G2, and so on. The step-wise synthesis of arborescent polymer is illustrated in Scheme 2.6.



Scheme 2.6 Schematic representation of the synthesis of an arborescent polymer⁹

The tree-like architecture with multiple branching levels thus obtained, characteristic of arborescent polymers, results from the successive grafting cycles. These polymers can be synthesized by both *grafting onto* and *grafting from* methods, although the *grafting onto* method (illustrated in Scheme 2.6) has been most widely applied.

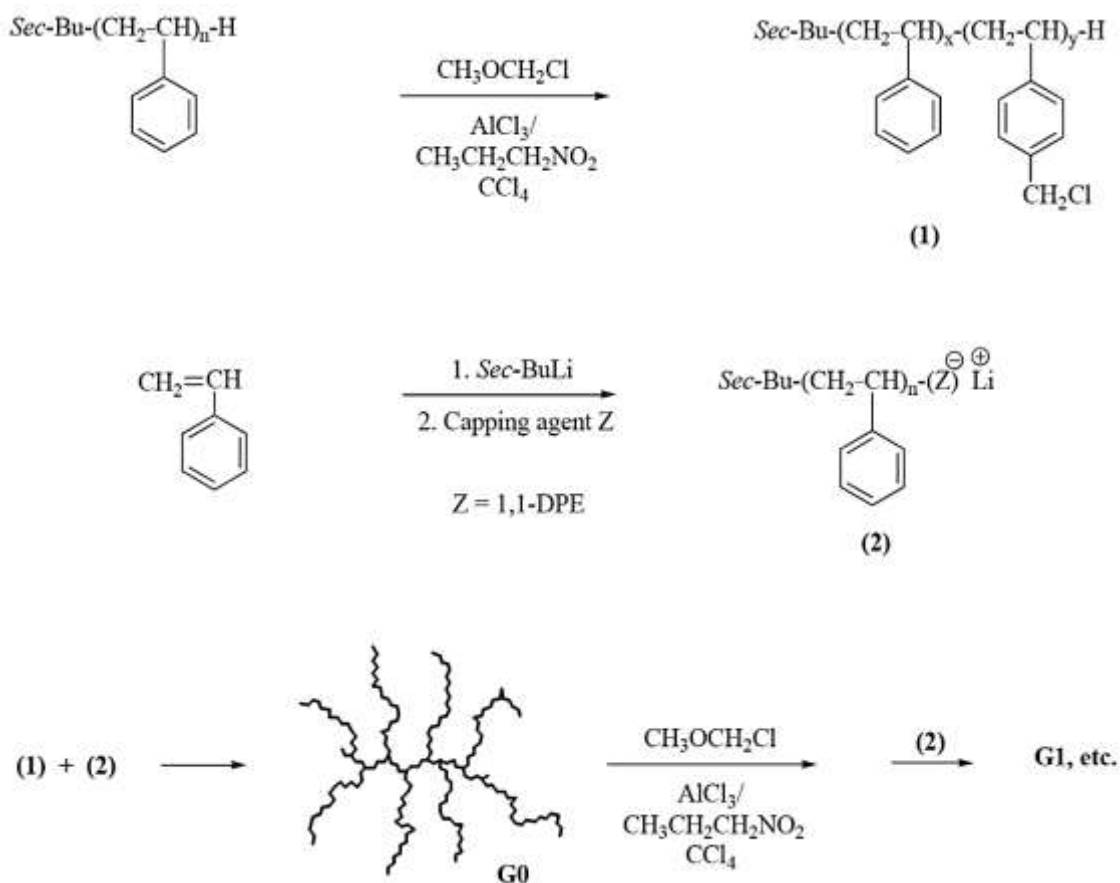
2.2.7 Synthetic Strategies for Dendrigraft or Arborescent Polymers

Dendrigraft polymers have been synthesized using both divergent (core first) approaches, which includes *grafting onto* and *grafting from* methods; and convergent (arms first) approaches, which are essentially *grafting through* methods. The synthetic work presented in this thesis is based on the core first *grafting onto* and *grafting from* methods.

2.2.7.1 Synthesis by Anionic Grafting Onto Method

The anionic *grafting onto* method was first used by Gauthier and Möller⁴² to synthesize arborescent polystyrenes. This approach relies on cycles of either chloromethylation⁴² or acetylation,⁴⁹ and anionic grafting reactions. The random introduction of coupling sites onto a linear polystyrene substrate is followed by their reaction with living polystyryl macroanions to obtain the G0 arborescent polymer. A fundamental requirement in the arborescent polymer synthesis is the ability to reintroduce coupling sites on the newly grafted side chains. If this can be achieved, the functionalization and grafting cycles can be repeated to obtain arborescent polymers of generations G1 and above, with molecular weights and branching functionalities increasing geometrically for successive generations. In order to obtain well-defined graft polymers by this approach, several requirements must be satisfied. The macroanions need to have good living character, a narrow molecular weight distribution (MWD), and be sufficiently reactive. The side chains grafted in each generation must allow further introduction of coupling sites without intermolecular cross-linking. Finally, the coupling reaction must proceed without side reactions and in high yield. Styrene is one monomer which satisfies these requirements, in

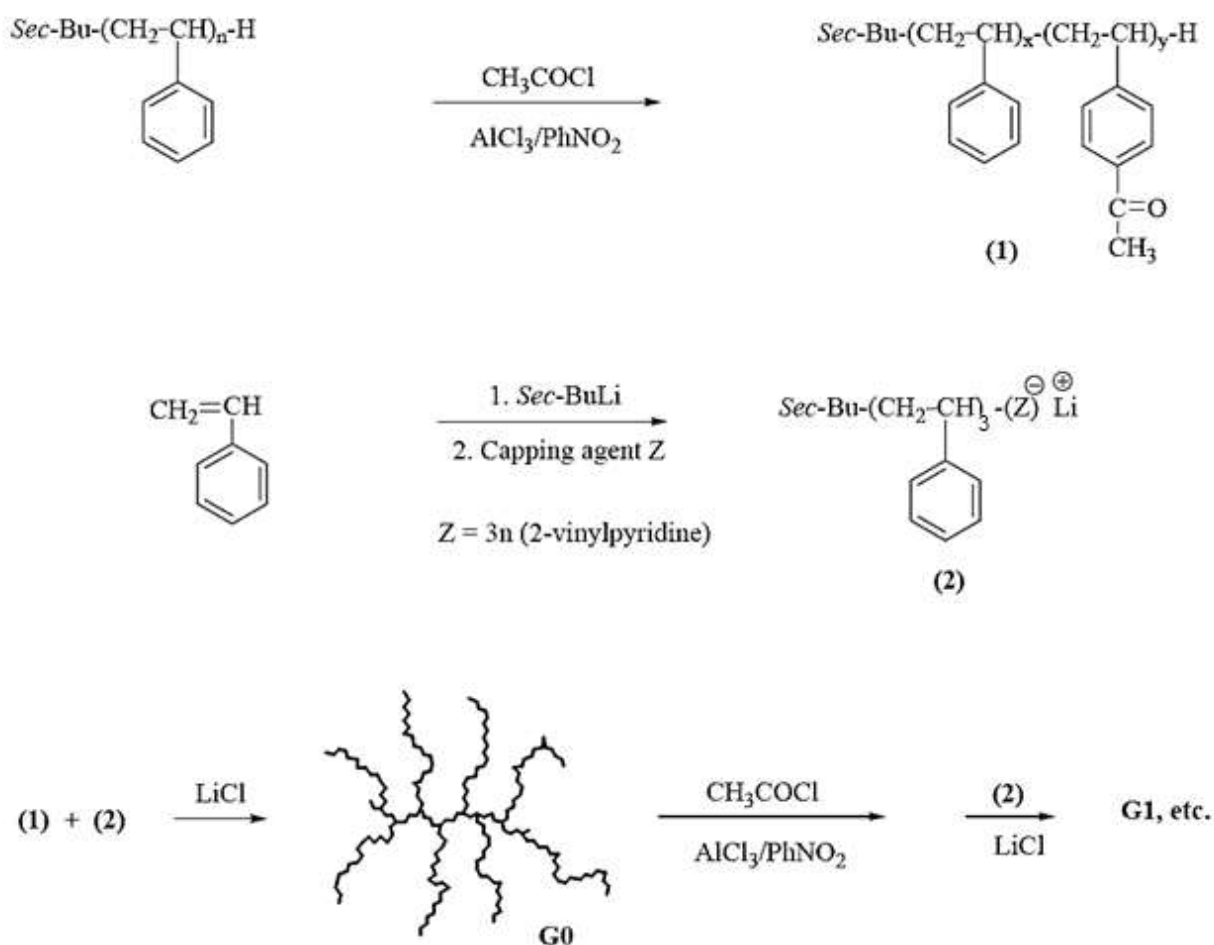
that the anionic polymerization of styrene produces reactive macroanions with exceptional living characteristics. Additionally, a wide range of functional groups can be introduced on the pendent phenyl rings via electrophilic substitution. Chloromethylation and acetylation reactions have both been applied to the synthesis of arborescent polystyrenes.^{42,49} The steps involved in the synthesis of arborescent polystyrene using chloromethyl coupling sites are illustrated in Scheme 2.7. In this approach, the chloromethylated linear substrate is coupled with living polystyryllithium after capping the chains with a 1,1-diphenylethylene (DPE) unit. The use of DPE capping for the polystyryl anions aims to avoid side reactions with the chloromethylated substrate: Due to a competing metal-halogen exchange reaction, reacting non-capped polystyryllithium with a linear chloromethylated polystyrene substrate can decrease the yield to as low as 50 percent. In contrast, the yield reaches 96 percent in THF at -30 °C after capping with DPE.



Scheme 2.7 Arborescent polystyrene synthesis by grafting onto chloromethylated polystyrene substrates⁹

Styrene was also used as one of the monomers in the current project, but random acetylation of the polystyrene substrates with acetyl chloride in nitrobenzene was followed by coupling with polystyryllithium after capping with 3-5 equivalents of 2-vinylpyridine units to minimize the side reactions of the macroanions and increase the grafting yield, as shown in Scheme 2.8. In this alternate method developed previously, it was determined that the grafting yield is maximized in THF at 0 °C, by capping the living chains with 3 equivalents of 2-vinylpyridine, and by adding 5

equivalents of LiCl per chain end in the reaction. Repetition of the acetylation and grafting reaction cycles leads to arborescent polystyrenes of generations G1 and above, and the grafting yield attained depends on the substrate generation and the molecular weight of the side chains used in the reaction.



Scheme 2.8 Arborescent polystyrene synthesis by grafting onto acetylated polystyrene substrates⁹

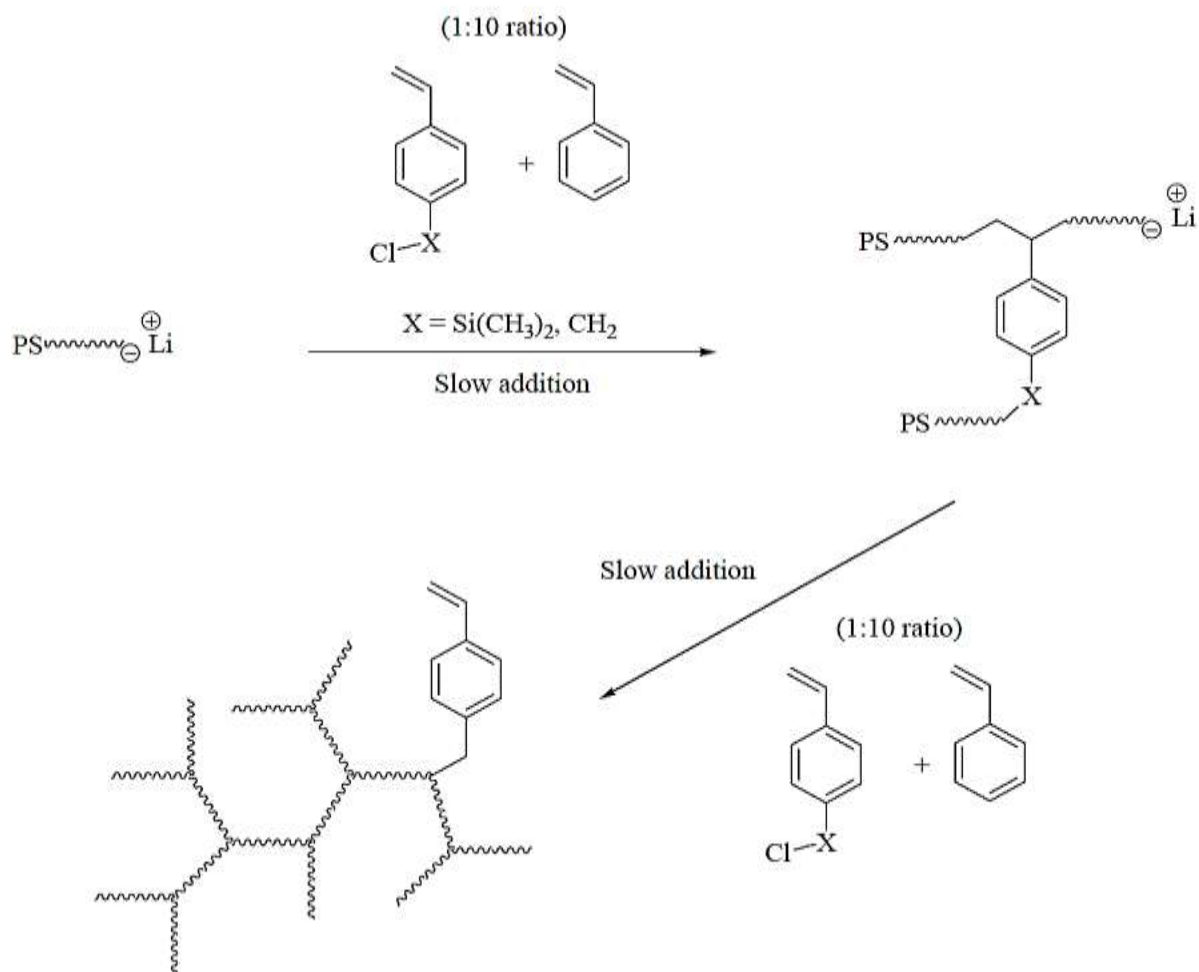
2.2.7.2 Synthesis by Anionic Grafting From Method

This procedure involves the growth of side chains from the substrate. Unfortunately it is difficult to characterize the structure of the graft polymers obtained by these methods, and the MWD of the products is generally broader. In spite of these limitations, *grafting from* schemes have allowed the synthesis of novel macromolecular architectures that would be inaccessible by other methods. As an example of this methodology, the synthesis of amphiphilic arborescent copolymers will be explained in more detail below.

2.2.7.3 Synthesis by Anionic Grafting Through Method

A one-pot self-branching convergent technique for the synthesis of branched polymer structures was first described by Knauss et al.^{50,51} This method relies on the formation of macromonomers *in situ* from living macroanions, and the slow addition of a “bifunctional” monomer, carrying a polymerizable vinyl group and a second chemical functionality able to couple with the living chains. The macromonomers formed by slow addition of the coupling agent react further with living chains, yielding branched polymers with a relatively narrow MWD. 4-(Chlorodimethylsilyl) styrene⁵⁰ (CDMSS) and vinylbenzyl chloride⁵¹ (VBC) were two of the bifunctional monomers proposed for the synthesis of dendritic polystyrenes, as demonstrated in Scheme 2.9. Linear polystyrene segments were synthesized, and a bifunctional monomer (CDMSS or VBC) was added to the living polymer in the presence of THF. The chlorosilyl and chloromethyl functionalities react at a faster rate with polystyryllithium than the vinyl group under these conditions, thereby yielding macromonomers with a terminal vinyl

group. These macromonomers then dimerize by reacting through their vinyl groups with the leftover living chains, if a less than stoichiometric amount of coupling agent is added. This produces branched polystyrene molecules with one single propagating centre located at the centre (focal point) of the molecule. To favor dendritic growth and avoid premature chain termination, the addition rate of the coupling agent must be slow enough to allow the reaction of both of its reactive moieties. Since the propagating centre is always located at the focal point, steric hindrance increases rapidly with the branching functionality and ultimately limits molecular growth. Thus, it is difficult to synthesize branched polymers with both a high molecular weight and a high branching density by this method. In order to alleviate this problem, a mixture of the coupling agent and styrene was added to introduce polystyrene spacer segments between the branching points, as shown in Scheme 2.9. With a molecular weight of 1000 g/mol for the primary polystyrene chains and a styrene : coupling agent (VBC) molar ratio of 5, for example, the molecular weight of the dendrigraft polymer was limited to $M_n = 24,000$ g/mol, while it reached 41,000 g/mol for a styrene : coupling agent (VBC) ratio of 15. The downside of this approach is that the branching density decreases as the styrene : coupling agent ratio is increased.

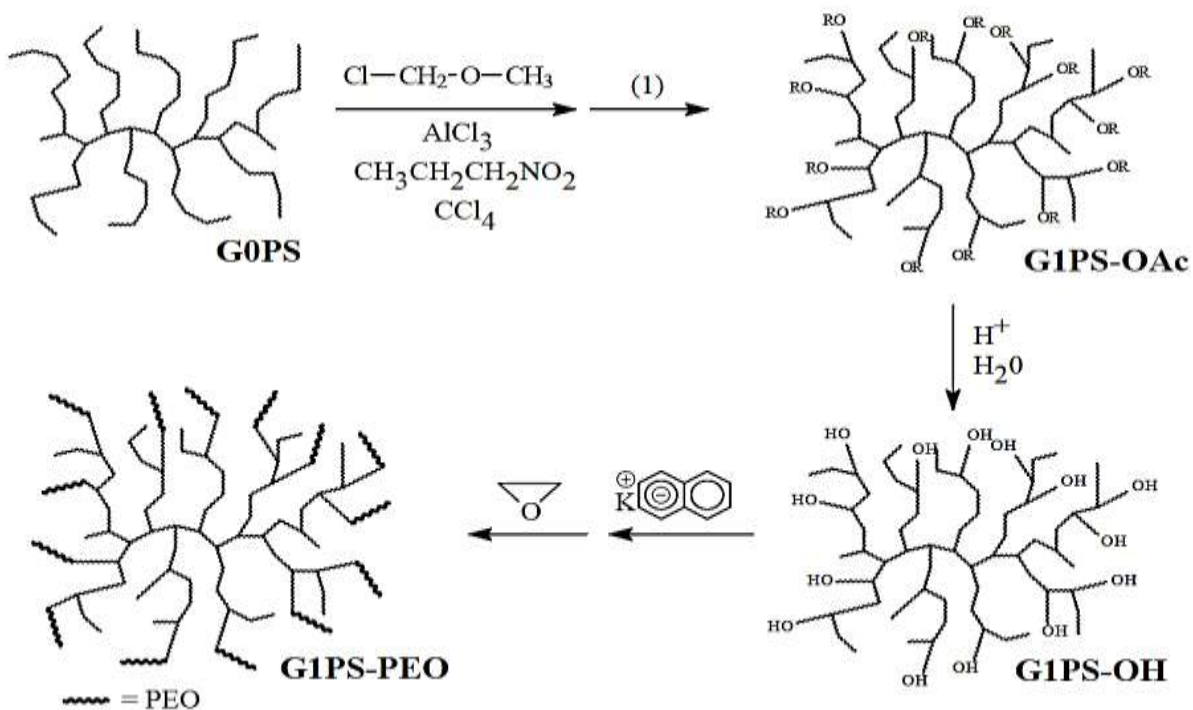
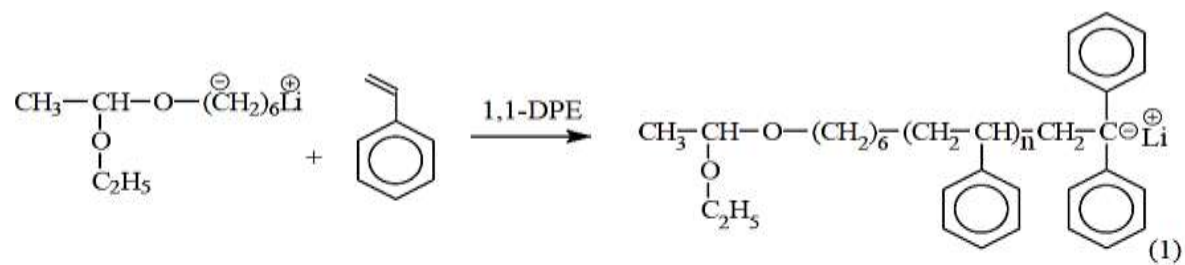


Scheme 2.9 Synthesis of dendritic polystyrene by convergent anionic polymerization⁹

2.2.8 Arborescent Core-shell Copolymers

Gauthier et al.³⁹ synthesized core-shell copolymers by a variation of the "graft-upon-graft" technique, using a combination of *grafting onto* and *grafting from* techniques. The arborescent polystyrene substrates serving as hydrophobic cores were synthesized by the *grafting onto* method described above, and hydroxyl chain ends were introduced on the outside of the

molecules in the final grafting reaction through a bifunctional initiator containing a protected hydroxyl group. After deprotection the end groups were titrated with potassium naphthalide to generate potassium alcoholate functionalities, and ethylene oxide was added to grow hydrophilic poly(ethylene oxide) segments from the chain ends as shown in Scheme 2.10.⁴² Figure 2.3 provides a schematic representation of the core-shell polymers with poly(ethylene oxide) segments and hydroxyl groups at the chain ends. Since these polymers have a hydrophilic poly(ethylene oxide) shell and a hydrophobic polystyrene core, they are expected to display the characteristics of micellar solutions. In contrast to polymeric micellar systems obtained by self-assembly, these micelles consist of individual branched molecules with a well-defined structure and a low polydispersity. Their highly branched structure should result in a more stable morphology as compared to block copolymer micelles, due to the limited ability of arborescent polymers to rearrange in solution. The current project focused on a synthetic procedure similar to the one outlined in Scheme 2.10, except for the use of a different bifunctional initiator and the addition of glycidol acetal to the alcoholate-functionalized substrate, to obtain polyglycidol chains (after deprotection of the acetal) as a hydrophilic ‘shell’ covalently bonded to the core polymer. The detailed characterization of these polymers and the investigation of their morphology is a goal for future work.



Scheme 2.10 Synthesis of amphiphilic arborescent polystyrene-*graft*-poly(ethylene oxide) by a *grafting from* scheme⁴¹

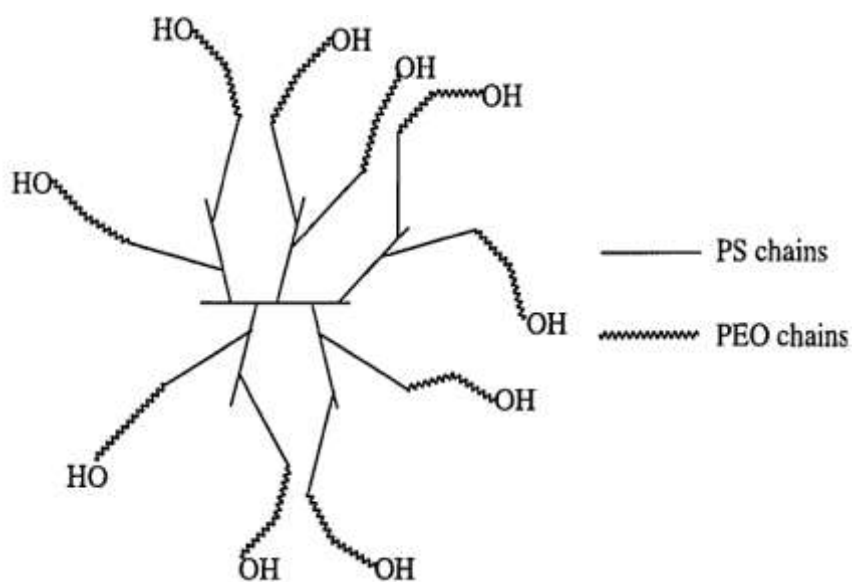
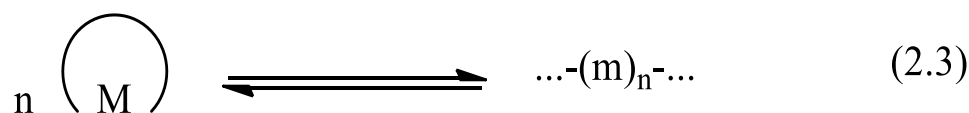


Figure 2.3 Schematic representation of a core-shell arborescent copolymer based on a generation 1 (G1) arborescent polystyrene substrate⁴¹

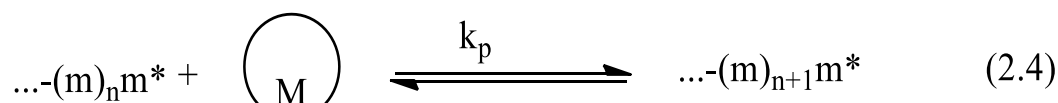
2.3 Ring-opening Polymerization

Besides step and chain polymerizations, cyclic monomers with various structures, including “compounds containing heteroatoms in the ring: oxygen [ethers, acetals, esters (lactones, lactides, and carbonates), and anhydrides], sulfur (polysulfur, sulfides and polysulfides), nitrogen [amines, amides (lactams), imides, *N*-carboxyanhydrides and 1,3-oxaza derivatives], phosphorus (phosphates, phosphonates, phosphites, phosphines and phosphazenes), or silicon (siloxanes, silyl ethers, carbosilanes and silanes)”⁵²⁻⁵⁵ have been polymerized via ring-opening polymerization.

The ability of a cyclic compound to polymerize according to a ring-opening mechanism is determined by two important factors.⁵⁶ First, the conversion of monomer molecules into macromolecules must be allowed both thermodynamically and kinetically. Practically, this means that the equilibrium must be shifted from the monomer to the macromolecule side, and the conversion of the monomer molecules to repeating units should be possible within an operable polymerization time, as shown in Eq 2.3. The net equation for the polymerization process can be written as:



where M is the monomer, and m represents the repeating units in the macromolecule derived from that monomer. An elementary reaction step for the macromolecular chain growth can be written as in Eq. 2.4:



where m^* is the active species and k_p and k_d are the propagation and depropagation rate constants, respectively.⁵²

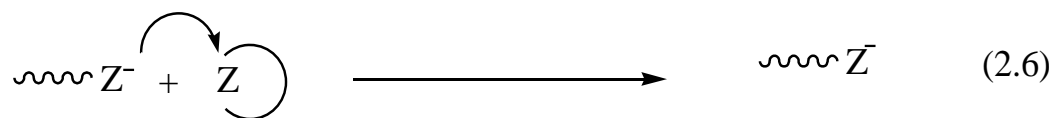
The initiators used for cyclic monomers are the same types as for the cationic and anionic polymerizations of monomers with carbon-carbon double bonds.⁵⁶ Most cationic ring-opening polymerizations of cyclic compounds containing oxygen or nitrogen as the heteroatoms lead to

the formation of oxonium or immonium ion propagating centers. A reaction that proceeds via nucleophilic attack by the monomer on the oxonium ion is presented in Eq. 2.5:



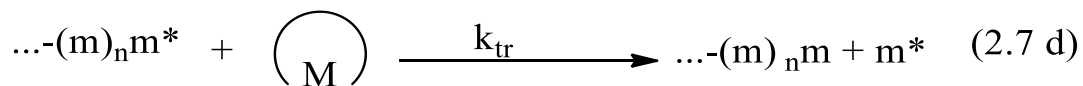
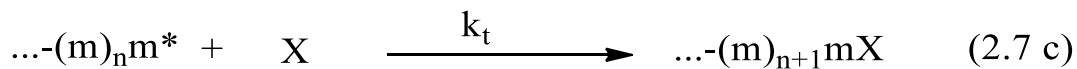
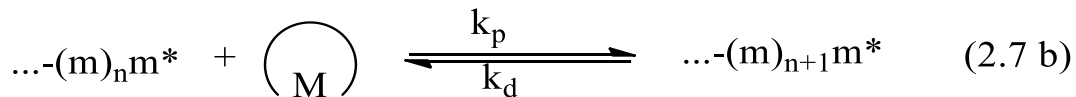
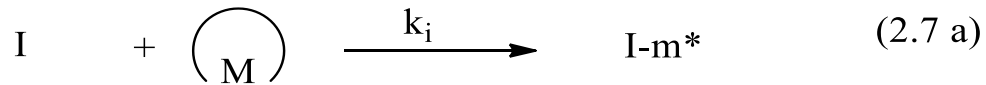
where Z represents a functional group such as O, NH, Si-O, CO-O, and CO-NH present in ethers, amines, siloxanes, esters and amides, respectively.

Anionic ring-opening polymerization involves the formation and propagation of anionic centers. Eq. 2.6 shows how the reaction proceeds via nucleophilic attack of the propagating anion on the monomer:



where Z⁻ represents an anionic propagating centre such as an alkoxide or carboxylate, derived from the cyclic monomer.⁵⁷

The reaction of a monomer with an initiator should generate active species as illustrated in Eq. 2.7a. These active species are capable of adding new molecules, as shown in Eq. 2.7b. Moreover, the addition of those molecules should occur faster than any side reactions including termination or chain transfer to the monomer, as shown in Eq. 2.7c and 2.7d, respectively.



In Equations 2.7 a-d, I is the initiator molecule, m^* is the active species, X is a terminating agent, and k_p , k_d , k_t , and k_{tr} are the rate constants for propagation, depropagation, termination, and chain transfer, respectively.⁵²

In the case of ring-opening polymerization, a large number of monomer units must be added in the propagation step to form a macromolecule. The Gibbs equation given in Eq. 2.8 must yield a negative free energy change for the propagation reaction if a high molecular weight is to be achieved,⁵⁶

$$\Delta G_p(xy) = \Delta H_p(xy) - T\Delta S_p(xy) \quad (2.8)$$

where x and y represent the monomer and polymer states, respectively, T is the absolute temperature, and $\Delta H_p(xy)$ and $\Delta S_p(xy)$ are the corresponding enthalpy and entropy of polymerization, respectively. The structure of the cyclic ring can affect the free energy of polymerization in numerous ways, including the size and ring strain associated with the monomer, the presence of substituents on the ring, geometrical or stereochemical chain isomerism, and the solid state morphology (e.g. crystallinity) that might be observed for the resulting macromolecule.⁵⁶

In general, the polymerization of cyclic monomers agrees with the rules established for the hypothetical polymerization of cycloalkanes: The main driving force for the polymerization of many cyclic compounds is their ring strain. This reflects the deviation from nondistorted bond angle values, bond stretching and/or compression, repulsion between eclipsed hydrogen atoms, and nonbonding interactions between substituents such as angular, conformational, and transannular strain. The enthalpy of polymerization can serve as a measure of ring strain for a system, whereas the specific monomer – polymer – solvent interactions can be neglected.

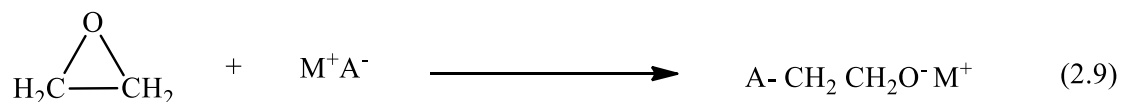
The polymerization of most monomers is usually accompanied by an entropy decrease due to the loss in translational degrees of freedom. Thus, polymerization is thermodynamically allowed only when the enthalpic contribution to ΔG_p prevails; that is when $\Delta H_p < 0$ and $\Delta S_p < 0$, the inequality $|\Delta H_p| > -T \Delta S_p$ is required. So the higher the ring strain, the lower the resulting monomer concentration obtained at equilibrium.

The angle and bond deformations in three- and four-membered cycles lead to high ring strain and negligible $[M]_{eq}$ values. However five- and six-membered cycles are the least strained and some of these compounds are unable to undergo polymerization. The ring strain for these

monomers is essentially derived from the gauche interactions between C–H bonds in neighboring –CH₂– groups, or between C–H bonds and the lone electron pairs of endocyclic oxygen or nitrogen atoms. Five-membered cycles such as THF show only moderate enthalpies of polymerization that lead to relatively high [M]_{eq} values. However, introducing a sulfur atom or a carbonyl group into the five-membered ring structure renders it incapable of high polymer formation under normal conditions.

2.3.1 Cyclic Ethers

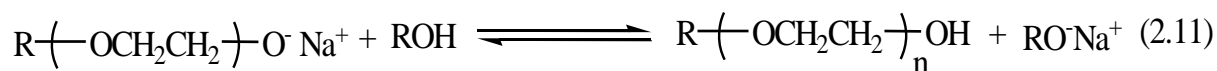
The 3-, 4-, 5-, and 6-membered cyclic ethers are oxirane, oxetane, oxolane, and oxane, respectively. The carbon-oxygen bond in ethers is in effect a strong bond.⁵⁷ The ring-opening polymerization of cyclic ethers is generally initiated by cationic species except for the epoxides, which can be polymerized by both cationic and anionic initiators due to the high degree of strain present in 3-membered rings. The anionic polymerization of epoxides such as ethylene and propylene oxides can be initiated by metal hydroxides, alkoxides, oxides and amides, as well as metal alkyls and aryls, including radical anion species such as sodium naphthalene. The initiation of ethylene oxide by M⁺A⁻ gives anionic species as shown in Eq. 2.9,



followed by the propagation step shown in Eq. 2.10:

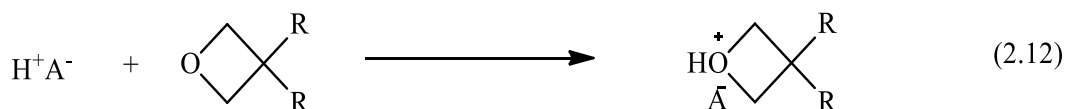


Epoxides can be polymerized even in the presence of protonic substances such as water or alcohols, added to produce a homogeneous system by solubilizing the initiators, including metal alkoxides and hydroxides. The increase in polymerization rate under these conditions does not only happen by solubilizing the initiator, but also by increasing the concentration of free ions and loose ion pairs. In the presence of an alcohol an exchange (chain transfer) reaction between a propagating chain and the alcohol is also possible, as illustrated in Eq. 2.11.

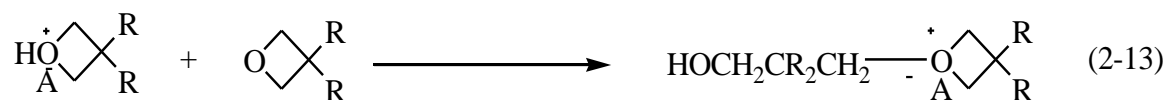


Similar exchange reactions take place between the newly formed polymeric alcohol and other polymer chains. These exchange reactions clearly lower the molecular weight of the polymer obtained. Not surprisingly, the literature only contains few reports on polymers with molecular weights above 10,000 g/mol for poly(ethylene oxide) obtained under these conditions.

The initiators used in the cationic polymerization of alkenes generate tertiary oxonium ion propagating species. Strong protonic acids such as trifluoroacetic and trifluoromethanesulfonic acids can also initiate polymerization via the initial formation of a secondary oxonium ion, as illustrated in Eq. 2.12.



This secondary oxonium ion then reacts with a second monomer molecule to form a tertiary oxonium ion, as shown in Eq. 2.13.



2.4 Glycidol Polymers

2.4.1 Linear Polyglycidol

2,3-Epoxy-1-propanol, also known as glycidol, is a hydroxyl-functional epoxide that holds a unique position among oxiranes: The hydroxyl group is located next to the oxirane ring, thus increasing its polarity, as shown in Figure 2.4.⁵⁸

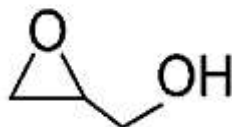


Figure 2.4 Structure of glycidol⁵⁸

This monomer, containing both epoxide and hydroxyl functions, is very well suited to studying the competition between the active chain end (ACE) and activated monomer (AM) mechanisms of propagation in epoxide polymerization.⁵⁹ The bifunctional structure of that monomer can influence its behavior during polymerization as well as the properties of the

materials obtained.⁶⁰ Polyglycidol, which is a water-soluble polymer, is of great interest for biomedical applications because of its biocompatibility and hydroxyl functionalities.⁶¹ Linear and hyperbranched polyglycidols have both been synthesized using anionic and cationic polymerization techniques.⁶¹

2.4.2 Anionic Polymerization of Glycidol

According to the literature aluminum chloride, mineral acids, as well as organometallic compounds of the group **II** or **III** metals and their alkoxides are useful catalysts for the polymerization of glycidol.⁶² However the lack of useful experimental data in the literature on polyglycidol formation led Sandler et al.⁶² to further investigate these polymers. Their work first examined in detail the polymerization of glycidol with a base. The polymerization has a similar mechanism to propylene oxide. Furthermore, polyglycidol (I) and poly(propylene oxide) (II) are related structurally, but differ in that I has an additional –OH substituent on the side chain, as shown in Figure 2.5.

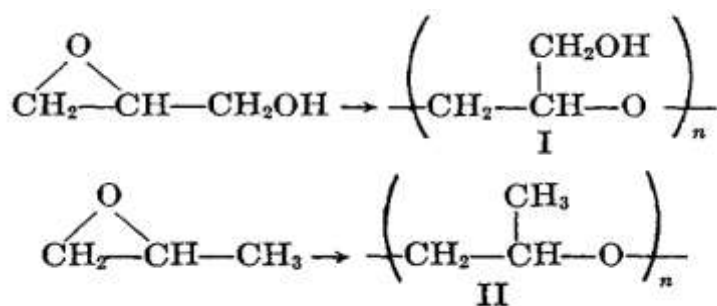
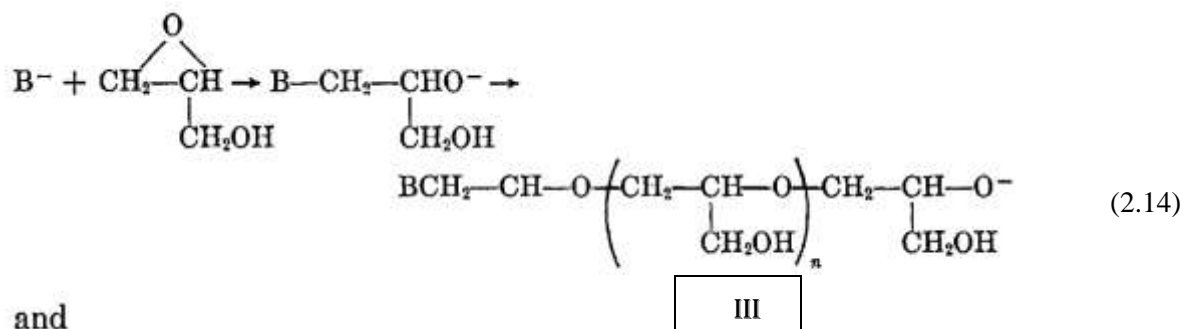


Figure 2.5 Polyglycidol (I) and poly(propylene oxide) (II)⁶²

Sandler et al. used different bases as catalysts at room temperature, which only produced linear polyglycidol of low molecular weight (III), as described in Figure 2.6.



and

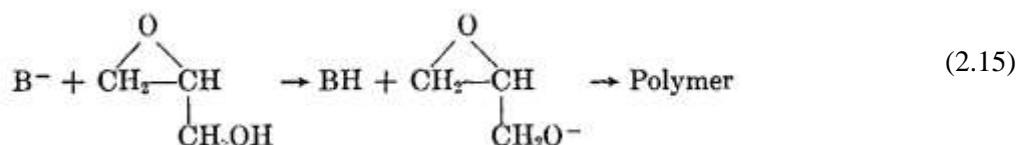
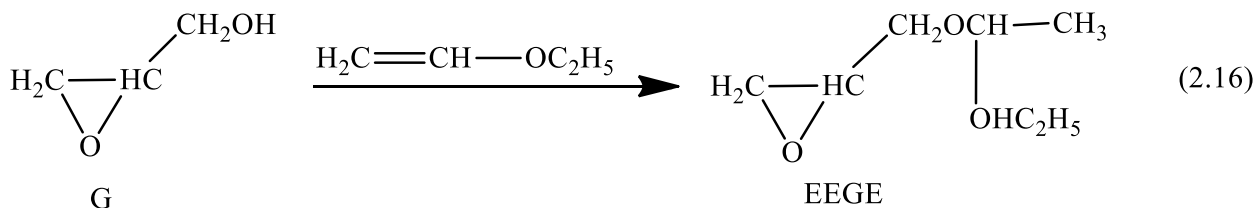


Figure 2.6 Linear polyglycidol with low molecular weight⁶²

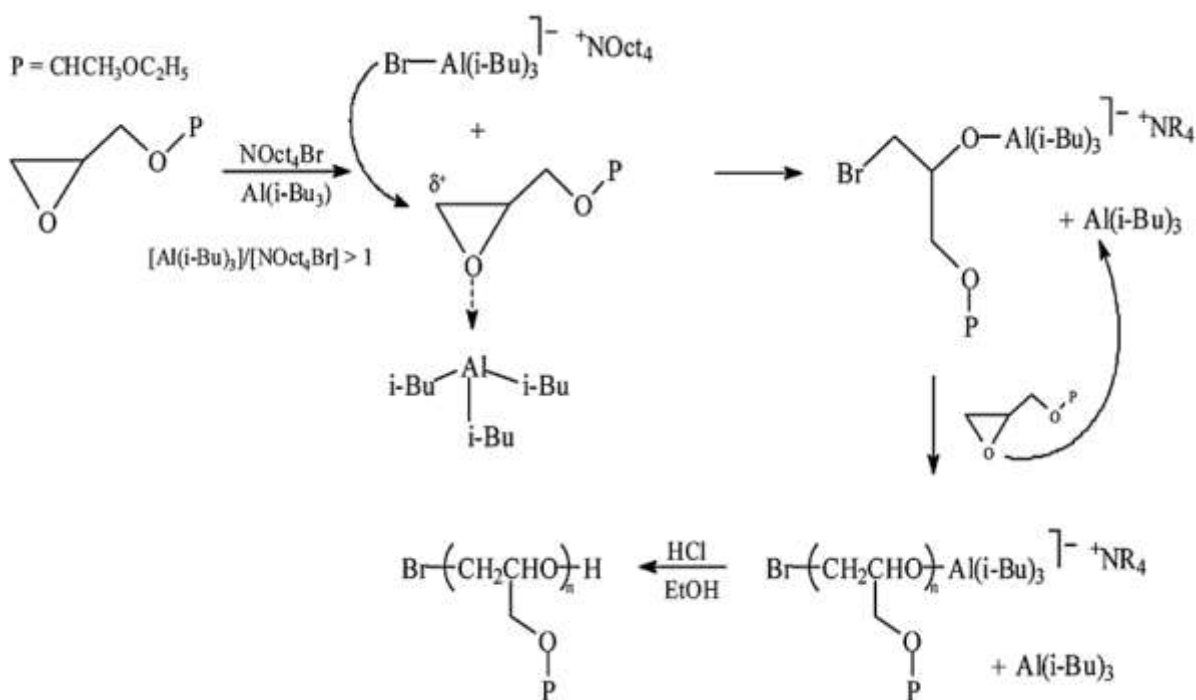
In this scheme, Eq. 2.14 likely accounts for the formation of the low molecular weight polymers, since the hydroxyl group can act as a ‘chain-terminating agent’ for the growth of the polymer with a terminal alkoxide group as shown in Eq. 2.15.⁶² These oligomers have a complex structure, with isomerized units and extensive branching due to chain transfer reactions. Vandenberg et al.⁵⁸ reported an indirect method to synthesize both isotactic and atactic polyglycidol via coordination or anionic polymerizations of glycidol protected with a trimethylsilyl group. Linear polymers with higher molecular weight were also obtained by that method.

This protection method is satisfactory with coordination initiators; however it can be cleaved by anionic initiators such as *tert*-BuOK. Furthermore, control of the molecular weight is not possible with coordination initiators.⁵⁸ Fitton et al.⁶³ also reported the reaction of glycidol with ethyl vinyl ether to yield 2,3-epoxypropyl-1-ethoxyethyl ether (EEGE), usually referred to as glycidol acetal, as illustrated in Eq. 2.16. This protecting group leads to a monomer that is easy to purify, stable under anionic polymerization conditions, and is easy to remove. Spassky et al.⁶⁴ used this monomer with anionic initiators such as cesium hydroxide (CsOH). Fairly high molecular weight polymers reaching up to 30,000 g/mol were thus obtained without cleavage of the protecting group.⁶⁴



The anionic initiator used (CsOH) produced molecular weights higher than expected from the reaction stoichiometry, indicating that only a fraction of the initiator contributed to the reaction. This was due to the heterogeneity of the reaction medium since CsOH was insoluble, which caused difficulty in controlling the process and a broad molecular weight distribution. Dworak et al.⁶⁰ rather initiated the polymerization of glycidol acetal with an alkali metal alcoholate (potassium *tert*-butoxide) in THF, which proceeded as homogenous reactions, and obtained polymers with well-controlled structures.⁶⁰

The synthesis of linear high molecular weight polyglycidol up to 85,000 g/mol by the so-called monomer-activated anionic polymerization mechanism has also been reported by Gervais et al.⁶¹ The mechanism of the monomer-activated anionic polymerization of EEGE is illustrated in Scheme 2.11.



Scheme 2.11 Mechanism for the monomer-activated anionic polymerization of EEGE initiated by the NOct₄Br/*i*-Bu₃Al system⁶¹

The use of tetraalkylammonium salts as initiators, in the presence of triisobutylaluminum (*i*-Bu₃Al) as activator/catalyst, has been useful to control the anionic polymerization of epoxides in hydrocarbon media. The EEGE monomer was thus polymerized in toluene at low temperature (0

°C) with [*i*-Bu₃Al]/[NOct₄Br] ratios ranging from 2 to 5. Quantitative conversion required the use of ratios higher than 3 however. Table 2.1 summarizes these reactions in terms of conversions and molecular weights obtained.

Table 2.1 Polymerization of *EEGE* with NOct₄Br/*i*-Bu₃Al in toluene at 0 °C⁶¹

run	[<i>i</i> -Bu ₃ Al]/[NOct ₄ Br]	[EEGE] (mol/L)	yield ^a (%)	time (h)	\overline{M}_n th ^b (g/mol)	\overline{M}_n exp (g/mol)		$\overline{M}_w/\overline{M}_n$ ^c
						SEC ^c	osmo ^d	
1	2	0.5	63	18	18 900	18 000		1.03
2	2	2	68	28	68 000	50 000		1.18
3	3	1.5	70	24	35 000	35 000		1.30
4	4	0.5	100	9	10 000	10 300	11 000	1.06
5	4	1	100	19	30 000	29 600	31 000	1.06
6	5	2	100	15	100 000	85 000		1.27

^aDetermined gravimetrically. ^b \overline{M}_n th = [EEGE]₀/[NOct₄Br] × *M*_{EEGE} × yield. ^cDetermined by size exclusion chromatography in tetrahydrofuran using a calibration with polystyrene standards. ^dDetermined by osmometry in toluene.

The molecular weight of PEEGE increased linearly with monomer conversion and narrow molecular weight distributions were obtained. Expected kinetic behavior was observed, with conversion as well as ln([M]₀/[M]) versus time plots as shown on Figure 2.8 for [*i*-Bu₃Al]/[NOct₄Br] ratios of 2 and 4. For 2 equivalents of *i*-Bu₃Al, the monomer consumption leveled off at 60 percent conversion without reaching completion. This behavior can be explained by a living reaction mechanism, without side reactions such as termination or chain transfer, but in which the Lewis acid (*i*-Bu₃Al) used to activate the reaction is trapped by complexation with the oxygen atoms along the PEEGE chains, as illustrated in Figure 2.7. In contrast, for 4 equivalents of *i*-Bu₃Al, the monomer conversion reached 90 percent. In

conclusion, the formation of a 1 : 1 initiating and propagating complex of low basicity, which minimizes chain transfer reactions to the monomer, along with a high degree of nucleophilicity, are due to the activating role of the excess Lewis acid, which allows fast reactions at low temperatures.⁶¹

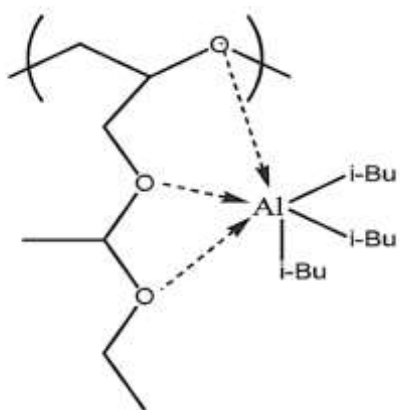


Figure 2.7 Complexation of triisobutylaluminum by the oxygen atoms of poly(EEGE)⁶¹

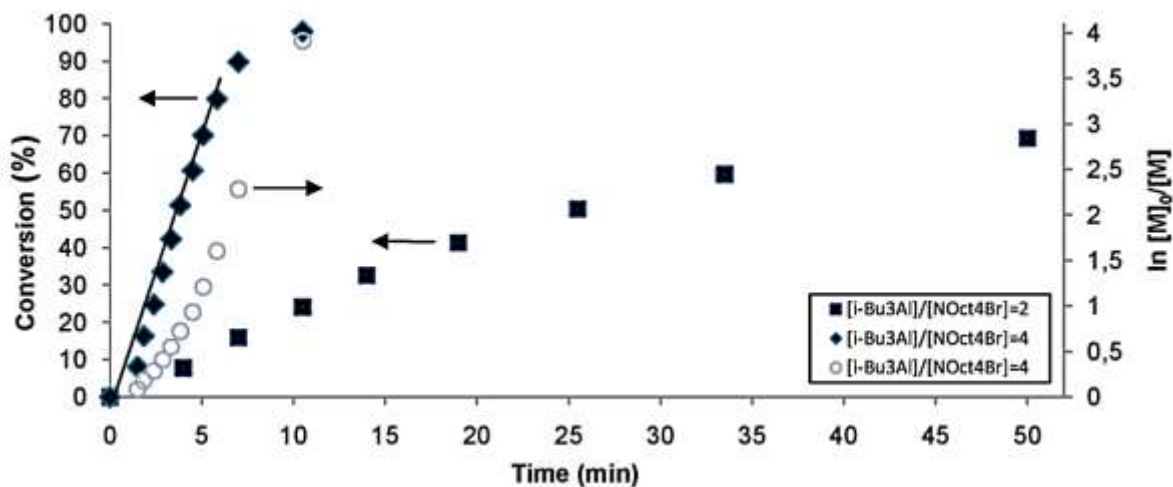
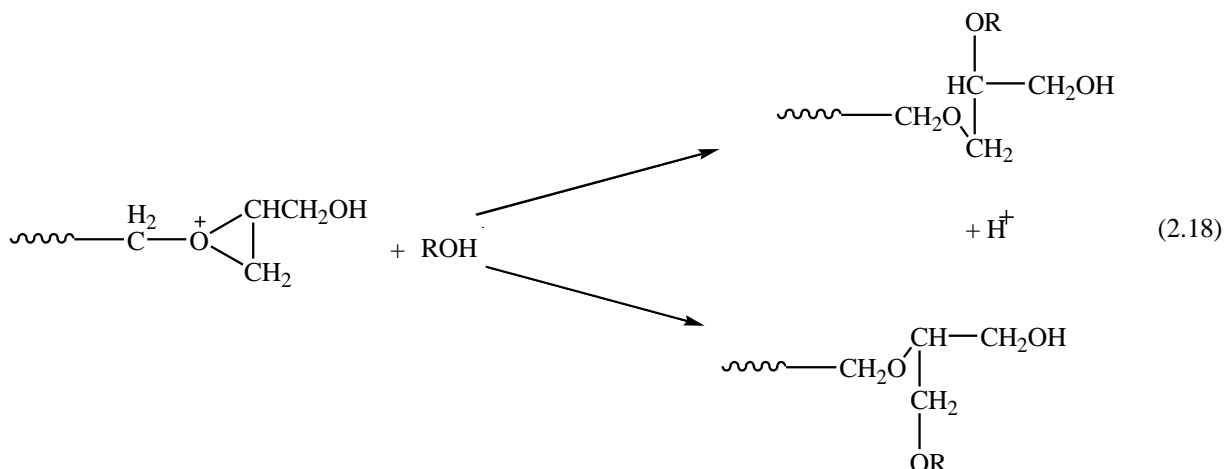
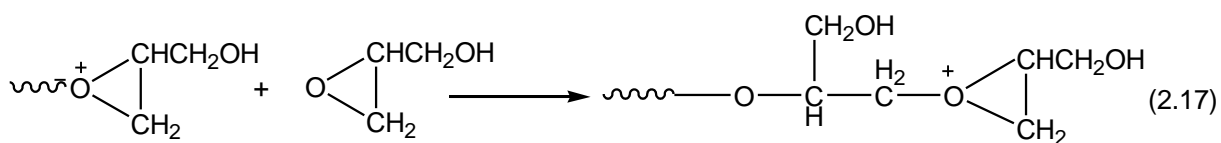


Figure 2.8 Conversion (filled squares) and $\ln[M]_0/[M]$ (open circles) versus time plots for the polymerization of ethoxyethyl glycidyl ether (EEGE) in toluene at 0°C , $[\text{EEGE}] = 0.5 \text{ M}$, $[\text{NOct}_4\text{Br}] = 7 \times 10^{-3} \text{ M}$, with $[i\text{-Bu}_3\text{Al}]/[\text{NOct}_4\text{Br}] = 2$ (■) or 4 (○)⁶¹

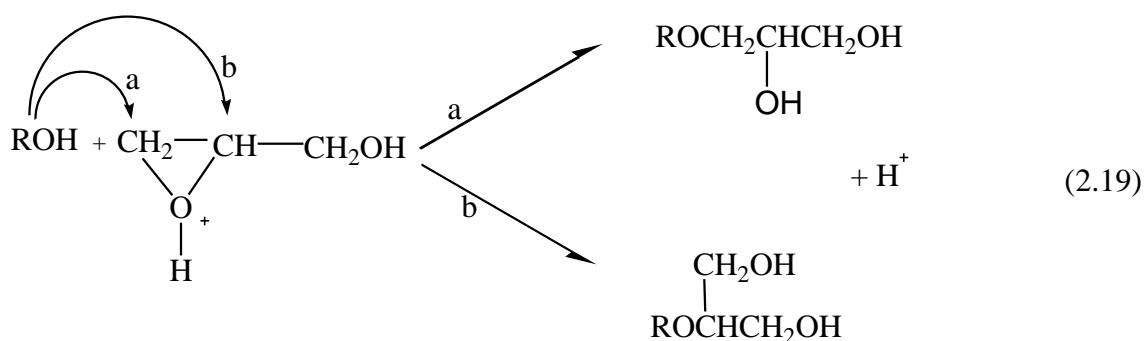
Block copolymers^{65,66} and star-shaped polymers⁶⁷ based on glycidol have also been synthesized. Arborescent polyglycidols⁶⁸ with high molecular weights were thus obtained using successive reactions *grafting from* the substrates. A linear polyglycidol was first synthesized through the anionic polymerization of glycidol acetal initiated with potassium *tert*-butoxide in THF, followed by hydrolysis of the acetal group. The polyanion thus obtained was used to initiate the polymerization of glycidol acetal, which yielded after hydrolysis polyglycidol-*graft*-polyglycidol, as shown in Scheme 2.12. This procedure was again repeated twice to produce three generations of arborescent polyglycidol samples with molecular weights reaching 10^6 g/mol while maintaining relatively narrow molecular weight distributions ($\text{PDI} < 1.43$).⁶⁸

2.4.3 Cationic Polymerization of Glycidol

The cationic polymerization of glycidol, first reported by Goethals et al., ultimately led to branched polyols.⁵⁹ Subsequently, Dworak et al.⁶⁹ developed a cationic polymerization technique for glycidol involving two competing propagation mechanisms, namely the activated monomer (AM) mechanism and the active chain end (ACE) mechanism. Nucleophilic attack of the monomer on the tertiary oxonium ion active species, corresponding to the ACE mechanism, produces a polymer which consists exclusively of $-\text{CH}_2-\text{CH}(\text{CH}_2\text{OH})-\text{O}-$ repeating units. Thus only primary hydroxyl ($-\text{CH}_2\text{OH}$) groups should be present as substituents in the polyether chain in this case. The situation is similar for chain transfer involving the hydroxyl groups on the monomer or the polymer, as shown in Eq. 2.17 and 2.18.



On the other hand, if the polymerization of glycidol proceeds via attack of the hydroxyl group of the polymer on the protonated monomer the AM mechanism comes into play, which leads to two types of repeating units, in which ROH is either a chain end or a side group. In the latter case branching occurs, as illustrated in Eq. 2.19 below.



In the study of Dworak,⁶⁹ polymers with molecular weights of up to 10,000 g/mol were obtained with a complex structure containing comparable amounts of primary and secondary OH groups. The (1-3) polymer units were formed by the ACE mechanism, while the (1-4) polymer units were formed by AM mechanism, as shown in Figure 2.9.

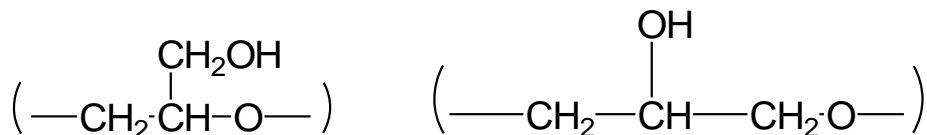


Figure 2.9 The 1-3 and 1-4 polymer units of polyglycidol⁵⁹

To gain a better understanding of the structure of these polymers, Lewis acids (BF_3OEt_2 , SnCl_4) and protonic acids (CF_3COOH , $\text{CF}_3\text{SO}_3\text{H}$) were also used as initiators. When the initiation was completed with BF_3OEt_2 or protonic acids, almost one half (42-54%) of all the structures obtained were 1-3 units, 25-29% were 1-4 units, and the rest were branches. On the other hand, the initiation with SnCl_4 produced fewer 1-3 units (18-26%) and many more branches (36-52%).⁶⁹

This study also found that temperature had a strong influence on the polymerization outcome: An increase in the reaction temperature increased the amount of branching, as shown in Table 2.2. The influence of the monomer-to-initiator ratio was less significant however.

Table 2.2 Structure of polyglycidol as a function of the polymerization temperature⁶⁹

Initiator	Temp. in °C	Content in mol-%		
		1-3 units	1-4 units	branches
BF_3OEt_2	-30	49	30	21
BF_3OEt_2	-15	43	25	31
BF_3OEt_2	15	39	22	39
SnCl_4	-15	18	46	36
SnCl_4	15	20	27	52

2.5 Ring-opening “Multibranching Polymerization”[®] by Slow Monomer Addition

Branched macromolecules such as the hyperbranched polymers have attracted much attention in nanotechnology.⁷⁰ These polymers exhibit unique characteristic features such as a low viscosity in solution, enhanced solubility, and a large number of terminal groups as compared to their linear polymer analogues. Kim and Webster first synthesized hyperbranched polymers in 1988 by the polycondensation of AB_m-type monomers.⁷¹ The main drawbacks of these hyperbranched polymer syntheses include very broad molecular weight distributions and relatively low degree of branching (DB) values, which limit the usefulness of hyperbranched polymers in many applications. In contrast, the slow monomer addition (SMA) method developed more recently is a highly effective technique to produce hyperbranched polymers with controlled molecular weights, higher DB values, and narrow molecular weight distributions.⁷⁰

2.5.1 Anionic Ring-opening Multibranching Polymerization of Glycidol

Linear polyglycidol has been obtained using various catalyst systems, but branching is generally considered an undesirable side reaction in these systems. The controlled synthesis of hyperbranched polyglycidol was thus difficult to achieve. However in 1999, Sunder et al.⁷¹ reported the anionic ring-opening multibranching polymerization of glycidol under slow monomer addition conditions, leading to polymers with molecular weights up to 6000 g/mol, narrow molecular weight distributions, and a high degree of branching using alkoxide initiators according to the mechanism shown in Figure 2.10.

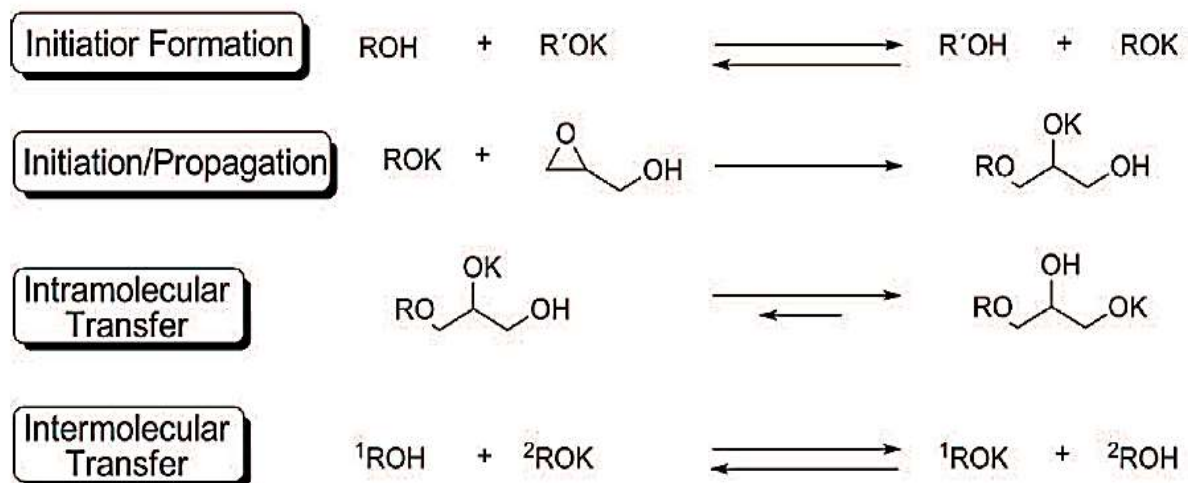


Figure 2.10 Mechanism for the anionic ring-opening polymerization of glycidol, employing partially deprotonated alcohol moieties as initiating sites⁷²

The use of partial deprotonation provides control over the concentration of active sites (alkoxides) in the polymerization. This results in simultaneous growth from all the chain ends, and thus molecular weight control and a low polydispersity. A deprotonating agent such as potassium methylate was used with the alcohol initiator (alkoxide) to convert only 10 percent of the hydroxyl groups to the alkoxide. In the propagation step, a secondary alkoxide is generated by reaction of the alkoxide initiator with the epoxide ring on its unsubstituted end. In the subsequent intramolecular chain transfer step, the formation of the more stable and highly reactive primary alkoxide is achieved to a certain extent. As the polymerization proceeds, the concentration of active species, initially set to 10 percent of the hydroxyl end groups present, gradually decreases since the incorporation of each glycidol monomer generates a new hydroxyl group that represents a dormant chain end.⁷¹

The architecture of the hyperbranched macromolecules prepared by anionic ring-opening multibranching polymerization is shown schematically in Figure 2.11. The initiator (a monofunctional alcohol or a polyol) is incorporated as the core unit. Since it is likely that all the hydroxyl groups remain active during the polymerization, dendritic (D), linear (L), and terminal (T) units are incorporated at each position of the structure, as illustrated in Figures 2.11 and 2.12.

If a secondary hydroxyl group can propagate, a linear 1,3-unit (L13) is generated. If the primary hydroxyl group propagates, a linear 1,4-unit (L14) is formed. If both the secondary and primary hydroxyl groups react with monomer, however, a branched dendritic unit (D) is obtained. If a monomer unit is deactivated by proton exchange or by the addition of an acid, a terminal unit (T) with two hydroxyl end groups is formed.⁷²

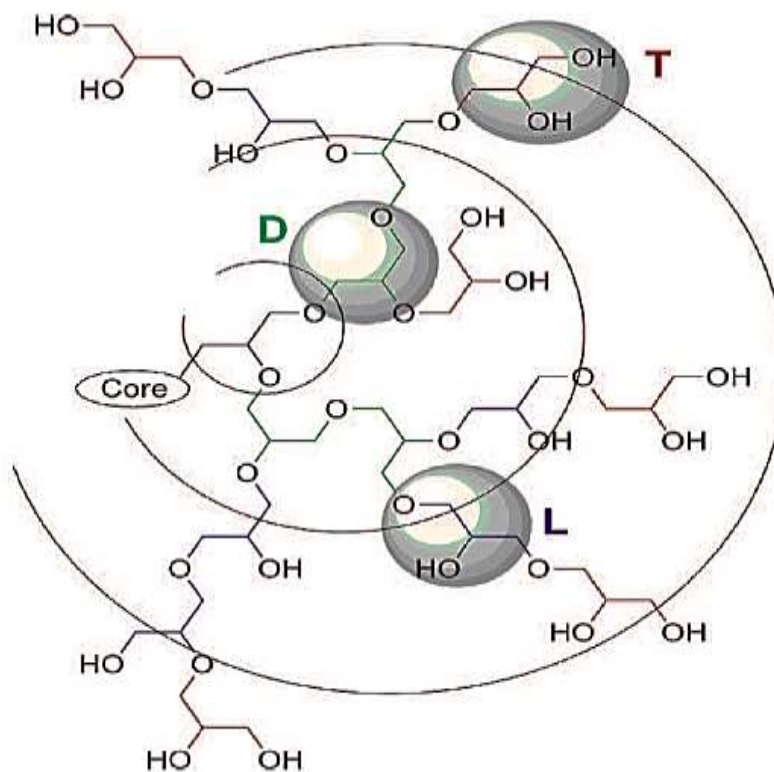


Figure 2.11 Schematic architecture of a hyperbranched polyglycerol derived from glycidol, with examples of terminal (T), dendritic (D), linear 1,3- (L13), and linear 1,4-units (L14) shaded; pseudogenerations are indicated by concentric lines, and the core is attached to the focal monomer unit⁷²

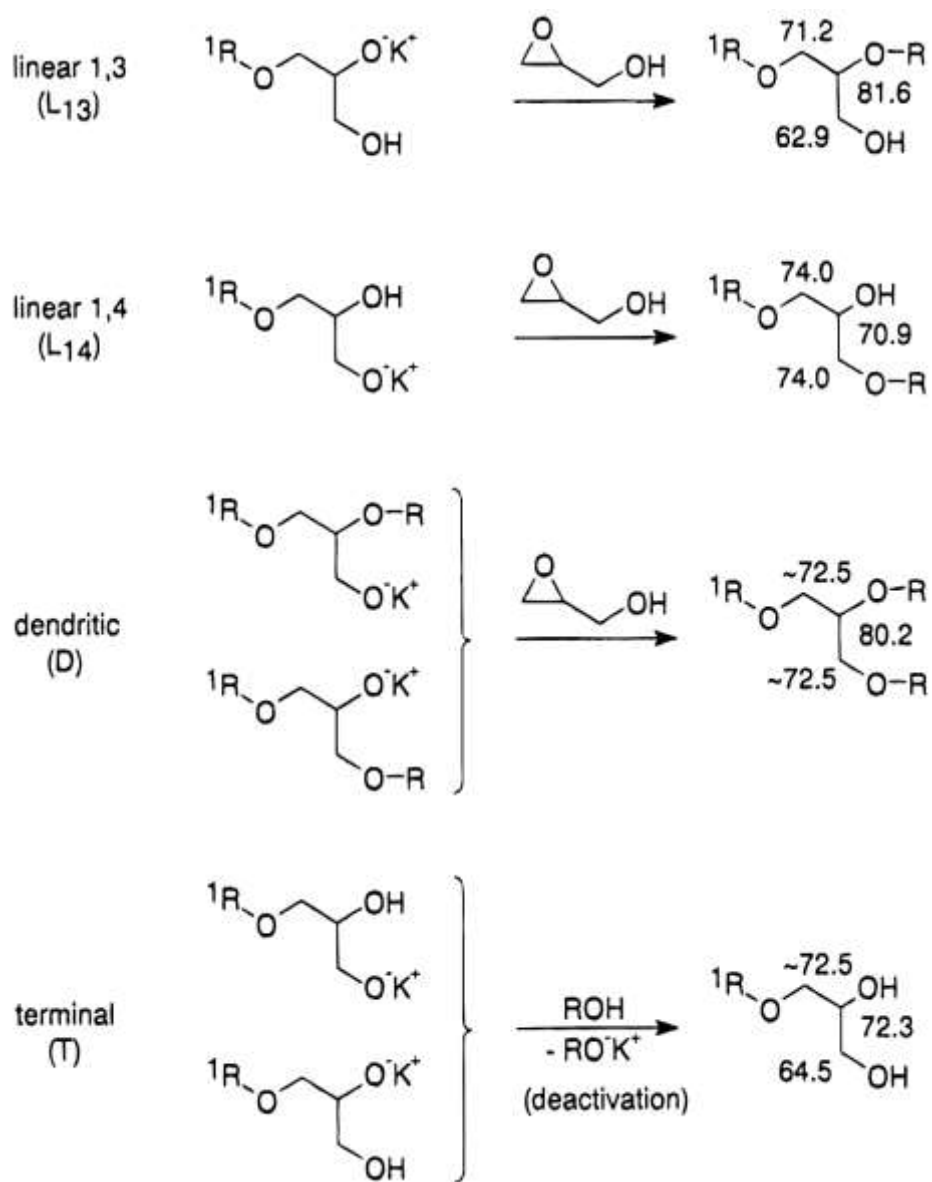
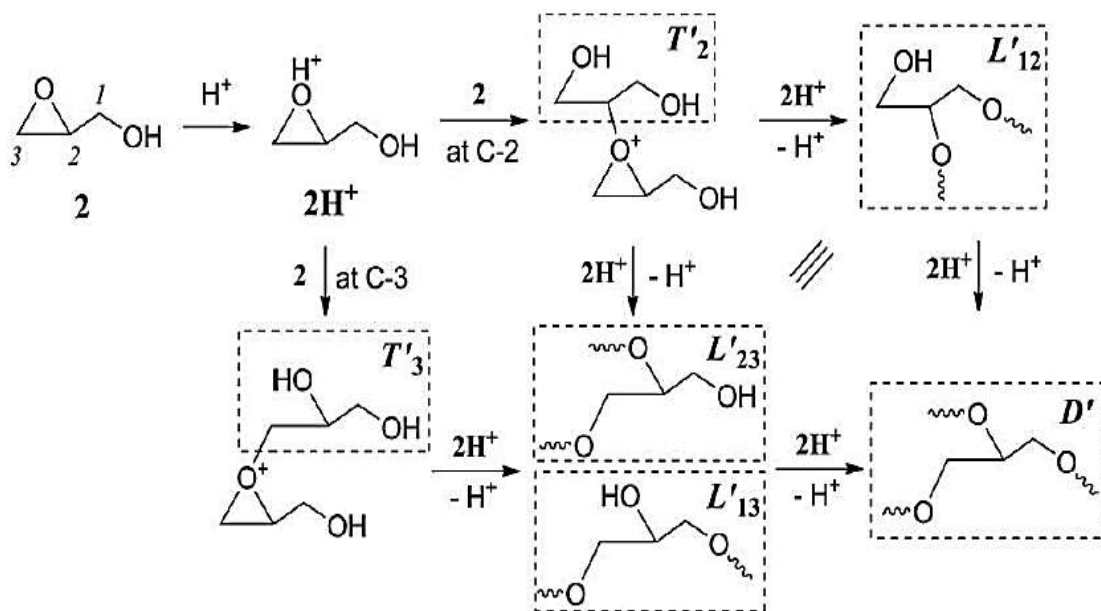


Figure 2.12 Formation of structural units and respective ^{13}C NMR shifts (in ppm) ⁷¹

2.5.2 Cationic Ring-opening Multibranching Polymerization of Glycidol

The polymerization of glycidol may also be catalyzed by trifluoromethanesulfonic acid ($\text{CF}_3\text{SO}_3\text{H}$) or boron trifluoride diethyl etherate ($\text{BF}_3\cdot\text{OEt}_2$) using the SMA method.⁷³ The yield of hyperbranched polymer was increased by using the SMA method as compared to a batch-wise polymerization protocol. For instance, the conversions attained in 2 h by polymerization without the SMA and with slow addition were 81 and 91%, respectively. In the cationic polymerization mechanism, the polymer obtained should consist of five different types of repeating units: the 2- and 3-linked terminal units (T_2 and T_3); the 1,3- and 2,3-linked (1,2-linked) linear units (L_{13} , and L_{23} ($=L_{12}$)); and the 1,2,3-linked dendritic unit (D') as shown in Scheme 2.13.



Scheme 2.13 Proposed mechanism for the cationic ring-opening multibranching polymerization of glycidol⁷³

The relative amounts of structural units of the types T^* , L^*_{23} and D^* were found to slightly increase by increasing the duration of the monomer addition, while the L^*_{13} units decreased. The degree of branching also increased when increasing the time of monomer addition.

Finally, a new surface-initiated polymerization method was developed to synthesize hyperbranched polyglycidol brushes covalently linked on Si/SiO₂ surfaces via the anionic ring-opening multibranching polymerization of glycidol at 110 °C.⁷⁴ Figure 2.14 describes the proposed mechanism for the polymerization of glycidol in this case. The growth of polyglycidol from the Si/SiO₂ surfaces was initiated by deprotonating the Si-OH bonds with sodium methoxide. The alcoholate deprotonated the silanol groups which attacked the glycidol monomer at the unsubstituted side, thus producing a secondary alkoxide. This alkoxide could then attack another glycidol monomer or exchange a proton with a neighboring primary alcohol group.⁷⁴

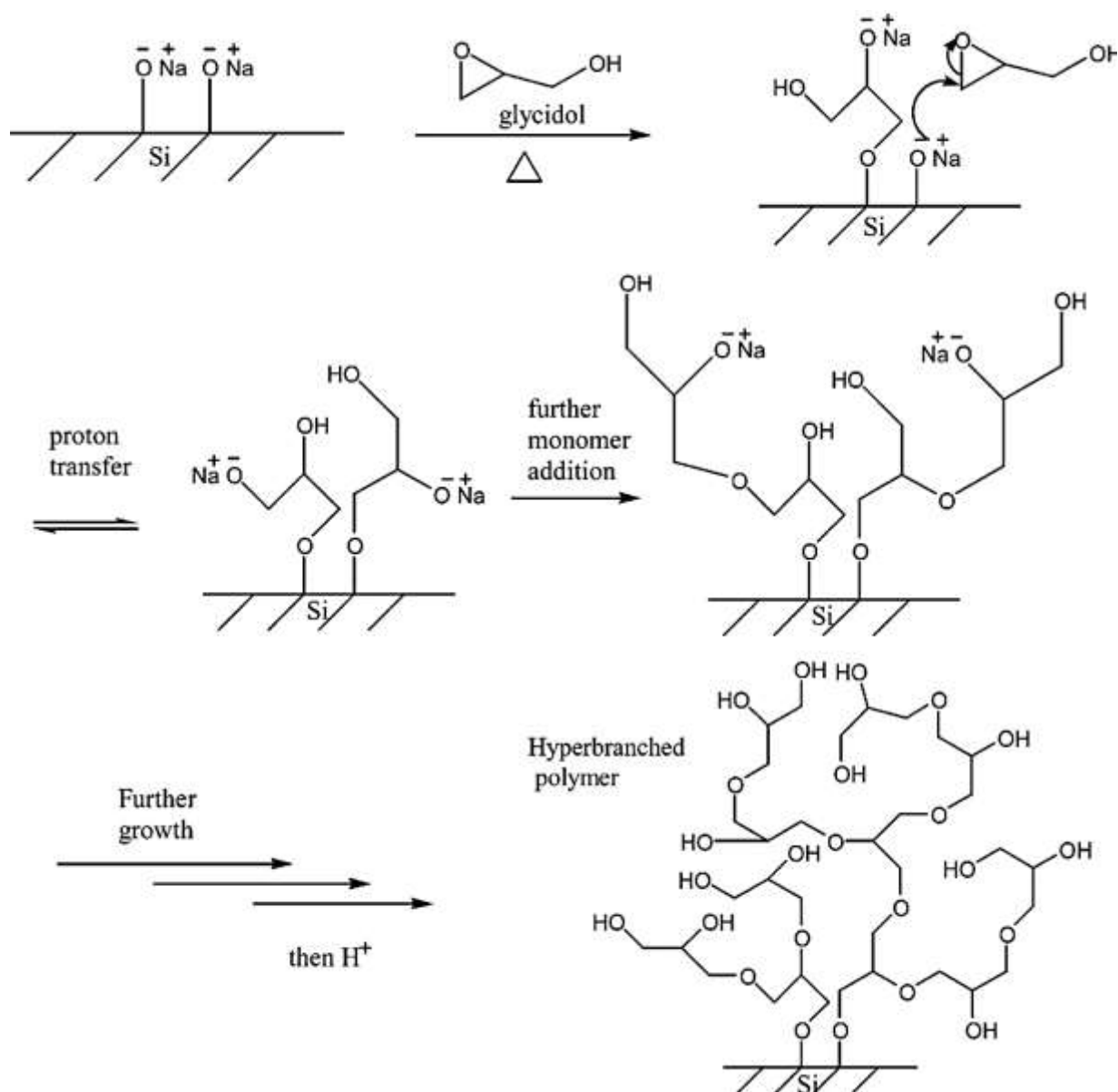


Figure 2.13 Proposed mechanism for the formation of hyperbranched polyglycidol on a Si wafer surface via anionic ring-opening multibranching polymerization⁷⁴

Since initiating sites are only present on the surface of Si/SiO₂, their concentration is low as compared to the amount of monomer added. For each monomer reacting with a propagating

center, two potential active sites are attached to the surface. Therefore the concentration of active sites decreases relatively to hydroxyl groups, but the total number of active sites remains constant as the reaction proceeds. The low concentration of active sites on the polymer brushes was found to be the key to the controlled growth of the brushes. The optimal reaction conditions for brush formation yielded a maximum thickness of approximately 15 nm. To further increase the thickness of the polyglycidol brushes, reinitiation was achieved by exposing the brush films to sodium methoxide and using the same polymerization method applied initially.⁷⁴

2.6 “Click” Chemistry in Polymer Synthesis

2.6.1 Azide–Alkyne Click Chemistry in Polymer Science

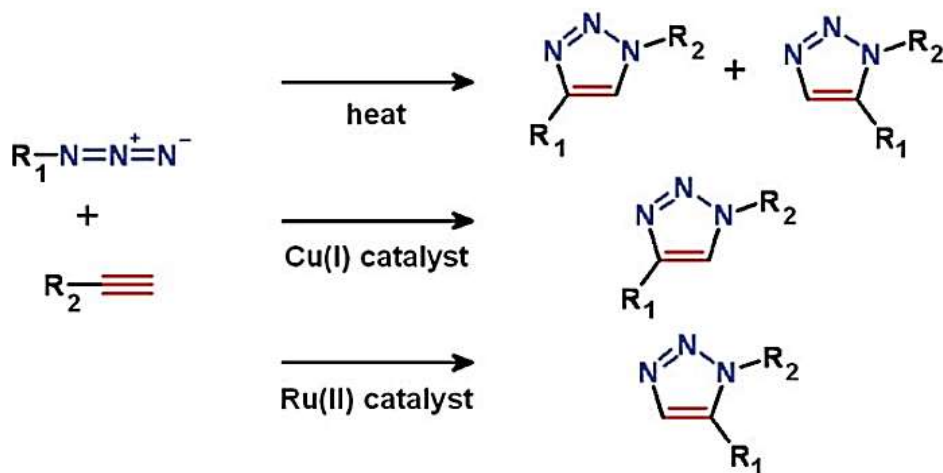
Living/controlled polymerization techniques have been used to synthesize a variety of different well-defined copolymer structures. However it is often impossible to combine specific polymers into one single copolymer architecture due to incompatibility between the different polymerization methods used to synthesize them. Thus polymer chemists have explored various approaches to combine different polymer chains beyond copolymerization. The combination of synthetic organic chemistry and polymer chemistry is a very promising approach to build novel structures by coupling preformed polymers using well-known organic coupling methods.⁷⁵ The concept of “click” chemistry was recently introduced to polymer science by Sharpless.^{76,77} Click chemistry is defined as a reaction that is ideally modular, wide in scope, high in yield, has little side products that are easily removed by non-chromatographic methods (for example

crystallization or distillation), is stereospecific but not necessarily enantioselective, uses simple reaction conditions, is not very sensitive to oxygen or water, uses easily accessible reagents, requires either no solvent or a solvent that is easily removed or benign such as water, enables simple product isolation, has a high thermodynamic driving force, and goes rapidly to completion. The concept of click chemistry thus appears ideal for coupling preformed polymer chains, and it is indeed an established method for the preparation of well-defined macromolecular architectures. For the synthesis of such well-defined structures, click chemistry must be combined with living/controlled polymerization methods allowing the preparation of well-defined polymeric building blocks functionalized with alkyne, azide, or other desired groups. The literature reported so far largely relied on the chemical modification of previously formed hydroxyl-terminated polymers. However, the use of ammonium salts as initiators in the presence of triisobutylaluminum (*i*-Bu₃Al) as activator can directly serve to synthesize linear high molecular weight polyglycidol from the protected monomer, and thus allows its direct α -azido functionalization.⁷⁸ In the current project, the synthesis of polyglycidol acetal with α -azide end groups, and the modification of hydroxyl-terminated polystyrenes with alkyne end groups was achieved, and copper (I) was used to couple these polymers. The reactions are discussed in more detail below.

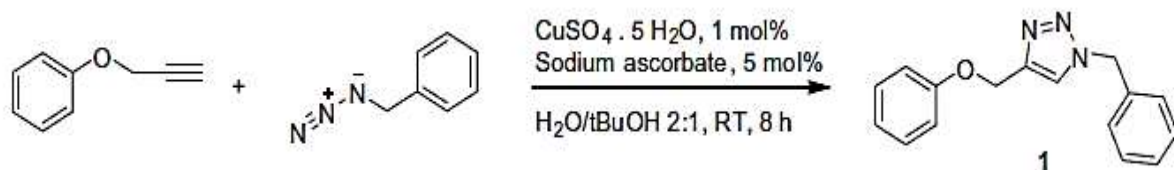
2.6.2 Cycloaddition of Unsaturated Molecules

Although various click chemistry reaction types have been developed, most reports are still concerned with the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction. Originally the

azide–alkyne (Huisgen)⁷⁹ cycloaddition reaction was performed at high temperatures, resulting in the formation of both 1,4- and 1,5-substituted-1,2,3-triazoles, conflicting with both the requirements of simple reaction conditions and stereospecificity. The use of a ruthenium(II) catalyst in the azide–alkyne cycloaddition reaction was found to change its stereospecificity, by leading solely to the 1,5 regioisomer of 1,2,3-triazole. Sharpless⁸⁰ and Meldal⁸¹ further reported a system of copper(I) catalyst for the 1,3-dipolar cycloaddition of azides and alkynes. The use of a copper(I) catalytic system leads to the exclusive formation of the 1,4-substituted 1,2,3-triazole product, accelerates the reaction tremendously, and allows room-temperature cycloadditions as shown in Scheme 2.14. In practice,⁸² the copper(I) catalyst can be generated in situ from copper(II) sulfate and sodium ascorbate as a reducing agent, or a copper(I) halide can be used together with a stabilizing ligand, as shown in Scheme 2.15.



Scheme 2.14 1,3-Dipolar thermal cycloadditions between alkynes and azides, leading to the formation of a mixture of regioisomers of 1,2,3-triazole in the absence of catalyst, the 1,4-regioisomer with copper(I) catalysts, or the 1,5-regioisomer with ruthenium(II) catalysts⁷⁵

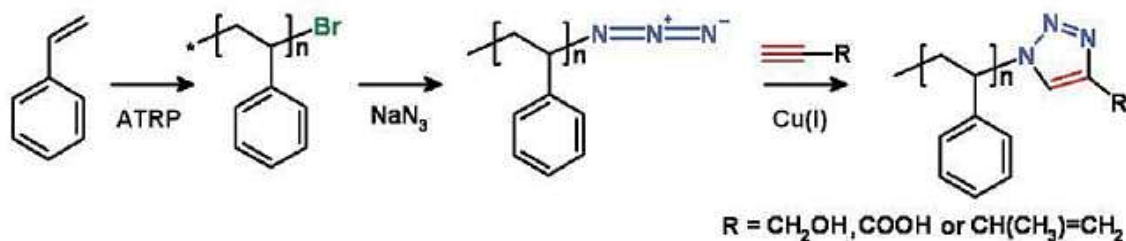


Scheme 2.15 Example of a Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (91% yield)⁸²

This reaction belongs to the hetero-Diels–Alder addition family, and is considered to be the most reliable type of these reactions because azides and alkynes are very stable towards dimerization and hydrolysis. Furthermore, this reaction is powerful due to its tolerance to a wide variety of functional groups and the easy accessibility of the starting compounds.

2.6.3 End-functionalization of Well-defined Polymers

Well-defined polymeric building blocks with one or two azide and/or alkyne functionalities at the chain ends can be synthesized by atom transfer radical polymerization (ATRP) or anionic polymerization. The first approach has been explored widely for the chain end functionalization of polystyrene.⁸³ For example, the copper(I)-catalyzed cycloaddition of several functional acetylenes with azido-polystyrene has allowed the quantitative formation of polystyrene end-functionalized with primary alcohol, carboxylic acid, or vinylic groups, as shown in Scheme 2.16.



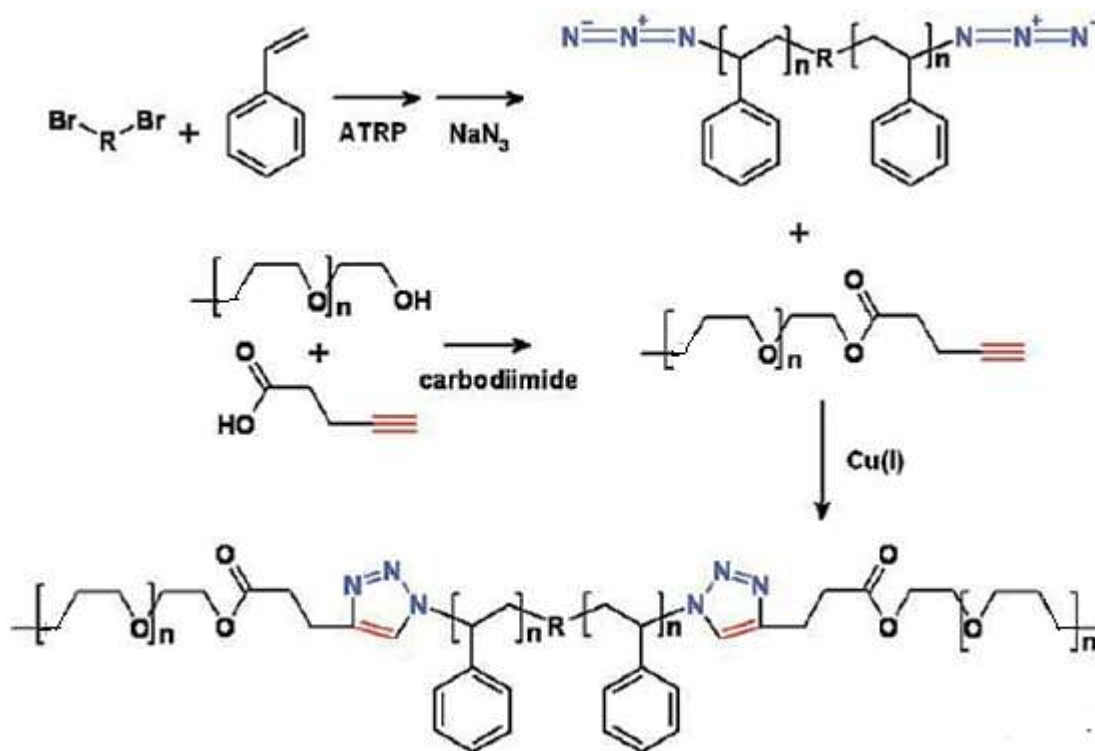
Scheme 2.16 Preparation of end-chain functionalized polystyrene via a combination of ATRP and click chemistry⁷⁵

Cornelissen and co-workers⁸⁴ also used click chemistry to prepare amphiphilic polystyrene bioconjugates that self-assembled into micellar structures in aqueous solutions. The most significant advantage of the copper(I)-catalyzed cycloaddition is its functional group tolerance, which allows the preparation of bioconjugates without the commonly required functional group protection and deprotection steps.

2.6.4 Block Copolymers

Copper(I)-catalyzed 1,3-dipolar cycloaddition was first explored for the preparation of block copolymers by Opsteen and Van Hest.⁸⁵ A variety of acetylene- and azido-functionalized polymers were prepared including azido and diazido polystyrene, acetylene-functionalized poly(methyl methacrylate) (PMMA), as well as azide- and acetylene-functionalized poly(ethylene oxide). These building blocks were then combined using the copper(I)-catalyzed 1,3-dipolar cycloaddition to prepare a series of amphiphilic diblock copolymers. In addition, the

synthesis of an amphiphilic triblock copolymer based on polystyrene and acetylene-functionalized poly(ethylene oxide) segments was demonstrated as depicted in Scheme 2.17.



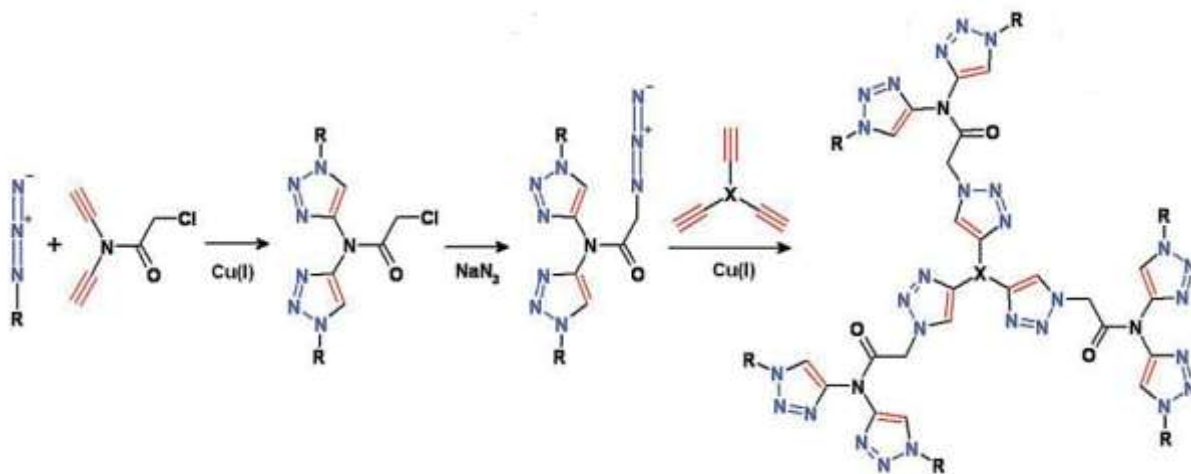
Scheme 2.17 Synthesis of a triblock copolymer via click chemistry. The diazido polystyrene was prepared by ATRP from a bifunctional initiator, and the acetylene-functionalized PEO was prepared by carbodiimide-catalyzed esterification⁷⁵

2.6.5 Hyperbranched and Dendritic Macromolecules

Voit et al.⁸⁶ explored the synthesis of hyperbranched polymers by 1,3-dipolar cycloaddition of monomers having one alkyne and two azide functionalities, or alternately two alkynes and one azide. The uncatalyzed polymerization of these monomers proceeded at ambient temperature,

yielding soluble hyperbranched polymers consisting of a mixture of both the 1,4- and 1,5-regioisomers of 1,2,3-triazole. The addition of a copper(I) catalyst to the polymerization mixture yielded only the 1,4-disubstituted 1,2,3-triazole rings, albeit the resulting hyperbranched polymer was insoluble in common solvents.

Hawker, Sharpless, and Fokin⁸⁷ were the first to explore the convergent synthesis of 1,2,3-triazole-based dendrimers using a variety of azide and acetylene precursors. Well-defined dendrimers of up to the fourth generation could be obtained in quantitative yield, as demonstrated by size exclusion chromatography analysis. The approach used is illustrated in Figure 2.18, for the preparation of a first-generation dendron that was subsequently coupled with a trifunctional core molecule. The synthetic methodology used to prepare the first-generation azide dendron could also be repeated for the preparation of higher-generation dendrimers.



Scheme 2.18 Synthesis of a first-generation 1,2,3-triazole-based dendritic wedge (G1) and subsequent coupling with a trifunctional core molecule⁷⁵

In summary, the copper(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition reaction has already been explored for the synthesis of a variety of controlled polymer architectures including end-functionalized polymers, block copolymers, cyclic polymers, graft copolymers, star-shaped copolymers, dendrimers, and crosslinked materials. Unfortunately, the presence of copper(I) in the azide–alkyne click chemistry may hinder its use in certain applications, for example in drug or gene delivery, and limit the biocompatibility of the resulting products, thereby suggesting the need for the development of alternate click reactions.

Chapter 3

Objectives

The main objectives of this project were as follows:

1. Synthesis of linear polystyrene, and arborescent substrates using cycles of acetylation and grafting reactions.
2. Synthesis of hydroxyl-functionalized polystyrenes using a bifunctional initiator.
3. Glycidol acetal synthesis and purification.
4. Growth of poly(glycidol acetal) chains from the hydroxyl-functionalized cores to form a shell around hydrophobic polymers of linear, and arborescent polymers of generations G0 and G1.
5. Modification of hydroxyl-functionalized polystyrene core with alkyne groups at the chain ends.
6. Synthesis of azide-functionalized poly(glycidol acetal) using activated monomer anionic polymerization.
7. Coupling of alkyne-functionalized polystyrenes with azide-functionalized poly(glycidol acetal) using a click reaction.

3.1 Justification

The acetylation of polystyrene was preferred to introduce the coupling sites on the substrates in this study. In past work, the reaction to introduce chloromethyl coupling sites was not very practical due to safety and environmental concerns. Acetyl chloride is much more innocuous than chloromethyl methyl ether (CMME) used in the latter reaction. Control of the substitution level in the acetylation reaction is also easier to achieve with nearly stoichiometric amounts of AlCl_3 and acetyl chloride, while in the chloromethylation reaction a large excess of CMME must be used and leads to the deactivation of variable amounts of AlCl_3 . Moreover, chloromethylation is prone to cross-linking reactions while acetylation is not. The acetal-protected organolithium initiator used in the original work has been replaced with a silyl ether-protected initiator because of its greater storage stability. Another modification concerns the replacement of ethylene oxide with glycidol acetal to add the hydrophilic shell. Ethylene oxide is extremely flammable and explosive when mixed with air. The International Agency for Research on Cancer classifies ethylene oxide as a Group 1 (proven) carcinogen.⁹² Even though glycidol and glycidol acetal are irritants to the skin, the eyes, the mucous membranes, and the upper respiratory tract, ethylene oxide is much more toxic. Poly(ethylene oxide) is also prone to crystallization, while polyglycidol is amorphous, which should lead to easier dissolution of the unimolecular micelles.

Potential applications for the arborescent polystyrene-*graft*-polyglycidol copolymers synthesized concern microencapsulation and drug delivery.

Chapter 4

Experimental Procedures

4.1 Purification of Solvents and Reagents

Anionic polymerization is very sensitive to impurities such as moisture and oxygen. Established techniques were therefore used to purify the solvents and monomers in order to achieve a high purity. Tetrahydrofuran (anhydrous, 99%, Aldrich) was purified by distillation from sodium (99.9%, Aldrich) and benzophenone (99%, Aldrich) under nitrogen, and toluene (anhydrous, 99.8%, Aldrich) was distilled from oligostyryllithium under nitrogen in the apparatus shown in Figure 4.1. The solvents were transferred directly to the polymerization reactor or manifolds through polytetrafluoroethylene tubing.

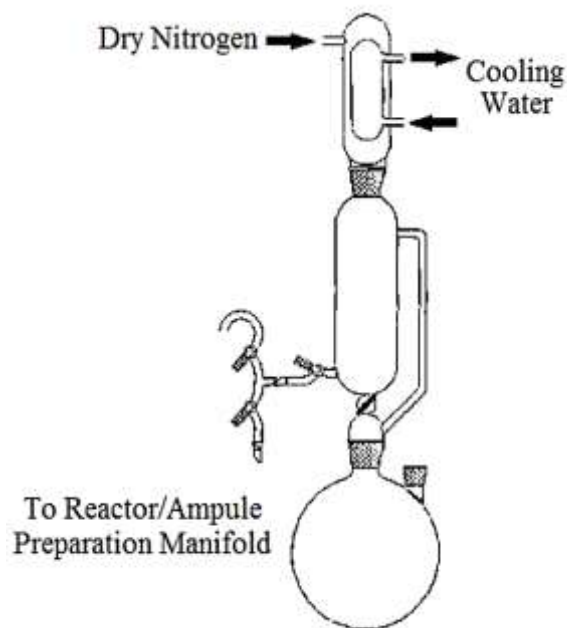


Figure 4.1 Apparatus for solvent distillation⁸⁸

Styrene (Aldrich, 99%), glycidol (2,3-epoxypropan-1-ol, Aldrich, 96%), ethyl vinyl ether (Aldrich, 99%), and the capping agent 2-vinylpyridine (2VP, Aldrich, 99%) were distilled under reduced pressure after stirring overnight in the presence of CaH_2 . The monomers were stored under nitrogen in a refrigerator until a second purification step was conducted immediately before use. *sec*-Butyllithium (Aldrich, 1.4 M in cyclohexane) serving as initiator was used as received, but its exact concentration was determined by the method of Lipton et al.⁸⁹ The bifunctional initiator 6-*tert*-butyldimethylsiloxyhexyllithium (TBDMS-O-Hexyl-Li) and diphenylmethylpotassium were synthesized according to published procedures.^{90,91} Acetyl chloride (Aldrich, 98%) was distilled under nitrogen and nitrobenzene (Aldrich, 99%) was distilled under vacuum. Anhydrous aluminum chloride (Aldrich, 99%), *p*-toluenesulfonic acid (Aldrich, 99%), triisobutylaluminum solution (1.0 M, 25% wt solution in toluene, Aldrich), potassium *tert*-butoxide (Aldrich, 95%), tetrabutylammonium azide (Aldrich), tetrabutylammonium fluoride solution (1.0 M in THF, Aldrich), lithium chloride (99%, Alfa Aesar), *N,N,N',N'',N'''*-pentamethyldiethylenetriamine (Aldrich, 99%), propargyl bromide (80 wt % in toluene, Aldrich), copper(I) bromide (Aldrich, 98%), and phenylmagnesium chloride (PhMgCl, Aldrich, 2.0 M solution in THF) were used without further purification.

4.2 Styrene Polymerization

Styrene was purified with phenylmagnesium chloride on the high-vacuum line shown in Figure 4.2, using the manifold shown in Figure 4.3. An ampoule (A) was connected to the

manifold and the whole system was evacuated and flamed. The manifold was then purged with dry nitrogen, PhMgCl solution (4 mL) was added to flask (B), and the system was evacuated for 30 min to remove the THF. After purging with dry nitrogen, styrene (19.4 g, 186 mmol) was added to flask (B) containing the PhMgCl, and the solution was degassed with three freeze-pump-thaw cycles. Finally the monomer was recondensed to ampoule (A).

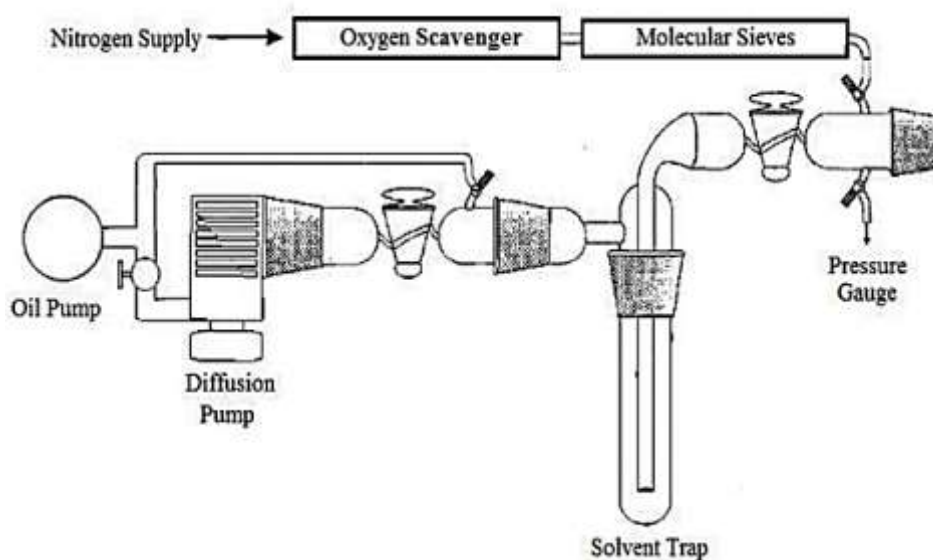


Figure 4.2 High-vacuum line system⁸⁸

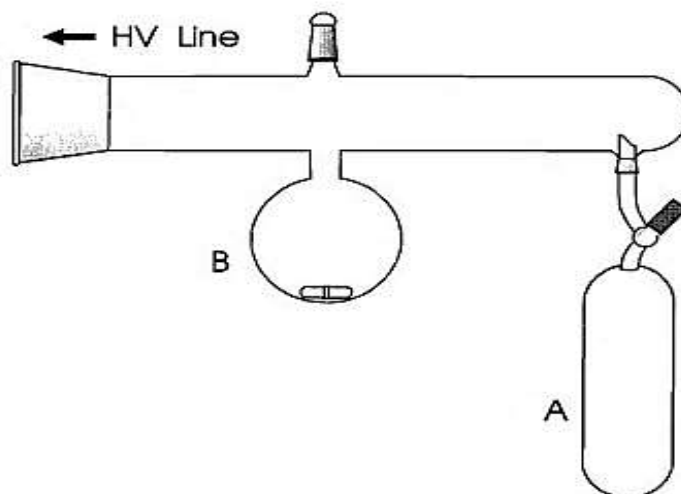


Figure 4.3 Apparatus for monomer purification⁴⁰

The glass polymerization reactor shown in Figure 4.4 was then connected to the high-vacuum line for the polymerization of styrene. The styrene ampoule and the THF line from the purification still were mounted on the reactor. A rubber septum was also used to cover one of the ground glass joints on the reactor to allow addition of the initiator with a syringe. The system was evacuated, flamed, and filled with dry nitrogen. After cooling to room temperature, toluene (200 mL) was added, followed by 2 drops of styrene and the initiator drop-wise to titrate the solvent and obtain a stable faint yellow coloration. Then the reactor was cooled to 0 °C and the whole amount of *sec*-butyllithium (2.7 mL, 30 mmol) solution was added (for a target $M_n = 5000$ g/mol), followed by the monomer. The coloration turned to orange-yellow. After 15 min the reactor was warmed to room temperature where it was maintained for 2 h; then it was cooled to -78 °C and dry THF (200 mL) was added. After 45 min the reaction was terminated with

degassed methanol (0.1 mL), the solution was concentrated on a rotary evaporator, and the polymer was recovered by precipitation in methanol, filtration, and drying under vacuum.

The bifunctional organolithium initiator synthesized (TBDMS-O-Hexyl-Li) (13 g, 0.075 M, 60 mmol), was also used to obtain polystyryllithium chains with a protected hydroxyl chain end in the polymerization of styrene (5.22 g, 49 mmol) in some cases. The same method described above for the synthesis of the linear polystyrene was used in that case.

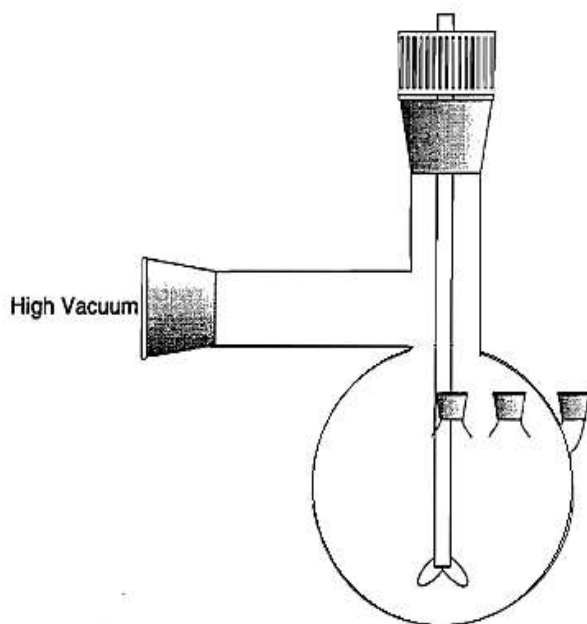


Figure 4.4 Polymerization reactor⁹

4.3 Acetylation of Polystyrene

A linear polystyrene sample was modified to introduce acetyl coupling sites for the grafting reaction. A sample of polystyrene (4.00 g, 38.4 meq styrene units, $M_n = 4770$ g/mol) was

dissolved in 100 mL of distilled nitrobenzene. Anhydrous AlCl_3 (3.15 g, 23.6 mmol) was dissolved in 10 mL of nitrobenzene and 2.04 g (26.0 mmol) of acetyl chloride was then added. This solution was added drop-wise to the polymer solution over 30 min and the reaction was left to proceed further for 30 min. The polymer was purified by two cycles of precipitation in acidified methanol, dissolution in chloroform, three extractions with a $\text{H}_2\text{O}/\text{HCl}$ mixture (50/50 v/v) and distilled water, and precipitation in methanol. ^1H NMR spectroscopy analysis was used to determine the acetylation level of the polymer.

4.4 Grafting Reactions

4.4.1 Synthesis of a G0 Arborescent Polystyrene

An arborescent polystyrene sample of generation G0 was prepared by coupling living polystyryl anions with the linear acetylated polystyrene substrate. An ampoule containing styrene (18.7 g, 179 mmol) was purified immediately before polymerization with PhMgCl (5 mL) as described above. Another ampoule containing 4 equivalents of 2-vinylpyridine (2VP, 1.2 mL in 10 mL of THF, 11 mmol) was prepared by further purification on a high-vacuum manifold with three freezing – evacuation – thawing cycles in the presence of CaH_2 powder (~1 g) followed by slow condensation under vacuum according to the procedure described for the purification of styrene. The monomer was diluted with ~10 mL of dry THF and the ampoule was filled with nitrogen.

Azeotropic drying of the acetylated polymer (31 mole %) was done using the vacuum manifold of Figure 4.5 which was first evacuated, flamed, and purged with dry nitrogen. The

polymer (1.51 g) was dissolved in 20 mL of THF and transferred to ampoule (A) with a syringe. The polymer solution was frozen in liquid nitrogen and the system was evacuated. After isolating the manifold from the vacuum line, the ampoule was warmed to room temperature and the THF was recondensed to flask (D). After closing stopcock (B), dry THF (30 mL) was added to flask (C) and condensed to ampoule (A) which was immersed in liquid nitrogen. The azeotropic distillation cycle was repeated three times and the polymer was finally dissolved in 20 mL of dry THF.

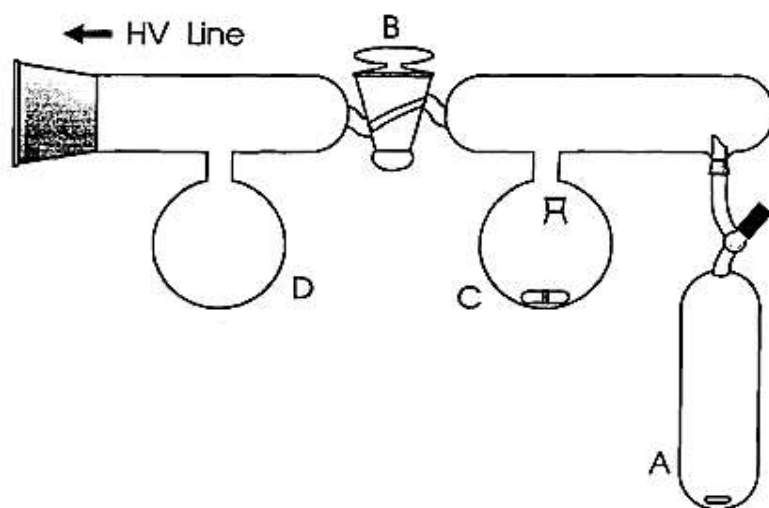


Figure 4.5 Apparatus for purification by azeotropic distillation⁴⁰

The two-liter glass polymerization reactor shown in Figure 4.4 was used to polymerize styrene and to prepare the graft polymer. The ampoules were installed on the reactor with the dry THF and toluene lines. A rubber septum was used to cover one of the ground glass joints of the reactor, to allow addition of the initiator with a syringe. Solid LiCl (0.79 g, 18 mmol) was also added to the reactor before it was evacuated, flamed, and filled with dry nitrogen. Toluene (200

mL) was then added, followed by 2 drops of styrene and the initiator drop-wise to titrate the solvent and obtain a stable faint yellow coloration. After that the reactor was cooled to 0 °C in an ice-water bath, the styrene was polymerized with 2.10 g (32 mmol) of *sec*-butyllithium solution (2.94 mL, for a target $M_n = 5000$ g/mol), resulting in a dark orange color. After 30 min the reactor was warmed to room temperature (23 °C) and the reaction was allowed to proceed for 2 h. The reactor was then cooled to -78 °C in a 2-propanol–dry ice bath and 200 mL of dry THF were added to increase the rate of polymerization, followed by the 2VP solution drop-wise, giving a dark red color. The reactor was warmed to 0 °C and the living polymer solution was titrated drop-wise with the acetylated polystyrene solution until the color became light red. Stirring was continued overnight and the remaining living polymer chains were deactivated by injecting 0.1 mL of degassed methanol. Finally the product was recovered by precipitation in methanol, filtration, and drying under vacuum. Analysis by size exclusion chromatography (SEC) was used to determine the molecular weight of the polymer and its polydispersity index (PDI).

4.4.2 Fractionation

This technique was used to remove the linear polystyrene contaminant (non-grafted chains) from the crude graft polymer. A crude polymer solution in toluene (4 g in 300 mL) was transferred to a cone-shaped flask at room temperature and methanol (ca. 250 mL) was slowly added with shaking until a cloudy solution was obtained. The solution was heated to 50 °C in a water bath for 40 min, methanol was again added to obtain a cloudy solution, and the flask was placed in a refrigerator overnight. The graft polymer settled at the bottom of the flask as a

viscous liquid which was removed, diluted with toluene, and recovered by precipitation in methanol, filtration, and drying under vacuum. Analysis of the purified product by SEC was used to confirm the removal of the side chain contaminant.

4.4.3 Synthesis of a G1 Arborescent Polystyrene

Polystyryllithium chains were synthesized from *sec*-BuLi (1.3 g, 20.3 mmol) and styrene (10 g, 96 mmol), capped with 2VP (0.92 g, 8.7 mmol), and coupled with a partially (20 %) acetylated G0 arborescent polystyrene substrate (1.83 g) in the presence of LiCl (0.46 g, 11 mmol) by the same method described for the synthesis of the G0 arborescent polymer.

4.4.4 Synthesis of a G0 Hydroxyl-functionalized Polymer

The bifunctional initiator TBDMS-O-Hexyl-Li was used to obtain polystyryllithium chains with a protected hydroxyl chain end in the polymerization of styrene. To synthesize a G0 hydroxyl-terminated polymer, styrene (20.8 g, 200 mmol) was polymerized with the bifunctional initiator (7.1 g, 0.31 M, 33 mmol) in toluene (200 mL) at 0 °C in the presence of LiCl (0.14 g) for 5 h to give an orange yellow solution. After cooling the reactor to -78 °C, dry THF (200 mL) was added followed by 3.7 g of 2VP (10% solution in THF), resulting in a dark red coloration. The acetylated linear polystyrene substrate (31 mole % substitution, 1.86 g in 10 mL of THF, 0.35 meq of acetyl groups) was dried azeotropically as described above. The reactor was warmed to 0 °C and the acetylated substrate solution was used to titrate the living polymer until the color became light red. The solution was stirred overnight and residual living polymer chains were

deactivated with 0.15 mL of methanol. Fractionation of the crude product was achieved in a toluene / methanol mixture.

4.4.5 Synthesis of a G1 Hydroxyl-functionalized Polymer

Polystyryllithium chains were obtained from TBDMS-O-Hexyl-Li solution (1.7 g, 8 mmol) and styrene (2.0 g, 19 mmol), capped with 2VP (0.36 mL, 3.3 mmol), and coupled with the acetylated G0 arborescent polystyrene substrate (20%, 0.27 g) in the presence of LiCl (0.08 g) by the same method described for the synthesis of the G0 hydroxyl-functionalized polymer. ¹H NMR spectroscopy and SEC analysis were used to confirm the presence of the protected hydroxyl groups and the molecular weight of the side chains.

4.5 Synthesis of Glycidol Acetal Monomer

p-Toluenesulfonic acid (TsOH, 1 g) was added portion-wise to a magnetically stirred solution of 40.0 g of 2,3-epoxypropanol (glycidol) in 200 mL of ethyl vinyl ether, to ensure that the temperature remained below 40 °C. The reaction mixture was stirred for 3 h, and then 100 mL of a saturated sodium bicarbonate (NaHCO₃) solution was added. The organic layer was isolated in a separatory funnel, dried over anhydrous magnesium sulfate (MgSO₄), and evaporated under reduced pressure. Distillation of the residue yielded a colorless liquid, which was stored under nitrogen in the refrigerator. ¹H NMR spectroscopy analysis was used to confirm the presence of the protecting group in the monomer.

4.6 Synthesis of Amphiphilic Copolymers

Deprotection of the silyl ether chain ends was achieved by treating the fractionated polymer with tetrabutylammonium fluoride (TBAF). To that end, the arborescent protected hydroxyl-terminated polystyrene (2.5 g) was dissolved in 250 mL of THF, and 2 g (7.8 mmol) of the TBAF solution was added. The reaction was maintained overnight at 77 °C. The solution then was evaporated to dryness, the polymer was again dissolved in 20 mL of THF, and purified with three cycles by azeotropic drying with THF.

A 1-L three-neck round-bottomed flask with a stirring bar was mounted on the high vacuum line, connected to the dry THF line, and a rubber septum was added on the last opening before it was evacuated and flamed. Approximately 20 mL of dry THF were added to the flask and titrated at room temperature with a diphenylmethylpotassium (DPMK, 0.30 M) solution via syringe to a yellow-brown color. Only a few drops of DPMK were required to reach a stable color. The polymer solution, with a number-average molecular weight $M_n = 69,000$ g/mol, was then added from the ampoule to the reaction vessel. The solution became clear and was titrated once more with the DPMK solution to generate active sites. Approximately 1.5 mL (0.45 mmol) of DPMK was needed to reach a stable endpoint. Glycidol acetal (4.5 g, 31 mmol) was further purified and stored under nitrogen immediately before polymerization by distillation of the monomer from triisobutylaluminum (1 mL). The monomer was then added via syringe to the round-bottomed flask. To achieve full monomer conversion, the reaction was left stirring for approximately 24 h in an oil bath at 65 °C. The reaction mixture obtained was light brown and slightly viscous. Approximately 2-3 drops of degassed acidified methanol were added to the reaction vessel to terminate the polymerization. The sample was purified by three cycles of

dialysis against THF, in a dialysis bag with a molecular weight cutoff (MWCO) of 1000. The solution was then filtered and the solvent was removed by rotary evaporation and dried under vacuum. Analysis by SEC and ^1H NMR spectroscopy served to determine the molecular weight and the composition of the copolymer, respectively.

4.7 Synthesis of Amphiphilic Copolymers by Click Chemistry

4.7.1 Synthesis of α -Azido Poly(glycidol acetal)

A linear polyglycidol sample with $M_n = 12,000$ g/mol and azide end groups was synthesized as follows. Glycidol acetal was purified immediately before polymerization by distillation. The initiator tetrabutylammonium azide (0.42 g, 1.5 mmol) was dried before use by three cycles of azeotropic distillation with dry toluene under vacuum, and stored under nitrogen after redissolution in 20 mL of toluene in a glass ampoule.

A 1-L, 5-neck round-bottomed flask was evacuated under high vacuum, flame-dried, purged with nitrogen, and dry toluene (100 mL) was added. The reactor was then cooled to -30 °C using a 2-propanol/water bath with dry ice. Glycidol acetal (15 g, 0.10 mol, for a target $M_n = 10,000$ g/mol) was added, followed by the initiator solution (15 mL) and 1.48 g (7.5 mmol) of triisobutylaluminum solution. The -30 °C bath was then removed, to allow the reaction to warm at room temperature and proceed overnight. The reaction was terminated with degassed acidified methanol. The polymer solution was purified three times by dialysis against THF in a bag with a MWCO of 1000, changed once after 8 h. The dialysis bag was then emptied into a round-bottomed flask and the THF was evaporated to give a clear viscous polymer. Analysis by SEC

and ^1H NMR spectroscopy (300 MHz, CDCl_3) were used to determine the molecular weight and to confirm the presence of the azide end groups.

4.7.2 Modification of Hydroxyl-functionalized Polystyrenes

The hydroxyl chain ends of the polystyrene substrates were converted into alkyne end groups. First, the arborescent deprotected polystyrene sample (0.5 g, 0.1 meq -OH groups) was dissolved in 50 mL of THF and potassium *tert*-butoxide (4 equiv, 0.16 g, 1.42 mmol) was added to activate the chain ends. After 2 h, propargyl bromide (0.16 mL, 1.8 mmol) was added. The color of the polymer solution changed from colorless to dark red. Analysis of the product by SEC and ^1H NMR spectroscopy (300 MHz, CDCl_3) was performed.

4.7.3 Click Reaction

For the “click” reaction, 0.1 g of alkyne-terminated polystyrene (0.02 meq of alkyne groups) and 3.5 g (0.21 mmol) of α -azido-functionalized poly(glycidol acetal) were dissolved in 50 mL of DMF, followed by 0.15 g (0.90 mmol) of PMDETA and 0.13 g (0.90 mmol) of copper(I) bromide. The reaction was stirred at room temperature for 48 h. The polymer was recovered by removing the solvent under vacuum, and a few cycles of dissolution in THF and precipitation in water. Analysis by SEC and ^1H NMR (300 MHz, CDCl_3) were used to determine the molecular weight and the composition of the resulting addition product.

4.8 Determination of the Concentration of the Initiators

The method of Lipton et al.⁸⁹ served to determine the exact concentration of the initiators used in this project. A 100 mL round-bottomed flask was connected to the high-vacuum line, evacuated, flamed and filled with dry nitrogen, and benzyl-benzamide (40 mg, 0.18 mmol) was added for the titration of the organolithium compounds. The flask was cooled to -35 °C and dry THF (100 mL) was added. A rubber septum was used to cover one of the ground glass joints on the flask to allow the addition of the initiator compounds being titrated with a syringe drop-wise until the solution just turned blue. The titration was repeated immediately before the reactions.

4.9 Sample Characterization

Size exclusion chromatography (SEC) analysis was performed for the polystyrene substrates before and after acetylation or modification, for the side chains, the crude grafting products, and the fractionated graft polymers. It was also performed for the protected polyglycidols and the amphiphilic polystyrene-polyglycidol copolymers. The system used consisted of a Viscotek GPCmaxVE 2001 instrument equipped with a Polyanalytik organic mixed-bed column and a triple detector array (consisting in differential refractive index, light scattering, and viscometer detectors), as well as an external UV detector. The polymer was analyzed in THF at a flow rate of 1 mL/min. The absolute number-average molecular weight (M_n) and polydispersity index (M_w/M_n) of the polymers were determined with the laser light scattering detector. Furthermore, SEC analysis in DMF was also used to determine the absolute number-average molecular weight

(M_n) and polydispersity index (M_w/M_n) of the deprotected polyglycidol with the laser light scattering detector.

^1H NMR spectroscopy analysis served to determine the acetylation level of the grafting substrates, and to detect the chain ends in reactions using the bifunctional organolithium initiator. This method was also used to determine the composition of the amphiphilic polystyrene-polyglycidol copolymers, and to confirm the introduction of alkyne and azide groups. The NMR spectra were recorded in CDCl_3 at a concentration of ca. 10 mg/mL on a Bruker-300 nuclear magnetic resonance spectrometer.

Chapter 5

Results and Discussion

5.1 Linear Polymers

5.1.1 Linear Polystyrene and Acetylation

The linear polystyrene sample obtained by anionic polymerization in toluene had a number-average molecular weight $M_n = 5200$ g/mol and a narrow molecular weight distribution ($M_w/M_n = 1.04$) by size exclusion chromatography (SEC) analysis in THF, as shown in Figure 5.1. Acetylation of that sample was performed with acetyl chloride and $AlCl_3$ in nitrobenzene according to a known procedure,⁵² yielding a grafting substrate with an acetylation level of 25 mole %, determined by 1H NMR spectroscopy analysis as shown in Figure 5.2.

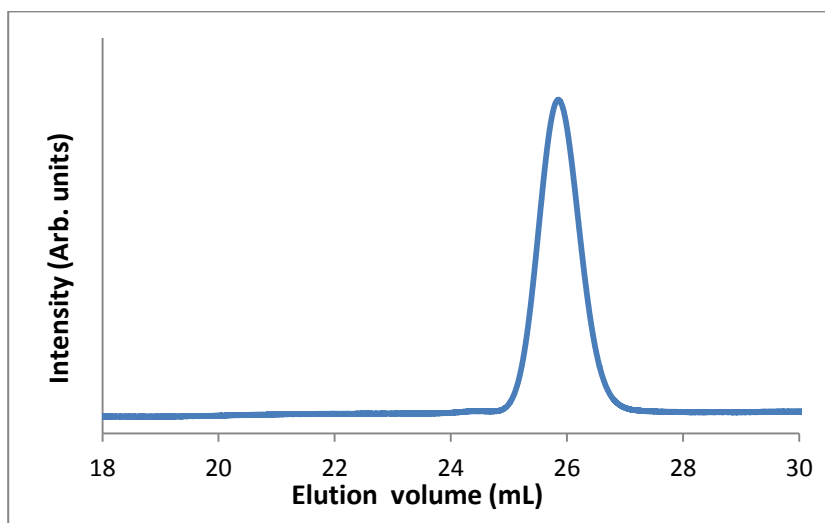


Figure 5.1 SEC analysis of linear polystyrene product

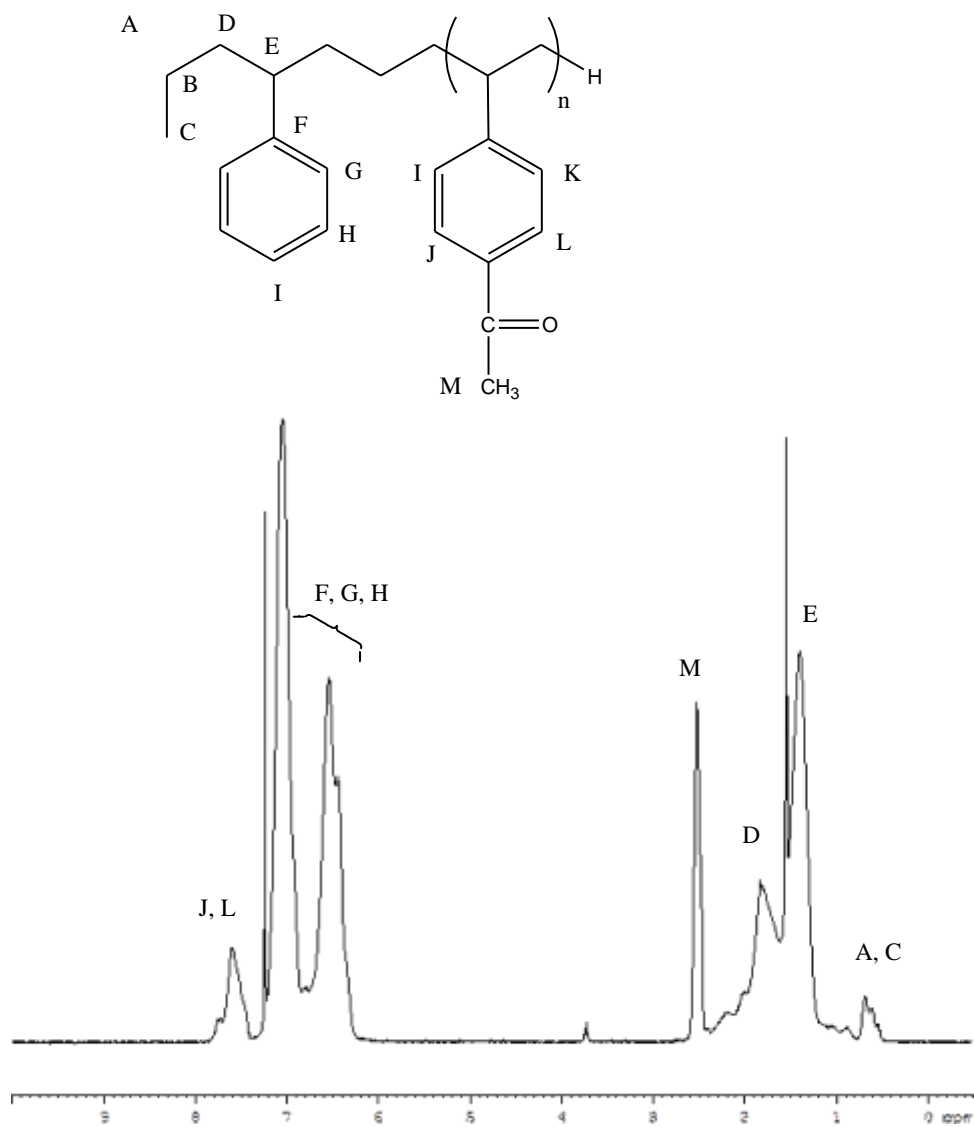


Figure 5.2 ^1H NMR spectrum for 25 mole % acetylated polystyrene

The introduction of the acetyl group causes two new resonances at δ 2.52 ppm (methyl protons of the acetyl group) and δ 7.59 ppm (phenyl protons ortho to the acetyl group). The functionalization level is easily controlled by adding nearly stoichiometric amounts of AlCl_3 and acetyl chloride in the reaction.

The use of the acetylation reaction rather than chloromethylation with methyl ether (CMME) has various advantages. First of all, acetyl chloride is less harmful than CMME. Second, the introduction of functional groups in acetylation is more easily controlled than in the chloromethylation reaction, which requires a large excess of CMME. This approach leads to the deactivation of variable amounts of catalyst. Finally, chloromethylation is prone to cross-linking, while acetylation is not.

5.1.2 Hydroxyl-functionalized Linear Polymer

The linear polystyrene sample with a hydroxyl chain end was obtained from the bifunctional organolithium initiator (TBDMS-O-Hexyl-Li), by anionic polymerization in toluene. It had a number-average molecular weight $M_n = 4200$ g/mol and a narrow MWD ($M_w/M_n = 1.07$) by SEC analysis in THF, as shown in Figure 5.3.

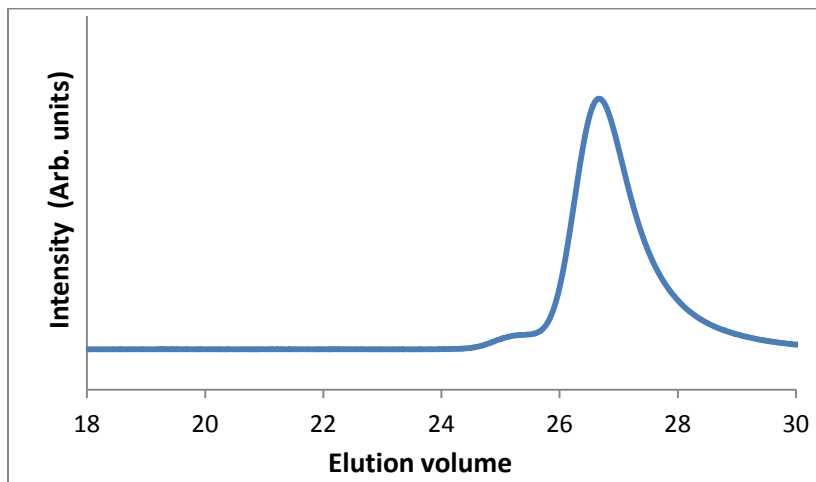
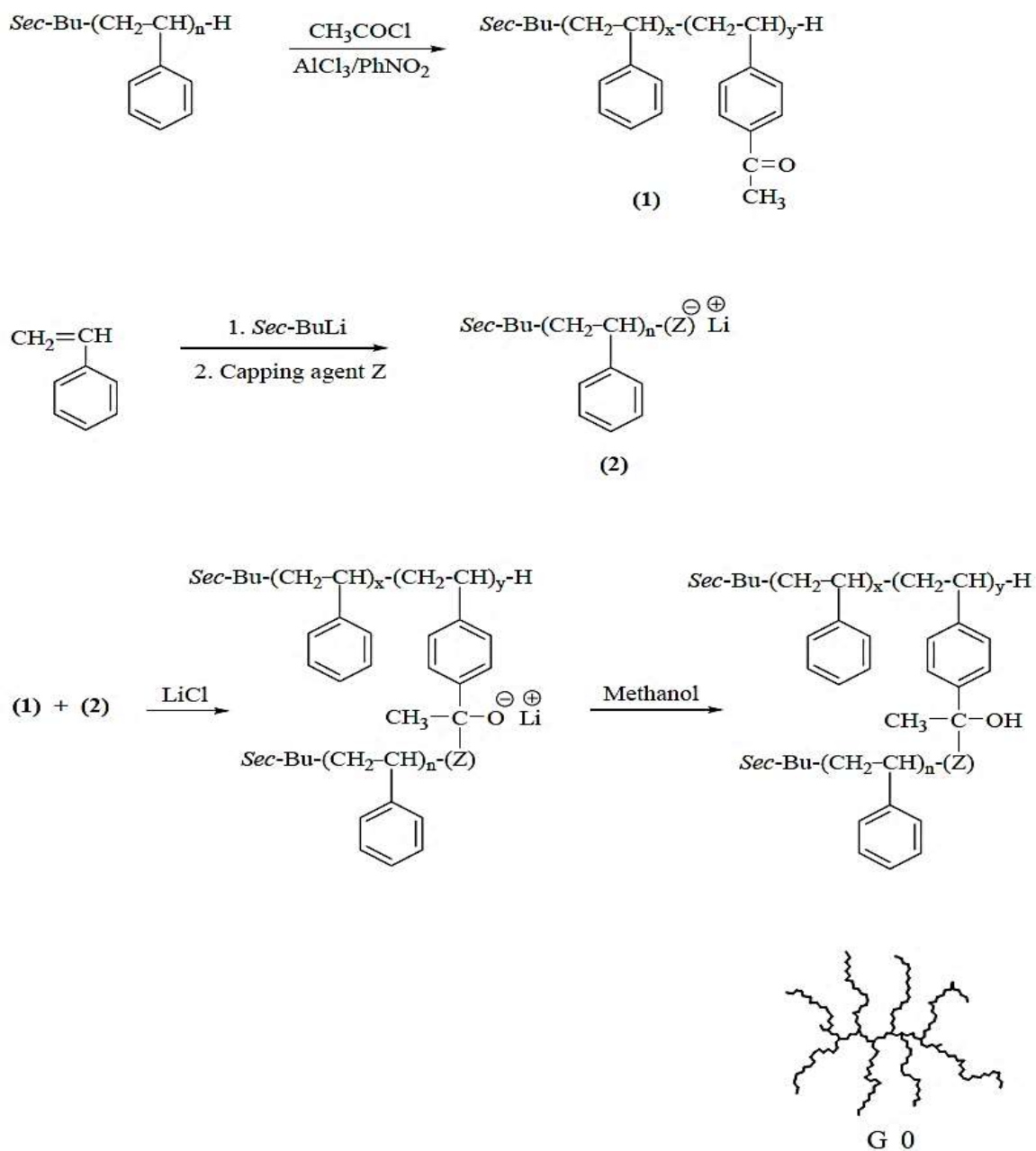


Figure 5.3 SEC analysis of hydroxyl-functionalized linear polystyrene

5.2 Graft Polymers

5.2.1 Arborescent Polystyrenes

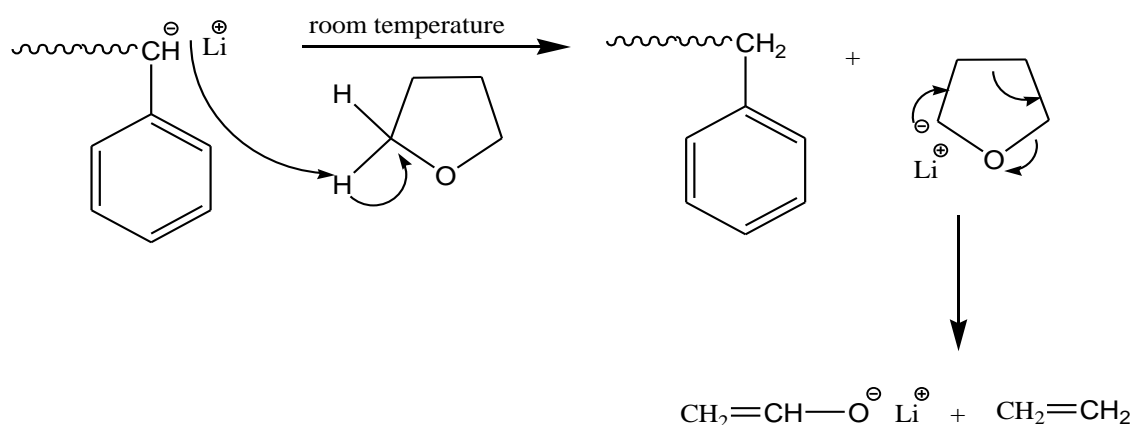
The synthesis of arborescent polymers involves three main steps. First of all, the substrate is acetylated to introduce coupling sites. Second, the polymerization of styrene with *sec*-butyllithium generates living polystyryllithium. Third, the living polymer is coupled by titration with the acetylated polystyrene substrate. The coupling reaction between the polystyryllithium species and acetylated polystyrene involves nucleophilic addition on the carbonyl group of the macroanions capped with 4 equivalents of 2-vinylpyridine (2VP), for side chains with a total $M_n = 5000$ g/mol as described in Scheme 5.1.



Scheme 5.1 Grafting reaction of acetylated polystyrene with capped polystyryllithium the capping agent Z is 2VP⁹

To maximize the grafting yield, defined as the fraction of living chains becoming attached to the substrate, optimized conditions were used for the reaction of the macroanions with the linear acetylated polystyrene substrate.⁴⁹ These correspond to a solvent mixture of toluene and THF, a grafting temperature of 0 °C, capping of the chains with 2VP, and the addition of LiCl to stabilize the living chain ends.

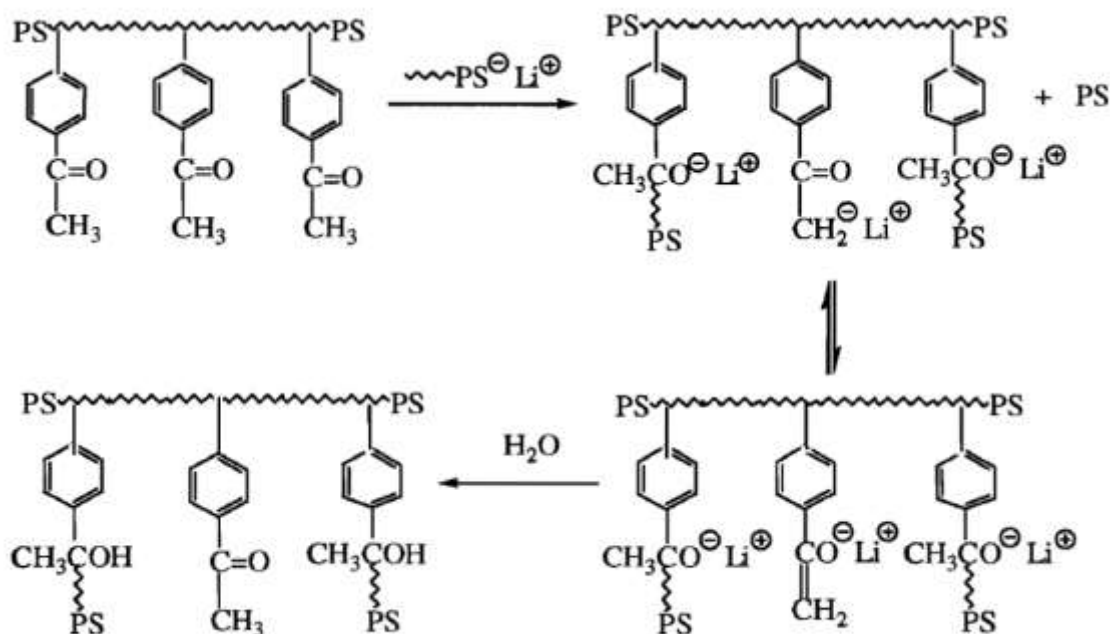
The grafting reaction was performed in a toluene/THF solvent mixture. Styrene was first polymerized with *sec*-butyllithium in toluene at 0 °C. After cooling to -78 °C, THF was added to increase the polymerization rate. Cooling must be used to avoid side reactions such as chain transfer to THF, which occurs at room temperature as shown in Scheme 5.2.



Scheme 5.2 Chain transfer to THF at room temperature

Because the polystyryl anions are highly reactive, they are sensitive to a number of side reactions such as protonation by the solvent leading to termination. The carbonyl functionality of acetylated polystyrene provides a site for nucleophilic addition in the grafting reaction, but it also

makes the methyl protons of the acetyl group acidic. Consequently, these protons are sensitive to abstraction by attack of the polystyryl macroanions, which leads to the formation of the corresponding enolate and chain termination rather than the desired coupling reaction, as shown in Scheme 5.3.



Scheme 5.3 Proton abstraction competing with nucleophilic addition in the synthesis of arborescent polystyrene⁵²

The method developed to avoid this side reaction is by capping the living polymer chains with a few 2VP units. End-capping reduces the reactivity of polystyryl anions about 100- to 1000-fold, thus making the living chain ends less likely to abstract a proton from the solvent or the acetylated substrate.⁵²

Furthermore, the addition of a salt to an anionic polymerization reaction can greatly reduce its propagation rate (or the reactivity of the living ends), by shifting the ion pair-free ion dissociation equilibrium in favor of ion pairs. These ion pairs have a very low reactivity (or a high stability) as compared with the free ions. Consequently the addition of LiCl to the grafting reaction further increases the grafting yield.

Analysis of the crude G0 product by SEC yielded $M_n = 71,000$ g/mol and $M_w/M_n = 1.13$ (Figure 5.4). The grafting reaction of polystyryllithium chains onto linear acetylated polystyrene was successful albeit the grafting yield, calculated from the ratio of the peak area for the graft polymer (leftmost, highest molecular weight peak) to the total peak area for the graft polymer and the linear chains, was only 84%. The rightmost peak on Figure 5.4 corresponds to linear chains deactivated by residual impurities present in the acetylated polystyrene solution or in the capping agent solution, or to chain deactivation according to the mechanism shown in Scheme 5.3. Essentially complete removal of the non-grafted side chains was achieved after 3 fractionation cycles (Figure 5.5). Precipitation fractionation is a procedure in which the crude polymer is dissolved in a good solvent (toluene), and a non-solvent (methanol) is added to selectively precipitate the less soluble, high molecular weight graft polymer while the more soluble linear polymer component is left in solution.

The number-average branching functionality (f_n) of the arborescent polymer, defined as the number of side chains added in the grafting reaction, can be calculated from the equation

$$f_n = \frac{Mn(G) - Mn(G-1)}{M_n^{br}} \quad (5.1)$$

where $M_n(G)$ and $M_n(G-1)$ represent the absolute number-average molecular weight of the G0 and linear polymers, respectively, and M_n^{br} is the number-average molecular weight of the side chains grafted. Since the linear substrate, the G0 polymer, and the side chains had M_n values of 4770, 71,000, and 5100 g/mol, respectively, a branching functionality $f_n = 13$ was obtained for the G0 polymer.

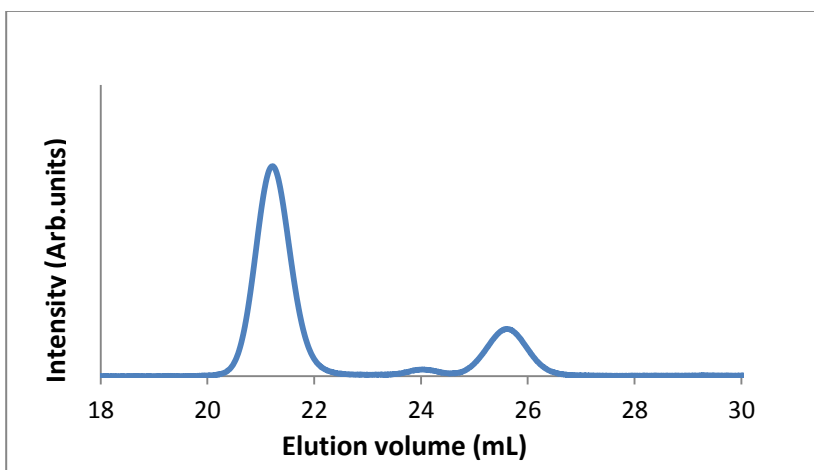


Figure 5.4 SEC analysis of the crude G0 product

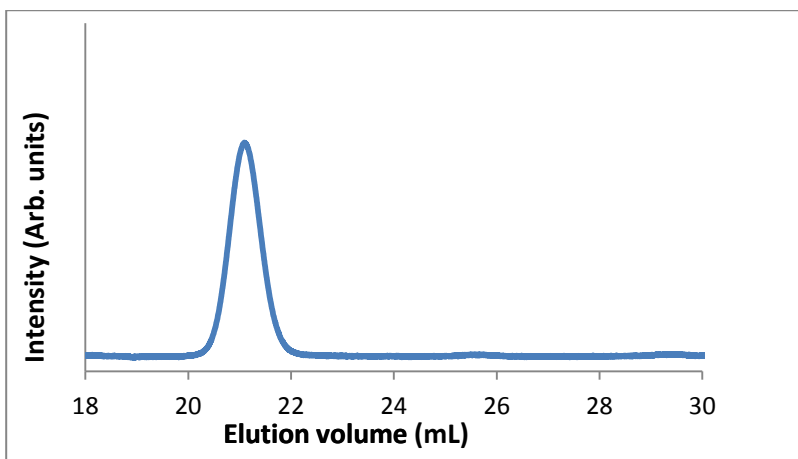


Figure 5.5 SEC analysis of the fractionated G0 product

The G1 arborescent graft polymer was obtained by acetylation of the G0 substrate ($M_n = 71,000$ g/mol) and coupling with linear side chains ($M_n = 5200$ mol/g). Analysis of the fractionated G1 product by SEC yielded $M_n = 733,000$ g/mol and $M_w/M_n = 1.06$, as shown in Figure 5.6. The grafting reaction of polystyryllithium chains onto the G0 acetylated polystyrene substrate proceeded with a grafting yield, calculated from the peak area ratio, of 78%. Removal of the non-grafted side chains was achieved after one fractionation cycle. Since the G0 substrate polymer, the G1 polymer, and the side chains had M_n values of 71,000, 733,000, and 5200 g/mol, respectively, a branching functionality $f_n = 127$ was obtained for the G1 polymer.

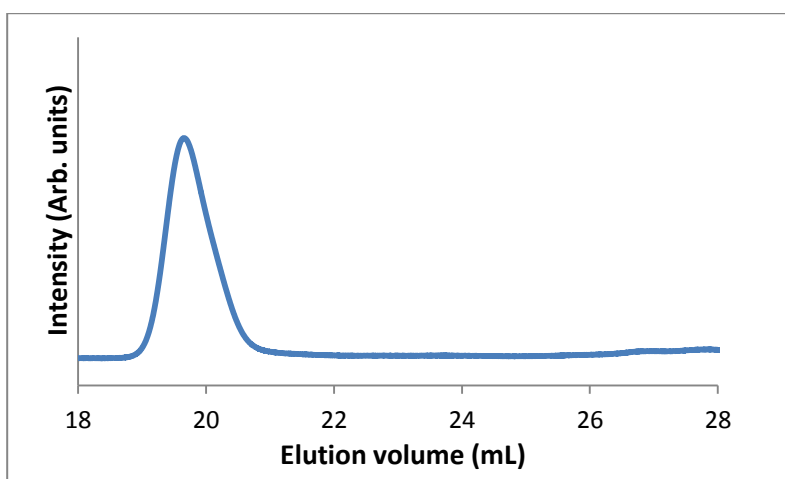
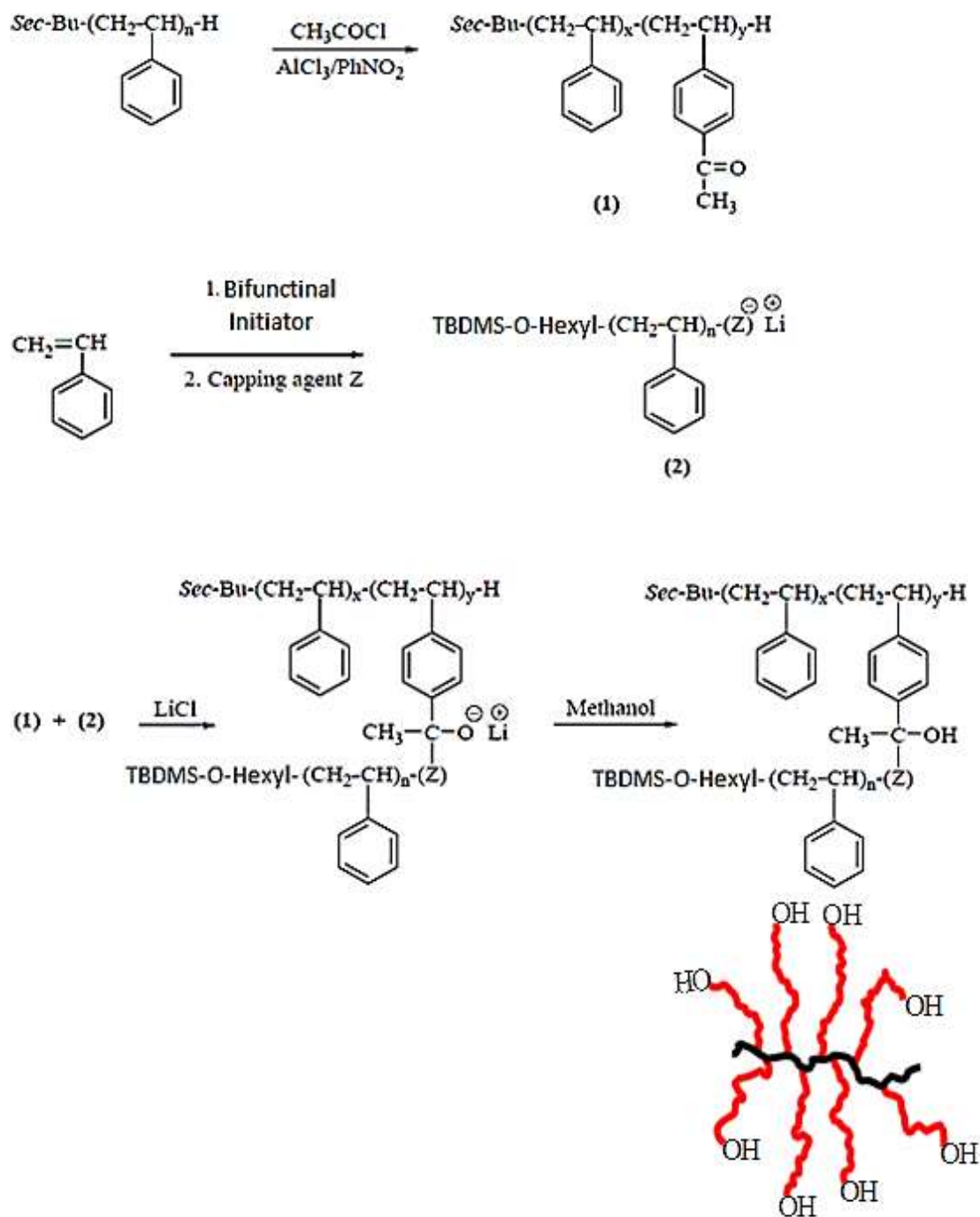


Figure 5.6 SEC analysis of the fractionated G1 product

5.2.2 Hydroxyl-functionalized Core Polymer

A G0 core polymer was synthesized to introduce functionalities acting as propagating centers for shell growth as shown in Scheme 5.4.



Scheme 5.4 Grafting reaction of acetylated polystyrene with capped polystyryllithium using the bifunctional initiator

In this case, the polystyryl anions were obtained from the bifunctional initiator TBDMS-O-Hexyl-Li, capped with 2VP, and coupled with the acetylated linear polystyrene substrate by the same method described for the synthesis of the G0 polymer, to yield a G0 polystyrene sample with protected hydroxyl groups. The ^1H NMR spectrum obtained for this G0 polymer (Figure 5.7) has signals characteristic for the chain ends at δ 3.53 ppm ($-\text{CH}_2\text{-O-Si-}$), δ 0.88 ppm (*tert*-Bu protons), and between δ 0.069-0.026 ppm (SiMe_2 protons).

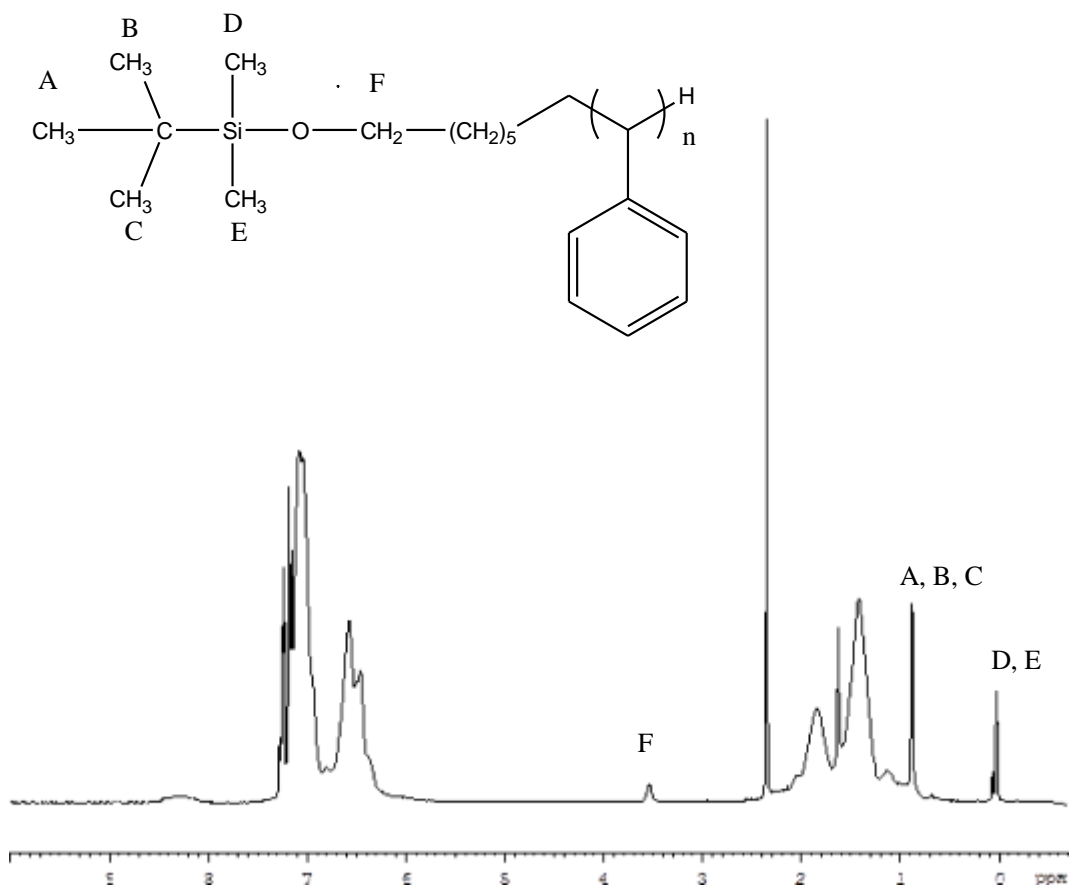


Figure 5.7 ^1H NMR spectrum for the G0 polymer with hydroxyl end groups

The grafting reaction was successful for the hydroxyl-functionalized G0 polymer (86% grafting yield), as confirmed by SEC analysis of the crude product shown in Figure 5.8. The G0 graft polymer had $M_n = 88,000$ g/mol and $M_w/M_n = 1.09$. The $M_n^{br} = 5400$ g/mol measured for the side chains and $M_n = 4770$ g/mol for the linear substrate yielded a branching functionality $f_n = 16$ for the hydroxyl-functionalized G0 substrate. Complete removal of the non-grafted side chains could be achieved after 3 cycles of precipitation fractionation (Figure 5.9).

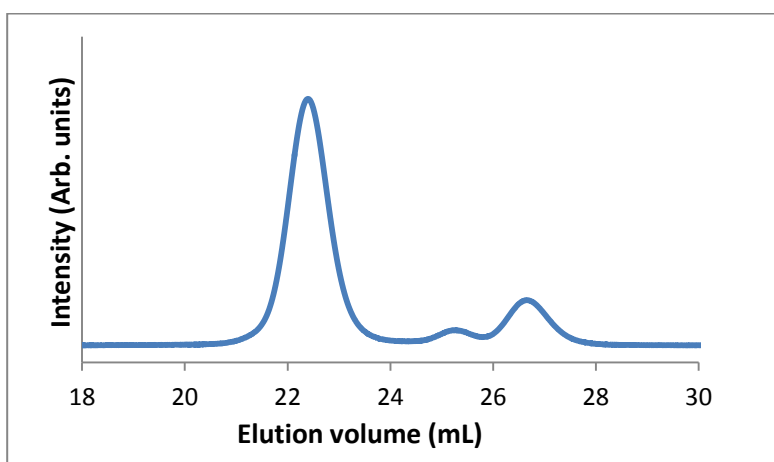


Figure 5.8 SEC analysis of the crude G0 hydroxyl-functionalized polymer

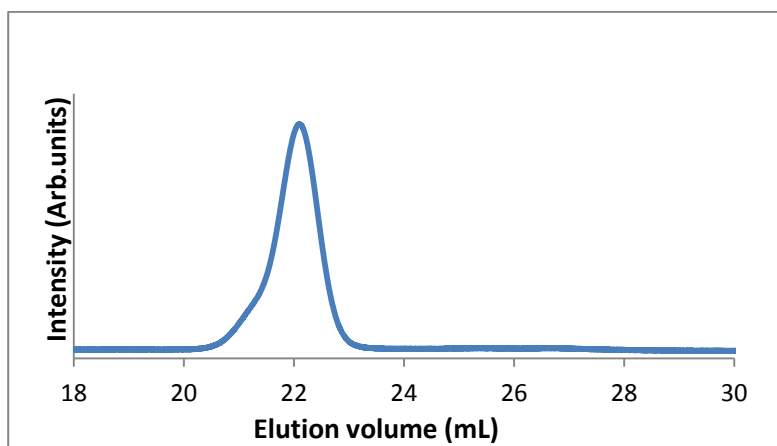


Figure 5.9 SEC analysis of fractionated G0 hydroxyl-functionalized polymer

A hydroxyl-functionalized G1 core polymer was obtained by the same method using a G0 acetylated substrate. However, the grafting reaction was slightly more successful in terms of avoiding side reactions for the hydroxyl-functionalized G1 polymer (80 % grafting yield) as compared to the G0 arborescent sample, as confirmed by SEC analysis of the crude product. The G1 graft polymer had $M_n = 501,000$ g/mol and $M_w/M_n = 1.2$. Since the side chains had $M_n^{br} = 4300$ g/mol and the arborescent G0 substrate had $M_n = 71,000$ g/mol, the branching functionality of the hydroxyl-functionalized G1 polymer was $f_n = 100$. One cycle of precipitation fractionation removed most of the non-grafted side chains, as shown in Figure 5.10.

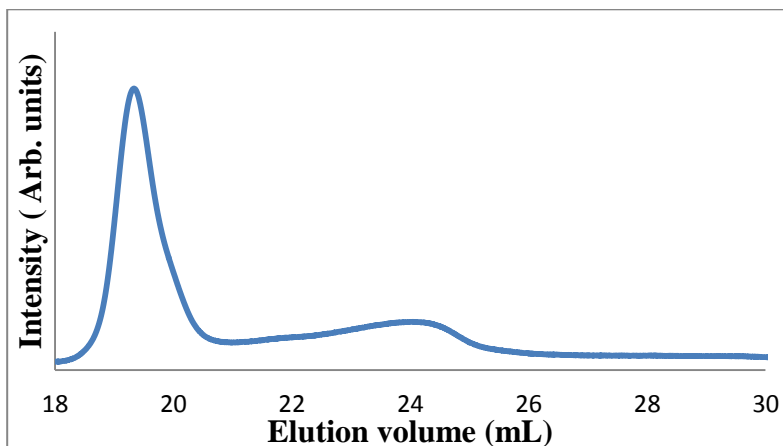
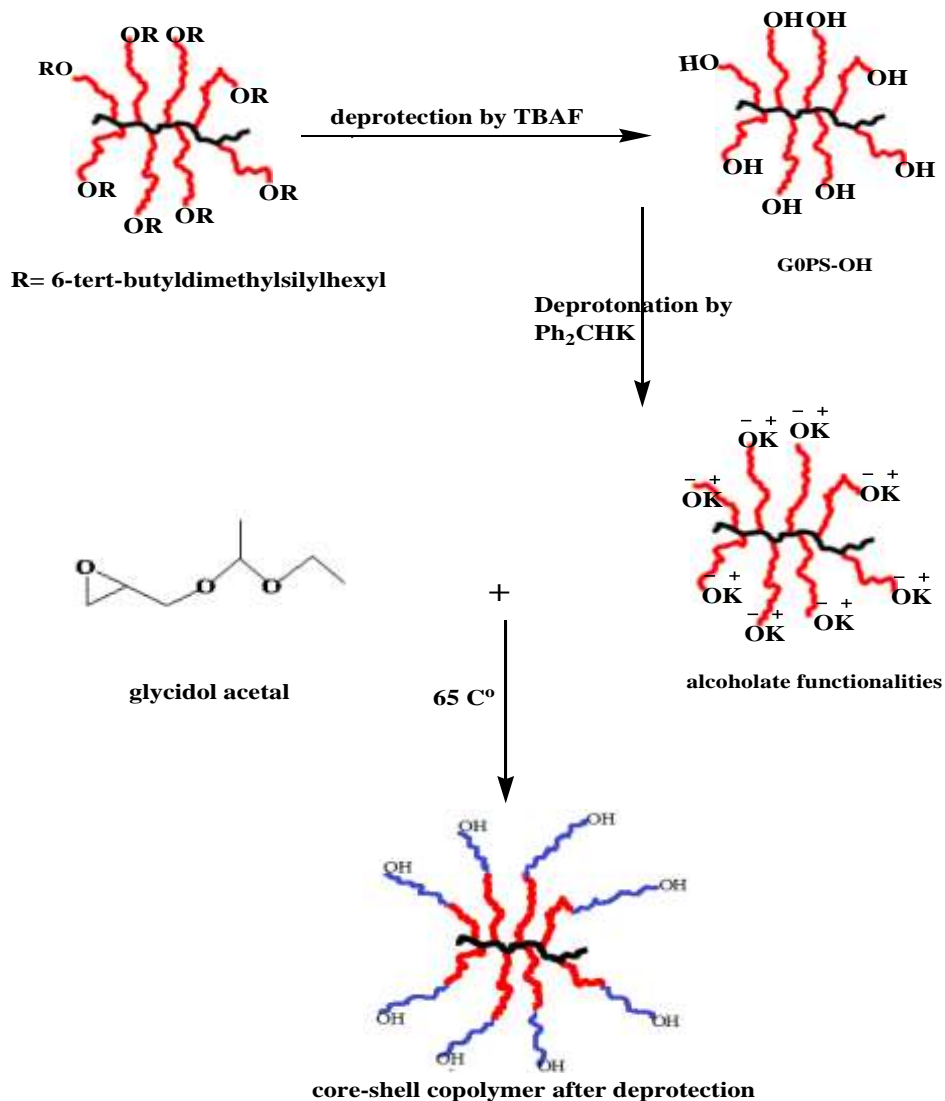


Figure 5.10 SEC analysis of fractionated G1 hydroxyl-functionalized polymer

5.3 Copolymers of Styrene and Glycidol Acetal

The amphiphilic polystyrene-*graft*-polyglycidol copolymers could be synthesized by either *grafting from* or *grafting onto* techniques. The synthesis of these copolymers, as originally

planned for the current project, involved three main steps: The synthesis of an arborescent core with hydroxyl chain ends; activation of the hydroxyl sites by deprotonation to generate living ends; and the anionic polymerization of glycidol acetal to allow the growth of the chains forming the shell, as described in Scheme 5.5.

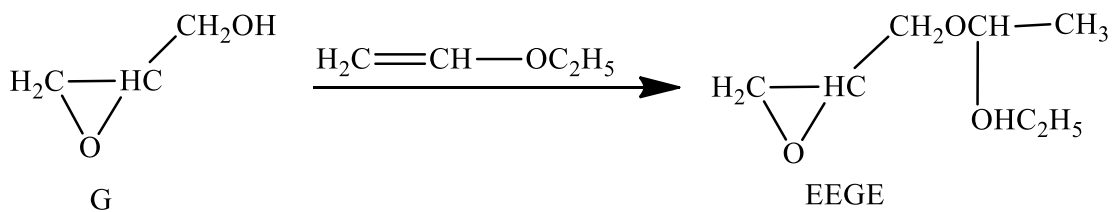


Scheme 5.5 Schematic overview of the polystyrene-*graft*-polyglycidol copolymers synthesis by a combination of *grafting onto* and *grafting from* techniques

The scheme shows that the hydroxyl-functionalized polystyrene serving as hydrophobic core is synthesized by the anionic polymerization and grafting techniques discussed earlier. The synthesis of the polyglycidol chains serving as hydrophilic shell material was attempted by the *grafting from* technique, using the core as an anionic initiator for ring-opening polymerization.

5.3.1 Synthesis of Glycidol Acetal

The synthesis of 2,3-epoxy-1-(1-ethoxyethoxy)propane (glycidol acetal) was achieved via the technique reported by Fitton et al.,⁶³ as shown in Scheme 5.6. The ¹H NMR spectrum obtained (seen in Figure 5.11) confirmed the structure and the purity of the product.



Scheme 5.6 Synthesis of 2,3-epoxy-1-(1-ethoxyethoxy)propane (glycidol acetal)

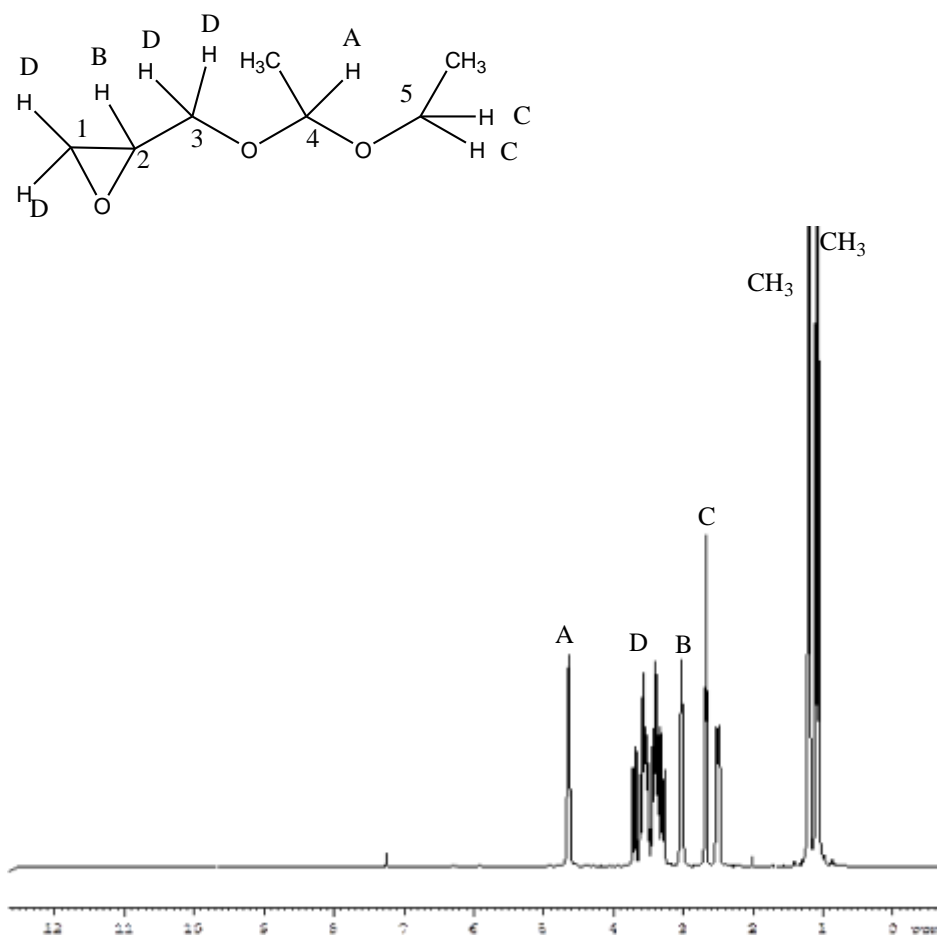
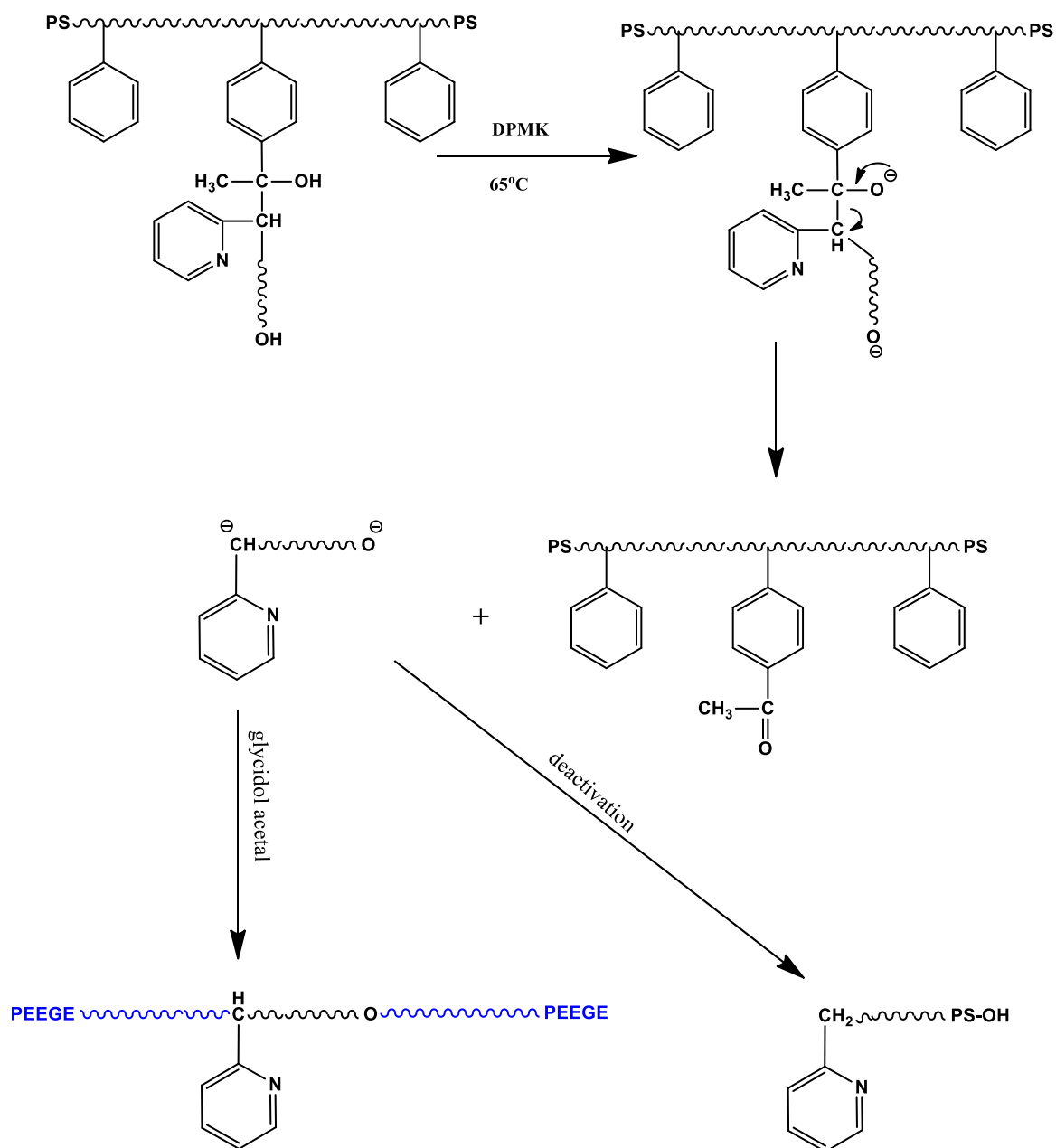


Figure 5.11 ^1H NMR spectrum for the glycidol acetal monomer

A large amount of ethyl vinyl ether was used in the reaction as reagent and as solvent, providing a yield of 85%. The protection reaction results in the formation of a chiral center in the monomer. The ^1H NMR spectrum of the monomer shows that the acetal proton on the C4 carbon atom is centered at δ 4.75 ppm, and the methyl protons of the acetal group are at δ 1.3 ppm. The rest of protons are centered at δ 2.7 (C5, 2HC and methyl protons), δ = 3.1 (C2, 1HB) and δ = 3.6 (C1 and C3, 4HD).

5.3.2 Synthesis of Amphiphilic Copolymers

The synthesis of the arborescent polystyrene substrates with hydroxyl end groups was discussed in Section 5.2.2, and yielded a well-defined G0 polymer with $M_n = 88,000$ g/mol and PDI = 1.09 (Figure 5.12). The living chains ends to initiate the polymerization of the glycidol acetal monomer were generated by deprotonating the hydroxyl end groups with diphenylmethylpotassium (DPMK), yielding alcoholate functionalities. The growth of the polyglycidol segments by ring opening polymerization was attempted at 65 °C over 48 h. Unfortunately, analysis by SEC of the crude product obtained by this method yielded unexpected results. While the polymerization of glycidol did occur, it did not result in the formation of a well-defined core-shell copolymer but rather in extensive cleavage of the side chains from the branched structure, characterized by a bimodal MWD (Figure 5.13). It is hypothesized that DPMK deprotonated not only the primary hydroxyl group at the side chain ends but also the secondary alcohols at the branching points, as shown in Scheme 5.7. This served as starting point for a reverse aldol reaction leading to chain cleavage as shown.



Scheme 5.7 The proposed mechanism for the cleavage of side chains from the branched polymer

After cleavage, two reaction paths exist for the macroanions formed. A large portion of the side chains may be deactivated during termination of the reaction with methanol, or otherwise by protic impurities. Second, the capped polystyryl macroanions formed with the hydroxyl-terminal side chains that may have been deprotonated, providing alcoholate initiating sites. These functions could initiate the polymerization of the glycidol acetal monomer, yielding polystyrene-*block*-polyglycidol copolymer chains.

The SEC analysis results for the crude product show that the molecular weight for the main peak of Figure 5.13 ($M_n = 4900$ g/mol; PDI=1.1) is much lower than for the polymer substrate before the reaction ($M_n = 88,000$ g/mol and PDI = 1.09, Figure 5.12). The molecular weight of the leftmost peak on Figure 5.13 is 9100 g/mol and PDI = 2.3. In other words, the SEC peak corresponding to the graft polymer shifted strongly to the right as the result of the extensive side chain cleavage reactions described in Scheme 5.7.

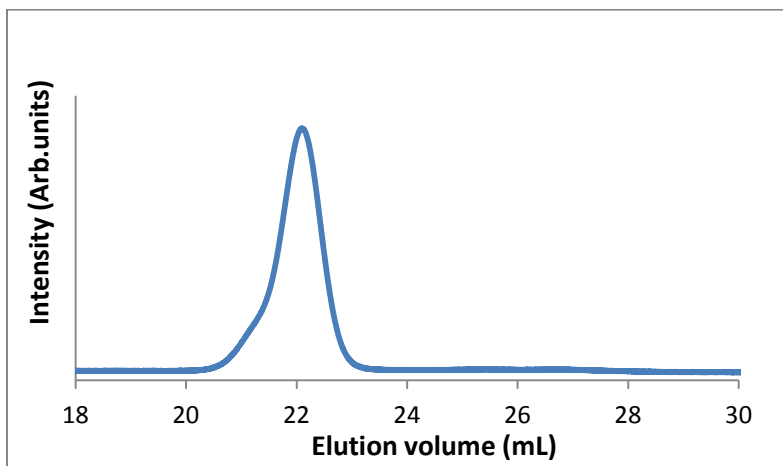


Figure 5.12 SEC analysis of fractionated G0 hydroxyl-functionalized polymer before the glycidol acetal grafting reaction

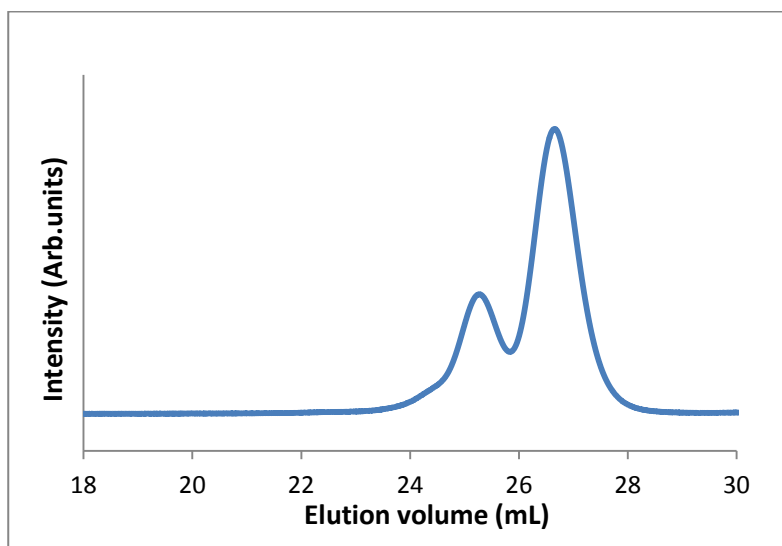


Figure 5.13 SEC analysis of the copolymer obtained after the addition of glycidol acetal

Analysis of the copolymer obtained by ^1H NMR spectroscopy (Figure 5.14) confirms the presence of both polystyrene and polyglycidol components in the crude product. While NMR analysis cannot provide support for the cleavage mechanism outlined in Scheme 5.7 (due to the low concentration of the specific signals of interest), it clearly shows that the growth of polyglycidol segments occurred. The experiments were repeated three times and gave identical results, further confirming the occurrence of chain cleavage.

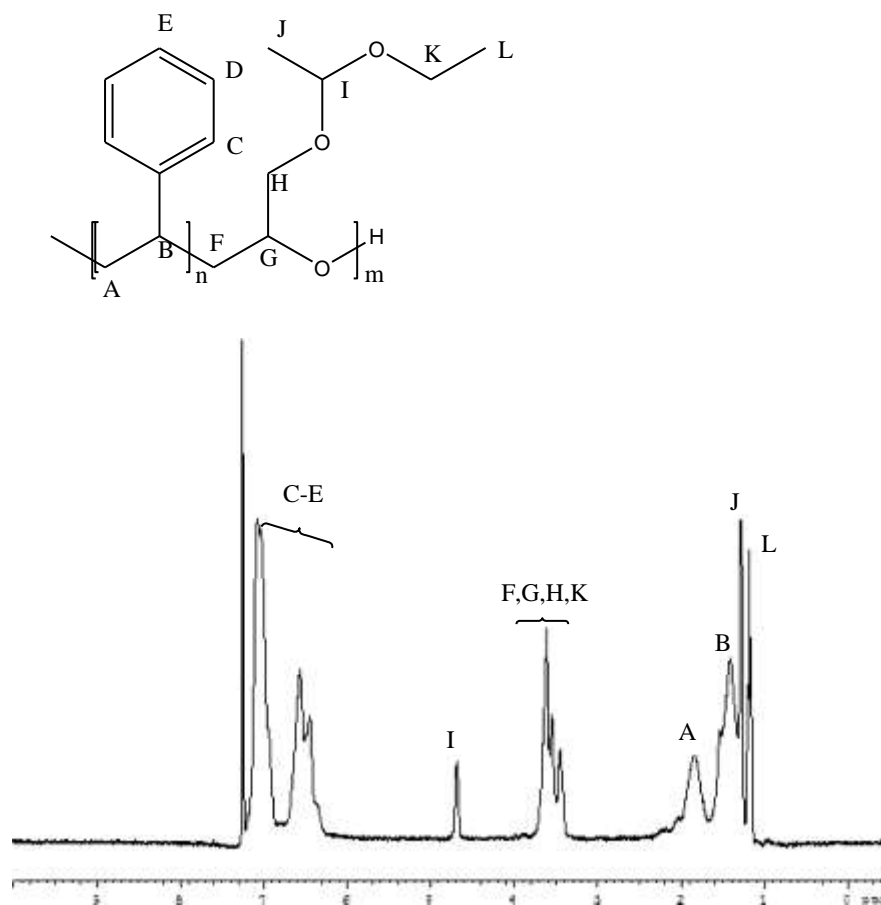


Figure 5.14 ¹H NMR spectrum for crude polystyrene-*block*-poly(glycidol acetal) copolymer in CDCl₃

Furthermore, the same method described for the synthesis of the amphiphilic arborescent copolymers, when used for the synthesis of linear amphiphilic polystyrene-*block*-poly(glycidol acetal) copolymers starting from a linear hydroxyl-functionalized polystyrene substrate, was successful. The SEC trace of Figure 5.15 for the linear hydroxyl-functionalized polystyrene yielded a number-average molecular weight $M_n = 4200$ g/mol and a PDI = 1.07. The addition of glycidol acetal led to a product with $M_n = 14,000$ g/mol and a PDI = 1.12, determined by SEC analysis in THF (Figure 5.16).

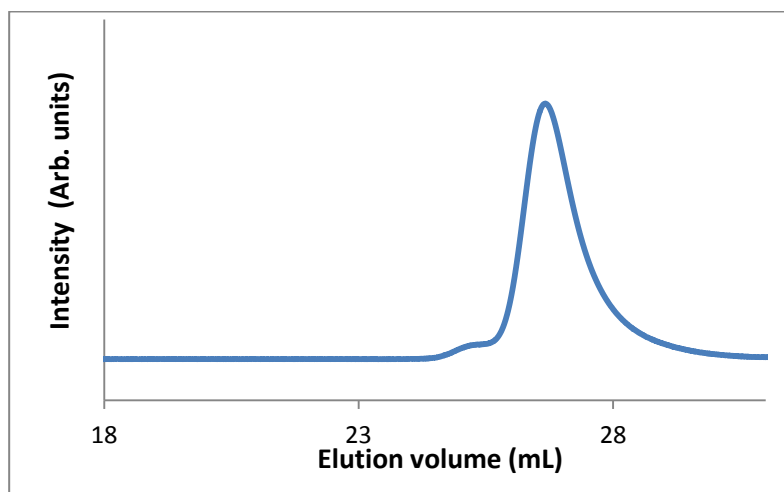


Figure 5.15 SEC analysis of hydroxyl-functionalized linear polystyrene substrate

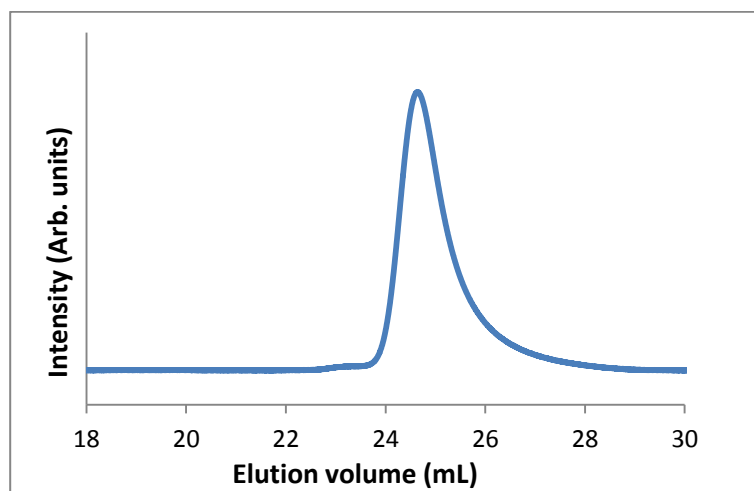


Figure 5.16 SEC analysis of polystyrene-*block*-poly(glycidol acetal) copolymer

5.4 Synthesis of Amphiphilic Copolymers by Click Reaction

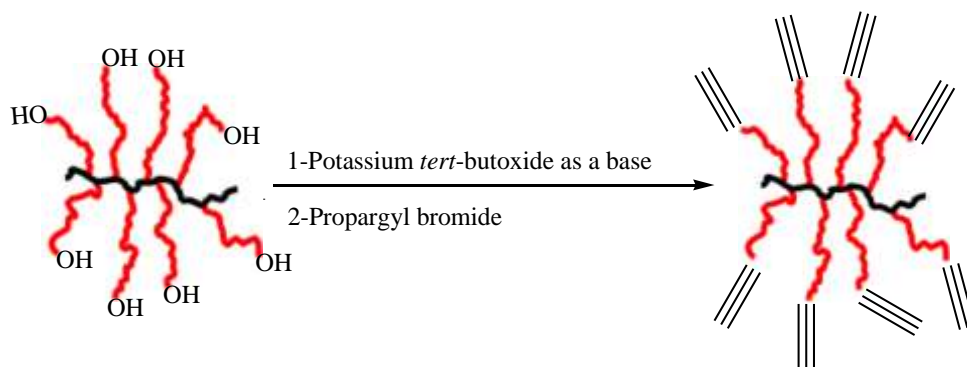
An alternate method developed for the synthesis of amphiphilic arborescent copolymers was also based on the anionic polymerization of glycidol acetal, in combination with the hydroxyl-

functionalized arborescent polystyrene substrates. In this case however, a coupling reaction with click chemistry was used for the addition of the hydrophilic shell segments, through the 1,3-dipolar cycloaddition of terminal alkynes with azides.

5.4.1 Modification of Hydroxyl-functionalized Polystyrene Substrates

The azide-alkyne coupling reaction was first tested in the synthesis of linear block copolymers. To this end, the polymerization of styrene was performed at 0 °C in toluene using the bifunctional initiator (TBDMS-O-Hexyl-Li) to obtain linear polystyrene with terminal hydroxyl groups.

In the first step, the terminal hydroxyl groups of the polystyrene substrate were used in a nucleophilic substitution reaction to generate alkyne chain ends as shown in Scheme 5.8, following a procedure reported by Huang.⁹³ This was achieved using potassium *tert*-butoxide as a base to deprotonate the hydroxyl chain ends, and the addition of propargyl bromide. The success of the reaction was confirmed by ¹H NMR analysis, showing the presence of the alkyne end group in Figure 5.17, through a weak resonance for CH₂-O at δ 1.3 ppm and a new signal assigned to the alkyne proton at 4.1 ppm.



Scheme 5.8 The modification of arborescent polystyrene with alkyne terminal groups

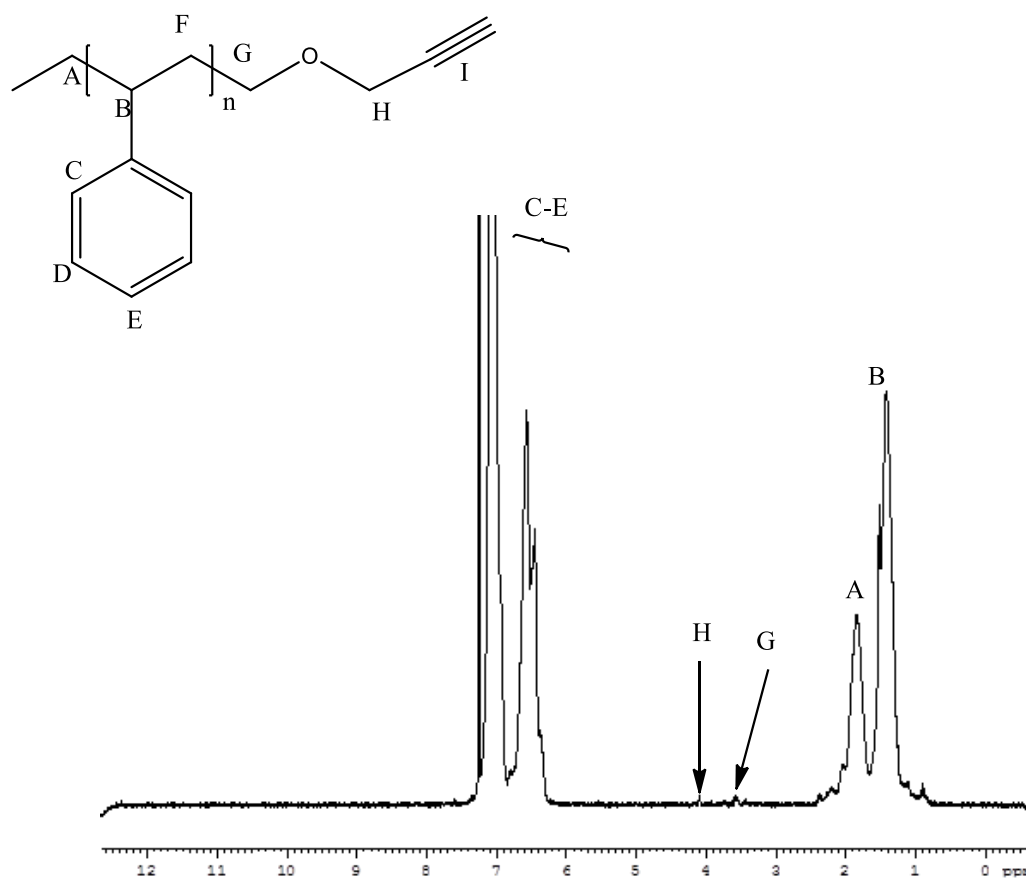
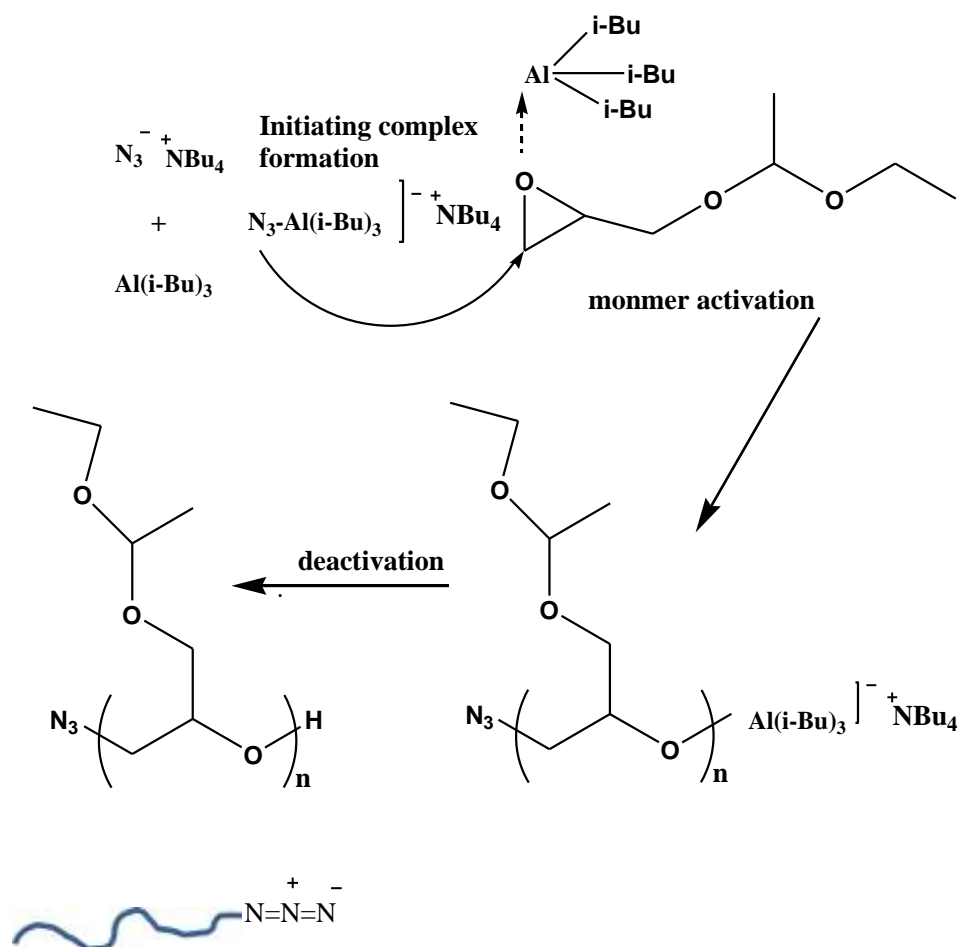


Figure 5.17 ^1H NMR spectrum for polystyrene with alkyne end groups

5.4.2 Synthesis of α -Azido Polyglycidol

α -Azido poly(glycidol acetal) was prepared by the monomer-activated anionic polymerization technique,⁶¹ using tetrabutylammonium azide as initiator in the presence of triisobutylaluminum as activator. The excess of activator used with respect to the initiator ($[i\text{-Bu}_3\text{Al}]/[n\text{-Bu}_4\text{N}_3] = 5$) allowed the synthesis of polyglycidol with controlled high molecular weight (M_n of up to 12000 g/mol) in a few hours. The initiation of glycidol acetal was performed at $-30\text{ }^\circ\text{C}$ in toluene; after a few minutes the temperature was allowed to increase to room temperature. Scheme 5.9 shows that the reaction involves strong activation of the oxirane ring on the monomer by the Lewis acid ($i\text{-Bu}_3\text{Al}$) via complexation.



Scheme 5.9 Mechanism of the reaction for the preparation of polyglycidol with azido end groups

The presence of an azido group was confirmed by ^1H NMR spectroscopy analysis CDCl_3 before deprotection of the acetal (Figure 5.18) and after deprotection (Figure 5.19, using DMSO).

The SEC analysis results, shown in Figure 5.20, serve to determine a molecular weight $M_n = 12,000$ g/mol and a PDI = 1.13 for the polymer. The protecting groups were removed with

hydrochloric acid, after which the polymer had a molecular weight dropping to $M_n = 6,000$ g/mol and a PDI = 1.11 as shown in Figure 5.21.

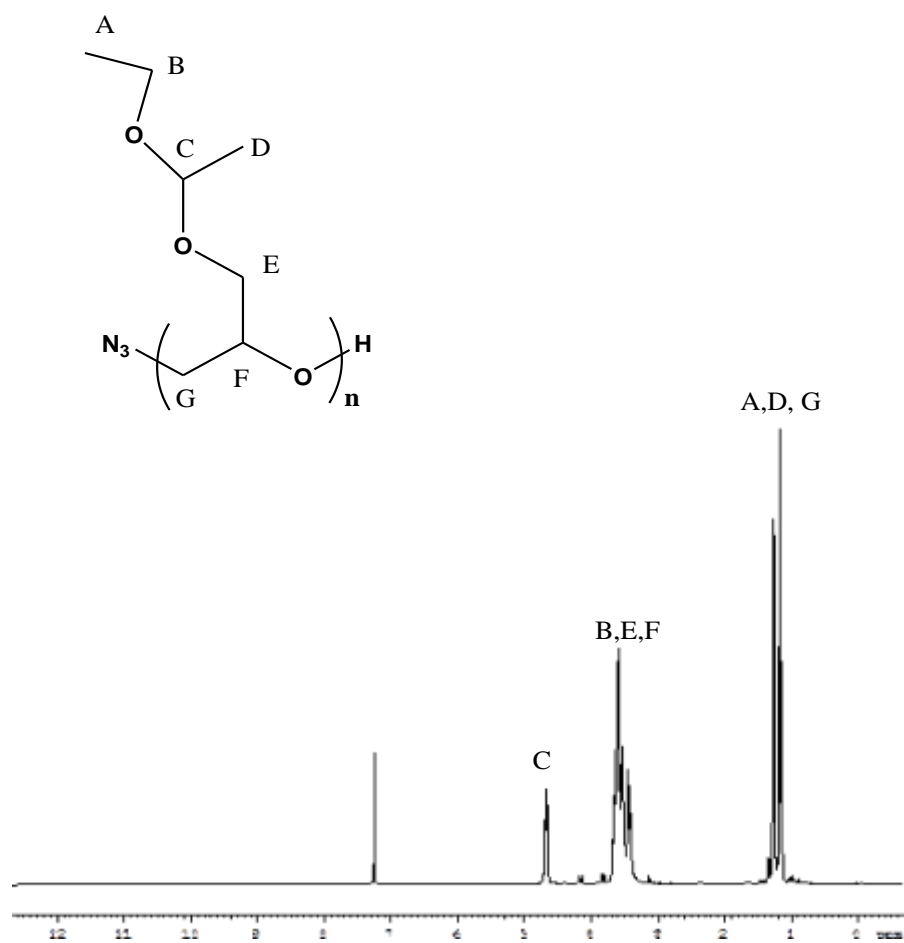


Figure 5.18 ^1H NMR spectrum in CDCl_3 for poly(glycidol acetal) with azide end groups

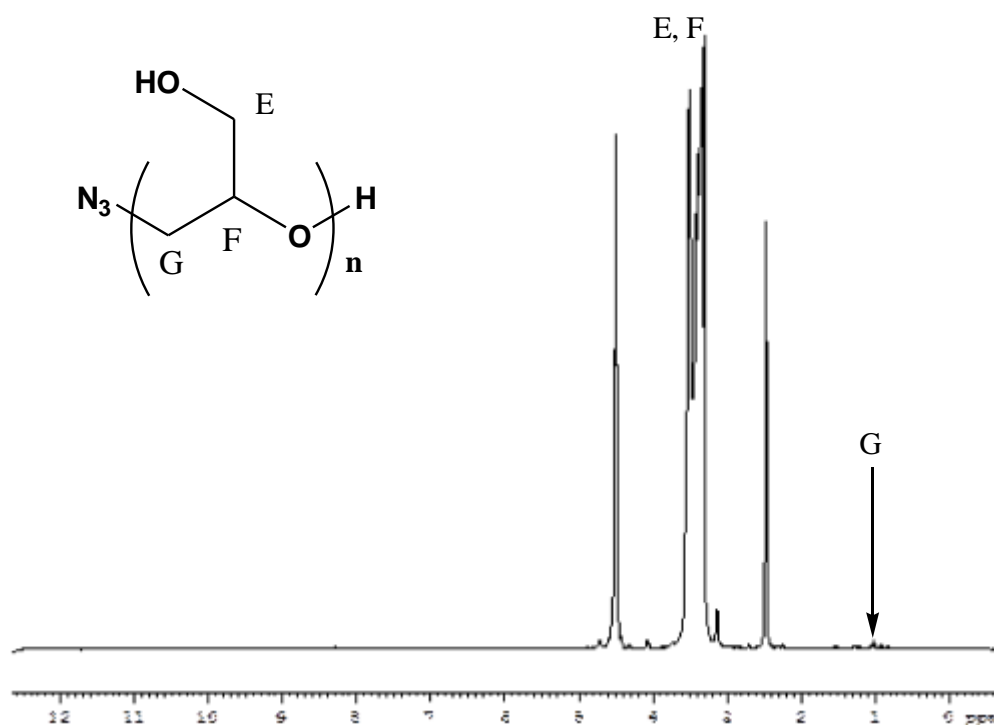


Figure 5.19 ^1H NMR spectrum for polyglycidol in DMSO-d_6 after deprotection

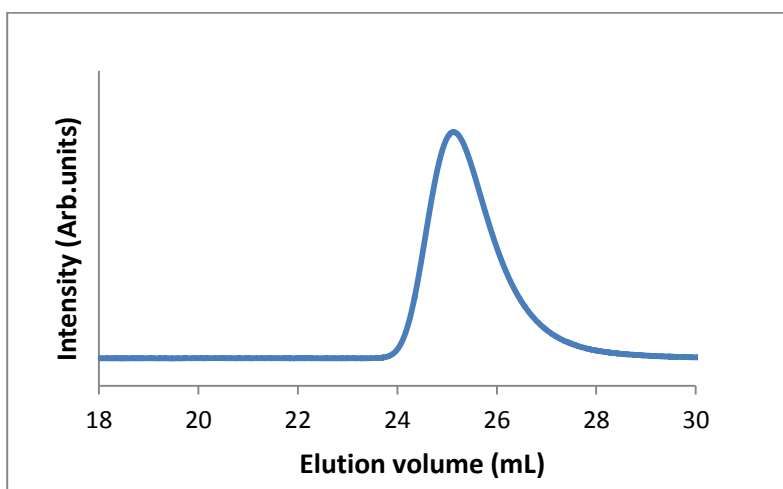


Figure 5.20 SEC analysis of the α -azido poly(glycidol acetal) side chains in THF before deprotection

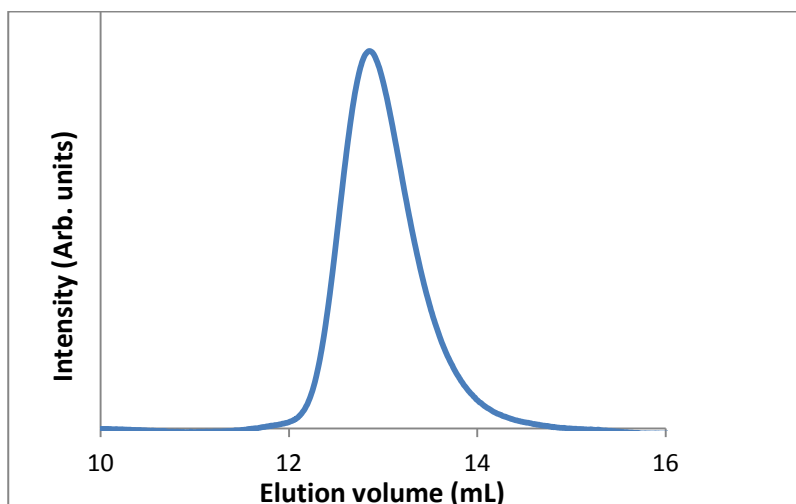
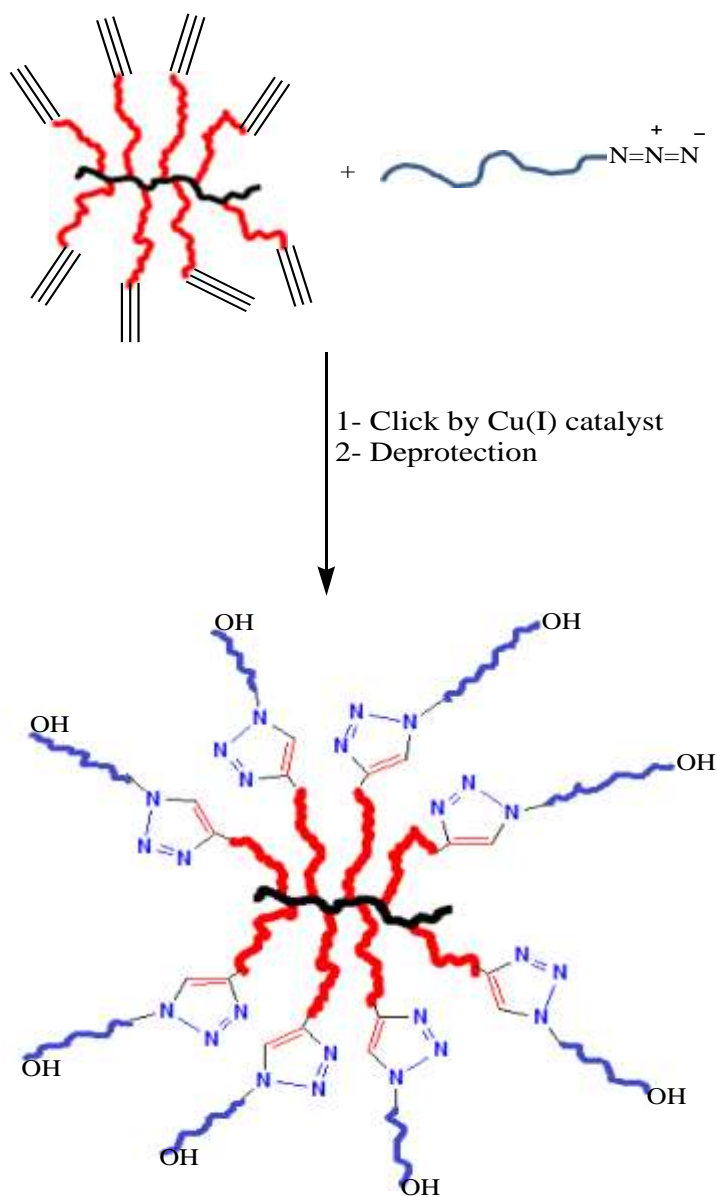


Figure 5.21 SEC analysis of the α -azido polyglycidol side chains in DMF after deprotection

5.4.3 Click Polymers

The copper(I)-catalyzed 1,3-dipolar cycloaddition of azide- and alkyne-terminated polymers was briefly explored for the preparation of amphiphilic diblock and core-shell arborescent copolymers. The well-defined linear and arborescent building blocks with alkyne functionalities at the chain ends, and poly(glycidol acetal) with azide chain ends were both synthesized by anionic polymerization. The click reaction between the alkyne-functionalized polystyrenes and azido polyglycidol in the presence of Cu(I) should yield only the 1,4-disubstituted triazole isomer under the reaction conditions shown in Scheme 5.10.⁷⁵



Scheme 5.10 Click reaction of alkyne-functionalized polystyrene and azide-functionalized polyglycidol

The synthesis and the modification of the linear and arborescent polystyrene substrates with alkyne end groups was discussed in Sections 5.1.2, 5.2.2 and 5.4.1, and yielded well-defined polymers with molecular weights $M_n = 4200$ and $88,000$ g/mol, respectively. On the other hand,

the synthesis of the linear of polyglycidol with azide end groups was discussed in Section 5.4.2. The coupling of these polystyrene substrates with the polyglycidol segments by click reactions was attempted at 40 °C over 48 h.

Analysis of the fractionated copolymer products by SEC in DMF yielded $M_n = 10,200$ with PDI = 1.2 and 177,000 g/mol with PDI = 1.28, as shown in Figures 5.22 and 5.23 for the amphiphilic polystyrene-*block*-poly(glycidol acetal) and G0 arborescent amphiphilic polystyrene-poly(glycidol acetal) copolymers, respectively.

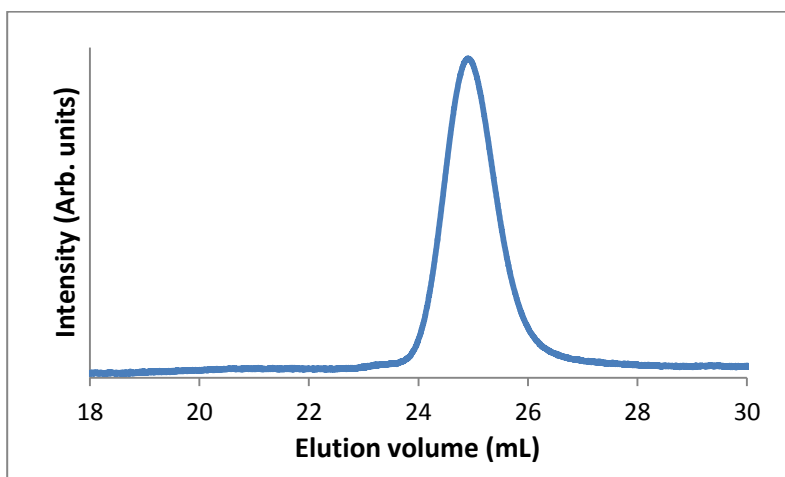


Figure 5.22 Amphiphilic linear polystyrene-*block*-poly(glycidol acetal)

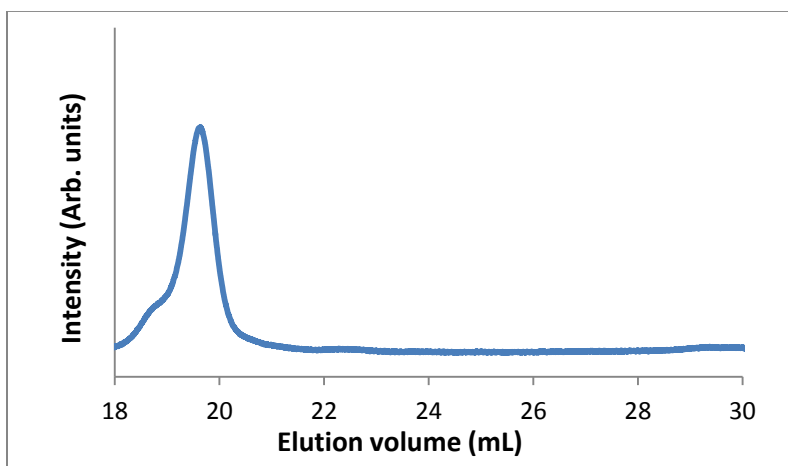


Figure 5.23 SEC analysis of fractionated G0 arborescent polystyrene-*graft*-poly(glycidol acetal) copolymer

Chapter 6

Conclusions and Future Work

6.1 Conclusions

Arborescent polystyrenes were synthesized through anionic polymerization and grafting procedures. The "graft-upon-graft" technique yielded samples with a high molecular weight and a narrow MWD in a few steps. The synthesis of arborescent polymers with hydroxyl groups at the chain ends was also demonstrated by initiating the polymerization of styrene with a bifunctional initiator, and coupling the living chains with acetylated polystyrene.

A "grafting from" technique was attempted to synthesize core-shell polymers with a shell of poly(glycidol acetal) chains, by titrating the hydroxyl groups on the core polymer with DPMK and adding the glycidol acetal monomer to the substrate. Unfortunately, this led to extensive cleavage of the chains on the substrate due to a reverse aldol reaction, so that this path could not be used as originally planned.

An alternate technique for the synthesis of the amphiphilic copolymers was developed based on click chemistry, by coupling polyglycidol side chains having an azide end groups with polystyrene substrates having alkyne groups at the chain ends in the presence of copper. While this approach could not be explored in as much detail as would have been desirable, due to time limitations, the preliminary results obtained by that method appear promising.

6.2 Future Work

To fully explore the potential of the novel amphiphilic arborescent structures synthesized, the following aspects of these molecules should be further explored:

1. To develop a method to remove the secondary alcohols present at the coupling sites of the arborescent polystyrene substrates obtained by the acetylation path. These indeed seem to be at the origin of the side chain cleavage reaction observed when the poly(glycidol acetal) side chains are grown via deprotonation with DMPK.
2. To synthesize two additional series of amphiphilic core-shell copolymers of generations G2 and G3 with 5000 g/mol polystyrene branches.
3. To characterize these amphiphilic copolymers by different methods such as the Langmuir balance technique (at the air/water interface), atomic force microscopy, and neutron scattering.
4. To investigate the solubilization and release properties of arborescent copolymers for different hydrophobes in aqueous media, to determine the influence of branching functionality, branch chain length, and polyglycidol content on the properties of arborescent core-shell copolymers.

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