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Molecular weight distribution and endgroup functionality of poly(2-ethyl-2-oxazoline) prepolymers

O. Celebi, S.R. Barnes, G.S. Narang, D. Kellogg, S.J. Mecham, J.S. Riffle*

Macromolecules and Interfaces Institute and the Department of Chemistry, Virginia Tech, Blacksburg, VA 24061, USA

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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 as the control, activated benzyl and xylyl halides, and non-activated alkyl iodides. Endgroup functionalities and molecular weight distributions were compared by SEC, ^{1}H NMR and titrations. PEtOx oligomers initiated with methyl triflate had polydispersities (PDI's) near 1.1 while those initiated with activated benzyl or xylyl halides had PDI's of 1.30–1.45. The difference was attributed to slower initiation and to covalent species in the activated halide-initiated reactions that were present in addition to the more active cations. ^{1}H NMR showed an approximately 1:1 endgroup functionality in these cases and titrations of the amine endgroups were in good agreement with the NMR endgroup data. 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. Non-activated alkyl iodides initiated these reactions quite slowly and there was a wider discrepancy between targeted and obtained molecular weights after isolation of the oligomers.

1. Introduction

Monofunctional and telechelic poly(2-oxazoline) prepolymers are candidates for components of block and graft copolymers for many applications provided that they can be synthesized with reasonable control over molecular weights and their distributions and that their endgroups can be 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 obtained 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 fluorinated phenyl-containing polymers. Moreover, 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) and polypeptides since they are comprised of a $-NCH_2CH_2-$ backbone and an amide in each repeat unit [3–6].

Structural features of poly(2-oxazoline)s offer good potential for biomedical applications [3,4,7–10]. Poly(2-methyl-2-oxazoline) and PEtOx are of 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 poly(2-methyl-2-oxazoline) 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 good endgroup functionality. Mono- [22,23] and difunctional [24] allyl or benzyl halides have been studied as

* Corresponding author.
E-mail address: judyriffle@aol.com (J.S. Riffle).

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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 poly(ethylene oxide) 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 poly(2-methyl-2-oxazoline)s 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. Alternatively, Volet and coworkers synthesized mono- and difunctional poly(2-methyl-2-oxazoline) oligomers utilizing iodomethane and 1,3-diiodopropane initiators, respectively, and terminated with sodium azide. Azido-functional polyoxazoline oligomers were then transformed to acrylate, epoxide, carboxylic acid and poly(ethylene oxide) functionalities utilizing heterobifunctional alkynes and click chemistry via Huisgen 1,3-dipolar cycloaddition reactions [38]. 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, then the allyl endgroup was reacted with trimethoxysilane by hydrosilylation [39]. Hoogenboom and Schubert et al. [40] also described the synthesis of a multifunctional copoly(2-oxazoline) scaffold containing α-anthracene and ω-azide termini as well as pendent alkenes in the side chain. In this study an anthracene moiety with an iodomethylene substituent was introduced at the initiation step, and 2-(dec-9-enyl)-2-oxazoline was copolymerized with 2-ethyl-2-oxazoline to introduce alkene pendent groups, then the polymerization was terminated with sodium azide. Their approach shows promise for selective attachment to bioactive agents.

While many homo- and copolymers containing poly(2-alkyl-2-oxazoline) 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, including step–growth reactions. 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 titrations were combined to assess the influence of reaction variables on molecular weights and endgroup functionality. Prepolymers with secondary amine and vinylsilane endgroups have been investigated.

2. Experimental

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. Diethylether (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 (1000 MWCO, wet in 0.05% aqueous sodium azide) were purchased from Spectrum Laboratories, Inc. 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 °C overnight.

2.2. Synthesis

2.2.1. Synthesis of a diiodo-p-xylene initiator

Diiodo-*p*-xylene was prepared from dibromo-*p*-xylene and sodium iodide in acetone. 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 °C 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 × 3). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum. The residue was recrystallized from 1,4-dioxane, and washed with cold dioxane and diethylether. The product was vacuum dried overnight at 50 °C. Yield was ~50%.

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, then the reaction was conducted at 60 °C for 24 h. The reaction mixture was cooled to room temperature and the salt by-products were allowed to precipitate over 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 °C, ~0.8 Torr, and collected as a colorless liquid. A 2-fold excess of NaI (0.034 mol, 5.1 g) was charged to a round-bottom flask equipped with a magnetic stir bar. The reaction vessel was sealed with a septum and flame-dried. Acetone (25 mL) was added via syringe to the flask. 3-Chloropropylmethyldivinylsilane (0.017 mol, 3.0 g) was charged to the reaction vessel via syringe. The reaction was stirred at 60 °C for ~48 h. The acetone was removed by rotary evaporation, and the reaction mixture was dissolved in chloroform (150 mL). The excess NaI and the NaCl salt byproducts were removed by vacuum filtration. The clear, colorless 3-iodopropylmethyldivinylsilane product was vacuum distilled at 70 °C and ~0.8 Torr. ^{1}H NMR confirmed the expected structures in each case. Yield was ~40%.

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) and a 2-fold excess of NaI was used in the second step. Yield was ~40%.

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 °C. 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 of $CDCl_3$. 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 °C 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. The product yields were ~70%.

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, then freeze-dried.

Synthesis of *boc*-piperazine-terminated PEtOx oligomers with benzyl bromide as the initiator followed a similar procedure to that described above and the yields obtained were ~60%.

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 ^{1}H 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 °C 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, then freeze-dried. The product yield was ~80%.

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.

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.

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. These heterobifunctional initiators yielded ~ 60% of polymer.

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 300 × 7.5 mm (polystyrene/divinylbenzene) connected in series with a guard column having 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 7000 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 by universal calibration was defined as 2 standard deviations (7–8%). The variation in M_n by light scattering was also defined as 2 standard deviations (11–13%). 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 system was performed by monitoring the molar mass of a known molecular weight polystyrene sample by light scattering with every sample set. The accepted variance of the 21,000 g/mole sample was defined as 2 standard deviations (11.5% M_n, 9% M_w) from a set of 34 runs over a 6-month time period.

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 micropipette. Equivalence (inflection) points were determined by plotting the first derivative of the pH curve ($\Delta pH/\Delta V$) against titrant volume.

3. Results and discussion

Prepolymers synthesized with three classes of initiators based on their rates of initiation and the relative 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, also more nucleophilic counterions). While triflates are ideal with regard to oligomerization conditions, their sensitivity to moisture makes triflate macromonomers more difficult to handle and purify. Alkyl halide initiators are much less sensitive to moisture and would be preferable if oligomers with good molecular weight distributions and terminal functionality can be achieved.

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 °C) with the same monomer and initiator concentrations and their molecular weights and endgroup structures were analyzed (Fig. 1, Table 1). It was reasoned that this set would serve as control materials since fast initiation relative to propagation and narrow molecular weight distributions have been reported earlier by several investigators [2]. 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 ($-NCH_2CH_2-$) [23,41], 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.

The structures and endgroups of these monofunctional PEtOx oligomers were characterized using ^{1}H NMR (Fig. 2a–c), titrations and SEC (Table 1). Polymerization resulted in broad NMR 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 (Fig. 2a) and 1.30 ppm (Fig. 2b) were 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 compared to assess the efficiency of termination (1:1 endgroup ratio). It should be noted that the *t*-butyl protons on the *boc*-piperazine terminated oligomers appear as a sharp singlet, while the piperidine proton resonances are broad, and thus it is expected that the ^{1}H NMR analyses may be more accurate for the *boc*-piperazine-functional polymers. However, a ± ~5% error was applied for all of the NMR analyses. In all cases, the ^{1}H NMR integrals were consistent with the expected 1:1 ratio of methyl groups on the initiator to secondary amines on the terminated end. Number average molecular weights were calculated by comparing the ratio of the integrals of PEtOx proton resonances to the endgroup protons (both CH_3 and either piperidine or *t*-butyl). Disappearances of the *t*-butyl resonances upon deprotection of *boc*-piperazine were also indicative of successful deprotection (Fig. 2c).

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-functional polymers were titrated with base and the titrant volumes between the two inflection points corresponded to the number of amine endgroups. To determine the equivalence points that resulted from abstraction of protons from piperazinium endgroups, the first derivative of the pH curve (Fig. S1a) ($\Delta pH/\Delta V$) was plotted against volume (Fig. S1b). When $\Delta pH/\Delta V$ is at its maximum value, it represents the inflection point of the titration. Titrant volumes between the two inflection points were utilized to determine the concentration of amine endgroups. Piperidine-functional polymers were titrated with acid. The NMR and titration data shown in Table 1 are within the error range for all of the triflate-initiated polymers. It is reasoned that the titration data is likely more accurate due to inherent line broadening in the NMR spectra. The endgroup data showed that the molecular weights were somewhat higher than the targeted values and this was attributed to loss of some low molecular weight species in the dialysis process used to purify the oligomers.

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 1). All of the polymerizations initiated

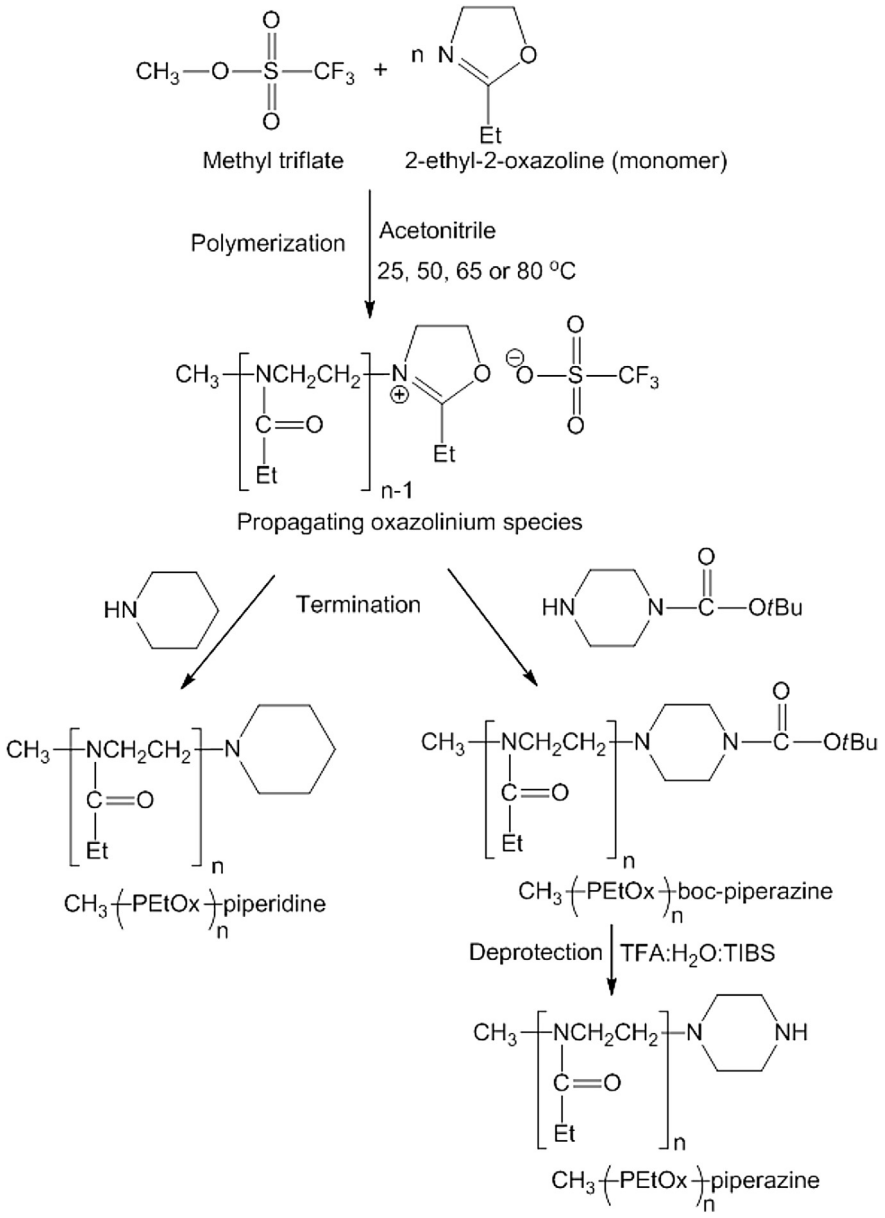

Fig. 1. Synthesis of controlled molecular weight poly(2-ethyl-2-oxazoline) oligomers with piperidine or piperazine endgroups.

with methyl triflate that were conducted over a range of temperatures (25–80 °C) and that were terminated at 70 to near 100% monomer conversion produced unimodal, symmetrical chromatograms (Fig. 3). While reactions proceeded faster as expected as temperature was increased, no effect on molecular weight distribution was observed with temperature in this range as long as the reactions were not continued after the monomers were depleted. M_n's were calculated from the SEC curves via both a universal

Table 1
Methyl triflate-initiated PEtOx oligomers prepared at different temperatures.

Reaction temperature (°C)	Reaction time (h)	Termination agent	M_n[a] target	M_n[b] ^{1}H NMR	M_n titration	M_n[c,d] SEC universal calibration	M_n[c,e] SEC light scattering	PDI
80	4	*boc*-Piperazine	5200	6250 ± 300	5750 ± 250	6800 ± 250	6500 ± 350	1.13
65	7	Piperidine	4500	5450 ± 250	5650 ± 150	6600 ± 250	6200 ± 350	1.15
50	24	Piperidine	4850	5650 ± 300	6000 ± 50	7000 ± 250	6800 ± 350	1.12
25	215	Piperidine	4400	4550 ± 250	–	6100 ± 250	5900 ± 350	1.11

[a] Corrected for monomer conversion at termination and includes the terminal *boc*-piperazine or piperidine endgroups.
[b] Error in the NMR spectra were estimated to be ± ~5% in the calculated M_n values.
[c] The dn/dc was 0.0515 ± 3%.
[d] The standard deviation varied from ±120 to 240.
[e] The standard deviation falls in the range of ±260 to 370.

calibration that was prepared with a series of monodisperse polystyrene standards and viscometric and differential refractive index detectors, and also by MALLS static light scattering and differential refractive index detectors. The intensity of the Raleigh ratio (R(θ)) 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). The universal calibration method is also more dependent on the higher molecular weight polymers because it depends on solution viscosity. All of the SEC analyses of the triflate-initiated polymers showed somewhat higher M_n's than the endgroup analyses (NMR and titration) (Table 1). This can likely be attributed to the SEC weighted dependence on the higher molecular weight side of the distributions with both light scattering and viscometric measurements.

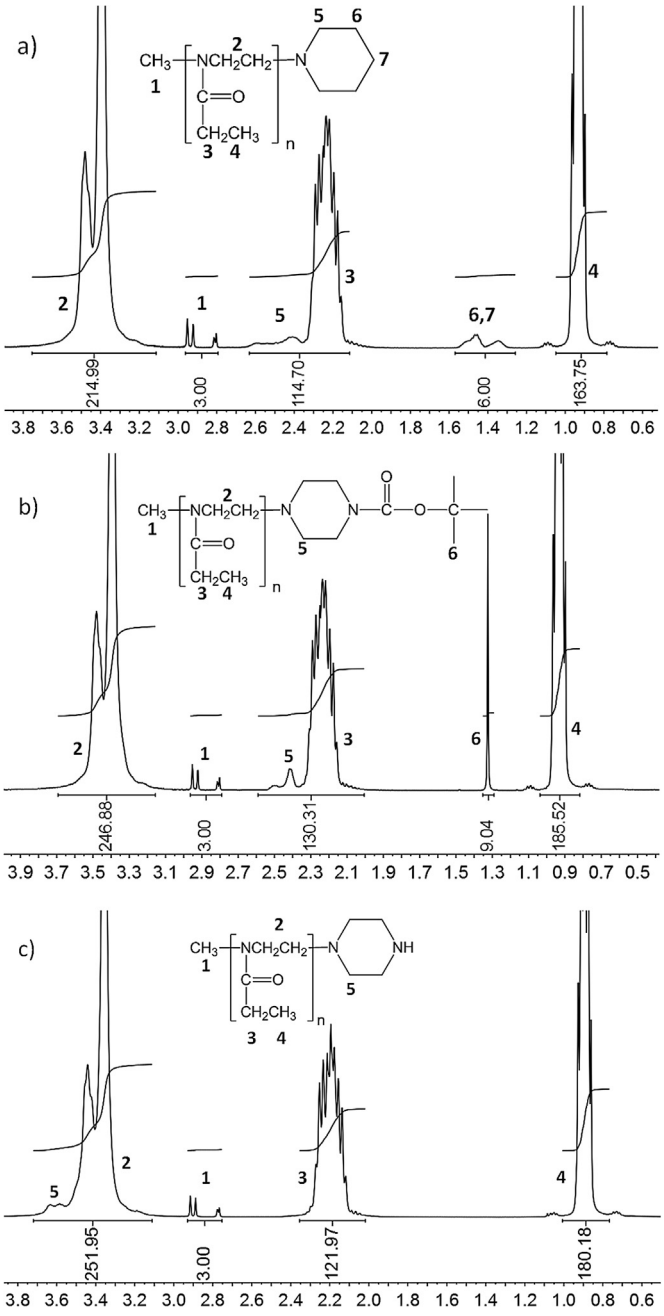

Fig. 2. ^{1}H NMR spectra of a) CH_3-PEtOx-piperidine synthesized using methyl triflate as the initiator at 65 °C and terminated with piperidine, b) CH_3-PEtOx-*boc*-piperazine synthesized using methyl triflate as the initiator at 80 °C and terminated with protected piperazine, and c) CH_3-PEtOx-piperazine (deprotected CH_3-PEtOx-*boc*-piperazine) prepared at 80 °C obtained in D_2O.

The refractive index increment (dn/dc) is critical to calculating molar mass by light scattering. It is also important for calculating molar mass using a 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 0.05 M LiBr were calculated 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 shown in Table 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 h), and the other was maintained at 80 °C well after all of the monomers had been consumed (24 h). The polymer that had been heated for ~24 h had a prominent high molecular weight shoulder in the SEC chromatogram, whereas the polymer heated for only 4 h had a symmetrical unimodal peak and a PDI of 1.13 (Fig. S2). Moreover, our studies indicated that as these side reactions occurred, there was no correlation between the integral ratios of protons from initiator fragments and terminal groups. This may be attributed to enamine formation and chain coupling as monomer was depleted as previously suggested by Litt et al. [42]. All of this data on molecular weights and endgroup structures of PEtOx oligomers suggests that materials with controllable molecular weights and narrow PDI's with the expected endgroup functionality can be prepared with methyl triflate as an initiator (Table 1). It is important, however, to terminate the reactions at times close to complete monomer conversion.

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, would be accessible by this method [25,43].

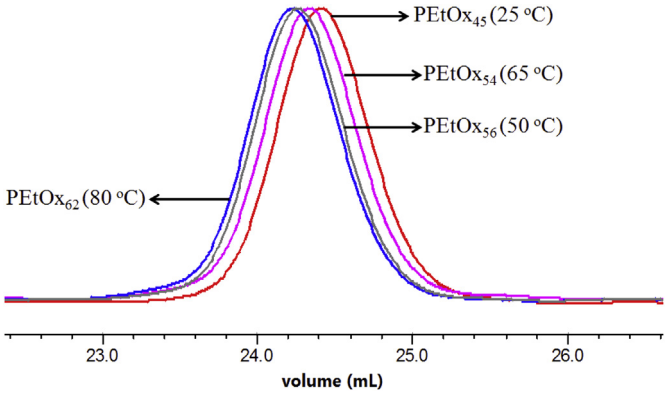

Fig. 3. Refractive index chromatograms of PEtOx oligomers initiated with methyl triflate and polymerized at 25, 50, 65 and 80 °C.

Monofunctional PEtOx oligomers were initiated with benzyl bromide at 25, 40, 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. Telechelic PEtOx oligomers were prepared using dibromo- and diiodo-*p*-xylene initiators. ^{1}H NMR indicated the successful conversion of dibromo-*p*-xylene to diiodo-*p*-xylene as confirmed by the upfield shift of aromatic and methylene protons in diiodo-*p*-xylene in reference to dibromo-*p*-xylene. The melting point of the diiodo-functional initiator was 178–179 °C and dibromo-*p*-xylene had a melting point of 145–147 °C, consistent with literature values [44].

^{1}H NMR again showed an approximate 1:1 correlation between *boc*-piperazine (*t*-butyl) resonances (9H) and benzyl endgroup aromatic protons (5H) at 7.10–7.35 ppm (Fig. 4). Chemical structures of the difunctional PEtOx oligomers with *boc*-piperazine endgroups and their deprotected forms were confirmed by ^{1}H NMR and titrations (Fig. 5a–c). Aromatic and methylene protons from the initiator resonated at 7.15 and 4.50 ppm, respectively. The integral values of *t*-butyl protons (18H) on the endgroups and resonances from the initiator (4H) suggested that difunctional polymers were formed (Fig. 5b). Disappearance of the *t*-butyl proton resonances upon deprotection of the chain ends indicated conversion to secondary amine endgroups (Fig. 5c). ^{1}H NMR also showed the expected downfield shifts of the protonated piperazinium resonances as they were formed under acidic conditions.

M_n values were calculated using the relative integral values of PEtOx protons in the repeat units and the endgroups (Table 2). As with the triflate-initiated oligomers, the amine endgroups of these oligomers were also titrated. With the exception of entry 4, Table 2 shows good agreement between M_n's derived from the titration and NMR endgroup data for the polymers that were initiated with benzyl and xylyl halides. We and others have observed that 2-ethyl-2-oxazoline polymerizations conducted using benzyl (and also initiated by non-activated alkyl halides) halides proceed via a mixture of covalent and cationic oxazolinium species due to some attack on the terminal cationic ring by the relatively nucleophilic halide counterions [23,41,45]. The reactivity of cationic propagating chains is much higher compared to the covalently-bound species [46]. However, since the NMR data show an ~1:1 ratio of benzyl to piperazine functionality and since both covalent and ionic propagating species were present in the benzyl halide-initiated polymerizations, this suggests 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 were present, the desired endgroup functionality was still obtained.

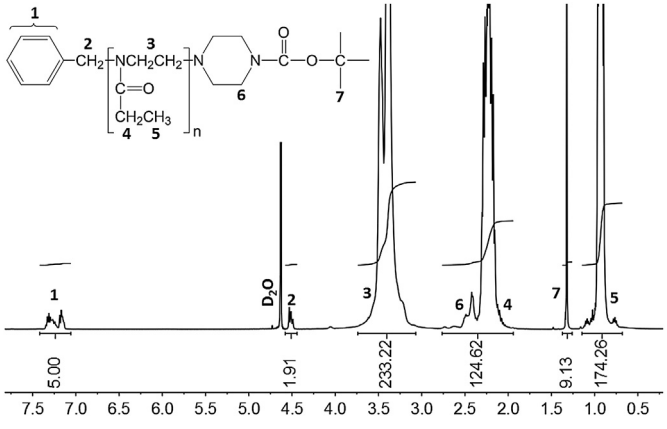

Fig. 4. ^{1}H NMR spectrum of a PEtOx oligomer that was initiated with benzyl bromide at 25 °C and terminated with *boc*-piperazine obtained in D_2O.

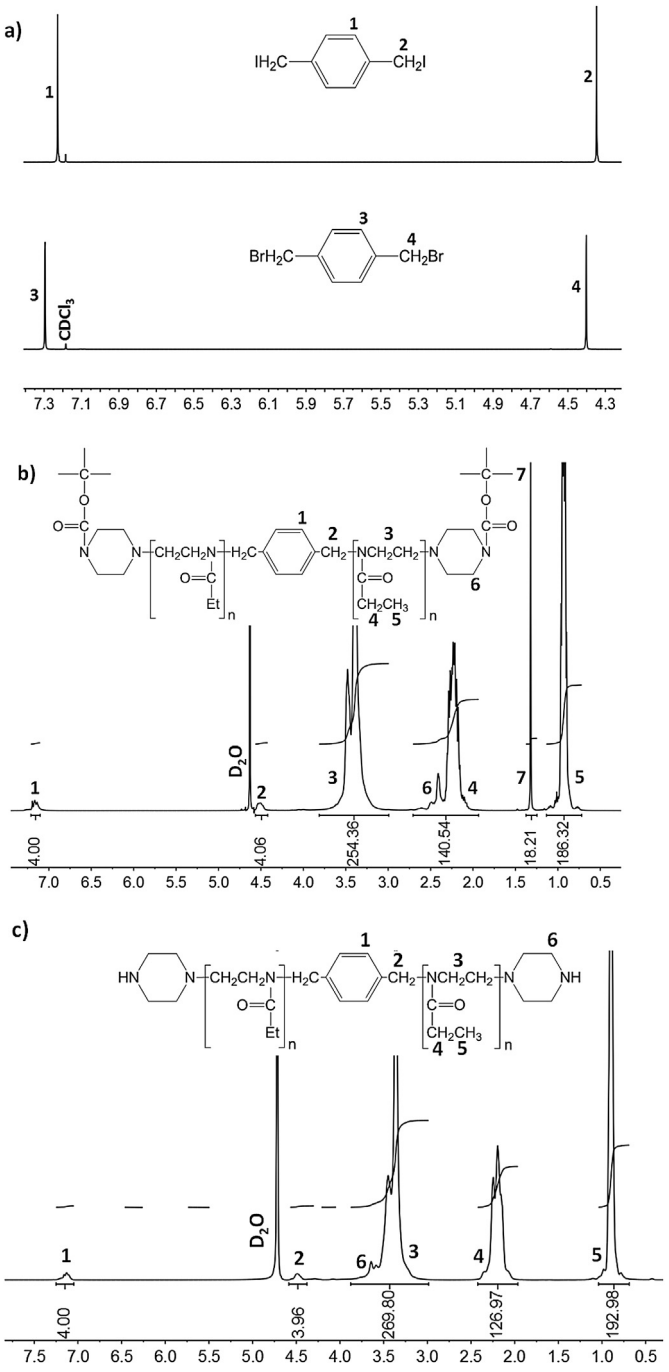

Fig. 5. ^{1}H NMR spectra of a) dibromo- and diiodo-*p*-xylene initiators obtained in $CDCl_3$, b) a telechelic PEtOx oligomer polymerized using diiodo-*p*-xylene at 60 °C and terminated with *boc*-piperazine obtained in D_2O, and c) piperazine-functional telechelic PEtOx (deprotected form) obtained in D_2O.

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 SEC sample recovery values yielded by the Astra software were higher than 100% (signifying 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 2 that were initiated with benzyl or

Table 2
Alkyl halide-initiated monofunctional and telechelic PEtOx oligomers terminated with *boc*-piperazine.

Initiator	Temperature (°C)	Reaction time (h)	Target[b] M_n	M_n[c] ^{1}H NMR	M_n titration	M_n[d] SEC universal calibration	PDI
Benzyl bromide	25	304	4650	6050 ± 300	5900 ± 100	4700	1.36
Benzyl bromide	40	33	4550	5500 ± 300	5600 ± 300	4900	1.34
Benzyl bromide	50	25	4850	6250 ± 300	6100 ± 250	4900	1.33
Benzyl bromide	65	19	5000	6150 ± 300	5650 ± 150	5600	1.30
Dibromo-*p*-xylene	60	8.5	7200	8300 ± 400	8600 ± 150	6300	1.45
Diiodo-*p*-xylene	60	4.5	5550	6750 ± 350	6975 ± 125	5000	1.37
Monovinyl alkyl iodide	60	13.5	4000	7300 ± 350	–	6500 ± 250	1.26
Divinyl alkyl[a] iodide	60	10.5	4300	7250 ± 350	6150 ± 125	5600 ± 250	1.33

[a] Terminated with piperidine.
[b] Corrected for the extent of monomer conversion at termination and includes the *boc*-piperazine or piperidine endgroups.
[c] Error in the NMR spectra were estimated to be ± ~5% for boc-piperazine functional oligomers and ±7% for piperidine functional polymers of the M_n values.
[d] Errors were not assigned to the SEC values for the cases of aromatic initiators due to the unknown error caused by deviations in the dn/dc across the molecular weight distribution.

xylyl halides (Fig. S3), this was 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 deviances in calculations of molecular weights, and the impact was greater for lower molecular weights. This implied 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 2 by adjusting them for each sample until the SEC software suggested 100% recovery of the sample. It is noted that the molecular weights derived from SEC for the polymers in Table 2 with the aromatic initiators were lower than their titrated and NMR values. This may indeed be attributable to a variance in dn/dc across the molecular weight distribution for those in Table 2 prepared with aromatic initiators due to the high refractive index of the initiator.

While absolute values for M_n's from SEC for the benzyl and xylyl-initiated polymers were not reliable, the molecular weight distributions for those materials were uniformly higher than for polymers initiated with methyl triflate (~1.30–1.45 versus ~1.1, Tables 1 and 2). RI chromatograms of the benzyl bromide initiated oligomers showed a slight tail on the low molecular weight side relative to the very symmetrical curves from the methyl triflate-initiated polymers (Fig. S4). The rather broad PDI values were attributed to slower initiation rates and slow propagation of covalent species that were present in addition to the cationic oxazolinium ions.

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

Heterobifunctional PEtOx's with vinylsilane functionalities on one chain end and an amine group on the other were attempted using mono- and divinylsilylpropyl iodide initiators (Fig. 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 Finkelstein reaction as described previously [28–30]. The molecular structures of these mono- and divinylsilyl alkyl iodides were confirmed by ^{1}H NMR (Figs. 7a and 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 protons appeared at 5.6–6.2 ppm. ^{1}H NMR analyses of the heterobifunctional PEtOx oligomers also showed the expected chemical structures (Figs. 7b and 8b). Endgroup analyses again confirmed efficient 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 (Fig. 7c). However, the initiation rate with these initiators relative to propagation was too slow and there were substantial amounts of low molecular weight species in the molecular weight distributions (Fig. S5). Yields of the polymerizations initiated by the two alkyl iodide initiators were ~60%. The data in Table 2 show a wider discrepancy between the targeted and acquired molecular weights than the polymers initiated with the activated benzyl halides, and this is attributed to more loss of the low molecular weight fractions during isolation and purification in cases where non-activated halides were the initiators. Moreover, the SEC chromatograms of polymers initiated with the non-activated halides had significant low molecular weight tails (Fig. S5) that were not observed with the activated halide initiators (Fig. S4). 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 products with significant low molecular weight fractions.

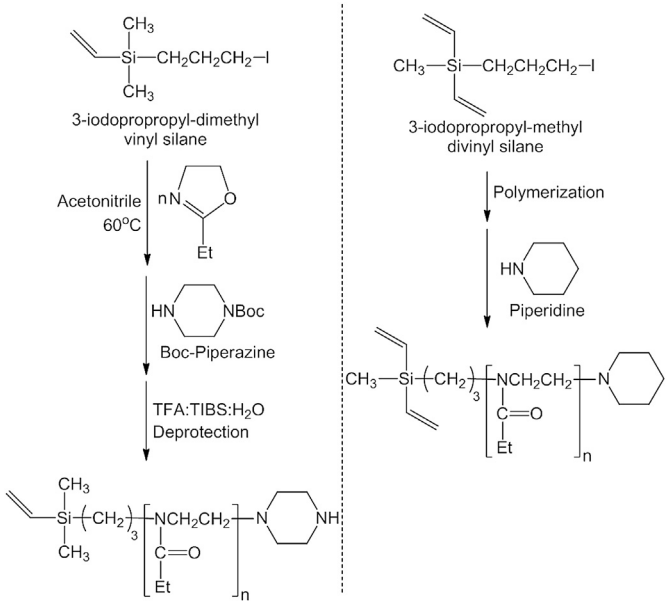

Fig. 6. Synthesis of heterobifunctional PEtOx oligomers initiated by mono- or divinyl alkyl iodides and terminated with aliphatic amines.

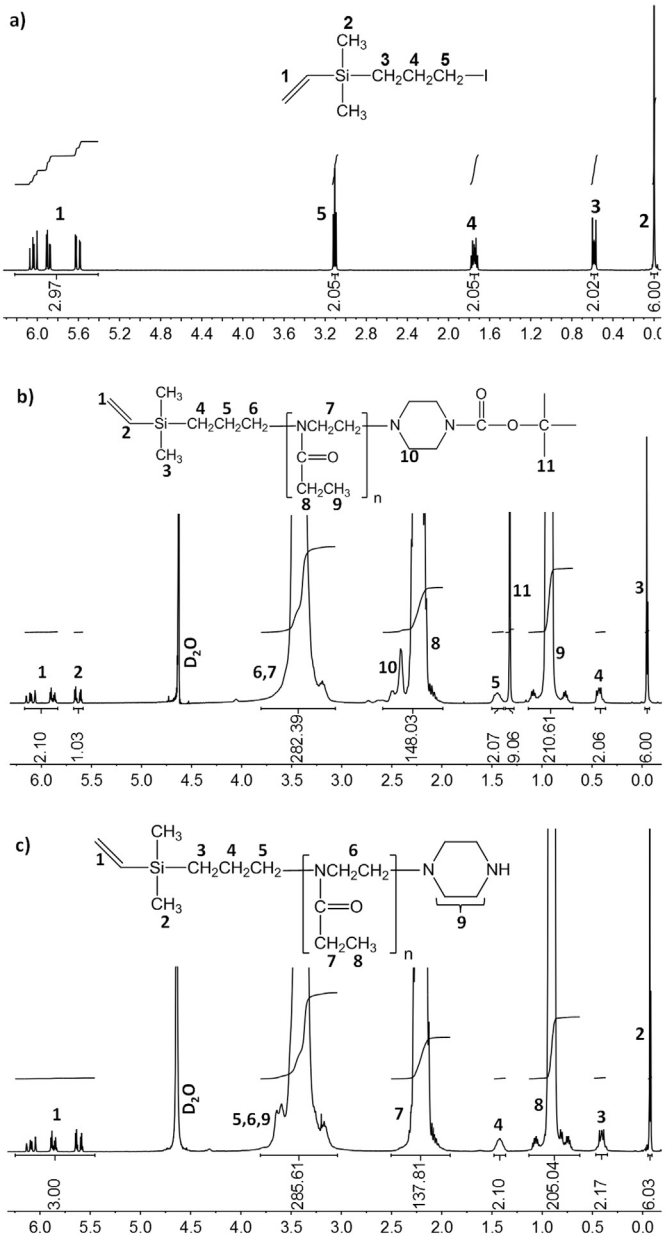

Fig. 7. ^{1}H NMR spectra of a) 3-iodopropyldimethylvinylsilane obtained in $CDCl_3$, b) dimethylvinylsilylpropoxy-PEtOx-*boc*-Piperazine obtained in D_2O, and c) dimethylvinylsilylpropoxy-PEtOx-Piperazine obtained in D_2O.

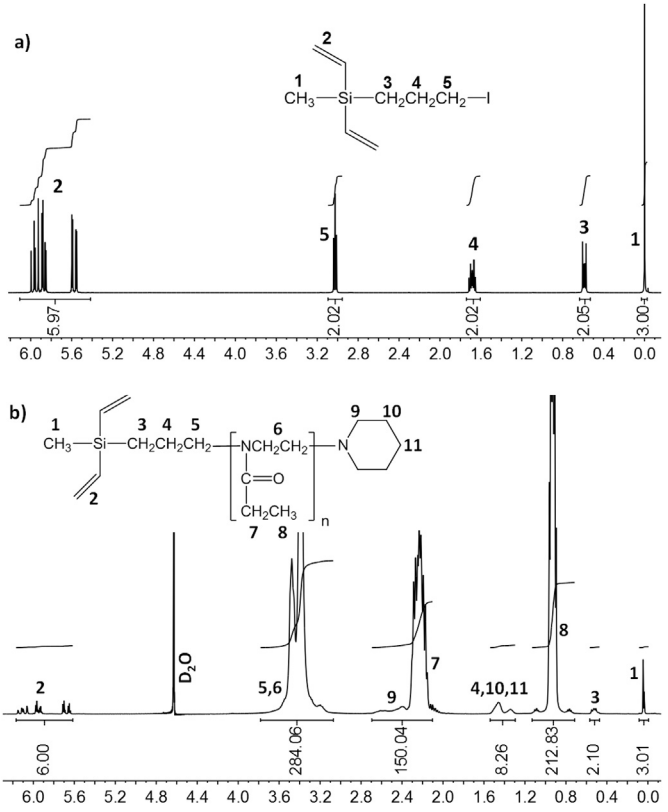

Fig. 8. ^{1}H NMR spectra of a) 3-iodopropylmethyldivinylsilane obtained in $CDCl_3$ and b) a methyldivinylsilylpropoxy-PEtOx-Piperidine oligomer obtained in D_2O.

4. Conclusions

Poly(2-alkyl-2-oxazoline) prepolymers were prepared with triflate, and activated and non-activated alkyl halide initiators, and their molecular weights and endgroup functionalities were examined with the objective of delineating synthetic parameters for oligomers that could be used as components of block and graft copolymers. Results showed that mono-functional PEtOx oligomers with the expected functionality utilizing triflate initiators as the control materials were prepared. The polymerizations were conducted between 25 and 80 °C and the reactions were terminated at 70–100% monomer conversion. No effects on molecular weight distributions were observed with temperature in this range. By terminating each reaction without allowing prolonged heating in the absence of monomer, side reactions such as the formation of chain-coupled products were minimized.

Activated and non-activated halide initiators were investigated and the polymer molecular weights and endgroup functionalities were compared with the methyl triflate-initiated controls. For the polymers initiated with methyl triflate and the activated halides, NMR data suggested that the endgroup structures were preserved. Thus, it is concluded that amines used in the termination step reacted with both the cationic and covalent endgroups on the polymers initiated with activated halides. Endgroup structures and their relative concentrations obtained from ^{1}H NMR and titration were in good agreement. In all cases, the polymers prepared with the halide-functional initiators had broader molecular weight distributions than the alkyl triflate-initiated controls and this was attributed to a combination of slower initiation and also to the relative nucleophilicity of the counterions that led to some covalent propagating species in addition to the cations in those cases. The purification steps that included dialysis also removed some low molecular weight polymers and this was more pronounced with the non-activated halide initiators, thus leading to wider discrepancies between targeted and obtained molecular weights.

SEC chromatograms showed some differences between oligomers prepared from fast and slow initiating species. The PEtOx oligomers had small dn/dc values in the SEC solvent and even a slight change caused significant deviations in molecular weights as in the case of benzyl and xylyl halide initiated oligomers due to the presence of an aromatic ring with a high refractive index. The variation in refractive index increment with concentration across the molecular weight distribution caused deviation in SEC molecular weights.

The materials that were initiated with methyl triflate and benzyl and xylyl halides are considered to be potential candidates for hydrophilic functional 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.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.polymer.2014.11.005.

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