Synthesis and Characterization of Poly(2-Ethyl-2-Oxazoline) Functional Prepolymers and Block Copolymers

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ABSTRACT

This dissertation focuses on the synthesis and characterization of functional poly(2-ethyl-2-oxazoline) (PEtOx) containing homo- and block copolymers that are potential materials for membrane-based water purification and gas separation, drug delivery, magnetic resonance imaging and tissue engineering applications.

The polymerization of 2-ethyl-2-oxazoline (EtOx) was investigated with regard to the effects of initiator structures and reaction parameters such as polymerization time and temperature on molecular weight control and molecular weight distribution, endgroup functionality, living characteristics, and mechanism and kinetics. The structure of initiators was shown to significantly affect the molecular weight control and molecular weight distribution of PEtOx oligomers. Methyl triflate initiated polymerizations were found to result in oligomers with low polydispersity (PDI) values around 1.10-1.15 and symmetrical chromatograms were obtained via size exclusion chromatography (SEC) studies with the use of refractive index, light scattering and viscosity detectors. However, EtOx polymerizations initiated by halide containing initiators such as benzyl chloride, dibromo- and diiodo-*p*-xylene, and vinylsilylpropyl iodides yielded PEtOx oligomers with higher PDI values ~ 1.30-1.40. Higher molecular weight distributions can be attributed to the presence of covalent species during polymerization and slower initiation rate as evidenced by kinetic studies when compared to PEtOx's prepared from methyl triflate initiators. In all cases, termination reactions with aliphatic cyclic amines were

quantitative. Mono- and diamine functional PEtOx oligomers with controlled molecular weight and excellent end-group functionality may be used as prepolymers for incorporation into multiblock and graft copolymer and crosslinked structures for a variety of applications such as membranes and hydrogels for tissue engineering matrices.

Poly(2-ethyl-2-oxazoline) containing block copolymers were prepared using the macroinitiator method. First, amphiphilic triblock copolymers with hydrophobic poly(arylene ether sulfone) (PSF) central block and hydrophilic PEtOx side blocks were synthesized via polymerization of EtOx sequences from tosylate functional telechelic PSF macroinitiators. PSFs are well-known engineering thermoplastics with excellent resistance to hydrolysis and oxidation, as well as displaying good mechanical properties, thermal stability and toughness. Phenol functional PSFs were prepared via step-growth polymerization of dichlorodiphenylsulfone and bisphenol-A (slight excess) monomers. Phenolic chain ends were then converted to aliphatic hydroxyethyl endgroups by reaction with ethylene carbonate. Upon treatment with *p*-toluenesulfonyl chloride, tosylate functional PSF macroinitiators were prepared. PEtOx-*b*-PSF-*b*-PEtOx triblock copolymers (pendent acyl groups of PEtOx side blocks) were partially hydrolyzed in an acidic medium to introduce random charged poly(ethylene imine) units to prepare ionomer structures that may show good salt rejection, water flux and antibacterial properties for membrane-based water purification applications.

Phosphonic acid modified poly(ethylene oxide)-*b*-poly(2-ethyl-2-oxazoline) (PEO-*b*-PEtOx) diblock copolymers were prepared via cationic ring opening polymerization of EtOx monomers from tosylate functional PEO macroinitiators and subsequent functionalization reactions on the polyoxazoline block. Post-modification

reactions included controlled partial pendent acyl group hydrolysis under an acidic medium to form the random block copolymers of PEtOx and poly(ethyleneimine) (PEI), Michael addition of diethylvinyl phosphonate groups to PEI units and hydrolysis of the ethyl groups on the phosphonates to yield pendent phosphonic acid groups on the polyoxazoline block. After each step of functionalization reactions, structures and compositions were confirmed utilizing ^{1}H NMR and the degree of phosphorylation was found to be > 95%. Both PEO and PEtOx are biocompatible polymers and the anionic quality of the phosphonic acid has the potential to be pH controllable and provide an environment where cationic drugs and contrast agents can be attached. Thus, these polymers have potential as drug carriers and contrast enhancement agents for magnetic resonance imaging applications.

This work is dedicated to my wife and daughter:

Secil and Nehir Birgul Celebi

My parents:

Emine and Selami Celebi

and

Sister:

Dilruba Celebi

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Attribution

Several colleagues and coworkers aided with the research presented in this dissertation. A brief description of their background and their contributions are included here.

Prof. Dr. Judy S. Riffle - Ph.D (Department of Chemistry and Macromolecular Science and Engineering Program, Virginia Tech) is the advisor and committee chair. Prof. Riffle provided extensive advice and discussion on the design, execution of the experiments, the analysis of the experimental data, and writing of the Ph. D. dissertation.

Chapter 3: Synthesis and Characterization of Polyoxazoline-Polysulfone Triblock Copolymers

Prof. Dr. James E. McGrath - Ph.D (Department of Chemistry and Macromolecular Science and Engineering Program, Virginia Tech) has coadvised chapter 3 with his innovative ideas on the preparation and potential uses of polysulfone-*b*-polyoxazoline-*b*-polysulfone triblock copolymers.

Dr. Yinnian Lin - Ph.D (Department of Chemistry and Macromolecular Science and Engineering Program, Virginia Tech) worked a research scientist in Dr. Judy Riffle's group over 15 years and retired in 2013 and contributed to the derivatization of polysulfone macroinitiators with ethylene carbonate to introduce hydroxy ethyl endgroups. He also kindly shared his many years of experience throughout all of the chapters presented here.

Dr. Chang Hyun Lee - Ph.D (Department of Chemistry, Virginia Tech) worked as a postdoctoral research in Dr. James McGrath's group for 3 years. I had many scientific discussions with him and he contributed extensively to the thermal characterization of polyoxazoline-polysulfone copolymers as well as the investigation of film properties prepared from these polymers such as water uptake measurements.

Chapter 4: Molecular Weight Distribution and Endgroup Functionality of Poly(2-ethyl-2-oxazoline) Prepolymers

Ms. Suzanne R. Barnes - M.Sc (Macromolecular Science and Engineering Program, Virginia Tech) has recently defended her master thesis under advisory of Dr. Judy Riffle and currently been working as an research and development analytical chemist for Ennis Flint in North Carolina. She has performed the size exclusion chromatographic analysis (SEC) of all the polymers presented in this dissertation.

Mr. Gurtej S. Narang – Ph.D student (Macromolecular Science and Engineering Program, Virginia Tech) has extensively contributed to the synthesis and characterization of mono- and difunctional polyoxazoline oligomers.

Ms. Danielle Kellogg – Senior student (Department of Chemistry, St. John Fisher College, Rochester, NY) was an intern at summer undergraduate research program held in 2011 at Virginia Tech. She contributed to the synthesis and characterization of preliminary polyoxazoline homopolymer syntheses presented in chapter 4 and phosphonic acid functional poly(ethylene oxide)-polyoxazoline diblock copolymers in chapter 5 as part of her summer project.

Dr. Sue J. Mecham - Ph.D (Department of Chemistry and Macromolecular Science and Engineering Program, Virginia Tech) is currently a research scientist and the manager for the analytical instruments laboratories. She has also extensively helped in the SEC characterization of polyoxazoline containing functional homopolymers and block copolymers.

Chapter 5: Synthesis and Characterization of Phosphonic Acid Functional Poly(ethylene oxide-b-2-ethyl-2-oxazoline) Diblock Copolymers

Mr. Alfred Y. Chen - M.Sc (Macromolecular Science and Engineering Program, Virginia Tech) has recently defended his master thesis under advisory of Dr. Judy Riffle. He contributed to the synthesis and characterization of phosphonic acid functional poly(ethylene oxide)-b-poly(2-ethyl-oxazoline) diblock copolymers.

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CHAPTER 1 – Introduction

Poly(2-oxazoline)s are prepared from five-membered cyclic imino ethers that are polymerized via cationic ring-opening polymerization. They have structural similarities to poly(ethylene oxide) and polypeptides since they are comprised of an ethyleneimine (CH_2CH_2N) backbone and an amide functionality in each repeat unit. Hydrophilic poly(2-ethyl-2-oxazoline) containing functional homo- and block copolymers are potential materials for drug delivery, magnetic resonance imaging, water purification and gas separation membrane applications.[1-4]

Polymeric membrane based separations are the primary choice of producing drinking water as being more energy-efficient and have lower operation costs compared to distillation,[5] to meet the increasing worldwide need for fresh drinking water.[6] Currently, polyamide (PA) membranes have widely been used due to their excellent salt rejection and flux properties. However, PA membranes exhibit very low resistance to chlorinated disinfectants. This problem necessitates the use of expensive dechlorination and rechlorination treatment steps.[7] Although poly(arylene ether sulfone)s (PSF)s have many excellent properties and are used as porous supports in PA thin film composite membranes, they are not used as the separation layer in membrane applications because of their hydrophobic nature.[8] Membranes used in water treatment require a hydrophilic character to provide better water flux and avoid membrane fouling (i.e. attachment of microorganisms, proteins etc).

Chapter 3 describes the synthesis and characterization of poly(2-ethyl-2-oxazoline-*b*-arylene ether sulfone-*b*-2-ethyl-2-oxazoline) and poly(2-ethyl-2-oxazoline-*co*-ethyleneimine-*b*-sulfone-*b*-2-ethyl-2-oxazoline-*co*-ethyleneimine) amphiphilic triblock copolymers with hydrophobic PSF central block and hydrophilic polyoxazoline endblocks via cationic ring-opening polymerization. This approach can lead to PSF-based water purification membrane candidates with enhanced water permeability, salt rejection, antibacterial and antifouling properties.

Chapter 4 presents the preparation of monofunctional, telechelic and heterobifunctional poly(2-oxazoline)s using different kinds of initiators and reaction conditions. Endgroup functionalities and molecular weight distributions were determined by size exclusion chromatography (SEC), ^{1}H NMR and titration. Monoamino-functional poly(2-ethyl-2-oxazoline)s (PEtOx)s initiated with methyl triflate had molecular weight distributions (MWD)s of approximately 1.1 while those initiated with benzyl bromide had MWDs of ~ 1.3. This was attributed to slow propagation of covalent species present in polymerizations initiated by halide containing initiators. Dibromo- and diiodo-*p*-xylene were used as initiators to form telechelic oligomers that were terminated with a protected piperazine. Titrations and ^{1}H NMR showed quantitative end group functionality in all cases. Due to the high control of functionality and relatively good control over molecular weights and their distributions, these polymers may be useful as prepolymers in step-growth polymerizations to form membranes and biomaterials.

Block ionomer complexes have recently found numerous applications as polymeric drug carriers.[9] Such complexes are formed between doubly hydrophilic block copolymers (block ionomers) containing ionic and nonionic blocks with the oppositely charged drug molecules, proteins, or metal ions. They can form micelles or vesicles depending on the structure of the block ionomer, changes in pH, temperature, and ionic strength. Ionic components with complementary charges associate via electrostatic interactions and form the core, however segregation of nonionic water-soluble blocks to the surface provides dissolution resulting in the formation of core-shell nanostructures. Such non-covalently bound structures are potentially ideal for encapsulating and releasing charged drugs and therapeutic proteins.[10]

Chapter 5 describes the synthesis and characterization of poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) (PEO-*b*-PEtOx) block copolymers via cationic ring opening polymerization of 2-ethyl-2-oxazoline sequences from tosylate functional PEO macroinitiators and the steps taken to functionalize the copolymers to introduce phosphonic acid groups by replacing pendent acyl groups of PEtOx block. This includes pendent group hydrolysis, Michael addition, and hydrolysis as well as ^{1}H NMR and SEC characterizations.

1.1 References

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(10) Bronich, T. K.; Popov, A. M.; Eisenberg, A.; Kabanov, V. A.; Kabanov, A. V. *Langmuir* **2000**, *16*, 481.

CHAPTER 2 - Literature Review

2.1 Chemistry, Properties and Applications of Poly(2-Oxazoline)s

2.1.1 Oxazolines

Oxazolines (OX)s are five-membered cyclic imino ethers that can be polymerized via a cationic ring-opening polymerization mechanism. They are heterocyclic compounds containing nitrogen, oxygen and one double bond in the ring. Depending on the location of the double bond, three types of oxazoline isomers are available (Figure 2.1). Among the oxazoline family, 2-oxazolines are the most extensively studied compounds in organic and polymer chemistry.[1] The substituents can be on the 2, 4, and 5 position of the 2-oxazoline ring. Polymerization of 2-substituted-2-oxazolines was discovered in the mid-1960s by four independent research groups.[2-5]

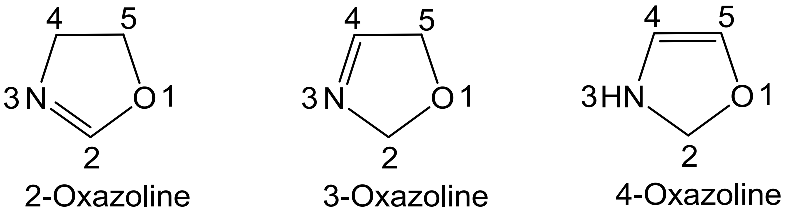


Figure 2.1 Ring structures of oxazoline isomers

Ring-opening polymerizations of many monomers such as cyclic ethers, cycloalkenes, lactones and lactams occur via the release of ring strain energy, and this value for tetrahydrofuran is estimated as 5.5 kcal mol^{-1}. However, the driving force for the ring opening polymerization (ROP) of 2-oxazolines is the extra enthalpy gain (~ 14 kcal mol^{-1}) caused by the isomerization from the imino ether functional group to the more stable amide group. The large difference between stability of the cyclic imine structure of 2-oxazoline monomer and the ring-opened tertiary amide repeat units facilitates polymerization.[6]

2.1.2 Polymerization of 2-oxazolines

Polymerization of 2-oxazolines follows ring-opening isomerization mechanism to produce the corresponding derivatives of poly(*N*-acylethylenimine). The reactions proceed via formation of cationic and/or covalent-bonded propagating chains (Figure 2.2), depending on the nucleophilicity of the monomer, counter-anion, and polarity of the solvent. If the counter-anion is more nucleophilic than the monomer, growing 2-oxazoline sequences have some covalent character. However, decreasing the nucleophilicity of the counter-anion increases the tendency of the polymerization to follow an ionic propagation mechanism. In both cases, initiation starts after nucleophilic attack of the nitrogen atom of a 2-oxazoline monomer onto an electrophilic initiator such as a benzyl halide, methyl iodide, methyl *p*-toluenesulfonate and methyl trifluoromethanesulfonate. Further monomer addition to the cationic oxazolinium ions or covalent species, selectively at its 5-position, results in ring-opening and isomerization of the cyclic oxazolinium species to a more stable amide group. Termination reactions can be conducted on both types of propagating species by addition of a stronger nucleophile.[7,8]

Substantial mechanistic and kinetic studies have been published to elucidate the monomer reactivity and chemical character of the intermediates (ionic or covalent), mostly utilizing *in situ* ^{1}H and ^{19}F NMR spectroscopic methods (Table 2.1). The substituents exert a significant influence on the polymerization mechanism of 2-oxazolines. The most nucleophilic monomer, 2-methyl-2-oxazoline, was found to propagate by the formation of oxazolinium ions with triflate,[7] tosylate,[9] iodide,[10] and bromide[11] counter-anions. However, the polymerization of 2-methyl-2-oxazoline initiated with benzyl chloride proceeded exclusively through covalently-bonded species.[11] In contrast, the least nucleophilic 2-perfluoro-2-oxazoline monomers cannot be polymerized with benzyl chloride or -bromide initiators.[8]

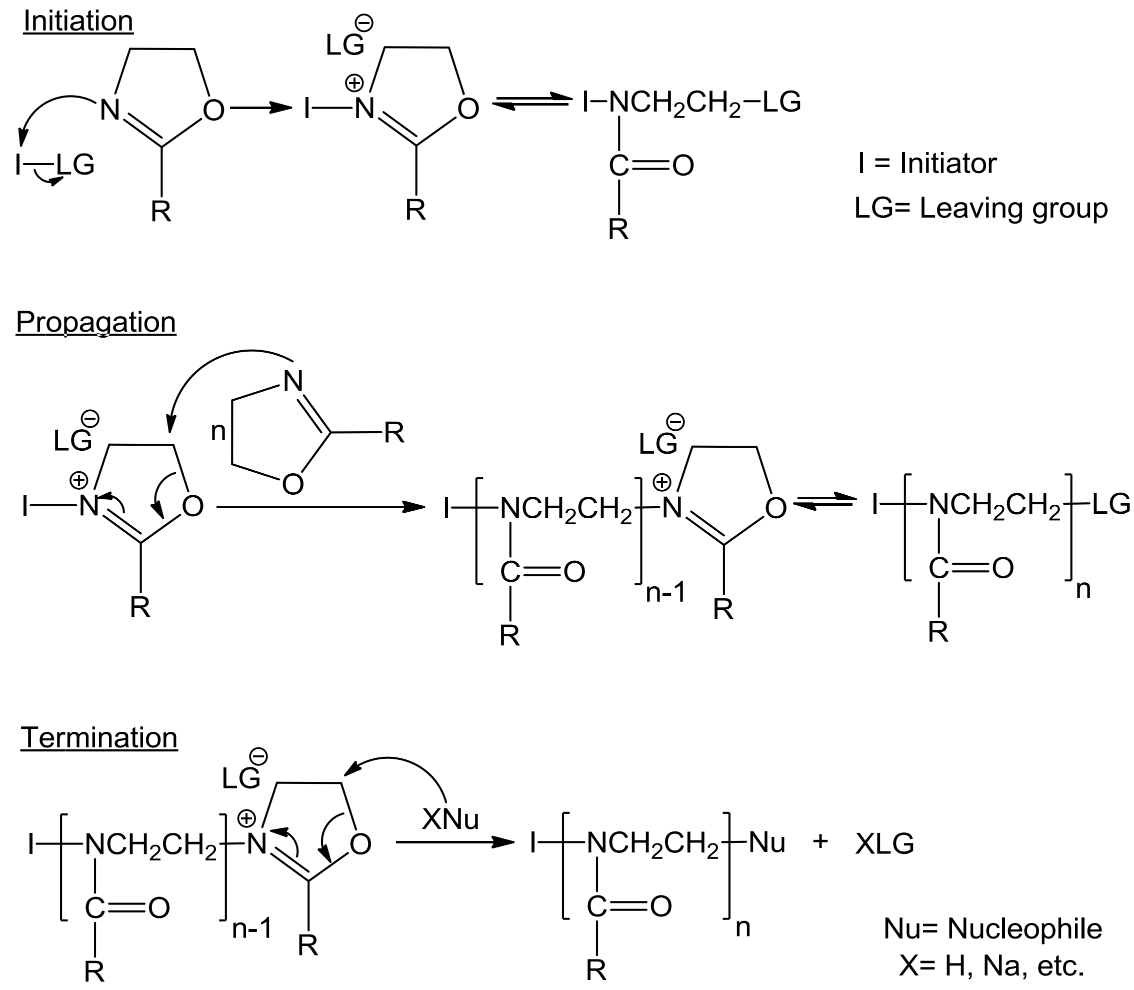


Figure 2.2 Cationic and covalent polymerization mechanism for 2-oxazolines [38,41,46]

However, with *p*-toluenesulfonate initiators, the growing 2-perfluoro-2-oxazoline chains are covalent esters and the corresponding oxazolinium ions are only formed with triflates as counter-anions.[12,13] The relative order of nucleophilicity between commonly utilized 2-oxazoline monomers and counter-anions derived from initiators are as shown below.[7,13]

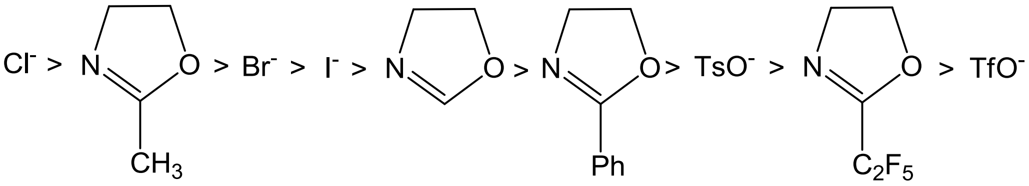
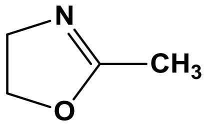
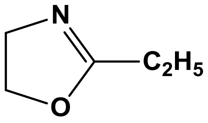
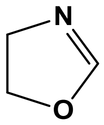
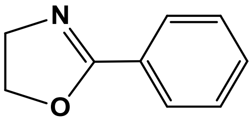
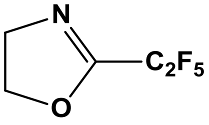


Table 2.1 Type of propagating species in the cationic ring-opening polymerization of commonly utilized 2-oxazoline monomers

	Counter-anions, LG$^-$				
Nucleophilicity ↑	← Nucleophilicity				
Monomer	Cl$^-$	Br$^-$	I$^-$	OTs$^-$	OTf$^-$
	Covalent[11]	Ionic[11]	Ionic[10]	Ionic[9]	Ionic[7,14]
	Covalent[15]	Covalent and Ionic[15]	Covalent and Ionic[16]	Ionic[15,17]	Ionic[7,14]
	Covalent[7]	Covalent[7]	Covalent and Ionic[18]	Ionic[18]	Ionic[7]
	---[14,15]	Covalent[15]	Covalent and Ionic[15]	Ionic[15,19]	Ionic[7,14]
	---[8]	---[8]	Covalent[7]	Covalent[12,13]	Ionic[12,13]

Monomers such as 2-ethyl-2-oxazoline,[15,16] 2-unsubstituted-2-oxazoline[7,18] and 2-phenyl-2-oxazoline[15] establish equilibria between covalent and ionic propagating chains with bromides and iodides as counter-ions. As a result, the relative nucleophilicity of monomer and counter-anion has a significant effect on the type of propagation species.

Chemical character of the intermediates is also significantly dependent on the solvent. Polar solvents stabilize the cationic species and increase the rate of propagation due to better solvation and stabilization of the ion pair. Polymerization of 2-methyl-2-oxazoline proceeds predominantly via cationic centers with bromide counter-ions in acetonitrile.[11] However, this monomer proceeds with 62% cationic species in nitrobenzene and less than 3% ionic growing chains in tetrachloromethane.[20] The use of extremely polar solvents such as ionic liquids for the polymerization of 2-ethyl-2-oxazoline were shown to have increased reaction rates in comparison to analogous polymerizations conducted in acetonitrile.[21] A cationic type mechanism is normally much higher in reactivity than a covalent type mechanism. Although there can be significant covalently-bonded species during polymerization, a major part of the monomer is consumed via the ionic mechanism because the rates of conversion between cationic and covalent active centers is much faster than the rate of propagation.[6,20]

2.1.3 Chain transfer reactions

Side-reactions are possible during 2-oxazoline polymerizations due to the reactive cationic species. Litt *et al.*[22] reported that chain transfer reactions can occur during the polymerization of alkyl oxazolines to a monomer by hydrogen abstraction from a position on the substituent adjacent to the cation, resulting in the formation of hindered enamines. The abstracted protons can initiate polymerization with remaining monomers. When almost all the monomer is consumed, the reactive chain ends (oxazolinium species, enamines) can couple to form undesired high molecular weight macromolecular structures (side-products) (Figure 2.3). Each of these couplings produces a branch point and regenerates another oxazolinium end-group. The evidence for such side-reactions has been found as high molecular weight shoulders in the size exclusion chromatography (SEC) chromatograms (Figure 2.4) during our preliminary studies. Therefore, it is recommended that polymerizations be performed under mild reaction conditions and terminated before complete monomer consumption to limit any side reactions.[23]

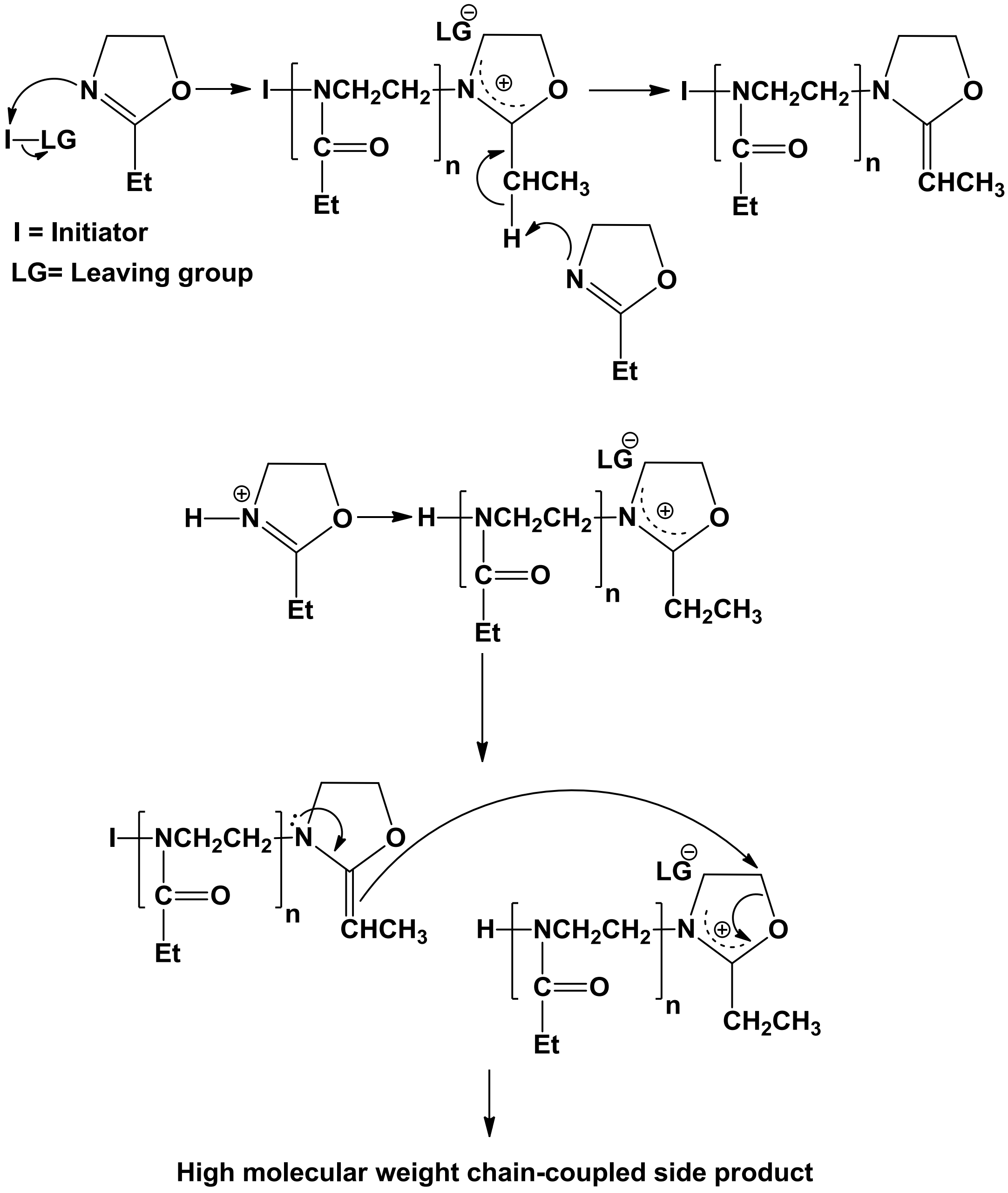


Figure 2.3 Chain-transfer mechanism during the polymerization of 2-oxazolines

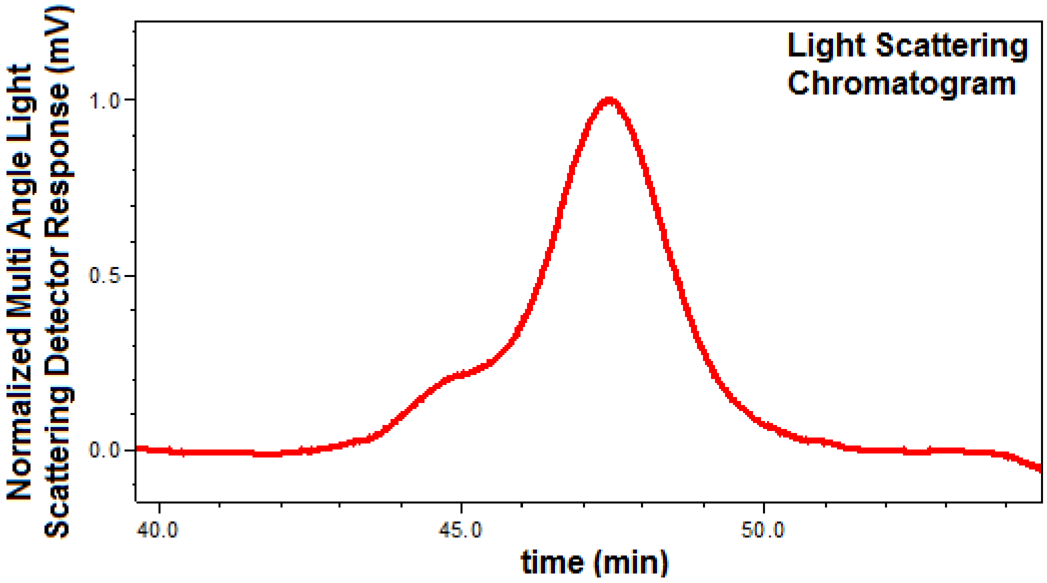


Figure 2.4 Light scattering chromatogram of poly(2-ethyl-2-oxazoline) obtained after polymerization at 80°C for 20 hours

Termination of 2-oxazoline polymerizations before chain-transfer reactions occur is important to obtain well-defined polymers with controlled endgroup functionality. Progress of the polymerizations can be monitored using ^{1}H NMR. A series of ^{1}H NMR spectra (in $CDCl_3$) (Figure 2.5) were used to obtain monomer conversion when methyl triflate and 2-ethyl-2-oxazoline were used as the initiator and monomer, respectively. The monomer protons resonating at 4.2, 3.8, 2.3 and 1.2 ppm shift and broaden once the monomer polymerizes. The ethylene monomer peaks are free of overlap with broadened polymer backbone protons, thus their integral ratios are used to calculate the unreacted monomer conversion.

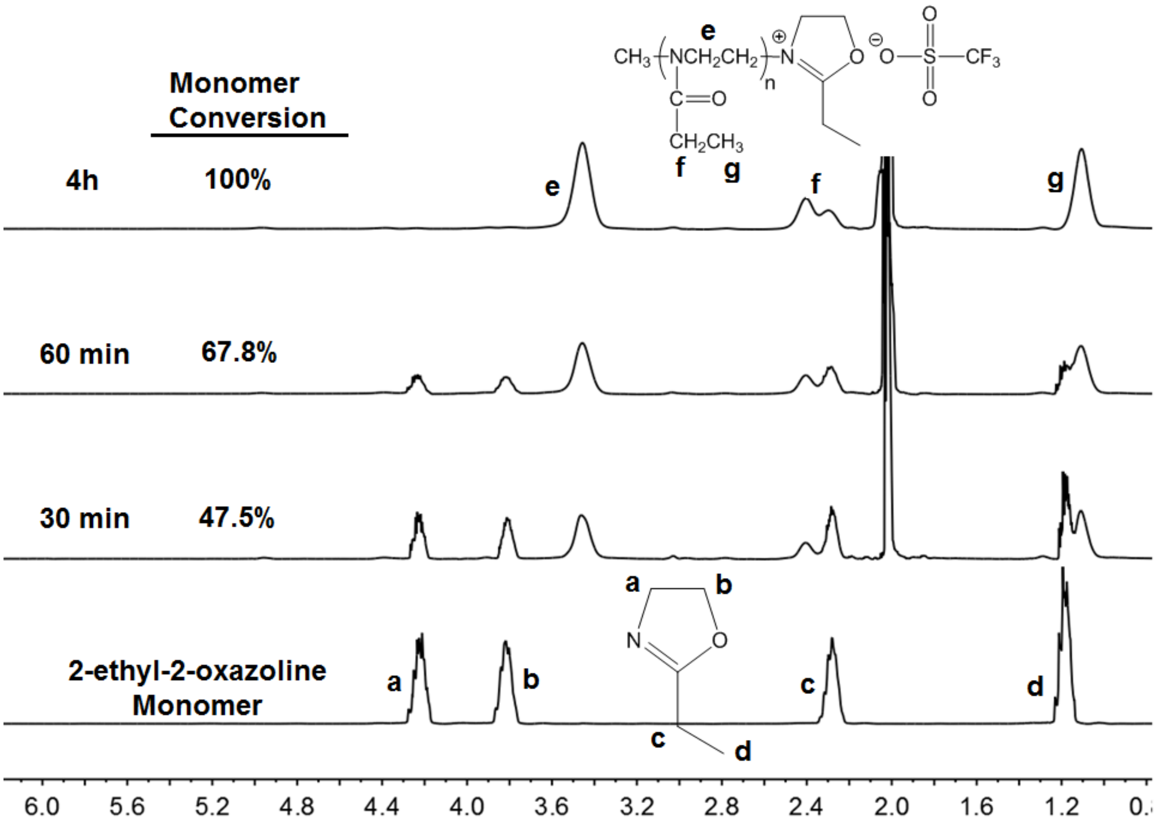


Figure 2.5 ^{1}H NMR spectra of the 2-ethyl-2-oxazoline polymerization kinetics initiated by methyl triflate at 80°C in acetonitrile

2.1.4 Chain-end functionalization

Various kinds of initiators have been employed in the form of Lewis acids (e.g. boron trifluoride),[7] strong protic acids,[7] halides,[24,25] and alkyl esters such as triflates[26-28] and tosylates[27,29,30] to prepare chain-end functional poly(2-oxazoline)s (POx) (Figure 2.6). Functional POx oligomers can be used as macromonomers in free radical polymerizations to obtain graft polymers,[31] prepolymers and macroinitiators for block copolymer synthesis[32] and further coupling reactions to form crosslinked structures.[33] Multifunctional initiators can also be utilized to prepare multifunctional architectures such as difunctional[34,35] and star-shaped polymers.[35,36]

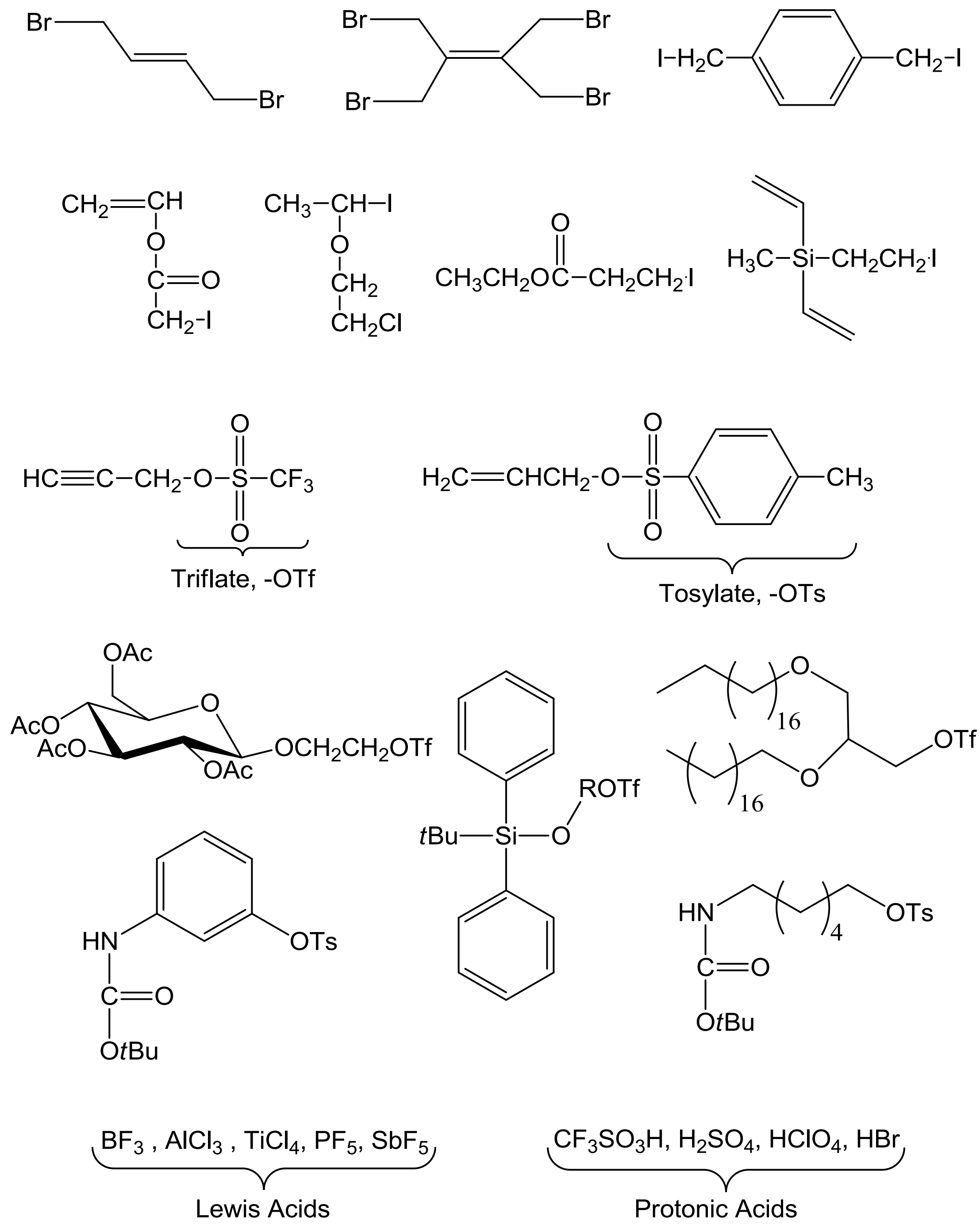


Figure 2.6 Initiators for the cationic ring opening polymerization of 2-oxazolines

Termination reactions of the cationic polymerization of 2-oxazolines with various nucleophiles also allows the introduction of functionalities to the chain-ends. Thus, telechelic, heterobifunctional and multifunctional polyoxazoline oligomers can be prepared by combining functional initiators and terminating agents. Nucleophiles may add to the cationic centers from either position “2” or “5” of the oxazolinium ring. Nucleophilic additions to position 2 are kinetically controlled and reversible, therefore the kinetic product can easily be hydrolyzed. However, irreversible addition onto position 5 results in a more stable thermodynamic product.

Poly(2-oxazoline)s with hydroxyl endgroups are commonly synthesized because they can be further functionalized and utilized as ideal prepolymers for incorporation into block copolymer and network structures. Hydroxyl functional POx has been reported with the propagating cationic chains terminated with H_2O/Na_2CO_3 or KOH in methanol.[6-8,37] However, H_2O/Na_2CO_3 does not completely yield –OH terminus at room temperature, because sodium hydrogen carbonate (sodium bicarbonate) molecules attack from the 2-position of oxazolinium ions and a significant amount of an ester endgroup is formed (Figure 2.7). Upon treatment with heat, the ester product is isomerized to a more stable amide alcohol via the intramolecular attack of the amino group on the ester carbonyl.[37] The most common method to introduce hydroxyl endgroups is to terminate the POx cationic chain ends with aqueous or methanolic KOH solution.[7]

Chain end functionalization of 2-oxazolines has also been reported using azides,[38] thiols,[27] methacrylic[39] and acrylic acid salts.[37,40] Another class of terminating agents are aliphatic amines especially in the form of secondary cyclic amines such as piperidine,[41] piperazine derivatives,[42,43] and morpholine.[44] Piperidine was found to result in fast (< 10 min) and quantitative termination.[45] Primary amines can also be utilized to introduce amine functionality but the resulting secondary amines can react again with cationic chain ends forming coupled polymer chains.[8]

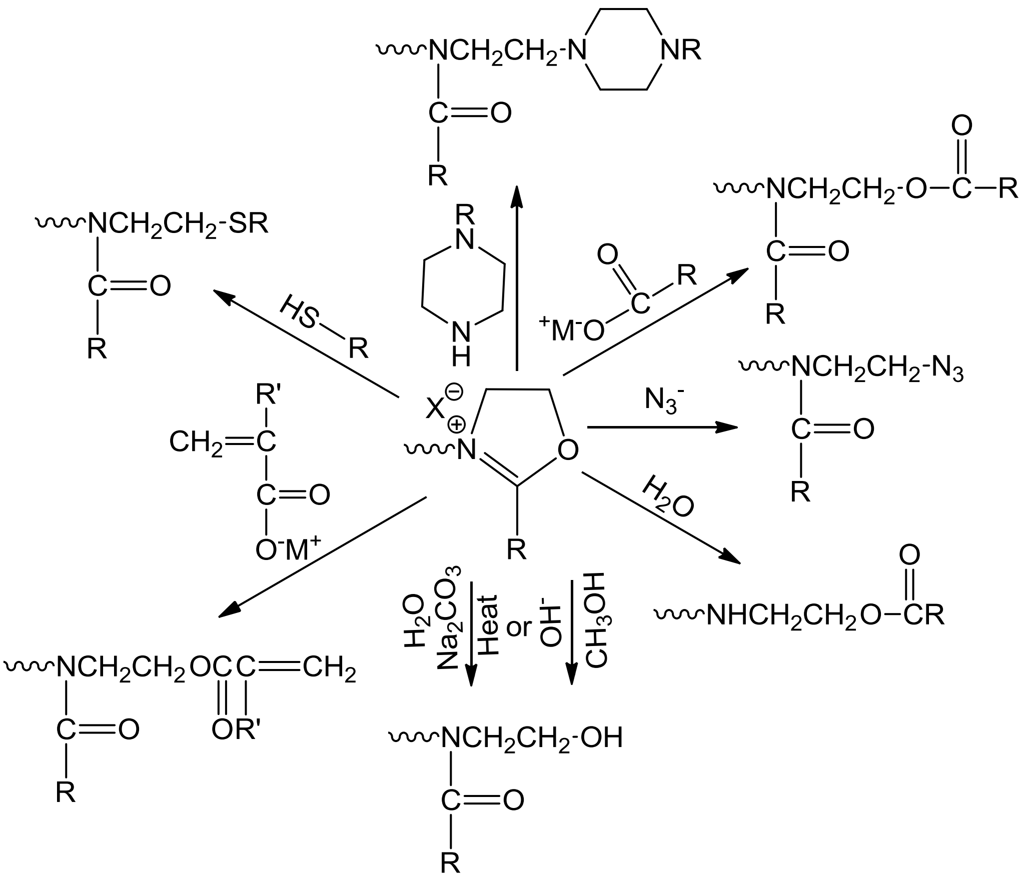


Figure 2.7 Nucleophiles utilized to terminate 2-oxazoline polymerizations and to obtain chain end functional polymers

2.1.5 Side chain functionalization

In addition to chain end functionalization of poly(2-oxazoline)s via the initiation and/or the termination method, side chain functionalities can also be introduced either by direct polymerization of 2-oxazoline monomers with different side "R" groups (Figure 2.8) or post-polymerization. Moreover, polymer properties can be tuned by simply varying the side-chains of 2-oxazoline monomers and their copolymerization.[46]

Alkyl chains of various lenghts ranging from methyl to nonyl,[6,7,10,14,16] iso-propyl,[47] iso-butyl,[48,49] *t*-butyl,[50] ethylpentyl[51] pendent groups are the most studied examples.

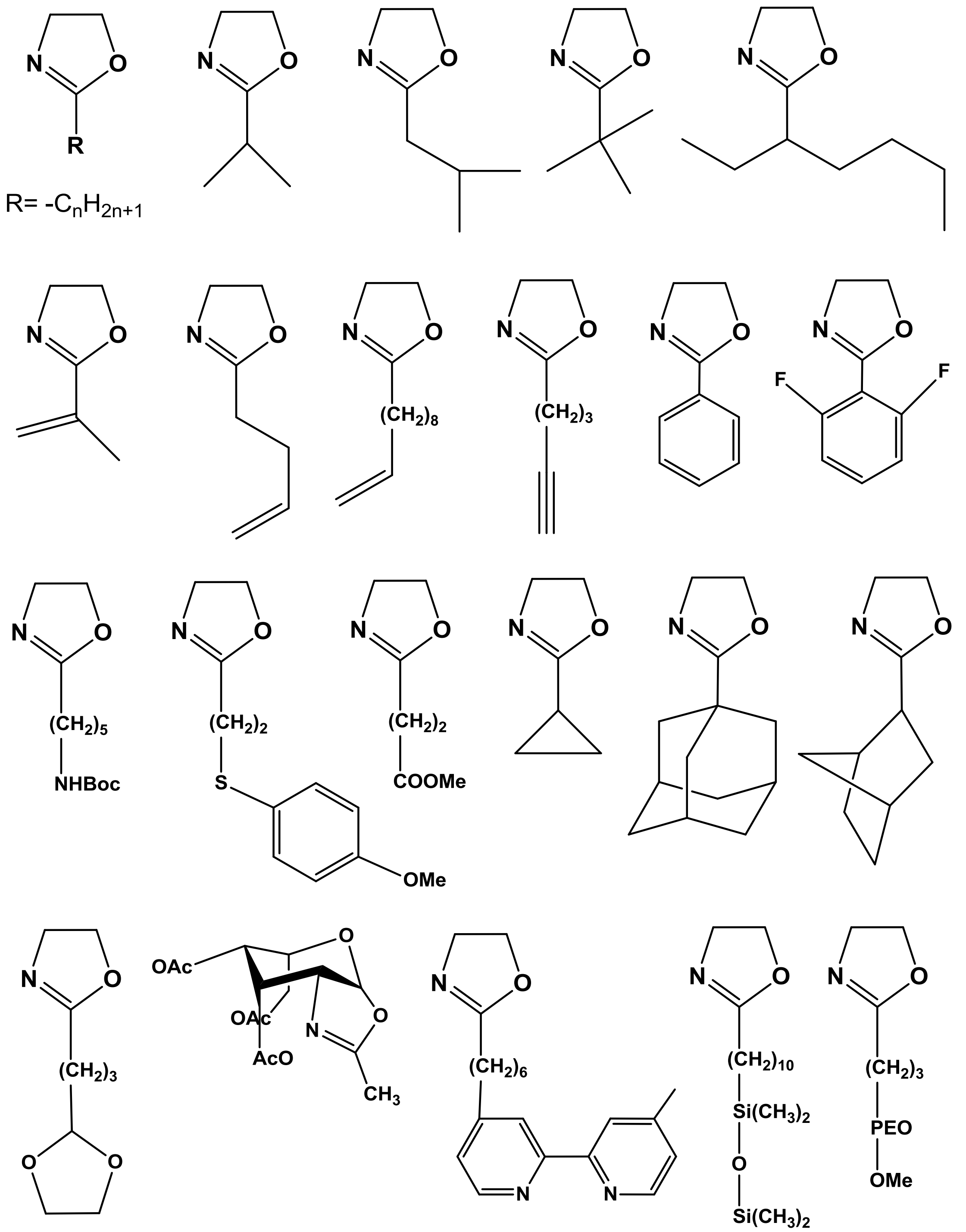


Figure 2.8 Common “R” side groups of 2-alkyl-2-oxazoline monomers

Side chains with unsaturated moieties,[43,52-54] cycloaliphatic[55,56] and aromatic groups with various substituents[15,57,58] have also been synthesized. When necessary, protecting groups have been used to avoid side reactions between pendent “R” groups (e.g. amine,[59] thiol[60] and carboxylic acid[61] and propagating species. One important class of “R” side groups is represented by polymer chains such as poly(ethylene oxide),[62] polystyrene[63] and poly(ε-caprolactone).[64] These macromonomers have been utilized to prepare graft copolymers. Halogenated derivatives of 2-(oxazoline)s cannot be utilized as side chains to obtain linear polymers due to their high reactivity as initiators that would result in branched polyoxazolines.[65] Even though most of the pendent groups are hydrocarbon-based compounds, a few silane pendent chains have also been studied.[66] Other interesting examples are glyco-[67,68] and pyridine-bearing 2-oxazoline monomers.[69] This variety offers good potential for preparing many different polymer conjugates for therapeutic applications.[70]

Poly(2-oxazoline)s are well-known precursors for the preparation of linear poly(ethylene imine)s (PEI) upon hydrolysis under acidic or basic conditions (Figure 2.9a).[71-73] The desired degree of deacylation can be at least somewhat controlled by the relative amounts of acid and cleavable amides.[74] Therefore, many different side chain functionalities can be introduced to PEI such as organic groups, bioactive compounds or nanoparticles. The high density of amino groups (15–20% of which are protonated at physiological pH) in a PEI structure allows complexation with negatively charged nucleic acids (e.g. DNA and RNA) and this can result in electrostatic compaction of polymer-DNA complexes to yield potential gene delivery vehicles.[75]

PEIs are also prepared by the cationic ring opening polymerization of aziridine (the nitrogen equivalent of ethylene oxide), but branched structures with primary, secondary, and tertiary amino groups are obtained (Figure 2.9b). The lack of structural (e.g. degree of branching) and molecular weight control during synthesis limits the use of PEIs.

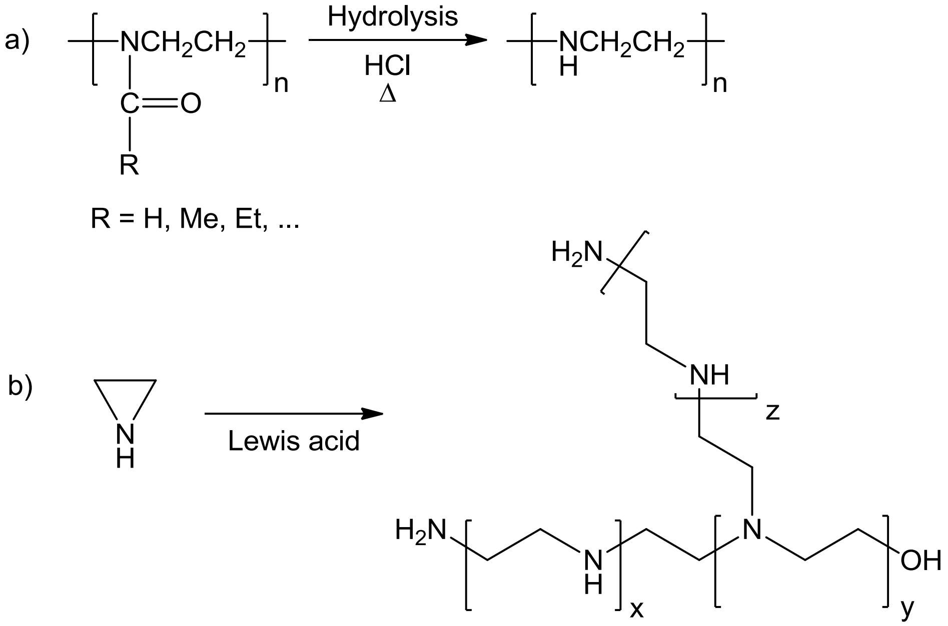


Figure 2.9 a) Hydrolysis of poly(2-oxazoline) to obtain linear poly(ethylene imine)

b) Polymerization of aziridine to branched poly(ethylene imine)

Moreover, PEIs show a strong cytotoxicity and reduced blood compatibility due to strong electrostatic interactions with cell membranes and extracellular matrices depending on the charge density and molar mass of the polymer.[76,77] However, linear PEI was found to have lower cytotoxicity than branched PEI.[78,79] Thus, subsequent backbone modifications are necessary to improve biocompatibility and drug delivery performance of PEIs.

Functionalization of PEI backbones via amino groups can open up the potential for their use in various applications with particular advantages such as targeted drug and gene delivery, long blood circulation time, formation of conjugates with bioactive substances etc. Reported modifications of PEIs include a) reductive *N*-methylation using formaldehyde/formic acid,[80] b) nucleophilic substitution with alkyl halides,[81] c) coupling reaction with epoxides,[82] d) Michael addition onto acrylates[83,84] and acrylonitriles,[84] e) acylation via addition of isocyanates[85] (Figure 2.10).

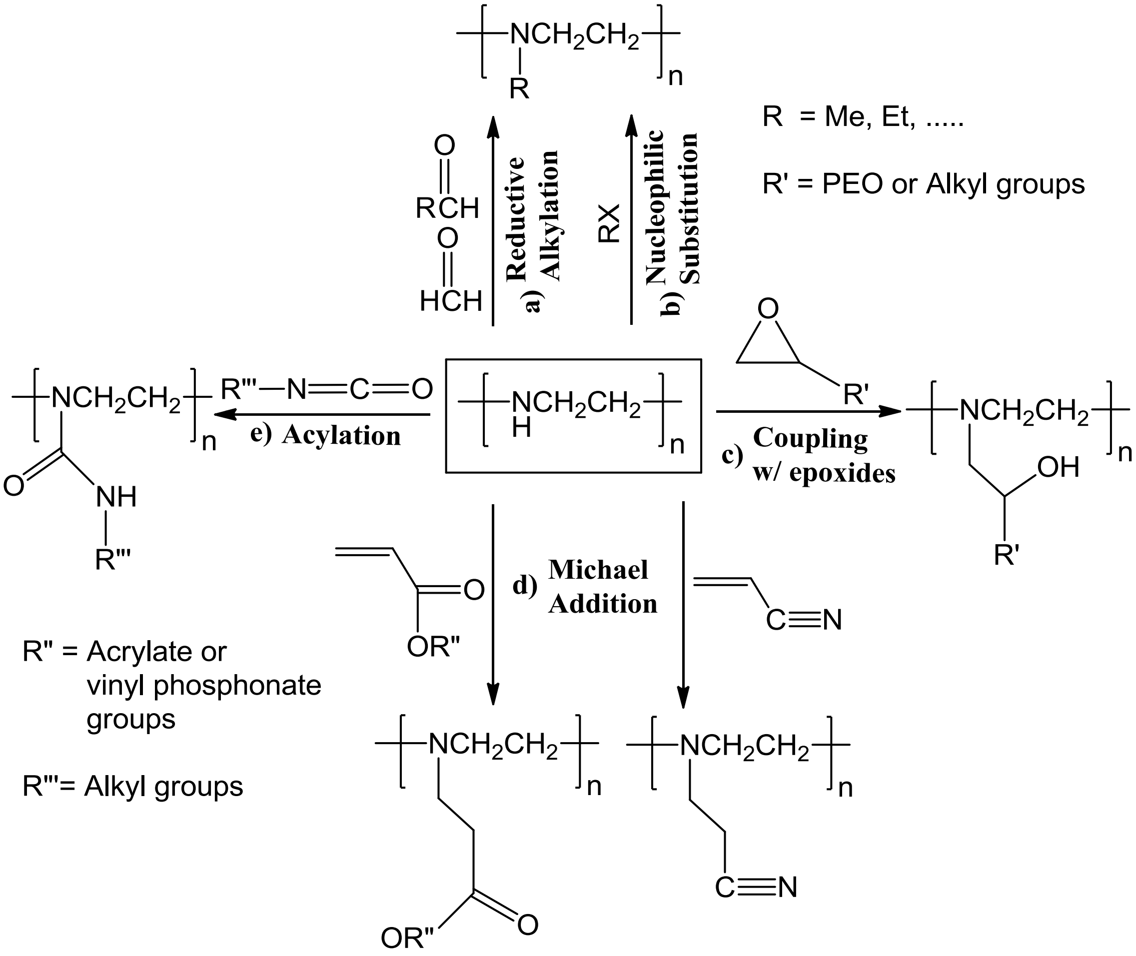


Figure 2.10 Introduction of various organic (functional) groups to poly(ethylene imine) backbones

2.1.6 Structure-property relationships

Poly(2-oxazoline)s have structural similarities to poly(ethylene oxide) (PEO) and polypeptides due to having (C-C-N) backbone repeat units and amide side chains. Furthermore, there is a significant influence of the type of pendent “R” groups on the final polymer properties. Especially, poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx) are strong alternatives to PEO as they were shown to have similar hydrophilicity,[86] biocompatibility,[42,87,88] blood circulation times[25,89] and stealth behavior.[25,90,91] The main advantage of poly(2-oxazoline)s over PEO is the versatility of monomer compositions as well as the introduction of various side-chain functionalities. The tertiary amide groups present in poly(2-oxazoline)s are more stable in physiological media (more resistant to hydrolysis by enzymes) than polypeptides.[46]

Solution properties also depend on the type of the alkyl chain. Poly(2-oxazoline)s with short side chains (R= ethyl, *n*- and *iso*-propyl), except for 2-methyl-2-oxazoline, exhibit lower critical solution temperature (LCST) behavior in aqueous solutions, whereas longer non-polar pendent alkyl chains or aromatic groups lead to an hydrophobic character and insolubility in aqueous media.[92,93] The cationic ring-opening polymerization allows easy access to amphiphilic and well-defined block copolymers via copolymerization of different types of 2-oxazoline monomers. These can solubilize hydrophobic drugs which is a key issue in drug delivery[27] and the LCST behavior can be tuned (e.g. cloud point) by composition[23] and the degree of polymerization[94] to prepare thermoresponsive materials.

Thermal and mechanical properties of poly(2-oxazoline)s such as glass transition temperature and Young's modulus strongly depend on the type of the side chains. Polymers with small side chains (e.g. methyl, ethyl, and propyl) are completely amorphous. However, when longer alkyl chains (2-butyl-2-oxazoline to 2-nonyl-2-oxazoline) (BuOx to NonOx) are introduced to the main chain, an endothermal peak around 150 ºC is observed, which is attributed to side chain crystallization. The glass-transition temperature (T_g) was found to decrease as the size of the side-chain increased (from MeOx to 2-pentyl-2-oxazoline) due to the increased distance between polymer chains (reduced packing density). However, no T_g was detected for polyoxazolines with a hexyl or longer alkyl chains and this may be due to higher degrees of crystallinity. Moduli of elasticity showed a similar trend to T_g and decreased with increasing length of the alkyl side chain from methyl to butyl groups.[95]

2.1.7 Poly(2-oxazoline) copolymers and applications

Cationic ring-opening polymerization of 2-oxazoline monomers with different nucleophilities provides straightforward access to well-defined block copolymers in one-pot using sequential monomer addition and “one-shot” copolymerization techniques to prepare random, quasi-diblock, and block (e.g. diblock, terpolymer, quarterpolymer) copolymers. This architectural variability of poly(2-oxazoline)s with tunable properties (e.g. solubility in water) as well as their combination with many different types of polymers allow the preparation of amphiphilic, double hydrophilic, graft and network polymer structures for use in a wide variety of applications.[6,8,27]

2.1.7.1 One-pot copolymerization

The difference in reactivity of a variety of 2-oxazoline monomers can in some cases enable preparation of random, alternating and block copolymers in one-pot. If both monomers are consumed at the same rate, random copolymers are obtained. On the other hand, if the monomer consumption rates differ significantly, gradient or even block copolymers are the products. If monomers with significantly different reactivities (nucleophilities) are simultaneously added to the reaction medium, the more reactive monomer selectively polymerizes first and the less reactive monomer subsequently polymerizes. Polymers obtained using this procedure have been called “quasi-diblock” copolymers.[8,96]

The statistical copolymerization of 2-oxazoline monomers was first demonstrated by Saegusa *et al.*[97] using 2-methyl-2-oxazoline (higher nucleophilic reactivity) and 2-(heptafluoro-*n*-propyl)-2-oxazoline (lower nucleophilicity) with methyl tosylate as the initiator at 120 ºC in nitromethane. Full conversion of 2-methyl-2-oxazoline was almost achieved in a very short time (about 2 min), while no fluorinated monomer was incorporated by that time. As the polymerization proceeded for 40 hours, chain-growth of 2-perfluoroalkyl-2-oxazoline sequences were completed. Hoogenboom *et al.*[98] prepared quasi-diblock copolymers using MeOx or EtOx with 2-phenyl-2-oxazoline (PhOx) in acetonitrile at 140 ºC via a microwave-assisted polymerization with methyl tosylate as the initiator. An alternative procedure was also developed for a "one-shot" block copolymerization. In this method, monomers are fed simultaneously but the polymerization is conducted with two-stage heating.[97] However, when 2-nonyl-2-oxazoline (NonOx) and EtOx are used, random block copolymers are yielded due to their close monomer reactivity ratios.[99]

The living polymerization of 2-oxazolines also allows the synthesis of well-defined block copolymers via sequential monomer addition method (one-pot block copolymerization with two or more-stage feeding of monomers). After complete conversion of the first monomer, a second monomer is introduced to the reaction mixture, and so on. Thus, well-defined diblock,[100] triblock[101] and tetrablock[102] structures are easily accessible (Figure 2.11). The sequential monomer addition method has also been applied to monomers from two different families using tetrahydrofuran (THF) and MeOx or EtOx to obtain diblock[103] or triblock[104] amphiphilic block copolymers. THF polymerization was initiated by either ethyl triflate or trifluoromethanesulfonic anhydride as monofunctional and difunctional initiators, respectively, and the polymerizations conducted in bulk at room temperature. MeOx or EtOx was then polymerized from the living ends of THF (oxonium ions) at 70 ºC in acetonitrile to prepare AB or ABA-type copolymers. This approach, however, also yielded some polyoxazoline homopolymers in the mixtures.

The potential access to well-defined (co)poly(2-oxazoline)s has led to their use in a wide variety of applications. Amphiphilic structures are prepared by the sequential polymerization of a monomer that results in a hydrophilic block [e.g., (MeOx) or (EtOx)] and one that forms a hydrophobic block [e.g., (NonOx) or (PhOx)].

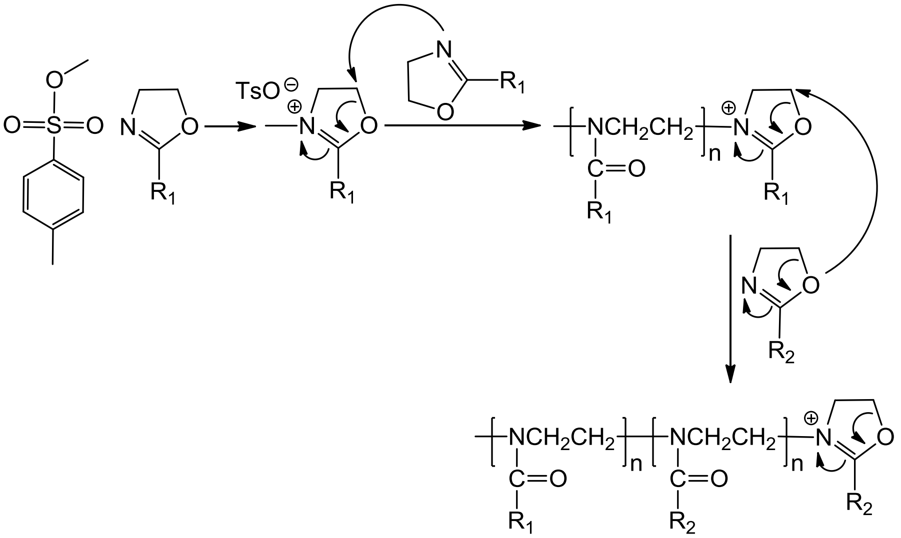


Figure 2.11 Synthesis of poly(2-oxazoline) block copolymers via sequential monomer addition method

Amphiphilic block copolymers can form thermodynamically stable micelles with low critical micelle concentrations, and thus, are interesting for biomedical applications.[27] Pluronics with a general structure of (PEO-*b*-PPO-*b*-PEO) are a prominent example and widely used as drug delivery systems due to (in general) their self-assembly into micelles in aqueous solutions as well as their solubilization of drugs with limited water solubility.[105,106] Polyoxazolines are also ideally suitable for micellar drug delivery with finely-tuned water-solubility as an analog to PEO.

Tiller *et al.*[107] demonstrated the synthesis and self-organization of P(MeOx)-*b*-P(PhOx)-*b*-P(MeOx) triblock copolymers with varying block lengths that formed at least three types of structures: unimolecular micelles, micellar aggregates, and polymersomes (a class of artifical vesicles prepared from amphiphilic synthetic block copolymers). A central block was first synthesized using dibromo-*p*-xylene as a bifunctional initiator at 160 ºC in a microwave reactor. Subsequently, MeOx sequences were grown from cationic chain-ends of middle block at 100 ºC to prepare ABA-type copolymer structures. P(PhOx) was chosen as an inner block because of its high T_g (~107 ºC) to obtain stable polymersomes.

Luxenhofer and Kabanov *et al.*[108] investigated relationships among structures of poly(2-oxazoline) amphiphiles and cytotoxicity and cellular uptake. In this regard, a series of amphiphilic di- and triblock copolymers were synthesized using PMeOx, PEtOx, P*i*PrOx, P*n*PrOx and PBuOx with molecular weights ranging from 6000 to 15,000 g/mol using methyl triflate as the initiator in acetonitrile at 130 ºC under microwave irradiation. The cytotoxicity studies were performed using cancer or immortalized cell lines and no cyctotoxicity even at high concentrations were found. Similar cellular uptake behaviors of amphiphilic poly(2-oxazoline)s were explored compared to Pluronics, and copolymers with higher hydrophobic content were found to enter the cells more readily than the ones with higher hydrophilic compositions.

Kabanov and coworkers[109] formulated highly radical scavenging hydrophobic fullerene (C_{60}), a therapeutic antioxidant, with a P(EtOx-*b*-BuOx) (5K-3K) amphiphilic copolymer and obtained nano-complexes. These nanoformulations included fullerene up to 1 wt % and charge-transfer complexation formation was proposed to occur between alkene groups in C_{60} as an inner core and nitrogen atoms in polyoxazoline repeat units as the outer shell. The cytotoxicity of these systems were also examined and no cytotoxicity was found at concentrations up to 50 μM.

Luxenhofer *et al.*[110] prepared an amphiphilic diblock P(EtOx-*b*-BuOx) and a series of triblock P(MeOx-*b*-BuOx-*b*-MeOx) copolymers to solubilize a well-known anti-cancer drug, Paclitaxel. A high drug-loading capacity up to 45% was obtained. Physicochemical properties of the drug-polymer formulation with a high solubility and stability for weeks in aqueous media as well as low toxicity and immunogenicity suggested that amphiphilic poly(2-oxazoline)s are promising candidates for drug delivery applications. High-drug loading capacity is attributed to the hydrophobic P(BuOx) central block as the micellar core and also to polar interactions between drug molecules and the tertiary amide groups. Further investigations in collaboration with Kabanov *et al.*[111] showed that P(MeOx-*b*-BuOx-*b*-MeOx) amphiphiles could also serve as carriers of multiple chemotherapeutic agents such as paclitaxel, docetaxel, etoposide and bortezomib with large amounts of loading capacities.

Poly(2-alkyl-2-oxazoline)s with short side chains (ethyl, *n* or *iso*-propyl) are thermosensitive materials showing an LCST behavior in aqueous solutions. Uyama and Kobayashi reported that poly(2-isopropyl-2-oxazoline) P(*i*PrOx) exhibits a cloud point in the range of 36-39 ºC that is very close to body temperature,[112] and it is therefore considered to be a promising candidate for biomedical applications. It is an alternative to its isomer poly(*N*-isoproplyacrylamide) (PNIPAM; LCST=32 ºC).[113] Another structural isomer P(*n*PrOx) exhibits a cloud point at 24 ºC.[114] Figure 2.12 depicts the structures and LCSTs of PEtOx,[115] P*i*PrOx[112] and P*n*PrOx.[114] Solubility studies of PEtOx indicated that the presence of salts, molecular weight of the polymer, and the concentration of the polymer solution affect the LCST behavior.[115] The addition of NaCl decreased the LCST of PEtOx, while the presence of tetrabutylammonium bromide increased the cloud point. As the molecular weight of the PEtOx increased, the cloud point temperature decreased. The minima in the cloud point curves occur at about 63.5, 63, and 61°C for polymer molecular weights of 20,000, 50,000, and 500,000 g/mol respectively. Jordan *et al.*[116] investigated the effect of end-group polarity on the thermosensitivity of P*i*PrOx and found that the introduction of hydrophilic end-groups increased the cloud point whereas hydrophobic chain-ends decreased the LCST.

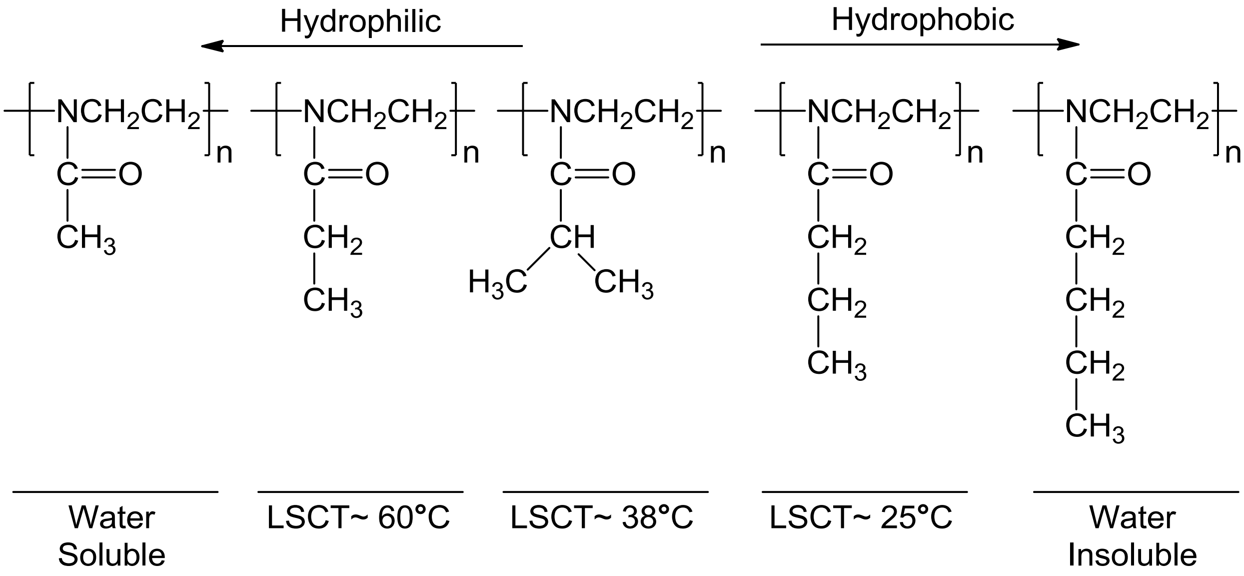


Figure 2.12 Phase transition temperatures of poly(2-oxazoline) homopolymers in water

Besides the LCSTs of homopolymers exhibiting thermosensitive behavior, there is also significant interest in copolymerization of 2-oxazoline monomers to be able to control the cloud points over a wide range of temperatures. Park and Kataoka precisely tuned the LCST of P*i*PrOx via copolymerization with hydrophilic EtOx. The monomer reactivity ratios of 1.78 and 0.79 were derived for EtOx and *i*PrOx from the cumulative and instantaneous compositions of the copolymers determined from the ^{1}H NMR and MALDI-TOF mass spectrometry. The formed gradient copolymers showed a linear increase in LCST from ~38 ºC to 67 ºC with an increasing molar amount of EtOx (up to 75%) for a 1.0 wt% polymer solution.[23] Huber and Jordan showed that cloud points below room temperature are also accessible for the polymers obtained via the gradient copolymerization of *i*PrOx with hydrophobic NonOx.[117]

2.1.7.2 Poly(2-oxazoline) containing block copolymers

End-group and side-chain functional macroinitiators are important prepolymers to prepare block and graft copolymers of poly(2-oxazoline)s with other polymer families. Various types of polymers have been combined with poly(2-oxazoline)s via macroinitiator approaches to benefit from the characteristics of each polymer in a wide variety of applications.

2.1.7.2.1 Poly(2-oxazoline) and poly(lactide) copolymers

Wang and Hsiue synthesized a series of poly(L-lactide)-*b*-poly(2-ethyl-2-oxazoline)-*b*-poly(L-lactide) (PLLA-*b*-PEtOx-*b*-PLLA) triblock copolymers for drug delivery applications.[32] The synthetic strategy was to first prepare a dihydroxy-functional PEtOx (HO-PEtOx-OH) using a difunctional initiator (1,4-dibromo-2-butene) in acetonitrile at 100 °C with termination by methanolic KOH at room temperature. Telechelic PEtOx was then utilized as a macroinitiator to grow poly(L-lactide) sequences from –OH chain-ends with stannous octoate as the catalyst system in dry chlorobenzene at 140 °C (Figure 2.13). Triblock copolymers formed micelles at lower concentrations when the molecular weight and crystallinity of hydrophobic PLLA blocks increased.

These polymer solutions also formed precipitates as the temperature was increased. These pH and thermosensitive materials were investigated as polymeric micelles for intracellular delivery of the anticancer drug (doxorubicin, DOX).[118] In vitro drug release studies indicated that release of DOX from micelles was successfully inhibited at pH 7.4. However, an accelerated release of DOX from micelles was observed at lower pH values ~5.0, thus suggesting that the lower intracellular pH’s may be suitable for faster release.

2.1.7.2.2 Poly(2-oxazoline) and poly(dimethylsiloxane) copolymers

Meier and coworkers described the synthesis of cross-linkable poly(2-methyl-2-oxazoline)-*b*-poly(dimethylsiloxane)-*b*-poly(2-methyl-2-oxazoline) (PMeOX-*b*-PDMS-*b*-PMeOx) triblock copolymers with methacrylate groups at both chain ends (Figure 2.14).[119] The polymer consists of a flexible, hydrophobic middle block and two water-soluble end-blocks. An α,ω-bis(3-hydroxypropyl) PDMS reacted with trifluoromethanesulfonic anhydride under strictly anhydrous conditions to introduce triflate end-groups.

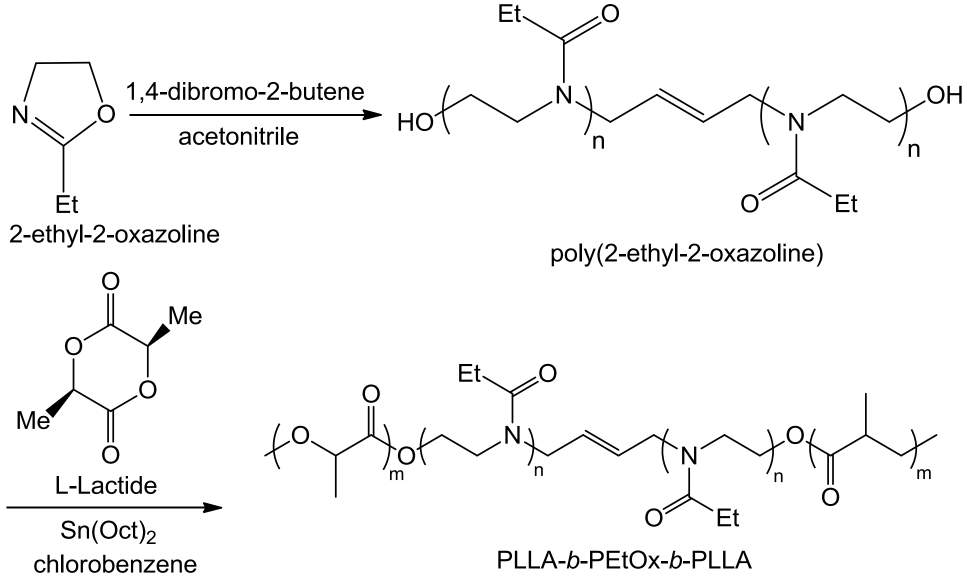


Figure 2.13 Synthesis of PLLA-*b*-PEtOx-*b*-PLLA triblock copolymers

The polymerization was then performed with the addition of 2-methyl-2-oxazoline using dichloroethane as the solvent at 40 ºC and terminated by KOH in ethanol. Hydroxy-functional (PMeOX-*b*-PDMS-*b*-PMeOx) were also derivatized through reaction with 2-isocyanatoethylmethacrylate. The methacrylate functional triblock copolymers were then cross-linked using UV-induced free radical polymerization. Morphological studies indicated the formation of vesicular structures. Cross-linking did not cause any change in morphology. Moreover, mechanical integrity was gained upon crosslinking due to the covalent linkages between copolymer molecules. Furthermore, these copolymer network structures were shown to form ultrathin (10-nm) free-standing membranes that mimicked lipid bilayers.[120]

Other synthetic methods to prepare PDMS-Polyoxazoline block copolymers have also been reported. Riffle *et al*.[121] synthesized (PDMS-*b*-PEtOx) diblock copolymers with narrow molecular weight distributions. The first step was to prepare benzyl chloride functional PDMS oligomers using hexamethyltrisiloxane and *sec*-butyllithium as a monomer and initiator, respectively. The PDMS oligomers were then terminated with dimethylsilylethyl benzyl chloride. Diblock materials were prepared by polymerizing 2-ethyl-2-oxazoline from the monofunctional benzyl-chloride terminated PDMS. Sodium iodide was added to these systems to produce iodobenzyl macroinitiators *in situ*. Montemagno *et al*.[122] used a similar method to prepare a telechelic PDMS macroinitiator system with benzyl chloride functionality, with subsequent polymerization of EtOx sequences in the presence of NaI yielded PEtOx-*b*-PDMS-*b*-PEtOx triblock copolymers.

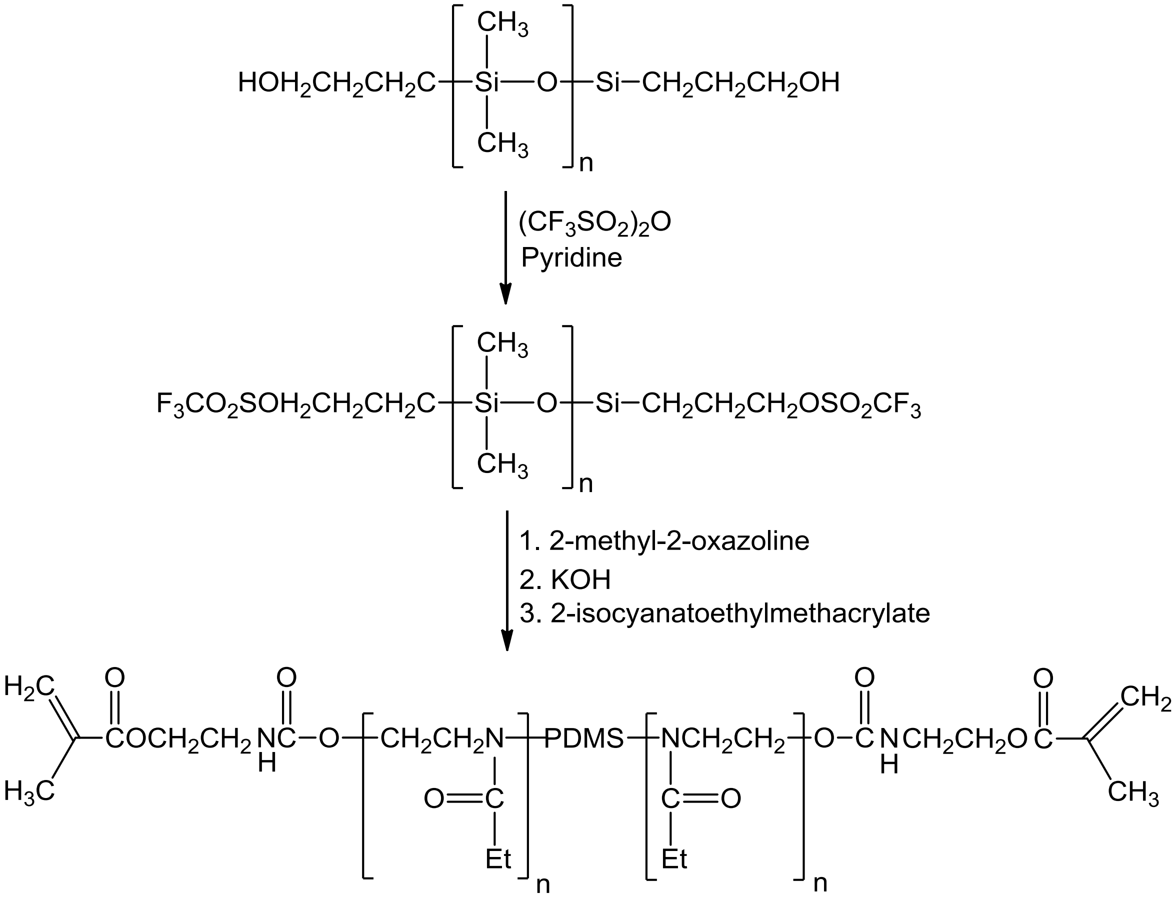


Figure 2.14 Synthesis of PEtOx-*b*-PDMS-*b*-PEtOx triblock copolymers

2.1.7.2.3 Poly(2-oxazoline) and poly(ethylene oxide) copolymers

The synthesis of poly(ethylene oxide)-poly(alkyl oxazoline) diblock copolymers was first reported by Kataoka and coworkers.[123] In the first step, a heterobifunctional PEO macroinitiator with an acetal group at one end and a methanesulfonate (mesylate) group at the other end was prepared by anionic ring opening polymerization of ethylene oxide using potassium 3,3-diethoxypropan-1-olate as the initiator in THF at room temperature. The growing anionic chains were terminated by methanesulfonyl chloride. Acetal-PEO-SO_2CH_3 was then utilized as a macroinitiator for the polymerization of 2-methyl-2-oxazoline to introduce the second block in nitromethane at 60 ºC for 70 hours

(Figure 2.15). Molecular weight distribution (MWD) of the PEO-*b*-PEtOx diblock copolymer was reported to be ~1.4 as obtained by SEC analysis with a refractive index detector.

Cheradame *et al*.[124] conducted a kinetic study on the synthesis of PEO-*b*-PMeOx diblock copolymers utilizing two different PEO-macroinitiators with 4-chloromethylbenzoate and tosylate functional groups (Figure 2.16) in acetonitrile at ~ 80 ºC. In each polymerization, slow initiation was observed. Interestingly, tosylated PEO macroinitiators were found to initiate the methyl oxazoline polymerizations only slightly faster than the benzyl chloride ones under identical conditions. However, it is known that initiation rate constant of methyl tosylate (k_i=4.00x10^{-4} L/(mol.sec) at 50 ºC)[9] is much higher than that of benzyl chloride (k_i=0.47x10^{-4} L/(mol.sec) at 85 ºC)[11] for polymerization of MeOx in acetonitrile performed with the same monomer and initiator concentrations. Thus, slow initiation of alkyl oxazoline polymerizations from PEO-macroinitiators is a prominent issue regarding preparation of well-defined diblock copolymers.

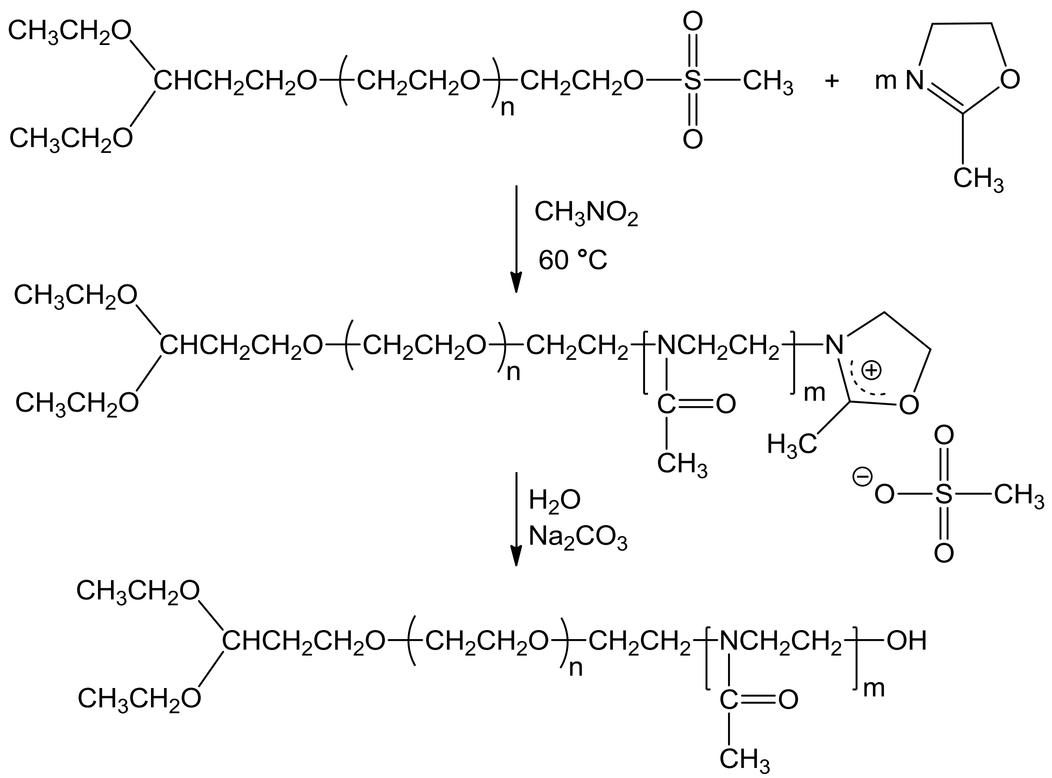
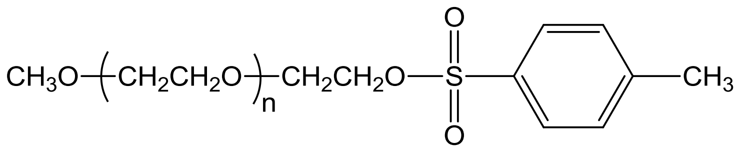
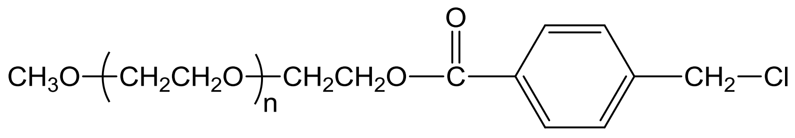


Figure 2.15 Synthesis of a poly(ethylene oxide)-*b*-poly(methyl oxazoline) diblock copolymer with a mesylate functional PEO macroinitiator



Tosylate ended PEO macroinitiator



Chloromethyl benzoate ended PEO macroinitiator

Figure 2.16 Tosylate and chloromethyl benzoate functional poly(ethylene oxide) macroinitiators

Poly(ethylene oxide)-*b*-poly(alkyl oxazoline) block copolymers are interesting materials because of their easy transformation to poly(ethylene oxide)-*b*-poly(ethylene imine) under acidic or alkaline conditions. The high efficiency of cationic PEIs to complex with nucleic acids make them very attractive for gene delivery applications. However, PEIs display a severe cytotoxicity due to their strong electrostatic interactions with cell membranes. Therefore, chemical modifications of PEI with biocompatible polymers is required for their use in a variety of bioapplications.[125,126]

2.1.7.2.4 Other copolymers containing poly(2-oxazoline)s

Hwang and Hsiue *et al*.[127] prepared amphiphilic PEtOx-*b*-poly(ε-caprolactone) (PCL)-*b*-PEtOx triblock copolymers in three steps. First, monohydroxy-functional PEtOx was synthesized using methyl *p*-toluenesulfonate as the initiator and terminated with methanolic KOH. Secondly, ε-caprolactone was polymerized using a tin(II) octoate catalyst from the hydroxyl-ended PEtOx macroinitiator to introduce poly(ε-caprolactone) as the second block. Hydroxy-ended diblock copolymers were then coupled with hexamethylene diisocyanate to form PEtOx-*b*-PCL-*b*-PEtOx triblock copolymers. The resulting copolymers formed a hydrogel in aqueous solution showed a reversible sol (room temperature)-gel(physiological temperature) phase transition. The gel was used to extend the release of the antibody bevacizumab (Avastin^{TM}) to treat intraocular neovascular diseases. These hydrogels did not exhibit cytotoxicity in vitro.

Besides the use of macroinitiator approach to prepare block copolymers of poly(2-oxazoline)s, grafting,[129-131] coupling[132] and crosslinking[33] reactions have also been applied to obtain novel poly(2-oxazoline) macromolecular structures for a wide variety of applications.

2.2 Polymeric Membranes for Water Purification

Today, more than 1 billion people are suffering from a lack of potable water and about 2.3 billion people (41% of Earth's population) live in regions with water scarcity. This number is estimated to be 3.5 billion by 2025.[133] More than 96% of world’s water is found in seas and oceans. Water conservation, dam construction, thermal distillation and membrane processes have been applied to overcome water shortage problems, but membrane-based water purification is increasingly becoming the choice for effective solutions.[134] Membrane technology for desalination, such as reverse osmosis (RO), is an attractive and energy efficient means for developing new sources of fresh water globally.[133,134]

Commercial reverse osmosis desalination membranes are mainly prepared from aromatic polyamide thin film composites (TFC’s) due to their excellent rejection of salt and organic impurities, their high water flux and good permeability properties, their stability over a wide pH range at ambient temperatures, and their good mechanical properties.[134-138] The polyamide barrier layers used for desalination are synthesized by reaction of *m*-phenylene diamine with trimesoyl chloride and related monomers.[138] TFC membranes are comprised of a thin, highly selective aromatic polyamide layer interfacially polymerized onto a reinforced microporous sublayer (mostly polysulfone (UDEL) supports). However, the aromatic amide groups of these polyamides have low resistance to chlorinated disinfectants (e.g. HOCl). Chemical degradation (chain scission) begins at the amide nitrogen and proceeds primarily through N-Cl formation.[139,140] Polyamide backbone degradation results in an irreversible loss of membrane performance and necessitates the use of expensive dechlorination and rechlorination treatment steps before and after passage of seawater through the membranes.[139,141-144]

2.2.1 Hydrophilic modifications of poly(arylene ether sulfone)s

Poly(arylene ether sulfone)s are important engineering thermoplastics with excellent resistance to hydrolysis and oxidation, and they display excellent mechanical properties, thermal stability and toughness. The most important commercially available polymer belonging to this family is bisphenol A polysulfone (UDEL polysulfone) (Figure 2.17), which is prepared by step growth polymerization of bisphenol A and 4,4'-dichlorodiphenylsulfone.[145,146]

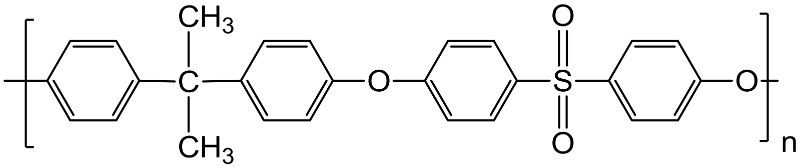


Figure 2.17 Chemical structure of bisphenol-A polysulfone

Poly(arylene ether sulfone)s are used as the porous supports in polyamide TFC membranes and they do not possess the vulnerable amide bond that is susceptible to chlorine attack.[147] Membranes used in water treatment require a hydrophilic character to provide better water flux and show improved fouling resistance towards colloidal matter, microorganisms, organic and inorganic substances.[134,141,148,149] The hydrophobicity of the polysulfone causes the membranes to have an absorptive surface and results in undesired accumulation of a variety of foulants that compromise membrane pores.[145] Thus, more hydrophilic polysulfones hold great promise as future water purification membranes with high stability against chlorinated disinfectants and resistance to (bio)fouling. Controlling the compositions of hydrophilic blocks in the amphiphilic polysulfone copolymers can be utilized to tune transport properties such as water permeability in the final membranes.[150-153]

Hydrophilic modification of poly(arylene ether sulfone)s has been a goal of many investigations. One main method has been sulfonation of polysulfones (PSF). Sulfonation procedures fall into two main categories, post-sulfonation[154] and direct polymerization utilizing sulfonated monomers.[147,150] Sulfonated polysulfones prepared by post-sulfonation methods show excellent salt rejection and water flux at high concentrations of feed water. However, strong acids (e.g. chlorosulfonic acid) used as sulfonating agent lead to undesirable side reactions such as partial cleavage of the bisphenol A polysulfone at the isopropylidene link or branching and crosslinking. There are also difficulties in controlling the degree of sulfonation and the distribution of the sulfonate groups in the final polymer at low levels.[145,150] Although sulfonated polysulfones show very good membrane performance, synthetic difficulties in their preparation have hindered their acceptability for desalination applications.[150]

Disulfonated poly(arylene ether sulfone) random copolymers including both hydrophobic and hydrophilic segments have been prepared by direct copolymerization of a disulfonated monomer (3,3'-disulfonato-4,4'-dichlorodiphenyl sulfone (SDCDPS)) with non-sulfonated monomers such as (e.g. 4,4'-dichlorodiphenyl sulfone (DCDPS) and 4,4'-biphenol (BP), (Figure 2.18).[150,155,156]

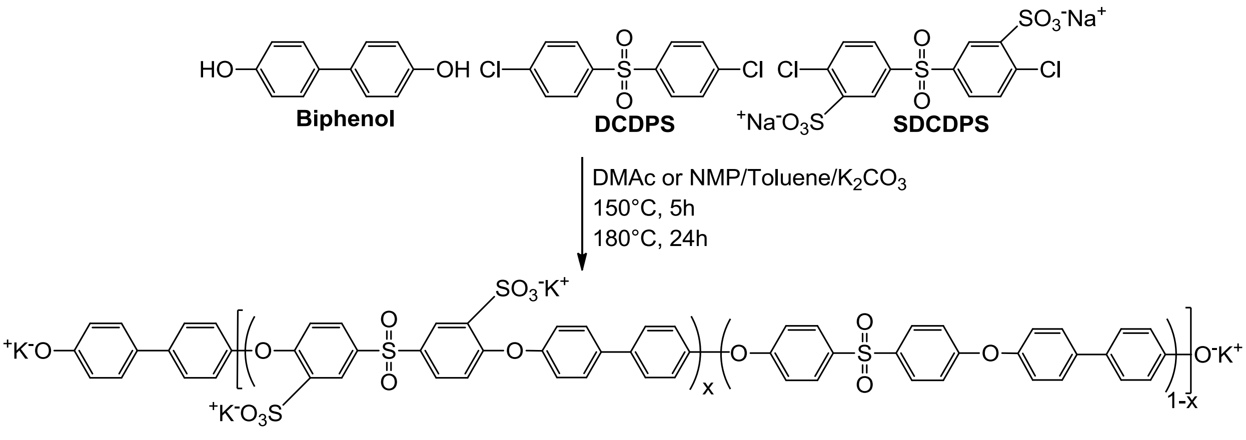


Figure 2.18 Synthesis of phenoxide endcapped partially sulfonated biphenyl sulfone copolymer[147]

Directly copolymerized disulfonated PSFs consist of hydrophobic (non-sulfonated) and hydrophilic (sulfonated) segments. The direct polymerization method allows control over molecular weight, degree of sulfonation and microstructure of these random copolymers. This synthesis procedure yields poly(arylene ether sulfones) that are more favorable for desalination applications since side reactions (e.g. degradation of polymer backbone, crosslinking) are also avoided. These polymers are highly chlorine-tolerant over a wide range of pH (4-10), as well as being mechanically and thermally stable, and they have good salt rejection and water flux. It was demonstrated that as the degree of sulfonation was increased, water uptake (a measure of hydrophilicity) increased.[150] The recovered yields from these copolymerizations are very high.

In addition to the use of block copolymer and post-modification approaches, surface modification and blending have also been utilized to hydrophilize polysulfone-based membranes. Surface modifications can be applied in the form of plasma treatment, grafting, adsorption and coating. Promising membrane performance has been obtained, but shortcomings such as limited long term stability, the changes of pore sizes and pore size distributions after coating and grafting, and required additional processing steps during membrane fabrication are issues.[157] Polymer blends have also been investigated to increase hydrophilicity. To make appropriate blends, the two polymers should be soluble in the same solvent so that the solution can be further processed. One limitation of this method has been to identify common solvents that solubilize both hydrophilic and hydrophobic polymers. Another issue has been that the blended polymer membranes have to date suffered from less stability compared to copolymers, since physical interactions in the blends polymers are weaker than chemical interactions (covalent chemical bonds) present in block copolymers (i.e. the chemical bond between hydrophilic and hydrophobic segments).[158]

Linking hydrophilic polymers such as PEO and poly(2-oxazoline)s with polysulfone has the potential to form new membrane materials while retaining the unique properties of individual components. These block copolymers may also provide modified surfaces that will improve resistance to (bio)fouling and increase water flux. Furthermore, the tertiary amide structures of hydrophilic poly(alkyl oxazoline)s may resist attack by chlorine-containing disinfectants since they lack the amidic hydrogens on the aromatic polyamides that are the source of initial degradation of the current amides used in the TFC’s.

Poly(ethylene oxide) (PEO) is a linear or branched polyether, generally synthesized via anionic ring opening polymerization of ethylene oxide (EO) under pressure. PEO is highly hydrophilic and biocompatible and molecular weight can be controlled. Its applications include drug delivery, bioseparations, protein modification, dispersants for magnetite nanoparticles and modification of surfaces (implants, membranes) to give them a non-fouling character.[159,160]

Poly(ethylene oxide) has a polydispersity around 1.1, because it is polymerized using living anionic polymerization. The initiators for EO polymerizations are generally hydroxide or alkoxide functional groups. The reaction mechanism, when a base catalyst is used (Figure 2.19), include the nucleophilic attack by a base on an ethylene oxide ring.[159] Ethylene oxide polymerizations are also conducted from a hydroxyl group containing initiator utilizing a double metal cyanide catalyst (e.g. $Zn_3[Co(CN)_6]_2$) with a proposed mechanism shown in (Figure 2.20).[161]

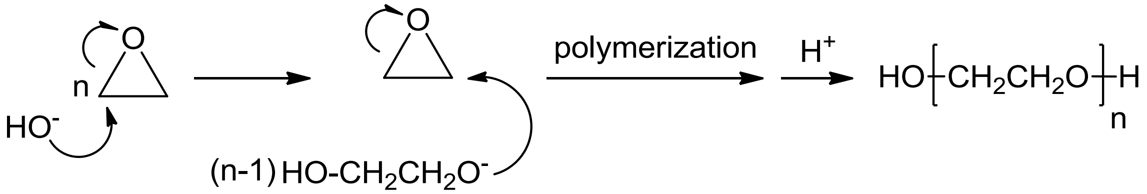


Figure 2.19 Synthesis of PEO oligomer via ring opening polymerization of EO initiated by a base (hydroxide ion)

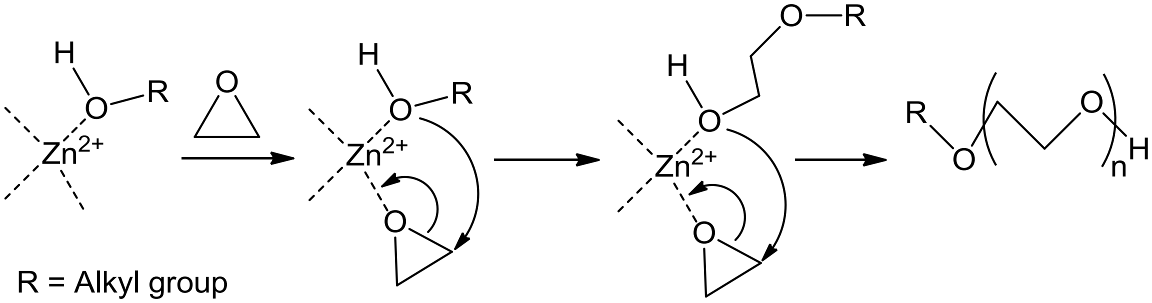


Figure 2.20 Proposed ethylene oxide polymerization via metal coordinated catalyzed ring opening polymerization

Different synthetic methods have been applied to obtain amphiphilic PEO-*b*-PSF block copolymers. One strategy to prepare ABA block copolymers, where B is a hydrophobic polysulfone (PSF) central block, and A is a hydrophilic PEO side block, is via atom transfer radical polymerization (ATRP), using a bromoalkyl-terminated difunctional PSF as a macroinitiator to polymerize acrylate-functional PEO macromonomers.[157,162] These polymers are also promising for bioapplications (e.g. artificial stents, implants, drug release studies).

Shi *et al.*[163] synthesized PEO-polyethersulfone via reaction of chlorosulfonated PSF with an oligomeric PEO, and proposed to use this as a hydrophilic modifier for PSF-based ultrafiltration membranes. Chlorosulfonic acid was used during the chlorosulfonation step. This sulfonating agent leads to side reactions such as molecular weight degradation, and crosslinking.[150] Hancock and Fagen[164] prepared aryl-chloride-terminated PSF and PEO oligomers separately, then condensed these two polymers with each other via nucleophilic aromatic substitution.[164,165]

Our initial synthetic method was to prepare amphiphilic, ABA-type PEO-*b*-BisA PSF-*b*-PEO triblock copolymers using a double metal cyanide catalyzed coordinated ring-opening polymerization of ethylene oxide monomers from the ends of phenol functional telechelic bisphenol A polysulfone (BisA PSF) macroinitiators (Figure 2.21). One proposed advantage of this approach was to control molecular weight of the PEO units while obtaining stable materials under membrane processing conditions. A series of PEO-*b*-BisAPSF-*b*-PEO triblock copolymers including varying amounts of PEO (between 30% and 70%) were synthesized. In all cases, ~80% of phenolic endgroups on PSF macroinitiator were found to initiate the polymerization of PEO while about 20% of phenol groups remained unreacted as evidenced by ^{19}F NMR data (after derivatizing the phenolic and aliphatic alcohol endgroups with trifluoro acetic anhydride).

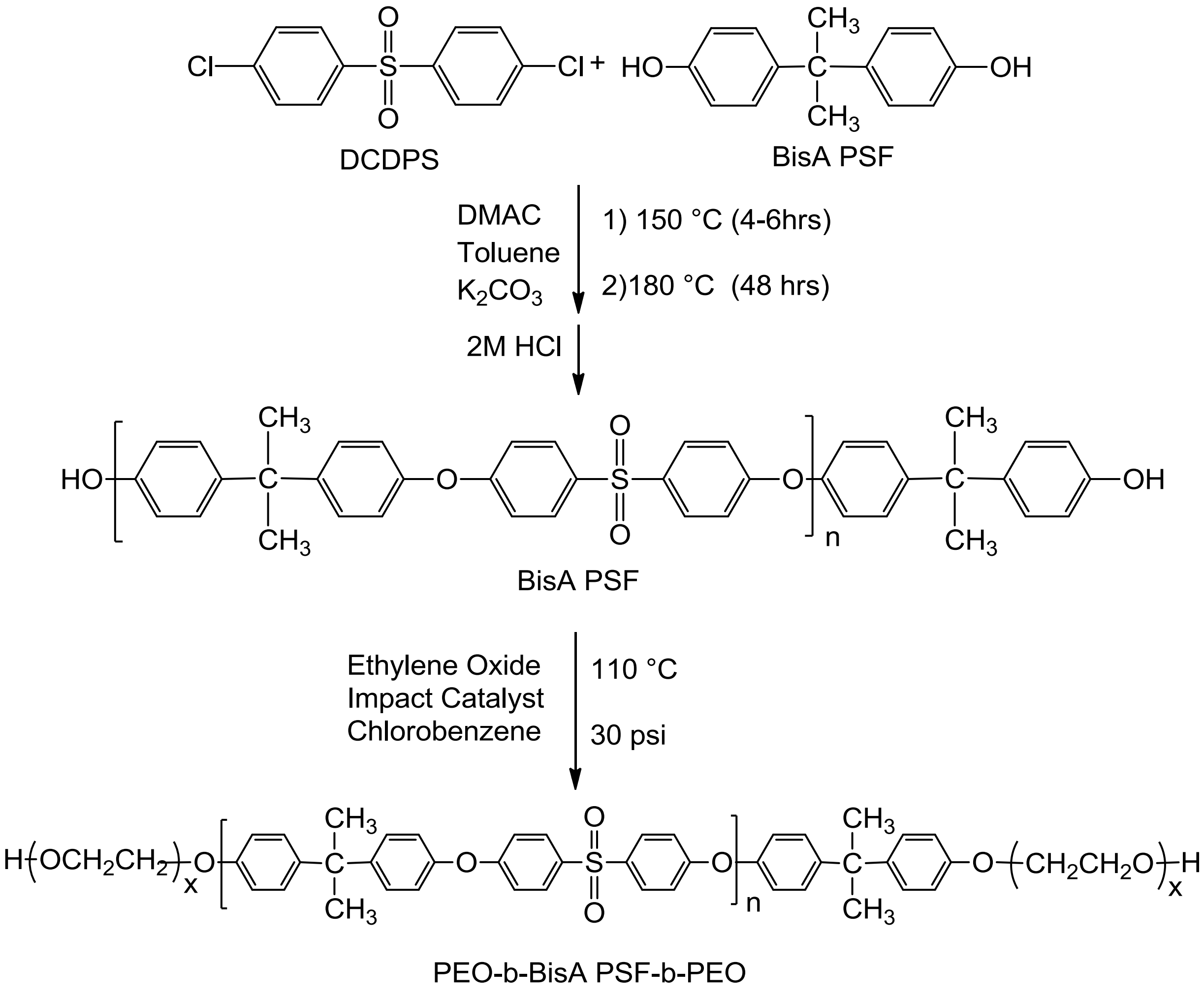


Figure 2.21 Synthesis of poly(ethylene oxide)-bisphenol A polysulfone (PEO-*b*-BisA PSF-*b*-PEO) triblock copolymers via metal coordinated catalyzed ring-opening polymerization

The synthetic challenges encountered with the catalyst to synthesize PEO-PSF triblock copolymers lead us to investigate polyoxazolines with small side chains (e.g. methyl or ethyl) as an analog to PEO to prepare amphiphilic PEtOx-*b*-PSF-*b*-PEtOx triblock copolymers.[151] The details of this study are presented in the subsequent research chapters. Our study was also honored to be published in a virtual special issue of "Polymer" on living and controlled polymerizations dedicated to Professor Axel

Muller.[166] In a recent study, amphiphilic graft copolymers of polysulfones with poly(2-oxazoline) side chains were synthesized via cationic ring-opening polymerization of 2-ethyl-2-ozaxoline and 2-propyl-2-ozaxoline from a chloromethylated polysulfone/potassium iodide macroinitiator system (with 15% benzylchloride content).[129] The graft copolymer showed temperature-dependent surface hydrophobicity due to the thermoresponsive character of utilized poly(2-oxazoline)s.

Besides the potential use of hydrophilic polymers in water purification membranes, hydrophilic polyoxazolines are also promosing materials for gas separations. Crosslinked PEO was found to selectively remove polar and acid gases such as CO_2 and H_2S from mixtures of light gases, such as H_2 and N_2, and hydrocarbons. Polymers containing polar moieties such as ether groups achieve high selectivity based upon their high solubility selectivity favoring CO_2 transport.[167-170] Thus, gas separation membranes prepared from poly(2-oxazoline)s may exhibit good separation properties with polar gases due to their structural and functional similarities to PEO and their amorphous nature.

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CHAPTER 3 - Synthesis and Characterization of Polyoxazoline-Polysulfone Triblock Copolymers

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Abstract

Amphiphilic triblock poly(2-ethyl-2-oxazoline-*b*-sulfone-*b*-2-ethyl-2-oxazoline) (PEOX-*b*-PSF-*b*-PEOX) and poly(2-ethyl-2-oxazoline-co-ethyleneimine-*b*-sulfone-*b*-2-ethyl-2-oxazoline-co-ethyleneimine) (PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI) copolymers were synthesized for potential use as water purification membranes. Poly(arylene ether sulfone) (polysulfone) oligomers of controlled molecular weight were prepared by nucleophilic step polymerization of 4,-4’-dichlorodiphenyl sulfone with a molar excess of bisphenol-A. The phenolate endgroups were then reacted with ethylene carbonate to afford telechelic aliphatic hydroxyethyl groups. These were tosylated to produce macroinitiators for ring-opening cationic polymerization of 2-ethyl-2-oxazoline. Subsequently, the pendent amides on the hydrophilic PEOX blocks were also hydrolyzed to generate positively charged PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymers. Compositions with high polysulfone compositions relative to the hydrophilic blocks were of particular interest because they maintained good mechanical integrity in water. Water

uptake at room temperature increased up to 18 wt% for copolymers with 22 wt% of the hydrophilic components. Solid-state thermal properties suggested some phase mixing of the components in the PEOX-*b*-PSF-*b*-PEOX copolymers but better phase separation of the blocks in the partially hydrolyzed PEOXcoPEO-*b*-PSF-*b*-PEOXcoPEI materials.

3.1 Introduction

There is an increasing worldwide need for fresh drinking water[1] and desalination processes can provide potable water from oceans and seas which contain ~97% of the water. Membrane-based separations are now the major technology for producing drinking water because they are energy-efficient and have lower operation costs compared to distillation.[2,3] Reverse osmosis (RO) and nanofiltration are the dominant membrane processes for desalination. RO membranes do not have distinct pores, but rather rely on free volume within the polymer films for separations.[4] Thus, these membranes can efficiently reject monovalent ions such as sodium and chloride. RO membrane separations depend highly on the chemical and physical structure of the membrane materials.[1,2,4,5] They should be chemically stable in the presence of substances utilized as disinfectants and should resist adhesion of microorganisms and growth of biofilms. They must also be stable both mechanically and structurally over a long time, and possess ideal separation properties such as high water flux and salt rejection.

Polyamide thin film composite membranes are currently widely used for desalination.[6] However, their sensitivity to chlorinated disinfectants is a major disadvantage. Chlorinated disinfectants, typically in the form of aqueous hypochlorite, are inexpensive and highly effective biocides that are extensively used in water purification.[7] Unfortunately, these disinfectants degrade polyamide membranes which results in structural changes that are accompanied by loss of salt rejection properties.[8]

Thus, pre-treatment steps including disinfection, removal of the disinfectants before the feedwater is passed through these membranes, then subsequent disinfection are required.[9]

Poly(arylene ether sulfones) (PSFs) are important engineering thermoplastics with excellent resistance to chlorinated disinfectants, hydrolysis and oxidation, as well as good mechanical properties, thermal stability and toughness.[10] Conventional PSFs made from bisphenol-A and dichlorodiphenyl sulfone are used as porous supports for polyamide thin film composite membranes, but they are not used as the separation layer because of their hydrophobic nature.[11] Membranes for the separation layer in water treatment require a hydrophilic character to provide better water flux and improve resistance to membrane fouling (i.e. adhesion of microorganisms, proteins, etc.).

Hydrophilic modifications of PSFs have been the goal of many investigations.[10-19] One of the main hydrophilic modifications has been sulfonation of the PSF backbones. Sulfonation procedures fall into two main categories, post-sulfonation[12] and direct copolymerization of disulfonated comonomers.[2,13] PSF random and block copolymers including both hydrophobic and hydrophilic sequences have been synthesized with disulfonated comonomers. Poly(ethylene oxide)-polysulfone block copolymers have also been prepared to render PSF more hydrophilic. Hancock and Fagan[14] prepared aryl chloride-terminated PSF oligomers and condensed them with hydroxyfunctional poly(ethylene oxide) by step-growth polymerization to obtain poly(ethylene oxide)-PSF multiblock copolymers. Wang *et al.*[15] and Gaynor and Matyjaszewski[16] reported syntheses of poly(ethylene oxide)-*b*-PSF-*b*-poly(ethylene oxide) amphiphilic triblock copolymers via atom transfer radical polymerization utilizing a bromoalkyl-terminated difunctional PSF as a macroinitiator for acrylate-functional poly(ethylene oxide) macromonomers. Surface modifications such as plasma treatment, grafting, adsorption and/or coating, as well as blending, have also been used to prepare PSF-based membranes with hydrophilic character.[17-20]

This paper describes the synthesis and characterization of PEOX-*b*-PSF-*b*-PEOX amphiphilic triblock copolymers, and partial hydrolysis of the pendent amides in the PEOX blocks to form PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI. The focus has been on copolymers wherein the major component was the hydrophobic PSF with minor compositions of the hydrophilic blocks in order to examine the composition range that may yield good films for water purification. It is reasoned that high compositions of the hydrophilic blocks would lead to films that absorb too much water to maintain good mechanical properties during use as water purification membranes.

2-Oxazolines are five-membered cyclic imino ethers that can be polymerized via living cationic polymerization.[21] Poly(2-oxazolines) are comprised of C-C-N backbone repeat units, and therefore have some structural similarity with poly(ethylene oxide).[22-24] They possess low toxicity and good hydrolytic stability in aqueous solutions. The nature of the alkyl side chain of poly(2-oxazoline)s is directly related to their solubilities and hydrophilic-hydrophobic character. Poly(2-oxazolines) with short alkyl side chains such as methyl and ethyl are hydrophilic and water-soluble.[25-29] Several studies have focused on incorporating poly(2-oxazoline)s into block copolymer structures to obtain materials with novel properties.[30-33] It is reasoned that the hydrophilicity of PEOX and the cationic charge of PEOXcoPEI as flexible endblocks of block copolymers may yield membrane surfaces that resist protein and microorganism adhesion. This approach may lead to PSF-based water purification membranes with enhanced water permeability, salt rejection, and antibacterial and antifouling properties.

3.2 Experimental

3.2.1 Materials

N,N-Dimethylacetamide (99%), potassium carbonate (>99%), dimethylformamide (99.8%), ethylene carbonate (98%), *p*-toluenesulfonyl chloride (TsCl, >98%), calcium hydride (>90%), dioxane (>99%), trifluoroacetic anhydride (>99%) and 4,4'-dihydroxy-2,2-diphenylpropane (bisphenol-A, >99%) were purchased from Aldrich and used as received. 4,4'-Dichlorodiphenyl sulfone (DCDPS, 99%) was purchased from Alfa Aesar and used as received. 2-Ethyl-2-oxazoline and chlorobenzene, both from Aldrich, were dried over CaH_2 and vacuum distilled into a dry flask under nitrogen. Triethylamine (TEA, >99.5%) was purchased from Fluka and used as received. Aqueous hydrochloric acid (2M, LabChem) was used as received. Methanol, chloroform, diethyl ether and toluene (Fisher Scientific) were used as received.

3.2.2 Synthesis

3.2.2.1 Synthesis of controlled molecular weight poly(arylene ether sulfones) (PSFs) with phenol endgroups

PSFs were prepared with phenol endgroups by using an excess of bisphenol-A relative to DCDPS calculated with the Carothers equation. A reaction to produce a relatively high molecular weight oligomer with a predicted M_n of 15,600 g/mol was conducted as follows. Bisphenol-A (12.268 g, 53.74 mmol), DCDPS (15.000 g, 52.23 mmol) and K_2CO_3 (8.86 g, 64 mmol) were added to a three-neck, 250-mL flask equipped with a condenser, Dean Stark trap, nitrogen inlet/outlet, and a mechanical stirrer. DMAc

(175 mL) and toluene (72 mL) were added to the flask to dissolve the monomers. The solution was heated under reflux at 145 °C for 4 h while the toluene-water azeotrope was removed from the reaction mixture, and then the toluene was completely removed by slowly increasing the temperature to 170°C. The reaction was continued for 36 h at this temperature. The reaction mixture was cooled to room temperature and diluted with 500 mL of chloroform. It was filtered to remove most of the salt, then stirred with excess 2M HCl (200 mL) for 2 h at 25°C, and precipitated by addition to stirring methanol. The polymer was filtered and dried under vacuum at 100°C for ~24 h. The polymer was dissolved in chloroform, passed through a 0.45-μm Teflon® filter, then isolated by precipitation in methanol. The product was dried at 100°C under vacuum for 24 h.

Synthesis of a PSF with a predicted molecular weight of 4400 g/mol was conducted in a similar manner utilizing bisphenol-A (13.200 g, 57.80 mmol), DCDPS (15.000 g, 52.23 mmol), K_2CO_3 (8.92 g, 65 mmol), DMAc (145 mL) and toluene (103 mL).

3.2.2.2 Synthesis of diethoxylated poly(arylene ether sulfone) (Diethoxylated PSF)

Phenol terminated PSFs were ethoxylated with ethylene carbonate to yield oligomers with hydroxyethyl endgroups. A representative procedure is as follows. Phenol terminated PSF (10.53 g, 2.34 mmol), ethylene carbonate (4.03 g, 45.8 mmol), K_2CO_3 (0.63 mg, 4.58 mmol) and DMF (60 mL) were charged to a 100-mL flask containing a magnetic stir bar and enclosed with a rubber septum bound with steel wire. The reaction was placed in an oil bath and purged with nitrogen for 15 min, then the temperature was gradually increased to 125°C and the reaction was stirred for 20 h. The solution was cooled to room temperature and acidified with 2M $HCl_{(aq)}$ (5 mL, 10 mmol). The polymer was recovered by precipitation into methanol, then was filtered and dried at 100°C overnight under vacuum.

3.2.2.3 Synthesis of tosylated poly(arylene ether sulfone) macroinitiators

A PSF with hydroxyethyl endgroups (7.2 g, 1.57 mmol) was dissolved in 50 mL of chlorobenzene in a 100-mL flask equipped with a magnetic stir bar. TEA (2.18 mL, 15.6 mmol) and TsCl (2.98 g, 15.6 mmol) were added into the flask. The reaction mixture was stirred for 24 h at 25°C. The reaction mixture was diluted with 250 mL of chloroform and washed 4X with 400-500 mL of DI water in a 1-L separatory funnel to remove salts and unreacted toluenesulfonic acid. The organic phase was concentrated using a rotary evaporator under reduced pressure. The polymer-chloroform solution was passed through a 0.45-μm Teflon® filter, then the macroinitiator was isolated by precipitation into diethyl ether, collected by filtration and dried at 100°C *in vacuo* overnight.

3.2.2.4 Synthesis of PEOX-b-PSF-b-PEOX triblock copolymers

Amphiphilic PEOX-*b*-PSF-*b*-PEOX triblock copolymers were synthesized via cationic polymerization of 2-ethyl-2-oxazoline from the ends of the tosylated PSF macroinitiators. A procedure for preparing a targeted composition of ~2:1 wt:wt PSF:PEOX using a 4900 g/mol macroinitiator is as follows. A tosylated PSF macroinitiator (3.14 g, 0.641 mmol) was dried overnight *in vacuo* at 120°C in a 100-mL flask equipped with a magnetic stir bar and enclosed with a rubber septum bound with steel wire and Parafilm. Chlorobenzene (20 mL) was added via a syringe to dissolve the macroinitiator at room temperature. 2-Ethyl-2-oxazoline (1.52 mL, 1.49 g, 15 mmol) was added via syringe, and the temperature was raised to 115°C and maintained for 24 h. The solution was cooled to room temperature and the polymer was terminated with 1M $KOH_{(aq)}$ (5 mL, 5 mmol) and the mixture was stirred for 2 h. The triblock copolymer was recovered by precipitation in diethyl ether, collected by filtration and dried under vacuum at 100°C overnight.

3.2.2.5 Partial acid hydrolysis of a PEOX-b-PSF-b-PEOX triblock copolymer to afford an ionomer

A procedure for removing a portion of the pendent amide groups from the PEOX blocks by acid hydrolysis is provided. A PEOX-*b*-PSF-*b*-PEOX triblock copolymer with 2100 g/mol PEOX:15,200 g/mol PSF:2100 g/mol PEOX (0.83 g, 0.043 mmol, 1.82 meq of amides) was dissolved in 10 mL of dioxane in a 100-mL flask containing a magnetic stir bar and enclosed with a septum. 2M $HCl_{(aq)}$ (0.73 mL, 1.46 mmol) was added and the reaction temperature was raised to 90°C and maintained for 24 h. The PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI block copolymer was isolated by precipitation into diethyl ether and the extent of hydrolysis was estimated using ^{1}H NMR.

3.2.3 Characterization

Water uptake of the PEOX-*b*-PSF-*b*-PEOX and PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymers was evaluated for film membranes. Films were fabricated via solution casting from $CHCl_3$. Each copolymer was dissolved in $CHCl_3$ (10 wt %), filtered through a 0.45-µm Teflon® filter, and cast onto a clean glass plate. The cast solutions were maintained under ambient conditions for 24 h to allow most of the solvent to evaporate, then the films were dried at 110°C under vacuum for 24 h and weighed to obtain the dry weights. To obtain fully-hydrated membrane weights, each film was immersed in DI water at ambient temperature for 24 h, patted dry, then weighed. The water uptake was calculated from the ratio of the increase in membrane weight divided by the dry weight and expressed as a weight percent.

^{1}H NMR spectra were obtained on a Varian Unity 400 NMR spectrometer operating at 399.95 MHz. The NMR parameters included a pulse width of 30° and a relaxation delay of 1 s at room temperature with 64 scans. All spectra of the polymers were obtained in $CDCl_3$ at a concentration of 0.25 g/mL, with the exception of the PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI triblock copolymers that were measured in 90:10 v:v $CDCl_3$:DMSO-d_6.

The PSFs with phenol and hydroxyethyl endgroups were reacted with trifluoroacetic anhydride to produce the respective trifluoroacetate derivatives, then analyzed by ^{19}F NMR to assess the endgroup structures. For example, a PSF with hydroxyethyl endgroups (200 mg, 0.044 mmol) was dissolved in 5 mL of $CHCl_3$ in a 25-mL flask and trifluoroacetic anhydride (0.5 mL, 3.53 mmol) was added to the polymer solution. The reaction mixture was held at 25°C for 12 h. DI water (100 mL) was added to the reaction mixture to hydrolyze the remaining anhydride, and the mixture was stirred at room temperature for 2 h. The organic phase was analyzed by ^{19}F NMR. ^{19}F NMR spectra were collected utilizing the same NMR spectrometer operating at 376.29 MHz with a pulse width of 45° and a relaxation delay of 3 s with 64 scans.

PSF molecular weights and polydispersities were analyzed by size exclusion chromatography (SEC). An Alliance Waters 2690 Separations Module with a Viscotek T60A dual viscosity detector and laser refractometer equipped with four Waters Styragel HR columns (HR4 7.8 x 300 mm, HR3 7.8 x 300 mm, HR2 7.8 x 300 mm, and HR0.5 7.8 x 300 mm) was used for chromatographic analysis. Chloroform was employed as the mobile phase at 30°C and a flow rate of 1.0 mL/min. Polystyrene standards were used to construct a universal calibration to determine absolute molecular weights. Samples were passed through a 0.45-μm Teflon® syringe filter before measurement.

The thermal decomposition behavior of polymer samples was determined using a thermogravimetric analyzer (TGA, TA Instruments, TGA Q500) with a heating rate of 10°C/min under nitrogen. TGA measurements were conducted from 50 to 600°C. Prior to each measurement, all samples were held at 90°C for 15 min in the TGA instrument to minimize moisture content.

Thermal transitions of the polymers were investigated by differential scanning calorimetry (DSC, TA Instruments, DSC Q1000). The samples were placed in aluminum pans and preheated to 200°C for 5 min under a nitrogen atmosphere and cooled to 30°C. All samples were heated from 30 to 300°C at a heating rate of 5°C/min under a nitrogen flow rate of 60 mL/min. The glass transition temperature (T_g) of each sample was taken from the second scan.

3.3 Results and Discussion

3.3.1 Synthesis of phenol terminated PSFs and modifications to obtain hydroxyethyl endgroups and tosylated PSF macroinitiators

PSFs with phenol endgroups were synthesized from DCDPS and bisphenol-A via nucleophilic aromatic substitution (Figure 3.1). ^{1}H NMR spectra were used to determine their chemical compositions and confirm the phenol endgroup functionality (Figure 3.2). Resonances at 6.8 and 7.1 ppm were assigned to endgroup protons, and the peaks at 7.0, 7.2 and 7.8 ppm were assigned to aromatic protons in the polymer repeat units. The ratio of the integrals of aromatic protons at 7.8 ppm to the endgroup protons at 6.8 ppm were used to estimate the number average molecular weights of the PSF oligomers assuming they were quantitatively terminated with phenol.[34] Methyl protons from the isopropylidene link resonated at 1.7 ppm. The predicted number average molecular weights utilizing the calculated excesses of bisphenol-A relative to DCDPS were 15,600 and 4400 g/mol, in close agreement with the values obtained from the NMR analyses of 15,100 and 4500 respectively.

Reaction of the phenolic endgroups on the PSF oligomers with an excess of ethylene carbonate in the presence of the weak K_2CO_3 base was an effective method for converting to aliphatic hydroxyethyl endgroups (Figure 3.1).[35-37] Nucleophilic attack of the phenoxide ion on one of the alkyl carbons of the cyclic ethylene carbonate causes ring-opening and loss of CO_2 to yield the ethanol derivative.[38] ^{1}H NMR confirmed that the endgroup modification had occurred (Figure 3.2). The appearance of aliphatic ($–CH_2$) peaks at 3.94 and 4.06 ppm showed the presence of hydroxyethyl endgroups, and integration of those peaks indicated the presence of approximately one hydroxyethyl unit for each phenol endgroup on the precursor polymer. To determine whether all of the phenols had been converted to hydroxyethyl endgroups, the phenol-functional precursor oligomers and the corresponding polymers with hydroxyethyl endgroups were reacted with trifluoroacetic anhydride to produce the respective trifluoroacetates. ^{19}F NMR spectra can distinguish the aromatic versus aliphatic trifluoroacetates.[39] A PSF with the aromatic trifluoroacetate resonated at 75.13 while the aliphatic derivative resonated at 75.25 ppm (Figure 3.3). The ^{19}F spectrum for each polymer had only a single peak, which indicated the presence of only one type of hydroxyl group in each case.

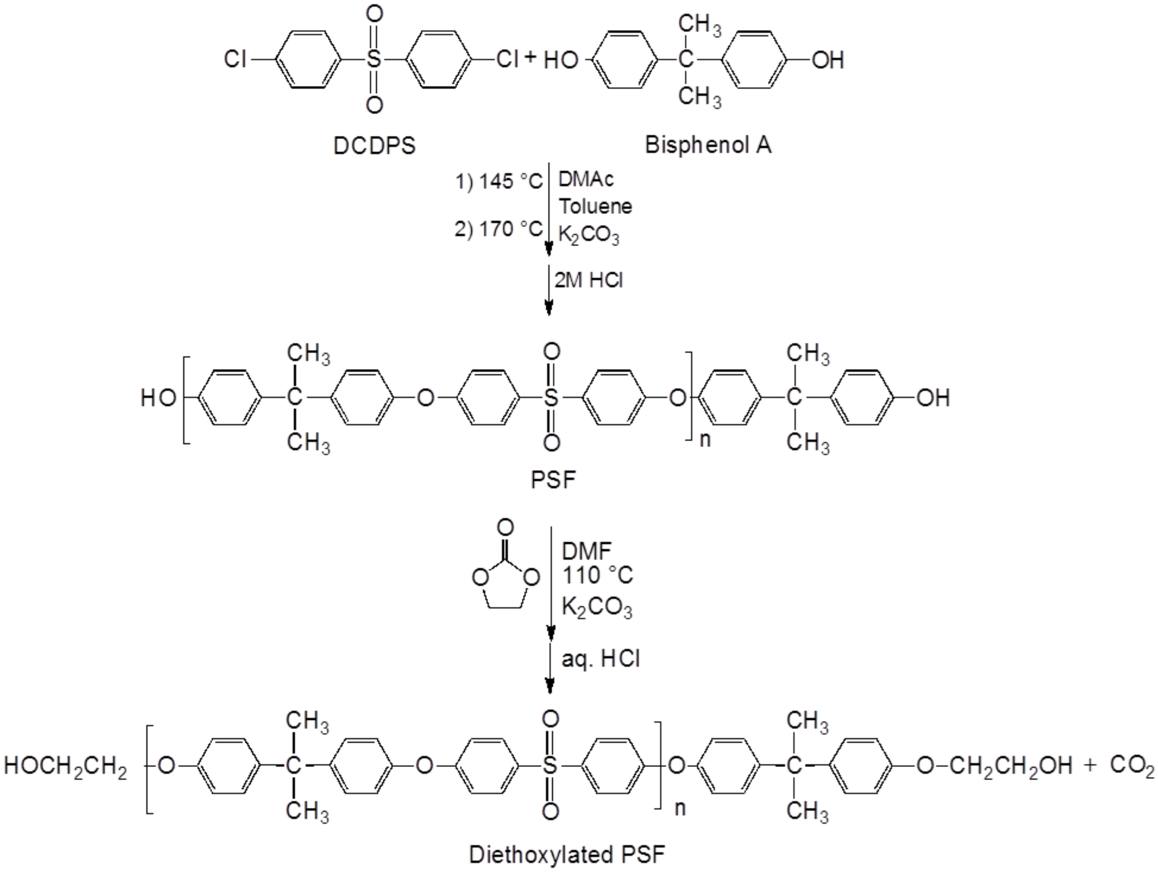

Figure 3.1 Synthesis of controlled molecular weight PSF oligomers with phenol and hydroxyethyl endgroups

Thus, the combined ^{1}H and ^{19}F spectra showed that the phenol endgroups had been converted to aliphatic hydroxyl groups and that little, if any, oligomerization of the ethylene carbonate had occurred. SEC data for the PSFs with the hydroxyethyl endgroups showed number average molecular weights of 4200 and 14,200 g/mol, in reasonable agreement with the predicted values and the experimental values derived from ^{1}H NMR.

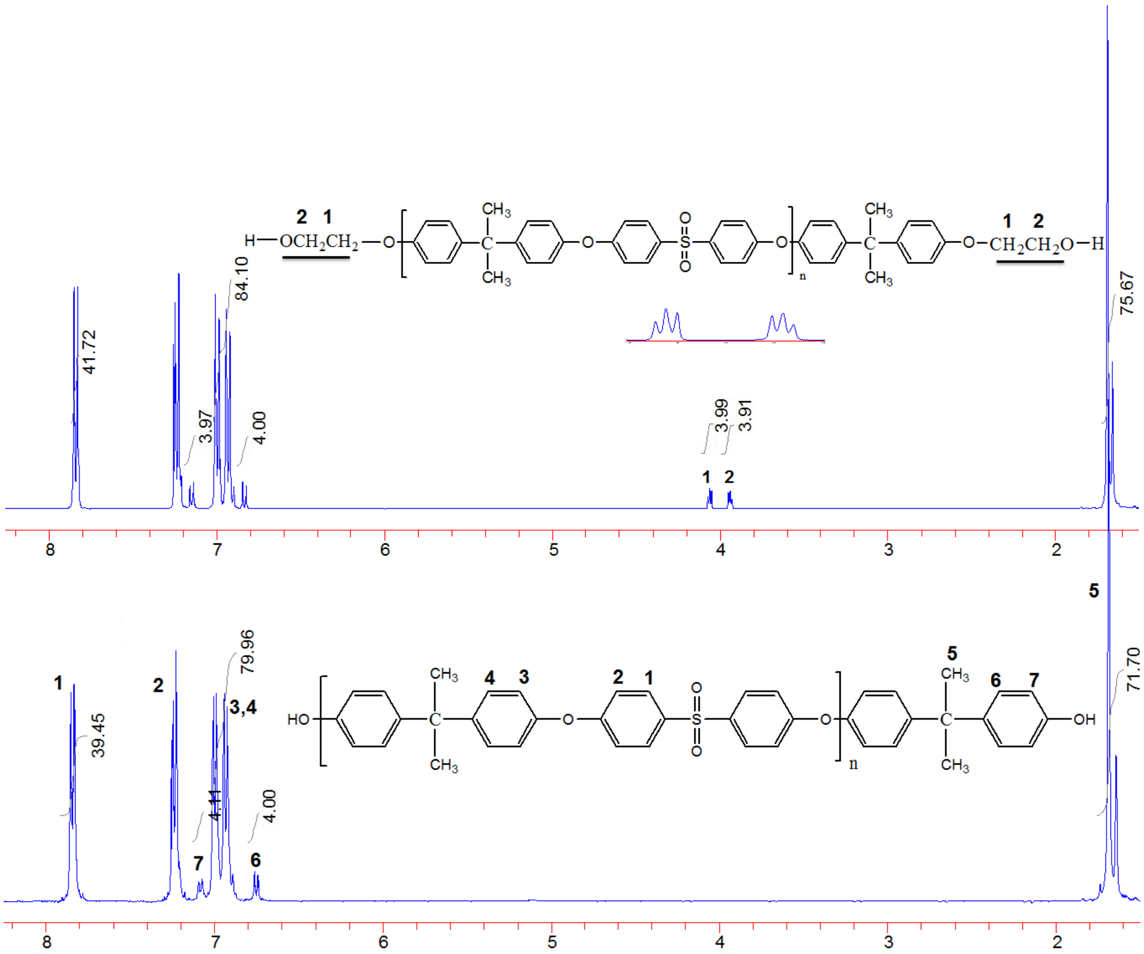

Figure 3.2 ^{1}H NMR spectra of PSFs with phenol and hydroxyethyl endgroups obtained in $CDCl_3$

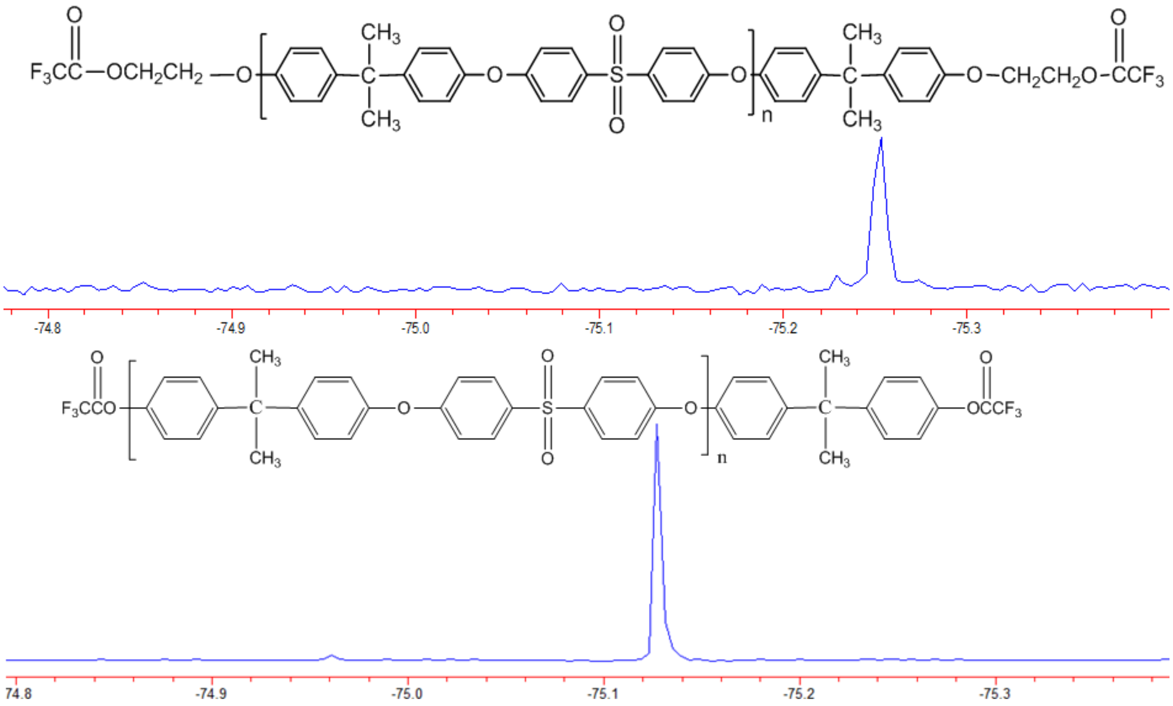

Figure 3.3 ^{19}F NMR spectra of trifluoroacetate derivatives of PSF with phenol and hydroxyethyl endgroups obtained in $CDCl_3$

The aliphatic alcohol-functional PSFs were tosylated to provide macroinitiators for the 2-ethyl-2-oxazoline polymerizations (Figure 3.4). ^{1}H NMR showed the expected downfield shifts of the methylene resonances on the hydroxyethyl endgroups as they were converted to tosylates, with the expected integral ratio of the ester methylene of the tosylate relative to the methyl peak of the tosyl group being 2:3 (Figure 3.5). These results suggest that the PSF macroinitiator was quantitatively tosylated. TGA data of the macroinitiator with an M_n of 4900 g/mol (calculated from the ^{1}H NMR data) indicated the onset of degradation at ~300°C (Figure 3.6). Quantitative measurement of the mass change at ~300 °C yielded a weight loss of 8.7%, which was close to the endgroup composition estimated from ^{1}H NMR of 8.2%.

3.3.2 Synthesis of PEOX-b-PSF-b-PEOX amphiphilic triblock copolymers

PEOX-*b*-PSF-*b*-PEOX triblock copolymers were prepared via cationic ring-opening polymerization of 2-ethyl-2-oxazoline from both ends of the tosylated PSF macroinitiators (Figure 3.4). An orange color was observed during these reactions, which is indicative of the propagating cationic oxazolinium species. After the monomer was consumed, the cationic chain ends were neutralized with KOH.

A ^{1}H NMR spectrum of a PEOX-*b*-PSF-*b*-PEOX triblock copolymer is shown in Figure 3.7. Formation of the PEOX end blocks resulted in the appearance of broad peaks in the region around 3.45 ppm due to the methylene backbone protons of PEOX ($-NCH_2CH_2$) and pendent group protons at 2.35 ($-CH_2$) and 1.12 ppm ($-CH_3$). The PEOX M_n was calculated by comparing the relative ratio of the integrals of PEOX proton resonances to the aromatic and aliphatic endgroup proton resonances on the PSF. The resulting M_n values of the PEOX blocks were in good agreement with the targeted block lengths (Table 3.1). The values derived from SEC measurements for the PEOX-containing materials were different than anticipated based on both the synthetic procedures and the NMR data and it is not clear why this occurs. We have encountered difficulties with SEC analyses of poly(2-ethyl-2-oxazoline) homopolymers previously, and attributed the problems at least partially to the polar amide groups adsorbing onto the SEC column walls and compromising the elution times.[30,40]

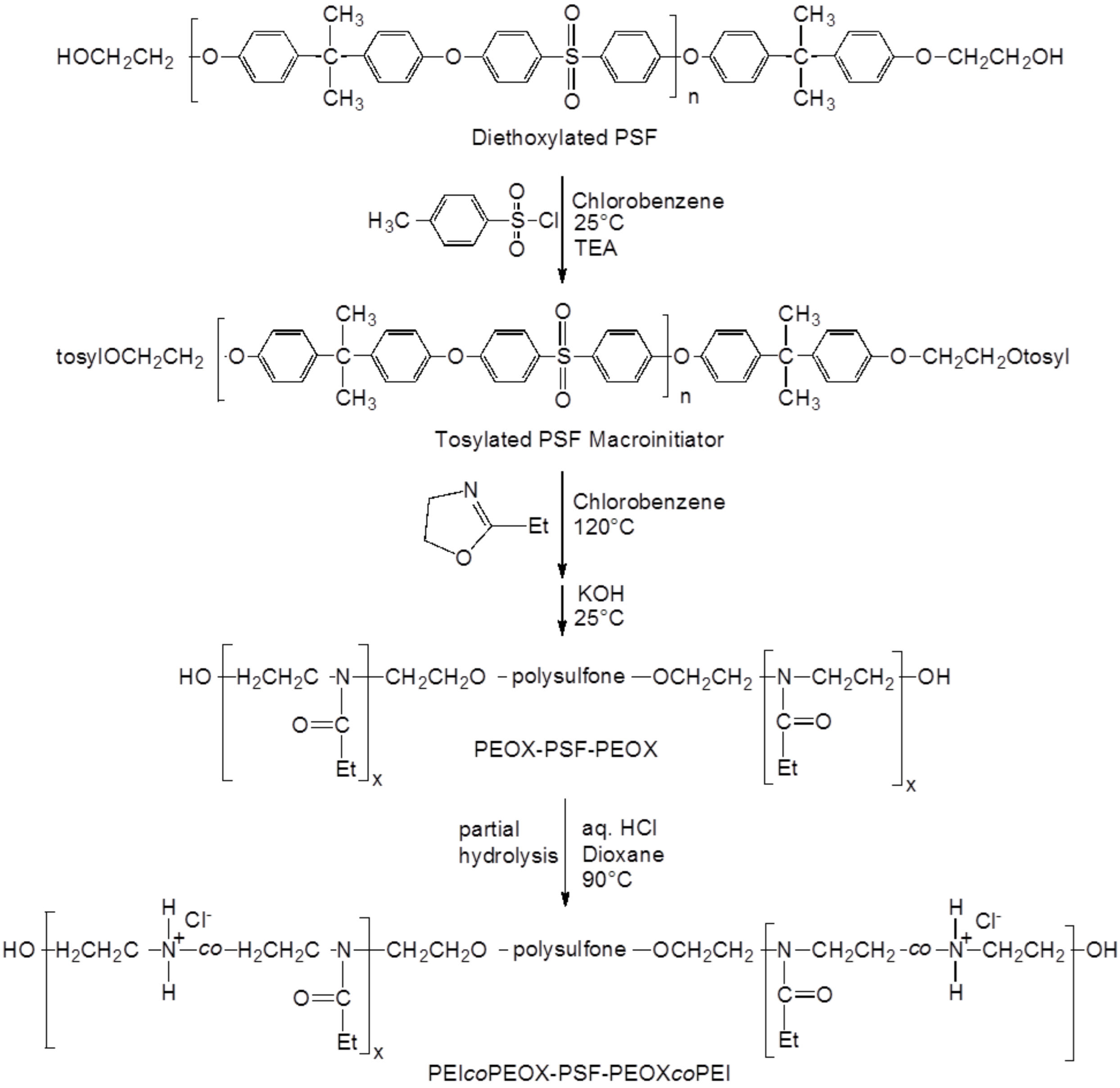

Figure 3.4 Synthesis of PEOX-*b*-PSF-*b*-PEOX and PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymers

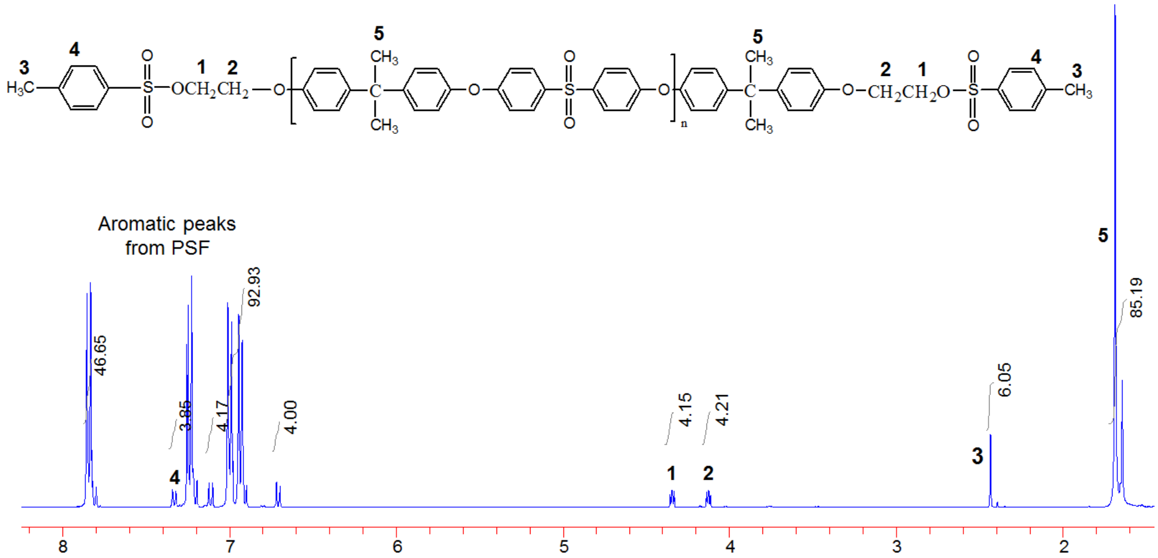

Figure 3.5 ^{1}H NMR spectrum of a PSF macroinitiator obtained in $CDCl_3$

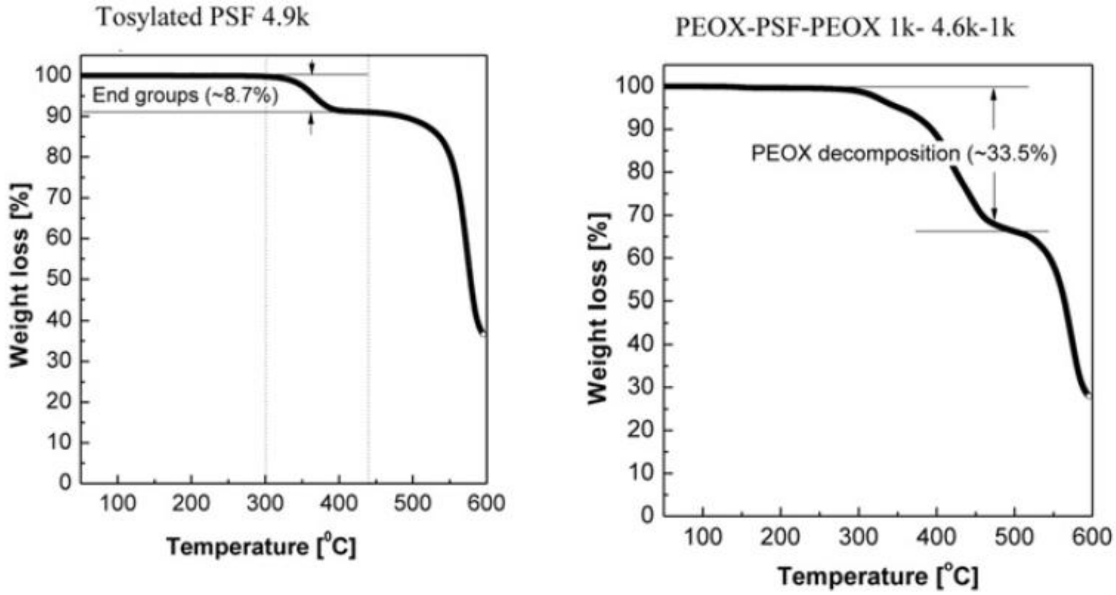

Figure 3.6 TGA thermograms of a PSF macroinitiator and PEOX-*b*-PSF-*b*-PEOX triblock compositions

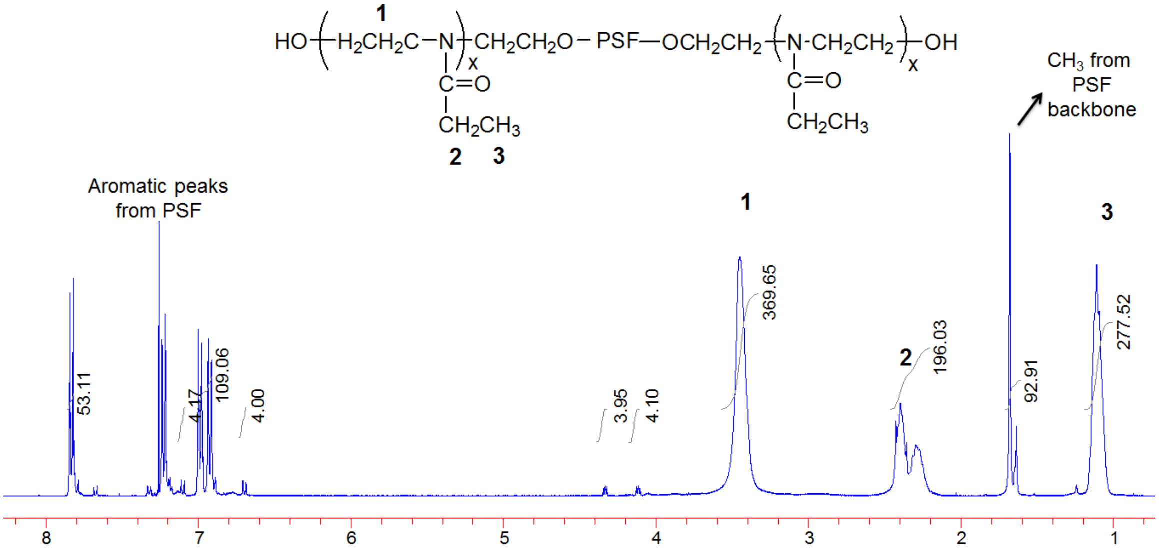

Figure 3.7 ^{1}H NMR spectrum of a PEOX-*b*-PSF-*b*-PEOX copolymer obtained in $CDCl_3$

Table 3.1 Properties of polyoxazoline-polysulfone block copolymers

Polymer (M_n)[a]	**Composition hydrophobic:hydrophilic (wt:wt)**	**Degree of Hydrolysis (%)[b]**	**Water Uptake (%)**	**Glass Transition Temperature(s) (°C)[c]**
PSF (15.2k)	100:0	----	5.3	170
PEOX-*b*-PSF-*b*-PEOX (0.8k-*b*-15.2k-*b*-0.8k)	90:10	----	10.5	163
PEOX-*b*-PSF-*b*-PEOX (1.4k-*b*-15.2k-*b*-1.4k)	86:14	----	14.9	160, 52 (weak)
PEOX-*b*-PSF-*b*-PEOX (2.1k-*b*-15.2k-*b*-2.1k)	78:22	----	18.6	156, 60
PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI (0.55k-*b*-15.2k-*b*-0.55k)	93:7	57	13.3	177
PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI (0.85k-*b*-15.2k-*b*-0.85k)	90:10	68	12.8	174
PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI (1.15k-*b*-15.2k-*b*-1.15k)	86:14	80	19.8	180

[a] Calculated using ^{1}H NMR

[b] Calculated using ^{1}H NMR (Each hydrolyzed copolymer was prepared from PEOX-PSF-PEOX with different side lengths)

[c] Determined from second heating scans measured by DSC

3.3.3 Synthesis of charged PEOXcoPEI-b-PSF-b-PEOXcoPEI copolymers

A series of PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymers were prepared by acid hydrolysis of a portion of the pendent amides on the PEOX-*b*-PSF-*b*-PEOX end blocks. The degree of hydrolysis was characterized by ^{1}H NMR (Figure 3.8) in a solvent mixture of 90:10 v:v $CDCl_3$:d_6-DMSO by taking the ratio of backbone proton resonances at 3.00 ppm corresponding to ethyleneimine units relative to the peaks at 3.45 ppm on 2-ethyl-2-oxazoline units (Table 3.1).[41] d_6-DMSO was added to the NMR solvent so that the backbone methylene resonances corresponding to the ethyleneimine units appeared at 3.00 ppm. It has been previously suggested that the polar sulfoxide oxygen hydrogen bonds to acidic hydrogens on nitrogen on quaternary ammonium ions in water:DMSO mixtures.[42,43] It is reasoned that this may also occur in the $CDCl_3$:d_6-DMSO solvent mixture utilized for these measurements, and that this may explain the upfield shift of the charged ethyleneimine units relative to amides.

Hydrolyses of PEOX-*b*-PSF-*b*-PEOX copolymers were conducted in a dioxane:water solvent mixture. The PEOX-*b*-PSF-*b*-PEOX copolymers were dissolved in dioxane, then 0.8 moles of aqueous HCl per amide equivalent were added. The polymer precipitated upon addition of the aqueous acid, so these hydrolysis reactions were heterogeneous. ^{1}H NMR spectra of the partially hydrolyzed copolymers showed no changes in the resonances of the PSF blocks. Thus, there is no evidence that the acidic hydrolysis conditions caused any changes in the PSF block structure.

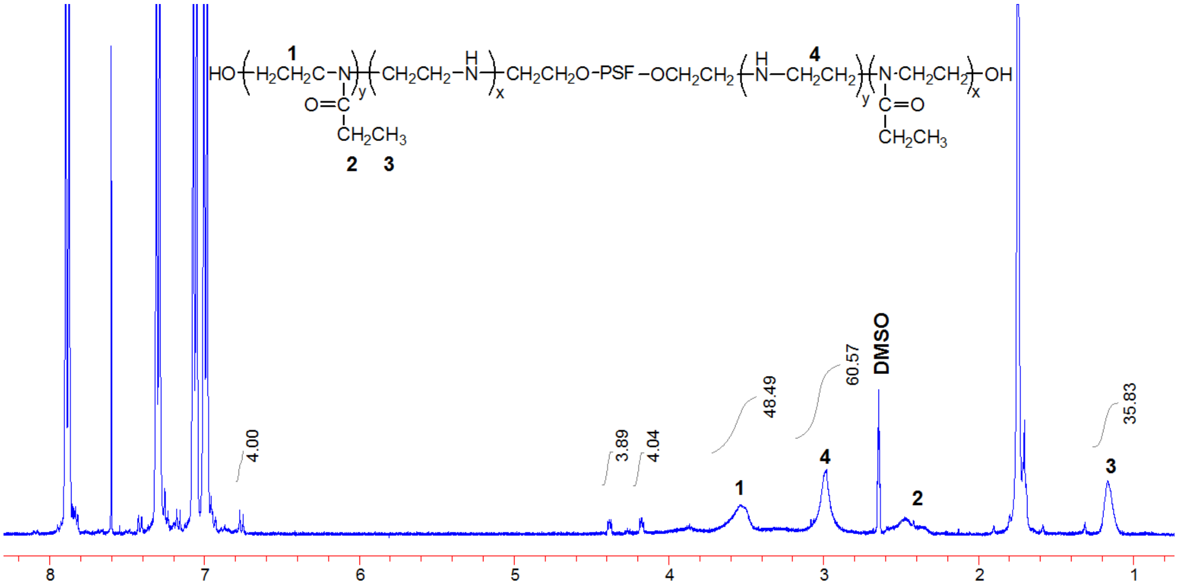

Figure 3.8 ^{1}H NMR spectrum of a PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymer showing the degree of hydrolysis obtained in a $CDCl_3$:d_6-DMSO (90:10 v:v) solvent mixture

3.3.4 Thermal properties of the copolymers

TGA temperature scans (Figure 3.6) of the PEOX-*b*-PSF-*b*-PEOX copolymers obtained under nitrogen revealed that the PEOX portions did not lose weight up to 300°C regardless of their composition in the copolymer. The PSF started to decompose at 450°C and displayed a distinct shoulder on the thermograms corresponding to their higher thermal stability. The copolymer compositions obtained from weight loss TGA data correlated well with those derived from ^{1}H NMR.

The solid-state phase behavior of these block copolymers was evaluated by examining their glass transition temperatures via DSC (Figure 3.9). The T_g's of the PSF blocks relative to the PSF macroinitiator were reduced by 5-15°C as PEOX content increased from 10 to 22 wt % (Table 3.1), indicating some phase mixing. When the

PEOX block length was increased in the PEOX-*b*-PSF-*b*-PEOX copolymers, especially when it was above 20% by weight, a second T_g corresponding to the PEOX component was detected.

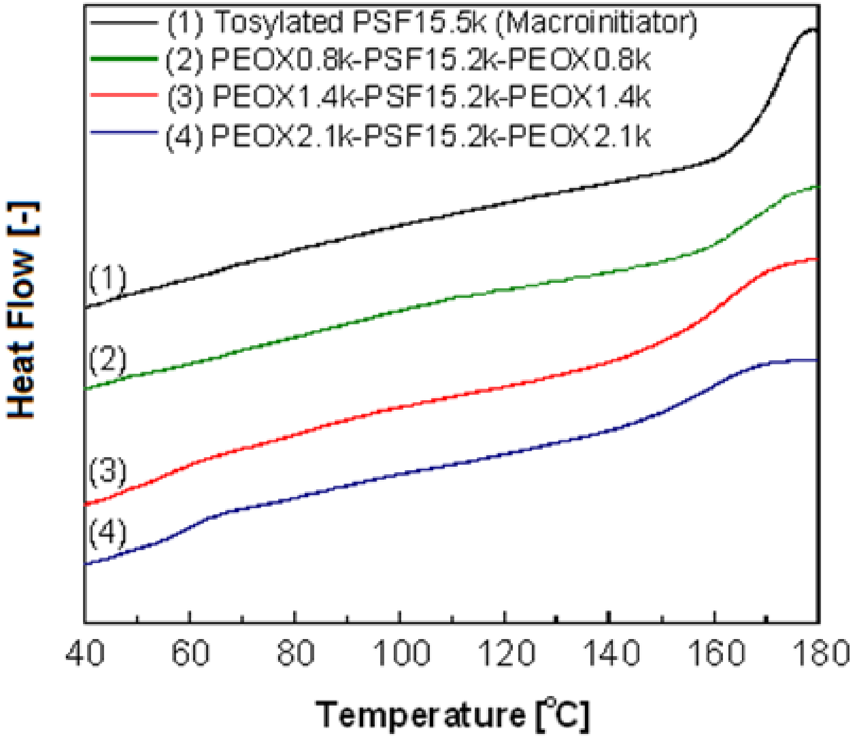

Figure 3.9 DSC thermograms of PEOX-*b*-PSF-*b*-PEOX copolymers with a 15,200 g/mol PSF obtained from second heating scans

DSC studies of the charged PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymers revealed that as the PEI content increased, the glass transition temperatures of the PSF block also increased (Figure 3.10). The increase in T_g of the PSF in the partially hydrolyzed copolymers relative to the macroinitiator can be ascribed to decreased mobility of PSF endgroups in these copolymers, and likely less phase mixing in the block copolymers. There were no detectable T_g's corresponding to the short PEOXcoPEI components and while this may simply be due to the low compositions of the

PEOXcoPEI component, this aspect will require further research to fully understand these phenomena.

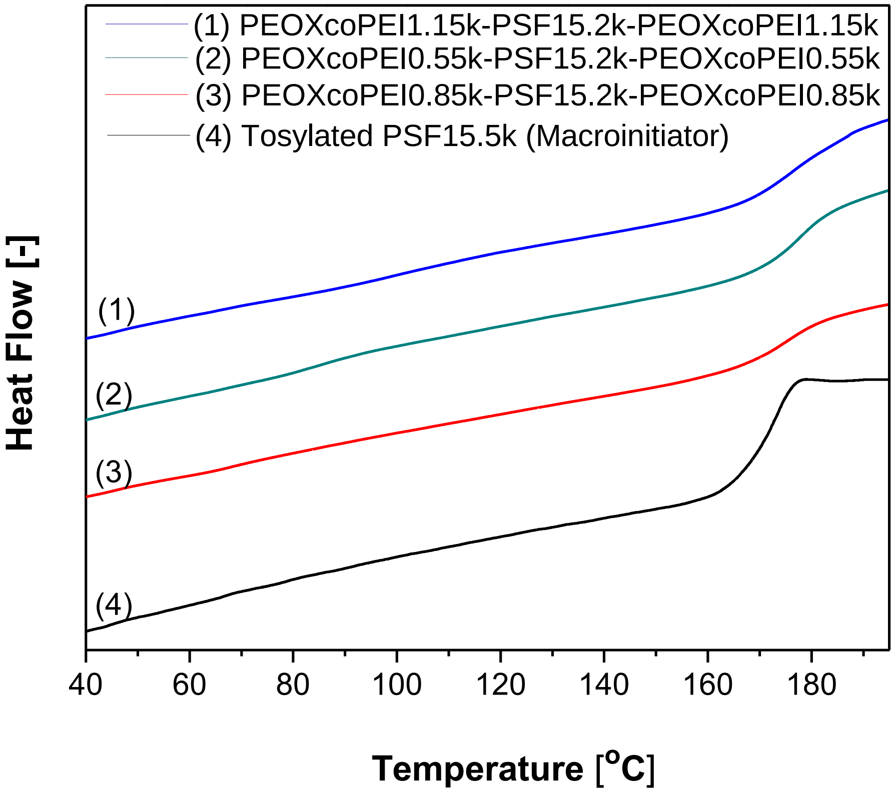

Figure 3.10 DSC thermograms of PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI copolymers with a 15,200 g/mol central PSF block obtained from second heating scans

3.3.5 Water uptake properties of copolymers

The hydrophilicity of a membrane is often characterized by its water uptake.[44] Increasing the composition of PEOX from 10 to 22 wt % in the triblock copolymers with the 15,200 g/mol PSF block leads to an increase in the water uptake to approximately 18 % (Table 3.1). These results compare well with a series of disulfonated PSFs investigated previously by McGrath and Freeman et al. that had excellent water flux and salt rejection properties.[45] Significant differences were not observed between the water uptake of the PEOX-*b*-PSF-*b*-PEOX relative to the PEOXcoPEI-*b*-PSF-*b*-PEOXcoPEI membranes. It is reasoned that this may be at least partially attributable to the low compositions of the end blocks in these materials.

3.4 Conclusions

In this study, the synthesis of amphiphilic triblock copolymers with hydrophobic PSF central blocks and hydrophilic PEOX end blocks was demonstrated via a cationic ring-opening polymerization. The methodology depends on quantitatively converting phenol endgroups on the PSF to aliphatic hydroxyl groups and reaction of the precursor PSF oligomers with an excess of ethylene carbonate proved to be an efficient means for this reaction. Partial hydrolysis of the PEOX amides under acidic conditions resulted in charged PEOXcoPEI end blocks. Depression of the PSF T_g's in the PEOX-*b*-PSF-*b*-PEOX copolymers with short PEOX components suggested that the components were miscible, and a separate PEOX T_g was only detected as the block length of the PEOX was lengthened. By contrast, when the PEOX components were partially hydrolyzed to form PEOXcoPEI, the T_g's of the PSF central block increased, thus suggesting that the increased polarity of the end blocks produced a better phase separated morphology. As expected, water uptake of the copolymers increased with increasing hydrophilic content. The focus of ongoing research is to prepare membranes from these new materials and define relationships among chemical and morphological structure and membrane water flux and salt rejection.

Acknowledgements

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CHAPTER 4 - Molecular Weight Distribution and Endgroup Functionality of Poly(2-ethyl-2-oxazoline) Prepolymers

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Abstract

Control over molecular weight distribution and endgroup functionality is important for prepolymers that are to be further incorporated into block and graft copolymers. Monofunctional, telechelic and heterobifunctional poly(2-ethyl-2-oxazoline) (PEtOx) oligomers were prepared by cationic ring-opening polymerization with different classes of initiators including methyl triflate, activated alkyl halides (e.g., benzyl halides), and non-activated alkyl halides. Endgroup functionalities and molecular weight distributions were studied by SEC, ^{1}H NMR and titrations. PEtOx oligomers initiated with methyl triflate had molecular weight distributions (PDI's) near 1.1 while those initiated with activated benzyl or xylyl halides had PDI's of 1.3-1.4. The difference was attributed to slow propagation of covalent species in the activated halide-initiated reactions that were present in addition to the more active cations. Titrations and ^{1}H NMR showed quantitative endgroup functionality in all cases. Due to the control of functionality and relatively good control over molecular weights and dispersities, it was concluded that these polymers should be suitable as prepolymers for membrane, hydrogel and drug-

delivery applications. By contrast, non-activated alkyl halides initiated these reactions quite slowly and the targeted molecular weights were not achieved.

4.1 Introduction

Monofunctional and telechelic poly(2-oxazoline) prepolymers are excellent candidates for components of block and graft copolymers for a myriad of applications provided that they can be synthesized with reasonable control over molecular weights and their distributions and that they can be perfectly functionalized. They are prepared from five-membered cyclic imino ethers that are polymerized via cationic ring-opening polymerization.[1,2] Ideally, the endgroup functionality can be controlled by employing a functional initiator and/or a termination agent. Monomer compositions can be varied to obtain hydrophilic (e.g. having methyl or ethyl side chains), hydrophobic (butyl, nonyl, phenyl), thermoresponsive (primarily ethyl and *n*- and *iso*-propyl) and fluorophilic (fluorinated phenyl) polymers. Moreover, many different side chain functionalities can be introduced post-polymerization to attach a variety of bioactive compounds or nanoparticles. Poly(2-oxazoline)s have structural similarities to poly(ethylene oxide) (PEO) and polypeptides since they are comprised of a -NCH_2CH_2- backbone and an amide in each repeat unit.[3-6]

The structural features of poly(2-oxazoline)s render it a good polymer for potential biomedical applications.[3,4,7-10] Poly(2-methyl-2-oxazoline) (PMeOx) and PEtOx are of great interest due to their hydrophilicity, biocompatibility,[11-13] stealth behavior,[14-16] and prolonged blood circulation times.[15,17] Promising chemical and biological properties of poly(2-oxazoline)s have revealed a new class of polymer candidates for high-capacity delivery systems for hydrophobic drugs,[18] chemotherapeutic agents,[19] enhanced cellular delivery of proteins,[20] and brain delivery.[21]

Mono- and difunctional PEtOx and PMeOx prepolymers can potentially be incorporated into hydrophilic or amphiphilic linear or graft copolymers or cross-linked networks. These are of interest for polymeric membranes, as components of bioimaging agents and as hydrogels for tissue engineering matrices. A key to those copolymers, gels or nanostructures is the preparation of polyoxazoline oligomers with controllable molecular weights and quantitative endgroup functionality. Mono-[22,23] and difunctional[24] allyl or benzyl halides have been studied as initiators for poly(2-oxazoline)s. These halides are good electrophiles and many of them are commercially available or easily synthesized. Kobayashi *et al.*[25] reported controlled molecular weight hydroxyfunctional telechelic poly(alkyl oxazoline)s utilizing difunctional allylic or benzylic initiators followed by termination with potassium carbonate. Our group previously reported poly(alkyl vinyl ether-*b*-2-ethyl-2-oxazoline)[26] and poly(dimethylsiloxane-*b*-2-ethyl-2-oxazoline)[27] block copolymers using non-activated iodoethyl and activated benzyl iodide-containing macroinitiators respectively.

Numerous studies have been conducted on the synthesis and applications of heterobifunctional PEO oligomers as well as some post-functionalization reactions.[28-34] However, there are few reports of controlled molecular weight poly(2-oxazoline)s with precise endgroup functionality. Reif and Jordan[35] synthesized α-hydroxyalkyl-ω-amino functional amphiphilic PMeOx from *t*-butyldiphenylsiloxyalkyltriflate hydrophobic initiators followed by termination with *boc*-piperazine and subsequent deprotection reactions. Kataoka *et al.*[36] described an alternative method to prepare α-amino-ω-hydroxy-poly(2-oxazoline)s by initiating the polymerization with a phthalimide-functional tosylate initiator and terminating the reactions with sodium hydroxide. This was followed by conversion of the phthalimide group to an amine by treatment with hydrazine. Hoogenboom and Schubert *et al*.[37] demonstrated the synthesis of “clickable” poly(2-oxazoline)s with alkyne and hydroxyl groups utilizing propargyl- and 3-butynyl tosylate initiators. Zalipsky *et al.*[15] prepared hydrophilic poly(2-oxazoline) oligomers with carboxylic acid and hydroxyl groups using ethyl 3-bromopropionate/potassium iodide as the initiator system and utilized potassium hydroxide to hydrolyze the ethyl ester groups and simultaneously terminate the polymerization. Allyl-functional poly(2-oxazoline)s were also prepared by initiating the polymerization with allyl tosylate, and then reacting the allyl endgroup with trimethoxysilane by hydrosilylation.[38]

While many homo- and copolymers containing polyalkyloxazoline compositions have been reported, there has not been sufficient attention given to molecular weight and functionality. This paper describes a detailed investigation of the level of control over molecular weight and endgroup functionality of oligomeric PEtOx’s with the aim of achieving prepolymers for incorporation into block or graft copolymers. Monofunctional, telechelic and heterobifunctional PEtOx oligomers were prepared using different initiators and termination agents, and size exclusion chromatography (SEC) with multiple detectors, ^{1}H NMR spectroscopy, and endgroup titrations were combined to assess the influence of reaction variables on molecular weights and quantitative functionality. Prepolymers with secondary amine and vinylsilane endgroups have been investigated.

4.2 Experimental

4.2.1 Materials

Methyl trifluoromethanesulfonate (methyl triflate, ≥98%), α,α’-dibromo-*p*-xylene (97%), benzyl bromide (98%), *t*-butyl piperazine-1-carboxylate (*boc*-piperazine, 97%), piperidine (>99.5%), triisobutylsilane (TIBS, 99%), ammonium chloride (>99.5%), dichloromethane (>99.8%), dioxane (>99%), calcium hydride (CaH_2, 95%), isopropanol (>99.5%) and standard hydrochloric acid solution (0.1 M) were purchased from Sigma-Aldrich and used as received. Acetonitrile (EMD chemicals, 99.8%) and 2-ethyl-2-oxazoline (Sigma-Aldrich, ≥99%) were dried over CaH_2 and distilled into a flame-dried flask under nitrogen. Sodium iodide (Sigma-Aldrich, ≥ 99.5%) was dried under vacuum at 100 °C. Diethyl ether (99.9%), methanol (99.9%), chloroform (99.98%) and acetone (99.5%) (Fisher Scientific) were used as received. 3-Chloropropylmethyldichlorosilane and 3-chloropropyldimethylchlorosilane (both from Gelest, Inc.), vinylmagnesium bromide (Tokyo Chemical Industry, Inc., 14% in THF, ca. 0.1 M), magnesium sulfate (E.M. Science), trifluoroacetic acid (TFA, Alfa Aesar, 99%) and 0.1 M (standard) KOH (Alfa Aesar) were used as purchased. Deuterated solvents ($CDCl_3$ and D_2O) were acquired from Cambridge Isotope Laboratories, Inc. Cellulose acetate dialysis membranes (Spectrum Laboratories Inc., 1000 MWCO, wet in 0.05% aqueous sodium azide). The SEC mobile phase, *N*-methylpyrrolidone (NMP), was purchased from Fisher Scientific, stirred over phosphorus pentoxide (P_2O_5), distilled under vacuum, and filtered through a 0.2 µm PTFE filter before use. After distillation but before filtration, 4.34 g of lithium bromide (LiBr) was added per liter of NMP to provide a 0.05 M solution. LiBr was purchased from Sigma-Aldrich and dried under vacuum before use at 100 ºC overnight.

4.2.2 Synthesis

4.2.2.1 Synthesis of diiodo-p-xylene

Diiodo-*p*-xylene was prepared from dibromo-*p*-xylene and sodium iodide in acetone by the Finkelstein reaction. A mixture of dibromo-*p*-xylene (2.00 g, 7.58 mmol) and sodium iodide (6.81 g, 45.5 mmol) in acetone (18 mL) was placed in a 100-mL flask and the reaction was conducted at 60 ºC for 48 h. The solvent was removed under vacuum and the residue was dissolved in chloroform (250 mL) and extracted with DI water (500 mL x 3). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum. The residue was recrystallized from *p*-dioxane, and washed with cold dioxane and diethylether. The product was vacuum dried overnight at 50 ºC.

4.2.2.2 Synthesis of 3-iodopropylmethyldivinylsilane and 3-iodopropyldimethylvinylsilane

3-Iodopropylmethyldivinylsilane was prepared similarly to a previously reported procedure.[29] 3-Chloropropylmethyldichlorosilane (6.70 g, 34.5 mmol) was added via a syringe to a flame-dried, 250-mL round-bottom flask with a magnetic stir bar under N_2. Vinylmagnesium bromide (98 mmol, 98 mL of a 1 M vinylmagnesium bromide solution in THF) was transferred into the flask that was in an ice bath. The reaction was conducted at 60 °C for 24 h. The reaction mixture was allowed to precipitate the salt byproducts at RT for 1 h. The liquid portion was decanted and concentrated using a rotary evaporator. The crude product was diluted with dichloromethane (200 mL) and washed 4x with saturated aqueous ammonium chloride solution (500 mL each) in a 1-L separatory funnel. Anhydrous magnesium sulfate was added to the organic layer to remove residual water, followed by vacuum filtration. Dichloromethane was removed under vacuum, and the product, 3-chloropropylmethyldivinylsilane, was vacuum distilled at 75 ºC, ~ 0.8 Torr, and collected as a colorless liquid. ^{1}H NMR confirmed the expected structure.

Synthesis of 3-iodopropyldimethylvinylsilane was performed in a similar procedure utilizing 3-chloropropyldimethylchlorosilane (10.0 g, 58.4 mmol) and vinylmagnesium bromide (70.2 mmol, 70.2 mL).

4.2.2.3 Synthesis of monofunctional poly(2-ethyl-2-oxazoline) oligomers with piperidine or piperazine endgroups

A procedure for the synthesis of a PEtOx oligomer initiated with methyl triflate and terminated with an aliphatic amine is provided. Methyl triflate (0.280 mL, 0.404 g, 2.46 mmol), EtOx monomer (12.5 mL, 12.3 g, 124 mmol), and acetonitrile (12.5 mL) were syringed into a flame-dried, 100-mL, round-bottom flask containing a magnetic stir bar and enclosed with a rubber septum bound with steel wire at room temperature. The solution was stirred for ~ 5 min. Four different oligomers were prepared with the same initiator and monomer concentrations, and the polymerizations were conducted at 25, 50, 65 and 80 ºC. The monomer conversion was monitored using ^{1}H NMR spectroscopy by analyzing samples prepared from 0.1-mL aliquots from the reaction mixture in 0.4-0.5 mL $CDCl_3$. The polymerization was terminated with an excess of piperidine (2.43 mL, 2.10 g, 24.6 mmol) or *boc*-piperazine (1.83 g, 9.84 mmol) solutions in 20 mL of acetonitrile. The solutions were stirred overnight and the polymers were isolated by adding each solution dropwise into stirring diethylether (300 mL). Each PEtOx oligomer was dried under vacuum at 50 ºC overnight and diluted to 200 mL with DI water. The polymer solution was placed in a 1000 g/mol MWCO cellulose acetate dialysis membrane and dialyzed against 4 L of DI water for 48 h. The contents of the dialysis membrane were transferred to a 250-mL flask and freeze-dried. ^{1}H NMR confirmed the expected chemical structures.

Deprotection of the *boc*-piperazine endgroups was performed utilizing a similar procedure to that reported previously.[11] A $PEtOx_{62}$-*boc*pip (700 mg, 0.113 mmol) was dissolved in a 4-mL mixture of 95:2.5:2.5 TFA:water:TIBS (v:v:v) and stirred for 30 min. The reaction mixture was diluted with 5 mL of methanol and 2 mL of water. The solution was dialyzed against 4 L of DI water for 48 h and freeze-dried.

Synthesis of *boc*-piperazine-terminated PEtOx oligomers with benzyl bromide as the initiator followed a similar procedure to that described above.

4.2.2.4 Synthesis of diiodo-p-xylene or dibromo-p-xylene-initiated and piperazine-functional telechelic poly(2-ethyl-2-oxazoline) oligomers

An exemplary procedure for synthesizing a diiodo-*p*-xylene-initiated and piperazine-functional telechelic PEtOx is provided. Diiodo-*p*-xylene (0.212 g, 0.593 mmol) was placed in a dry, 100-mL, round-bottom flask. EtOx monomer (3.61 mL, 3.54 g, 35.7 mmol) and acetonitrile (3.5 mL) were added via a syringe to the flask enclosed with a rubber septum, and the solution was stirred for ~5 min to dissolve the initiator. The temperature was raised to 60 °C. The polymerization was maintained for 4 h and 40 min (~85 % conversion as measured by ^1H NMR). The reaction mixture was cooled to RT and the polymer was terminated with *boc*-piperazine (1.10 g, 5.91 mmol) in 10 mL of acetonitrile and stirred overnight. The telechelic polymer was recovered by precipitation in diethylether, collected by filtration and dried under vacuum at 50 ºC overnight. The polymer solution was dialyzed against 4 L of DI water for 48 h using a 1000 g/mol MWCO cellulose acetate dialysis membrane and freeze-dried. The product yield was 80-85 %.

Deprotection of the *boc*-piperazine endgroups followed the same procedure described previously using a *boc*Pip-PEtOx$_{59}$-*boc*pip (700 mg, 0.111 mmol, 0.222 mmol *boc*-piperazine endgroups).

Telechelic PEtOx oligomers prepared from dibromo-*p*-xylene were synthesized using the same procedures for the polymerization and deprotection reactions described above with adjusted stoichiometric amounts of reagents.

4.2.2.5 Synthesis of heterobifunctional poly(2-ethyl-2-oxazoline)s with one vinylsilane endgroup and one piperazine endgroup

An exemplary procedure for preparing a heterobifunctional PEtOx with one terminal vinyl group and a piperazine group at the other end is provided. EtOx monomer (8.06 mL, 7.91 g, 79.8 mmol) was charged via a syringe to a 100-mL, flame-dried, round-bottom flask enclosed with a rubber septum. 3-Iodopropyldimethylvinylsilane (0.405 g, 1.59 mmol) and acetonitrile (8 mL) were syringed into the flask, and the solution was stirred for ~5 min at RT. The reaction flask was placed in an oil bath and the temperature was raised to 60 °C. The cationic polymerization was monitored using ^{1}H NMR, and at ~74% conversion of monomer (7 h, 20 min), the growing chains were terminated with an excess of *boc*-piperazine (1.48 g, 7.95 mmol) solution in acetonitrile (15 mL). The solution was stirred overnight. The polymer was recovered by precipitation in diethylether, then dialyzed and freeze-dried as described above.

4.2.2.6 Synthesis of divinyl and piperidine-functional poly(2-ethyl-2-oxazoline) oligomers

Synthesis of a 3-iodopropylmethyldivinylsilane-initiated and piperidine-terminated PEtOx oligomer followed a similar procedure to that described above, with

EtOx (8.38 mL, 8.23 g, 83.0 mmol), 3-iodopropylmethyldivinylsilane (0.365 g, 1.37 mmol), acetonitrile (8.20 mL), and piperidine (0.677 mL, 0.584 g, 6.85 mmol). The polymerization was terminated at ~67% conversion of monomer.

4.2.3 Characterization

^{1}H NMR spectra were obtained using a JEOL Eclipse Plus 500 NMR operating at 500.16 MHz or a Varian Unity Plus spectrometer operating at 399.87 MHz at room temperature with 64 or 128 scans. The spectra of the polymers and initiators were obtained in D_2O (0.10 g/mL) and $CDCl_3$ (0.03 g/mL), respectively.

Size exclusion chromatography (SEC) was conducted on the materials to measure molecular weight distributions. The column set consisted of 3 Agilent PLgel 10-μm Mixed B-LS columns 300x7.5mm (polystyrene/divinylbenzene) connected in series with a guard column of the same stationary phase. An isocratic pump (Agilent 1260 infinity, Agilent Technologies) with an online degasser (Agilent 1260), autosampler and column oven was used for mobile phase delivery and sample injection. A system of multiple detectors connected in series was used for the analysis. A multi-angle laser light scattering (MALLS) detector (DAWN-HELEOS II, Wyatt Technology Corporation), operating at a wavelength of 658 nm, a viscometer detector (Viscostar, Wyatt Technology Corp.), and a refractive index detector operating at a wavelength of 658 nm (Optilab T-rEX, Wyatt Technology Corp.) provided online results. The system was corrected for interdetector delay, band broadening, and the MALLS signals were normalized using a 21,000 g/mol polystyrene standard obtained from Agilent Technologies or Varian. Data acquisition and analysis were conducted using Astra 6 software from Wyatt Technology Corp. A universal calibration curve was constructed using polystyrene standards with narrow PDI's. Seventeen standards were used to establish the calibration curve with molecular weights ranging from 2000 to 1.4 million g/mol, but the low molecular weight range was of particular interest for this study. Five standards in the range of 2000 to 10,000 g/mol were used to cover this range. The uncertainty of the universal calibration molecular weight measurements of the PEtOx homopolymers was determined by preparing and running replicate samples of 3 different methyl triflate-initiated PEtOx oligomers in the range of 7,000 g/mol. Each sample was prepared 3 times and each specimen was run and analyzed 3 separate times producing 9 analyses of each of the 3 samples. The variation in M_n was 2-3% and the variation in the PDI was 0-2%. All of these measurements were carried out based on the same calibration curve and therefore this evaluation takes into account the sample preparation and run-to-run variations of the SEC samples. Validation of the run conditions was performed by monitoring the molar mass of a known molecular weight polystyrene sample by light scattering with every sample set.

Titrations were performed to determine the number average molecular weights of poly(2-oxazoline) oligomers by endgroup analysis. An Orion 3 Star pH meter with gel-filled pH electrodes was utilized for pH measurements. A piperidine- or piperazine-functional polymer solution (~200-300 mg in 20 mL) in water or isopropanol, respectively, was charged to a 50-mL, 3-necked, round-bottom flask containing a stir bar. The solution, while being stirred slowly, was titrated with a 0.05 M $KOH_{(aq)}$ or $HCl_{(aq)}$ standard solution by addition of 0.05-mL increments using a micro-pipette. Equivalence (inflection) points were determined by plotting the first derivative of the pH curve ($\Delta pH/\Delta V$) against titrant volume.

4.3 Results and Discussion

Prepolymers synthesized with three classes of initiators based on their rates of initiation and the nucleophilicity of the counterions have been compared. These include methyl triflate (fast initiation, weakly nucleophilic counterion), activated alkyl halides including initiators with benzyl and xylyl groups (slower initiation, more nucleophilic counterions), and non-activated alkyl iodides (very slow initiation, more nucleophilic counterions). While triflates are ideal with regard to oligomerization conditions, their sensitivity to moisture makes triflate macromonomers difficult to handle and purify. Alkyl halide initiators are much more versatile provided oligomers with good molecular weight distributions and terminal functionality can be achieved.

4.3.1 Monofunctional poly(2-ethyl-2-oxazoline) oligomers initiated by methyl triflate and terminated with secondary amines

A series of methyl triflate-initiated PEtOx oligomers were prepared at different temperatures (25, 50, 65 and 80 ºC) with the same monomer and initiator concentrations to serve as control materials and their molecular weights and endgroup structures were analyzed (Figure 4.1, Table 4.1). The propagating cationic chains were terminated at 25 °C with either piperidine or *boc*-piperazine in a similar manner to that described by Luxenhofer *et al.*[11] Monomer conversion was monitored using ^{1}H NMR spectroscopy from the integral ratios of resonances corresponding to the monomer and polymer backbone (-NCH$_2$CH$_2$-)[23,39], and the polymers were terminated at 80-100% conversion. Polymers with *boc*-piperazine endgroups were deprotected by cleaving the *t*-butyloxycarbonyl groups under acidic conditions to form secondary amine-functional chains.

Table 4.1 Methyl triflate-initiated PEtOx oligomers prepared at different temperatures

Reaction Temperature (°C)	Termination Agent	Target[a] M_n	M_n ^{1}H NMR	M_n Titration	M_n[b] SEC Universal Calibration	M_n[b] SEC Light Scattering	PDI
80	*boc*-Piperazine	5200	6250	5750 ± 250	6800	6500	1.13
65	Piperidine	4500	5450	5650 ± 150	6600	6200	1.15
50	Piperidine	4850	5650	6000 ± 50	7000	6800	1.12
25	Piperidine	4400	4550	--	6100	5900	1.11

[a] Corrected from the monomer conversion at termination and includes the terminal *boc*-piperazine or piperidine endgroup

[b] The dn/dc was 0.0515 with a standard deviation of ±3%.

The structures and endgroups of these monofunctional PEtOx oligomers were characterized using ^{1}H NMR (Figure 4.2a-c), titrations and SEC (Table 4.1). Polymerization resulted in the formation of broad peaks around 3.45 ppm due to methylene backbone protons ($-NCH_2CH_2-$) and pendent group protons at 2.25 ($-CH_2-$) and 0.90 ppm ($-CH_3$). The methyl endgroup introduced in the initiation step resonated at 2.8 and 3.0 ppm, thus reflecting cis and trans amide endgroups. The signals around 1.40 (Figure 4.2a) and 1.30 ppm (Figure 4.2b) are assigned to piperidine (6H) and *t*-butyl (9H) in *boc*-piperazine endgroups, respectively. The integral ratios of methyl protons on the initiator end to piperidine or *t*-butyl groups on the terminated end were utilized to assess the efficiency of termination (1:1 endgroup ratio). In all cases, the ^{1}H NMR spectra suggested that these polymers were quantitatively terminated with secondary amines.

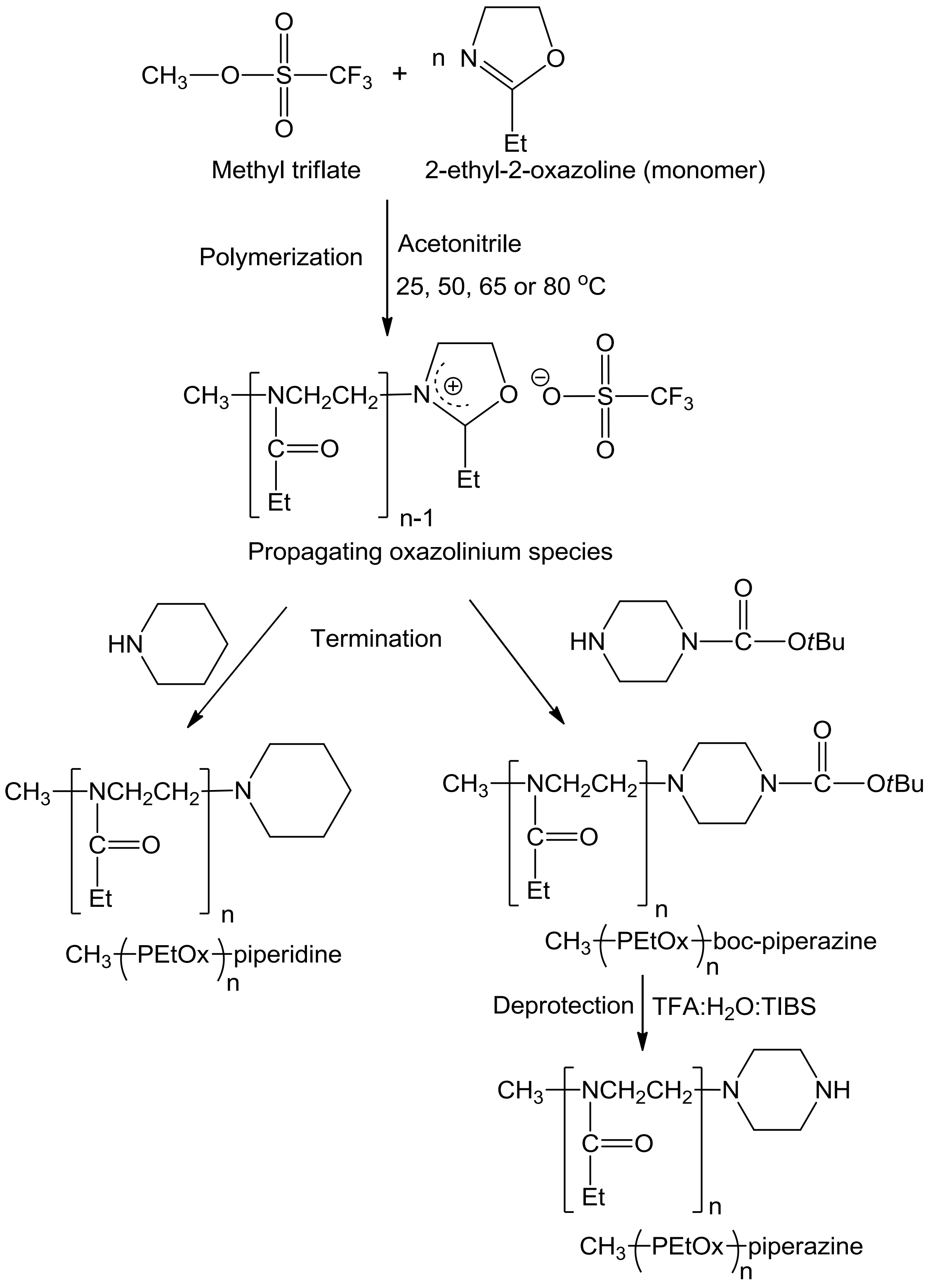
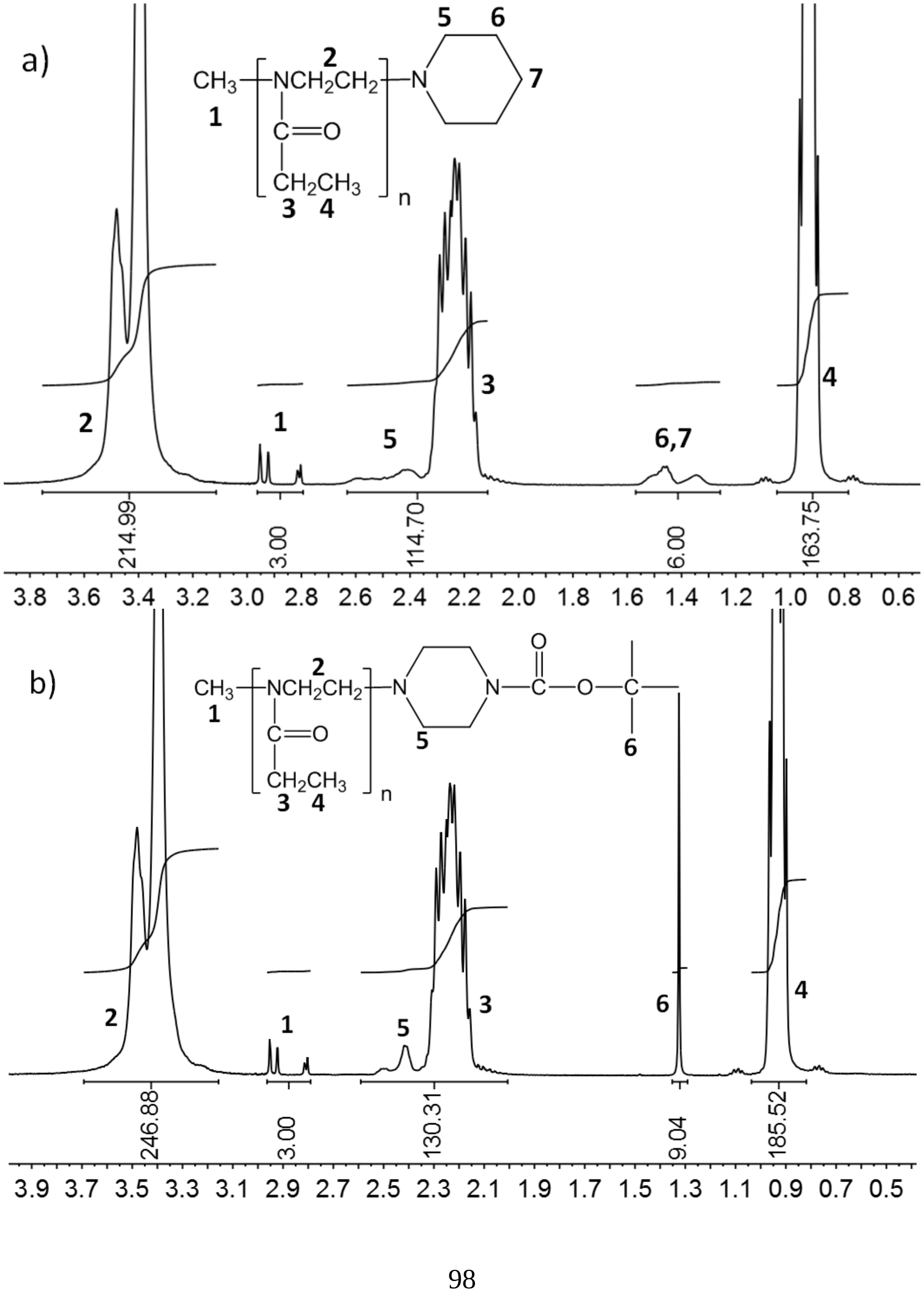


Figure 4.1 Synthesis of controlled molecular weight poly(2-ethyl-2-oxazoline) oligomers with piperidine or piperazine endgroups

Number average molecular weights were calculated by comparing the ratio of the integrals of PEtOx proton resonances to the endgroup protons (CH_3 and either piperidine or *t*-butyl). Disappearance of the *t*-butyl resonances upon deprotection of *boc*-piperazine also indicated quantitative deprotection (Figure 4.2c).



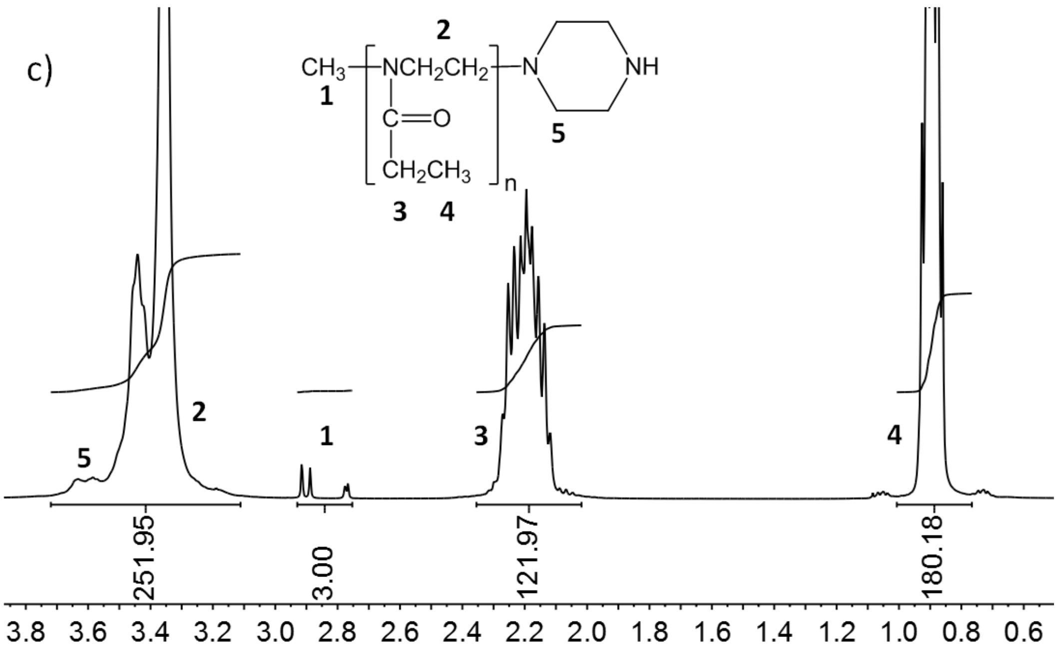


Figure 4.2 ^{1}H NMR spectra of a) CH_3-PEtOx-piperidine synthesized using methyl triflate as the initiator at 65 ºC and terminated with piperidine, b) CH_3-PEtOx-*boc*-piperazine synthesized using methyl triflate as the initiator at 80 ºC and terminated with protected piperazine, and c) CH_3-PEtOx-piperazine deprotected form of CH_3-PEtOx-*boc*-piperazine prepared at 80 ºC obtained in D_2O

The piperazine and piperidine endgroups were titrated to determine the concentrations of amine and to correlate this data with the ^{1}H NMR endgroup analyses. Titrations showed the expected two inflection points for piperazine endgroups and one for piperidine-terminated polymers. Piperazinium-terminated polymers were titrated with base and the titrant volumes between the two inflection points corresponded to the number of amine endgroups. Piperidine-functional polymers were titrated with acid. While the concentrations of amines measured by titration matched the endgroup data obtained from ^{1}H NMR reasonably well, it is reasoned that the titration data should be more accurate due to inherent line broadening in the NMR spectra. The molecular weights obtained via these endgroup analyses were always somewhat higher than the targeted values and this is attributed to the loss of some low molecular weight species in the precipitation and dialysis isolation processes.

Molecular weights of the PEtOx oligomers were measured by SEC in *N*-methylpyrrolidone containing 0.05 M LiBr and compared to number average molecular weights (M_n’s) calculated from the endgroup analyses (Table 4.1). All four polymers initiated with methyl triflate produced unimodal, symmetrical chromatograms (Figure 4.3). M_n’s were calculated from the SEC curves using both a universal calibration that was prepared with a series of monodisperse polystyrene standards using the viscometric and differential refractive index detectors, and also by the MALLS static light scattering and differential refractive index detectors. The intensity of the Raleigh ratio ($R(\theta)$) signal from the light scattering detector is a function of the refractive index increment (dn/dc), the sample concentration, and the molar mass of the molecules in solution. Due to the dependence on molar mass, light scattering is more sensitive to higher molecular weight polymers as opposed to the lower oligomeric range investigated herein, whereas the refractive index signal only depends on concentration (not on molar mass). Thus, SEC values from the universal calibration may be more accurate than light scattering for these low molecular weight oligomers.

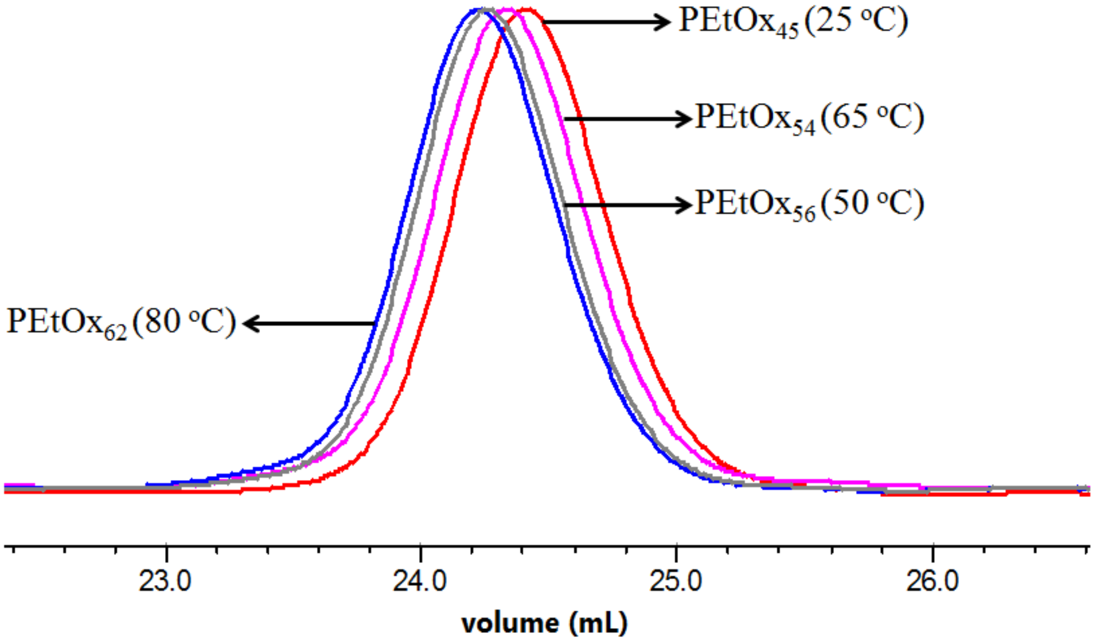


Figure 4.3 Refractive index chromatograms of PEtOx oligomers initiated with methyl triflate and polymerized at 25, 50, 65 and 80 °C

The refractive index increment (dn/dc) is critical to the calculation of molar mass by light scattering. It is also important for calculating molar mass using universal calibration because an accurate measure of the concentration of the polymer molecules at each increment is necessary to determine the molar mass averages for a polymer distribution. The dn/dc's of PEtOx in NMP with 0.05M LiBr were determined using two methods. The dn/dc of the samples used for the uncertainty study was measured for each replicate based on the assumption of 100% recovery. The average dn/dc of the 27 data points was 0.0514. A high molecular weight standard was used to determine a dn/dc of 0.0516 offline. Therefore a dn/dc value of 0.0515 was used to calculate M_n's of the methyl triflate-initiated polymers in Table 4.1.

We also compared molecular weight distributions of two PEtOx oligomers that were polymerized at 80 °C, where one was terminated immediately after monomer conversion (4 hours), and the other was maintained at 80 ºC well after all of the monomers had been consumed (24 hours). The polymer that had been heated for ~24 hours had a prominent high molecular weight shoulder in the SEC chromatogram, whereas the polymer heated for only 4 hours had a symmetrical unimodal peak and a PDI of 1.13. Moreover, the polymer that had been heated too long could not be quantitatively terminated with the aliphatic amines. This may be attributed to enamine formation and chain coupling as monomer was depleted as previously suggested by Litt *et al.*[40] All of this data on molecular weights and endgroup structures of PEtOx oligomers suggests strongly that materials with molecular weights near the targeted values with narrow PDI's and quantitative endgroup functionality can be prepared with methyl triflate as an initiator (Table 4.1). It is important, however, to terminate the reactions at times close to complete monomer conversion.

4.3.2 Comparison of prepolymers initiated with activated benzyl and xylyl halides

Benzyl and xylyl halide initiators were investigated due to their ease of handling and because mono- or telechelic prepolymers, respectively, are accessible by this method.[25,41] Monofunctional PEtOx oligomers were initiated with benzyl bromide at 25, 50 and 65 °C under identical reaction conditions to those conducted with methyl triflate so that the degree of control over molecular weight and endgroup functionality could be directly compared. ^{1}H NMR again indicated quantitative termination with *boc*-piperazine as confirmed by the integral ratios of the benzyl endgroup aromatic protons (5H) at 7.10-7.35 ppm relative to the *t*-butyl resonances (9H) (Figure 4.4). M_n values were calculated using the relative integral values of PEtOx protons in the repeat units and the endgroups (Table 4.2).

Table 4.2 Alkyl halide-initiated monofunctional and telechelic PEtOx oligomers terminated with *boc*-piperazine

Initiator	Temperature (°C)	Target[b] M_n	M_n ^{1}H NMR	M_n Titration	M_n SEC Universal Calibration	PDI
Benzyl Bromide	25	4650	6050	5900 ± 100	4700	1.36
Benzyl Bromide	50	4850	6250	6100 ± 250	4900	1.33
Benzyl Bromide	65	5000	6150	5650 ± 150	5600	1.30
Dibromo-*p*-xylene	60	7200	8300	8600 ± 150	6300	1.45
Diiodo-*p*-xylene	60	5550	6750	6975 ± 125	5000	1.37
Monovinyl alkyl iodide	60	4000	7300	--	6500	1.26
Divinyl alkyl[a] iodide	60	4300	7250	6150 ± 125	5600	1.33

[a] Terminated with piperidine

[b] Corrected for the extent of monomer conversion at termination and includes the *boc*-piperazine or piperidine endgroups

SEC results, however, showed that when employing the same dn/dc value for the benzyl and xylyl halide-initiated polymers that was measured for the methyl triflate-initiated oligomers, the indicated SEC sample recovery values were higher than 100% (indicating that the dn/dc value was too low for those polymers). The refractive index increment is independent of molar mass as long as the chemical structure is independent of molar mass. For the polymers in Table 4.2 that were initiated using benzyl or xylyl halides, this is not the case. Just one aromatic ring on the endgroup (or in the middle of the chain for xylyl halide initiation) impacted the dn/dc sufficiently to cause deviations in calculations of molecular weights, and the impact was greater for lower molecular weights as the weight percentage of the aromatic groups increased.

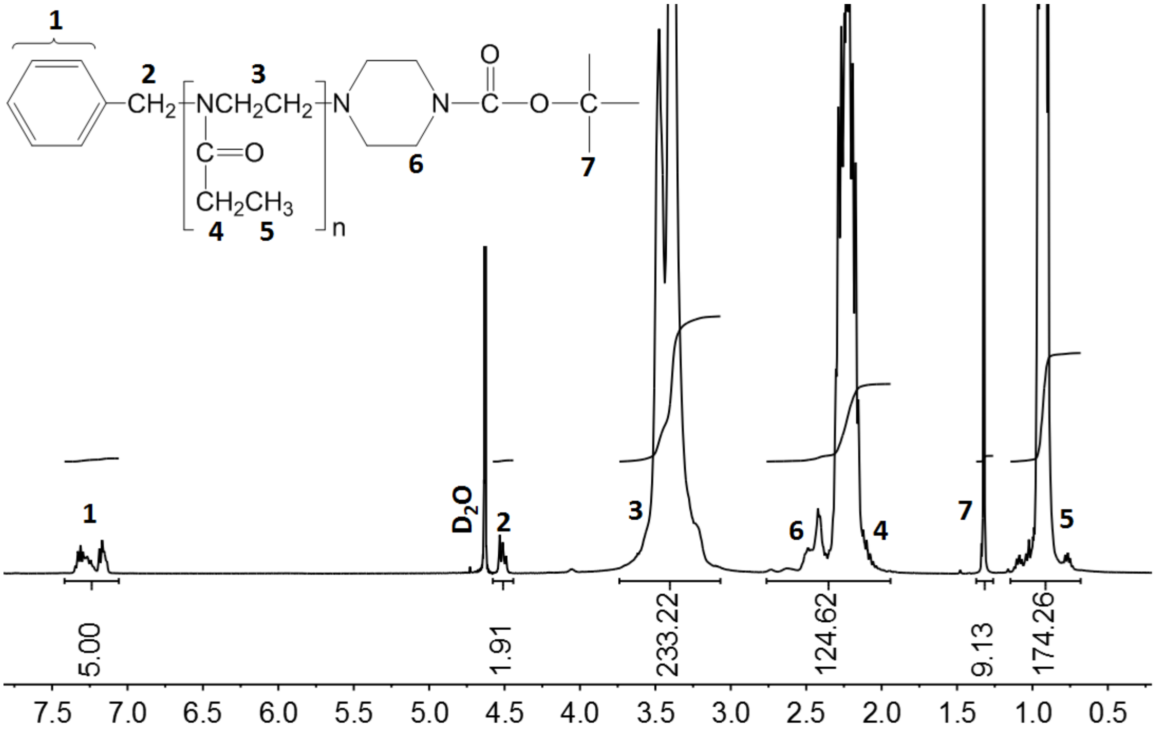
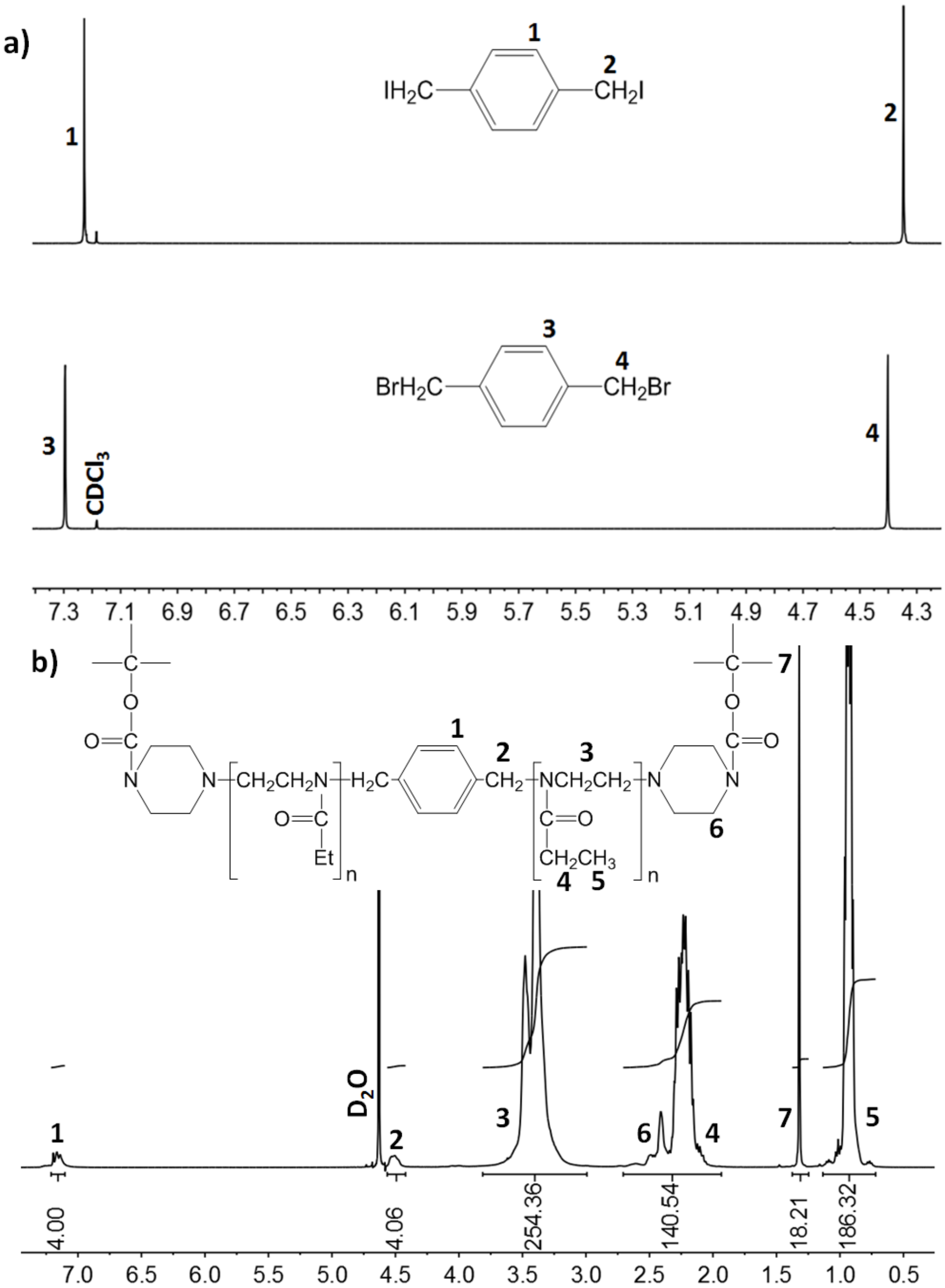


Figure 4.4 ^{1}H NMR spectrum of a PEtOx oligomer that was initiated with benzyl bromide at 25 ºC and terminated with *boc*-piperazine obtained in D_2O

This implies that dn/dc varied as a function of molecular weight and therefore it varied significantly across the distribution. Thus, it was necessary to estimate the dn/dc values of the benzyl and xylyl-initiated PEtOx oligomers shown in Table 4.2 by adjusting them for each sample until the SEC software suggested 100% recovery of the sample. It is noted that the molecular weights from SEC were higher than the titration values for the polymers shown in Table 4.1 that were initiated with methyl triflate, while the SEC values for the polymers in Table 4.2 with the aromatic initiators were lower than their titrated values. This may indeed be attributable to a variance in dn/dc across the molecular weight distribution for those in Table 4.2 prepared with aromatic initiators due to the high refractive index of the initiator.

We and others have observed that 2-ethyl-2-oxazoline polymerizations conducted using alkyl (including benzyl) halides proceed via a mixture of covalent and cationic species (oxazolinium ions) due to some attack on the terminal cationic ring by the relatively nucleophilic halide counterions.[23,39,42] The reactivity of cationic propagating chains is much higher compared to the covalently-bonded species.[43] Thus, it is reasonable that polymers from benzylic halide initiators should have somewhat broader molecular weight distributions compared to triflate-initiated polyoxazolines. Consistent with this premise, PDI's for these benzyl halide-initiated polymers were ~1.3 whereas those prepared with methyl triflate were ~1.1 (Tables 4.1 and 4.2). RI chromatograms of the benzyl bromide initiated oligomers also showed a slight tailing on the low molecular weight side relative to the very symmetrical curves from the methyl triflate-initiated polymers. However, the combined facts that quantitative piperazine functionality is obtained with the benzyl halide initiated polymers and that both covalent and ionic propagating species are present demonstrate that both the covalent and ionic species react with piperazine in the termination step. This is important because even though two types of propagating species are present, quantitative endgroup functionality is still obtained.

Telechelic PEtOx oligomers were prepared using dibromo- and diiodo-*p*-xylene initiators (Table 4.2). ^{1}H NMR indicated the successful conversion of dibromo-*p*-xylene to diiodo-*p*-xylene (Figure 4.5a) and the melting point of the diiodo-functional initiator was 178-179 ºC, consistent with literature values.[44] Chemical structures of the difunctional PEtOx oligomers with quantitative *boc*-piperazine endgroups and their deprotected forms were confirmed by ^{1}H NMR and titrations (Figures 4.5a-b). Aromatic and methylene protons from the initiator resonated at 7.15 and 4.50 ppm, respectively. The integral values of *t*-butyl protons (18 H) on the endgroups and resonances from the initiator (4H) indicated quantitative termination and the formation of difunctional polymers (Figure 4.5b). The relative signal intensities between endgroup and initiator protons also showed the absence of side reactions. Disappearance of the *t*-butyl proton resonances upon deprotection of the chain ends indicated complete conversion to secondary amine endgroups (Figure 4.5c). ^{1}H NMR also showed the expected downfield shifts of the protonated piperazinium resonances as they were formed under acidic conditions. Relative ratios of the integrals of PEtOx proton resonances to the endgroup or initiator proton resonances in the telechelic materials were used to calculate M_n (Table 4.2), and the results were consistent with those obtained with the monofunctional benzyl bromide initiator. Molecular weight distributions of ~1.4 were obtained. As expected, these were somewhat broader than those obtained with triflate initiators, but still quite reasonable. Thus, these telechelic oligomers have good potential to be used as prepolymers for developing step-growth block copolymers and as components of novel hydrogels.

a)
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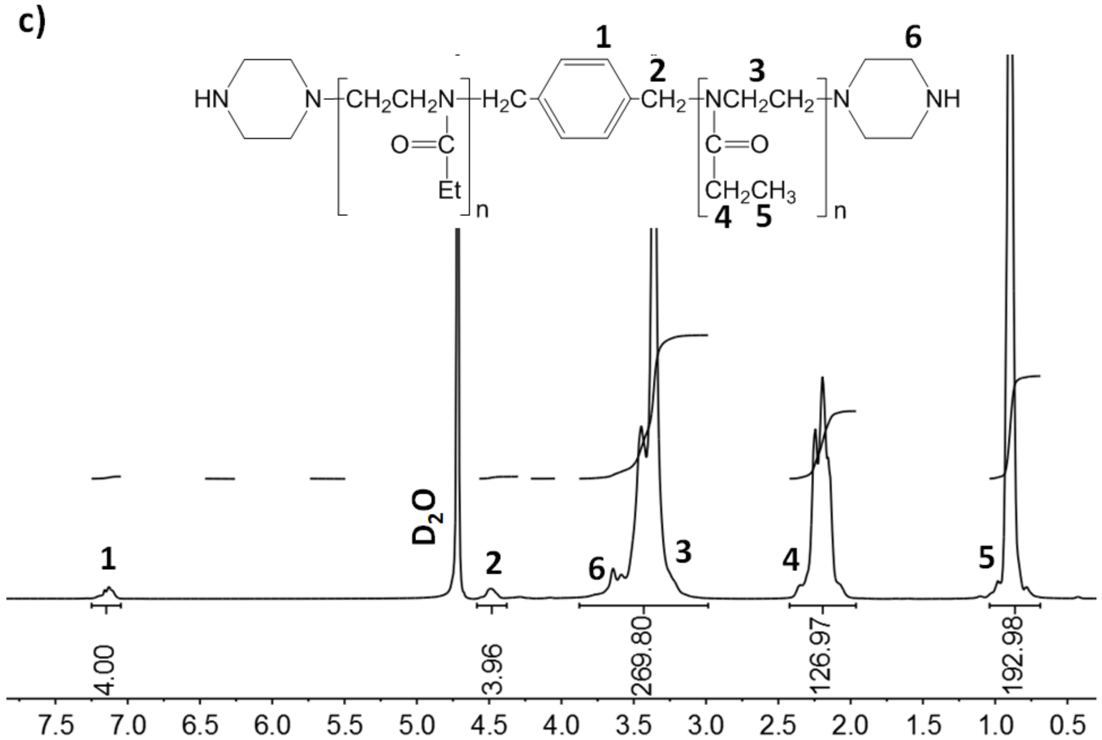


Figure 4.5 ^{1}H NMR spectra of a) dibromo- and diiodo-*p*-xylene initiators obtained in $CDCl_3$, b) a telechelic PEtOx oligomer polymerized using diiodo-*p*-xylene at 60ºC and terminated with *boc*-piperazine obtained in D_2O, and a c) piperazine-functional telechelic PEtOx (deprotected form) obtained in D_2O

4.3.3 Heterobifunctional PEtOx oligomers from vinylsilane-functional non-activated alkyl halide initiators

Heterobifunctional PEtOxs with vinylsilane functionalities on one chain end and an amine group on the other were attempted using mono- and divinylsilylpropyl iodide initiators (Figure 4.6). These initiators containing one or two vinyl groups were synthesized from 3-chloropropylchlorodimethylsilane and 3-chloropropyldichloromethylsilane, respectively, by reaction with vinylmagnesium bromide. The alkyl bromides were then converted to the corresponding iodides by a

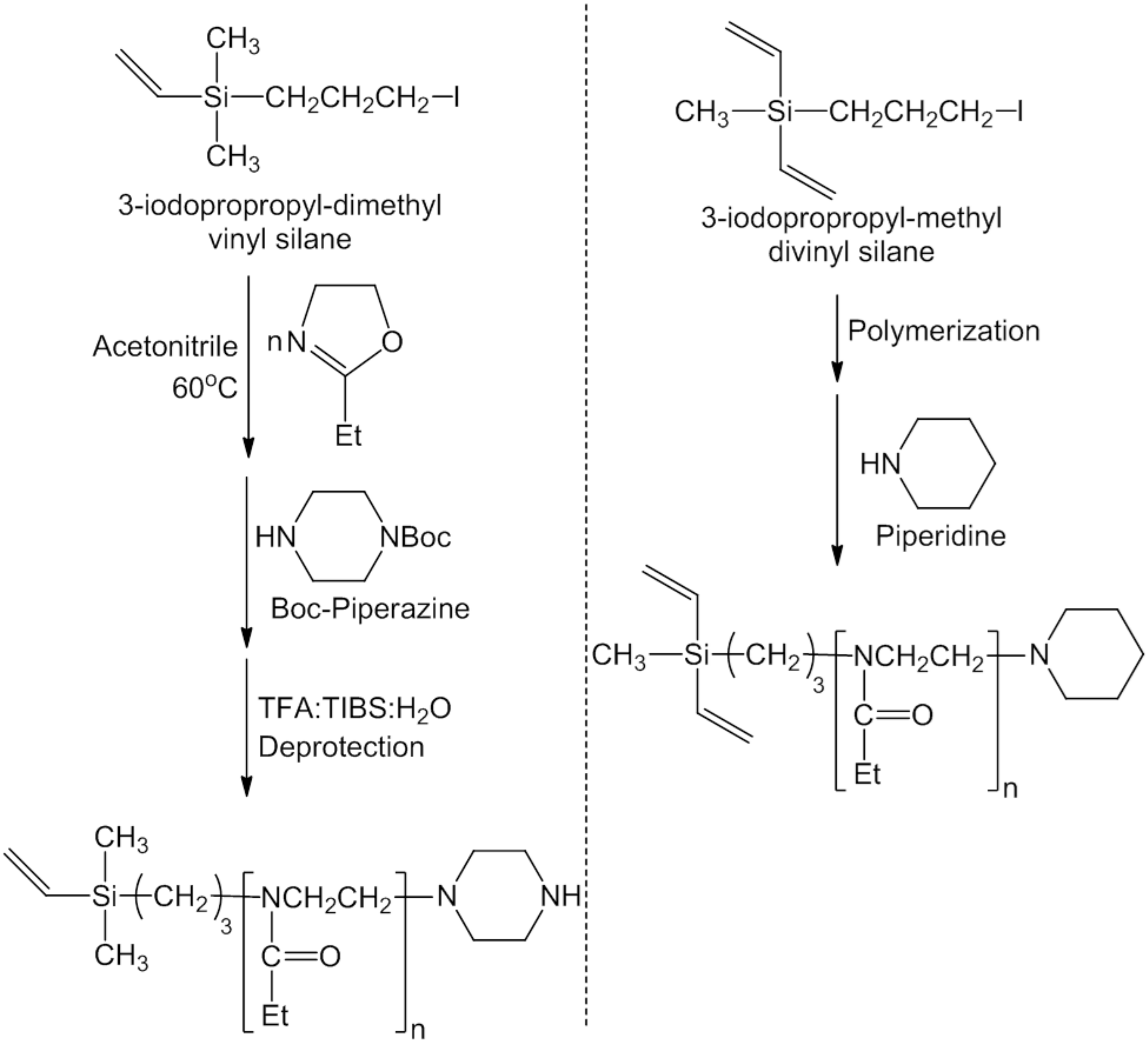
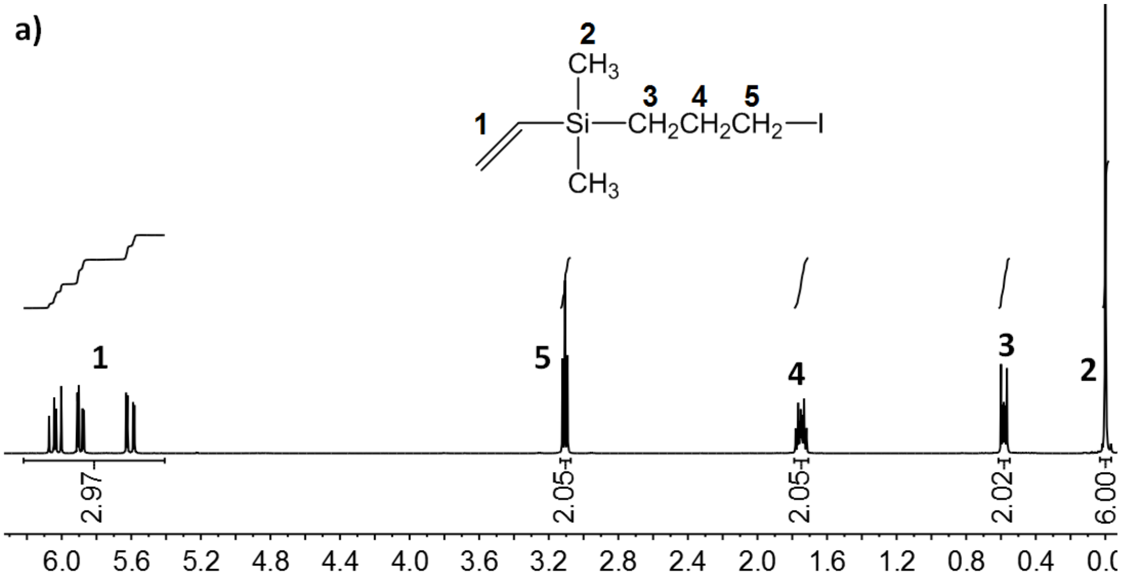


Figure 4.6 Synthesis of heterobifunctional PEtOx oligomers initiated by mono- or divinyl alkyl iodides and terminated with aliphatic amines

Finkelstein reaction as described previously.[28-30] The molecular structures of these mono- and divinylsilyl alkyl iodides were confirmed by ^{1}H NMR (Figures 4.7a and 4.8a). The methylene protons adjacent to the silicon atom resonated at 0.6 ppm, and the middle (-CH_2) protons on the propyl group were observed at 1.7 ppm. The signals at 3.1 ppm were assigned to the methylene group directly attached to the iodine. Vinyl group protons appeared at 5.6-6.2 ppm. ^{1}H NMR analyses of the heterobifunctional PEtOx oligomers also showed the expected chemical structures (Figures 4.7b and 4.8b). Endgroup analyses again confirmed quantitative termination by either piperidine or *boc*-piperazine. Methyl and vinyl groups attached to the silicon atom remained intact under acidic conditions during cleavage of the protecting groups (Figure 4.7c). However, the initiation rate with these initiators relative to propagation was too slow and there were substantial amounts of very low molecular weight species in the molecular weight distributions. Thus, it was reasoned that the combination of very slow initiation with the non-activated alkyl iodides combined with the nucleophilicity of the iodide counterions that caused some slowly-propagating species resulted in ill-defined products.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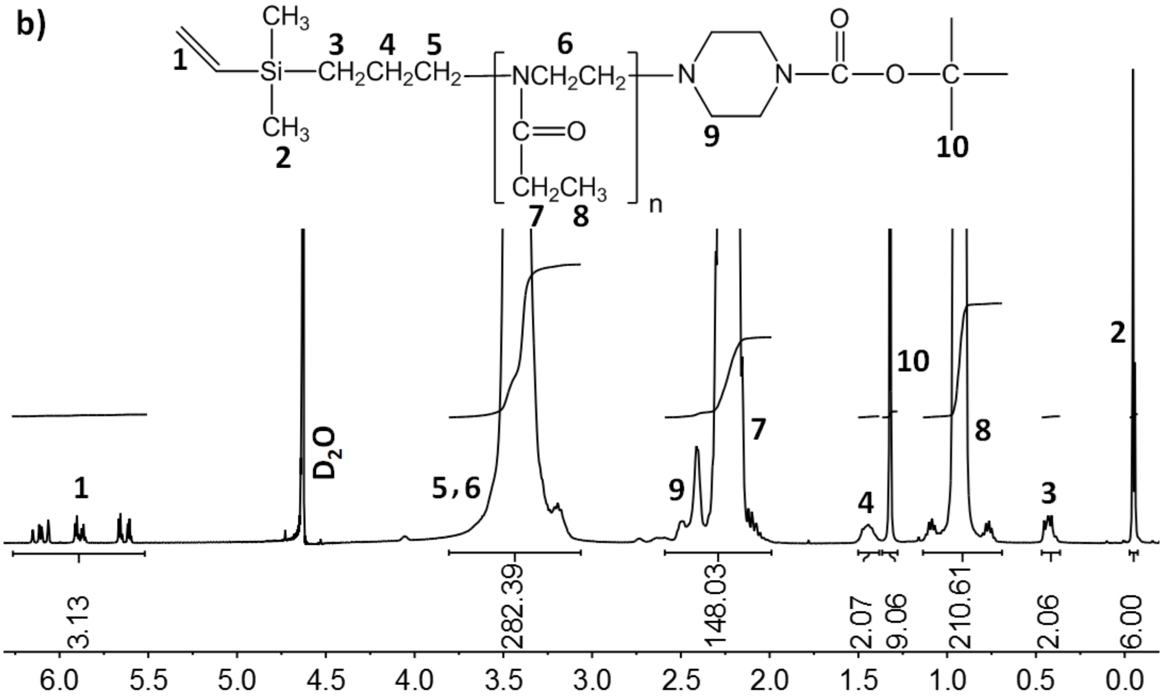
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148.03
2.07
9.06
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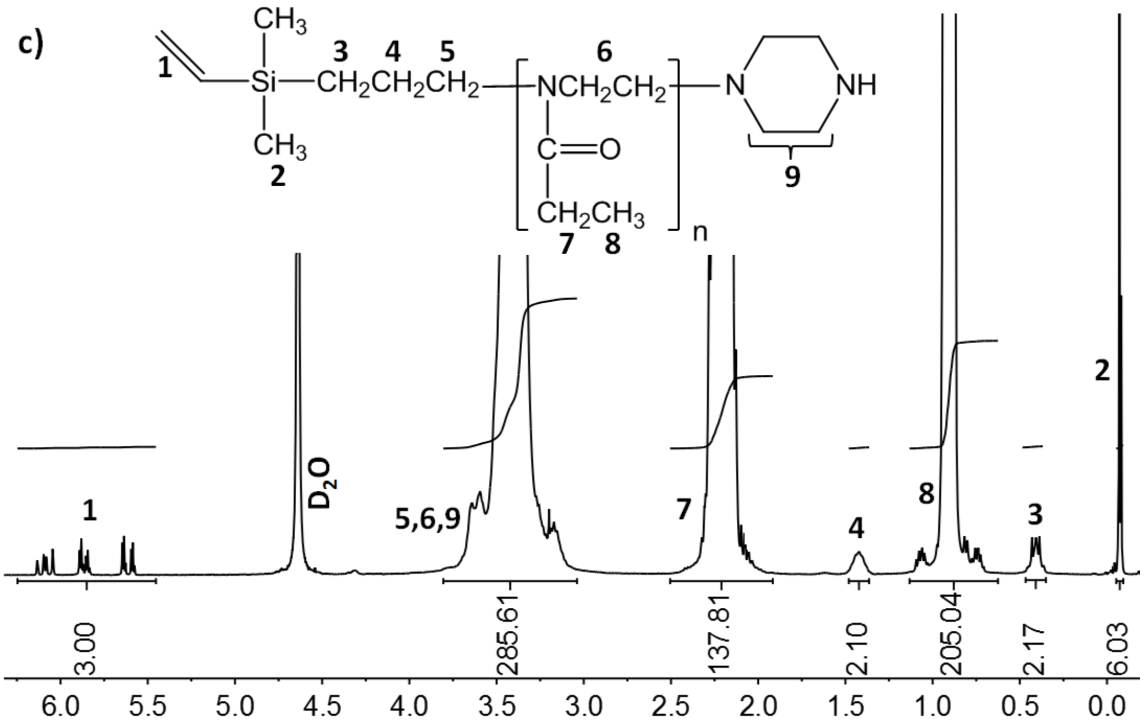

Figure 4.7 ^{1}H NMR spectra of a) 3-iodopropyldimethylvinylsilane obtained in $CDCl_3$,

b) dimethylvinylsilylpropoxy-PEtOx-*boc*-piperazine obtained in D_2O, and

c) dimethylvinylsilylpropoxy-PEtOx-piperazine obtained in D_2O*

*Protons attached to nitrogen atoms on piperazine endgroups may be substituted with deuterium atoms in D_2O. Therefore, it is difficult to observe proton resonances attached to nitrogen in D_2O.

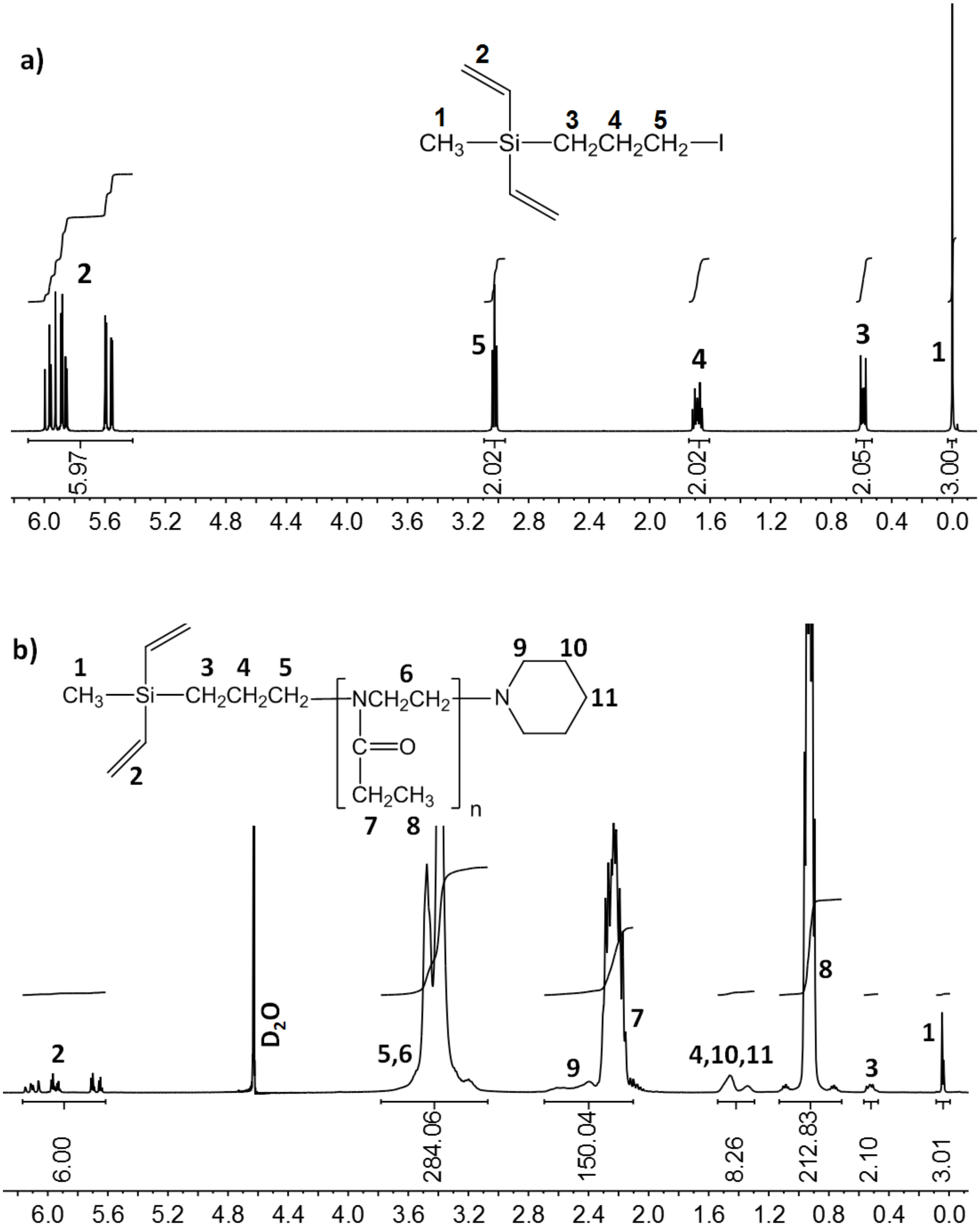

Figure 4.8 ^{1}H NMR spectra of a) 3-iodopropylmethyldivinylsilane obtained in $CDCl_3$ and b) a methyldivinylsilylpropoxy-PEtOx-piperidine oligomer obtained in D_2O

4.4 Conclusions

In summary, the monofunctional PEtOx oligomers initiated with methyl triflate showed excellent agreement between targeted and experimental molecular weights, symmetrical SEC curves and narrow molecular weight distributions, and excellent terminal functionality. By contrast, non-activated alkyl halides initiated these polymers very slowly and molecular weights significantly higher than those targeted were obtained, likely due to loss of very low molecular weight fractions during isolation. Probably the most important findings in this work were in regard to the molecular weight distributions of about 1.3-1.4 and excellent functionality of the monofunctional and difunctional PEtOx oligomers initiated with the activated alkyl halides. These materials are considered to be excellent candidates for hydrophilic monofunctional macromonomers or telechelic difunctional oligomers for incorporation into novel block and graft copolymer structures that may find use in novel membranes and various medical applications from hydrogels to drug-delivery.

Acknowledgements

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CHAPTER 5 - Synthesis and Characterization of Phosphonic Acid Functional Poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) Diblock Copolymers

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Abstract

This study presents the synthesis, functionalization, and characterization of phosphonic acid functional poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) (PEO-*b*-PEtOx) copolymers. PEO-*b*-PEOX diblock copolymers were prepared via cationic ring-opening polymerization of EtOx sequences from monofunctional CH_3-PEO-tosylate macroinitiators. Two samples of 1:2 and one sample of 1:3 (wt:wt) of PEO-to-PEtOx block copolymers were synthesized. These samples were then partially hydrolyzed to form the random copolymer poly(ethylene oxide)-*b*-poly(2-ethyl-2-oxazoline)-*co*-poly(ethyleneimine) (PEO-*b*-PEtOx-*co*-PEI). The degree of hydrolysis was dependent on the volume and concentration of the acid. PEI units were subsequently modified with diethyl vinyl phosphonates via Michael addition where less than 5 % of PEI units remained unfunctionalized. As a next step, phosphonic acid groups were introduced by the removal of the ethyl ester groups in the presence of trimethylsilyl bromide and anhydrous methanol. The composition and structure of each product was confirmed by

^{1}H NMR. SEC studies of the diblock copolymers indicated a PEO-macroinitiator peak which was attributed to the slow initiation mechanism relative to propagation though further functionalizations were not affected by this. These novel materials may bind strongly to oppositely charged drugs, metal ions and nanoparticles and be used for biomedical applications.

5.1 Introduction

In recent years, amphiphilic block copolymers have been extensively investigated as potential drug carriers due to their self-assembly in aqueous solutions into various kinds of morphological structures. Double hydrophilic block copolymers represent a special type of amphiphile that are comprised of at least two water-soluble blocks with different chemical compositions. Thus, each block in such materials shows a different affinity for substrates, molecules, and solvents. In many cases, one of the blocks is designed to interact with a substrate while the other interacts primarily with the medium to dissolve or disperse the materials.[1-3]

One important subclass of doubly hydrophilic block copolymers is “block ionomers” which are comprised of ionic and nonionic blocks.[4-6] These charged hydrophilic block copolymers can combine with proteins, drugs, or metal ions to form block ionomer complexes. These complexes can induce micelle or vesicle formation depending on the structure of the block ionomer, changes in pH, temperature, and ionic strength. Association of the ionic blocks with opposite charges, and steric stabilization by nonionic chains has lead to the formation of nanoscale core-corona structures. Therefore, these systems were found to be ideal nanocarriers for pharmaceutical agents. For example, charged drug molecules can be encapsulated into these nanostructures via electrostatic interactions with ionic blocks. This forms the core which is surrounded by nonionic blocks representing the corona. Nonionic chains prevent aggregation and macroscopic phase separation, and thereby disperse these nanostructures in water or physiological media.[4,6,7]

It is well known that poly(ethylene oxide) PEO is a biocompatible polymer used in a variety of biomedical applications due to its high solubility in water, low toxicity, and absence of immunogenicity. When conjugated to proteins, and drug molecules, PEO increases their solubility in aqueous media and sizes of the resultant complexes, and this can increase circulation times in the bloodstream.[8,9] However, the use of PEO is limited due to its low drug-loading capacity. One strategy to incorporate PEO in drug conjugating systems is to employ block copolymers.[10]

Poly(2-oxazoline)s (POXs) also represent an excellent class of biocompatible polymers,[11-14] and they resemble PEO in terms of their biocompatibility and stealth behavior.[15,16] POXs are sometimes regarded as pseudo-polypeptides since each repeat unit includes an amide bond.[17] POX possesses a poly(ethylene imine), $(C\text{-}C\text{-}N)_n$, backbone with amide-bonded pendent groups in each repeat unit. Short alkyl side groups such as methyl or ethyl, result in hydrophilic, water soluble POX. However, longer alkyl chains or aromatic side groups give rise to a hydrophobic structure leading to insolubility in aqueous media.[18] Monomer compositions and side-chain functionalities of poly(2-oxazolines) can be modified to allow for attaching a variety of bioactive compounds.[19]

Incorporation of POX into block copolymers has resulted in promising drug carriers.[12] Jeong *et al.*[20] prepared poly(2-ethyl-2-oxazoline-*b*-ε-caprolactone) (PEtOx-*b*-PCL) amphiphilic diblock copolymer micelles, and loaded paclitaxel, an anticancer drug with poor aqueous solubility, into these systems. Wang and Hsiue[21] studied micellization of biodegradable poly(L-lactide)-*b*-PEtOx-*b*-poly(L-lactide) triblock copolymers and showed that the central PEtOx block was sensitive to pH and temperature. The anticancer drug doxorubicin showed an enhanced release mechanism from these micelles under acidic conditions (pH~5), suggesting a pH triggered drug delivery system.[22] PEtOx-*b*-poly(ethylene imine) (PEtOx-*b*-PEI) diblock copolymers were also prepared for use as nonviral gene carriers through formation of pH-sensitive polyplexes with DNA.[23] Previously our group reported the synthesis of (PEO-*b*-PEtOx) and (PEO-*b*-PEtOx-co-PEI) copolymers.[24,25] Moreover, POXs have been combined with polypeptides[26-28] and polysaccharides[29-32] to provide potential biocompatible materials for therapeutic applications.

In this study, we demonstrate a novel approach to prepare poly(ammoniumbisphosphonate) block copolymers with PEO. This builds upon previous work with PEO-*b*-PEtOX-*co*-PEI through functionalization reactions on the PEI component. These materials have potential as drug delivery vehicles and contrast enhancement agents in magnetic resonance imaging (MRI).

5.2 Experimental

5.2.1 Materials

Poly(ethylene glycol) methyl ether (M_n = 5800 g/mol), *p*-toluenesulfonyl chloride (TsCl, >98%), anhydrous methanol (>99.8%), calcium hydride (>90%), manganese (II) chloride tetrahydrate (99.9%) were purchased from Aldrich and used as received. 2-Ethyl-2-oxazoline and chlorobenzene, both from Aldrich, were dried over CaH_2 and vacuum distilled into a dry flask under nitrogen. Triethylamine (TEA, 99.5%) was obtained from Fluka. Bromotrimethylsilane (TMS-Bromide, 97%) and aqueous potassium hydroxide (1 M) were purchased from Alfa Aesar and used as received. Dialysis tubing (3500 g/mol MWCO) was obtained from Spectra/Por. Aqueous hydrochloric acid (2 M, LabChem) was used as received. Diethyl vinyl phosphonate (98%) was obtained from Epsilon Chiminie. Diethyl ether, methanol and dichloromethane (Fisher Scientific) were used as received. Anhydrous dichloromethane (>99.8%) was obtained from EMD Chemicals.

5.2.2 Synthesis

5.2.2.1 Synthesis of CH_3-PEO-tosylate macroinitiator

The synthesis of poly(ethylene oxide) methyl ether tosylate macroinitiator is provided. A 5800 g/mol M_n PEO oligomer (30.2 g, 5.21 mmol) was added to a 250-mL flask equipped with a magnetic stir bar and enclosed with a rubber septum bound with steel wire. The PEO oligomer was vacuum dried at 70°C for 24 h and dissolved in dichloromethane (70 mL). Et_3N (3.67 mL, 26.3 mmol) was added to serve as an acid scavenger. In a separate flask, TsCl (2.04 g, 10.7 mmol) was dissolved in 50 mL of CH_2Cl_2. The tosyl chloride solution was syringed into the reaction flask. The reaction was stirred for 24 h at 25 °C. The reaction mixture was passed through a 0.2-μm Teflon® filter, then transferred to a separatory funnel, and washed with DI water 4X to remove salts. The organic phase was concentrated via rotary evaporation, and the resulting macroinitiator was collected via precipitation into diethyl ether, and then was dried overnight under vacuum at 50 °C.

5.2.2.2 Synthesis of poly(ethylene oxide-b-2-ethyl-2-oxazoline) diblock copolymers

Double hydrophilic poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) (PEO-*b*-PEtOx) block copolymers were synthesized via cationic ring opening polymerization of 2-ethyl-2-oxazoline from the end of the tosylated PEO macroinitiator. A representative procedure for preparing a targeted composition of ~2.5:1 wt:wt PEO:PEtOx is as follows. A tosylated PEO macroinitiator (3.3 g, 0.57 mmol) was dried overnight at 80 °C in a 100-mL flask equipped with a magnetic stir bar and enclosed with a rubber septum. Chlorobenzene (20 mL) was added to dissolve the PEO macroinitiator, and then 2-ethyl-2-oxazoline (5.51 mL, 5.41 g, 55 mmol) was syringed into the macroinitiator solution. The reaction was performed at 110 °C for 24 h. The reaction mixture was cooled to room temperature and the polymer chains were terminated with 1 M KOH (1 mL, 1 mmol) in methanol. The diblock copolymer was isolated by precipitation into diethyl ether, and collected by filtration and dried at 50 °C *in vacuo* overnight.

5.2.2.3 Acid hydrolysis of poly(ethylene oxide-b-2-ethyl-2-oxazoline)

An acid hydrolysis procedure for removing a portion of the pendent amide groups from the PEtOx blocks is provided. A PEO-*b*-PEtOx diblock copolymer with 5800 g/mol PEO:14,300 g/mol PEtOx (5 g, 0.25 mmol, 36 meq of amides) was charged to a 100-mL flask containing a magnetic stir bar and enclosed with a septum. $HCl_{(aq)}$ (2 M, 10.5 mL, 21 mmol) and 4.5 mL of DI water were syringed into the flask. The reaction was conducted at 90 °C and maintained for 24 h, then cooled to room temperature. The reaction mixture was diluted to 50 mL with DI water and placed in a 3500 g/mol MWCO cellulose acetate dialysis membrane and dialyzed against 4 L of DI water for 48 h. The pH of the receptor medium was adjusted to ~9 with KOH to remove acetates and other salts. The contents of the dialysis membrane were transferred to a 250-mL flask and freeze-dried. ^{1}H NMR was used to confirm the extent of hydrolysis.

5.2.2.4 Synthesis of phosphonic acid functional PEO-*b*-PEtOx-co-PEI

The ethylene imine groups of the partially hydrolyzed copolymers were reacted via Michael addition with diethyl vinyl phosphonate. A representative procedure for addition of phosphonate groups to the PEO-*b*-PetOx-co-PEI copolymer is as follows. A PEO-*b*-PEtOx-co-PEI (4.07 g, 0.25 mmol, 19.3 meq of amides, 16.7 meq of imines) was charged to a 100-mL flask equipped with a stir bar, and dissolved in DI water (10 mL). Diethyl vinyl phosphonate (7.75 mL, 8.22 g, 50 mmol) was added to the polymer solution. The reaction was performed at 80 °C for 24 h. The reaction mixture was diluted with DI water (40 mL) and placed in a 3500 g/mol MWCO cellulose acetate dialysis bag and dialyzed against 4 L of DI water for 48 h to remove excess diethyl vinyl phosphonate. The contents of the dialysis membrane were transferred to a 250-mL flask and freeze-dried.

PEO-*b*-PEtOx-co-PEI-phosphonic acid was prepared by removal of the ethyl ester groups from PEO-*b*-PEtOx-co-PEI-phosphonate.[33,34] In a representative procedure, PEO-*b*-PEtOx-co-PEI-phosphonate (0.50 g, 0.031 mmol, 0.625 meq of phosphonate groups, 1.25 meq of ethyl groups) was dissolved in anhydrous dichloromethane (5 mL) in a flame-dried 100-mL flask equipped with a stir bar, and enclosed with a rubber septum. TMS-Br (0.25 mL, 0.29 g, 1.88 mmol) was syringed into the reaction flask and stirred at 25 °C for 24 h, then the solvent and excess TMS-Br were removed via rotary evaporation. The product was further processed under vacuum at 60 °C for 4 h utilizing a KOH trap system. The resultant polymer was dissolved and reacted in methanol (3 mL) for 6 h to cleave the trimethylsilyl groups. PEO-*b*-PEOX-co-PEI-phosphonic acid was recovered by precipitation into diethyl ether and vacuum-dried at 25 °C for 24 h.

5.2.3 Characterization

^{1}H NMR spectral analyses of polymers were performed using a Varian Inova 400 NMR spectrometer operating at 400 MHz. The NMR parameters included a pulse width of 30° and a relaxation delay of 1 s at room temperature with 32 scans. All spectra of the polymers were obtained in D_2O at a concentration of 0.05 g/mL.

Size exclusion chromatography was performed using an Agilent Technologies 1260 Infinity series HPLC pump equipped with a degasser, autosampler, and temperature controlled column compartment. The detectors used were a Dawn Heleos-II multi-angle laser light scattering detector and Optilab T-rEX refractive index detector both by Wyatt Technologies. The mobile phase was *N*-methylpyrrolidone containing 0.05 M LiBr and the stationary phase consisted of two alpha M mixed bed columns from Tosoh Bioscience. The column compartment was maintained at 80 °C and the detectors at 50 °C. Samples were dissolved at approximately 1 mg/ml and filtered with a 0.2 µm Teflon® filter prior to sample loading.

The thermal decomposition behavior of polymer samples was determined using a thermogravimetric analyzer (TGA, TA Instruments, TGA Q5000) with a heating rate of 10°C/min under nitrogen. TGA measurements were conducted from 50 to 600 °C. Prior to each measurement, all samples were held at 100 °C for 15 min in the TGA instrument to remove any moisture.

5.3 Results and Discussion

5.3.1 Synthesis of poly(ethylene oxide-b-2-ethyl-2-oxazoline) diblock copolymers and their acid hydrolysis and functionalization with phosphonic acid

Syntheses of the PEO-*b*-PEtOx diblock copolymers were performed using cationic living ring-opening polymerization of 2-ethyl-2-oxazoline from one end of PEO-tosylate macroinitiators (Figure 5.1). After polymerization reaction was complete, the cationic chain ends were neutralized with KOH in methanol at 25 ºC to form a hydroxyl endgroup. A portion of the pendent amide groups were then hydrolyzed to obtain a series of PEO-*b*-(PEtOx-co-PEI) copolymers (Figure 5.2). It has been reported that the degree of deacylation on PEtOx could be controlled by the stoichiometric molar ratio of HCl to amide up to a degree of deacylation of 0.4.[35] Thus, various concentrations of HCl were used to control the extent of hydrolysis so that copolymers with different relative amounts of amide versus ethyleneimine units could be investigated. Ethyleneimine units on PEO-*b*-(PEtOx-co-PEI) were post-functionalized with diethylphosphonate (DEVP) via Michael addition in water to introduce pendent ammonium phosphonate groups as precursors for the corresponding phosphonic acids (Figure 5.2).

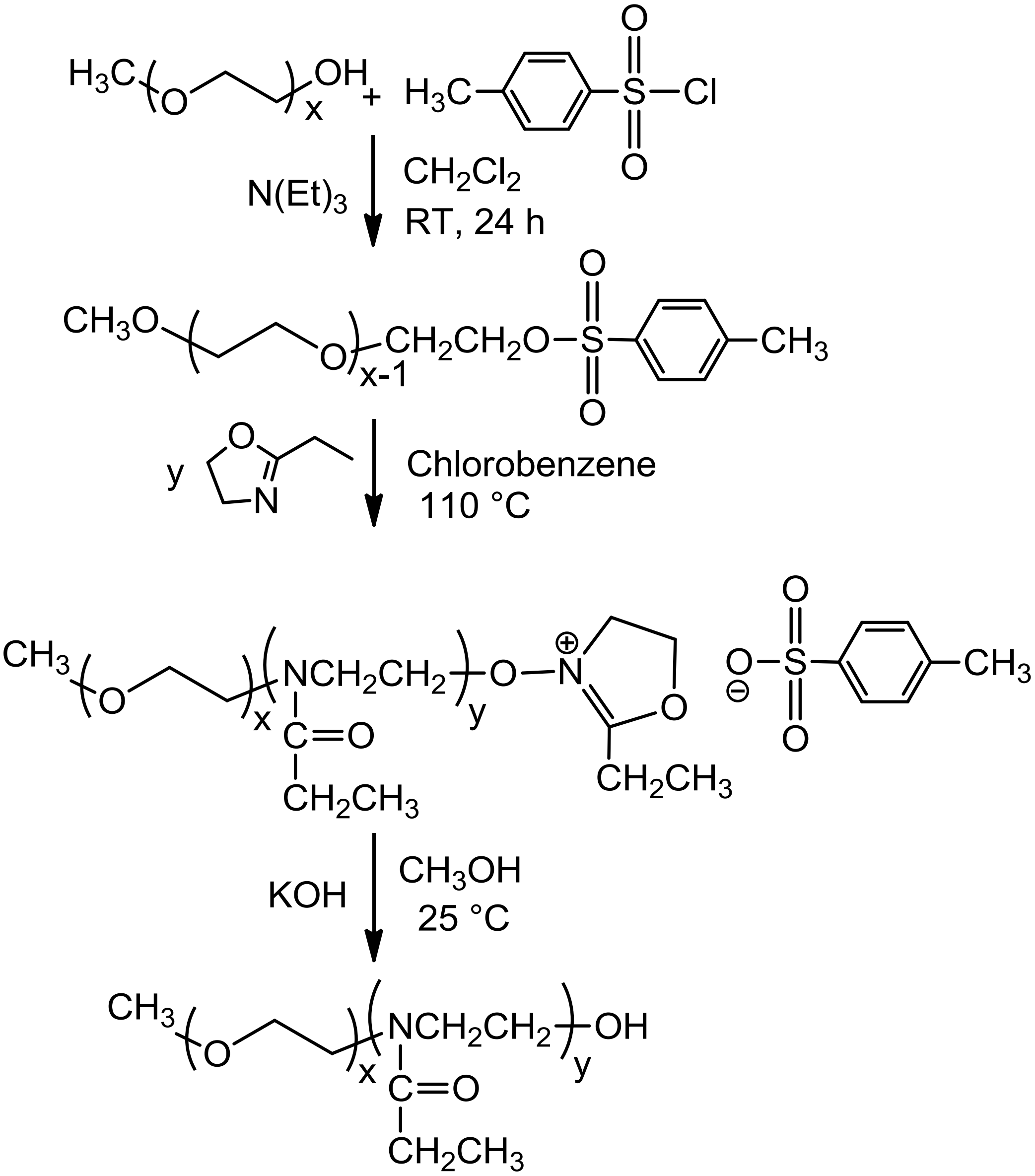

Figure 5.1 Synthesis of poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) copolymers

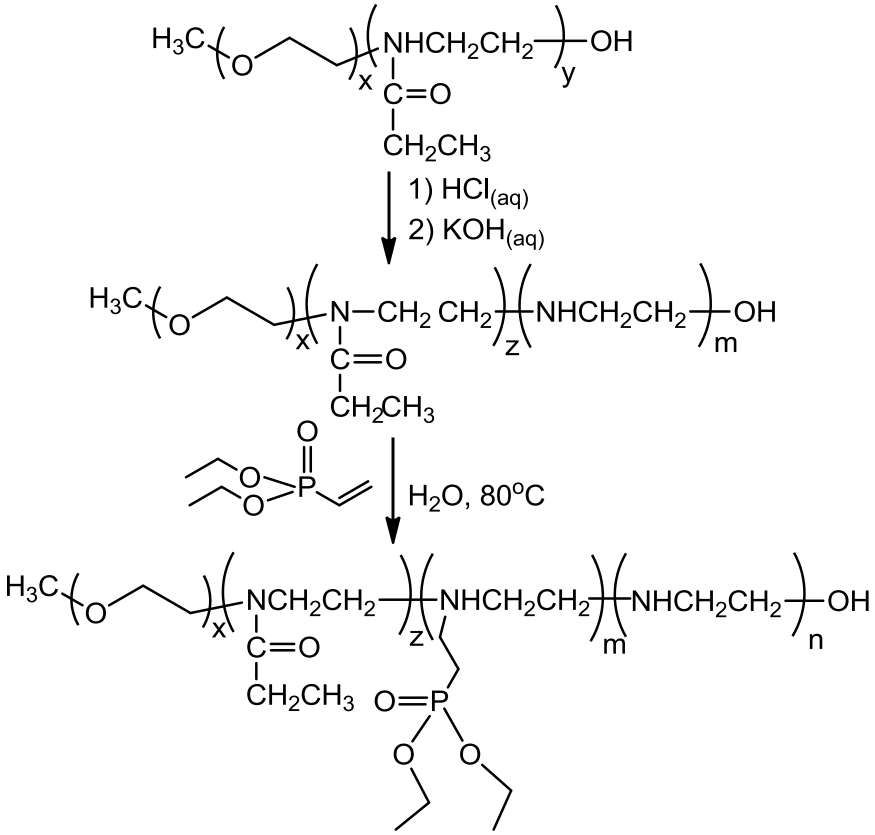

Figure 5.2 Synthesis of diethyl phosphonate derivatives of poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) diblock copolymers through acid hydrolysis and Michael addition

Water likely accelerated the reactions based on the literature reports.[36] The reactions were conducted with 3 equivalents of diethylvinylphosphonate per equivalent of ethyleneimine and resulted in 92-96% addition. The ethyl esters on the phosphonate pendent groups were removed by reacting the polymers with an excess of TMS-Br in anhydrous dichloromethane to form trimethylsilyl-phosphonates (Figure 5.3), then the silylated intermediates were converted to the corresponding phosphonic acid derivatives by methanolysis. These reactions were conducted under strict anhydrous conditions to avoid TMS-Br hydrolysis.

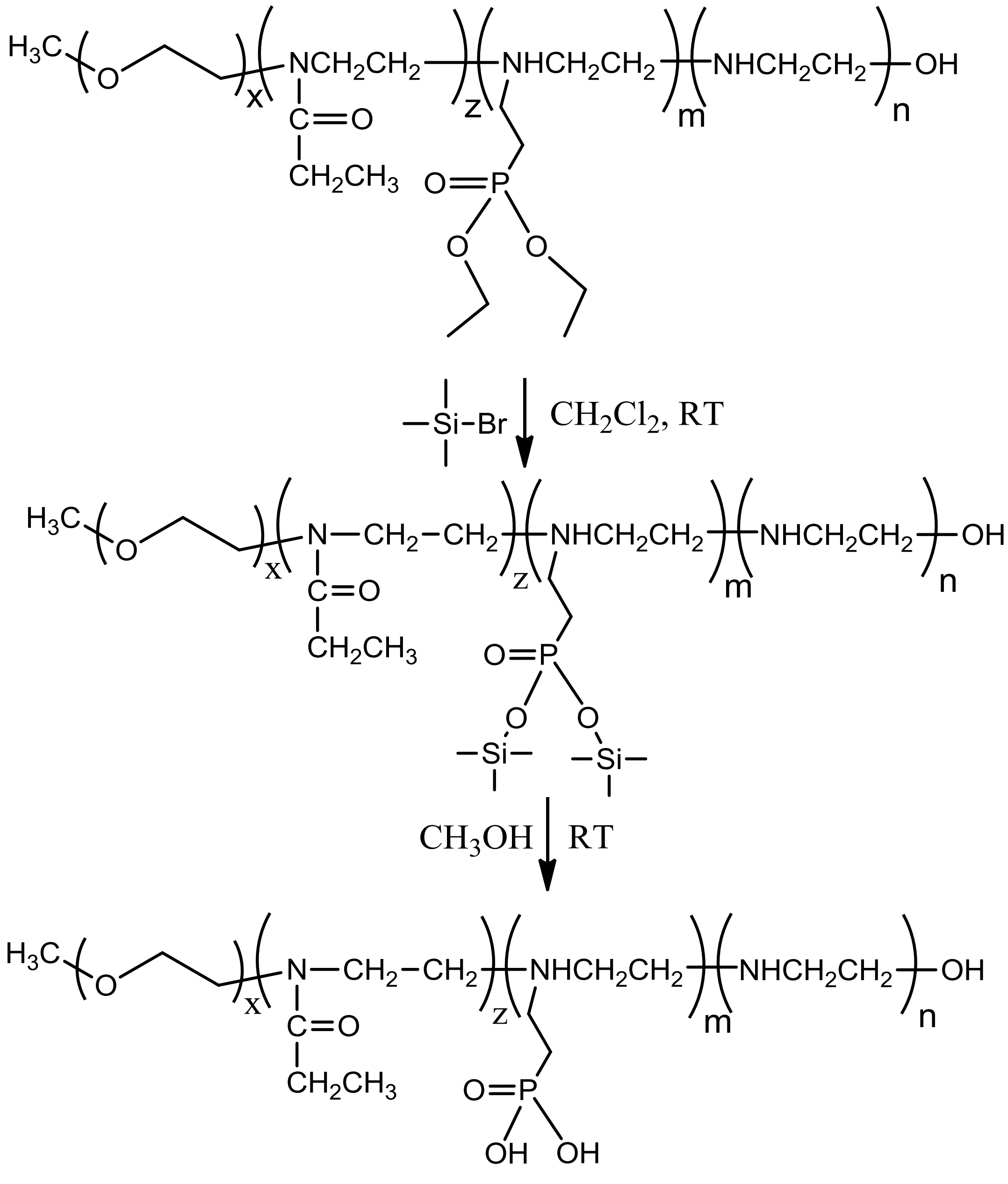

Figure 5.3 Conversion of diethyl phosphonate group to phosphonic acid

Size Exclusion Chromatography (SEC) was used to analyze the molecular weight distributions of the copolymers in NMP containing 0.05 M LiBr with multiple detectors (differential refractive index, viscosity, and multi-angle laser light scattering). The viscosity curves of these PEO-*b*-PEOX copolymers were bimodal (Figure 5.4). The low molecular weight peak coincided with the SEC curve of the PEO-macroinitiator, and this signified that there was a substantial amount of PEO-macroinitiator remaining. The refractive index curves had a negligible peak in the macroinitiator region since the refractive index of the solvent and PEO were very similar. This allowed clear identification of residual macroinitiator as the source for the low molecular weight peak. It was reasoned that the rate of initiation relative to propagation was too slow to yield well-defined block copolymers. Thus the materials were blends containing a major amount of the desired diblock copolymer combined with the residual PEO macroinitiator.

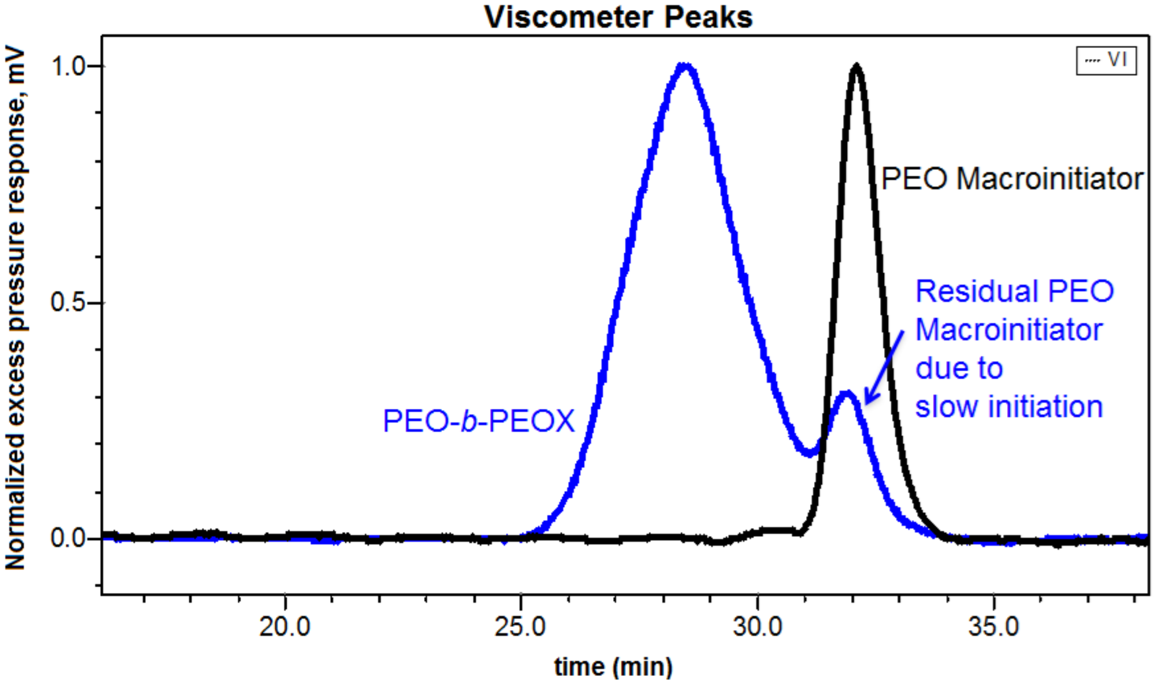

Figure 5.4 SEC chromatogram of a PEO-*b*-PEtOx diblock copolymer showing a bimodal viscosity* curve in comparison to a PEO macroinitiator

* Specific viscosity can be measured by the viscometer detector from an equation relating the differential pressure across a capillary bridge.

5.3.2 ^{1}H NMR analyses to predict the copolymer compositions before and after the acid hydrolysis and phosphonic acid modification

^{1}H NMR spectra of the PEO-*b*-PEOX diblock copolymer-PEO blends provided the PEO to PEtOx compositions (Table 5.1). A representative spectrum is shown in Figure 5.5. Formation of the PEtOx end blocks resulted in the appearance of broad peaks in the region around 3.3-3.5 ppm assigned to the methylene backbone protons of PEtOx (-NCH_2CH_2) and pendent group protons at 2.2 ppm (-CH_2) and 0.9 ppm (-CH_3). The experimental compositions determined via ^{1}H NMR were in good agreement with the targeted compositions.

Table 5.1 Compositions of PEO to PEtOx in copolymers

PEO-b-PEtOx Copolymer	**Targeted Composition (wt:wt)**	**Experimental PEO to PEtOx Composition (wt:wt)**
1	0.37:0.63	0.39:0.61
2	0.37:0.63	0.37:0.63
3	0.28:0.72	0.29:0.71

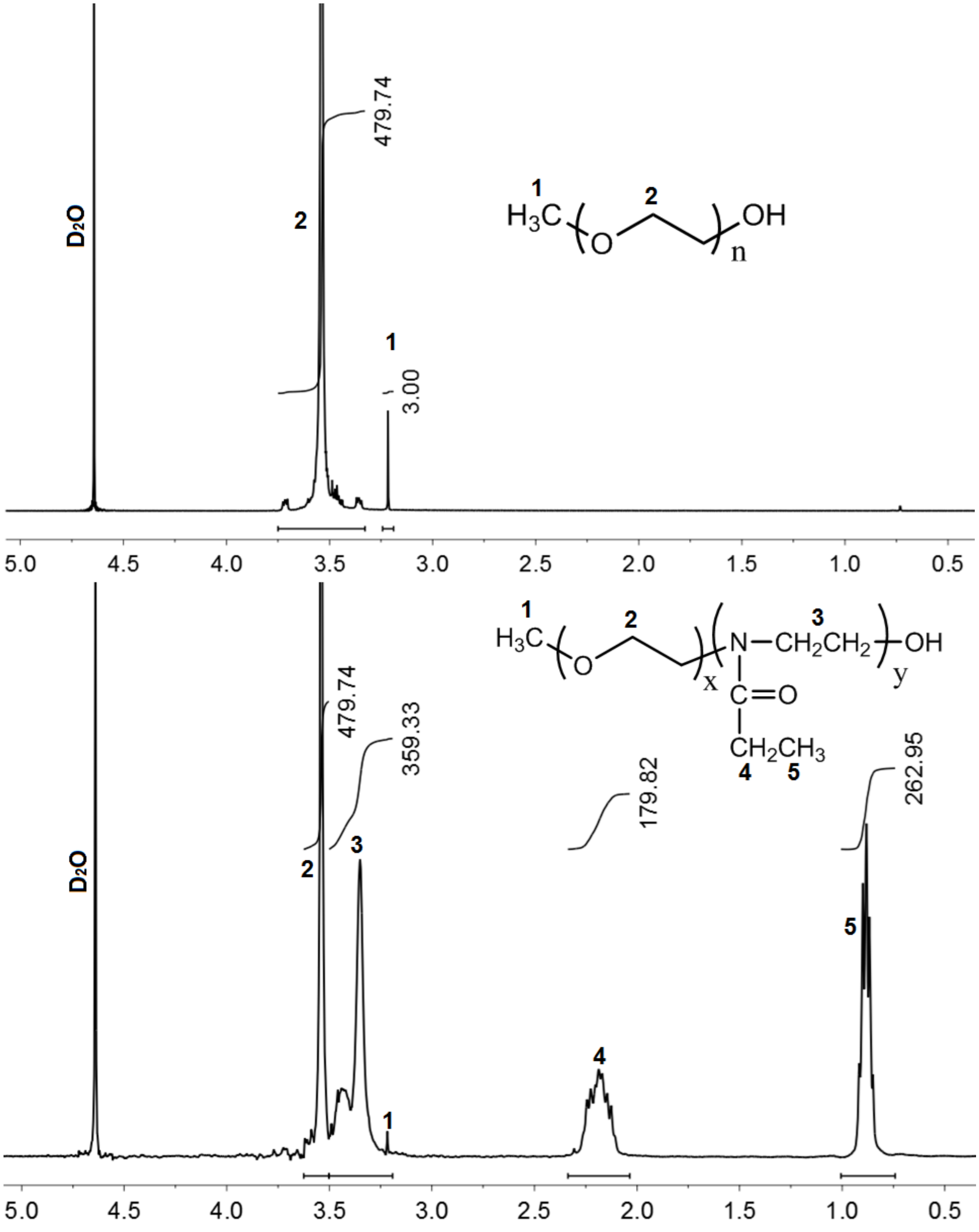

Figure 5.5 ^{1}H NMR PEO 5K and PEO-PEtOx diblock obtained in D_2O*

* Upon dissolution of -OH terminated PEO in D_2O, the substitution of deuterium may occur with the PEO hydroxyl endgroup protons resulting in CH_3-PEO-OD.

As the concentration of HCl in the amide hydrolysis modification was increased, the extent of hydrolysis also increased (Table 5.2), but the exact degree of hydrolysis that were achieved were always somewhat smaller than targeted. As discussed by Kem *et al.*[35], this may be related to a polyelectrolyte effect where hydrolysis becomes slower as polymer units become protonated, especially at higher degrees of hydrolysis. This does, however, provide a means to prepare copolymers with different degrees of hydrolysis.

Table 5.2 PEO-*b*-PEtOx hydrolysis to form PEO-*b*-PEtOx-co-PEI*

Copolymer**	**Targeted Hydrolysis**	**Experimental Hydrolysis**
2A	60.0%	51.4%
3	58.8%	46.0%
2B	40.0%	27.4%

* PEI segments are randomly distributed.

** Copolymer 2 described in Table 5.1 was hydrolyzed with 2 different concentrations of HCl. The third entry was derived from copolymer 3.

^{1}H NMR spectra reflected the pH sensitive character of the PEO-*b*-(PEOX-co-PEI) copolymers (Figure 5.6). The hydrolysis by-product after neutralization with KOH, propionate ion, was ionically bound to secondary ammonium groups on the ethyleneimine units of the backbone. The alkyl group proton resonances at 1.1 and 2.5 ppm on the associated propionate ions appeared on the ^{1}H NMR spectra (Figure 5.6) when the polymers were dialyzed against deionized water. The backbone methylene protons on the secondary ammonium and 2-ethyl-2-oxazoline units were shifted downfield relative to those on the unharged polymer. When a hydrolyzed copolymer solution was dialyzed against high pH (~9) water, resonances from propionate ions completely disappeared (since they had been removed by dialysis) and resonances due to

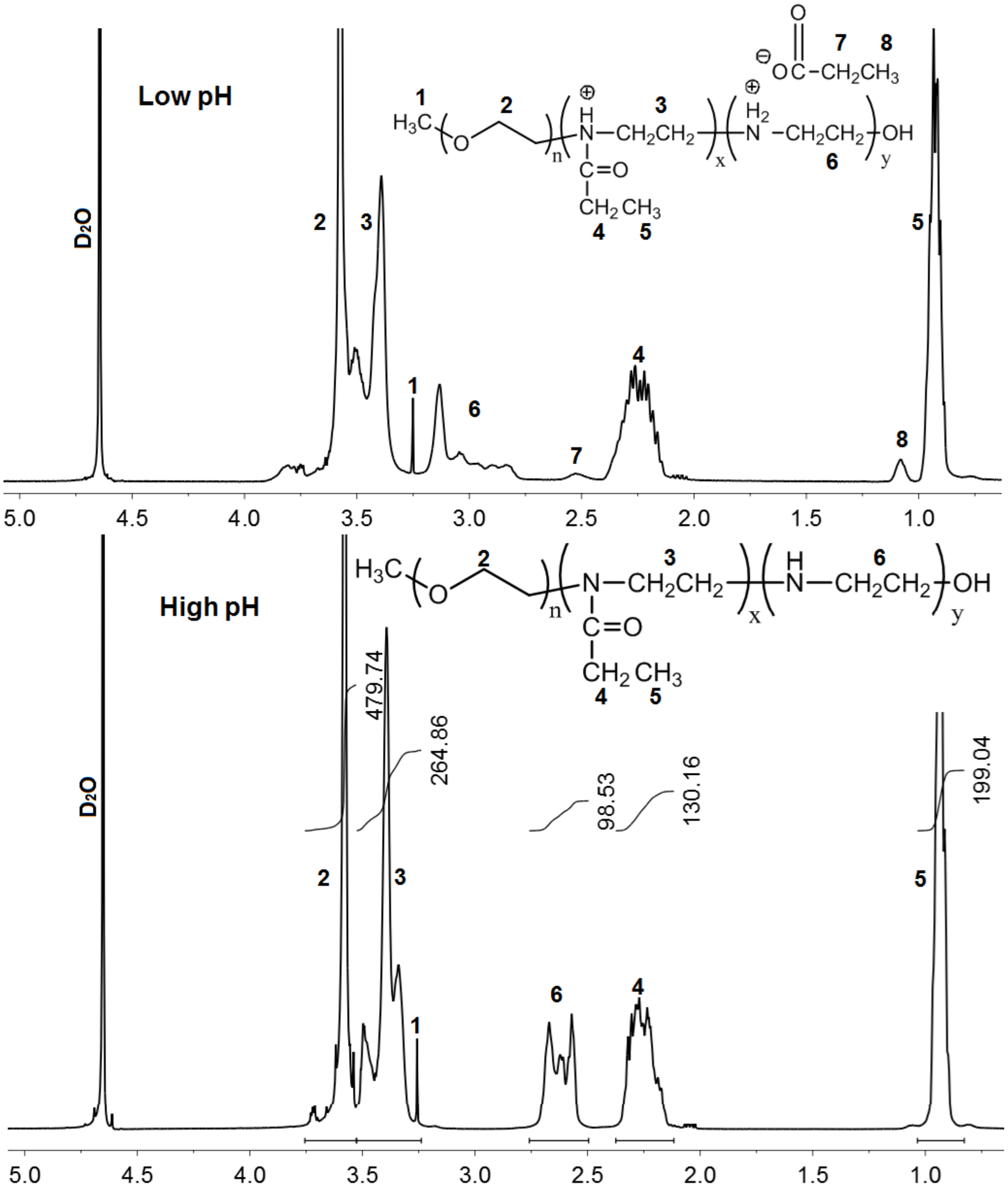

Figure 5.6 ^{1}H NMR comparison illustrating pH influence on polymer mixture obtained in D_2O*

* Deuterium-exchange reactions with D_2O may also be applicable to the protons attached to nitrogen atoms as well as hydroxyl endgroups.

uncharged ethyleneimine and 2-ethyl-2-oxazoline units were shifted upfield. This demonstrated the complete removal of propionate and neutralization of ethyleneimine units to form free amines. The hydrolysis degrees of PEtOx component were determined by calculating the relative areas of proton resonances in the ethylenimine units relative to the pendent group protons of PEtOx.[24,25]

A representative spectrum (Figure 5.7) denotes the difference between PEI units and the ones with phosphorylated. The appearance of the ethyl peaks at 1.2 and 4.0 shows that the Michael addition was succesful. The ^{1}H NMR spectra of the PEO-*b*-(PEOX-*co*-PEI-*co*-phosphonate) copolymers were used to analyze the relative amounts of oxyethylene, amide, ethyleneimine, and diethylphosphonatoethyl pendent groups (Table 5.3). Figure 5.8 (top) shows three different characteristic signals for the diethylphosphonatoethyl groups: (1) methylene protons adjacent to the phosphorus at 1.9 ppm, and (2) ethyl ester group resonances at 4.0 for -CH2- and (3) 1.2 ppm for -CH_3 groups. The resonances at 2.4-2.8 ppm represent a combination of the methylene adjacent to nitrogen and the backbone methylenes in the phosphorus-containing units (total of 6 protons per unit), and also the backbone methylenes in residual ethyleneimine units (4 protons per unit). The relative amounts of the phosphorus-containing units and ethyleneimine were calculated by subtracting the resonance integral at 1.2 ppm from the total integral at 2.4-2.8 ppm. The remaining part of the integral at 2.4-2.8 ppm was then representative of the small residual amount of ethyleneimine units. The peak integral at 0.9 ppm due to the methyl groups on the amides was utilized to calculate the relative amounts of those units. The resonances due to the ethyleneoxy and backbone amide units overlap, so the relative number of ethyleneoxy units could only be estimated by subtracting the appropriate component due to the amides from the total resonance at ~3.2-3.7 ppm.

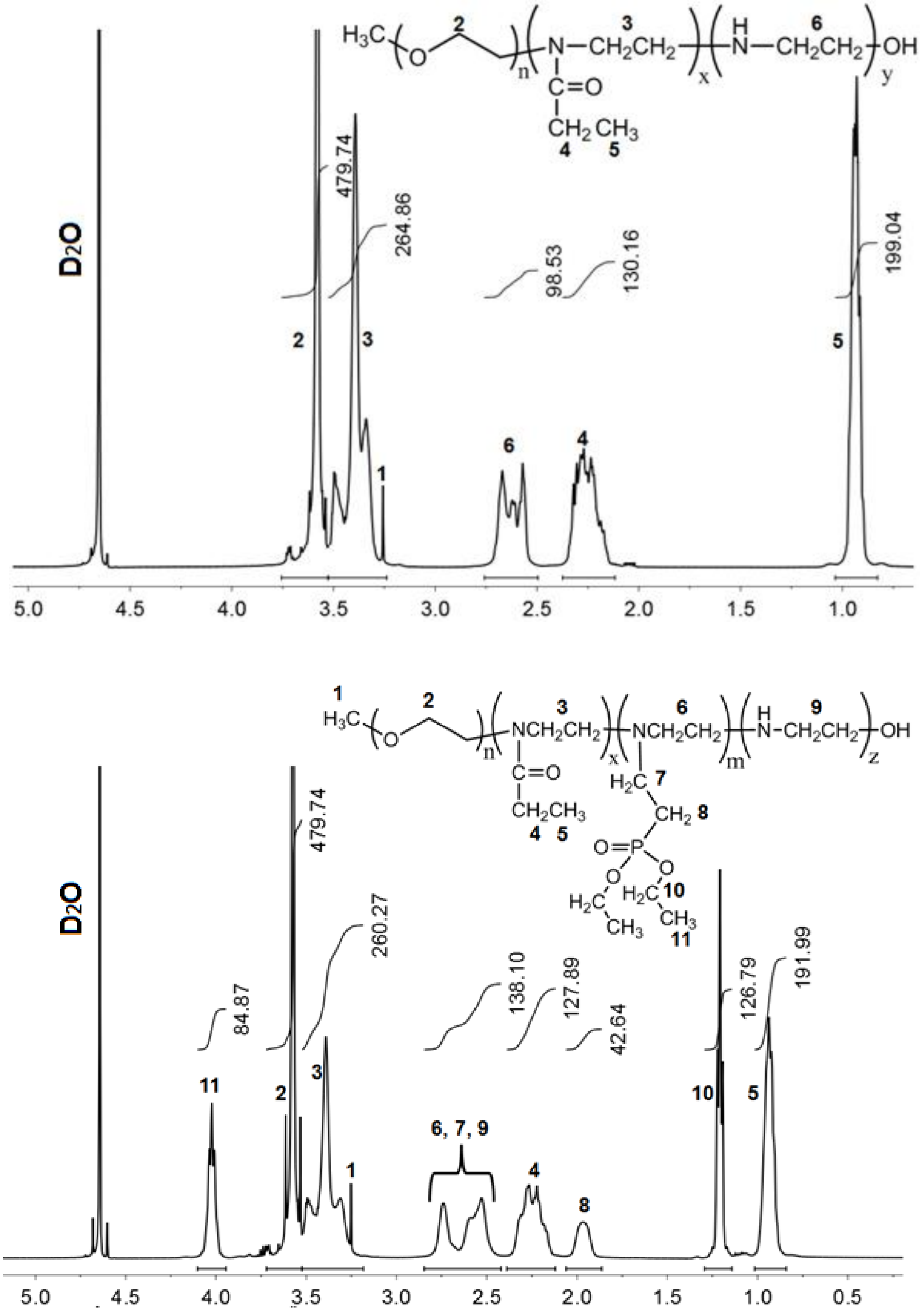

Figure 5.7 ^{1}H NMR of PEO-*b*-(PEtOx-co-PEI) phosphorylation obtained in D_2O

Table 5.3 Compositions of PEO-*b*-(PEOX-*co*-PEI-*co*-phosphonate)*

Copolymer	Ethyleneoxy	Amides	Phosphorus-Containing units	Ethyleneimine
2A	120	42	42	2
2B	129	71	23	2
3	119	64	53	2

* Phosphonate groups are randomly distributed.

The conversion to the corresponding phosphonic acid was demonstrated by the disappearance of the diethylphosphonatoethyl signals at 1.2 (-CH_3) and 4.0 (-CH_2) ppm (Figure 5.8) (bottom). In addition, the methylene group proton resonances on the PEtOx backbone as well as the methylene protons that have similar chemical environments (labeled **6**, **7** and **9**) showed a significant downfield shift that can be explained by the positive charge on the ammonium ions formed after phosphonic acid modification. The efficiencies of the Michael addition were high ranging between 92-96% phosphorylation of ethyleneimine units.

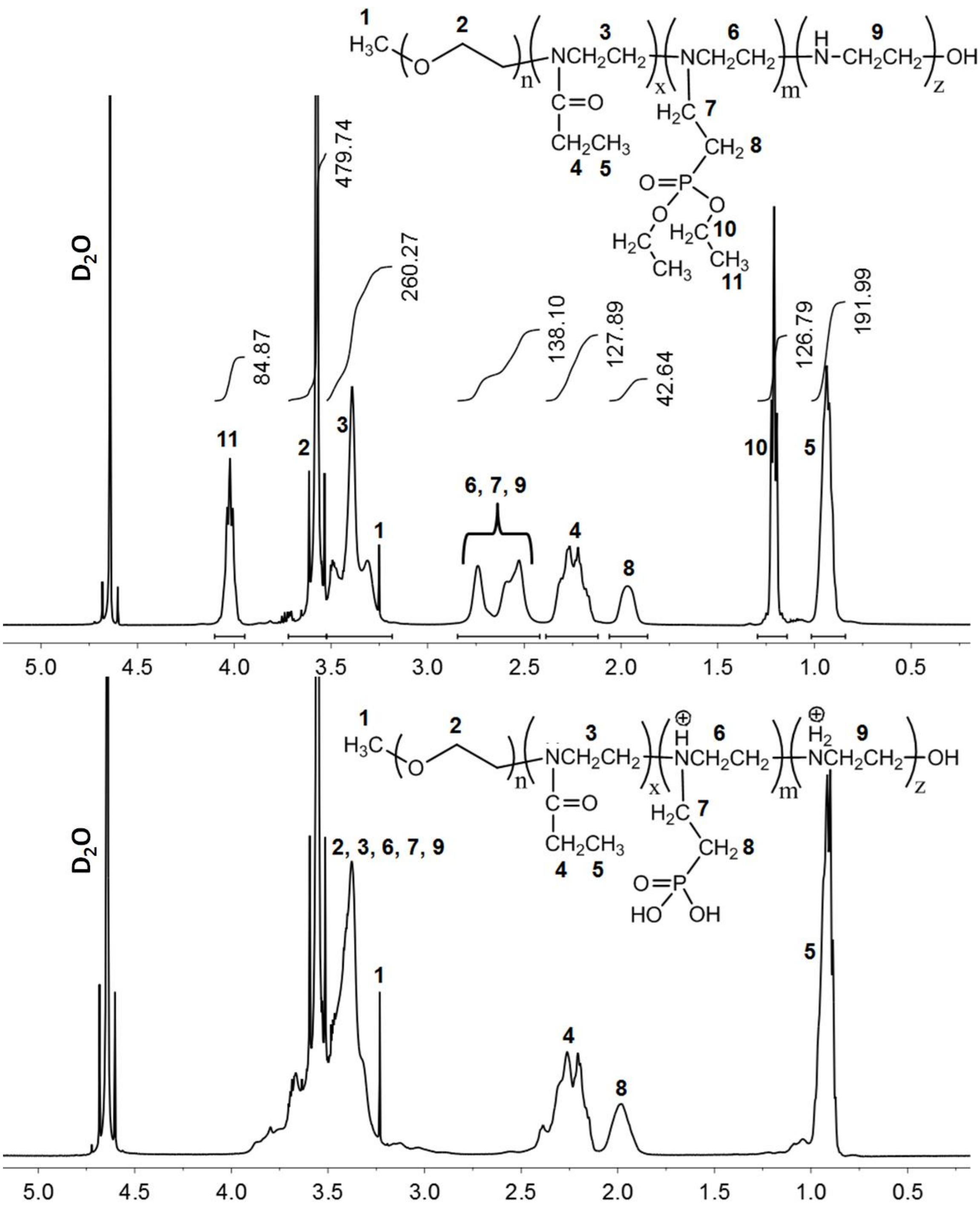

Figure 5.8 ^{1}H NMR of diethyl phosphonate conversion to phosphonic acid

5.3.3 Effect of acid hydrolysis and post-phosphorylation on thermal stability

Thermogravimetric analyses (TGA) of PEO homopolymers, PEO-*b*-PEOX copolymers and their derivatives were conducted under nitrogen atmosphere (Figure 5.9). The thermograms show the weight loss profiles of each polymer as they were converted from the PEO to the PEO-*b*-(PEOX-*co*-PEI-*co*-phosphonic acid). TGA temperature scans revealed that both PEO and PEO-*b*-PEOX and the PEO-*b*-(PEOX-*co*-PEI) showed similar degradation behavior and did not lose a significant amount of weight up to 300-330 °C, and then they completely decomposed without the formation of char. By contrast, the phosphorus- containing copolymers began weight-loss somewhat earlier (220-260 °C) but formed significant levels of char (10-17%). It has been reported that at elevated temperatures, dialkyl phosphonates pyrolyze to monoalkyl derivatives, and then condense to form P-O-P crosslinks that result in char.[37-39] Consistent with this premise, the amount of char after these tests corresponds to the weight percentages of the pendent phosphonates in these materials.

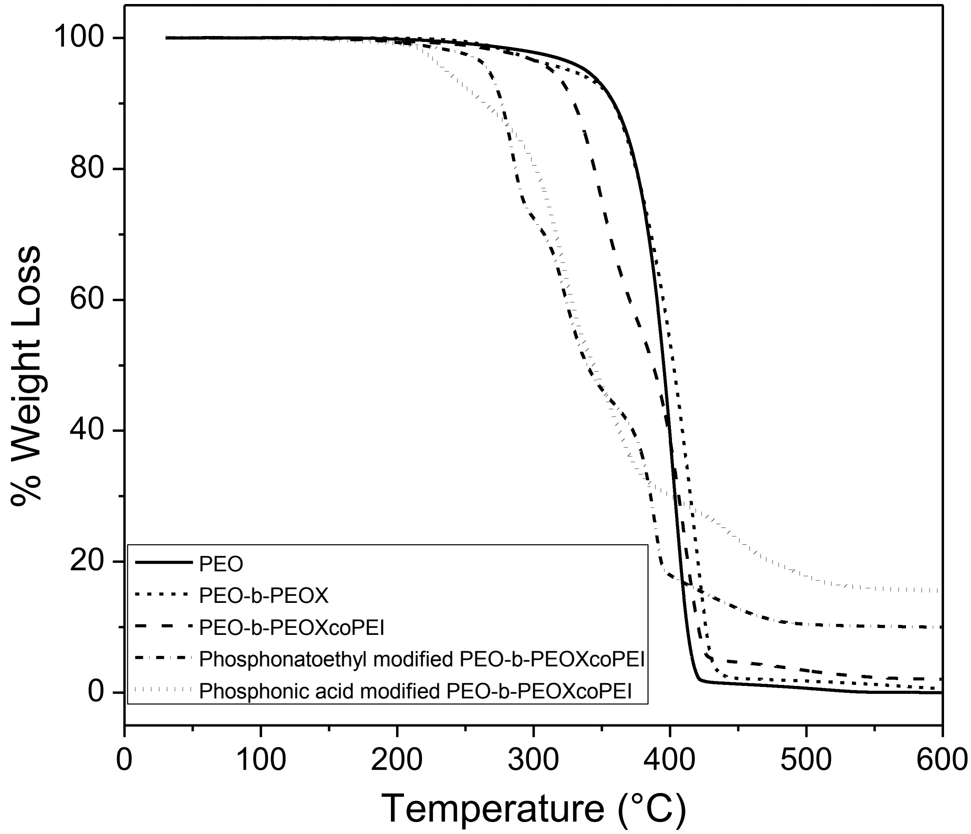

Figure 5.9 TGA graph depicting diblock series from PEO-b-PEtOx to phosphonic acid modified final form

5.4 Conclusions

PEO-*b*-PEOX diblock copolymers were prepared using cationic ring-opening polymerization. However, it was found that CH_3-PEO-tosylate macroinitiators resulted in blends of PEO-*b*-PEOX copolymers with residual PEO-macroinitiators which is attributed to the relatively slow initiation of PEtOx relative to propagation. However, the post-functionalization reactions were controllable and lead to the formation of ammonium phosphonate zwitterions. ^{1}H NMR data confirmed the structures of phosphonic acid-modified random copolymers. These novel materials with pH sensitive phosphonate functionality may exhibit strong complexation toward many types of nanoparticles such as magnetite, ions (e.g. manganese) and cationic (e.g. gentamicin) drugs. Non-ionic PEO block may also provide steric dispersion stability in water for micellar complexes with metal oxide nanoparticles, ions or drugs in their cores.

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CHAPTER 6 - Conclusions and Recommendations

Several synthetic strategies have been developed for preparing functional poly(2-ethyl-2-oxazoline) (PEtOx) containing homo- and block copolymers as potential components of water purification membranes and biomaterials. Controlling the membrane transport properties such as water flux, salt and organic solute rejection via utilization of polysulfone(hydrophobic)-poly(2-oxazoline)(hydrophilic)-based amphiphilic block copolymers is a promising approach to prepare future water purification membranes with high stability against chlorinated disinfectants and over a wide pH ranges. Moreover, poly(2-oxazoline)s are attractive candidates for use in a variety of bioapplications such as drug delivery vehicles, magnetic resonance enhancement agents, and tissue engineering matrices because they can be synthesized with controlled molecular weights, endgroup and side-chain functionalities and molecular architectures.

Our initial approach was to prepare poly(2-ethyl-2-oxazoline-*b*-arylene ether sulfone-*b*-2-ethyl-2-oxazoline) (PEtOx-*b*-PSF-*b*-PEtOx) amphiphilic triblock copolymers via cationic ring opening polymerization of 2-ethyl-2-oxazoline monomers from telechelic tosylate functional PSF macroinitiators. Thermal analyses indicated high thermal stability and the presence of two different glass transition temperatures might be indicative of a phase separated morphology. The triblock copolymers were then hydrolyzed to form poly(2-ethyl-2-oxazoline-*co*-ethyleneimine)-*b*-poly(arylene ether sulfone)-*b*-poly(2-ethyl-2-oxazoline-*co*-ethyleneimine) (PEtOx-*co*-PEI-*b*-PSF-*b*-PEtOx-*co*-PEI) ionomers. Promising water uptake values were obtained even though short polyoxazoline end blocks were introduced. However, it was reasoned that high compositions of the hydrophilic components in triblock copolymer structures might result in films with poor mechanical properties due to absorption of too much water during use as water purification membranes. Therefore, multiblock copolymers based on copolymerizations of poly(arylene ether sulfone) oligomers with hydrophilic poly(alkyloxazoline) prepolymers have been proposed since they were expected to have better mechanical integrity with higher hydrophilic compositions. Thus, telechelic and heterobifunctional PEtOx oligomers with controlled molecular weights and endgroup functionality (e.g. secondary amine, vinylsilane) have been synthesized. Such endgroup structures are suitable for further coupling and/or crosslinking reactions with multifunctional isocyanates, epoxides or acrylamides to form amphiphilic multiblock structures. Telechelic, heterobifunctional or multifunctional poly(alkyl oxazoline)s are also interesting materials for incorporation into hydrogel structures as support materials.

Multiblock amphiphilic copolymers can be prepared via copolymerization of diisocyanate functional hydrophobic PSF and telechelic hydrophilic PEtOx oligomers with secondary amine endgroups. Isocyanate functional telechelic PSFs can be prepared by reacting hydroxyethyl endgroups on PSF termini with diisocyanates (Figure 6.1). Alternatively, multiblock nonionic copolymers can be synthesized using multifunctional PEtOx prepolymers with vinylsilane endgroups. In this approach, first, heterobifunctional PEtOx oligomers with vinyl silane and secondary amine functional endgroups will be prepared as described in chapter 4. Subsequently, these prepolymers will be coupled with either di-, triisocyanates or di-, tetraepoxy functional reagents to form multivalent hydrophilic PEtOx prepolymers for incorporation into crosslinked selective layers for thin film composite membranes (Figure 6.2). Multifunctional PEtOx oligomers with

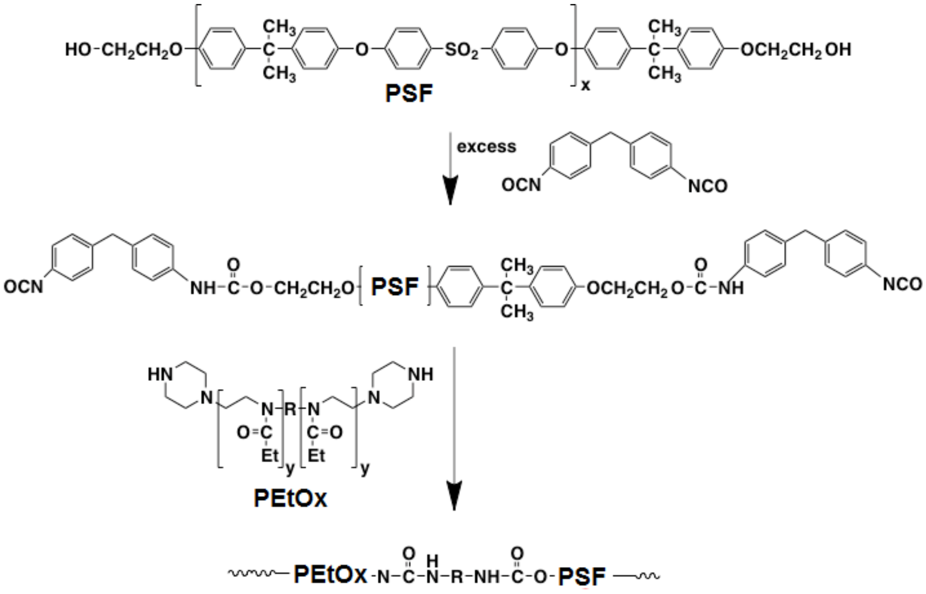


Figure 6.1 Linear random amphiphilic PSF-PEtOx-polyurethane multiblock copolymers

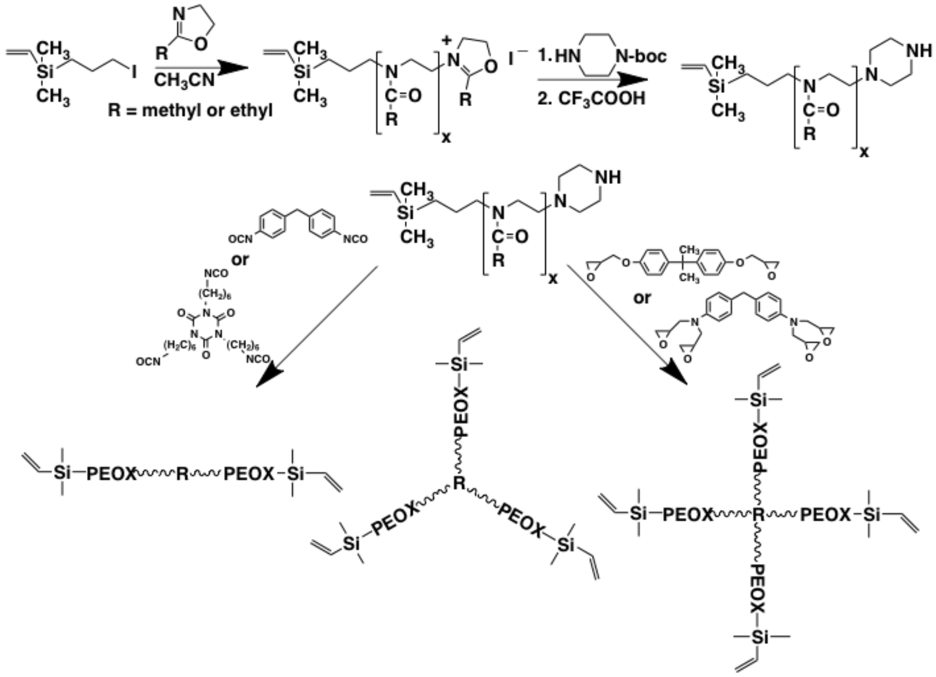
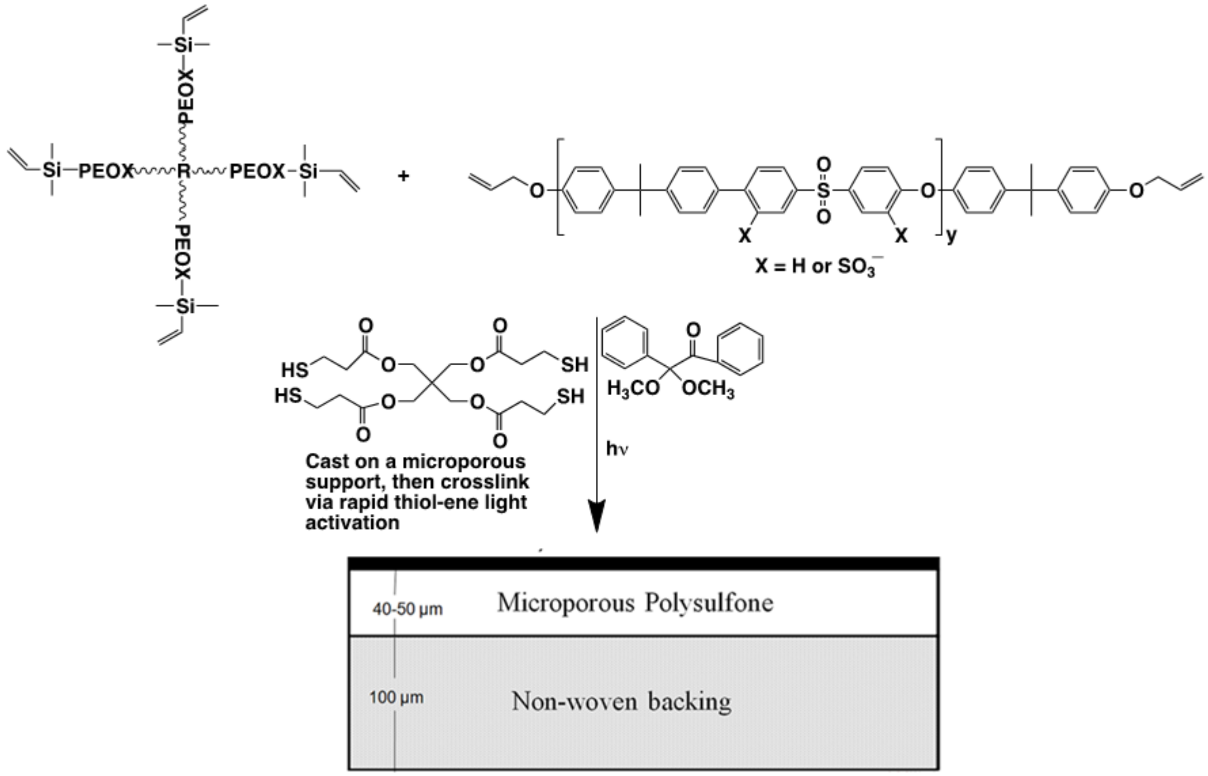


Figure 6.2 Synthesis of multifunctional PEtOx oligomers with vinylsilane endgroups

vinylsilane functionality are suitable for thiol-ene free radical crosslinking reactions with vinyl functional telechelic PSF oligomers that are initiated with light (Figure 6.3).

Amphiphilic network membranes based on PSF and PEtOx polymers can be generated using these potential methodologies.



Cast on a microporous support, then crosslink via rapid thiol-ene light activation

Figure 6.3 Light induced crosslinking reaction to form polysulfone-poly(alkyloxazoline) networks as barrier layers for thin film composite membranes

Phosphonic acid modified poly(ethylene oxide-*b*-2-ethyl-2-oxazoline) (PEO-*b*-PEtOx) diblock copolymers have also been synthesized through functionalization reactions on the polyoxazoline block. The poly(alkyloxazoline) block was partially hydrolyzed with HCl to form the random copolymer PEO-*b*-PEOX-*co*-PEI. These copolymers were dialyzed in pH ~ 9 to neutralize the imine group for an efficient Michael addition reaction onto diethyl vinyl phosphonate to form PEO-*b*-PEOX-*co*-PEI-*co*-phosphonate copolymers. Further hydrolysis of the phosphonate groups formed the final product, PEO-*b*-PEOX-*co*-PEI-*co*-phosphonic acid. The polyelectrolyte block can form complexes with drugs or ions with a complementary charge and the non-ionic water soluble block (PEO) provide steric stabilization in physiological media. Thus, the formed nanostructures can be utilized as promising drug delivery vehicles. ^{1}H NMR spectra confirmed the formation of phosphonic acid functional copolymers. However, detailed SEC investigations with a multiple (multi-angle laser light scattering, viscometry, and differential refractive index) detector system indicated the presence of PEO-macroinitiators remained unreacted during the polymerization of EtOx monomers. While the refractive index and light scattering chromatograms only showed unimodal relatively narrow distributions, the viscometer curves clearly displayed the PEO macroinitiator content in a second lower molecular weight peak. Hence, the final product is a blend of phosphonate functional copolymer with a residual PEO macroinitiator. Both PSF and PEO macroinitiators have the same type of endgroup structures and EtOx polymerizations were performed under identical conditions, however we have not observed any side shoulders in the SEC chromatograms of triblock copolymers prepared using PSF macroinitiators. PSF may be more dominating in SEC runs than PEtOx and we might have a mixture of diblock and triblock copolymers. However there is no indication for this conclusion after detailed SEC studies with a multiple-detector system and triblock copolymers with different block lenghts.

Phosphonic acid functional PEO-*b*-PEtOx diblock copolymers may still be interesting materials for biomedical applications due to the biocompatibility of PEO. However, it is much easier to work with well-defined systems to have a better control over the desired applications. Thus, alternative and easily handled PEO macroinitiator structures (e.g. benzyl iodide functional PEO) (Figure 6.4) should be developed that will show a faster initiation mechanism for alkyl oxazoline polymerizations than tosylate functional PEO macroinitiators. Moreover, copper catalyzed azide/alkyne click chemistry may be a viable approach to prepare PEO-*b*-PEtOx diblock copolymers. In the first step, an azido functional PEtOx can be prepared using methyl triflate and sodium azide as the initiator and termination agent, respectively. As a next step, monofunctional PEO (e.g. CH_3-PEO-OH) can be functionalized with an alkyne group at one chain end using a base (e.g. sodium hydride, NaH) to abstract hydroxyl protons and propargyl bromide ($CH{\equiv}C{-}CH_2Br$) to introduce an alkyne group. Finally, functional PEO and PEtOx can be coupled using the Huisgen 1,3-dipolar cycloaddition reaction in the presence of a copper catalyst (sodium ascorbate/copper (II) sulphate) to form the desired diblock copolymer structures (Figure 6.5). This diblock copolymer is also believed to be stable under acidic conditions that are utilized during post-modification reactions to introduce phosphonate/phosphonic acid groups.

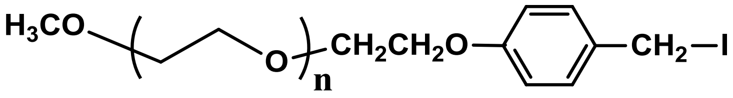


Figure 6.4 Chemical structure of a benzyl iodide functional PEO macroinitiator

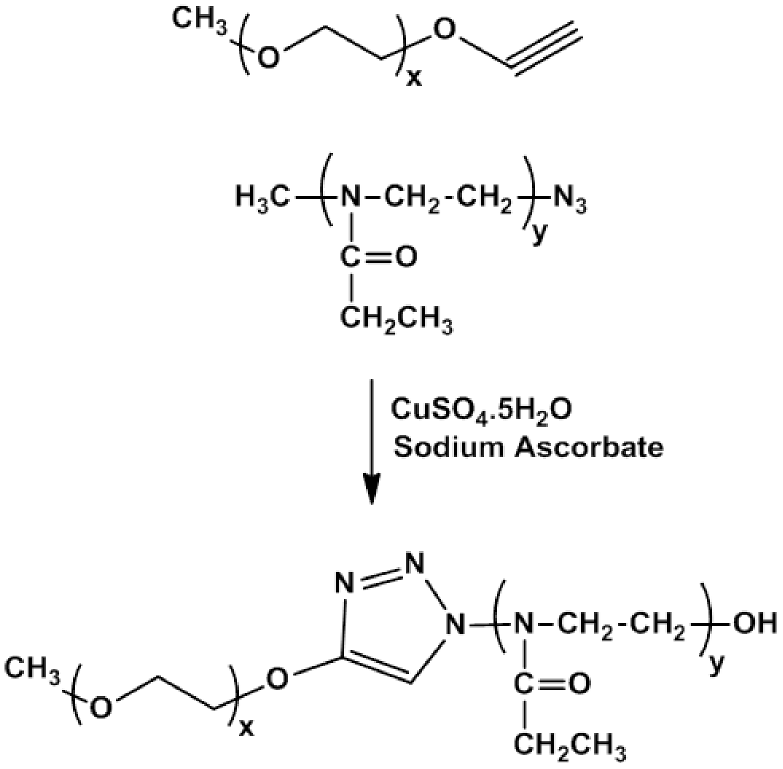


Figure 6.5 Synthesis of PEO-*b*-PEtOx diblock copolymers using copper catalyzed azide/alkyne click chemistry