Published in final edited form as:

Aust J Chem. 2009 November 20; 62(11): 1496–1500. doi:10.1071/CH09398.

Synthesis of Michael Acceptor Ionomers of Poly(4-Sulfonated Styrene-co-Poly(Ethylene Glycol) Methyl Ether Acrylate)

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Abstract

Ionomers containing sodium 4-styrene sulfonate (4SS) and poly(ethylene glycol) methyl ether acrylate (PEGA) were synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization. The polymerization was mediated by 1-phenylethyl dithiobenzoate chain transfer agent in a dimethylformamide/water solvent system. Well-defined copolymers of pPEGA-co-4SS were produced with molecular weights ranging from 10 kDa to 40 kDa and polydispersity indices (PDIs) of 1.06–1.18 by gel permeation chromatography (GPC) against monodisperse poly(methyl methacrylate) (PMMA) standards. Post polymerization, the dithioester was reduced and trapped *in situ* with divinyl sulfone to produce a well-defined, semitelechelic pPEGA-co-4SS Michael acceptor polymer. UV-vis, infrared, and ¹H NMR spectroscopy confirmed that the integrity of the polymer backbone was maintained and that the vinyl sulfone was successfully incorporated at the chain end.

Ionomers are polymers that have both neutral and ionic units incorporated into the polymer backbone. The charge distribution in the polymer matrix increases and strengthens the intermolecular forces between different units, improving their mechanical properties compared to a neutral polymer.^[1] Poly(sodium 4-styrene sulfonate) (p4SS), one of the most widely studied ionomers, is a water-soluble, anionic polymer that has been utilized in diverse applications as in the formation of polymer electrolytic membranes for fuel cell design and as an anticoagulant biomaterial coating.^[2, 3] Polymerization of sodium 4-styrene sulfonate (4SS) has previously been accomplished using free radical polymerization. An industrial method for the production of p4SS is the post polymerization modification of polystyrene by sulfonation. However, this results in non-specific sites of sulfonation.

Recently, controlled radical polymerizations (CRPs) such as atom transfer radical polymerization (ATRP)^[4, 5] and reversible addition-fragmentation chain transfer (RAFT)^[6–9] polymerization have been used to access well-defined 4SS-containing polymers with narrow polydispersity indices (PDIs). ATRP was the first CRP implemented in the formation of linear^[10] and brush^[11, 12] homopolymers of 4SS. The 4SS was protected with an alkyl ester before polymerization; subsequent deprotection of the p4SS alkyl ester revealed free sulfonates and led to well-defined polymers.^[13, 14] A caveat to this approach is that extra purification steps were required for the protection of the monomer, as well as deprotection of the polymer. RAFT polymerization has also been utilized to polymerize a wide range of functional monomers, including sulfonates.^[6–9, 15] McCormick and coworkers have extensively demonstrated the ability to use aqueous RAFT polymerization mediated by water-soluble CTAs to synthesize diverse polymeric scaffolds with negative charge.^[16–18]

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Others have used RAFT to copolymerize 4SS along with acrylic acid (AA) stepwise to form block copolymers for use in multilayer assembly to form polymer capsules.^[19] In our approach, the monomer poly(ethylene glycol) methyl ether acrylate (PEGA) solubilized a dithioester chain transfer agent (CTA) that had poor water solubility.^[20] Additionally, the PEGA aided in solubilizing the 4SS in a H₂O:DMF solvent system for polymerization. Kinetic data indicated that with approximately equal feed ratio of 4SS:PEGA that the 4SS was consumed more rapidly than PEGA, generating a gradient ionomer. Gradient polymers can have interesting properties compared to block and random copolymers.^[8, 21-23] Herein, we report that this technique enabled efficient synthesis of anionic, water-soluble copolymers with narrow PDIs for a variety of different molecular weights. Post polymerization, the dithioester was reduced and trapped with divinyl sulfone to yield semi-telechelic pPEGA-*co*-4SS-vinyl sulfone polymers

1-Phenylethyl dithiobenzoate (**1**) was synthesized as previously described.^[24] RAFT polymerization of 4SS and PEGA was mediated by **1** in a 1:1 mixture of DMF and H₂O at 80°C using [1]:[0.5]:[8]:[8] of **1**:AIBN:PEGA:4SS (Scheme 1). Prior to addition of PEGA the solution was heterogeneous consisting of phase separated CTA and 4SS. The ratio of DMF to H₂O was a key factor. Excess water caused the CTA and AIBN to phase separate and with the addition of excess DMF, the 4SS precipitated. Previously, we had explored homopolymerization of 4SS and noticed phase separation of the homopolymer (unpublished results). As a result we believe that the PEGA plays a key role in maintaining monomer and polymer solubility of this highly charged system.

The polymerization was terminated after 11.5 h (>99% 4SS, 90% PEGA conversion). The crude reaction mixture was then dialyzed against water for 24 h, followed by MeOH (MWCO 1000 dialysis tubing) to generate **2a**. The molecular weight and end group retention of **2a** could not be determined unambiguously from the ¹H NMR spectrum due to the overlap of the R- and Z-groups with the sulfonated styrene proton peaks (Figure 1a). Analysis by GPC against monodisperse PMMA standards indicated the synthesis of a well-defined polymer; a number average molecular weight (*M_n*) of 10.4 kDa and a PDI of 1.06 were obtained (Figure 2). The targeted molecular weight was 5.2 kDa. ¹H NMR spectroscopy was useful to estimate the final ratio of monomers within the polymer. The methyl ether, poly(ethylene glycol), and ester protons of the PEGA units were averaged and compared to that of the protons on 4SS. From this, the copolymer was found to have a final ratio of approximately 1:1 PEGA to 4SS at this high conversion.

To determine if the monomers polymerize at the same rate, a reaction was monitored by ¹H NMR. To target a molecular weight of 8.8 kDa, the ratio used was [1]:[0.5]:[13.8]:[12.4] of **1**:AIBN:PEGA:4SS. Samples were taken over a 10 h period and analyzed by ¹H NMR and aqueous size exclusion chromatography (SEC). The results indicated that 4SS was consumed faster than PEGA, determined by monitoring the disappearance of the vinylic protons of the 4SS and PEGA units to the ether protons of PEGA over time (see supporting information). This suggested that a gradient polymer was formed and indicated that to obtain a 1:1 ratio in the final polymer that high overall conversions must be achieved.

Favorable results obtained with **2a** led to applying this strategy towards the synthesis of larger molecular weight polymers. Ratios of [1]:[0.5]:[30]:[30] and [1]:[0.5]:[61]:[61] of **1**:AIBN:PEGA:4SS were quenched at 96% 4SS, 82% PEGA conversion and >99% 4SS, 90% PEGA conversion to generate **3** and **4**, respectively. The targeted molecular weight for **3** was 17.4 kDa, with GPC indicating a *M_n* of 22.8 kDa and a PDI of 1.10. The targeted molecular weight for **4** was 37.5 kDa, with GPC indicating a *M_n* of 42.3 kDa and a PDI of 1.18 (Figure 2). Thus, different molecular weights of well-defined polymers were obtained. The GPC traces of **3** and **4** each contained a small shoulder at approximately double the

molecular weight. This indicated chain-chain coupling during the synthesis of these higher molecular weight polymers.

Again, because of the overlapping 4SS polymer peaks, it was not possible to unambiguously detect the R- and Z-group peaks within the aromatic region. Thus, the polymers were characterized by UV-vis spectroscopy. All three polymers exhibited a strong UV absorbance at 306 nm in water, indicative of the presence of the dithioester. Furthermore, these highly charged polymers had excellent solubility in a wide range of solvents including water, acetonitrile, methanol, ethanol, tetrahydrofuran, and dimethylformamide. This latter feature was advantageous in that the resulting polymers could be characterized by GPC in organic media.

We, and others, have demonstrated that post polymerization, chain end thiocarbonylthio moieties can be transformed into a variety of reactive functional groups.^[24-31] This is often achieved by reduction to and subsequent reaction of the thiol. We have recently described a facile strategy to quantitatively reduce the dithioester and trap it with divinyl sulfone.^[24] Therefore, we investigated if this approach was amenable to this copolymer system. Briefly, three Schlenk tubes were filled with butylamine, polymer dissolved in methanol, and divinyl sulfone dissolved in phosphate buffer (PB) with reducing agent, respectively, and the oxygen was removed. The polymer solution was added to the tube containing the amine to reduce the dithioester to the thiol, after which the divinyl sulfone solution was added to trap the resulting free thiol. Analysis of the semitelechelic poly(pPEGA-co-4SS)-vinyl sulfone **2b** indicated that the reaction had occurred. There was a new broad peak centered at 6.25 ppm (*, Figure 1b) corresponding to the geminal hydrogen on the vinyl group (Figure 1b). UV analysis of **2b** showed no absorbance at 306 nm confirming the absence of the dithioester. The infrared spectra of **2a** and **2b** showed no difference in the percent transmittance of peaks corresponding to the PEGA compared to that of the 4SS, indicating that the chemical functionality of monomers was not significantly altered by the transformation. Taken together, these results suggested that the phenyl dithioester end group had been replaced with the vinyl sulfone. Vinyl sulfone groups were installed at the ends of polymer **3** and **4** in a similar manner.

In conclusion, we demonstrated the ability to effectively copolymerize sulfonated styrene and PEGA by RAFT polymerization. A CTA that exhibits poor aqueous solubility was utilized. The addition of the PEGA monomer aided the solvation of both the negatively charged sulfonated styrene and the hydrophobic CTA. It also rendered the final polymer soluble in both aqueous and organic media. Different molecular weights were targeted, the molecular weight distributions were narrow, and the copolymer ratios were similar to the feed ratios at high conversions. At lower conversions, more 4SS monomer was present in the polymer. Post polymerization, the dithioester groups were reduced with butylamine and trapped with divinyl sulfone generating semitelechelic pPEGA-co-4SS-vinyl sulfone polymers.

Experimental

Materials

All chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Acros, and EMD and used as received unless otherwise specified. Tetrahydrofuran (THF) was distilled over sodium/benzophenone and stored under argon.

Analytical Techniques

¹H and ¹³C NMR spectra were acquired on a BrukerAvance 500 MHz or 600 MHz DRX and spectra were processed using Topspin 1.2 NMR software. UV-Vis spectra were

obtained on a Biomate 5 Thermo Spectronic UV-Vis spectrometer using quartz cells. IR absorption spectra were recorded using a PerkinElmer FT-IR equipped with an ATR accessory. Merck 60 (230-400 Mesh) silica gel was used for column chromatography. GPC was conducted on a Shimadzu HPLC system equipped with a refractive index detector RID-10A, one Polymer Laboratories PLgel guard column, and two Polymer Laboratories PLgel 5 μm mixed D columns. LiBr (0.1 M) in DMF at 40 °C was used as the eluent (flow rate: 0.80 mL/min). Calibration was performed using near-monodisperse poly(methyl methacrylate) standards from Polymer Laboratories. Aqueous GPC was also conducted on a Shimadzu HPLC system equipped with a refractive index detector RID-10A, one Polymer Laboratories PLAquagel guard column and two Polymer Laboratories PLAquagel-OH 8 μm mixed columns. Ethylenediaminetetraacetic acid (EDTA) (5 mM) in PB (20 mM) at a pH of 7.44 was used as the eluent (flow rate: 0.40 mL/min). Calibration was performed using near-monodisperse poly(sulfonated styrene) standards from Polysciences Inc. Chromatograms were processed using the EZStart 7.2 chromatography software.

Synthesis of 1-phenylethyl dithiobenzoate

Magnesium (0.279 g, 11.5 mmol) was added to a flask. Bromobenzene (1.50 g, 9.55 mmol), dry THF (8.0 mL) and iodine (6.0 mg, 0.024 mmol) were added slowly and stirred for 1.5 h at 50 °C. Carbon disulfide (0.873 g, 11.5 mmol) was added drop wise after the temperature was reduced to -78 °C and subsequently stirred for 1.5 h. (1-Chloroethyl)benzene (1.61 g, 11.5 mmol) was added drop wise after the reaction mixture was warmed to 23 °C and stirred for 27 h. 5 mL H₂O was then added and the THF was removed *in vacuo*. The aqueous layer was washed with 3 $\times$ 50 mL of EtOAc. The organic layers were combined and dried over MgSO₄, filtered, and the solvent was removed *in vacuo*. The crude product was purified via silica gel chromatography. 10/1 Hexane/ethyl acetate was used as the eluent. **1** was obtained as red oil in 81.0 % yield (2 g). δ_{H} (500 MHz, CD₃CN): 7.91 (dt, J = 1.0, 8.4 Hz, 2H), 7.56 (tt, J = 1.1, 7.4 Hz, 1H), 7.46 (dt, J = 1.4, 7.4 Hz, 1H), 7.41-7.34 (m, 4H), 7.28 (tt, J = 1.1, 7.3 Hz, 1H), 5.22 (q, J = 7.1 Hz, 1H), 1.76 (d, J = 6.9 Hz, 3H). δ_{C} (500 MHz, CD₃CN): 228.97, 145.97, 142.44, 133.60, 129.69, 129.55, 128.82, 128.72, 127.61, 51.65, 21.47. UV (DCE): $\lambda_{\text{max}}(\epsilon)$ = 306 (15790 L $\cdot$ mol⁻¹ $\cdot$ cm⁻¹). IR (neat): 3681, 3026, 2967, 2922, 2865, 1800, 1679, 1589, 1491, 1443, 1371, 1333, 1311, 1222, 1178, 1105, 1080, 1039, 1023, 999, 908, 874, 838, 683, 695 cm⁻¹.

Typical polymerization of PEGAcSS

1 (50.0 mg, 0.193 mmol), AIBN (16.0 mg, 0.0974 mmol), PEGA (0.645 mL, 1.55 mmol), and 4SS (.319 g, 1.55 mmol) were loaded into a Schlenk tube. Dimethylformamide and water (1:1) (2.45 mL) were added to give a 1.25 M solution of both monomers. The Schlenk tube was subjected to three freeze-pump-thaw cycles and immersed into an 80 °C oil bath. After 11.6 h (90% conversion PEGA, >99% conversion SS) the reaction flask was removed from the oil bath, immediately opened to the atmosphere, resealed, and placed into liquid nitrogen. The polymer was purified by dialysis against water (24 h, changed twice) and then methanol (24 h, changed twice) (MWCO 1,000 Da). Polymer conversions were calculated from the ¹H NMR spectra by averaging of the integrations of the vinylic proton peaks of PEGA and the peak centered at 4.10 ppm (COOCH₂) of pPEGA and PEGA and the vinylic proton peaks of SS and the aromatic peaks from 8.0-6.4 ppm in CD₃CN. δ_{H} (500 MHz, CD₃CN): 8.0-6.4 (Na⁺ SO₃⁻ C₆H₄, C₆H₅CSS Z-group and C₆H₅CHCH₃ R-group), 4.5-3.9 (COOCH₂), 3.9-3.35 (OCH₂CH₂O), 3.35-3.2 (OCH₃), 2.5-1.8 (polymer backbone peaks, CH(CH₃)Ph R-group). M_n g/mol (GPC): 10,400. PDI: 1.06. UV-vis (H₂O): absorbance C=S (λ = 306 nm). IR (neat): 3449, 2903, 1727, 1652, 1601, 1467, 1451, 1409, 1349, 1326, 1289, 1218, 1196, 1122, 1094, 1037, 1010, 947, 833, 773, 737, 668 cm⁻¹.

Typical aminolysis and *in situ* conjugation of 2a with divinyl sulfone to afford pPEGA-vinyl sulfone (2b)

2a (65.0 mg, 0.00627 mmol) was dissolved in MeOH (1.15 mL) in Schlenk tube one. *N*-Butylamine (0.058 mL, 0.587 mmol) was added to Schlenk tube two. Schlenk tube three contained divinyl sulfone (0.120 mL, 1.20 mmol) dissolved in a 0.1 M pH 8.6 phosphate buffer (PB) (with 10 mM tris(2-carboxyethyl) phosphine hydrochloride (TCEP) and 10 mM ethylenediaminetetraacetic acid (EDTA)) (1.2 mL). All three tubes were freeze-pump-thawed three times under argon. The contents of tube one (dissolved polymer) was cannulated into tube two (*N*-butylamine) and stirred for 10 minutes. Then tube three (divinyl sulfone in buffer) was cannulated to tube two and stirred for 30 min at 23 °C. The crude **2b** was dialyzed against H₂O (24 h, changed twice) and then MeOH (24 h, changed twice) (MWCO 1000 Da) to afford **2b**. δ_{H} (500 MHz, CD₃CN): 8.0-6.4 (Na⁺ SO₃⁻ C₆H₄ polymer, C₆H₅CHCH₃R-group, and CH=CH₂), 6.4-6.2 (CH=CH₂), 4.40-3.80 (COOCH₂), 3.75-3.35 (OCH₂CH₂O), 3.35-3.2 (OCH₃), 2.5-1.8 (polymer backbone peaks, CH(CH₃)Ph R-group). M_n g/mol (GPC): 7,100. PDI: 1.10. UV-vis (H₂O): absorbance at $\lambda = 306$ nm was 0. IR (neat): 3452, 2909, 1727, 1657, 1642, 1601, 1452, 1409, 1349, 1289, 1216, 1195, 1119, 1091, 1036, 1010, 947, 833, 775, 734, 669 cm⁻¹.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was funded by the National Science Foundation (CHE-0809832). SNSA thanks the NIH sponsored Chemistry and Biology Interface (CBI) Training Program. GNG thanks the Christopher S. Foote Graduate Research Fellowship in Organic Chemistry and the NIH Biotechnology Training Grant. NMM thanks the UC LEADS program. HDM thanks the Alfred P. Sloan Foundation for additional funding.

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Fig. 1.
 ^1H NMR spectra of a) **2a** and b) **2b** in CD_3CN .

Fig. 2.
GPC trace overlay of **2a**, **2b**, **3**, **4**.

Scheme 1.a) Synthesis of copolymer **2a**, **3**, and **4**. b) Transformation of **2a** to **2b**.