Synthesis and Characterization of New Multifunctional Initiators for Anionic Polymerization and the Use of Poly(4-hydroxystyrene) as a Template for New Polymers

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Degree

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Christopher Michael Hurley

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DEDICATION

This work is dedicated to my father, Dr. John P. Hurley, whose commitment to hard work and enduring attitude has been a guiding light to his children.

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I would like to express my sincerest appreciation towards all the individuals who contributed to making this dissertation a possibility. A work of this nature is impossible without the direct and indirect contributions of a large number of great people.

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ABSTRACT

This dissertation explores the synthesis and use of multifunctional anionic polymerization initiators for the purpose of opening the gateway to the synthesis of polymer architectures of greater complexity. First the multifunctional oxyanion initiator generated by reacting poly(4-hydroxystyrene) with sodium hydride was used to synthesize a previously unknown polymer containing an aryl halide functional group. The homopolymer solution self-assembly behavior of poly(4-hydroxystyrene) and the newly synthesized poly (4-(4-bromophenyloxy)styrene) were both investigated. This is followed by the synthesis and characterization of multifunctional alkyne core molecules and random copolymers of polystyrene-co-poly(4-hydroxystyrene) which served as templates for the synthesis of new random copolymers of polystyrene-co-poly(4-(2-propynyloxy)styrene). The newly formed multifunctional alkyne core molecules and alkyne functionalized random copolymers served as polymer backbones in a “grafting to” strategy. Previously prepared azide terminated polymers were grafted to the multifunctional alkyne core molecules and polymer backbones by copper (I) catalyzed alkyne-azide cycloaddition reactions. Lastly, the synthesis of a new hydrocarbon soluble multifunctional initiator was undertaken. The resulting molecule was shown to be an efficient initiator of anionic polymerization in non-polar solvent in the absence of polar additives, necessary in all previous attempts to combat large scale aggregation of such multifunctional initiator. This new initiator will open the way to facile synthesis of well-defined star polymers, star-block copolymers, and more complex polymer architectures.

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CHAPTER 1 INTRODUCTION

Background

Anionic polymerization is a living ionic polymerization method that is characterized by the narrow molecular weight distribution ($M_w/M_n<1.10$), stoichiometric control over the molecular weight, complete monomer consumption and the absence of chain transfer and termination.[1] Synthetic polymer chemistry has been guided by the pursuit of control over the variables that affect the properties of polymers. Although many techniques have been developed for the synthesis of macromolecules, with a large emphasis lately on controlled radical polymerization techniques, the zenith of control is achieved through living anionic polymerization. The successful demonstration of the living anionic polymerization of styrene by Szwarc et al. in 1956, sparked a large scale interest in such polymerization systems.[2,3] A diverse array of alternative polymerization techniques have since been developed by researchers, bringing many benefits including increased tolerance to impurities and wider array of viable monomers.[4] Ultimately these techniques have fallen short of the control provided by anionic polymerization. The method of initiation and propagation of anionic polymerization by sodium naphthalenide has been identified as electron transfer from the organometallic species to the monomer, thereby forming a new bond between two activated monomers and transferring the metal counterion to the newly formed living chain ends.[2] The following nine criteria to define a living polymerization system were laid out by Quirk et al.[5,6]

- Polymerization proceeds until all of the monomer has been consumed. Further addition of monomer results in continued polymerization
- The number average molecular weight (M_n) is a linear function of conversion
- The number of polymer molecules is a constant, which is sensibly independent of conversion
- The molecular weight is controlled by the stoichiometry of the reaction
- Narrow molecular weight distribution polymers are produced
- Block copolymers can be prepared by sequential monomer addition
- Chain-end functionalized polymers can be prepared in quantitative yield
- Linearity of the kinetic plot of the rate of propagation as a function of time

- Determination of linearity of a kinetic plot of the left side of the following equation versus time

$$ln\left(1-\frac{[I_o]}{[M_o]}\overline{DP_n}\right) = -k_p[I_o]t$$

$[I_o]$=initial monomer concentration; $[M_o]$=initial monomer concentration; $\overline{DP_n}$=number average degree of polymerization; k_p=rate constant of propagation; and t=time

Anionic polymerization has led to breakthroughs both in academic research and in commercial endeavors.[7] A multitude of fascinating and practical polymers have been synthesized by anionic polymerization over the past several decades as the technique has been shown to be effective in polymerizing dienes, methacrylates, acrylates, epoxides, episulfides, cyclic siloxanes, lactones and styrenic monomers.[6] Adept researchers using specific initiators, functionalized monomers and terminating agents have created a variety of complex polymer architectures, including random and block copolymers, star polymers, comb and brush polymers, H polymers, dendrimers, etc. Commercially, the anionic polymerization of dienes has led to a variety of beneficial products, namely synthetic rubbers.

The selection of a proper initiator is paramount for the success and control of anionic polymerization. In the presence of hydrocarbon solvents, organometallic initiators can suffer from aggregation and in polar solvents the presence of multiple types of ion pairs with different reactivity can affect the control over the polymerization reaction.[6] A vital key to selecting a proper initiator for anionic polymerization is understanding the role reactivity plays between the two species. In general, a relationship has been observed between the reactivity of a monomer and the stability of the anion that it forms, that is directly reflected in the pK_a value of the conjugate acid of the anion.[6] Higher pK_a value corresponds to lower stability of the propagating anion, which in turn leads to a lower reactivity of the monomer towards anionic polymerization. Lower reactivity monomers necessitate the use of highly reactive initiator species. In an instance where the initiator reactivity is too low compared to the monomer, initiation may not occur or may be

incomplete or slow relative to propagation. Conversely, an initiator of reactivity much greater than the monomer being polymerized can lead to side reactions.[8] Reactivity of monomer species must also be considered in the case of block copolymer synthesis, as the first polymer block functions as a macroinitiator for the second block. A more reactive propagating anion is required to initiate a second polymer block that forms more stable propagating anions.[6] For example, a living polystyrene anion is capable of initiating 2-vinyl pyridine but the living chain end of poly(2-vinyl pyridine) is incapable of initiating the polymerization of styrene.

Organolithium initiators have played an important role in anionic polymerization due to their quantitative and controlled initiation of styrenes and dienes. The polymerization of dienes by organolithium species in non-polar solvent leads to a high percentage (>90 %) of the desirable 1,4 microstructure. Natural rubber, which consists of cis-1,4-polyisoprene, has highly prized elastomeric properties. Lithium is unique among the alkali metal counterions in its ability to produce polydienes of high 1,4-microstructure. The presence of a Lewis base (ex. THF) is often necessary to help facilitate the solubility of initiators in non-polar solvents. This is particularly true of higher functionality initiator where several anions may be in close proximity, such as a difunctional initiator. These polar additives, even in small quantities generally have a large effect on the polydiene microstructure. A large shift away from the cis-1,4-microstructure towards 1,2 or 3,4 occurs, with dire results with regard to the elastomeric properties of the resulting polymer. The pursuit of multifunctional initiators soluble in non-polar solvents has thus been ongoing for decades.[9]

The synthesis of simple organolithium species is performed by reacting lithium metal with the desired alkylhalide species.[10] These reactions produce monofunctional organolithium initiators, with varying levels of solubility in non-polar solvents.[6] On the market today, there are several widely available organolithium species sold in solution with non-polar solvents, and these are commonly used directly as initiators in anionic polymerization.[11] Attempts to produce difunctional organolithium initiators using an analogous reaction with alkyldihalides does not produce high yields of the desired dilthium species. These reactions suffer from several issues including α-lithium halide elimination

and intermolecular coupling reactions.[9,12] Also, aggregation of multilithiated species in non-polar solvents is another factor that limits their potential as multifunctional initiators.

For the past several decades a number of synthetic strategies have been pursued all of which fall into one of two general categories: direct reaction with an alkali metal or reaction with an organoalkali species. Among the initiators synthesized by direct reaction, those formed from the reaction with aromatic hydrocarbons have been some of the most popular, even finding use as purging solutions and drying agents for preparing anhydrous solvents due to the vivid colors of the active initiators in solution.[11] Aromatic hydrocarbons (naphthalene, fluorene, anthracene, etc.) are known to react with alkali metals to form radical anions in polar aprotic solvents such as ethers. A commonly used and classic example of these initiators is sodium naphthalenide, used by Szwarc in his seminal paper in 1956.[3] The reaction of the aromatic radical anion with the monomer forms the corresponding monomer radical anion by reversible electron transfer, which promptly dimerizes to form a difunctional initiator (Figure 1.1). These difunctional initiators have been instrumental in synthesis of triblock copolymers of narrow and monomodal molecular weight distribution.{Ahn, 2003 #648;Rahman, 2006 #649;Baskaran, 2007 #1057;Claes, 1961 #650} Aromatic hydrocarbon initiators require polar solvents to promote solubility. Polar solvents are known to accelerate the rate of propagation relative to the rate of initiation in anionic polymerizations. The increase in propagation rate can make the polymerization reactions difficult to control and lead to a broadening of the molecule weight distribution. In order to control the rate of propagation and to suppress side reactions, low temperatures (ex. -78℃) are used in these reactions. Unfortunately, in the case of polydienes, the high reactivity of the growing chain ends in polar solvent results in a large increase in the percentage of 1,2 and 3,4 microstructures which produce polymers with higher glass transition temperatures (T_g) and thus less desirable elastic properties.[6]

Direct reaction of alkali metal with α-substituted vinyl monomers is another popular method of synthesizing initiator species.[13-23] The reaction of the α-substituted vinyl monomer mirrors that of the aromatic hydrocarbons. A monomer radical anion species is produced from the reaction with lithium which then quickly dimerizes leaving a homogeneous difunctional carbanion species.[14] The reaction of the alkali metal with

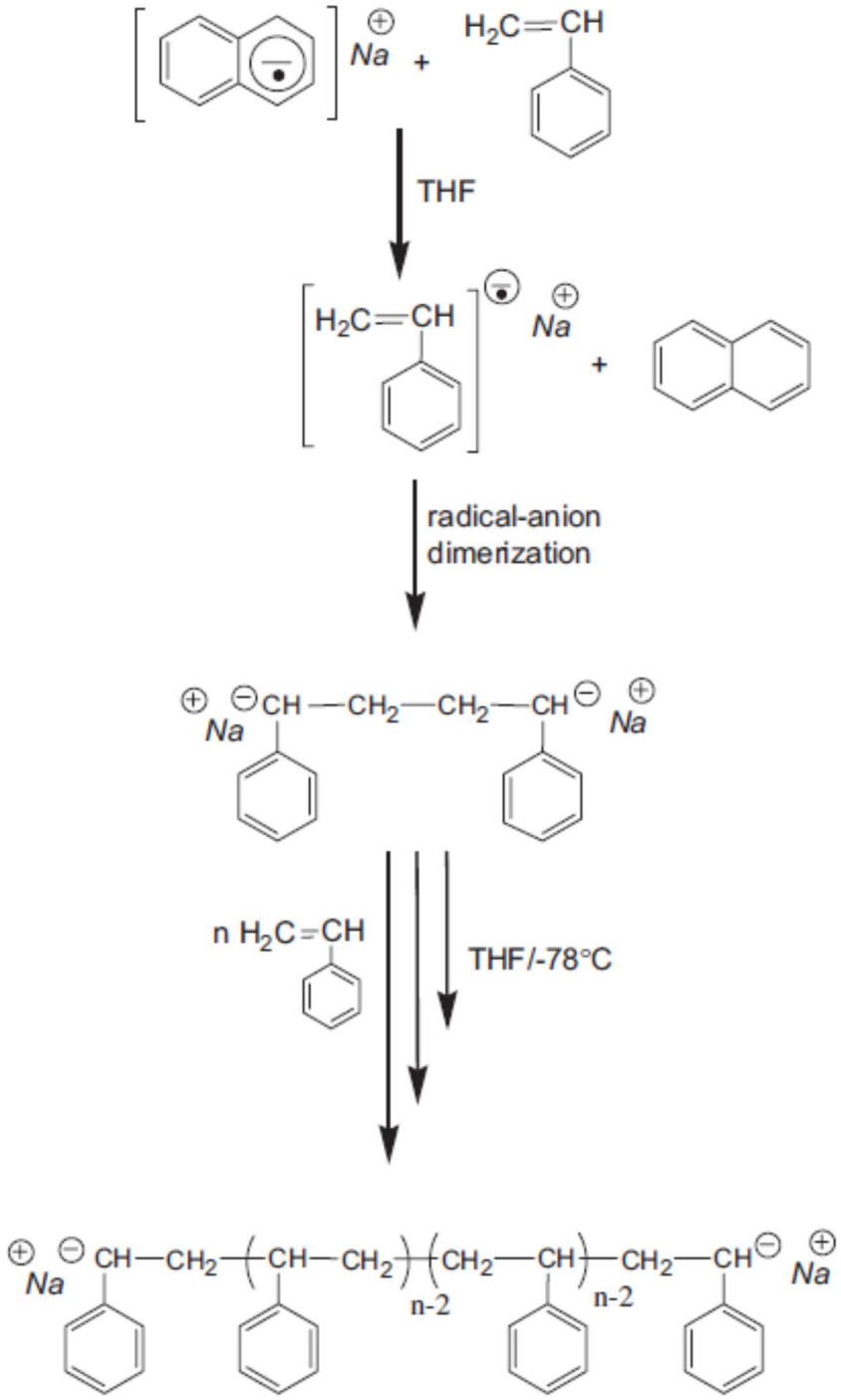


Figure 1.1 Dimerization of styrene radical anion to form difunctional initiator for polystyrene synthesis in THF. Adapted from reference 7.

the monomer requires the presence of polar additives, such as THF, for the formation of the difunctional initiator. As such, when employed for the polymerization of dienes the polar additives lead to a high percentage of 1,2 and 3,4 addition of monomer resulting in poor elastic properties.

Multifunctional Initiators

The synthesis of multifunctional organolithium initiators by reaction with a Lewis base (RLi) has also received a large amount of attention. Although, as previously noted, the reaction of alkyl dihalides results in poor conversion to the desired dilithium species because of side reactions, the synthesis of multilithiated species starting from aryl halides does not have the same impediments. The Wurtz coupling reaction that plagues the synthesis of alkyl dilithium species does not occur in the reaction of aryl halides due to the lower nucleophilicity of the phenyllithium with respect to bromide compounds.[24] Several experimental conditions can affect the yield of the exchange reaction including bromide species concentration, the nature of the alkyllithium used, the solvent and the temperature of the reaction. Experimental observation has concluded that the most appropriate concentration for aryl bromide species in the lithium-halogen exchange is ~5.3×10^{-2} M.[25-29] The lithium-halogen exchange reaction has been shown to be viable in both polar and non-polar solvents.[25-30] For those reactions done in polar solvents such as THF, low temperatures are required to control the kinetics of the polymerization and prevent side reactions. In the case of non-polar solvents, the exchange reaction is much less sensitive to the temperature of the reaction and is commonly conducted at room temperature for simplicity sake.

The quantitative nature of this reaction under proper experimental conditions was exploited by several research groups. Nithyanandhan and Jayaraman utilized this reaction to functionalize the terminal branching points of dendrimers.[31] Generations of dendrimer were grown by Williamson etherification reaction, yielding terminal aryl bromide groups of 3, 6, 12 and 24 for zero through third generations, respectively. The quantitative conversion of all terminal groups of each generations of dendrimer to aryl lithium was confirmed by observing ^{1}H and ^{13}C NMR shifts after the quenching of the

lithiated species with D_2O. The end groups were further functionalized by termination with CO_2 to yield carboxylic acid functionalities which were then converted to methyl esters.

The utility of the lithium-halogen exchange of aryl bromides for organic chemistry was in part demonstrated by Saa et al. They were able to produce multilithiated species from bromo-substituted salicylic and oligosalicylic acids without the need to utilize protecting groups to prevent side reactions.[32] In another study, Tsitsilianis et al. took advantage of the rigidity of α,ω-dibromo-oligophenylenes to produce model coil-rod-coil block copolymers in a two-step reaction.[33] First, an oligophenylene dilitihium initiator was produced by performing a halogen-lithium exchange reaction with α,ω-dibromo-oligophenylene. The second step entailed the introduction of monomer (styrene and 2-vinylpyridine were investigated), polymer growth and termination with degassed methanol. Although n-BuLi had been the most commonly used Lewis base in these reactions, Tsitsilianis et al. showed no adverse effects were encountered when utilizing *sec*-BuLi, and in the case of lithium-iodide exchange *tert*-BuLi has been shown to be the most effective butyllithium isomer.[33,34]

The application of the lithium-halogen exchange reaction of aryl bromides for the synthesis of carbanionic initiators was advanced further by Gnanou et al. In order to utilize a core first method for the synthesis of polymer stars, tri and tetracarbanionic initiators were first synthesized.[35,36] The exchange reaction to produce these initiators, conducted in benzene, was modelled with a 4,4'-dibromobiphenyl which resulted in an insoluble species that was incapable of initiation in the presence of monomers (styrene, butadiene, 1,1-diphenylethylene). The addition of 1:1 ratio of N,N,N',N'-tetramethylethylenediamine (TMEDA) in benzene solubilized the initiator and allowed for polymerization reactions to proceed. The same insolubility was found with tri and tetrafunctional initiators and could again be alleviated by addition of TMEDA.[36] Further investigation of the efficacy of different additives to solubilize these initiators showed lithium 2-methoxyethoxide to be the most efficient additive in a 4:1 ratio to butyllithium.[35] It was found that the most straightforward manner of addition for lithium 2-methoxyethoxide was to generate the species in situ by addition of sec-BuLi to 2-methoxyethanol. After first displaying the efficiency of these initiators for the

homopolymerization of three- and four-arm star polymers of polystyrene and polybutadiene, the sequential addition of monomer was used to synthesize star-block terpolymers. Star-block terpolymers with arms consisting of PS-b-PBd-b-PMMA were synthesized with narrow molecular weight distribution (PDI< 1.2). Aliquots taken after completion of the synthesis of each block reveal that molecular weight control was maintained throughout the process. The polymerization of the PMMA block was conveniently facilitated in this case by lithium 2-methoxyethoxide previously generated within the system. Potential application of these initiator systems was demonstrated by the synthesis of three- and four-arm amphiphilic star polymers having PBd-b-PEO block arms.[37] The first step in the polymerization begins with homopolymer polybutadiene star polymers synthesis followed by functionalization with hydroxyl end groups. The hydroxyl end groups were then converted to oxyanions by reaction with diphenylmethyl potassium (DPMK), the oxyanions then initiate the polymerization of ethylene oxide before being quenched. The molecular weight of each polymer block was determined by comparing the ratio of ^{1}H NMR signals of PBd to PEO against the known molecular weight of the PBd polymer star. Such amphiphilic star polymers with a hydrophobic polybutadiene core and a hydrophilic polyethylene oxide corona, to date can only be synthesized by core first initiation process, as the initiation of PBd by PEO is not known to occur. These star polymers having diblock arms were synthesized with good control over the molecular weight (PDI<1.32).[37]

Another popular technique for the creation of multifunctional initiators using organolithium as a reactant is conducted in two steps: 1) synthesis of an aromatic multivinyl macromonomer 2) initiation of the multiple vinyl bonds with equal reactivity and without self-propagation of the initiator species. The strategy for synthesizing an aromatic multivinyl macromonomer has centered around the design of molecules incorporating multiple moieties of 1,1-diphenylethylene (DPE).38 DPE is unique among vinyl monomers because it is known to propagate to a dimer ony in the presence of a large excess of BuLi (6.4 fold excess); at lower concentrations the formation of a monoadduct with BuLi is rapid and quantitative.39 Although structurally similar to the α-substituted styrenes, like α-methyl styrene, the sterically hindered monomer under normal experimental conditions can only complete the initiation reaction and does not propagate,

making it an ideal end-capping agent. When applied to multifunctional initiators, this property means that the possibility of intra- and intermolecular propagation of initiator species is eliminated. This unique characteristic of DPE has been taken advantage of by many research groups with exciting synthetic results. The simple monoaddition of n-BuLi to DPE to form 1,1-diphenylhexyllithium (DPELi) helped to pioneer the controlled anionic polymerization of PMMA.40 With the inclusion of additives such as lithium chloride (LiCl), DPELi has become the initiator of choice for polymerization of methacrylates with well controlled molecular weight and narrow molecular weight distribution.41-47 Additions of simple and polymeric organolithium species to DPE both result in diphenylalkyllithium species that can be used as initiators for a variety of monomers including styrene, dienes and methacrylates.6 By end-capping the first block of a block copolymer with DPE the living chain end can be retained while adjusting the stability of the carbanion to allow for the polymerization of a second block that would not be attainable otherwise (ex PS-b-PMMA).38

Functionalized 1,1-Diphenylethylene

A multiplicity of functionalized DPE molecules have been utilized for the synthesis of complex polymer architecture by taking advantage of the monoaddition characteristic of DPE.[38] The first functionalized DPE used to synthesize a miktoarm star (heteroarm) terpolymer was introduced by Isono et al.[48] By attaching a silane functionality to one of the phenyl rings of DPE they were able to form an initiation site for the growth of polydimethylsiloxane. The oxyanion of the growing PDMS chain proved too weak to effect the vinyl bond of DPE. With the vinyl bond intact and the PDMS chain terminated the PDI of the resulting macromonomer were unfortunately fairly broad (1.29-1.36).[48] Subsequent addition of living PS followed by reduction of the reaction temperature and polymerization of tert-butyl methacrylate resulted in a multimodal and broad PDI copolymer. The research of several groups followed a similar general methodology as that presented by Isono et al. which resulted in miktoarm star copolymers (ABC), four arm stars (A_2B_2) and five arm stars (A_2B_2C).[49-54] Abetz et al. took advantage of the monoaddition characteristic to direct the termination of living PS and PBd end-capped

with DPE to selectively terminate on the bromomethyl functionality of a DPE derivative to form a macromonomer. The macromonomer was then used for the synthesis of ABC miktoarm star terpolymers consisting of (PS)(PBd)(P2VP) and (PBd)(PS)(PMMA). Dumas et al. utilized a silane protected DPE to synthesize the amphiphilic star polymer (PS)(PEO)(PεCL) by first polymerizing a diblock using the DPE moiety to terminate the first block and initiate the second. The third arm was synthesized after the silane protecting group moiety was removed and the resulting functional group was used to polymerize ε-caprolactone.

Extensive research has been put forth by Hirao et al. on an iterative method of star polymer synthesis that utilizes cyclical steps of termination of living polymer by functionalized DPE, initiation of DPE moiety by living polymer, followed by termination of the living DPE by functionalized DPE (Figure 1.2).[55,56] As each iteration of the steps generates a new DPE moiety at the core of the molecule, the number of times this method can be use is theoretically limitless but in practical application it is limited by the steric hindrance each additional arm imposes. The drawback to such a synthetic technique is the precise stoichiometric control required and the purification requirement between iterations.

Divinylbenzene based multifunctional initiators have represented a simple strategy that has shown mixed results. Divinylbenzene is often used in order to achieve crosslinking in polymerization reactions. The reaction of 1,4-divinylbenzene with butyllithium or lithium naphthalenide in benzene at low concentration yields oligomeric poly(divinylbenzene) species with intact vinyl bonds.[57-60] Solubility issues due to crosslinking in the oligomers means that these species form a microgel in solution. The adducts formed by the reaction of these oligomers with *sec*-butyllithium can be used as multifunctional initiators for star polymer synthesis. In this case, the functionality of the oligomers is difficult to control so the branching of the star polymers is unpredictable. By using living polymers of low molecular weight to synthesize the poly(divinylbenzene) core particles issues with solubility are eliminated.[59-62] Despite greater control ove solubility the reactions using these multifunctional initiators still resulted in multimodal molecular weight distributions, corresponding to polymers of a multitude of different arms. The structurally similar m-diisopropylbenzene has been successfully employed as a

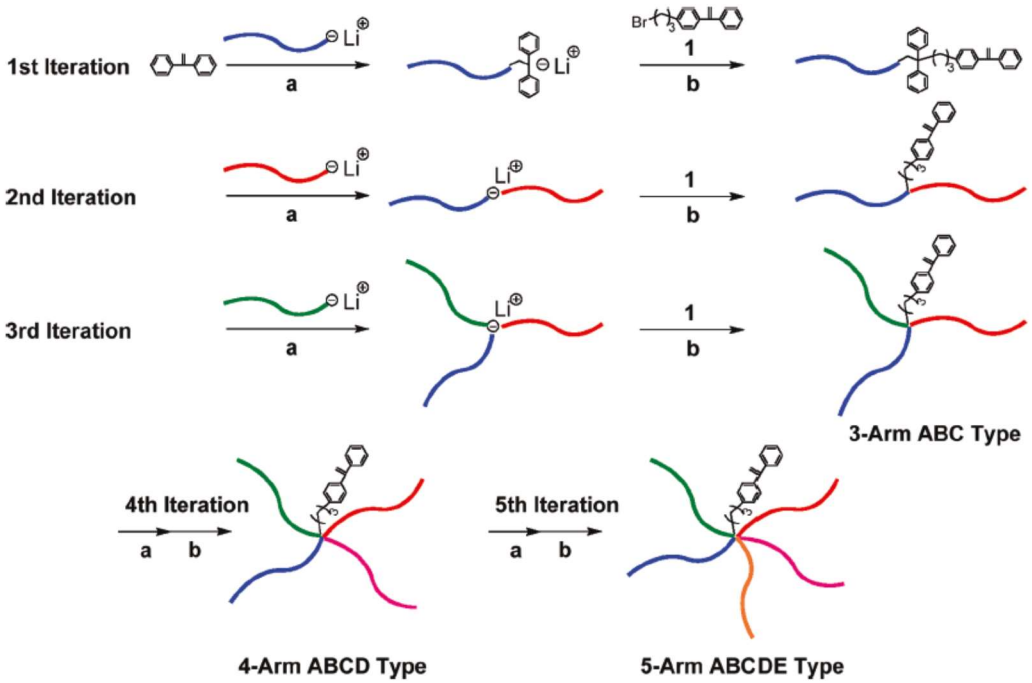


Figure 1.2 Iterative synthesis of star polymers through the use of functionalized DPE. Figure adapted from Reference 60.

difunctional initiator.[63-65] In order to avoid the precipitation of the initiator formed from the reaction of *sec*-BuLi and m-diisopropenylbenzene in non-polar solvent the addition of polar additive was deemed necessary. The addition of triethylamine was found to alleviate the solubility issues presented by the adducts formed.[64,66] Unfortunately, the quantitative formation of difunctional initiator does not occur under these conditions, a mixture of higher functionality species was detected along with the intended difunctional initiator.[66,67] Further experimental investigation revealed that by using *tert*-BuLi instead of *sec*-BuLi, while maintaining the presence of triethylamine, quantitative formation of a difunctional initiator can be achieved.[68-70] The use of a number of different polar additives, including several ethers and N,N,N'N'-tetramethylethylenediamine can also lead to difunctional initiators. In order to achieve equal reactivity of initiation sites the use of oligomeric species to initiate the difunctional initiator in the presence of a weakly polar additive such as anisole or lithium *tert*-butoxide was needed. Sanderson et al. reported the synthesis 2,2-bis[3-(1-propenyl)-4-methoxyphenyl]propane, a divinyl molecule similar in structure to p-diispropenylbenzene.[71] Used as difunctional initiator, it was found to polymerize butadiene to predictable molecular weight with monomodal and narrow molecular weight distribution. The initiator was said to be soluble in non-polar solvent and well controlled in the absence of polar additives. Without polar additives the polymers produced had high 1,4-microstructure. It was reasoned that the presence of methoxy ether moieties was responsible for the enhanced solubility and control over polymerization. The low molecular weight of the polymers prepared by this method cast some doubt on the lucidity of this claim.

Difunctional Double 1,1-Diphenylethylene Initiators

The success of 1,1-diphenylethylene as a monofunctional initiator, prompted a series of attempts to synthesize a difunctional initiator based around the idea of having two DPE moieties in the same molecule, a type of double DPE (DDPE).[9] In 1969 Fetters and Morton were able to dimerize DPE by direct treatment with lithium metal.[72] The direct reaction of DPE with lithium metal formed a monomer radical anion before dimerizing in

a corresponding manner to the same reaction as other α-substituted styrenes previously discussed. The presence of a small amount of aromatic ether was found necessary for the synthesis of the initiator. The polymerization of this initiator succeeded in producing monomodal molecular weight distribution ABA triblock copolymers. The first multivinyl macromonomers designed with multiple DPE moieties were introduced in the literature by Tung et al in 1978.[73] The addition of *sec*-BuLi to the DDPE molecules used by Tung et al. (Figure 1.3), was found to be rapid and produced an insoluble fine suspension of initiator. Reaction of these initiators when freshly prepared with a small amount of diene monomer resulted in their full solubility. Alternatively, initiation of these DDPEs by oligomeric polystyryllithium resulted directly in fully soluble initiators. Synthesis of the

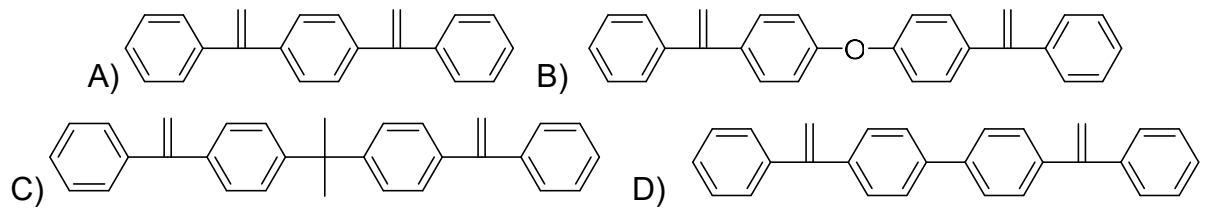
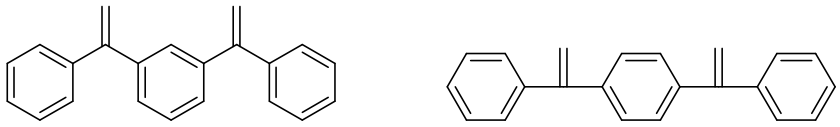


Figure 1.3. Four different DDPE molecules used by Tung et al. to form hydrocarbon soluble difunctional initiators

commercially important block copolymer polystyrene-b-polybutadiene-b-polystyrene (SBS) by initiators formed by the Tung et al. chemistry gave narrow molecular weight distributions but suffered from significantly lower tensile strength. Two years later, Shulz and Höcker reported the solubility in toluene and benzene of a difunctional initiator synthesized from the rapid reaction of two equivalents of *sec*-BuLi with MDDPE.[74] The difunctionality of the initiator was confirmed by mass spectrometry of quenched initiator.

Kinetic studies of the addition of *sec*-BuLi 1,3-bis(phenylethenyl)benzene (MDDPE) and 1,4-bis(phenylethenyl)benzene (PDDPE) by Leitz and Hocker revealed an important difference in the rate of addition in non-polar solvent (Figure 1.4).[75] For



MDDPE PDDPE

Figure 1.4. Structures of 1,3-bis(phenylethenyl)benzene (MDDPE) and 1,4-bis(phenylethenyl)benzene

PDDPE in toluene the rate of the first addition of *sec*-BuLi is significantly faster than the rate of the second addition. This is in contrast to the equal rates of addition found for MDDPE. The rates of first addition of *sec*-BuLi were comparable for both molecules. In addition, when MDDPE was handled in cyclohexane by McGrath et al. the rate of the second addition was actually found to be an order of magnitude greater than the first.[76] The explanation put forth has to do with resonance of the anion formed after the first addition of *sec*-BuLi. After the first addition of *sec*-BuLi, PDDPE is capable of the two resonance forms shown in Figure 1.5. The meta isomer is not capable of the same type of delocalization as PDDPE. The resonance of the anion would be expected to reduce the reactivity of the vinyl bond towards nucleophiles. Without the interference of resonance the meta isomer is allowed to freely react with organolithium species. Using molecule PDDPE Quirk et al. were able to synthesize A_2B_2 and A_4 star polymers by initiating the divinyl species with living polystyrene and then using the activated DPE moieties for the polymerization of polystyrene or polybutadiene arms.[5] The second phase of arm growth from the activated DPE centers resulted in bimodal molecular weight distribution. The addition of polar additives (THF for PS growth and s-BuOLi for PBd growth) resulted in the formation of monomodal polymers.

The initiation of DDPE species in non-polar solvents favors diaddition while the initiation of DDPE in polar solvent (THF) results in monoaddition. Quirk et al. were able to take advantage of this phenomena to form a macromonomer with a single polymer chain attached to the DDPE, leaving an unsaturated DPE moiety that was further utilized for the synthesis of a three arm star polymer.[77,78] The monoaddition of the living polystyrene to the DDPE was monitored by SEC and observed to be quantitative.

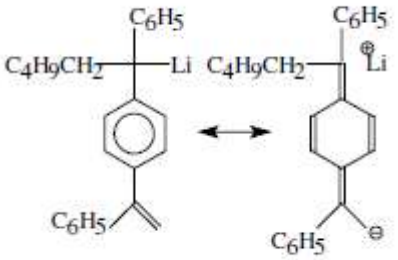


Figure 1.5. Resonance structure of monoaddition of BuLi to PDDPE

Additional analysis of the macromonomer by UV-vis spectroscopy and ^{1}H NMR yield estimates of functionality of 0.6 and 0.83, respectively. Further confirmation of the monoaddition to DDPE in THF was presented in the literature.[76,79,80]

Beyond the use of DDPE initiators to synthesize star polymers, the solubility of these initiators in non-polar solvents allows them to be used to synthesize ABA triblock copolymers. These reactions are analogous to the ABA triblock copolymers synthesized in two steps by difunctional aromatic hydrocarbon initiators (ex. sodium naphthalenide) with the exception that DDPEs are soluble in non-polar solvents and aromatic hydrocarbon initiators are not. The solubility difference opens up the possibility of middle polymer blocks which could not have been synthesized previously. McGrath et al. conducted the polymerization of polydienes in non-polar solvent with DDPE in order to obtain high 1,4 microstructure. THF was then added to the reaction and the temperature was reduced to -78℃ before *tert*-butyl methacrylate was added to the solution. The resulting triblock however lacked the desired control over molecular weight distribution as PDI was broad (1.10-1.25) or in some case bimodal.

Inconsistencies with regard to the control over molecular weight and molecular weight distribution when employing MDDPE as a difunctional initiator in non-polar solvent led to scrutiny of the reported results.[81] Previous researchers had performed polymerizations with MDDPE not under high vacuum conditions and in some case with excess BuLi.[82] In 1991, Quirk and Ma found that when performed with high vacuum technique and high purity reagents the dilithium initiator of MDDPE forms polystyrene and polybutadiene with multimodal molecular weight distributions and no control over the

molecular weight by stoichiometry. Previous observation of this result had been explained by imprecise addition of *sec*-BuLi.[83] When the polymerization is done with stoichiometric concentrations of THF highly controlled narrow molecular weight products are observed. In the event of stoichiometry being the cause of the discrepancies one of two scenarios exist: excess MDDPE or excess BuLi. Excess MDDPE would lead to an increase in the branching observed as living polymer chains would cross initiate unsaturated MDDPE molecules. Excess BuLi would results in polymer chain growth from the difunctional species and polymer chain growth from the monfunctional excess BuLi. In the event that chain end aggregation was the cause addition of polar additive would resolve the situation. To distinguish between the two possibilities, a carefully run set of reactions using high vacuum techniques with and without THF additive were conducted.[81] The findings showed bimodal molecular weight distributions without polar additive and narrow monomodal molecular weight distributions with polar additive. By careful consideration, the origin of the inconsistencies of the results was determined to be the in situ formation of the polar additive lithium butoxide. The excess BuLi added in some experimental procedures was intended to scavenge impurities prior to the initiation of MDDPE. By doing so the BuLi has the chance to react with small amounts of oxygen and hydroxyl groups present which is known to form lithium butoxide. The hypothesis was confirmed by the addition of previously synthesized lithium *sec*-butoxide (s-BuOLi) to difunctional initiator. The subsequent polymerization resulted in monomodal molecular weight distribution of polydienes (M_n=25,000, PDI=1.10). Previous observation that lithium alkoxides cause an increase in the rate of initiation and decrease the rate of propagation of isoprene with alkyllithium initiators support the assertion that the complexation of lithium alkoxide can account for the observed results.[84,85] The complexation behavior of alkyllithium and lithium alkoxide in solution has been thoroughly studied. [86-92] UV-vis absorption studies shed some insight on the state of aggregation with no polar additive present. Absorption at 438 nm characteristic of diphenylalkyllithium suggests that initiation is slow relative to propagation, leaving diphenylalkyllithium present throughout the polymerization process.[81] In 1998, the optimization of the ratio of the concentration of living chain end to sec-BuOLi for the polymerization of polyisoprene was investigated by Hadjichristidis et al.[93] A multitude of experiments with increasing ratio of

s-BuOLi:C-Li from 0.5 to 18 were conducted. The ratio of 8:1 (s-BuOLi:C-Li) was determined to most advantageous in regard to obtaining a low PDI polymer and also limiting the percentage of 3,4-microstructure below 15%. The desirable elastomeric properties of polyisoprene are retained at this percentage of 3,4-addition.

An explanation for the bimodality of the polymerization of hydrocarbon monomers with difunctional initiators in non-polar solvents without additives was put forth by Estrin in 2004.[94] It was reasoned that the bimodality was the result of two different phases present in the reaction, the first phase being an insoluble oligomeric sediment that is the consequence of the tetrameric association of lithium active sites of the difunctional initiators. The second phase consisted of those difunctional initiators that remain soluble in the reaction solution. The difference in rates of propagation for the two populations was put forth as being responsible for the bimodal molecular weight distribution. A mathematical model was advanced by Estrin that showed satisfactory agreement with experimental observations.[94]

In 1990, Sigwalt et al. noted the concentration of the living chain ends in the difunctional polymerization of isoprene in hexane by dilithio-oligoisoprene can have an effect on the state of aggregation in solution.[95] Through the use of ^{7}Li NMR they were able to establish two sets of behaviors for growing chain ends. For reaction with concentration below 5×10^{-4} M, an autoacceleration effect is seen up to a degree of polymerization of ~500 which is explained by the presence of different types of aggregates in solution. For concentrations above 5×10^{-4} M, the system behaves in an analogous manner to monofunctional BuLi systems. The autoacceleration effect can be seen in the first-order plot of monomer conversion of isoprene by α,ω-dilithio-oligioisoprene initiator (DP=20). The upward curvature evident in the lower concentration samples is indicative of autoacceleration (Figure 1.6).

More recently Hadjichristidis et al. have investigated the effect of growing chain end concentration of the difunctional initiator in solution in the presence of s-BuOLi on the modality of the polymer.[96] In similar findings to those of Sigwalt et al., differences in growing chain end concentration were linked to the modality of the polymers produced. The molecular weight distribution was found to be monomodal for concentrations above ~7×10^{-4} M. For those below 6×10^{-4} M, the distribution is found to be bimodal. The

explanation put forth centered around small amounts of protic impurities within these reaction systems. With the acceptance that protic impurities are an inevitability even with carefully executed high vacuum technique, it can be assumed that these impurities are generally equivalent from one reaction to another. A lower concentration of living chain ends means that the termination caused by protic impurities has a more drastic effect. The difference in molecular weight from difunctional growing chain ends and monofunctional growing chain ends (formed from protic termination of one of the difunctional sites) causes the bimodality seen. In higher concentration reactions the effect of monofunctional growing chain ends is masked by an overwhelming percentage of difunctional chain ends leading to a monomodal PDI. In addition, this paper reported that the ideal concentration of *sec*-BuOLi for the synthesis of high 1,4-microstructure polybutadiene was within the range of 1.2-1.6:1 (*sec*-BuOLi:C-Li). Small increases in the concentration of *sec*-BuOLi was observed to have a sizeable effect on the 1,4-microstructure of polybutadiene underlining the importance of keeping the ratio low to achieve better elastomeric properties

To date the method of choice for utilizing a DDPE initiator for anionic polymerization at high vacuum conditions in non-polar solvents requires the addition of a polar additive. In polymerization systems where microstructure of the polymer is not a concern (ex. polystyrene), the addition of THF or tertiary amines (ex. TMEDA) has been proven effective in maintaining the solubility of the difunctional initiator. In the case of polydienes, the microstructure of which is sensitive to the polarity of the solvent used, lithium alkoxides in low equivalencies have emerged as the additives of choice to maintain a high 1,4-microstructure.

Higher Complexity Polymer Architecture

Expanding upon the research done on functionalized DPE and difunctional initiators, the synthesis of higher complexity macromolecular architectures such as dendrimers and comb-like polymers have been accomplished. The synthesis of such.

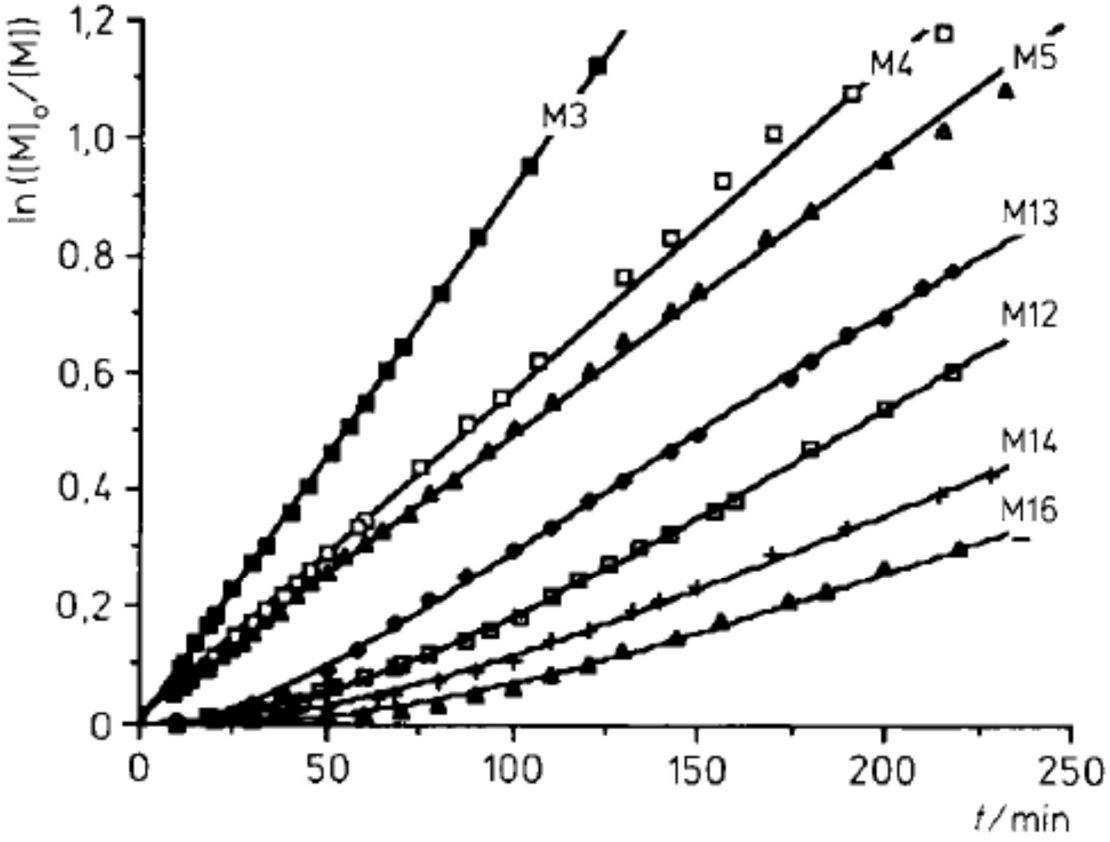


Figure 1.6 First-order plot for monomer conversion in the polymerization of isoprene with α,ω-dilithio-oligoisoprene (DP=20) as initiator in hexane at 30°C. Initial monomer concentration [M₀] and organolithium c are respectively (■) 0.70 M; 6.74 × 10 $^{-3}$ M, (□) 0.70 M; 1.10 × 10 $^{-3}$ M, (▲) 0.71 M; 0.53 × 10 $^{-3}$ M, (♦) 0.31 M; 0.29 × 10 $^{-3}$ M (⧈) 0.34 M, 0.097 × 10 $^{-3}$ M, (+) 0.12 M, 0.039 × 10 $^{-3}$ M, (▲) 0.14 M. 0.027 × 10 $^{-3}$

architectures requires clever planning of the synthetic route and the utmost purity and control over the reagents used. Dendrimers are polymers with dendritic (tree-like) architecture. They are characterized by a single core starting point, with symmetrical branching around it of equal chain length that ends in a branching point from which two new branches emerge. The succession of branching points each grow branches of equal length and are referred to by generation number denoting their distance from the core. Terminal functional groups are located at the end of the penultimate generation. These macromolecules are synthesized by one of two methods: core-first, divergent method or arm-first, convergent method. The core–first, divergent method was pioneered by Tomalia et al. in 1985 and the convergent method followed later in 1990.[97-99] The highly branched symmetrical architecture of these macromolecules. results in globular structures unique from those that can be formed by linear polymers. The potential of these materials has been investigated across a number of fields including drug transport, lithography, electron transfer and biological applications[100-107]

The divergent design to dendrimer growth requires a multifunctional core molecule to grow the initial star polymer. Functionalities at the terminal end of branches leave open the possibility of growing two more branches from the functionalized branching point. Each generation is grown in an iterative pattern with the branches of each generation capable of growing two more. After the initial demonstration of the concept by Tomalia et al. and Newkome et al., many examples of divergent growth dendrimers can now be found in the literature.[108,109] The diversity of dendrimer synthesis reported in the literature is such that while dendrimers of organic skeletons represent the majority of examples, there has been a number of main group element based skeletons including those of silicon, phosphorus and boron.[110] The number of published articles and the variety of dendrimers seen shows that with the appropriate branch terminating functionality and reactivation steps most any functionality can be used to synthesize these molecules.

Despite the great success with the divergent model of dendrimer growths there have been some drawbacks to this synthetic model. As the number of generations increases, a large excess of reagents becomes necessary to ensure the complete reaction of each branching point. The excess reagents must then be removed after each successive generation growth. In addition, the more generations that are grown, the

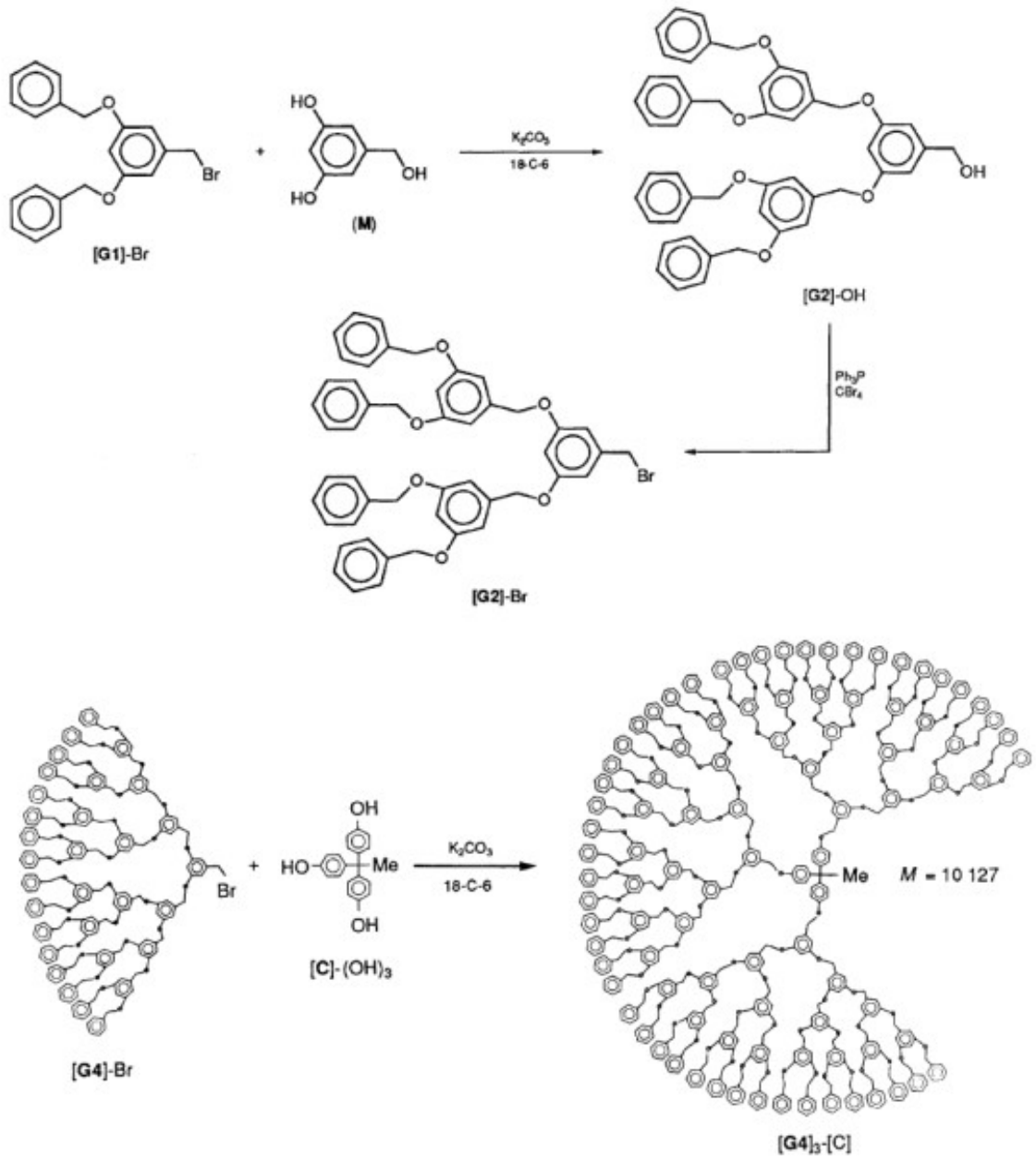


Figure 1.7 Dendrimer synthesis by the convergent method of poly(benzyl ether). Adapted from Reference 103.

number of terminal functional groups increases. The increasing number of functional groups means an increase in the potential for a failed or incomplete reaction. Imperfections introduced in this way threaten the quality of the dendrimers produced. A large total number of functional groups also leaves open the possibility of side reaction which could also decrease the quality of the dendrimer produced.

The convergent method of dendrimer synthesis introduced by Frechet et al. allows the dendrimer arms to be synthesized first and then efficiently merged together by a central linking agent. Successive Williamson etherification reactions followed by a bromination step were used to first synthesize several generations of arm growth before unifying the arms by attaching them to a trifunctional linking core (Figure 1.7).

There are several advantages of the convergent method over the divergent method. The amount of excess reagents necessary for the dendrimer synthesis is greatly reduced in the convergent method. Purification steps can be taken between the stages of dendrimer arm growth. The advantage that is in greatest contrast to the divergent method is the control over the degree of perfection. In the divergent model with increasing generations the control over degree of perfection begins to break down but in the convergent method a high degree of perfection can be maintained to several generations. In addition, several distinctive architectures can be accessed through this method that cannot be accomplished with a divergent method.[111-114]

Another classification of dendritic polymers exist known as dendrimer-like polymer stars. These polymeric materials are different from previously discussed dendrimers because they are the result of living chain polymerization with regular branching points and a central core.[115] Regular dendrimers are restricted to those polymers synthesized solely by step growth polymerization. As with dendrimers, the synthesis of dendrimer-like polymer stars can be classified as either divergent or convergent based on the overall synthetic strategy. An important recent development in the divergent synthetic strategy of dendrimer-like polymer stars is the use of a TERMINI. TERMINI is a phrase used to describe a terminating multifunctional initiator. The TERMINI molecule is used to endcap a growing chain while providing moieties that can be directly used to initiate new chain growth or moieties that must be slightly modified before being able to provide initiation sites. First proposed by Percec et al. in the context of living radical polymerization, the

idea is highly adaptable to other techniques.[116,117] The first example of the use of a TERMINI in anionic polymerization was put forth by Gnanou et al.[118] For the TERMINI, 4,4'-dibromodiphenylethylene was exploited to endcap a living anion, before terminating with methanol. The bromine atoms present on both the aromatic rings were then removed to yield carbanions in aryl halide-lithium exchange reactions previously encountered for the synthesis of multifunctional initiators. The TERMINI was shown to be effective in the synthesis of three arm star polymers and A_2B miktoarm star polymers by varying the monomer used before and after termination. Using the multifunctional initiator as the core and the TERMINI in an iterative approach, dendrimer-like star polymers of polystyrene were synthesized out to seven generations with narrow molecular weight distribution (Figure 1.8).[118]

Hirao et al. were able to utilize a divergent strategy where two protected functionalities were present on a 1,1-diphenylethylene anionic initiator were used first to initiate polymerization. After chain growth was terminated, the functionalities were deprotected and used as termination sites for living polymers also containing protected functionalities. By continuing with this iterative strategy, dendrimer-like polymer stars of poly (methyl methacrylate) were synthesized up to seven generation (Figure 1.9).[119]
Hadjichristidis et al. used a functionalized styrene to synthesize dendrimer arms prior to attaching the arms in a convergent manner to a chlorosilane core molecule. The key to this strategy lies in the ability to selectively direct the living chain end of the first living polymer to the chlorosilane rather than to the vinyl group of the functionalized styrene molecule. Dropwise addition and strict control over the stoichiometry was used to promote addition to the silane. The second step entailed the addition of another living polymer to the residual vinyl functionality of the macromonomer. The living chain end produced through addition to the macromonomer was used to polymerize additional monomer. Upon complete consumption of the monomer, the living chain ends were terminated using trichloromethylsilane to yield a two generation dendritic polymer star.[120]
In a subsequent publication by Hadjichristidis et al., this same strategy was pushed further to yield a dendrimer-like polybutadiene star of three generations.[121] The first generation was synthesized by terminating living polybutadiene chain ends using 4-(dichloromethylsilyl)-1,1-diphenylethylene. The diphenylethylene is then initiated by *sec*-

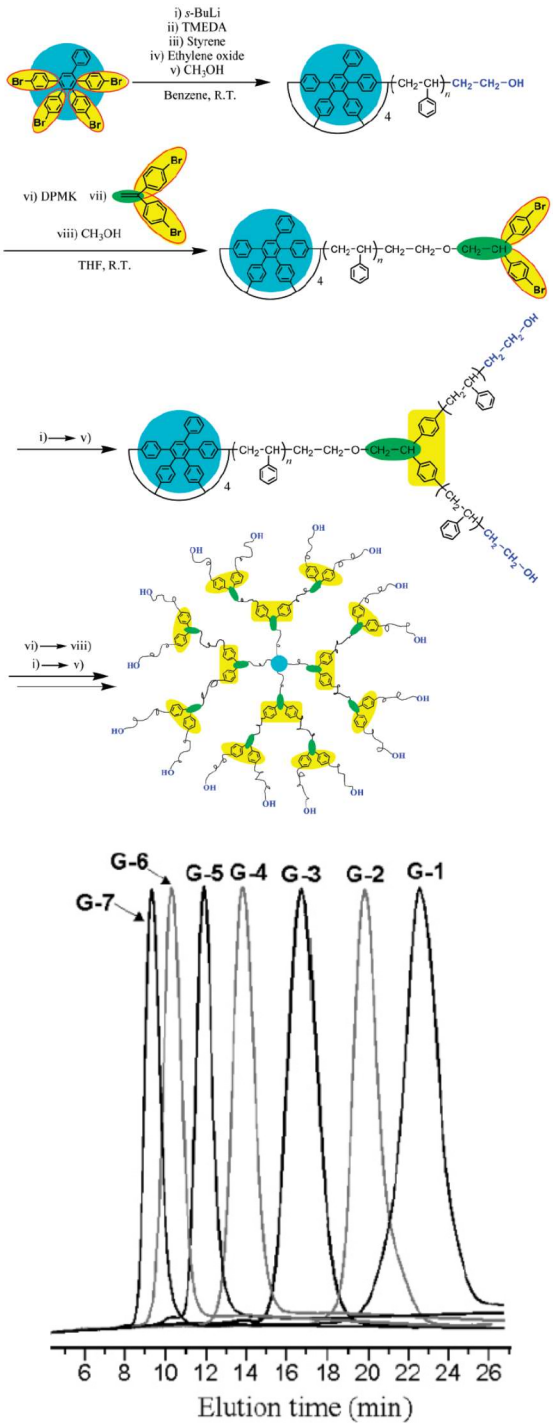


Figure 1.8 Synthetic Pathway for Dendrimer-like Polystyrene and Polybutadiene Stars. Adapted from Reference 123.

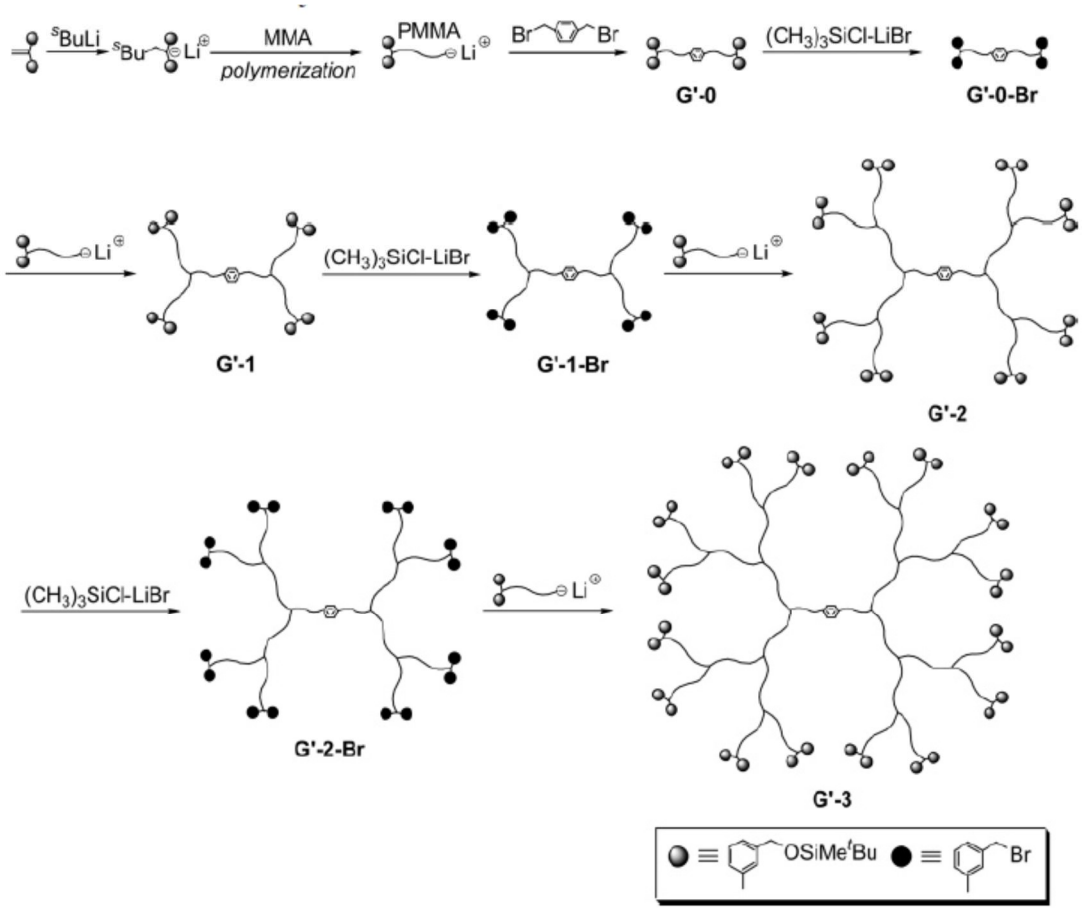


Figure 1.9 Synthetic Pathway for Dendrimer-like Poly (methyl methacrylate) Stars. Adapted from Reference 124

BuLi and used to polymerize polybutadiene. These polymer arms were then terminated onto a new 4-(dichloromethylsilyl)-1,1-diphenylethylene, where the cycle of initiation and monomer addition was repeated. Finally, these living chain ends were tethered together by using trichoromethylsilane to terminate.

Building on the success of their trifunctional initiator, Quirk et al. used the trifunctional living chain ends to polymerize polystyrene before terminating the living chain end with chlorosilanes such trichloromethylsilane and tetrachlorosilane. Terminating with these chlorosilanes provide termination sites for living polymer chain ends to attach as a second generation. Dendritic polymer stars with narrow molecular weight distribution and up to 13 branches were recovered using this technique.[122]

The generation of oxyanions is used extensively in the synthesis of dendrimers and dendrimer-like polymer stars. Beyond the scope of dendritic polymers, oxyanions find use as small molecule multifunctional initiators and as initiation sites for graft copolymers and hyperbranched polymers.[123-130] Oxyanions are weaker initiators than carbanion which leaves them limited to use with cyclic monomers such as lactones andoxiranes that can be initiated through anionic ring opening polymerization.[6] In 1988 Gnanou et al. introduced a set of strategies for the synthesis of polyethylene oxide (PEO) based around the oxyanion initiator.[126] A small molecule with three hydroxyl functionalities, trimethylolpropane, was selected in order to synthesize three arm PEO stars. Oxyanions were generated by converting the hydroxyl groups to alkoxides using diphenylmethylpotassium (DPMK), a common initiator for anionic polymerization. The metalation process requires several hours and the resulting alkoxide species has a reduced solubility which necessitates vigorous stirring. Addition of ethylene oxide monomer results in the slow growth of a three arm star. Graft copolymers were also synthesized from 4-(2-hydroxyethyl)styrene by first forming an alkoxide from the pendant hydroxyl group using DPMK as before. An additional initiator, potassium naphthalenide, was then added to the reaction in order to polymerize the vinyl functionality of styrene. Upon complete consumption of the styrene, ethylene oxide was added resulting in grafted polymer chain growth. Deprotonation of terminal hydroxyl groups of hyperbranched polyglycerol and polyglycerol with oligomeric propylene oxide was used to form multifunctional oxyanionic initiators for the polymerization of ethylene oxide.[131] DPMK

was used to generate the oxyanions, resulting in aggregation in the polyglycerol example. The incorporation of oligomeric propylene oxide at the terminal ends allowed for greater solubility of the initiator. The resulting polymers had broad polydispersities ranging from 1.4-2.2.

Another example of a graft copolymer using oxyanions to generate polymer side chains in a "grafting from" technique was the synthesis of poly(methyl methacrylate)-g-poly(β-butyrolactone) put forth by Jedlinski et al.[130] PMMA homopolymers were first polymerized anionically before being reacted with KOH and 18-crown-6 in toluene. The reaction with KOH and 18-crown-6 results in the removal of a percentage of the distal methyl groups. These newly generated carboxylate oxyanions were then used as initiation sites for β-butyrolactone, terminating grafting chain growth by the addition of methyl iodide. The average number of initiation site per chain varied from 7 to 65 and was shown to be controllable. Stadler and Bayer were able to synthesize $(PEO)_nPS(PEO)_n$ dumbbell shaped copolymers by generating oxyanions at the polymer chain ends for the polymerization of PEO side chains.[132] The high vinyl content of polydienes synthesized in the presence of polar solvent was exploited in the synthesis of these dumbbell copolymers. The difunctional initiator potassium naphthalenide was used to first polymerize polystyrene followed by the polymerization of several units of butadiene. Due to the influence of the polar solvent, a majority of the butadiene units took on a 1,2-microstructure with a pendant vinyl group. These vinyl groups were then subjected to a hydroboration-oxidation to convert to hydroxyl groups. From there the same strategy was followed as before, deprotonating the hydroxyl group to yield an oxyanion followed by the introduction of ethylene oxide and termination.

Poly(4-hydroxystyrene) has been another popular backbone for multifunctional initiators of anionic ring opening polymerization of graft copolymers.[123,124,127,133] The anionic polymerization of 4-hydroxystyrene requires the use of a protecting strategy similar to that used by Hirao et al. (Figure 1.10) to avoid quenching the chain end anion with the acidic proton from phenolic moieties.[6] Acetals, silanes and tert-butyl groups have been used as protecting groups for hydroxystyrene.[133-136] After deprotection, poly(4-hydroxystyrene) is easily converted to poly(phenoxide)s by the introduction of a strong base. By synthesizing a triblock ABA copolymer of polystyrene-b-poly(4-

hydroxystyrene)-b-polystyrene with a difunctional initiator, Se et al. were able to create a backbone with grafting sites selectively placed in the middle block.[124] Polymer chains of PEO were grown from these grafting sites to yield a narrow molecular weight distribution graft copolymer with grafting selectively in the middle block. These graft copolymers showed promise as a potential new class of solid polymer electrolytes. Frey et al. demonstrated the potential that poly(4-hydroxystyrene) has as an multifunctional initiator by using the oxyanion to synthesize hyperbranched polyglycidol.[137] Narrow molecular weight distributions (<1.4) were achieved with this method and control over the ratio of backbone to hyperbranched side chains was displayed by simply varying the length of the polymer backbone and the ratio of hydroxystyrene monomer to glycidol monomer. Deprotonation was limited to 10% to curtail the insolubility experienced with highly deprotonated polymer. The rapid proton exchange from hydroxyl to alkoxides allowed for each monomer unit to have hyperbranched growth. Mays et al. utilized a random copolymer of 4-hydroxystyrene and styrene in order to randomly disperse oxyanion initiation sites along the polystyrene backbone. After the Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization of acetoxystyrene and styrene, the protecting group was cleaved by hydrazine hydride and titrated with DPMK while applying mild heating. The added solubility provided by polystyrene and the heating process allowed deprotonation to reach 50%. The anionic polymerization of acetal-protected hydroxystyrene was introduced recently.[133,134] Acetal protecting groups offer rapid removal of the protecting group under milder conditions than the more commonly used *tert*-butoxystyrene. Frey et al. utilized acetal protected hydroxystyrene for the synthesis of amphoteric block copolymers with 2-vinyl pyridine (PHS-b-P2VP) which served as a multifunctional initiator for Anionic Ring Opening Polymerization (AROP) of ethylene oxide.[133]

Functionalized Styrene Monomers

The hydroxyl functionality of poly(4-hydroxystyrene) can be utilized for synthetic applications other than as a multifunctional initiator for AROP. The adaptation of the well-

studied reactions of the small molecule phenol to macromolecules has been quite limited, but holds huge potential.[138,139] Today, polystyrene is the most studied polymer system in anionic polymerization and has found extremely wide application in both commercial and academic endeavors.[4] The well-controlled synthesis of functionalized polystyrenes by anionic polymerization would allow for enhanced tailoring of materials to suit their intended application. The direct synthesis of functionalized polystyrene is hampered by the incompatibility of the living carbanion chain end with most functional groups. Although the direct anionic polymerization of styrene monomers with active hydrogens results in quenching of the anion, a number of functional groups have been shown to be stable towards the carbanion chain end. A limited number of monomers with functional groups have been shown to tolerate anionic polymerization conditions with functionalities of alkenes, alkynes, cyclobutanes, adamantanes, ethers, thioethers, aromatics, oligo(fluorenes), tert-amines, diphenylamines, fluorines, and those containing substituents with carbon bonded to heteroatoms (Ge, Sn, Bi, P,Si). Also included are substituents with Si bonded to Si, OR, NR_2, and H. The specific monomers that tolerate anionic polymerization conditions are shown in Figure 1.10.

The living anionic polymerization of halostyrenes has produced mixed results. Conflicting reports exist in the literature of whether the polymerizations of 4-bromostyrene and 4-chlorostyrene can be controlled or not, with one report of well controlled products and one report of broad or multimodal products, shed doubt on whether these qualify as living anionic polymerization.[35,140-142] It is likely that these polymers would suffer from halogen-lithium exchange reactions similar to those used by Gnanou et al. to synthesize multifunctional initiators.[35] The polymerization of 2- and 4-fluorostyrene has been shown to be well-controlled in THF at -78 ℃, resulting in polymers of narrow molecular weight distribution.

Two strategies have been developed to realize the anionic polymerization of styrenes with functional groups. The first techniques is to introduce electron withdrawing groups on the benzene ring of styrene to lower the reactivity of the benzyl carbanion chain end. The second technique is to use protecting groups and deprotect in a post-polymerization reaction to yield the desired polymer. The use of electron withdrawing

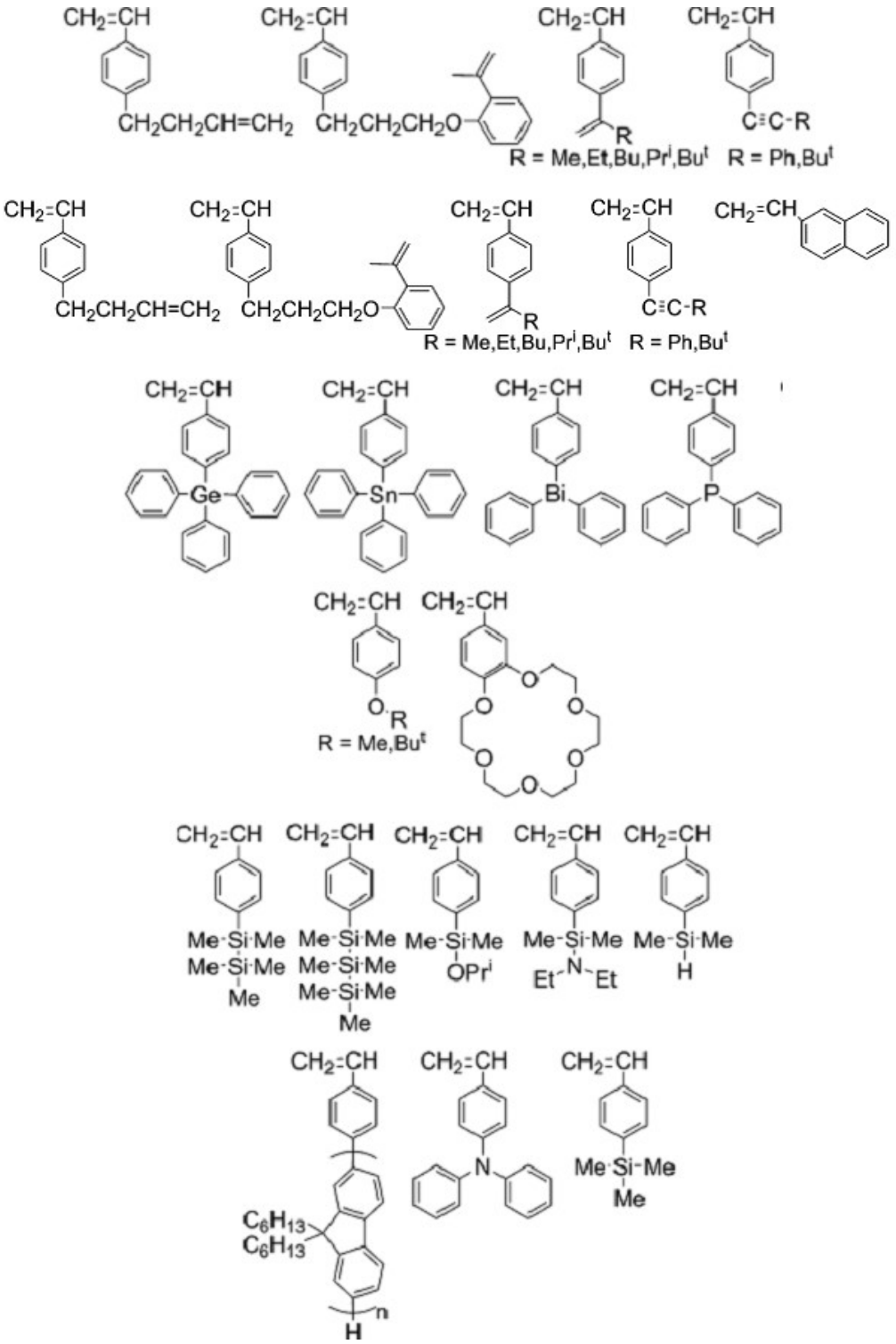


Figure 1.10 Functionalized styrene monomers that undergo anionic polymerization. Adapted from Reference 156.

groups was first proposed by Ishizone and Hirao with the intention that the introduction of an electron withdrawing group would reduce the electron density around the living carbanion, thereby reducing its reactivity and eliminating side reactions.[139,143] The first successful demonstration of this strategy was the polymerization of 4-vinyl(N,N-diisopropylbenzamide) in THF at -78 ℃. A quantitative yield of narrow molecular weight distribution polymer of predictable molecular weight was produced in this way. The lowered reactivity of the carbanion relative to polystyryllithium was demonstrated by the inability of poly(vinyl(N,N-diisopropylbenzamide)) to initiate the polymerization of either α-methylstyrene or isoprene, monomers that are normally initiated by living polystyrene. The apparent increase in the stability of the carbanion can be explained by taking into account that the addition of the N,N-diisopropylamido groups cause the extension of the π-conjugated system to include the carbonyl bond, resulting in an increase in the resonance effect.[139] A whole class of functionalized styrene monomers with N,N-dialkylamido functionalities were shown to be well controlled under identical reaction conditions to that of 4-vinyl(N,N-diisopropylbenzamide) (Figure 1.11). [144]

A different nitrogen-containing electron withdrawing group used in the polymerization of functionalized styrene is N-substituted imines (Figure 1.12). The facile nature of the conversion of N-alkyl and N-arylimines to aldehydes by acidic hydrolysis make this an attractive functionality. N-[(4 vinylphenyl)methylene]cyclohexamine was polymerized at -78 ℃ in THF producing a polymer of predictable molecular weight and narrow molecular weight distribution.[145] As with the previous example, a series of monomers underwent anionic polymerization at these conditions - The investigation of monomers with different alkyl and arylimine groups revealed that steric hindrance provided by the N-substituents has a direct effect on the ability to polymerize it anionically. All monomers investigated, including the least sterically hindered monomer with N-methyl substituents, underwent anionic polymerization at -78 ℃ in THF. Upon complete consumption of the monomer broadening of molecular weight and crosslinking occurred for the least sterically hindered monomers. For monomers containing isopropyl or *tert*-butyl groups more stable carbanions were produced.

The incorporation of oxazolines electron withdrawing groups, used frequently in small molecule organic synthesis as a protecting group for carboxylic acids, in the

benzene ring of styrene polymerized to narrow molecular weight distribution under normal anionic conditions for styrene of -78 ℃ in THF.[146,147] Oxazoline was expected to proceed smoothly due to the stable nature of these protecting groups even under highly basic conditions.[148] The cleavage of the oxazoline protecting group required significantly harsher conditions when compared to those used in the cleavage of the protecting group in small molecule organic synthesis. The full cleavage the oxazoline protecting group was confirmed by ^{1}H NMR. A series of oxazoline protected monomers were investigated with serious side reactions occurring in the case of 2-[2-(4-vinylphenyl)ethenyl]-4,4-dimethyl-2-oxazoline. The double bond between the benzene ring and the oxazoline group is necessary to provide resonance between the two ring structures but is vulnerable to attack by the carbanion. To suppress this effect a methyl group was added substituent to the double bond and polymerization of 2-[1-methyl-2-(4-vinylphenyl)ethenyl]-4,4-dimethyl-2-oxazoline proceeded to yield product exhibiting a narrow molecular weight distribution. Exposure of the polymer to UV radiation caused it to become insoluble, most likely due to crosslinking of the double bond. This could lead to potential photo-crosslinking applications.

Despite the high reactivity and the known susceptibility of cyano groups to both nucleophiles and electrophiles functionalized styrene, 4-cyanostyrene, was shown to polymerize quantitatively to predictable molecular weights and narrow molecular weight distributions.[149,150] The carbanion of poly(4-cyanostyrene) was shown to be stable through 24 hours at -78 ℃ in THF. When the position of the cyano group was moved from *para* to the *meta* and *ortho* positions, sluggish polymerization reactions and side reactions were encountered. No polymerization was seen in reactions of 3-cyanostyrene at -78 ℃ in THF. At slightly higher temperature, -30 ℃, the reaction proceeded but with a broad molecular weight distribution, indicative of side reactions. The reaction of 2-cyanostyrene proceeded at -78 ℃ but conversion was incomplete, reaching only 30 % after 200 hrs Despite the high reactivity and the known susceptibility of cyano groups to both nucleophiles and electrophiles functionalized styrene, 4-cyanostyrene, was shown to polymerize quantitatively to predictable molecular weights and narrow molecular weight distributions.[149,150] The carbanion of poly(4-cyanostyrene) was shown to be stable

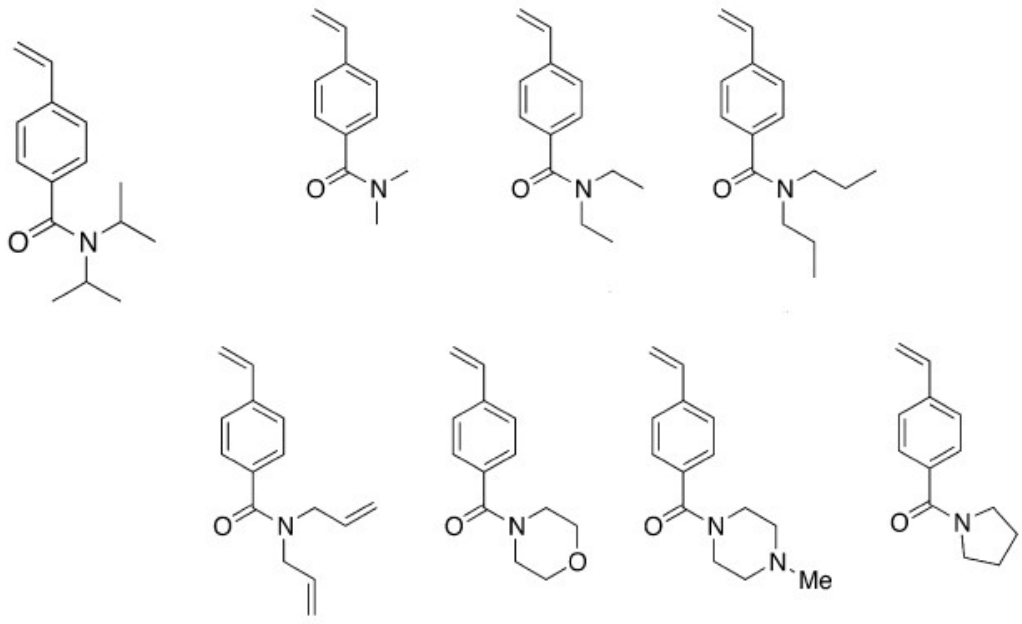


Figure 1.11 Class of dialkylamido functionalized styrene monomers that undergo anionic polymerization. Adapted from Reference 142.

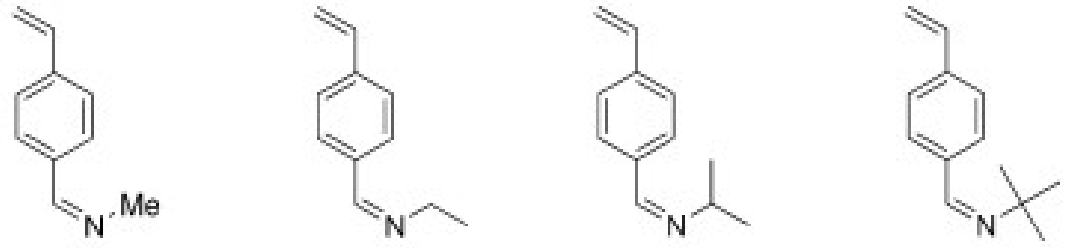


Figure 1.12 Class of N-substituted imine functionalized styrene monomers investigated for anionic polymerization.

through 24 hours at -78 ℃ in THF. When the position of the cyano group was moved from *para* to the *meta* and *ortho* positions, sluggish polymerization reactions and side reactions were encountered. No polymerization was seen in reactions of 3-cyanostyrene at -78 ℃ in THF. At slightly higher temperature, -30 ℃, the reaction proceeded but with a broad molecular weight distribution, indicative of side reactions. The reaction of 2-cyanostyrene proceeded at -78 ℃ but conversion was incomplete, reaching only 30 % after 200 hrs.

Literature reports of sterically hindered esters that are stable under strongly basic conditions, including in the presence of organolithium and Grignard reagents, led Hirao et al. to investigate the anionic polymerization of sterically hindered vinyl benzoates.[151,152] Starting with *tert*-butyl 4-vinyl benzoate, reaction with cumyl potassium and potassium naphthalenide at -78 ℃ in THF produced polymers with slightly broader than expected molecular weight distributions. With longer reaction times the appearance of multimodal molecular weight distributions developed, indicative of side reactions. Lower reaction temperature was used to reduce side reaction. The polymerization of *tert*-butyl 4-vinyl benzoate at -95 ℃ proceeded to produce polymers having predictable molecular weights and narrow monomodal molecular weight distributions. The removal of the *tert*-butyl group to yield poly(vinyl benzoic acid) was performed using $(CH3)_3SiCl$–NaI to cleave. Less sterically hindered ester monomers like methyl 4-benzoate and allyl 4-vinylbenzoate underwent no apparent polymerization at -78 ℃ in THF.[139] Attempts to polymerize aryl vinyl benzoates required *tert*-butyl groups in the 2,6 positions of the phenyl ring.[153] In the case of these *tert*-butyl substituted monomers, the polymerization with a stable living chain end at -78 ℃ and produced polymer of narrow molecular weight distribution.

Another class of substituent groups known to act as electron withdrawing groups and have stability towards electrophiles are N,N-dialkylsulfonamides.[154] The first N,N-dialkylsulfonamide substituted styrene to be tried was N,N-diethyl-4-vinylbenzenesulfonamide, proceeding quantitatively to a predictable molecular weight of narrow distribution.[155] Attempts to cleave the substituent group were largely unsuccessful even under harsh conditions. Instability was noted during the synthesis of the monomer N,N-dimethyl-4-vinylbenzenesulfonamide that resulted in polymerization of the monomer during column chromatography and at the bench top at room temperature. The isolated monomer did polymerize at -78 ℃ in THF to predicted molecular weight and narrow

distribution but the difficult in handling most likely precludes it from widespread use. In order to try to provide a more easily cleavable substituent group the monomer N-methyl-N0-[(4-vinylphenyl)sulfonyl]piperazine was synthesized. The polymerization reaction was well controlled, reaching predictable molecular weight and narrow molecular weight distribution at -78℃ in THF. Again, the substituent proved to be difficult to cleave despite harsh conditions.

The other strategy to polymerize functionalized polystyrene involves the use of protecting groups that render the functional group stable to the carbanion chain end without reducing the reactivity of the living chain end by electron withdrawing effects. In general three synthetic steps are followed in order to produce polymers using living anionic polymerization with reactive functional groups using this method. The first step entails the introduction of a protecting group to the monomer that prevents the functionality from being attacked. The second step is the polymerization of the protected monomer. The third step is the cleavage of the protecting group to yield the desired polymer.[6,139,156] In order for this strategy to be effective the protecting group must readily cleavable by a post-polymerization reaction. The first successful demonstration of this technique was used for the polymerization of poly(4-hydroxystyrene). Prior to polymerization the hydroxyl group was protected with tert-butyldimethylsilyl (TBDMS) to yield 4-*tert*-butyldimethylsilyloxystyrene.[136] The polymerization of the monomer proceeded at -78℃ in THF to predictable molecular weight and narrow molecular weight distribution. A litany of initiator were shown to be effective, including n-BuLi, *sec*-BuLi, lithium, sodium and potassium naphthalenides, all common initiators for the polymerization of styrene.[136] The removal of the protecting group after polymerization was done with either 2 N HCl in THF–H_2O (5/1, v/v) or $(C_4H_9)_4NF$ in THF at room temperature. Investigation of the polymerization of 2-tert-butyldimethylsilyloxystyrene and 3-*tert*-butyldimethylsilyloxystyrene produced insightful results. While the *meta* functionalized monomer proceeds exactly as the *para* functionalized monomer, the *ortho* functionalized monomer did not produce a polymer. The lack of polymerization was explained by an intramolecular reaction of the living chain end with the silicon atom of the protecting group due to the proximity. The intramolecular rearrangement results in the anion being transferred to the oxygen atom, the lower reactivity oxyanion is incapable of

polymerizing styrenic monomers. Variations in the bulkiness of the alkyl groups attached to the silyl protecting group were also tested. Monomers with protecting groups of bulkiness greater than that of TBDMS, *tert*-hexyldimethylsilyloxystyrene and triisopropylsilyloxystyrene, underwent anionic polymerization at -78 ℃ in THF to predictable molecular weight and narrow distribution.[157] When the same conditions were applied to polyhydroxystyrene monomers with protecting groups of reduced bulkiness or containing heteroatoms, trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, or *tert*-butoxydimethylsilyl, the reactions were unsuccessful.

Another well-established protected monomer for the synthesis of polyhydroxystyrene is *tert*-butoxystyrene.[135] The polymerization of *tert*-butoxystyrene proceeded at -78℃ in THF to predictable molecular weight and narrow molecular weight distribution. The removal of the protecting group was difficult, requiring the use of strong acid and reflux conditions. In an attempt to find a more easily removed protecting group, acetals were employed. The monomers, 4-(1-methoxymethoxy)styrene, 4-(1-ethoxyethoxy)styrene and 4-(2-tetrahydropyranyloxy)styrene, all proceeded in the same fashion as *tert*-butoxystyrene at the same conditions.[133,134,139] The cleavage of the acetal protecting groups was successful at much milder conditions, making these monomers highly desirable. Currently, only 4-(1-ethoxyethoxy)styrene is commercial available.

Protection of alkyl hydroxyl substituents on the benzene ring of styrene was also tested using silyl protecting groups. 4-(2-hydroxyethyl)styrene and 4-(2-hydroxypropyl)styrene, both shown to be polymerizable at -78 ℃ in THF to predictable molecular weight and narrow molecular weight distribution.[158] For 4-(2-hydroxyethyl)styrene, other protecting groups that led to successful reactions include isopropyldimethylsilyl, triethylsilyl, and trimethylsilyl groups.

The sulfur containing analogs of hydroxystyrene and4-(2-hydroxyethyl)styrene, 4-vinylthiophenol and 4-(2-mecaptoethyl)styrene, were protected for living anionic polymerization by TBDMS. At -78 ℃ in THF to the anionic polymerization of these monomers proceeded to predictable molecular weight and narrow molecular weight distribution.

The functional group amine is protected from the carbanion of a living chain end by converting the amines of 4-aminostyrene and 4-aminoethylstyrene to N,N-

bis(trimethylsilyl)aminostyrene and N,N-bis(trimethylsilyl)aminoethylstyrene, respectively. The polymerization of these monomers proceeded at -78 ℃ in THF to predictable molecular weight and narrow distribution.[159-161] The cleavage of the protecting group was successful under mild conditions, quantitatively producing the amine functionality at a pH ~5.

Another monomer class that employs silyl groups to protect during anionic polymerization is acetyl functionalized styrenes. The monomer, 4-[α-(1-tert-butyldimethylsilyloxy)ethenyl]styrene, protected with TBDMS, rearranges to a TBDMS enol ether functionality (Figure 1.13). Polymerization of the monomer proceeded at -78 ℃ in THF to predictable molecular weight and narrow distribution.[162] Two other acetyl functionalized styrenes, 4-vinylpropiophenone and 4-isopropenylacetophenone, were protected by TBDMS and polymerized anionically in well-controlled reactions at -78 ℃ in THF.

Attempts to polymerize the *meta* and *ortho*- vinylacetophenone found different results for each. *Meta*-vinylacetophenone was a well-controlled reaction, polymerizing under identical conditions to the *para* monomer. The *ortho* monomer, *ortho*-vinylacetophenone, did not polymerize. As was seen in TBDMS protected *ortho*-hydroxystyrene, the living chain end participates in an intra and intermolecular reaction with the silicon atom of the protecting group resulting in a rearrangement reaction and the development of an oxyanion.

A trimethylsilyl group is the protecting group of choice for the anionic polymerization of alkyne functionalized styrene monomers.[163] As with the previous investigations of anionic polymerization of functionalized styrenes, the effect of the position of the substituent was investigated. In this case it was found to have no effect, with 2, 3, and 4-Trimethylsilylethynylstyrene all polymerizing at -78 ℃ in THF to predictable molecular weights and narrow molecular weight distributions. The protecting group was easily cleaved by $(C_4H_9)_4NF$ in THF at room temperature.

Synthesis of poly(formylstyrene) by anionic polymerization requires a protecting group strategy. Despite the common use of acetals as protecting group against strong base and nucleophiles, attempts to use a number of different acetal groups to protect the

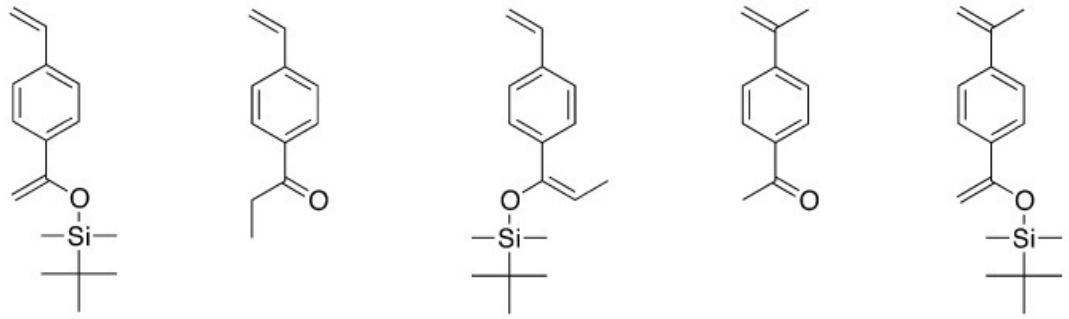


Figure 1.13 Class of acetyl functionalize styrene monomers and their corresponding TBDMS protected monomers. Adapted from Reference 142.

aldehyde functionality proved fruitless.[139] A cyclic N,N-acetal protecting group was used to synthesize the monomer 1,3-dimethyl-2-(4-vinylphenyl)imidazolidine, which was ableto polymerize anionically at -78 ℃ in THF to predictable molecular weights and narrow molecular weight distributions.

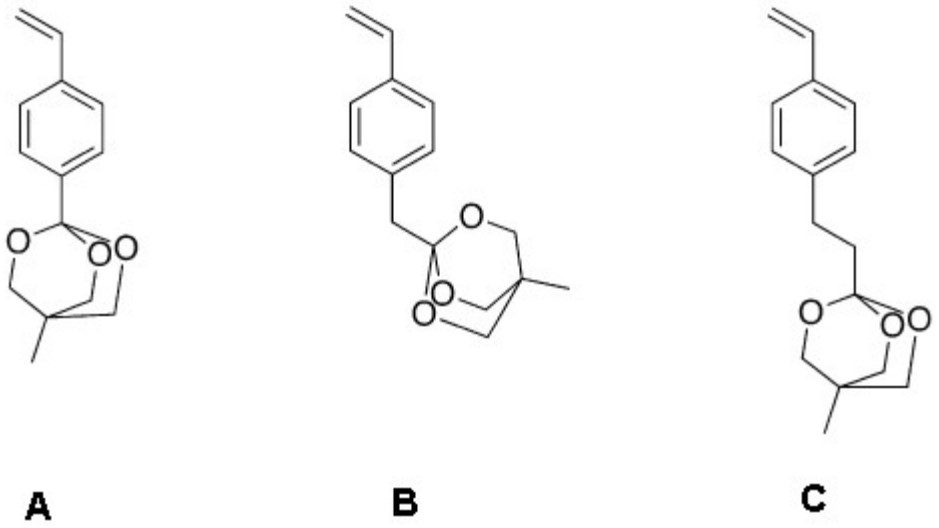
Silanol functionalized styrene monomers were protected by conversion to alkyoxysilylstyrene before polymerization. (4-vinylphenyl)dimethylmethoxysilane was shown to initiate but the living chain end population decreased over time, evidenced by the slow fading of the colored solution. The resulting polymers were of broad molecular weight distribution and obtained in less than quantitative yield. The anionic polymerization of (4-vinylphenyl)dimethyl-2-propoxysilane was stable at -78 ℃ as evidenced by the consistent reaction color for several hours. The resulting polymers were of predictable molecular weight, quantitative yield and narrow molecular weight distribution.

Lastly among styrene monomers with protected functional groups is a group of carboxylic acid protected styrenes. The functionality is protected by conversion to *ortho*ester functionalities. The reaction of 1-(4-vinylphenyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane with anionic polymerization initiators resulted in a low yield of insoluble polymer. In the case of 1-(4- vinylphenyl)methyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, 1-[2-(4-vinylphenyl)ethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (Figure 1.14,B and C,respectively), polymerization was conducted at -78℃ in THF to yielded polymer of predictable molecular weight and narrow

molecular weight distribution. The alkyl methylene carbons between the benzene ring are to prevent 1,6-elimination that occurs due to resonance of the carbanion in the polymerization of monomer A of Figure 1.13 .

Conclusions

Anionic polymerization has come a long way since the pioneering work of the 1950s and 1960s but many challenges still remain. The goal of synthesizing multifunctional initiators that require no polar additives, thereby allowing for the polymerization of polydienes of high 1,4-microstructure, remains to be met. The synthesis of functionalized polystyrenes by anionic polymerization continues to be challenges. As polymers continue to push into every sector of industrial life, demand from the commercial sector for materials that can be tailored to meet specific applications will continue to grow. Only by undertaking new synthetic strategies and understanding the fundamental of those currently in use will these challenges be met.



1,6 ELIMINATION

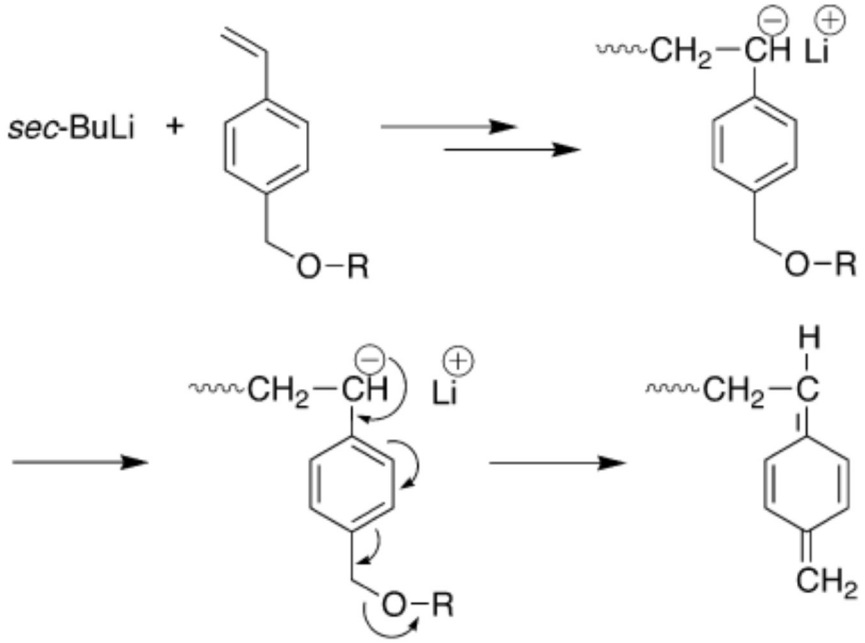


Figure 1.14 Class of orthoester protected styrene monomers (top)and 1,6-elimination reaction that occurs in monomer A (bottom). Adapted from Reference 142.

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CHAPTER 2 SYNTHESIS, CHARACTERIZATION AND APPLICATION OF THE SELF-ASSEMBLY OF AMPHIPHILIC HOMOPOLYMERS POLY(4-HYDROXYSTYRENE) AND POLY(4-(4-BROMOPHENYLOXY)STYRENE)

A version of this chapter will be submitted for publication:

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The article has been revised to fit dissertation guidelines. All synthetic work, measurements and writing were performed by Christopher M. Hurley, with the exception of the growth, treatment and analysis of human cancer cells by Megan Johnstone. All work was performed under the guidance of Mohammad Changez, Nam-Goo Kang and Jimmy W. Mays.

Abstract

Amphiphilic homopolymers of poly(4-hydroxystyrene) and poly(4-(4-bromophenyloxy)styrene) were synthesized by post-polymerization reactions of poly(4-(1-ethoxyethoxy)styrene). Poly(4-(1-ethoxyethoxy)styrene) was synthesized by living anionic polymerization under high vacuum conditions. After acidic deprotection to yield poly(4-hydroxystyrene) and etherification reaction to yield poly(4-(4-bromophenyloxy)styrene, several characteristics of the homopolymers were studied, including thermal stability, solubility and self-assembly behavior in solvent mixtures. The self-assembly of both homopolymers was measured by dynamic light scattering (DLS) and confirmed by atomic force microscopy (AFM) and transmission electron microscopy (TEM). The formation of gold nanoparticles took place within vesicles of poly(4-hydroxystyrene), as confirmed by TEM. Lastly, vesicles of poly(4-hydroxystyrene) were loaded with the chemotherapy drug, doxorubicin, and transferred from deionized water/methanol solvent mixtures, dialyzed and then solubilized in basic PBS buffer solution (pH=10) as a treatment for the cancer cell line HTC-116.

Introduction

The self-assembly of amphiphilic homopolymers has emerged as a growing field of interest within polymer chemistry.[1] The self-assembly behavior of block copolymers is well known, as amphiphilic block copolymers have been shown to form a variety of nanostructures including micelles, vesicles, cylinders, and a variety of more complex structures. The impetus for the self-assembly of block copolymers is the chemical

incompatibility of one block in the chosen solvent, typically combinations of hydrophobic and hydrophilic blocks are used. By careful manipulation of parameters such as the solvent mixture used, block length, block ratio, solvophilicity/solvophobicity of the block segments used, the nanostructure of the block copolymer self-assembly can be tailored.[2,3] Interest in these materials has been spurred on by their potential application in a wide variety of fields, including drug delivery sensing, and nanotechnology.[4-7]

Thayumanavan et. al. were the first to show this same type of self-assembly behavior in a homopolymer by utilizing a specifically designed monomer with a hydrophilic and hydrophobic moiety on either side of the styrene backbone, thus inducing facial amphiphilicity.[8] This clever design allows for the formation of homopolymer micelles in both and aqueous and hydrophobic solutions. Lee et al. were able to demonstrate the amphiphilic behavior of poly(2-(4-vinylphenyl)pyridine) in which the polymer backbone provides the hydrophobic group and the pendant group acts as the hydrophilic group, allowing for the formation of vesicles.[9-12] Thayamanavan et al. further demonstrated the potential of amphiphilic homopolymers by performing a rearrangement reaction using the core of the micelle as a microreactor. When compared to micelles formed from commonly used small molecules and a diblock copolymer, those micelles constructed of homopolymer were more rigid and confined.[13]

Since the discovery of homopolymer self-assembly behavior two techniques have been developed to synthesize these macromolecules: the “monomer-induced” method and the “hydrophobic-group-induced” method.[1] The “monomer-induced” method relies upon specially designed monomers, with hydrophobic and hydrophilic moieties or hydrophobic polymer backbones with hydrophilic pendant groups, to cause self-assembly.[8,10-12,14-20] The “hydrophobic-group-induced” method relies upon a hydrophilic homopolymer attached to a large hydrophobic end group to cause self-assembly.[21-30] Amphiphilic homopolymer self-assembly is achieved through an intramolecular phase separation and non-covalent intra and intermolecular interactions.[1]

Poly(4-hydroxstyrene) (PHS) represents an ideal candidate for amphiphilic homopolymer self-assembly. The rigid and polar nature of the pendant group and the flexible and non-polar polymer backbone are analogous to the poly(2-(4-vinylphenyl(pyridine)) used by Lee et al.[10,11] The recent introduction of acetal

functionalized styrene monomers has caused interest in poly(4-hydroxystyrene) to grow.[31-35] Poly(4-hydroxystyrene) has already attracted attention for a variety of applications including photoresist materials, physical gels composites and pH responsive materials[36-41] The direct polymerization of 4-hydroxystyrene by anionic polymerization is not viable due to the acidic nature of the functional group. Anionic polymerization provides the ability to produce narrow molecular weight distribution polymers with stoichiometric control over the molecular weight.[42] The utilization of protecting groups, to be cleaved after the polymerization to yield poly(4-hydroxystyrene), is the singular successful strategy for anionic polymerization. The acetal functionalized monomers represent another element of this same protecting group strategy[1,43]. The common utilization of acetals as hydroxyl protecting groups in small molecule chemistry is attributed to their straightforward synthesis and facile deprotection. The mild conditions required to cleave the acetal groups from these monomers to produce poly(4-hydroxystyrene) make 4-(1-ethoxyethoxy)styrene an attractive alternative to 4-tert-butoxystyrene, 4-tertbutyldimethylsiloxystyrene, or 4-acetoxystyrene.

The stability of acetal functionalized polystyrenes to anionic polymerization conditions was demonstrated by Frey et al. when polymerizing in THF at very low temperature (-90 ºC).[32] It was successfully shown that homopolymers of poly(4-(1-ethoxyethoxy)styrene) could be produced with narrow molecular weight distribution over a range of molecular weights (2700-69000 g/mol). Furthermore, they confirmed that the living nature of the chains ends was retained through the synthesis of block copolymers with 2-vinyl pyridine. Hirao et al. first referenced the anionic polymerization of 4-(2-tetrahydropyranyloxy)styrene as well-controlled chain length and narrow PDI in a footnote as “unpublished research”.[44] The report of anionic polymerization of 4-(2-tetrahydropyranyloxy)styrene and the demonstration of its living nature by homo- and block copolymerization was demonstrated by Gopalan et al.[34]

The chemical reactions of the small molecule phenol have been thoroughly studied in the literature and play an important role in the pharmaceutical industry.[45] The potential to adapt known phenol reaction chemistry to yield new polymeric materials by post-polymerization reactions on poly(4-hydroxystyrene) is an area in need of further investigation. The phenol functionality present in each monomer unit potentially allows for

the incorporation of previously difficult to achieve functionalities. Etherification reactions utilizing the phenol functionality have been used in order to incorporate several desirable functionalities already but many remain to be realized.[46-52]

Halogen bonding is a non-covalent intra- or intermolecular force defined by IUPAC in 2013 as a "net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity."[53] Although several examples of halogen bonding for polymeric materials have been presented in the literature, the investigation of this molecular force is limited.[54-56]

In this work, poly(4-(1-ethoxyethoxy)styrene) is produced by anionic polymerization. Post-polymerization reactions yield poly(4-hydroxystyrene) and poly(4-(4-bromophenyloxy)styrene) (PBPOS). The homopolymer self-assembly solution behavior of these two polymers was investigated by dynamic light scattering (DLS) in aqueous and organic solvent mixtures, and by atomic force microscopy (AFM), transmission electron microscopy (TEM). The capacity of PHS vesicles in solution to facilitate the formation of gold nanoparticles was also investigated.

Experimental Section

Chemicals

4-Bromobenzyl bromide 98% (Sigma Aldrich), sodium hydride 60% dispersion in mineral oil (Aldrich), concentrated HCl (Fisher), tetrahydrofuran (Fisher), methanol (Fisher), 4-(1-ethoxyethoxy)styrene (Synquest Laboratories), doxorubicin hydrochloride (Fisher), trimethylamine (Aldrich), . Tetrahydrofuran was distilled into the reactor from a purified solvent reservoir on the vacuum manifold.[57] *Sec*-butyllithium was diluted to the desired concentration by hexanes distilled into the appropriate apparatus from a purified solvent reservoir on the vacuum manifold. 4-(1-Ethoxyethoxy)styrene (Synquest Labs) was first dried by CaH_2 under high vacuum before being passed through a glass filter and separated into ampules. The ampules of monomer were then further distilled twice under dynamic vacuum using moderate heating to assist. Ampules of purified monomer were then diluted to the desired concentration with purified THF. All anionic polymerization

reactions were performed under high vacuum in custom built all glass reactors according to standard protocol.[57,58]

Characterization

All ^{1}H NMR analyses were performed on a Varian VNMR 500 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as the solvents. Molecular weights were determined by an RI detector based on calibration with polystyrene standards (6000-7500000 Da) by size exclusion chromatography (SEC) measurements performed using a Tosoh EcoSEC System equipped with two Tosoh TSKgel SuperMultiporeHZ-M and one TSKgel SuperMultipore HZ-M guard column. All polymers were eluted with THF at 40 °C with a flow rate of 0.35 ml/min and a run time of 15 minutes. Dynamic light scattering was used to determine the hydrodynamic radius R_H of polymer particles in solution using a PD Expert Instrument (Precision Detectors) with ten repetitions performed at a scattering angle of 95°. Atomic force microscopy (AFM) samples were drop-cast either on to freshly cleaved mica or onto clean glass slides depending on the microscope used. Freshly cleaved mica was used as the stage for AFM measurements performed using a Nanoscope IIIa Microscope with Multimode Controller (Veeco Instrument) in tapping mode at room temperature. Measurements utilizing glass slides as the stage were performed using an Asylum Research MFP3D in contact mode at room temperature. TEM images were obtained using a Zeiss Libra 200 MC TEM/STEM. TEM samples were prepared by depositing 10 µL of vesicles solution onto a carbon coated copper grid and allowing the solution to dry for several hours. UV-vis spectrophotometry was performed in the wavelength interval 250-900 nm using a Thermo Scientific Evolution 600 UV-Vis Spectrometer with using a quartz cuvette. Thermogravimetric analysis was performed on a TA Instruments Q-50 TGA. The sample was heated from 25 °C to 800 °C at a rate 20 °C/min in the presence of compressed air (Airgas) at a flow rate of 40 ml/min. Fourier-Transform Infrared Spectroscopy (FT-IR) was carried out using a Varian 4100 FT-IR using KBr (Aldrich, Spectroscopy) as a reference and precursors for background subtraction.

Anionic Polymerization of 4-(1-ethoxyethoxy)styrene

A typical example of the synthesis of poly(4-(1-ethoxyethoxy)styrene) is as follows:

The main reactor for polymerization of 4-(1-ethoxyethoxy)styrene was washed with (3-methyl-1,1-diphenylpentyl)lithium solution in hexanes to remove impurities from the reactor. The washing solution was then recollected by rinsing with distilled hexanes into the purge flask before it was removed from the apparatus.

Sec-butyllithium (1 mmol) was introduced by fracturing a breakseal and the ampule was rinsed by distilled hexanes to ensure correct stoichiometry. The reactor was then cooled to -98 °C by a liquid N_2/methanol bath. 10 mins were allowed for temperature of the reactor to equilibrate. The ampule of 4-(1-ethoxyethoxy)styrene (0.97 g/15 ml) was cooled to -98 °C before being introduced by fracturing the breakseal. The reaction was allowed to proceed for 1.5 hours before being terminated by the introduction of methanol by fracturing a breakseal. The polymer was precipitated by into methanol at -25 °C. The polymer was filtered, redissolved in tetrahydrofuran and rotary evaporated to dryness before being dried in a vacuum oven.

Deprotection of poly(4-(1-ethoxyethoxy)styrene)

1 g of poly(4-(1-ethoxyethoxy)styrene) was dissolved in 20 ml of THF at room temperature. To the solution, 1 ml of concentrated HCl was added with continuous swirling for 5 minutes. The polymer was then precipitated in to deionized water. The precipitated product was then collected by filtration, rinsed with deionized water to remove HCl and dried in a vacuum oven.

Williamson Etherification Reaction of poly(4-hydroxystyrene) and 4-bromobenzyl bromide

0.500 g of poly(4-hydroxystyrene) (4.16 mol of OH functional groups) 0.250 g of NaH 60% dispersion in mineral oil (6.24 mol) and a stir bar were placed in a two neck round-bottom flask and attached to the vacuum line. 25 ml of THF was distilled into the flask. The polymer and base were allowed to react until a characteristic light orange color

was seen indicating the formation of the phenoxide. At this point the round-bottom flask was removed from the vacuum line, connected to a reflux condensor and quickly put under a blanket of argon gas. 2.08 g of bromobenzyl bromide (8.32 mol) was dissolved in 10 ml of THF in a septa capped flask under argon gas. The bromobenzyl bromide solution was then transferred by cannula to the round-bottom flask and the solution was brought to reflux for eight hours. The reactor was then allowed to cool to room temperature before the solution was filtered to remove solid salt byproduct. The salt was rinsed several times with THF to remove any polymer product. Rotary evaporation was used to reduce the volume of the solution before the polymer was precipitated into a large excess of methanol. The polymer was collected by filtration and dried in a vacuum oven.

Self-assembly of homopolymers in solvent mixtures

In clean dry vials poly(4-hydroxystyrene) and poly(4-(4-bromophenyloxy)styrene) were dissolved in methanol and THF, respectively, to a concentration of 10 mg/ml to be used as stock solution. All solvents used were freshly filtered and centrifuged at 20,000 RPMs for 30 min to ensure purity. Vials were filled with the desired ratio of solvent mixtures before 0.5 ml of stock solution was added dropwise with vigorous shaking between drops to fully disperse solution. Visual changes in the turbidity of the solution were used as indication of the development of particles in solution. Vials were left unperturbed overnight to allow for settling in solution. The presence of self-assembled particles was confirmed by DLS, AFM and TEM.

Formation of gold nanoparticles

Small aliquots of vesicle solutions were taken and placed in clean, dry vials to which the appropriate amount of $HAuCl_4$ was added and allowed 6 hours to fully disperse in the vesicle solution. Hydrazine was then added to reduce the $HAuCl_4$ in solution, which caused a color shift from a yellow solution to a purple or purplish red solution. The vials were allowed to sit overnight before UV-vis spectroscopy was performed on the solutions.

Preparation of doxorubicin loaded poly(4-hydroxystyrene) Vesicles

5 mg of doxorubicin hydrochloride was converted to the free base doxorubicin by dissolving in 5 ml of DMSO and reacting with 2.0 molar equivalent of trimethylamine for 24 hours. 50 µl of free base doxorubicin solution (50 µg) was added to 2.5 ml of methanol and 0.5 ml of a solution of PHS 4 in methanol (10 mg/ml). 7 ml of deionized water was slowly added to the solution. The sample was shaken vigorously and allowed to sit overnight to allow the solution to settle. An analogous solution of PHS 4 vesicles was formed in the same 70/30 ratio of water/methanol to serve as a model for comparison. Both solutions were loaded into dialysis tubing with a molecular weight cut off of 3,500 g/mol. The solutions were stirred in DI water for 48 hours to remove any free doxorubicin. These aqueous solutions were used directly for cancer cell treatments at basic pH.

Cell Culture

HCT-116's, a colon cancer cell line, were counted and seeded at 100,000 per 60 mm2 dish with DMEM supplemented with 10% FBS and 5 mM Glucose. Briefly, the cells were trypsinized, pelleted and counted using an automated cell counter, CellScepter 2.0 EMD Millipore according to manufacturer instructions. Cells were left to grow over 24 hours before beginning treatment.

Treatment of HCT-116 cancer cells with Doxorubicin loaded Poly(4-hydroxystyrene) Vesicles

Treatments were as follows:

The control group, 24 hours after seeding, had its media replaced. Empty vesicles and vesicles loaded with doxorubicin groups were made as follows. The vesicles were measured to have the following concentrations 82,000 vesicles/ml. Vesicles with and without doxorubicin were mixed in a 1:1 ratio with PBS (pH 10.0). 500 µL of the PBS solution were added to 4.5 ml of cell culture media (as described above) to give a final concentration of 41,000 vesicles per 5 ml of media or ~8,000 vesicles per ml. Treatments

were left on for 24 hours and done in duplicate. At the end of this timepoint cells were trypsinized, pelleted and re-counted.

Results and Discussion

Well defined homopolymers of poly(4-(1-ethoxyethoxy)styrene) were synthesized by anionic polymerization at -98 °C using high vacuum techniques, followed by cleavage of the acetal protecting group to yield narrow molecular weight poly(4-hydroxystyrene). Subsequently, the poly(4-hydroxystyrene) was reacted with 4-bromobenzyl bromide, in a Williamson etherification reaction, to yield a new aryl halogenated polymer, poly(4-(4-bromophenyloxy)styrene). The results of the polymerization and subsequent post-polymerization modification steps are summarized in Table 2-1. Insight into the molecular structure of the polymers was achieved through ^{1}H NMR (Figure 2.1). The anionic homopolymerization of 4-(1-ethoxyethoxy)styrene and acidic deprotection had previously been recorded in the literature so the structure of these polymers were confirmed against previously reported ^{1}H NMR spectra.[32] The quantitative conversion of PHS to PBPOS was confirmed by the disappearance of the hydroxyl singlet peak at 9.0 ppm and the integration of a newly developed singlet at ~4.90 ppm corresponding to the methylene protons and the two additional broad singlets between 7.5 ppm and 7.0 ppm corresponding to the four additional aromatic protons (Figure 2.1). Further confirmation was seen in the FT-IR of both polymers as the broad OH stretch apparent in the spectra of poly(4-hydroxystyrene) disappears in the spectra of poly(4-(4-bromophenyloxy)styrene) (Figure 2.3) The Williamson etherification reaction of PHS was achieved with similar ease to the analogous small molecule reaction of phenol. The possibility of directly synthesizing a targeted molecular weight and narrow molecular weight distribution PBPOS by anionic polymerization of the monomer (4-bromophenyloxy)styrene is dubious due to the likelihood of lithium halogen exchange reactions. The exchange reaction would likely cause crosslinking and carbanion species in solution of different reactivities. Characterization of the thermal porperties of all three polymers, PpEES, PHS and PBPOS was conducted using TGA and DSC. The

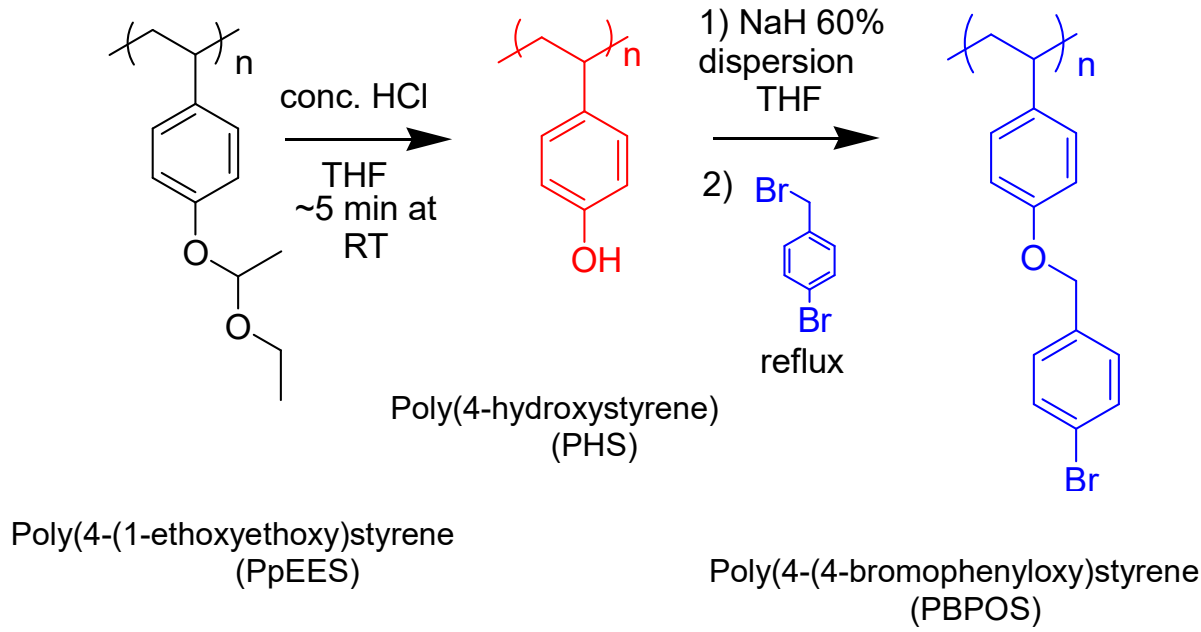


Figure 2.1 Conversion of PpEES to PHS intermediate product and the conversion of PHS TO PBPOS.

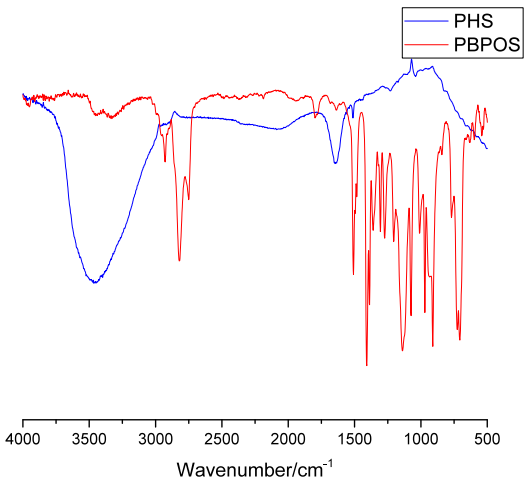


Figure 2.2 FTIR spectra of PHS and PBPOS.

Table 2-1 Molecular Characteristics of Amphiphilic homopolymers Poly(4-hydroxystyrene) and Poly (4-(4-bromophenyloxy)styrene) Made by Anionic Polymerization

sample	polymer	$M_{n,\,SEC}$	M_w/M_n
1a	PpEES	7000	1.04
1b	PHS	4700	1.08
2a	PpEES	10250	1.06
2b	PHS	5060	1.11
2c	PBPOS	10000	1.09
3a	PpEES	14600	1.07
3b	PHS	9700	1.14
3c	PBPOS	28600	1.21
4a	PpEES	10800	1.06
4b	PHS	10000	1.08
4c	PBPOS	27500	1.17

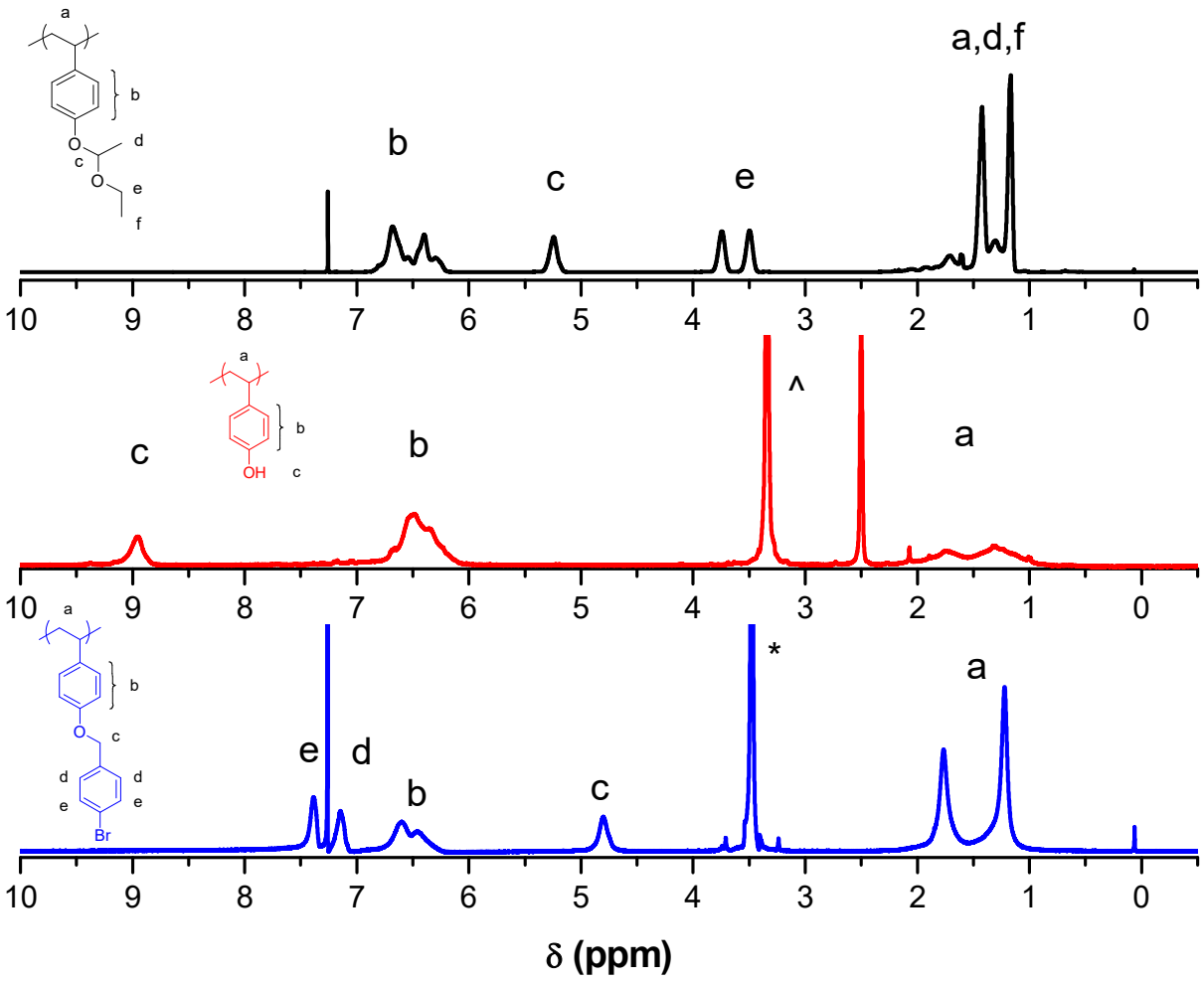
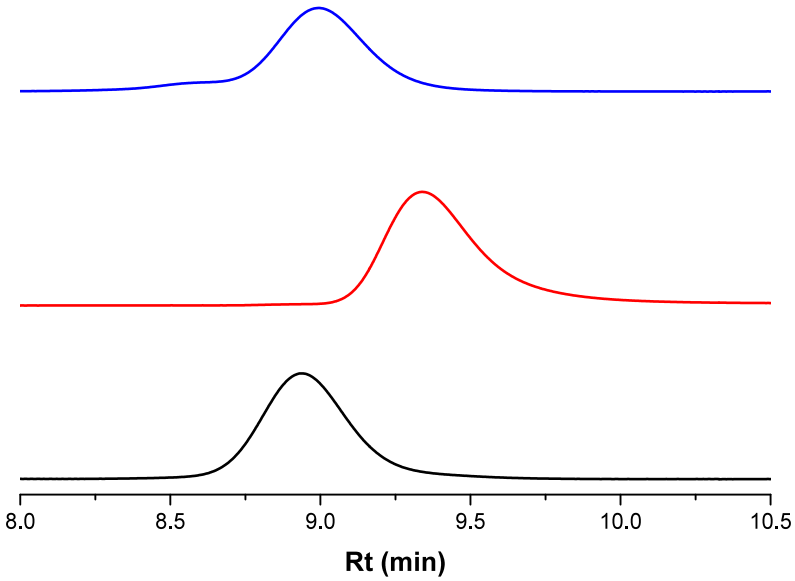


Figure 2.3 1H NMR (500 MHz) spectra of homopolymers 4a (CDCl3), 4b (DMSO-d6) and 4c (CDCl3).* Methanol, ^ H_2O



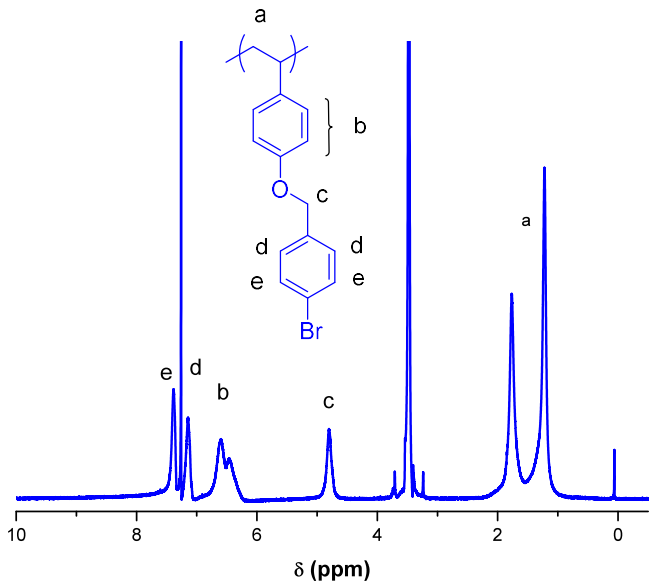


Figure 2.4 SEC traces for the conversion of PpEES to PHS to PBPOS (4a-c, Table 1) (top). ^{1}H NMR of poly(4-(4-bromophenyloxy)styrene) (4c) in $CDCl_3$ (bottom).

degradation temperature (T_d) values were determined at 5 % weight loss. As expected, PHS exhibits a single step thermal degradation with a T_d temperature of ~350 ℃, consistent with what is reported in the literature. The polymers PBPOS and PpEES both show a two step thermal degradation, although the effect is significantly more pronounced in PpEES (Figure 2.4). T_d values for PpEES and PBPOS were 291 ℃ and 300 ℃, respectively. In the thermal decomposition of PpEES approximately 30 % weight loss occurs in the first step which corresponds to the weight percentage of the acetal protecting group. Therefore, thermal deprotection of the acetal group can be assumed to occur upon annealing the polymer at elevated temperature. For PBPOS the onset of the first and second step of degradation are too close to make this type of observation. DSC was used to determine the T_g of the new homopolymer. T_g was observed to be between 58 ℃ and 67 ℃ (Figure 2.5).

The self-assembly of PHS in mixed solvent solution was investigated for mixtures of H_2O and methanol, H_2O and THF and hexanes and THF. Given the example set forth by Lee et al. where amphiphilic behavior in solution was achieved when 2-phenyl pyridine functioned as a hydrophilic head group, participating in hydrogen bonding and the flexible polymer backbone functioned as a hydrophobic group, similar behavior was hypothesized for poly(4-hydroxystyrene).[10] Where the pyridinyl moiety of poly(2-(4-vinylphenyl(pyridine)) interacts with water as a hydrogen bonding acceptor, the phenol moiety of poly(4-hydroxystyrene) can act as both a donor and acceptor. When the acidity of phenol is considered (pKa=10), the equilibrium of donor/acceptor would be most stable with phenol acting as a donor.[59]

To investigate the invertible nature of PHS in a similar manner to Thayamanavan et al. in their pioneering study, the self-assembly of PHS was investigated both in H_2O/THF and hexane/THF.[8] In addition, self-assembly behavior was also observed in the solvent mixture of H_2O/MeOH, where methanol is a good solvent for the homopolymer and H_2O is a non-solvent. Based on the DLS data reported in Table 2-2, a general trend of increasing hydrodynamic radius can be seen in those solution mixtures with decreasing H_2O content, best illustrated by the data obtained from polymer 3b in H_2O/MeOH. For the other solution mixtures the relationship between hydrodynamic radius and solvent composition is less clear.

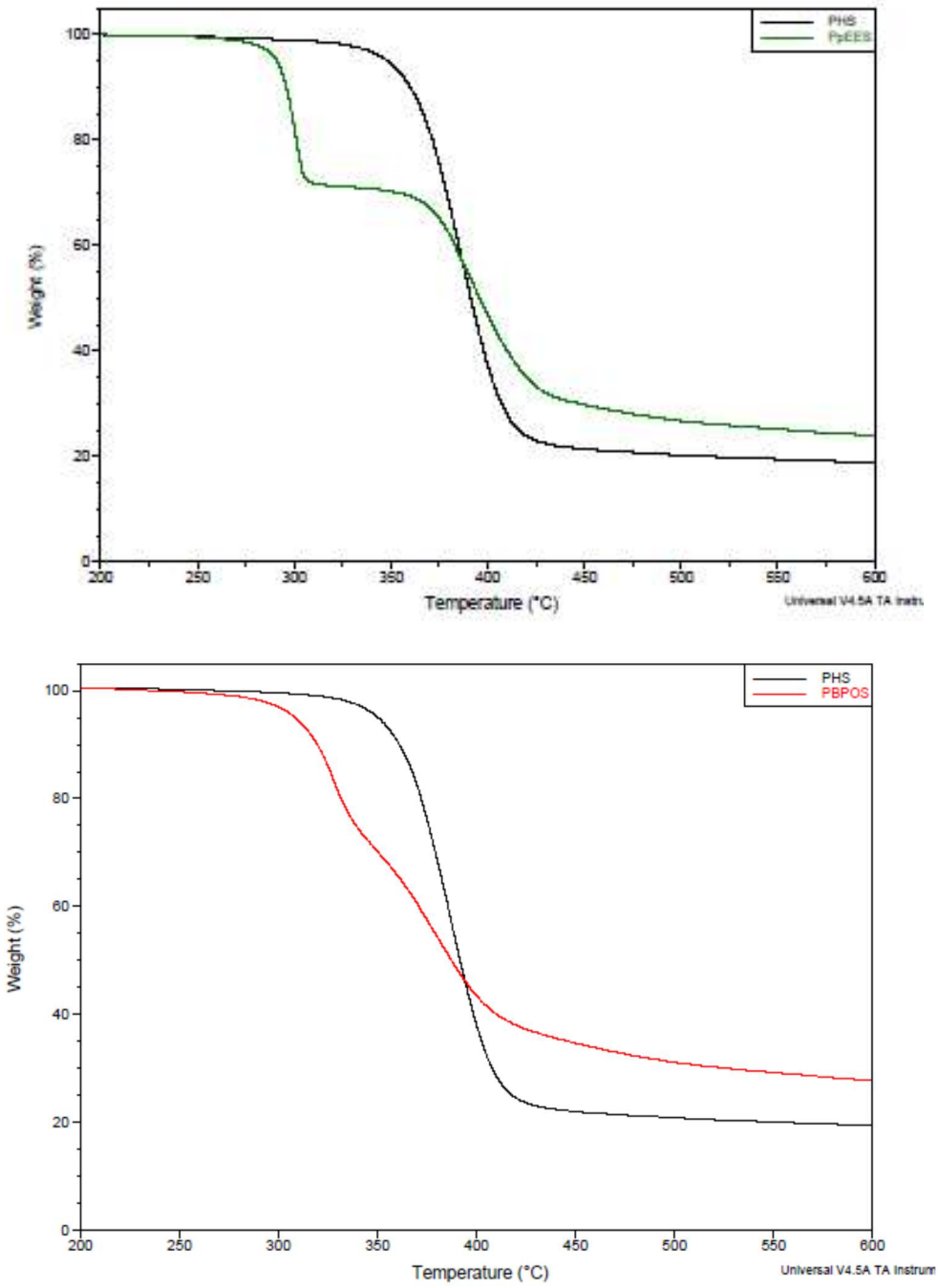


Figure 2.5 TGA Curves of the thermal degradation of PpEES vs. PHS (top) and the thermal degradation of PBPOS vs PHS (bottom).

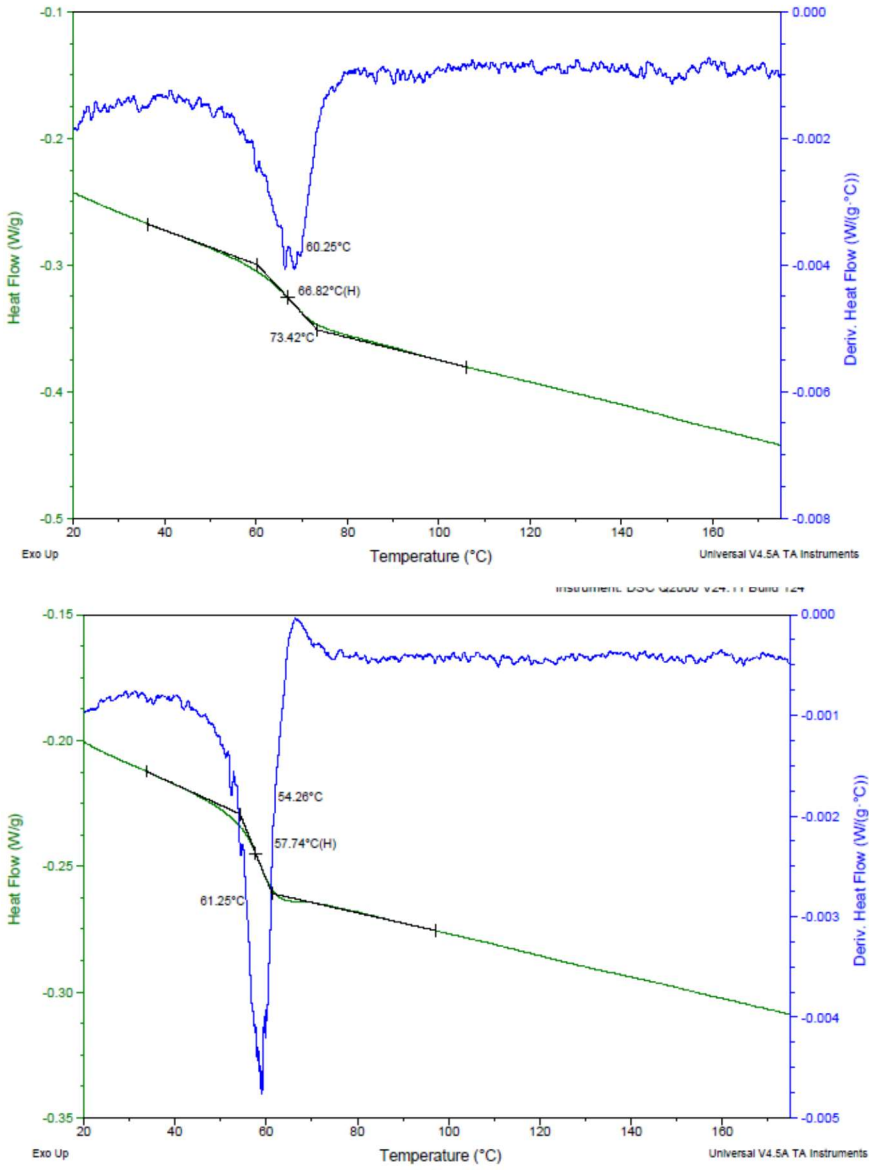


Figure 2.6 DSC traces of poly(4-(4-bromophenyloxy)styrene

Table 2-2 Summary of Average Hydrodynamic Radius for PHS and PBPOS in solution

polymer	% THF	% HEX	% H_2O	% MeOH	R_h (nm)
PHS 2	10	-	90	-	516
	20	-	80	-	617
	30	-	70	-	713
	40	-	60	-	523
	50	-	50	-	1670
	10	90	-	-	528
	20	80	-	-	418
	30	70	-	-	552
	40	60	-	-	198
	50	50	-	-	-
PHS 3	10	-	90	-	537
	20	-	80	-	586
	30	-	70	-	530
	40	-	60	-	484
	50	-	50	-	1500
	10	90	-	-	803
	20	80	-	-	381
	30	70	-	-	377
	40	60	-	-	-
	50	50	-	-	-
	-	-	90	10	77.2
	-	-	80	20	91.4
	-	-	70	30	115
	-	-	60	40	329
	-	-	50	50	-

Table 2-2 Continued

polymer	% THF	% HEX	% H_2O	% MeOH	R_h (nm)
PHS 4	10	-	90	-	553
	20	-	80	-	599
	30	-	70	-	582
	40	-	60	-	448
	50	-	50	-	1620
	10	90	-	-	679
	20	80	-	-	390
	30	70	-	-	419
	40	60	-	-	584
	50	50	-	-	-
	-	-	90	10	194
	-	-	80	20	208
	-	-	70	30	159
	-	-	60	40	344
	-	-	50	50	-
PBPOS 2	10	-	90	-	-
	20	-	80	-	695
	30	-	70	-	738
PBPOS 2	40	-	60	-	499
	50	-	50	-	337
PBPOS 3	10	-	90	-	435
	20	-	80	-	637
	30	-	70	-	605
	40	-	60	-	458
	50	-	50	-	308
PBPOS 4	10	-	90	-	418
	20	-	80	-	495
	30	-	70	-	617
	40	-	60	-	259
	50	-	50	-	430

In an analogous manner to the hydrogen bonding of PHS, the bromobenzene head group of PBPOS participates in halogen bonding. Halogen bonding is a non-covalent attraction that occurs between a covalently bonded halogen atom (donor) and a nucleophile (acceptor). Due to the anisotropic electron density of a bound halogenatom, a belt of predominantly negative elctrostatic potential forms orthogonal to the bond direction and is offset by a predominantly positive region on the end.[60] The effect of the predominant positive end is referred to as the σ-hole and is more frequently observed in the heavier halogens (Br, I). In the case of PBPOS, the bromobenzene head group acts as the halogen bond donor and the electron dense oxygen atom of water acts as the acceptor. The strength of this interaction coupled with the hydrophobicity of the hydrocarbon backbone is the driving force of the self-assembly of these homopolymer vesicles.

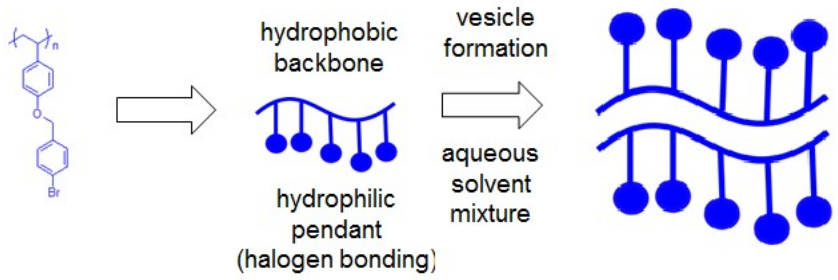


Figure 2.7 Formation of PBPOS vesicles in an aqueous solvent solution as a result of halogen bonding interaction

TEM imaging of the polymer vesicles of PBPOS in a 70/30 water/THF solution (v/v) required no staining in order due to the higher contrast provided by the bromine atoms. The bromine atoms appear to be on the surface of the vesicles as would be predicted if halogen bonding were the driving force of the self-assembly (Figure 2.6). The PBPOS vesicles shown in the TEM images were not uniform in size which could account for the lack of a consistent trend observed in DLS data with respect to the hydrodynamic size of the particles.

The nature of the self-assembled aggregates in solution was investigated by AFM, as shown in Figure 2.7. Image B of PHS in H_2O/MeOH show signs of vesicle fission.[61] The surface of the vesicles appears to be rough rather than smooth with what appear to be smaller vesicles partaking in either fusion or fission with the larger aggregate. Lee et al. reasoned that the fission process was responsible for the openmouthed vesicles seen in poly(2-(4-vinylphenyl)pyridine).[10] The process of vesicle fission is further illustrated in the TEM images of PHS which show the formation of an internal waist within the aggregate which will culminate in the separation of a new vesicle (Figure 2.8).

The formation of gold nanoparticle suspensions in polymer vesicles was conducted by first introducing $HAuCl_4$ into the polymer vesicles solutions for several hours before reducing the gold in solution by reaction with hydrazine.[62] The presence of gold nanoparticles was confirmed by UV-vis spectrophotometry measurements showing strong absorbance corresponding to the known absorbance band of gold nanoparticles between 500 and 600 nm (Figure 2.9). Interest in the formation of gold nanoparticles has been piqued recently as a consequence of the optical properties they possess. Gold nanoparticles could potentially find application as transistors, chemical sensors, and therapeutic agents among others.[63-68] Thorough investigation of the properties of gold nanoparticles in the literature has determined that the chemical, physical and surface plasmon resonance properties are dictated by their size, shape and surface morphology.[69-71] Moving forward, the ability to synthesize gold nanoparticles in a controlled manner of uniform size and morphology will prove ever more valuable. Visual confirmation of the gold nanoparticles can be seen in the TEM images portrayed in Figure 2.8.

Doxorubicin (DOX) is a common chemotherapy drug used for the treatment of several variant of leukemia, Hodgkin's lymphoma, breast stomach, lung and other cancers. It is commonly sold in the more aqueous soluble doxorubicin HCl salt, in order to encapsulate it in the hydrophobic vesicle layer, the salt must be reduced to free base. Doxorubicin HCl (DOX HCl) is converted to free base by reaction with triethylamine (TEA) in a 1:2 molar ratio of DOX HCl overnight in DMSO. 50 µL of the DOX/DMSO was added to 2.5 ml of methanol followed by 0.5 ml of PHS solution at 10 mg/ml and thoroughly mixed. To this mixture, 7ml of DI water was added to produce the formation of polymer

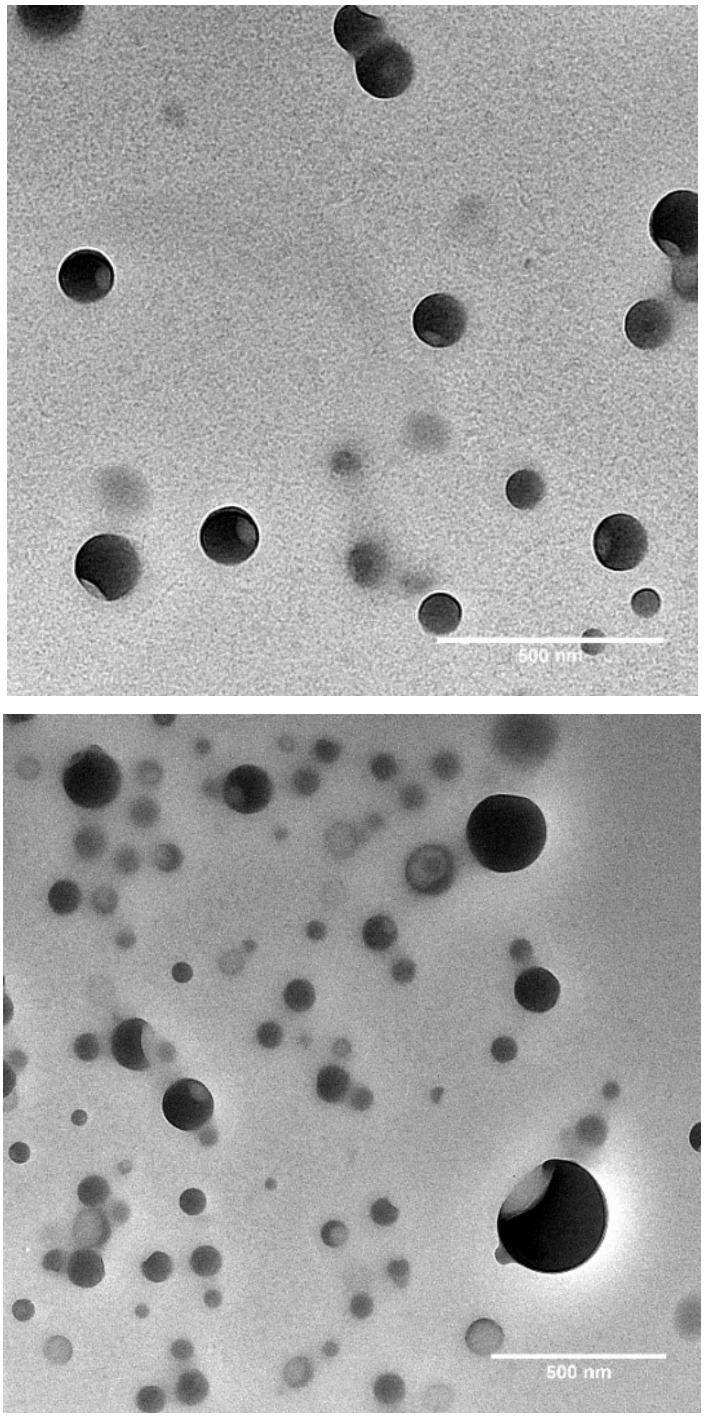
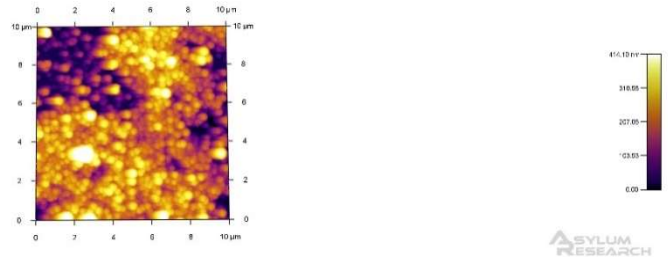
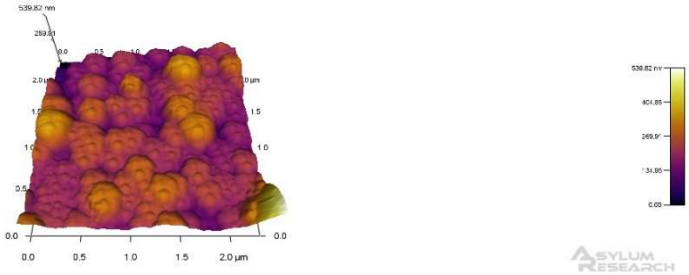


Figure 2.8 TEM images of PBPOS 4 in a 70/30 solvent mixture of water/THF.

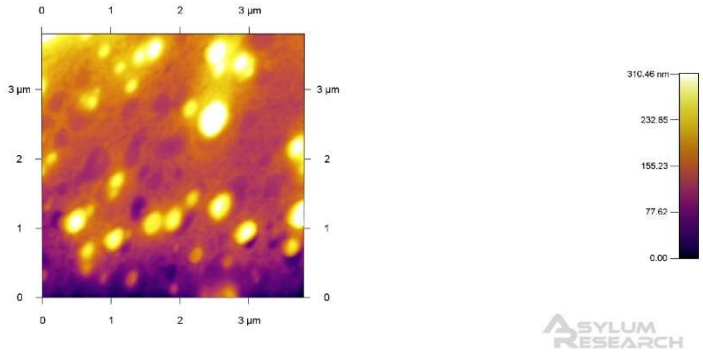
A)



B)



C)



D)

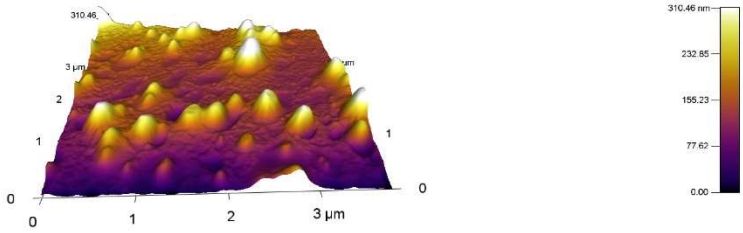


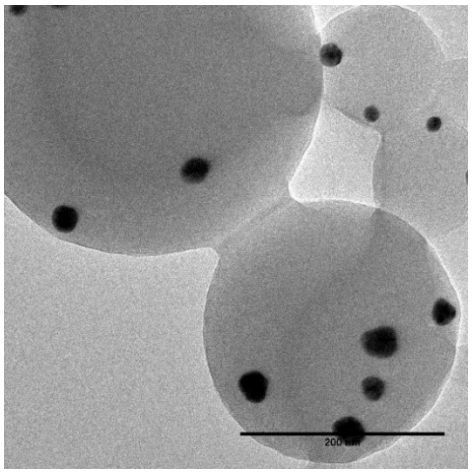
Figure 2.9 AFM images of PBPOS (4c) in a H_2O/THF solvent mixture of 70/30

vesicles. The mixture was dialyzed for 48 hours to remove nonencapsulated DOX. An analogous vesicle solution without DOX was prepared in order to compare the particle size by DLS. Visual inspection of the samples shows the presence of the red-orange color of doxorubicin in the solution after dialysis has been performed (Figure 2.10).

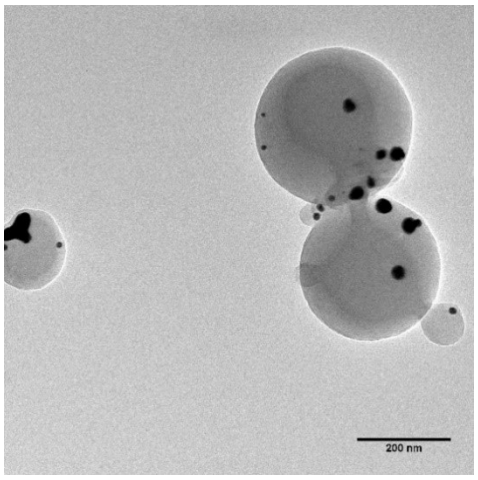
The HTC-116 cell line was incubated according to normal protocol before beginning treatment with DOX loaded vesicles. In order to exhibit proper controls for the effect of the release of the chemotherapy drug, two other treatments were run in parallel with the cell treated with DOX loaded vesicles. The first control was simply an untreated population of HTC-116 cells and the second was HTC-116 cells treated with empty vesicles. The treatment of empty vesicles was intended to account for any cytotoxic quality that might be inherent from the polymer itself. After 24 hours, the population of HTC-116 cells treated with vesicles loaded with DOX saw a 27% lower cell count than the untreated cells and 24% lower than the cells treated with empty vesicles. (Table 2-3) The 3% difference in cell count suggests a slight cytotoxcity inherent in the poly(4-hydroxystyrene) itself. Images of the cells taken after 24 hours of treatment show a significant difference between the populations (Figure 2.11).

The lowered cell count is assumed to be a result of the release of the chemotherapeutic drug, doxorubicin. In a basic environment, the phenolic hydrogen can be removed by base to form phenoxide monomer units within the polymer chain. The solubility of phenoxide in aqueous solutions is much greater than phenol allowing for the vesicles to become solubilize. The increased solubility of the polymer chains results in the release of the trapped doxorubicin, the result of which is decreased cell counts in HTC-116. DLS measurements performed on the dialyzed solutions revealed an increase in particle size for the solution with vesicles loaded with DOX relative to the empty vesicles. The average hydrodynamic radius over 15 scans was found to be 71 nm and 55 nm for the aqueous suspensions of vesicles loaded with DOX had empty vesicles, respectively. The incorporation of DOX in the polymer particle was anticipated to increase the size of particles and the presence of DOX is the only discernible difference between the two solutions.

A)



B)



C)

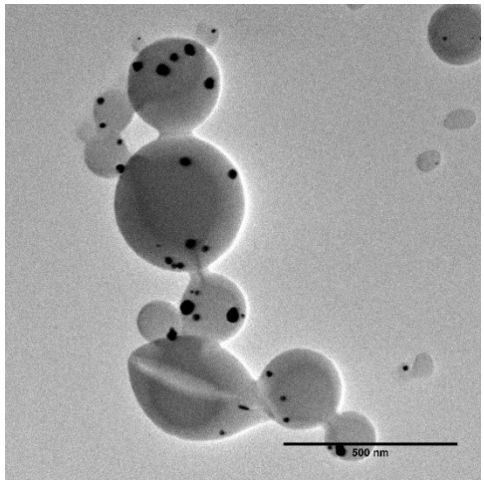


Figure 2.10 TEM Images of poly(4-hydroxystyrene) in a 70/30 solvent mixture of H_2O/MeOH with gold nanoparticles

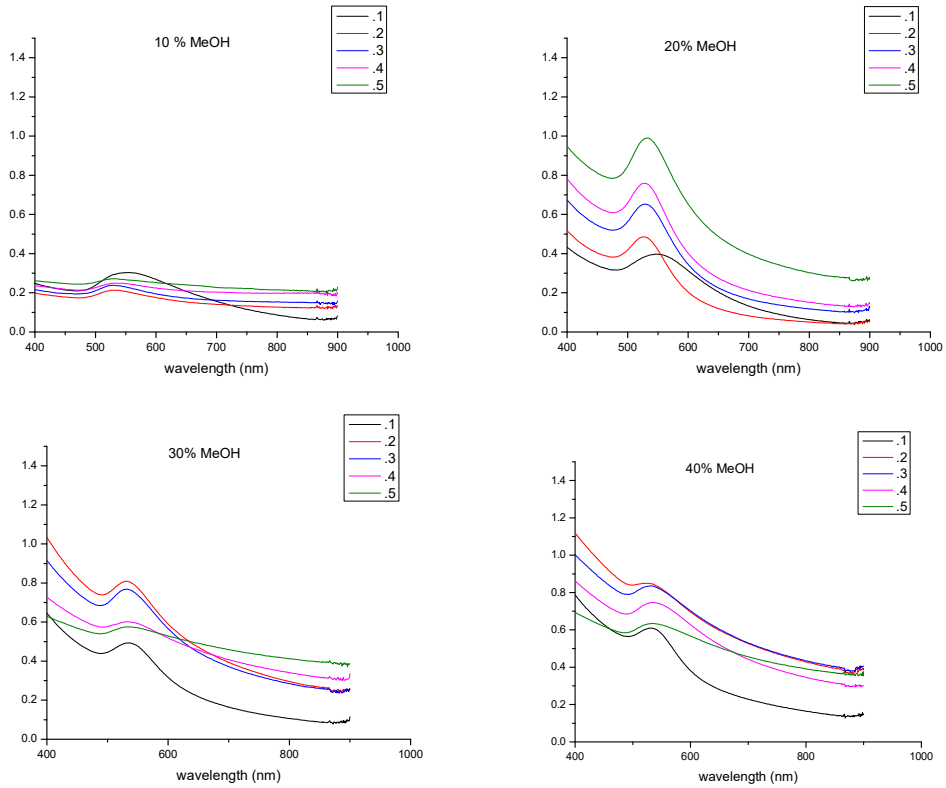


Figure 2.11 UV-vis spectra of gold nanoparticle colloid suspensions with molar ratios of PHS 1 to Au ranging from 1:0.1 to 1:0.5 in solution mixtures ranging from 90/10 to 60/40 H_2O to MeOH.

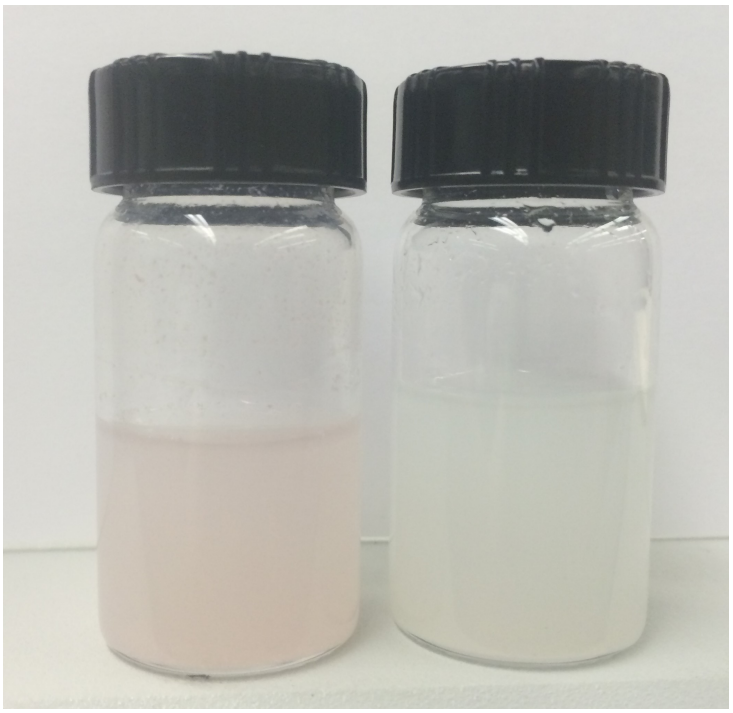


Figure 2.12 Solution of PHS in DI water with Doxorubicin encapsulated (left), solution of PHS in DI water without Doxorubicin (right).

Table 2-3 HTC 116 cell populations 24 hours after treatment

Cell Treatment	Cell Count	Cell Count	Avg	% change[a]
Untreated	270700	257200	263950	0
Empty vesicles	262000	247600	254800	-3
DOX loaded vesicles	193900	189900	191900	-27

[a] % change based on the direct population comparison with the untreated cells.

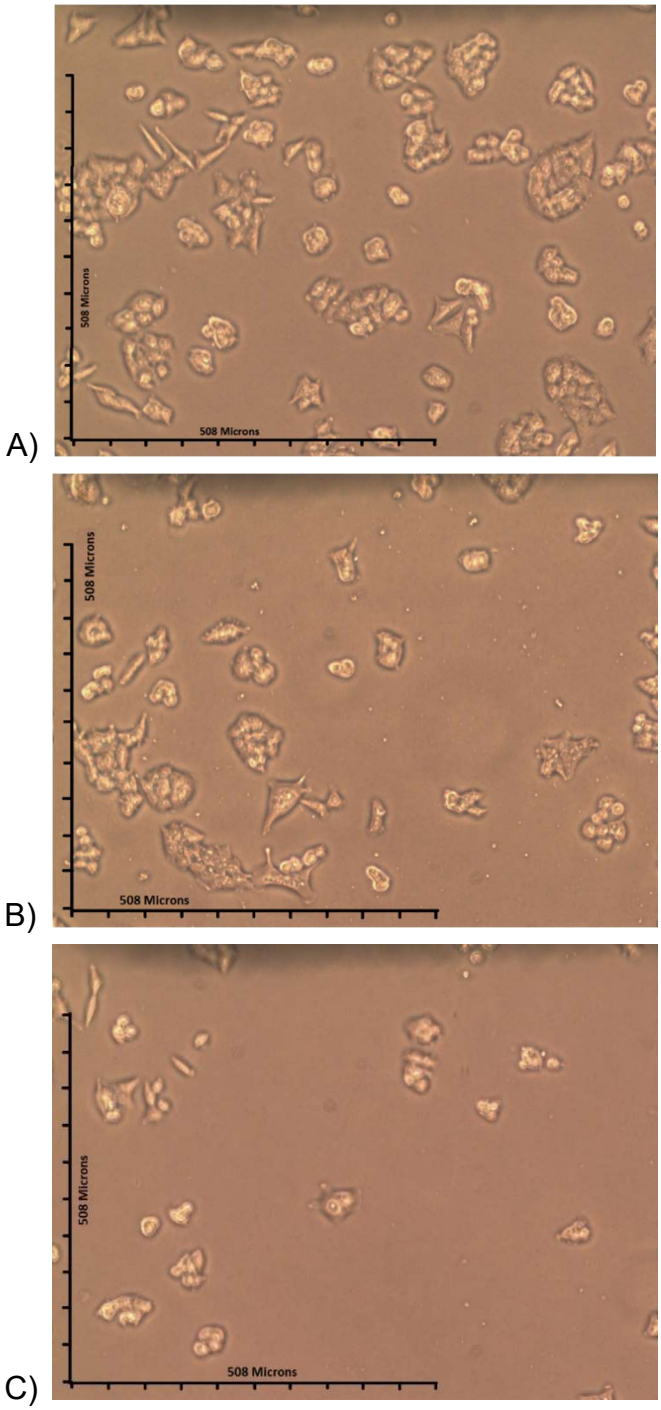


Figure 2.13 Images after 24 hours of untreated cells (A), empty vesicle treated cells (B) and DOX loaded vesicle treated cells (C)

Conclusions

The anionic polymerization of 4-(1-ethoxyethoxystyrene) at -98 ℃ yields polymers of predictable molecular weights and narrow molecular weight distributions. The acetal protecting group can be rapidly cleaved at room temperature to produce the homopolymer poly(4-hydroxystyrene). Williamson etherification reactions performed with poly(4-hydroxystyrene) and 4-bromobenzyl bromide quantitatively yield the new polymer poly(4-(4-bromophenyloxy)styrene. The strategy of accessing functionalized polystyrene by etherification reaction of poly(4-hydroxystyrene) and alkyl bromide species could be adapted to provide numerous polymers previously difficult or impossible to attain. The new polymer exhibits values of T_g between 57 ℃ and 67 ℃. Homopolymer self-assembly of PHS and PBPOS in aqueous mixture was driven by the intra and intermolecular forces of hydrogen bonding and halogen bonding. While hydrogen bonding has been used as the driving force for homopolymer self-assembly previously, this is the first example in which halogen bonding is believed to be responsible. The potential application of poly(4-hydroxystyrene) vesicles was displayed by their use in the formation of gold nanoparticles and the transport of chemotherapeutics.

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CHAPTER 3 SYNTHESIS AND CHARACTERIZATION OF STAR AND GRAFT COPOLYMERS OF POLY(4-(1-ETHOXYETHOXY)STYRENE) AND POLY(METHYL ACRYLATE) VIA CLICK REACTION

A version of this chapter will be submitted for publication:

Christopher M. Hurley, Nam-Goo Kang, Jimmy Mays. “Synthesis and characterization of star and graft copolymers of poly(4-(1-ethoxyethoxy)styrene) and poly(methyl acrylate) via click reaction.”

All synthetic work, measurements and manuscript writing were performed by Christopher M. Hurley under the guidance of Nam-Goo Kang and Jimmy W. Mays.

Abstract

A series of random copolymers, polystyrene-co-poly(4-(1-ethoxyethoxy)styrene) were prepared by anionic polymerization and in a two-step reaction converted to polystyrene-co-poly(4-(2-propynyloxy)styrene). These alkyne functionalized random copolymers were used as polymer backbones in graft copolymers. Bromide terminated poly(4-(1-ethoxyethoxy)styrene) and poly(methyl acrylate) were synthesized by anionic polymerization and atom-transfer radical-polymerization, respectively. An exchange reaction in DMF at room temperature with NaN_3 was used to convert terminal bromides to azides. These polymer sides chains were grafted first to tri- and tetra-alkyne functionalized core molecules by Copper(I)-catalyzed azide alkyne cycloaddition reaction (CuAAC) to form star polymers. Graft copolymer were synthesized in a similar manner using the prepared random copolymers with a maximum grafting percentage of 94%.

Introduction

The introduction of copper (I) catalyzed azide-alkyne click reactions (CuAAC) by Sharpless et al. in 2001 provided a tremendously powerful tool to aid organic chemists in the synthesis of small molecules.[1] Due to the robust, facile and efficient nature of these coupling reactions, CuAAC reactions were quickly adopted and applied to the synthesis of macromolecules with tremendous success.[2] CuAAC click reactions have been used to synthesize a variety of block copolymers, star, dendrimers, graft and hyperbranched polymers.[3-10] Other click reactions such as thiol-ene, thiol-yne and Diels-Alder reactions have also been employed in the literature, but CuAAC reactions remain dominant due to the fast reaction kinetics, high orthogonality and product yields, facile set up and a well-established tolerance to functional groups.[1, 11-13]

The CuAAC reaction has been important in the development of nanostructured polymer synthesis. These polymeric materials, in form of star, brush, dendrimer, hyperbranched polymers, etc., have shown promise in numerous fields including biomaterials, sensing and catalysis.[2,8,14-17] The combination of controlled polymerization techniques and CuAAC reactions allows for a great deal of command over chemical composition and structure. The tunable nature of the molecular weight and the level of control over placement of functional groups underlines the potential of these materials.

Graft copolymers consist of two components, a polymer backbone and polymer side chains. Three general strategies have been employed to synthesize graft copolymers: “grafting onto” (where polymer side chains are attached to the backbone), “grafting from” (where polymer chains are grown from initiator functionalities present of the backbone) and “grafting through” (where macromonomer side chains are polymerized to form the backbone).[18] The “grafting onto” strategy requires the separate preparation of polymeric side chains with terminal functionalities and a polymer backbone with complimentary functionalities. A subsequent reaction between the terminal functionality of the side chain and the functionality present on the backbone is necessary to form the graft copolymer. An advantage to synthesizing the backbone and side chain independently is that different polymerization techniques can be employed based on the desired monomer. In addition, characterization of each part prior to the formation of the graft copolymer allows for greater insight into the chemical structure and size of the graft copolymer. One drawback associated with this technique is that grafting density can be limited by steric hindrance from neighboring side chains. In an effort to combat this, CuAAC reactions have been used due to their high efficiency. A densely grafted cylindrical polymer brush was synthesized by Gao and Matyjaszewski utilizing Atom Transfer Radical Polymerization (ATRP) for polymer backbone and side chain synthesis and assembled by CuAAC reaction, reaching grafting efficiency as high as 88%.[10]

Block copolymers represent a significant portion of the polymer materials we encounter in our daily lives. The uniqueness and utility of block copolymers comes from their defining characteristic of covalently bonding together two chemically distinct polymer chains to form a single macromolecule. The covalent linkage of two different polymer blocks produces a polymer that shares characteristics of both blocks.[19] Living

polymerization methods are ideally suited for the synthesis of block copolymers. Although a number of living polymerization techniques have been developed, anionic polymerization remains the ideal polymerization method for block copolymer synthesis. Anionic polymerization is considered ideal for several reasons. The absence of chain termination and chain transfer reactions leads to stoichiometric conversion of monomer and polymers of predictable molecular weight. Anionic polymerization leads to polymers of narrow molecular weight distribution (PDI<1.10). The retention of living carbanion chain ends when control is maintained over experimental parameters such as temperature and monomer purity allows for stepwise addition of monomer.[20] Anionic polymerization has been used for decades to produce block copolymers of a number of different block arrangements including diblocks, triblocks and those of greater block diversity.[21]

Despite the great success of anionic polymerization in block copolymer synthesis, the technique remains hampered in comparison to radical techniques by the limited number of viable monomers.[19,20] Monomers with substituents that are reactive with the strongly basic carbanion living chain ends (ex. hydroxyl, carboxyl) are to be avoided or require a protecting group during anionic polymerization. In the case of alkynes, the acidic proton must be protected otherwise it will quench the initiator or propagating carbanion. In addition, the protons of adjacent methyls and methylenes are acidic and can be abstracted by the carbanion.[22] To date, the only successful strategy to synthesize a polymer with terminal alkyne functionalities by anionic polymerization has been to use the bulky trimethylsilyl protecting group.[23] The anionic polymerization of 2-, 3- and (4-trimethylsilylethynyl)styrene at -78 ℃ in THF yielded polymers of predictable molecular weight and narrow molecular weight distribution. Tetrabutylammonium fluoride in THF at room temperature is used in order to remove the trimethylsilyl group.

In this work, we present the synthesis and characterization of a series of new alkyne functionalized random copolymers, polystyrene-co-poly(4-(2-propynyloxy)styrene). The copolymers were synthesized by the post-polymerization reactions of polystyrene-co-poly(4-(1-ethoxyethoxy)styrene). These copolymers were used as polymer backbones for graft copolymer synthesis. Copper(I)-catalyzed azide-alkyne cycloaddition reactions, known as click reactions, were used to attach polymers

with terminal azide functionalities. Polymer of narrow molecular weight distributions and terminal bromide functionalities were prepared by either living anionic polymerization or ATRP. An exchange reaction was used to convert terminal bromides to azides. Azide terminated polymers were used as polymer side chains. The polymer side chains were grafted to alkyne functionalized random copolymer by CuAAC click reaction. In addition, the synthesis and characterization of three- and four-arm star polymers of poly(4-(1-ethoxyethoxy)styrene) and poly(methyl acrylate) are presented. A new tetra-alkyne functionalized core was prepared and it was shown to be efficient at coupling in Click reactions.

Experimental Section

Chemicals

Sec-Butyllithium (Acros,1.3 M in cyclohexane), 1,1-diphenylethylene (Acros, 98%), 1,3-dibromopropane (Acros, 98%), 4-(1-ethoxyethoxy)styrene (Synquest Laboratories), styrene (Sigma Aldrich), methyl acrylate (Acros 99%), THF (Fisher) , methanol (Fisher), ethyl α-bromoisobutyrate 98% (Aldrich), Copper (I) Bromide (Acros), N,N,N′,N″,N″-pentamethyldiethylenetriamine (Acros), propargyl bromide 80 weight % in toluene, stabilized(Acros), potassium carbonate (Acros), potassium iodide (Fluka), acetone (Fisher), sodium azide (Fisher), concentrated hydrochloric acid (Fisher). Tetrahydrofuran was distilled into the reactor from a purified solvent reservoir on the vacuum manifold.[11] *Sec*-butyllithium was diluted to the desired concentration by hexanes distilled into the appropriate apparatus from a purified solvent reservoir on the vacuum manifold. 4-(1-ethoxyethoxy)styrene (Synquest Labs) was first dried by CaH_2 under high vacuum before being passed through a glass filter and separated into ampules. The ampules of monomer were then further distilled twice under dynamic vacuum using moderate heating to assist. Ampules of purified monomer were then diluted to the desired concentration with purified THF. All anionic polymerization reactions were performed under high vacuum in custom-built all-glass reactors according to standard protocol.[24,25]

Characterization

Number-average molecular weight M_n and polydispersity index M_w/M_n (PDI) of all samples were determined by SEC using a Tosoh EcoSEC instrument equipped with two TSKgel Super Multipore HZ-V columns, calibrated using polystyrene and poly(methyl methacrylate) standards over a range of 600 to 7.5×10^6 Da. The polymer was eluted in THF at 40℃ with a flow rate of 0.35 ml/min, and a run time of 15 min. All ^{1}H NMR analyses were performed on a Varian VNMR 500 MHz spectrometer using either $CDCl_3$ or DMSO-d_6 as the solvent. Fourier-Transform Infrared Spectroscopy (FT-IR) was carried out using a Varian 4100 FT-IR using KBr (Aldrich, Spectroscopy) as a reference and precursors for background subtraction. Thermogravimetric analysis was performed on a TA Instruments Q-50 TGA. The sample was heated from 25℃ to 800℃ at a rate 20℃/min in the presence of compressed air (Airgas) at a flow rate of 40 ml/min. Differential scanning calorimetry was performed using a TA Instruments Q-2000 DSC with a nitrogen gas purge. Samples were heated in three cycles from 20℃ to 200℃ at a rate of 10℃/min.

Polymerization

Bromo-terminated polymers were synthesized by either ATRP or anionic polymerization according to standard protocols.

Synthesis of Bromo-Terminated Poly(4-(1-ethoxyethoxy)styrene) by Anionic Polymerization

A typical example of the synthesis of PpEES-Br is as follows:

A custom-made glass apparatus with previously collected ampules of 4-*(*1-ethoxyethoxy)styrene (15 ml solution in a 1:14 v/v monomer:THF), 1,1-diphenylethylene (1 ml, 0.5 mmol), sec-BuLi (1 ml, 0.1 mmol in hexanes), and 0.5 ml of 1,3-dibromopropane neat was attached to a high vacuum line and flame dried. The apparatus was purged with a potassium naphthalenide solution and thoroughly rinsed with distilled THF before the purge section was frozen with liq.N_2, flame sealed and removed. The *sec*-BuLi

ampule was then fractured and added to the reactor. The ampule was rinsed with distilled hexanes to ensure full addition to the reactor. The reactor was then cooled to -98 ˚C with a MeOH/liq. N_2 bath. The 4-(1-ethoxyethoxy)styrene ampule was then cooled to -98 ˚C before being added to the reactor. The temperature was maintained for 2 hours to allow the reaction to reach completion. 1,1-Diphenylethylene was cooled to -98 ˚C and added to the reactor. The temperature was maintained for fifteen minutes and the apparatus was shaken occasionally to ensure proper mixing. Lastly, the 1,3-dibromopropane ampule was cooled and its contents were added to the system. The deep red color of the solution quickly faded to a slight yellow. The apparatus was allowed two hours to come to room temperature and reach completion. The polymer was precipitated in MeOH at -25 ˚C. MeOH was decanted and the polymer was redissolved in THF, volume reduced by rotary evaporation and re-precipitated as before. This was repeated twice before polymer was dried by rotary evaporation and placed in a vacuum oven overnight.

Synthesis of Polymethyl acrylate (PMA) by Atom Transfer Radical Polymerization

Methyl acrylate (18 ml, 17.2 g), 15 ml of anisole, 80 mg of CuBr (0.56 mmol), 0.12 ml of PMDETA (0.57 mmol), 0.12 ml of ethyl α-bromoisobutyrate (EBiB, 0.82 mmol) were added to a glass apparatus with a stir bar. The reaction mixture was frozen with liq. N_2 and attached to the vacuum line. A freeze-pump-thaw cycle was performed three times before the apparatus was flame sealed from the vacuum line. The apparatus was placed in an oil bath at 80 ˚C for the desired time period. The reaction was terminated by freezing the reaction mixture in liq. N_2. The reaction solution was diluted with THF then passed through an alumina column in order to remove copper bromide. Rotary evaporation was used to then reduce the volume of the product before precipitating into methanol. The polymer was redissolved in THF and brought to dryness by rotary evaporation, followed by drying in a vacuum oven.

Conversion of Bromo Terminated Polymers to Azido Terminated Polymers

Several grams of the desired polymer were dissolved in a small amount of DMF (10-15 ml) and an excess of NaN_3 (ratio of 1:40, mol polymer: mol NaN_3 was added and stirred for 24 hours. The polymer solution was filtered and rotary evaporated to remove solvent. The polymer was redissolved in CH_2Cl_2 and washed three times with DI water. The organic layer is collected and $MgSO_4$ is added to remove moisture. The solution was again filtered and solvent is removed by rotary evaporation. The resulting polymer was dried further in a vacuum oven.

Anionic Polymerization of Random Copolymer of PS-co-PpEES

A typical reaction for the anionic polymerization of the random copolymer polystyrene-co- poly(4-(1-ethoxyethoxy)styrene) is as follows:

The main reactor for polymerization of 4-(1-ethoxyethoxy)styrene was washed with (3-methyl-1,1-diphenylpentyl)lithium solution in hexanes to remove impurities from the reactor which were removed by rinsing with distilled hexanes from a purge flask. The solvent and solution were collected in the purge flask before it was removed from the apparatus. *Sec*-butyllithium (1 mmol) was introduced by fracturing a breakseal and the ampule was rinsed using distilled hexanes to ensure correct stoichiometry. The reactor was then cooled to -78℃ by a dry ice/acetone bath. 10 mins were allowed for temperature of the reactor to equilibrate. Both the styrene (0.906 g/5 ml THF) ampule and the 4-(1-ethoxyethoxy)styrene **(**0.97 g/15 ml THF) was cooled to -78℃ before being introduced by fracturing the breakseal. The reaction was allowed to proceed for 2 hours before being terminated by the introduction of methanol by fracturing a breakseal. The polymer was precipitated into an excess of methanol. The polymer was filtered, redissolved in tetrahydrofuran and rotary evaporated to dryness before being dried in a vacuum oven.

Deprotection of PS-co-PpEES

Several grams of the desired PS-co-PpEES were dissolved in 20-25 ml of THF. To the solution 1-2 ml of concentrated HCl was added dropwise with continuous swirling over a period of 20 minutes. The polymer was then precipitated in to deionized water. The precipitated polystyrene-co-poly(4-hydroxystyrene) (PS-co-PHS) product was then collected by filtration, rinsed with deionized water to remove excess HCl and dried in a vacuum oven. The stoichiometric cleavage of acetal protection was confirmed by ^1H NMR.

Conversion of PS-co-PHS to polystyrene-co-poly(4-(3-propynyloxy)styrene) (PS-co-PPOS)

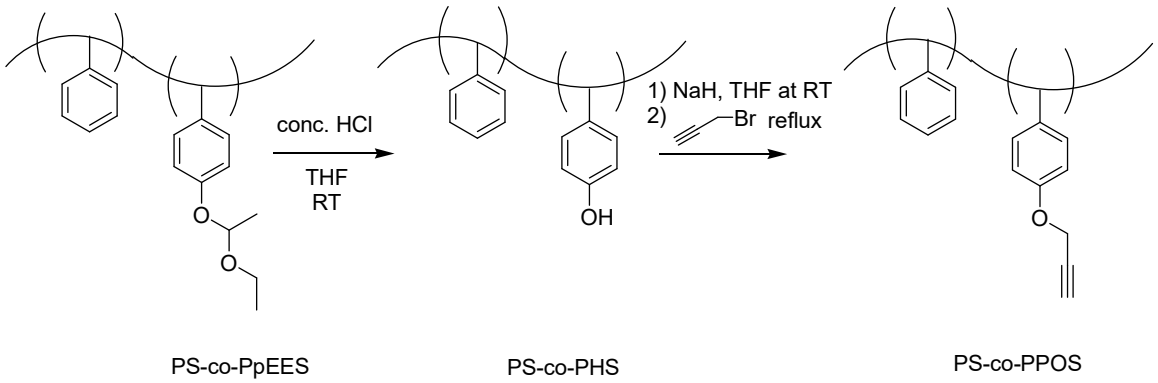


Figure 3.1 Conversion of PS-co-PpEES tp PS-co-PPOS in two steps

500 mg of the desired PS-co-PHS random copolymer was added to a round-bottom flask with 1.5 molar excess of NaH dispersion 60% in mineral oil before being attached to a vacuum line and evacuated. 20-50 ml of THF was distilled in to the round-bottom flask and the polymer solution was stirred for 1-2 hours. The round-bottom flask was then removed from the vacuum line and flushed with N_2 gas for several minutes, taking care not to evaporate off the solvent. A two times molar excess of propargyl bromide was added to the round-bottom flask by syringe before the round bottom flask was attached to a reflux condenser. The reactor was flushed with N_2 gas and brought to reflux for 12 hours. After, the round-bottom flask was brought to room temperature and

the reaction solution was filtered to remove salt byproduct. The THF solution was reduced in volume by rotary evaporation and then precipitated in hexanes. The polymer was filtered and dried before being redissolved in a small amount of THF and precipitated a second time in hexanes. The product was collected and dried.

Synthesis of 1,1,1-tris[4-(2-propynyloxy)phenyl]ethane and 1,1,2,2-tetrakis[4-(2-propylnyloxy)phenyl]ethane

Multi-alkyne functionalized species were synthesized in a manner similar to those previously presented in literature.[4,26,27] A typical example of the synthesis of 1,1,1-tris[4-(2-propynyloxy)phenyl]ethane is presented below:

5 grams (0.0163 mol) of 1,1,1-tris(4-hydroxyphenyl)ethane was added to a 250 ml two neck round-bottom flask along with 13.5 g (0.0980 mol) of freshly ground K_2CO_3 and 1.63 g (0.00980 mol) of KI were added to a round-bottom flask with ml of acetone, stirred and flushed with N_2 gas. 11 ml of propargyl bromide (0.0990 mol) was injected into the reactor and the solution was brought to reflux for 24 hours. The reaction mixture was cooled to room temperature and filtered, collecting the filtrate. Acetone was removed by rotary evaporation. The product was redissolved in CH_2Cl_2 and washed three times with distilled water. The organic phase was collected and dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The resulting product was purified by column chromatography using a mixture of ethyl acetate and hexanes (1:9) over silica gel. The solvent was removed from the resulting eluent by rotary evaporation. The product was dried further in a vacuum oven overnight.

1,1,1-tris[4-(2-propynyloxy)phenyl]ethane: 5.83 g, 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.01 (m, 6H Ar*H*), 6.87 (m, 6H Ar*H*), 4.67 (d, 6H HCC-C*H*$_2$), 2.52 (t, 3H *H*CC), 2.12 (s, 3H C*H*$_3$).

1,1,2,2-tetrakis[4-(2-propylnyloxy)phenyl]ethane: 5.46 g, 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 8H Ar*H*), 6.71 (m, 8H Ar*H*), 4.98 (s, 2H –CH), 4.63 (d, 8H HCC-C*H*$_2$), 3.46 (t, 4H *H*CC).

Click Reaction to Create Star, Comb and Brush Polymers

A multi-alkyne functionalized species, CuBr, PMDETA, the desired azide terminated polymer and 1-5 ml of toluene were added directly to a glass reactor and degassed three times using a freeze-pump-thaw cycle using liquid N_2 and a vacuum line. In the case of tetra-alkyne the reactants were dried for ~15 min before 1-5 ml of anhydrous THF was charged into the reactor from a reservoir. The reaction mixture was stirred until all the polymer and alkyne species had dissolved in solution. The reaction was then frozen, flame sealed and removed from the vacuum line. The reactor was then placed in an oil bath at 50 ˚C for several hours. After which time, the reaction solution was diluted with THF and passed through a neutral alumina column to remove the copper bromide. The volume was reduced by rotary evaporation and the polymer was precipitated into an appropriate solvent based on the polymer used. The resulting polymer was collected, filtered if necessary, and dried.

Results and Discussion

A series of well-controlled star and graft copolymers have been synthesized based on the conversion of phenol functionalities to propynyloxy phenyl functionalities. The tris and tetrakis alkyne functional star cores were synthesized by Williamson etherification reaction of the appropriate hydroxyphenyl precursor and propargyl bromide under N_2 atmosphere base on the method of Tang et al.[4] The etherification reactions were carried out with a molar ratio of OH: Br of 1:2. After 24 hours the initial reaction yield a viscous yellow liquid, which after washing and column chromatography was rotary evaporated to yield a yellow solid with yields of 85% and 79% for tris and tetrakis, respectively (Figure 3.2).

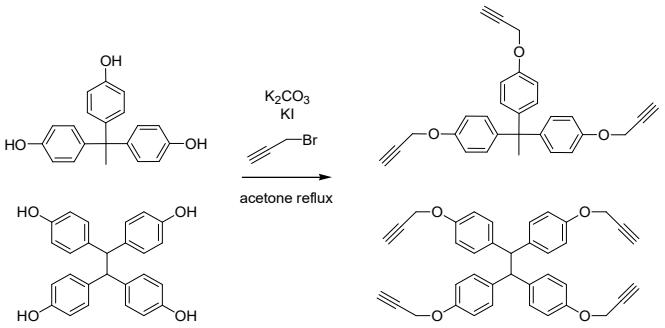


Figure 3.2 Synthesis of multi-alkyne functionalized star core molecule

In order to synthesize polymer backbones with a controlled number of grafting sites, the anionic polymerization of a polystyrene-co-poly(4-(1-ethoxyethoxy)styrene) (PS-co-PpEES) and PpEES homopolymer were chosen due to the report of well controlled polymerization of the protected hydroxystyrene monomer in THF.[28] In addition the facile and rapid deprotection of the hydroxystyrene monomers is advantageous from a viewpoint of efficiency and safety. Polymerization conditions of -98 ˚C in THF were attempted for the polymer backbone because this low temperature is necessary to suppress side reactions in the homopolymerization of 4-(1-ethoxyethoxy)styrene but after six hours the consumption of polystyrene was incomplete at this temperature. The polymerization of styrene and 4-(1-ethoxyethoxy)styrene at standard conditions for styrene of -78 ˚C in THF resulted in full monomer consumption and a slightly broader than expected molecular weight distribution (<1.2). Deprotection of the random copolymer resulted in the disappearance of the peaks at 5.27, 3.76 and 3.52 ppm from the protecting group and appearance of a peak at 9.01 ppm for the terminal hydroxyl group in agreement with the literature. Integration of the hydroxyl peak at 9.01 ppm with respect to the aromatic peaks for PS-co-PHS yielded the same ratio as the single hydrogen of the protecting group (Ar-O-C*H*) at 5.27 ppm to aromatic peaks. The disappearance of peaks associated with the protecting group and the appearance of a hydroxyl peak with matching integration strongly suggest full cleavage of the protecting group. The ^{1}H NMR spectra after attachment of alkyne functionalities allowed for further comparison of the ratio of aromatic protons to those of the pendant group. The integration of the CH_2 signal at 4.63 ppm from the newly attached propynyl functionality yielded the same ratio of

Table 3-1 Molecular Characteristics of Polystyrene-co-Poly(4-(1-ethoxyethoxystyrene)

sample	pEES (g)	Sty (g)	[I] (mmol)	M_{ntheo}	M_{nexp}[a]	PDI
10	0.323	0.906	0.2	6100	4700	1.14
11	0.323	1.812	0.1	21400	22100	1.25
13	0.350	1.812	0.1	21600	19300	1.20
14	0.323	0.906	0.2	12300	13200	1.11
15	0.350	0.906	0.2	6300	4900	1.19
16	0.350	1.812	0.1	21600	28000	1.18
17	0.970	0.906	0.1	18800	20400	1.16
19	1.067	0.906	0.53	3700	3200	1.19
20	1.325	2.718	0.53	7600	6000	1.17
21	1.681	0.906	0.53	4900	7200	1.16

[a,] M_n values determined by SEC calibrated from 600- 7.5×10^6 Da based on linear polystyrene and linear poly(methyl methacrylate) standards for PpEES and PMA, respectively. [b,] PDI and % graft based of the integration of the majority peak in the SEC chromatograms.

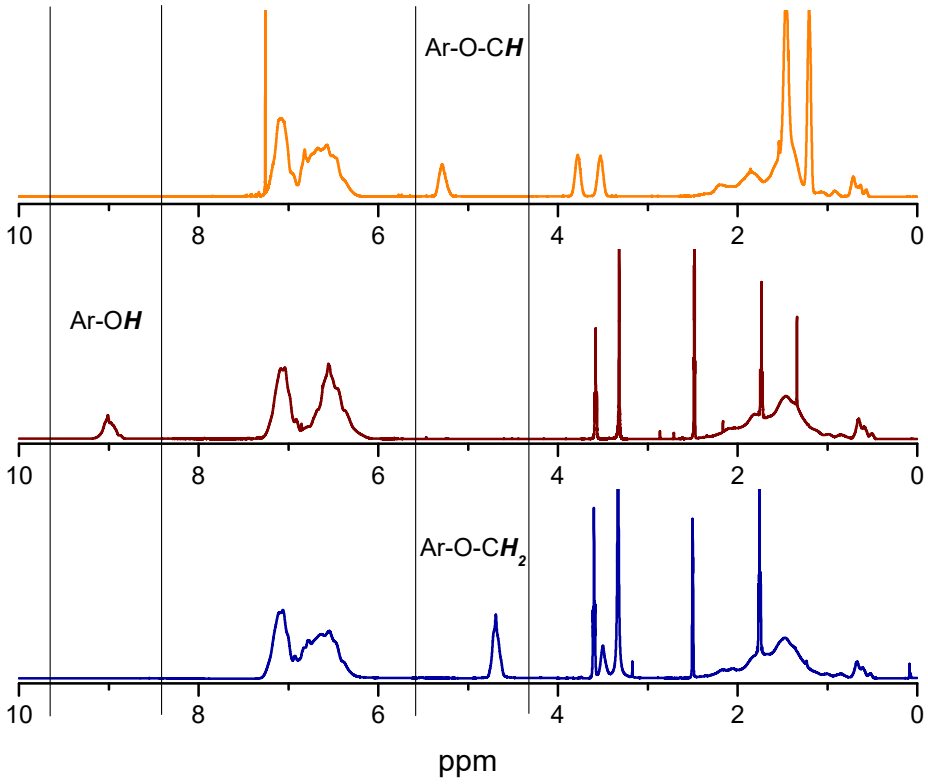


Figure 3.3 ^{1}H NMR comparison of random copolymers of PS-co-PpEES ($CDCl_3$, top), PS-co-PHS (DMSO-d_6, middle) and PS-co-PPOS (DMSO-d_6, bottom).

aromatic peaks giving evidence that a complete conversion of hydroxyl phenyl functionalities to propynyloxyphenyl functionalities has taken place (Figure 3.2). Changes in molecular weight of the random copolymers as a result of the removal of the acetal protecting group and addition of the alkyne functionality were also monitored by SEC measurement with the results summarized in Table 3-2 and illustrated by Figure 3.3.

Insight into the random nature of the backbone copolymers was gained by analyzing the DSC traces of the copolymers of PS-co-PPOS. The unknown nature of the T_g value of a homopolymer of poly(4-propynyloxy)styrene necessitated the synthesis of this homopolymer in order to know approximately where T_g might appear. A homopolymer of PHS was converted to PPOS following the same Williamson etherification reaction used previously. The quantitative conversion of PHS to PPOS was monitored by 1H NMR by comparing the integration of the methylene peak at 4.62 ppm to the aromatic peaks from 6.90-6.15 ppm. The single T_g for each copolymer between the experimental value of PPOS and the literature value for PS suggest a non-block copolymer monomer arrangement, i.e. a statistical copolymer (Figure 3.4).

The synthesis of narrow molecular weight side chains for grafting was performed by ATRP for PMA and anionic polymerization for PpEES. Through the ATRP process the use of the initiator ethyl α-bromoisobutyrate results in a terminal bromine that is converted to an azide group following examples in the literature.[26] The synthesis of azide terminated PpEES by anionic polymerization was performed in two step. The polymerization of pEES proceeded according to normal high vacuum protocol for this monomer, at -98 ˚C in THF. After complete consumption of the monomer, the living chain end was end capped with DPE to lower the reactivity of the living chain end. The living chain end was then terminated using 1,3-dibromopropane to yield polymer with a terminal bromide without any detectable trace of doubly quenched polymer chains.[29] In the second step, the terminal bromide is converted to azide in the same manner as PMA. The presence of a terminal azide was confirmed by FTIR and by attachment of the polymer to the multifunctional alkyne core molecules. Determination of number average molecular weight (M_n) of the polymer side chains is summarized in Table 3-3.

To date, the anionic polymerization of pEES has not been used to synthesize star polymers. By reacting in a 1:1 ratio of azide to alkyne for both tris and tetrakis alkyne

Table 3-2 Molecular Characteristics of Polystyrene-co-Poly(4-hydroxystyrene) and Polystyrene-co-Poly4-(2-propynyloxy)styrene)

polymer	M_n	PDI
PS-co-PHS 10	4400	1.11
PS-co-PHS 11	22700	1.24
PS-co-PHS 13	19700	1.18
PS-co-PHS 14	11700	1.12
PS-co-PHS 15	4700	1.13
PS-co-PHS 16	27400	1.14
PS-co-PHS 17	20400	1.16
PS-co-PHS 19	2800	1.17
PS-co-PHS 20	5400	1.19
PS-co-PHS 21	6200	1.13
PS-co-PPOS 15	28000	1.18
PS-co-PPOS 16	29300	1.16
PS-co-PPOS 19	3500	1.19
PS-co-PPOS 21	5400	1.17
PPOS	9000	1

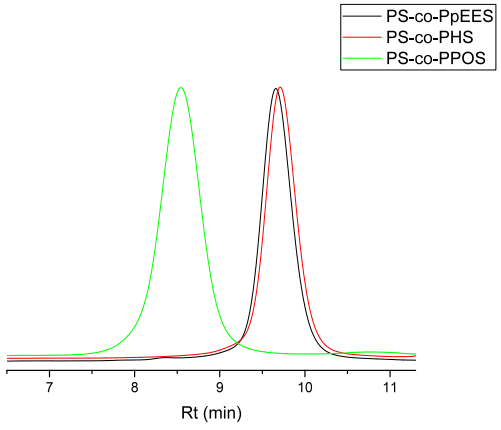


Figure 3.4 SEC curves for the conversion of PS-co-PpEES to PS-co-PHS acidic deprotection and the Williamson etherification reaction of PS-co-PHS to PS-co-PPOS.

Table 3-3 Molecular Characteristics of Azide Terminated Polymers, Star and Graft Copolymers

azide terminated polymer $(P\text{-}N_3)_r$								
Polymer				M_n		PDI		
PMA-N_3				9200		1.05		
PpEES-N_3				5000		1.07		
polymer stars by click reaction								
polymer	Mass of P-N_3	Alkynes/ core	mmol of alkyne core	$M_{n\,theo}$	$M_{n\,exp}$[a]	PDI[b]		
Tri-PMA	0.525 g	3	0.019	27600	24200	1.05		
Tri-PpEES	0.290	3	0.019	15000	13700	1.04		
Tri-PpEES	0.290	3	0.019	15000	14000	1.05		
tetra-PpEES	0.363	4	0.018	20000	16500	1.05		
graft copolymers by click reaction								
Reaction #	Polymer Backbone	P-N_3	$M_{n\,theo}$	$M_{n\,exp}$	Alkyne/ backbone theo	Alkyne/ backbone calc	PDI	% graft
1	16	PMA	204,100	71000	18	19	1.09	94
2	19	PMA	95500	43000	10	10	1.09	70
3	21	PMA	152600	81000	16	15	1.08	78
4	16	PpEES	124300	47000	18	19	1.15	79
5	19	PpEES	53500	25200	10	10	1.14	86

[a,] M_n values determined by SEC calibrated from 600- 7.5×10^6 Da based on linear polystyrene and linear poly(methyl methacrylate) standards for PpEES and PMA, respectively. [b,] PDI and % graft based of the integration of the majority peak in the SEC chromatograms.

core molecules, star polymers consisting of three and four arms, respectively, were synthesized with narrow molecular weight distributions (<1.10) and nearly complete conversions (Figure 3.5).

The determination of the number of 4-(2-propynyloxy)styrene) monomer units per copolymer was determined by calculating the mole fraction from 1H NMR of the copolymer PS-co-PPOS. By comparing the integration of the methylene peak at 4.62 ppm to that of the aromatic peaks from both monomers (Haromatic) and accounting for the hydrogens from poly(4-(2-propynyloxy)styrene) the integration from the aromatic hydrogens of polystyrene can be determined. This number is then divided by the number of hydrogens per styrene unit (5 H) to allow a direct comparison to the units of 4-(2-propynyloxy)styrene.

$$\frac{H_{aromatic} - 4}{5} = styrene\ /\ 2 - propynyloxystyrene \qquad \text{(Eq. 3-1)}$$

The number determined is then used to calculate the mole fraction of 4-(2-propynyloxy)styrene with 4-(2-propynyloxy)styrene set equal to one. The mole fraction is then converted to a mass fraction following Eq. 3-2.

$$\frac{x_1 M_1}{(1 - x_1)M_2 - x_1 M_1} = mass\ fraction\ of\ M_1 \qquad \text{(Eq. 3-2)}$$

M_1= molecular weight of 4-(2-propynyloxy)styrene; M_2= molecular weight of styrene; x_1= mole fraction of 4-(2-propynyloxy)styrene.

The mass fraction is then multiplied by the molecular weight of the copolymer to determine the mass of the copolymer that belongs to poly(4-(2-propynyloxy)styrene). By dividing this mass by the mass of the 4-(2-propynyloxy)styrene monomer unit, the number of 4-(2-propynyloxy)styrene monomer units per copolymer can be determined. The values calculated can be seen in Table 3-3. The theoretical values for the number of 4-

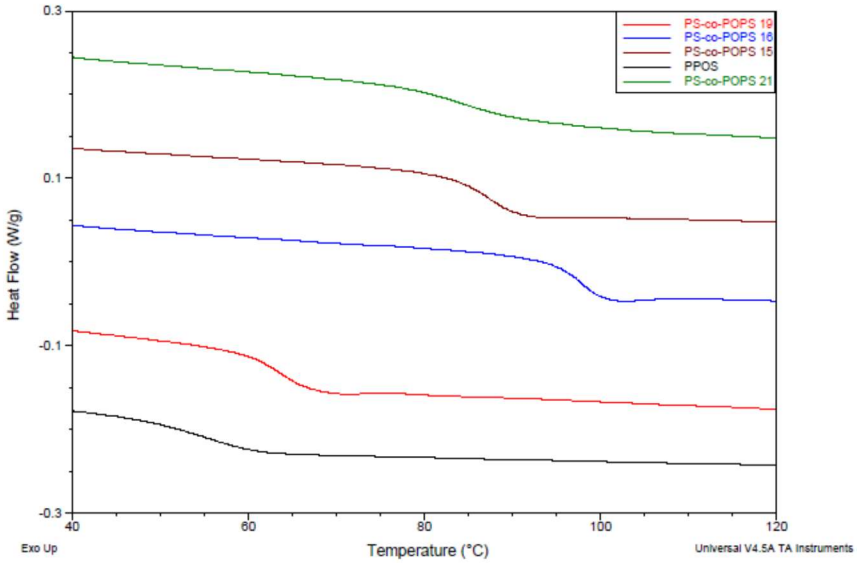


Figure 3.5 DSC traces of PS-co-PPOS and homopolymer PPOS

(2-propynyloxy)styrene per ccopolymer is calculated by dividing the moles of 4-(2-propynyloxy)styrene by the moles of initiator.

Click reactions were used to synthesize graft copolymers with side chain polymers of PMA or PpEES. Based on the theoretically calculated number of alkynes per polymer backbone an equimolar amount of polymer side chains were placed in the reactor along with CuBr, PMDETA and the solvent. Freeze-pump-thaw cycles were used to degas the reaction before the reactor was filled with N_2 gas to provide an inert atmosphere. Reaction were heated to 50 ℃ for 12 hours before being filtered through a column of neutral alumina to remove CuBr. The collected reaction solution was rotary evaporated the dryness, redissolved and precipitated. The collected polymers were dried, mass and characterized as summarized in Table 3-3.

In addition, a more accurate estimation of the graft copolymer mass can be calculated from the mass of azide terminated polymer used in the reactions adjusted by integral of graft percentage to determine an estimation of the mass of polymer attached during click reactions. By dividing this mass by the moles of alkyne functionalized polymer backbone used in the reaction an estimation of the molecular weight of the polymer arms attached can be made (Table 3-4, column three divided by column five). From this number the molecular weight of the backbone should be added to get a final estimate. The relatively narrow molecular weight distributions (PDI<1.2) makes the assumption that graft copolymers are all of similar molecular weight valid. Therefore, the mass of polymer grafted is assumed to be evenly distributed among the polymer backbones and can simple be divided moles of polymer backbone to calculate the total molecular weight of the grafted arms.

The Mn values obtained from the SEC for PpEES and PMA graft copolymers are estimated based on the hydrodynamic volume of linear standards of polystyrene and polymethyl methacrylate, respectively. By having known values for the Mn of the polymer side chains and calculating the area under the curve from the SEC chromatogram, more reasonable estimations of the molecular weight can be made. Some doubt will remain on the accuracy of such a method due to the lack of complete separation of the peaks for the graft copolymer and that of the linear homopolymer but some insight into the nature of the reaction is provided (Figure 3.6).

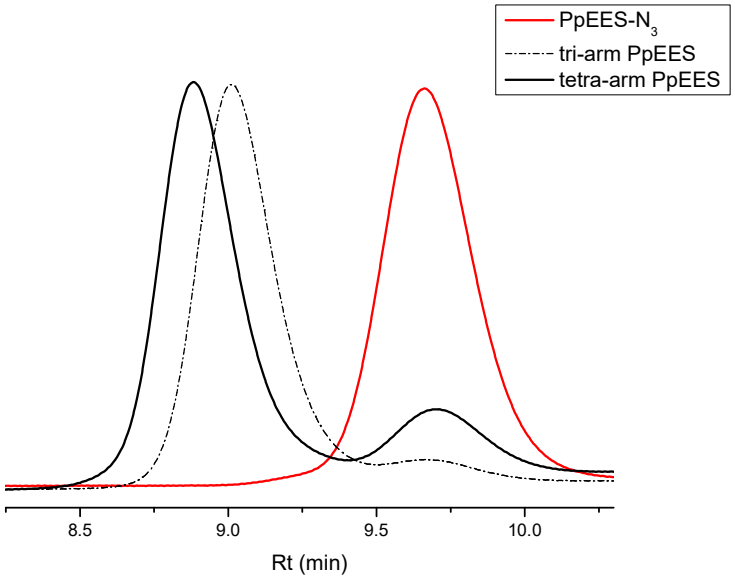


Figure 3.6 SEC Chromatograms of azide terminated PpEES and tri- and tetra-arm PpEES from CuAAC reaction with tri- and tetra-alkyne core molecules

Table 3-4 Estimation of graft copolymer molecular weight based on the percentage under the SEC curve for the majority peak

Reaction #	Mass of polymer used	Mass adjusted by graft %	Mass of backbone used	mol of backbone	Adjusted MW
1	0.113 g	0.106 g	0.020 g	6.8×10^{-7}	185200
2	0.267 g	0.187 g	0.010 g	2.9×10^{-6}	64500
3	0.997 g	0.778 g	0.036 g	6.7×10^{-6}	186300
4	0.200 g	0.166 g	0.064 g	2.2×10^{-6}	101100
5	0.090 g	0.075	0.010 g	2.9×10^{-6}	29400

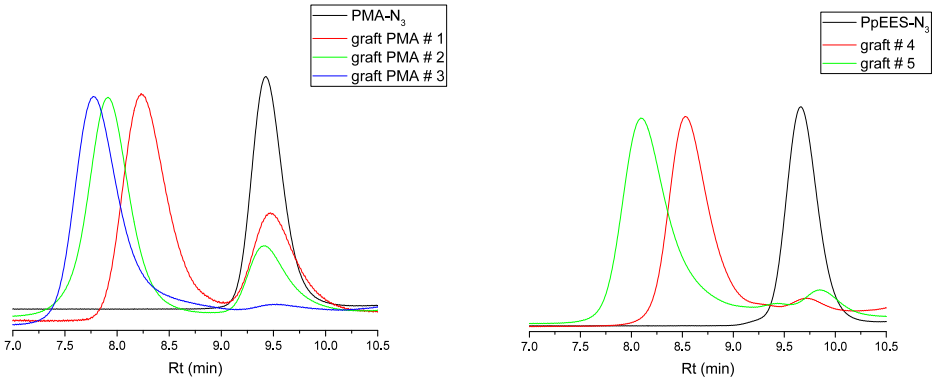


Figure 3.7 SEC chromatograms of azide terminated PMA and PMA graft copolymers (left). SEC chromatiograms of azide terminated PpEES and PpEES graft copolymer (right).

Conclusions

A series of random copolymers of PS-co-PHS were synthesized by anionic polymerization utilizing pEES as a protected monomer to provide PHS by acidic cleavage of the acetal protecting group. The conversion of the hydroxyl moieties of PS-co-PHS to 2-propynyloxy by Williamson etherification reaction was shown to be quantitative. The application of these random copolymers as polymer backbones onto which azide terminated polymers can be grafted by CuAAC reaction was demonstrated. In addition, a new tetra-alkyne functionalized core molecule was synthesized and shown to be effective in the synthesis of a four arm polymer star by copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC).

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CHAPTER 4 TRIFUNCTIONAL ORGANOLITHIUM INITIATOR FOR LIVING ANIONIC POLYMERIZATION IN HYDROCARBON SOLVENTS IN THE ABSENCE OF POLAR ADDITIVES

A version of this chapter has been accepted by the Royal Society of Chemistry journal *Polymer Chemistry* for publication pending minor revisions

George V. Theodosopoulos, Christopher M. Hurley, Jimmy W. Mays, Durairaj Baskaran, and Georgios Sakellariou. “Synthesis of Trifunctional Organolithium Initiator and Anionic Polymerization in Hydrocarbon Solvents in the Absence of Polar Additives.”
Synthetic work and measurements performed collaboratively by Christopher M. Hurley and George V. Theodosopoulos. Manuscript was written jointly by all authors.

Abstract

A novel hydrocarbon-soluble trifunctional organolithium initiator, with no polar-additive requirements, has been synthesized for use in anionic polymerization. The complete synthesis of the unsaturated tri-diphenylethylene compound, 4,4,4-(ethane-1,1,1-triyl)tris(((3-(1-phenylvinyl)benzyl)oxy)benzene) (I), is described and the efficiency of the new initiator is evaluated using 1H NMR and NALDI-TOF MS. Activation of precursor I, was performed in-situ using stoichiometric amounts of *sec*-BuLi in benzene. Three-arm polystyrene and polyisoprene stars with narrow molecular weight distributions were obtained in the case of relatively high total anion concentration, [*sec*-BuLi]$_0$ > 3.8 x 10-3 mol/L (3 x [I]$_0$). At low total anion concentrations, uncontrolled molecular weight and broad/bimodal distributions were obtained, plausibly attributed to the presence of partially solvated aggregation dynamics complicating the propagation. The ‘living’ nature of the polymerization was confirmed by the sequential polymerization of styrene, and isoprene. The viscometric branching factor g´ values of the final branched polymers were measured and compared to g´ values of three-arm stars reported in the literature.

Introduction

Anionic polymerization, since the proof of its ‘living’ nature demonstrated by Szwarc et al., remains over 60 years the gold standard by which other ‘living’/controlled polymerizations are judged today.[1] This is due to the ability to synthesize well-defined structures of various architectures such as linear and branched homo-, di-, tri- and multi-block copolymers with predefined molecular weights and extremely narrow molecular weight distributions (MWD), which has intrigued the scientific community for decades. Major accomplishments in designing new polymeric architectures in anionic polymerization were attributed to the understanding of carbanion stability, functionality, kinetic and aggregation dynamics during anionic polymerization in polar and non-polar

media.[2] The demand for even more complex architectures requires stable, new multifunctional initiators.[3-5]

Attempts to synthesize multifunctional initiators via direct multilithiation, using multifunctional alkyl halides, have been limited due to eliminations caused by lithium-halogen exchange and intermolecular coupling reactions.[6,7] Synthesis of difunctional anionic initiators in polar solvents is generally accomplished by radical anion dimerization, using alkali metal with naphthalene in combination with vinyl monomers.[8] However, alkyllithium compounds and their state of aggregation have complicated the synthesis of di- and trifunctional organolithium initiators in non-polar media. Adduct formation of alkyllithiums with difunctional vinyl monomers, such as diisopropenylbenzene and the non-homopolymerizable 1,1-diphenylethylene (DPE), was widely used in the literature.[9,10]

Highly studied difunctional organolithium initiators in non-polar solvents based on double DPE groups have been thoroughly studied by Tung, Quirk, Hocker, and Szwarc.[11-16] Mays, Hadjichristidis and their co-workers have demonstrated the use of difunctional (DPE-type) alkyllithium initiators for the synthesis of styrene-butadiene-styrene triblocks, hyperbranched polymers, H-shaped, centipedes, regular combs, barb wires and cyclic polymers in benzene.[17-21] In all these studies, a small amount of polar additives was used to suppress aggregation and assist simultaneous initiation at both sites of the initiator in benzene.

The development of trifunctional or polyfunctional alkylithium initiators, for living anionic polymerization, will greatly expand the tools available for the synthesis of more complex polymer architectures such as well-defined dendrimers and hyperbranched molecules, with precise control of architecture and narrow molecular weight distribution. Furthermore, these initiators will, due to their solubility in hydrocarbon solvents, allow synthesis of homopolymers and copolymers incorporating high 1,4-polydienes. These materials have excellent elastomeric properties and they are not amenable to controlled polymerization to high molecular weights and high conversions by any other living mechanism other than anionic polymerization in hydrocarbon solvents. Attempts were made in the past to generate trifunctional initiators for use in anionic polymerization.[22-24] A trifunctional initiator based on 1,3,5-tris(1-phenylethenyl)benzene adduct with sec-BuLi

was developed by Quirk and Tsai.[25] They reported inefficient initiation resulting in very high molecular weight polymers with broad molecular weight distributions (Mw/Mn = 1.55) in benzene in the absence of polar additive. However, the polymerization proceeded successfully and three-arm polystyrene with narrow MWD was obtained in the presence of THF as polar additive to assist solvation of lithium species. It is well-known that the polymerization of dienes in pure hydrocarbon solvents is necessary for maintaining high 1,4 microstructure of polydienes, which is essential to maintain low glass transition temperature (Tg) for target synthesis of styrene-diene elastomers.

Unfortunately, multifunctional organolithium initiators exhibit strong aggregation in non-polar media which leads to the formation of high molecular weight, three-dimensional structures with low solubility in hydrocarbon solvents.[26,27] The presence of aggregates and their dynamics with unimers govern the kinetics of initiation and propagation, with great impact on the molecular weight distribution. Initiator aggregation in di- or trifunctional DPE type sec-BuLi adduct initiators poses a challenge in achieving quick and simultaneous initiation at all sites for polymerization in non-polar medium. Polar additives, such as amines, ethers and alkoxides have heretofore been mandatory in order to break carbanion-Li aggregates.[28,29] A formation of dative covalent bonds, between lithium and polar atoms, enables rapid initiation and prevents gelation in non-polar medium. Introduction of polar additives enhances the solvation of counterion and the insertion of 1,2 diene microstructure, which is not desired when polydienes are synthesized in non-polar media.[30,31] Maintaining a high 1,4-microstructure in polydienes is critical for the development of ABA triblock copolymers with styrene and dienes having excellent elastomeric properties.[32] Thus, an avoidance of polar additive is important for di- or trifunctional anionic initiator particularly with lithium as the counterion in hydrocarbon media. Significant efforts have been made in the synthesis of hydrocarbon-soluble di-, and trifunctional initiators.[12,33] However, the synthesis of an effective hydrocarbon-soluble initiator, particularly a trifunctional initiator not requiring any polar additives, has not been reported in the literature.

Herein we present an approach to synthesize a hydrocarbon soluble trifunctional initiator based on a DPE derivative, which initiates styrene and isoprene in non-polar solvents homogeneously without the presence of a polar additive. To facilitate the

synthesis of such a trifunctional anionic initiator, a precursor compound with three DPE groups, all connected to a central core through ether linkages to suppress delocalization of the anions, was synthesized and characterized. The trifunctional carbanion adduct with sec-BuLi was formed using the precursor derivative and homo- and diblock (co)polymerizations were performed in the hydrocarbon solvent benzene. The synthesized three-arm star polymers were characterized using size exclusion chromatography (SEC), 1H NMR and viscometry.

Experimental Section

Chemicals

Benzene, hexane, styrene, isoprene (Acros), and tetrahydrofuran (THF, Fisher) were purified according to the standards of anionic polymerization high vacuum techniques as described elsewhere.[34,35] sec-BuLi (n-hexane solution) and sec-BuOLi (benzene solution) were prepared in vacuum by the reaction of lithium metal with sec-butyl chloride (Acros) and 2-propanol (Merck), respectively. Both sec-butyl chloride and 2-propanol were freeze-degassed three times on the vacuum line, fractionally distilled into calibrated ampoules, and stored at room temperature. sec-BuLi concentration was determined as described by Hadjichristidis and Mays.[34,35] sec-BuOLi concentration was determined by neutralizing a known amount with excess of standard aqueous HCl solution and back titrating the excess of HCl with standard NaOH aqueous solution. The rest of the chemicals were purchased from Sigma-Aldrich and used as received unless purification is described in the text below.

Characterization

Size exclusion chromatographic (SEC) analyses were conducted at 40 °C using a modular instrument consisting of a Waters Model 510 pump, a U6K sample injector, a 401 refractometer, and a set of four l-Styragel columns with a continuous porosity range of 106–103 Å. THF was the carrier solvent at a flow rate of 1 ml/min. The system was

calibrated with seven PS standards having MWs between 1,000 g/mol and 900,000 g/mol. Several samples were analyzed with a Polymer Laboratories GPC-120 size exclusion chromatograph at 40 ºC equipped with four PLgel columns 7.5x300 mm; 10 µm; 500, 10E3, 10E5, and 10E6 Å a Precision Detector PD2040 (two-angle static light scattering), Viscotek 220 differential viscometer, and a Polymer Labs refractometer. THF was again used as the carrier solvent with a flow rate of 1 ml/min.

Nuclear magnetic resonance (NMR) spectra were recorded in chloroform-d and deuterated dimethylsulfoxide (DMSO) at 25 °C with a Varian Unity Plus 300/54 NMR spectrometer and Liquid State Varian Mercury Vx 300 MHz spectrometer.

Nano-assisted laser desorption-ionization mass spectrometry (NALDI-TOF MS) was performed using a NALDI target (Bruker Daltonics, Billerica, MA) and were recorded on a Bruker Autoflex II mass spectrometer (Bruker Daltonics, Billerica, MA) equipped with a nitrogen laser operated at 337 nm, a frequency of 25 Hz, and an acceleration voltage of 20 kV. Silver trifluoroacetate (AgTFA) as the cationizing agent. The analyte and salt were dissolved in THF (10 mg/ml) and mixed in a 1:1 ratio prior to deposition on the target. Mass spectra were measured in reflectron mode, and the mass scale was externally calibrated with polystyrene standards.

Molecular weight measurements were carried out using an AB Sciex (Foster City, CA) Voyager-DE PRO matrix-assisted laser desorption/ionization time-of-flight (MALDI/TOF) mass spectrometer in reflectron mode. Dithranol was used as the matrix and prepared in chloroform at 10 mg/ml. Sodium chloride was used as the cationization reagent and prepared in methanol at 10 mg/ml. The sample was dissolved in chloroform at approximately 1 mg/ml. A volume of 1 µl sample solution was mixed with 10 µl of matrix solution and 0.5 µl of cationization reagent solution. A 1 µl aliquot of the solution was hand-spotted onto a stainless steel target and allowed to dry in air.

Weight-average molecular weights, Mw, were obtained by static light scattering measurements at 25 °C using a Chromatix KMX-6 low-angle light scattering photometer. Stock solutions were prepared, followed by dilution with solvent to obtain solutions with lower concentrations. All solutions were optically clarified by filtering through 0.22 µm pore size nylon filters directly into the scattering cell. The specific refractive index increment (dn/dc) values were measured using a Brice-Phoenix differential refractometer

(model BP-2000-V) at 25 °C for λ = 633 nm or by an Otsuka differential refractometer (model DRM-1020) under the same conditions. Aqueous NaCl solutions were used for the calibration of the instruments.

Viscometry experiments were performed using Cannon-Ubbelohde dilution viscometers in a water bath at 35 ± 0.01 °C. Intrinsic viscosities, [η], were obtained using both the Huggins

$$\eta_{sp}/c = [\eta] + K_H [\eta]^2 c$$

and the Kraemer equations

$$ln\eta_r/c = [\eta] + K_K [\eta]^2 c$$

where KH and KK are the Huggins and Kraemer coefficients, respectively, ηsp (= ηr -1) is the specific viscosity, and ηr, the ratio of the solution to solvent flow times, is the relative viscosity. The solvent flow time was greater than 200 s in all cases, so no kinetic energy corrections were made.

Synthesis of 1-(3-brom-methylphenyl)-1-phenylethylene

The bromide synthesis was completed by a two- step reaction, through an initial Witting reaction and a subsequent Wohl-Ziegler bromination.

Synthesis of 1-(1-methoxy-1-phenyl)-3-methylbenzene

Commercially available 3-methylbenzophenone, 1, (29 g, 147 mmol) was added to a round bottom flask and placed under N2 atmosphere. Anhydrous THF (300 ml) was added through a double headed needle (cannula) in the flask. The solution was brought at -78 °C using mixture of isopropanol and dry ice, methyllithium solution (100 ml, 1.6M in diethylether) was added drop-wise in the solution under vigorous stirring. After the

addition was completed the solution was slowly allowed to reach room temperature. Iodomethane (40 ml, 642 mmol) was then added and the solution was left under stir for three days. It was then poured in 5% w/v NaOH (500 ml) solution and stirred for an hour. The solution was then transferred into a separating funnel using hexane as the organic phase. The extraction on the aqueous solution was repeated for three more times. The hexane solution was then rotary evaporated down to a viscous liquid 2, hexane was added and the solution was dried with a small amount of magnesium sulfate. A color change was observed from a yellowish-greenish to a red-brown color. Purification of crude product by column chromatography (activated silica gel, 35-70 mesh, 300 g), with hexane as eluent gave 1-(1-methoxy-1-phenyl)-3-methylbenzene as yellow-green product, yield 91.7%. Thin layer chromatography TLC (silica gel F 254, hexane 95% and 5% ethylacetate) Rf = 0.32.

Synthesis of 1-(3-bromo-methylphenyl)-1-phenylethylene

CCl4 was washed with saturated NaOH, freeze-degassed three times on the vacuum line, fractionally distilled keeping the middle fraction (one third of the total volume) in a round bottom flask, containing molecular seaves. In this first reaction 2 g of the precursor 1-(1-methoxy-1-phenyl)-3-methylbenzene 2 (2 g, 8.84 mmol), where poured into a round bottom flask. N-Bromosuccinamide NBS (1.575 g, 8.85mmol) is quickly added in the flask, followed by a 2% molecular amount of AIBN (0.029 g, 0.177 mmol) compared to the precursor. The solvent, CCl4 (25 ml) was transferred through a double pointed needle bridge, under constant nitrogen flow. For the reaction an IR lamp was used, as a heat source and also to help create the radicals trough the emitted radiation. The system is left under reflux for 24 hrs. The solution is chilled, filtered and the filtrate is then rotovaporated. A red-brown viscous liquid is left. Purification of crude product by column chromatography with hexane as eluent, gave 3-bromomethyldiphenylethylene 3 as slightly yellow product, yield 68 %.

Synthesis of 4,4,4-(ethane-1,1,1-triyl)tris(((3-(1-phenylvinyl)benzyl)oxy)benzene), 3

Commercially available 1,1,1-Tris(4-hydroxylphenyl)ethane 2 (1 g, 3.3 mmol) was utilized as the starting material for initiator-precursor synthesis, and along with a small excess of 1 (3.178 g, 11.63 mmol, ~1.2 mol of 1 for each hydroxyl group), freshly ground K2CO3 (6 g, 43 mmol) and KI (0.3 g, 1.82 mmol) as catalyst, where placed under N2 flow. The synthetic route for 4,4,4-(ethane-1,1,1-triyl)tris(((3-(1-phenylvinyl)benzyl)oxy)benzene) 3 is illustrated in Scheme 1. The synthesis proceeded through a Williamson etherification. The solvent (acetone) was added through a double pointed needle, under nitrogen. Acetone was purified by stirring overnight, under vacuum, with calcium sulfate and fractionally distilled and stored in a flask containing molecular sieves under nitrogen. The reactor was placed in an oil bath at 90 °C and was left under reflux for 36 hrs. The compound was extracted with chloroform, filtered and the filtrate rotary evaporated down to a yellow viscous product. Purification of the crude product by column chromatography with mixture of hexane and ethyl acetate as eluent (97 %-3 %), gave a slightly yellow partially solid, viscous product 3, yield 92.5 %. TLC (silica F 254, hexane 90 % and 10 % ethyl acetate as eluent) Rf = 0.40.

Formation of tri-functional carbanion initiator

The synthesis of the trifunctional initiator, 4, was achieved upon activation of 3 with sec-BuLi (Scheme 2). The adduct formation was performed in a custom blown glass apparatus equipped with ampoules, break-seals, and glass magnets for reagent addition and constrictions for aliquots removal, under high vacuum. The apparatus was purged with a solution of n-BuLi and washed with benzene. Then 50 ml of benzene were distilled back into the reactor and the purge section was removed. The ampoule containing 3, tri-DPE (0.113 mmol) was broken and then rinsed with benzene to ensure that all the tri-DPE had been removed. A small amount of the solution was removed before addition of the sec-BuLi from the apparatus by heat sealing to check the purity and estimate the mass by NALDI-TOF MS (and MALDI-TOF MS) Figures 2 and S6. At this point sec-BuLi

was introduced in to the apparatus (~0.101 mmol), the solution initially obtained a pale yellow color that within minutes turned into orange, and finally became red-orange. After 2.5 h, an aliquot was removed and quenched. Then several more drops of sec-BuLi (~0.203 mmol) were added to the reactor. After another 2.5 h, a second aliquot was removed and quenched. At this point the remaining sec-BuLi was added (0.340 mmol). The solution had a clear deep-orange red color and the concentration of initiator solution was 2.3 × 10-3 M. At 7, and 9 h after the initial addition of sec-BuLi and tri-DPE aliquots of the solution were removed and quenched. The quenched aliquots were transferred to clean round-bottom flasks, rotary evaporated and then dried overnight in a vacuum oven before being subjected to testing by Matrix Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI TOF-MS) and Liquid Chromatography Mass Spectrometry (LC-MS) (Appendix, Figure).

Polymerization of Styrene or Isoprene by the Trifunctional Organolithium Initiator (4).

Styrene and isoprene were polymerized under high-vacuum using break-seal techniques in benzene using the trilithium initiator 4 in the absence of any polar additive. Deliberate termination was completed using degassed methanol. The polymerization reaction (entry 5, Table 1) was performed in a custom made glass reactor equipped with ampoules containing sec-BuLi (1.08 mmol), the unsaturated compound 3 (0.345 mmol in 10 ml of pure benzene), styrene (10 g, 96 mmol), and methanol (2 ml). Initially, the ampoules with compounds 3 and sec-BuLi were introduced by smashing the break-seals in the reactor containing 130 ml of purified benzene and left to react overnight at room temperature. The solution after a couple of minutes obtained a pale yellow color that within minutes turned into orange and finally accumulated a clear red-orange color. Then, styrene was added in to the reactor, the color faded from red-orange to orange (for styrene) and faint orange (for isoprene). The polymerization was left for 20 h and then was terminated by adding a small amount of degassed methanol.

Results and Discussion

Synthesis of tri-functional DPE precursor

Synthesis of the tri-functional DPE moiety-containing precursor is shown in Figure 4.1. The chemistry and functionality of the diphenylethylene compound, and the

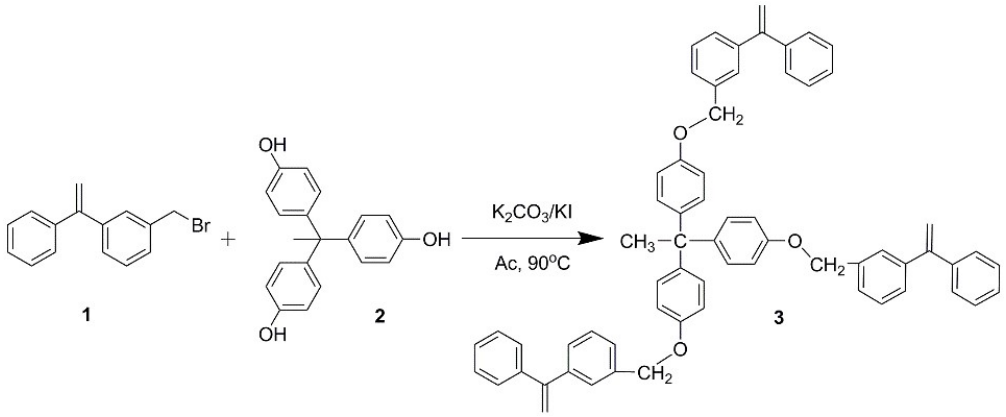


Figure 4.1 Synthetic route for preparation of 4,4,4-(ethane-1,1,1-triyl)tris(((3-(1-phenylvinyl)benzyl)oxy)benzene).

chemical advantages of a built-in ether group, were taken into consideration during its design.[11,16,33] The previously reported trifunctional DPE precursor by Quirk et al., formed aggregates upon stoichiometric amount of sec-BuLi addition and required the use of a polar additive for polymerization to simultaneously initiate at all three sites. This could be caused by the delocalization of carbanion adduct and the rigid conformation of the trifunctional carbanion.[25] In order to avoid extended delocalization of the final carbanion adduct, Williamson etherification reaction was performed between 3 moles of 1-(3-bromomethylphenyl)-1-phenylethane (Br-CH2DPE, 1) and commercially available 1,1,1-tris(4-hydroxylphenyl)ethane (THPE, 2) in the presence of K_2CO_3/KI as catalysts in acetone. The Br-CH2DPE was synthesized using a reported procedure via Witting

reaction of methylbenzophenone and subsequent Wohl-Ziegler bromination (Figure 4.1).[36]

The Williamson etherification reaction proceeded quantitatively. The purification of precursor 3 using silica column gave a slightly yellow viscous product. After recrystallization in methanol the product 3 acquired a white color and embraced the solid state. 1H NMR showed the presence of three DPE moieties in 3 as the integration of three protons of methyl group (a) of the core THPE matches with six photons of three olefins (c) and benzylic methylene (b) groups (Figure 4.2).

The main feature the ether group provides to the structure is an increase of solubility of trifunctional carbanion in hydrocarbon solvents (the long alkyl spacer also contributes) after forming the triadduct with sec-BuLi. It will also assist in avoiding extended pi-conjugation of the resulting carbanion and possibly to reduce inter/intra molecular cross-association. The ether group is very stable under basic conditions and does not react with carbanions. The advantages of a built-in ether group have also been described in the work of Sanderson et al.[33] The concept of intramolecular ether moieties in a multifunctional initiator was first presented by Tung et al.[11] Several bi-functional initiators based on DPE types have been extensively studied in many chemical variations in anionic polymerization.[15,16,37]

In order to reassure the presence of three DPE moieties in 3 and its molecular integrity as a whole, mass spectrum using NALDI-TOF was conducted. NALDI-TOF MS utilizes a target covered with a layer of inorganic nanostructures. These nanostructures absorb laser energy efficiently, resulting in laser desorption of the sample without the need for a matrix. The resulting mass spectra were obtained with higher sensitivity and lower chemical background than traditional MALDI-TOF MS, and the technique is especially useful for the analysis of low molecular weight compounds (< 2000 Da).38 The NALDI-TOF mass spectrum of compound 3 is shown in Figure 4.3. The main peak observed at m/z 989.57 which corresponds to the desired trifunctional DPE ([(C21H17O)3CCH3 □Ag]+, whose theoretically calculated monoisotopic mass is 989.31 Da. The smaller peak observed at 867.70 is likely due to fragmentation, and attributed

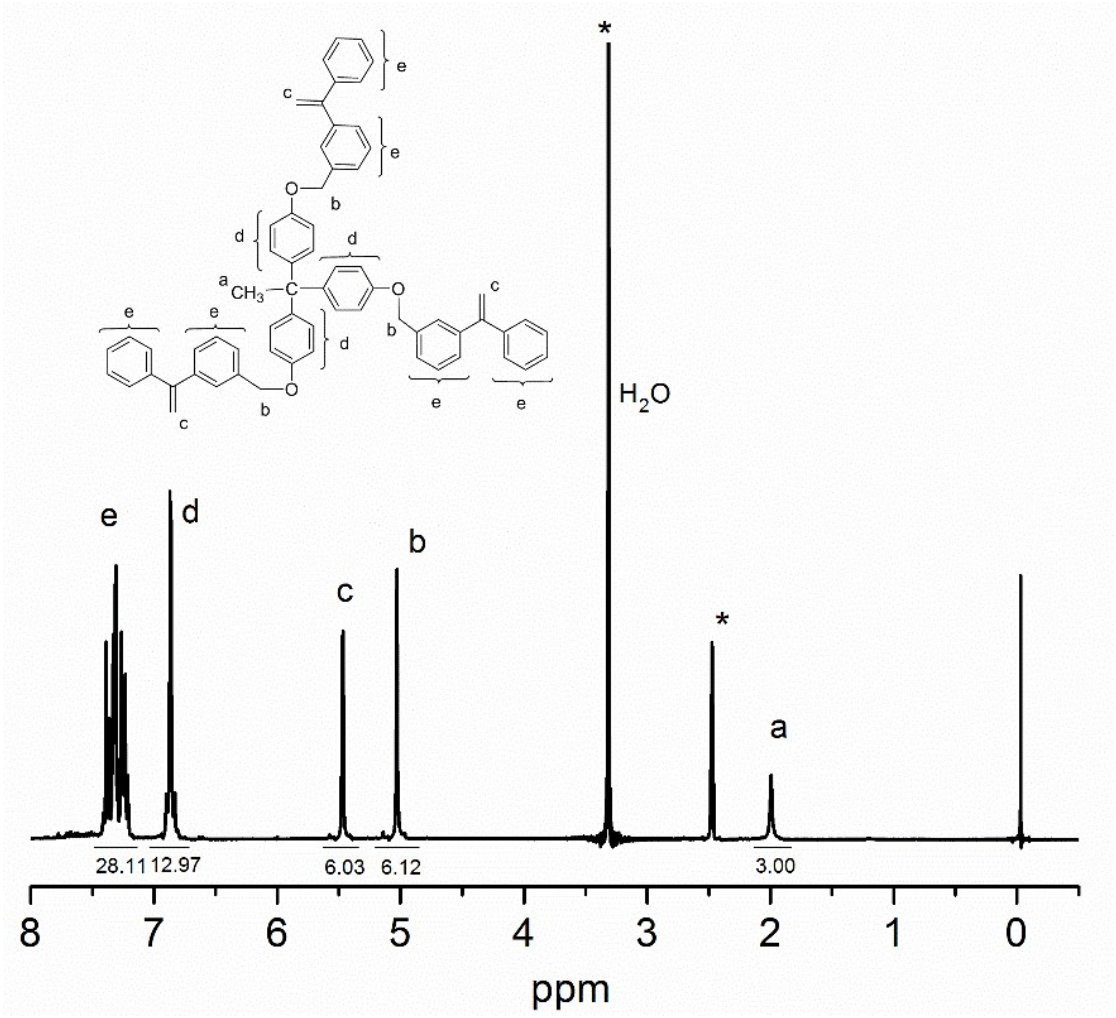


Figure 4.2 1H NMR of compound 3 in DMSO-d6

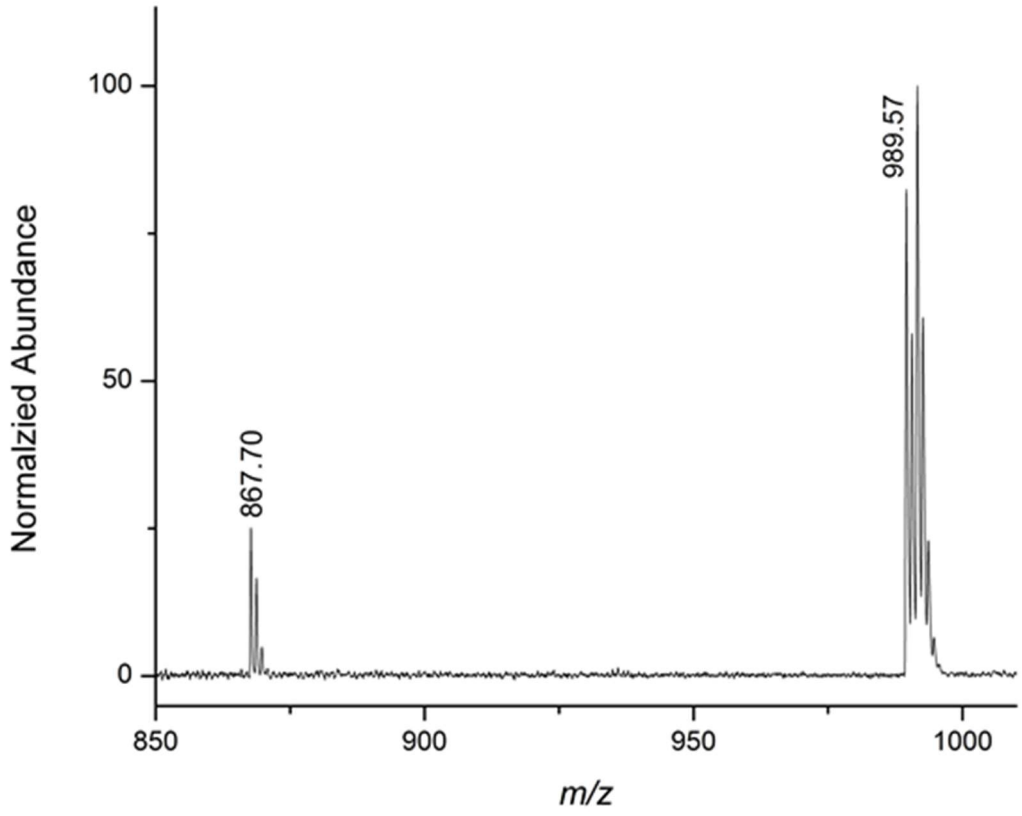


Figure 4.3 NALDI-TOF mass spectrum of unsaturated trifunctional DPE compound 3.

to the loss of a methyl group to form a radical cation (calc. monoisotopic mass 867.38 Da).

As previously mentioned, a trifunctional initiator, consisting of three DPE-moieties connected to an aromatic ring has been described by Quirk and Tsai.[25] This multifunctional initiator requires a Lewis-base, such as THF, to render its three DPE adducts with *sec*-BuLi equally active, and possessed limitations regarding the lowest targeted molecular weight, in order to obtain mono-modal and narrow molecular weight distributions.

Synthesis of three-arm star homopolymers of styrene($P(S)_3$) and isoprene ($P(I)_3$)

The synthesis of three-arm PS and PI was performed using a known concentration of 3 and a stoichiometric amount of sec-BuLi corresponding to the olefins in 3, in benzene under high vacuum (Figure 4.4). All the performed reactions are listed in Table 1. Upon mixing a calculated amount of sec-BuLi into the solution containing 3, a pale yellow color appeared indicating the formation of the anion adduct with the olefin. The color of the reaction mixture slowly became intense and changed to red-orange over few hours (Appendix Figure 4.9). The polymerization was initiated after aging the initiator solution over ~15 h, to be sure for complete adduct formation.

Several reactions were performed at different total concentrations of the initiator ([I]0), for both styrene and isoprene three-arm star polymer synthesis (Table 4.1). In some case, a slight excess of *sec*-BuLi was employed to make sure of complete conversion of all the double bonds into anions. Polymerization reactions were performed over 20 h and terminated with methanol. It should be mentioned here that the polymerization is expected to be completed within a few hours, it was merely for convenience that the propagation was continued over-night. The reaction performed with active total anion concentration, $[\text{sec-BuLi}]_0$ of 3.8 x 10-3 mol/L (3 x $[I]_0$), produced very high molecular weight three arm star polystyrene with a broad monomodal molecular weight distribution (MWD) (run 1, Table 4.1). Although in some cases, we observed bimodal distributions (results are not given here), many reactions gave broad distributions

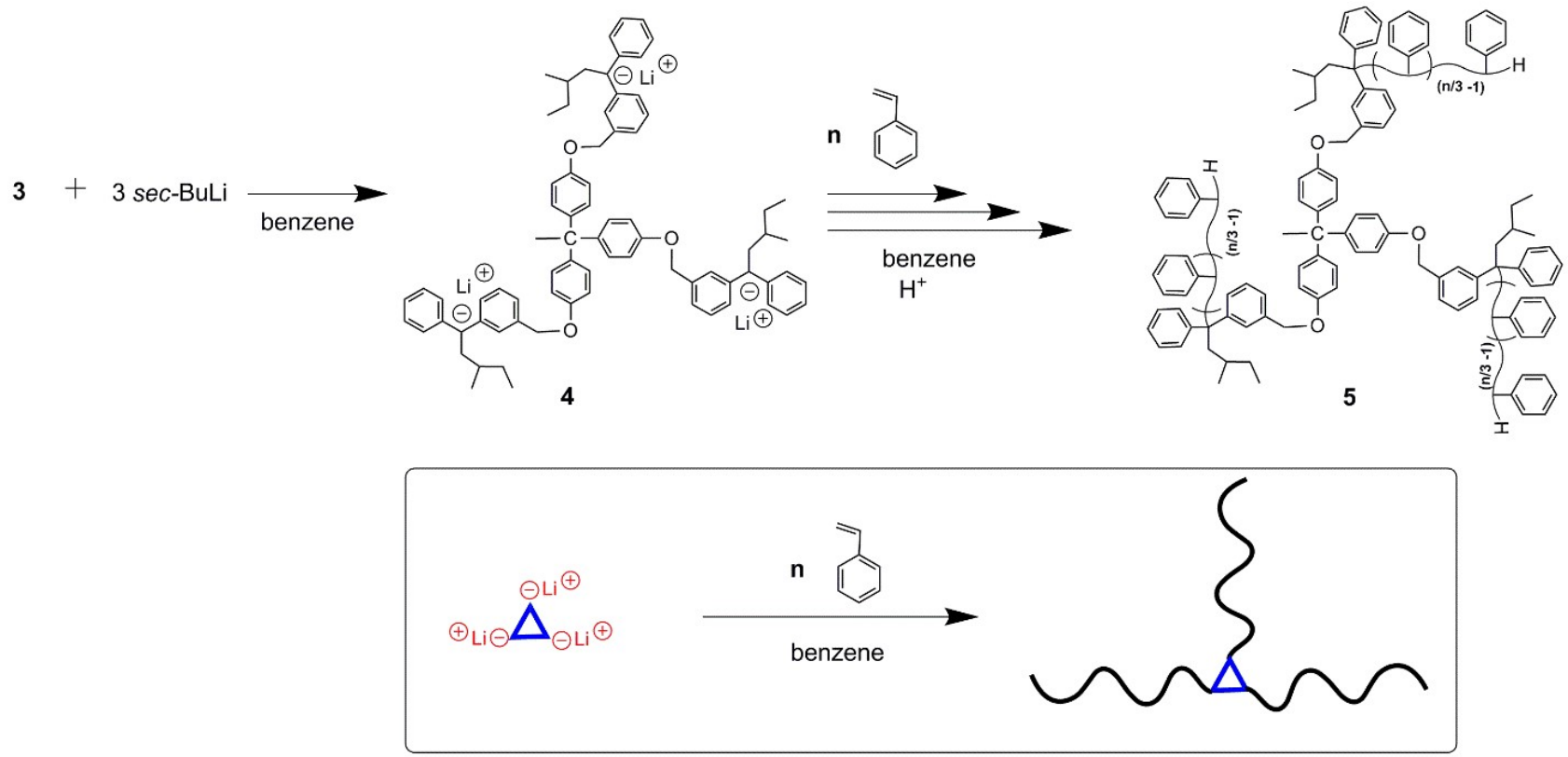


Figure 4.4 Formation of trifunctional carbanion adduct initiator 4, via reaction of *sec*-BuLi with 3, and the synthesis of three arm three-arm polystyrene, $P(S)_3$ in benzene at RT.

Table 4-1 Anionic polymerization of styrene and isoprene and synthesis of three-arm $P(S)_3$ and $P(I)_3$ their diblock copolymerization using the multifunctional initiator in benzene without any polar additive.

Entry	[TriDPE] 10^3 (mol/L)	[sBuLi] 10^3 (mol/L)	[olefin] [a] /[BuLi]	[S or I][b] 10^3 (mol/L)	$M_{n,th}$[c] 10^{-3} (g/mol)	$M_{n,SEC}$ [d] 10^{-3} (g/mol)	$M_{w,LS}$ [e] 10^{-3} (g/mol)	PDI[d] (M_w/M_n)
Styrene (S)								
1	1.27	3.80	1.0	0.99	81.4	116.0	-	1.23
2	2.13	6.58	0.97	0.61	29.0	-	31.0	1.05
3	6.20	18.6	1.0	0.71	12.0	-	12.6	1.06
Isoprene (I)								
4	0.38	1.20	0.95	0.24	43.0	152.0	490.0	1.47
5	0.75	2.40	0.94	0.52	47.0	224.0	360.0	1.48
6	5.50	16,5	1.0	0.81	10.0	-	11.0	1.03
Styrene (S) and Isoprene (I)								
7	6.20	18.6	1	[S] = 0.71 [I] = 0.29	12.0	-	12.6	1.06

a) 3 × [TriDPE]/[sBuLi], b) monomer concentration either styrene (S) or isoprene (I), c) 3 × (grams of monomer/[sBuLi], d) Size exclusion chromatography calibrated against standard PS in THF, for polyisoprene, the hydrodynamic volume factor 1.6 was used to calculate molecular weight. e) determined by Low Angle Laser Light Scattering in cyclohexane (PI) and toluene (PS) at 25 °C, or by laser light scattering with a laser of 680 nm at 15º and 90º angles using d*n*/d*c* values of 0.186 ml/g and 0.128 ml/g for PS and PI in THF, respectively.

with very high molecular weight for low concentration of total anion. This indicates that the initiation of all three sites of 4 is not uniform and aggregation dynamics of 4 might play a role for such a high molecular weight product. Similar observations were made for isoprene polymerization with [sec-BuLi] < 3.8 x 10-3 mol/L (run 4-5, Table 1). In run 4 and 5, a slight excess sec-BuLi was used to assure complete adduct formation for isoprene polymerization. These reactions also did not produce narrow MWDs. It was expected that we would see two peaks, one corresponding to the trifunctional initiator and the other to the excess sec-BuLi. The broad distribution of the high molecular weight polymers indicates that the excess sec-BuLi might be cross-associating with aggregated anions in benzene.

Interestingly, when we did the subsequent reactions at higher active anion concentration such as [sec-BuLi] < 3.8 x 10-3 mol/L, the three-arm $P(S)_3$ and $P(I)_3$ stars exhibit very narrow MWDs (Mw/Mn ≤ 1.06) in all cases, with very high initiator efficiency (run 2,3 and 6, Table 4.1, Figure 3.5). As shown in Table 1, the molecular weights determined from light scattering are very close to the theoretical ones which led us to the conclusion that all initiator sites participated in the polymerization and more importantly that all initiation centers are equally efficient. Our last conclusion is supported from viscometry studies, as discussed below.

In one of the experiments (run 2, Table 4.1), we used a small excess of sec-BuLi (3-4 %) compared to the double bonds of 4 in low concentration reaction. A second peak with higher molecular weight was seen in the SEC eluogram, which was attributed to a linear PS (Figure 3.5). The two peaks were separated by fractionation and the star branch structure was confirmed through the measurement of the branching parameter g´, as discussed below.

Throughout the polymerization for both low ([*sec*-BuLi] < 6.6 x 10-3 mol/L) and high ([*sec*-BuLi] up to 18.6 x 10-3 mol/L) concentration reactions, the propagating reaction solution was homogeneous and there were no particles or insoluble aggregates observed during the reaction.

It is evident by studying the data in Table 4.1 that two different behaviors are recorded in relation to the initiator concentration in solution. For initiator concentrations above ~3 × 10-3 mol/L the synthesized star polymers exhibit monomodal distribution

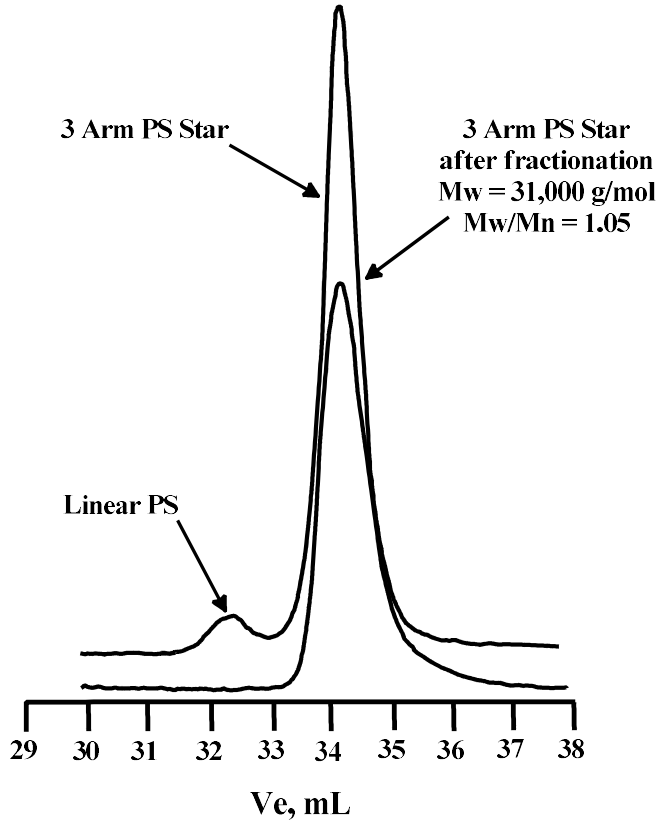


Figure 4.5 Size exclusion chromatography eluograms of the three-arm PS star before and after fractionation (run 2, Table 1).

where the polydispersity indices are below 1.1, while for concentrations lower than this value the polymers show broad/bimodal distributions with polydispersity indicesin the range of 1.25 < Mw/Mn < 1.50. The formation of very high molecular weight products only in low concentration reactions suggests that the aggregation of trifunctional carbanion, 4 undergoes dynamic equilibrium with different reactive solvated species that inserts styrene or isoprene at different rates leading to extremely high molecular weight and uncontrolled products (Figure 3.6). We believe that this behavior is due to the existence of partially active aggregates of different populations in fast dynamic equilibrium with the non-aggregated unimeric trifunctional initiator at low concentration of initiator.

An indication for the participation of such partially solvated aggregates at low concentration of difunctional anionic initiators can be obtained from the literature.[31] Vasilakopoulos and Hadjichristidis31 in their study of the influence of (1,3-Phenylene)bis(3-methyl-1-phenyl pentylidene)dilithium initiator (DLi) concentration on the modality of polybutadiene in non-polar solvent observed a similar behavior. They found that for a relatively high DLi concentrations ([I[$_0$ > 7 × 10-4 M) monomodal PBds with polydispersity indices less than 1.07 were obtained, whereas bimodal PBds were observed at lower concentrations. As shown in Scheme 3, we propose that at higher trifunctional initiator concentration ([sec-BuLi] > 6.6 x 10-3 mol/L), an equilibrium of intermolecular ion-pairs exists between exclusively active unimer ion-pair and dormant-intermolecular associated ion-pair (two state equilibrium). The dielectric constant of the non-polar medium may also influence this equilibrium position depending on the concentration of anions. However, at the lower initiator concentration studied in this work, a partial activation of aggregation may occur, which can produce reactive species for propagation. Although the origin of such species is not fully understood, a possible explanation could be an intramolecular solvation of delocalized anions that activates the aggregates and induce equilibrium shifts to less aggregated species which have some of the ion-pairs active in its aggregates. This multiple equilibrium dynamics must be responsible for the very high molecular weight products obtained with broad and bimodal distributions. It appears that critical concentrations exist for 4 to initiate monomers homogeneously at all sites in benzene.

Viscosity and branching factor studies of $P(S)_3$ and $P(I)_3$

The branched architecture of the star polymer can be identified using the branching factor, g', which is related to branching parameter g, a radius of gyration contraction factor. In order to confirm the formation of star polystyrene and examined the functionality, g´ values were compared to the ones reported in the literature for 3-arm stars. As it is well known, star polymers have smaller hydrodynamic volume, smaller radius of gyration, Rg, and smaller intrinsic viscosity, [η], as compared to linear polymers with the same composition and molecular weight. So, through measurements of intrinsic viscosity of the branched and the corresponding linear polymers, g´ values may be determined from the equation below:

$$g' = [\eta]_{br}/[\eta]_{lin} \quad (1)$$

The absolute molecular weights of the polystyrene star in toluene, and of polyisoprene star in cyclohexane were determined by light scattering and through the following equations,[39] the intrinsic viscosities of the linear analogous were determined.

$$[\eta]_{lin} = 9.27 \times 10^{-3} M_w^{0.734} \quad \text{PS in toluene (2)}$$

$$[\eta]_{lin} = 1.97 \times 10^{-2} M_w^{0.733} \quad \text{PI in cyclohexane (3)}$$

In Table 2 the values of intrinsic viscosities of the star samples, the g´, and the Huggins coefficients KH are shown. The KH coefficient was determined from the slope at the Huggins plot (4) and provides additional proof of the polymer's branched structure.

$$\eta_{sp}/c = [\eta] + K_H [\eta]^2 c \quad (4)$$

Table 4-2 Viscosity of tri-arm star polystyrene and polyisprene samples synthesized using tri-DPE adduct with sBuLi in benzene.

Entry	Sample	$M_{w,LS} \times 10^{-3}$ (g/mol)	$[\eta]_{star}$[a] (dL/g)	g´	K_H[a]
2	$(PS)_3$	31.0	0.148	0.81	0.43
3	$(PS)_3$	12.6	0.078	0.82	0.41
6	$(PI)_3$	11.0	0.163	0.84	0.37

a) determined by viscometry in cyclohexane (PI) and toluene (PS) at 35 °C

Literature values of g´ for three-arm star polymers are in the range between 0.8 and 0.94, but especially for three arm PS stars the values obtained in toluene at 35 °C are between 0.81 and 0.85.[40,41] These values are in very good agreement with the ones obtained from viscometry, in the same solvent and at the same temperature, for our two PS samples. Also, g´ values are sensitive to the asymmetry of the arms. It has been shown that PS stars with three arms of different molecular weights have increased g´ values (~0.92).[42] Additional evidence that the obtained polymers have star branch structure, comes from the Huggins coefficient, KH. The increased value of the Huggins coefficients for our materials, as compared to the ones obtained for analogous linear polymers in good solvents (KH~0.3), provides additional strong evidence for higher chain segment density, as expected for these three-arm stars, $P(S)_3$ and $P(I)_3$).

Synthesis of three-arm star copolymer containing diblock arms ($P(S\text{-}b\text{-}I)_3$)

To confirm the 'living' nature of the polymerization, diblock copolymerization was performed through sequential addition of second monomer (isoprene) after the polymerization of styrene. The reaction was performed using high concentrations to avoid non-uniform propagation of living arms in the synthesis of $P(S\text{-}b\text{-}I)_3$. Upon addition of isoprene, the color of the living polystyryl anion solution changed rapidly (within a few seconds) from orange to pale yellow, which confirms a fast initiation of the second block. The polymerization of the 2nd block was left to proceed for a day at room temperature before termination with methanol. The synthesis of three-arm star with diblock copolymer

arms was confirmed by SEC (Figure 4.6) where an obvious shift of the peak corresponding to the diblock (copolymer arm star formation) towards higher molecular weights was observed. Also, from the eluogram, at low molecular weights, a small peak (<3 %) is observed, corresponding to left over, unreacted three-arm polystyrene star.

This small unreacted fraction is not coming from the termination reaction as the polymerization was performed under high-vacuum using break-seals, but could have resulted from incomplete initiation of styryl anions. Further confirmation was obtained by 1H-NMR where resonances of both blocks are present in the spectrum (Figure 4.12, Appendix). The absence of high molecular weight products due to participation of partially solvated aggregates is confirmed using a triple detection method, which showed monomodal peak in low-angle light scattering (Figure 4.6). The formation of well-defined three-arm diblock containing star copolymer, P(S-b-I)$_3$ reconfirms the uniform initiation of multifunctional initiator that works well in benzene.

Conclusions

In summary, we report the synthesis of a novel trifunctional anionic initiator that is effective in hydrocarbon solvents without the addition of polar additives. Using this initiator, well-defined three-arm star homopolymers of PS and PI were synthesized, as well as star-block copolymers having arms of PS-b-PI. Rigorous molecular characterization by a combination of NMR, SEC, light scattering, mass spectrometry, and viscometry confirmed the well-defined three-arm star architecture of these materials and confirms the highly efficient nature of this initiator. Future work will report the use of this new initiator for the synthesis of highly complex macromolecular architectures.

Acknowledgements

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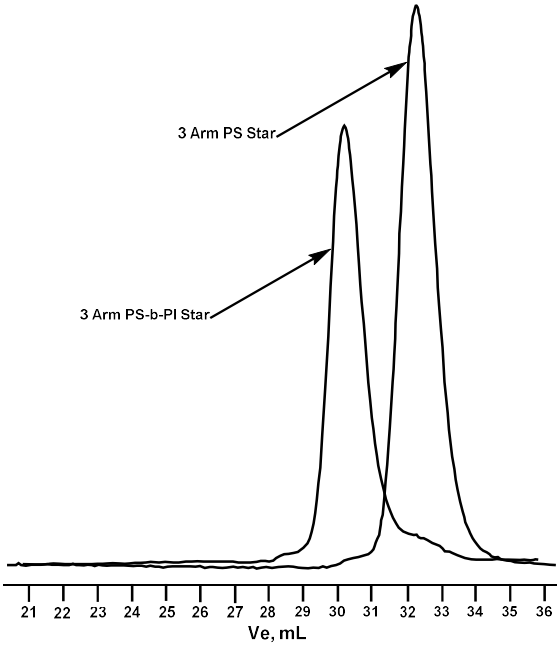


Figure 4.6 Size exclusion chromatography eluograms of the three-arm PS star and of the corresponding diblock copolymer star (P(S-*b*-I)$_3$) after the polymerization of isoprene (run 3 and 7, Table 1).

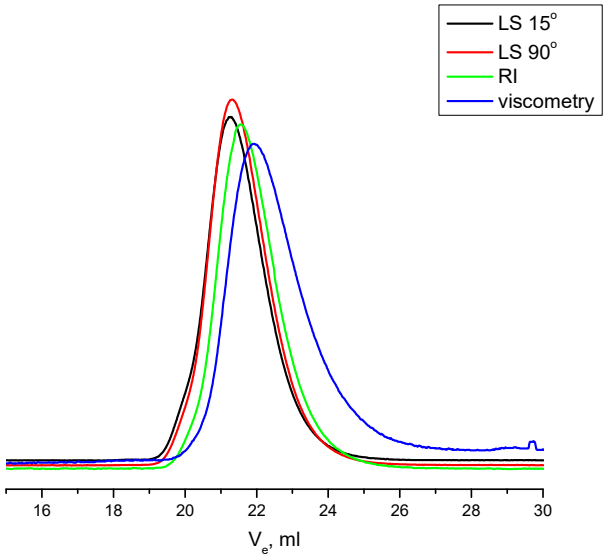


Figure 4.7 Size exclusion chromatography eluograms of broad molecular weight distribution polymer star. (Table 1, entry 5)

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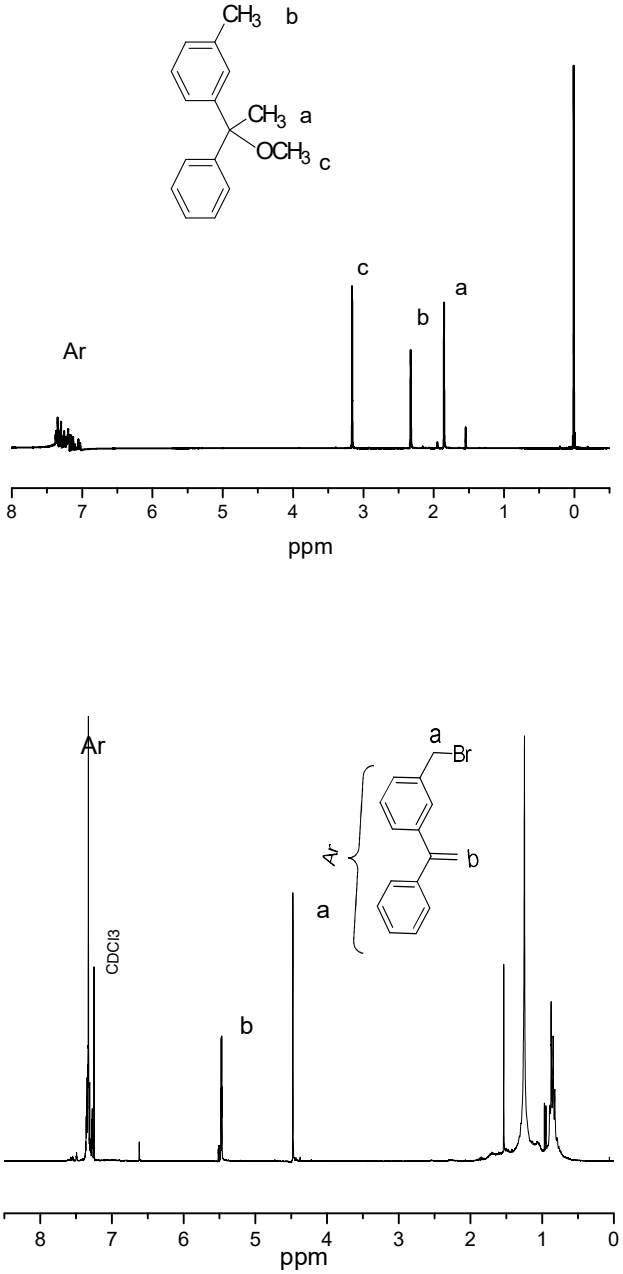


Figure 4.8 ^{1}H NMR of 1-(1-methoxy-1-phenyl-ethyl)-3-methylbenzene and 3-bromomethyl DPE

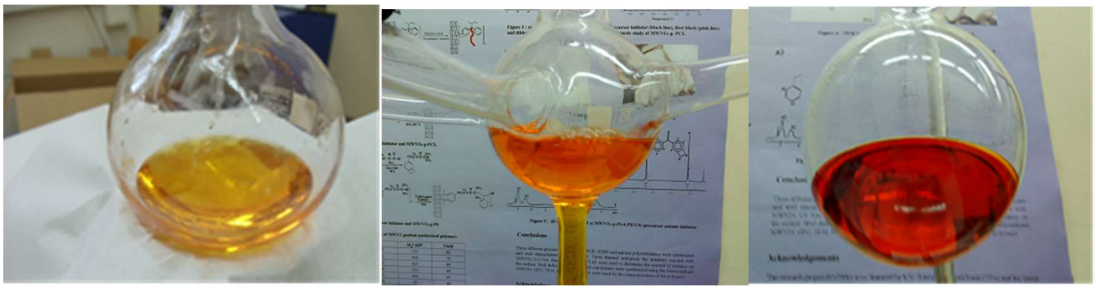


Figure 4.9 Photos during activation of 4,4,4-(ethane-1,1,1-triyl)tris(((3-(1-phenylvinyl)benzyl)oxy)benzene) with *sec*-BuLi.

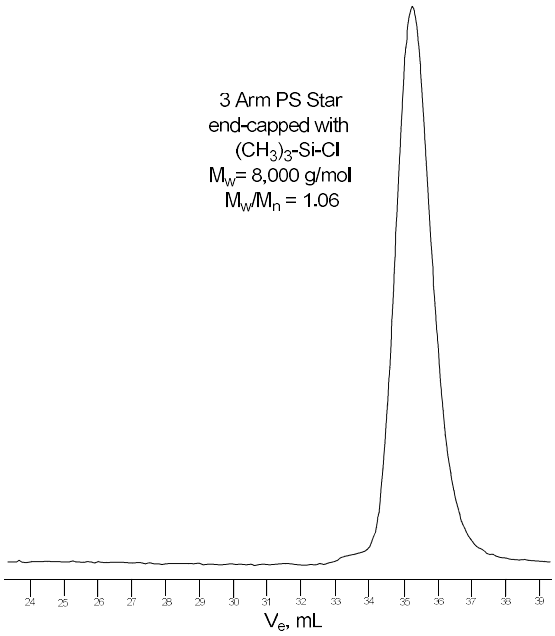


Figure 4.10 Size exclusion chromatography eluogram of the three-arm PS star after end-capping with (CH3)3-Si-Cl.

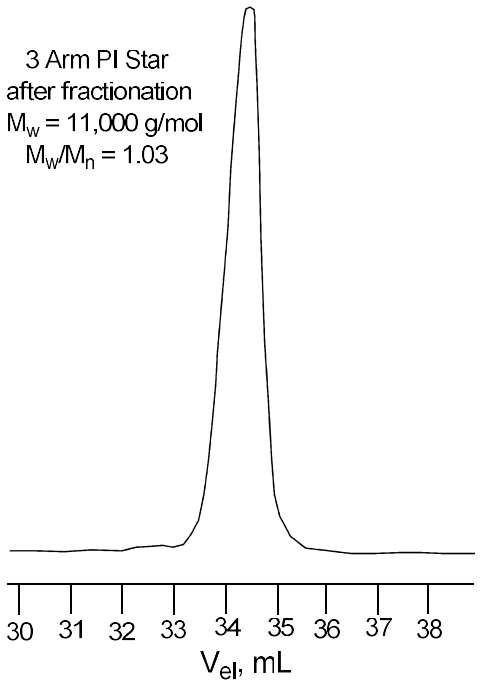


Figure 4.11 Size exclusion chromatography eluogram of the three arm PI star after fractionation.

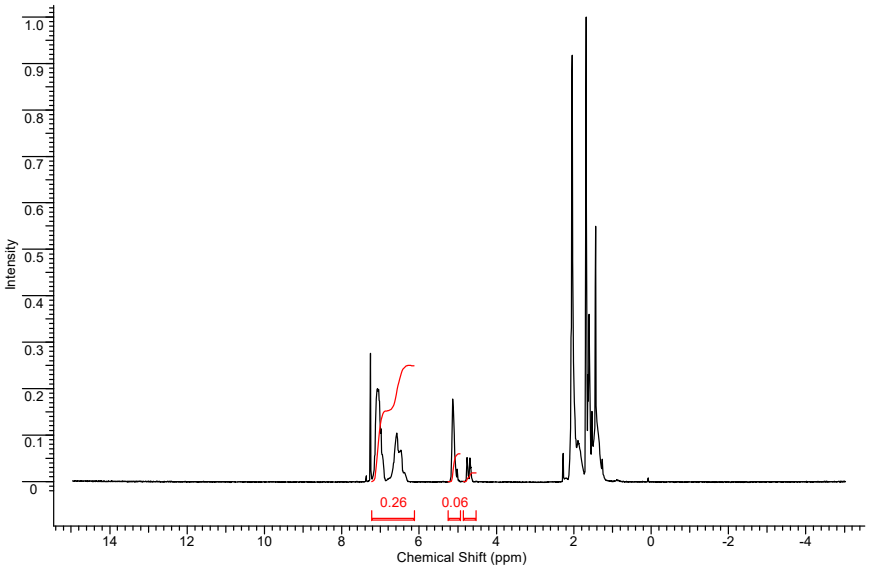


Figure 4.12 ^{1}H-NMR of PS-*b*-PI Star

Reactant ID Verified

Internal calibrated

$[C_{65}H_{54}O_3+H-CH_4]^+$ Fragment is dominant

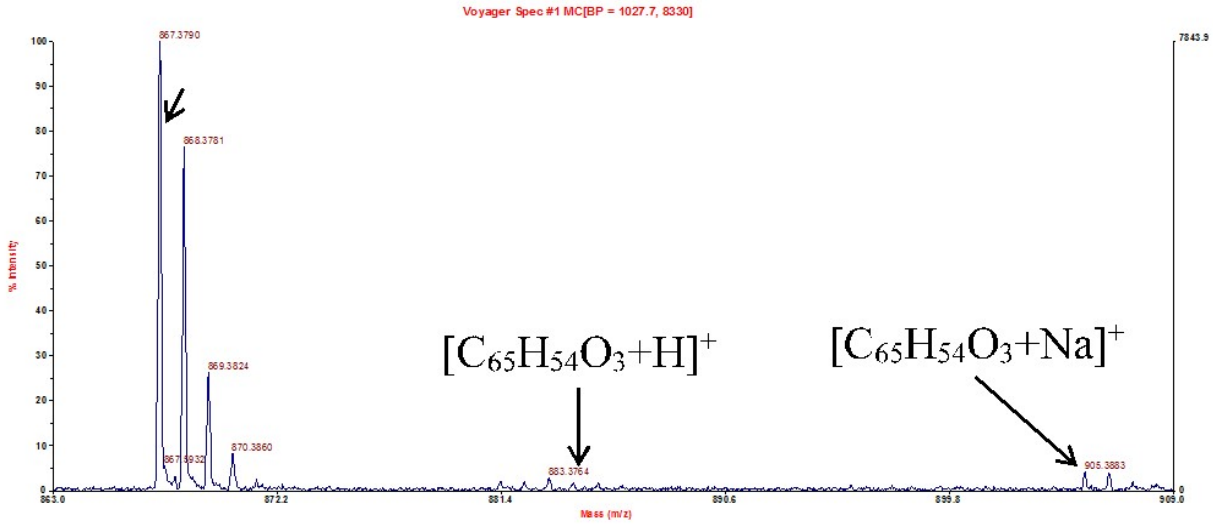


Figure 4.13 MALDI-TOF MS of compound 5, before the addition of sec-BuLi

CHAPTER 5 CONCLUSIONS AND FUTURE WORK

Conclusions

The fundamentals and challenges of the synthesis of initiators for anionic polymerization, especially multifunctional initiators, have been discussed and the prior experimental results were thoroughly reviewed in the Introduction chapter. In addition, the special role of 1,1-diphenylethylene in the experimental methods of anionic polymerization and the challenges of polymerizing functionalized styrene monomers by anionic polymerization were also discussed at length. By striving to develop new multifunctional initiators and synthetic pathways to address the obstacles encountered in anionic polymerization new materials can be developed to address real world problems.

A synthetic pathway to new materials based off of the well-known reactions of phenol has been developed. By using the well-known Williamson etherification reaction, the hydroxyl group of poly(4-hydroxystyrene) can be used to add functional groups that are normally incompatible with anionic polymerization. Greater insight has been gained into the non-covalent bonding forces that can drive the self-assembly of homopolymers in solvent mixtures, including hydrogen bonding and halogen bonding. Potential applications of the self-assembled homopolymer vesicles of poly(4-hydroxystyrene) have been investigated as possible vehicles for the transport of chemotherapeutics and the formation of gold nanoparticles.

Random copolymers of styrene and 4-(1-ethoxyethoxy)styrene were polymerized by anionic polymerization and had the acetal removed to yield polystyrene-co-poly(4-hydroxystyrene). Using the Williamson etherification reaction, the hydroxyl functionalities of the random copolymers, PS-CO-PHS, were converted propynyloxy functionalities by reacting with propargyl bromide. The alkyne functionalized polymer was used as a backbone for the synthesis of graft copolymer utilizing previously synthesized polymer side chains with terminal azide groups. Copper(I)-catalyzed azide-alkyne cycloaddition reactions were used to graft the side chains to the polymer backbones. Among these graft copolymers was the first example fully synthesized by anionic polymerization.

The organic synthesis of a trifunctional molecule to serve as trifunctional initiator upon reaction with sec-BuLi based on 1,1,1-tris(4-hydroxyphenyl)ethane was performed. 1-(3-bromo-methylphenyl)-1-phenylethylene was synthesized in a two-step reaction and purified before a Williamson etherification reaction and was used to covalently tether three

1,1-diphenylethylene functionalities to a single core molecule. Reaction conditions for solubilizing the initiator after the reaction of sec-BuLi with the triDPE molecule revealed a solubility dependence on concentration. The solubility of the initiator had an adverse effect on the quality of polymerization reactions.

For over 50 years the pursuit of a trifunctional initiator for anionic polymerization that is fully soluble in non-polar solvent in the absence of polar additives has been ongoing. The trifunctional initiator presented in this dissertation is the first to satisfy these conditions and has been demonstrated to synthesize three-arm star polymers to targeted molecular weights and narrow molecular weight distributions. The retention of the living carbanion was demonstrated by synthesizing star polymers with block copolymer arms by sequential monomer addition. Without the need for polar additives star polydienes of high 1,4-microstructure can be synthesized in one pot reactions for the first time, greatly reducing the complexity of polymer star synthesis by anionic polymerization. The introduction of this trifunctional initiator opens up a great many synthetic possibilities to the field of anionic polymerization.

Future Work

The potential for future work based off the insight gained from the work in this dissertation could lead to new materials and previously unseen polymer architectures. Synthetic polymer chemistry can go as far as the creativity of the individual chemist can take it. The relatively new study of homopolymer self-assembly in solution means that ample opportunity exist to investigate new systems. By adapting many of the organic reactions known to occur in phenol, polymers containing functional groups not previously attainable by anionic polymerization can be synthesized. The work of D. I. Packham in 1964 represents a great opportunity to synthesize by anionic polymerization narrow molecular weight polymers with a variety of functional groups starting from PHS.[1] This work showed that electrophilic aromatic substitution reactions on PHS are restricted to the ortho position allowing for the synthesis of substituted PHS such as poly(3-nitro -4-hydroxystyrene), poly(3-chloro-4-hydroxystyrene), poly(3-amino-4-hydroxystyrene). These functionalized polymers could find application in a variety of fields including ion-

exchange materials and anti-bacterial applications as well as having the potential for amphiphilic homopolymer self-assembly.

The use of click reactions in the synthesis of complex polymer architect continues to be an area of great possibilities. The conversion of a PHS homopolymer to poly(4-(2-propynyloxy)styrene gives the potential to use CuAAC for a densely grafted copolymer. The synthesis of star polymers with alkyne functionalities by converting star polymers of PHS or PS-co-PHS by Williamson etherification for further CuAAC reactions gives the possibility of grafted star copolymers. Conversion of the methylbromo group of 1-(3-bromo-methylphenyl)-1-phenylethylene to alkyne functionality by Williamson etherification reaction with propargyl alcohol would give the possibility of end-capping an azide terminated polymer with a DPE functionality for potential use in anionic polymerization.

The trifunctional initiator opens up a new avenue for the divergent synthesis of polymer star, dendrimers and hyperbranched polymers. Synthesis of these polymers with control over the microstructure of polydienes can now be investigated and could potentially lead to new and higher performance commercial materials. The continued investigation of the factors surrounding the solubility of the trifunctional initiator will be a crucial part of the effort of moving multifunctional initiators forward. The use of a TERMINI to synthesize dendrimer-like polymer stars by divergent strategy is a highly intriguing possibility. Investigations of the structure property relationships of block star copolymers synthesized by the trifunctional initiator, with high 1,4-microstructure of polydienes could be an area of great interest. These are just a handful of the possible directions in which a curious future investigator could take this work

VITA

Christopher M. Hurley was born in Atlanta, GA on March 24th 1987. He was raised and attended primary education in Amherst, NY, graduating from Amherst Central High School in 2005. He matriculated at Hobart College in Geneva, NY in the Fall of 2005 and graduated in the Spring of 2009 with a Bachelor of Science Degree in Chemistry. Upon graduation he was admitted to graduate school at the University of Tennessee Knoxville in Knoxville, TN in the Fall of 2009 as a graduate student in the Chemistry Department. During his time there he studied Polymer Chemistry in the laboratory of Dr. Jimmy W. Mays.