Reactive Polymer Zwitterions: Sulfonium Sulfonates

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ABSTRACT: Sulfonium sulfonate, or sulfothetin, zwitterionic monomers were synthesized by ring-opening of 1,3-propanesultone with dialkyl sulfides containing styrenic or methacrylic moieties. Reversible addition-fragmentation chain-transfer polymerization of these monomers was achieved in water or trifluoroethanol, and the resulting polymers exhibited higher upper critical solution temperatures than the analogous sulfobetaine polymers. Unlike typical polymer zwitterions, these polymeric sulfothetins possess an inherent reactivity that proved tunable based on their chemical structures. This reactivity makes them amenable to post-polymerization modification by nucleophilic dealkylation to rapidly access novel substituted polymers and gels. © 2016 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2016**, *00*, 000–000

KEYWORDS: functional polymer zwitterions; post-polymerization modification; RAFT polymerization; sulfonium cation; thetins

INTRODUCTION Polymer zwitterions are of considerable interest across the materials and medical communities due to their water-solubility, low cytotoxicity, and charge neutrality. Such polymers are employed in applications ranging from drug and gene delivery[1] to antifouling[2] and low friction materials.[3] Tailoring the properties of polymer zwitterions (e.g., aqueous solubility, solution transitions, and reactivity) is achieved by their integration into copolymers,[4] introducing functionality directly into the zwitterionic moiety[5,6] altering the polymer architecture[7] or backbone,[4,8–11] or inverting the zwitterion orientation relative to the backbone.[12,13] Moreover, altering the anion, cation, or the anion–cation separation distance has a profound effect on the temperature and salt responsiveness of polymer zwitterions.[4,6,14,15]

A literature survey reveals that most polymer zwitterions contain nitrogen-based cations derived from ammonium,[5,10,16,17] imidazolium,[15,18] benzimidazolium,[15] and guanidium.[19] Though sulfonium cations are susceptible to nucleophilic dealkylation,[20–23] polysulfonium salts are long known[22,24] with recent reports of their use in controlled polymerization.[20,21,25,26] Sulfonium-based zwitterions, or thetins, are found in living organisms[27]—dimethyl sulfonium propionate (DMSP) and its derivatives are present in algae[28,29] and coral reef invertebrates.[30] DMSP biosynthesis and function in transmethylation and osmoregulation are well-documented,[29] while the phosphatidylsulfocholines (sulfonium analogs of phosphatidylcholine) are found in cell membrane glycerolipids of diatoms and algae.[31]

Sulfothetin (i.e., sulfonium sulfonate) zwitterions are prepared by the reaction of dialkyl sulfides with 1,3-propanesultone and find use as active agents in herbicide formulations,[32] surfactants,[33] and intermediates in sulfonioalkanesulfonic ester synthesis.[34] Among the prior reports of sulfonium-based polymer zwitterions,[24,35–38] three involve carboxythetins (i.e., sulfonium carboxylates) prepared by conventional free radical polymerization or post-polymerization modification,[24,35,36] and two patents mention sulfothetin structures (Fig. 1).[37,38]

Here we describe the synthesis of sulfothetin-containing monomers and polymers. Both the styrenic and methacrylic monomers were synthesized on a multigram scale, in good yield, and without the need for chromatographic purification. Reversible addition-fragmentation chain-transfer (RAFT) polymerization of both monomers was achieved under aqueous conditions, or in trifluoroethanol (TFE), noting a significant influence of the selected chain transfer agent (CTA) and solution ionic strength. These polymeric sulfothetins presented upper critical solution temperature (UCST) and anti-polyelectrolyte behavior, and higher cloud point temperatures than their analogous sulfobetaines poly(3-(N,N-dimethylvinylbenzyl ammonio)-propanesulfonate) (**PSB1**) and poly(sulfobetaine methacrylate) (**PSB2**) (Fig. 1). Unlike typical polymer zwitterions, the sulfothetin polymers that we describe are inherently reactive and amenable to nucleophilic dealkylation, thus affording access to a diverse range of materials by post-polymerization modification.

Additional Supporting Information may be found in the online version of this article.

EXPERIMENTAL

Materials

Acetonitrile (anhydrous, 99.8%), 4,4′-azobis(4-cyanovaleric acid) (98%, ACVA), 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (>97%, CPDB), 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (97% CPTTC), 1,3-propanesultone (98%), 4-vinylbenzyl chloride (90% with 500 ppm t-butylcatechol), 2-(methylthio)ethyl methacrylate (96%), sodium thiomethoxide (95%), sodium bromide (>99%), and sodium trifluoroacetate (98%) were purchased from Sigma Aldrich. 2,2,2-Trifluoroethanol (TFE) (99+%), butylated hydroxytoluene (BHT, 99%), mercaptopyridine (98%), sodium azide, and sodium nitrate were purchased from Alfa Aesar. Spectra/Por7 dialysis membranes (3.5 kDa MWCO, pretreated regenerated cellulose tubing), sodium chloride, and sodium sulfate were purchased from Fisher Scientific. 4-Arm PEG-thiol(pentaerythritol) (>90% substitution molecular weight 5000 g/mol) was purchased from Jenkem Technology USA. Deuterated solvents were purchased from Cambridge Isotope Laboratories. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. All other materials were used as received. 2-(N-3-Sulfopropyl-N,N-dimethyl ammonium)ethyl methacrylate was purchased from Sigma Aldrich and polymerized according to literature procedures.[10] 3-(N,N-dimethylvinylbenzyl ammonio)-propane sulfonate was prepared and polymerized according to literature procedures.[10]

Characterization

NMR spectra were recorded on a Bruker 500 spectrometer with the solvent proton signal used as a reference point. Size exclusion chromatography, eluting in TFE with 0.02 M sodium trifluoroacetate at 40 °C, was performed on an Agilent 1200 series system equipped with a degasser, an isocratic pump operated at 1 mL/min, an auto-sampler, a Polymer Standards Service (PSS) PFG guard column (8 × 50 mm), three PSS PFG analytical linear M columns (8 × 300 mm, particle size 7 μm), and a refractive index detector. Molecular weights and molecular weight distributions were estimated relative to PMMA standards. ESI-TOF MS spectral data was recorded on a Bruker microTOFII using positive-ion mode. Cloud points were measured by turbidimetry using a Hitachi U-3010 spectrophotometer equipped with a *t*2 temperature-controlled cuvette holder and TC-1 temperature controller (Quantum Northwest). Transmittance was measured at 550 nm while cooling the solutions at 1 °C/min. Cloud points are reported as the onset transmittance decrease. Milli-Q® ultrapure water (18.2 MΩ cm) was used for these experiments.

Monomer Synthesis

3-(4-Vinylbenzylmethyl Sulfonio)Propane-1-Sulfonate (2)

First, 4-vinylbenzyl methyl sulfide (**1**) was synthesized. Sodium thiomethoxide (3.4 g, 49 mmol) was dispersed in dry THF (40 mL). The reaction vessel was immersed in an ice bath, and 4-vinylbenzyl chloride (6.3 g, 37 mmol) was added dropwise while stirring. The mixture was allowed to warm to room temperature, then stirred for 20 h. The mixture was filtered to remove sodium chloride and compound **1** was recovered as a yellow oil after concentration under vacuum (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.4 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H) 6.74 (dd, J = 10.9, 17.6Hz, 1H) 5.77 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 10.9 Hz, 1H), 3.70 (s, 2H), 2.02 (s, 3H) ^{13}C NMR (500 MHz, $CDCl_3$, δ): 137.9, 136.5, 136.3, 129.1, 126.3, 113.7, 38.1, 14.9.

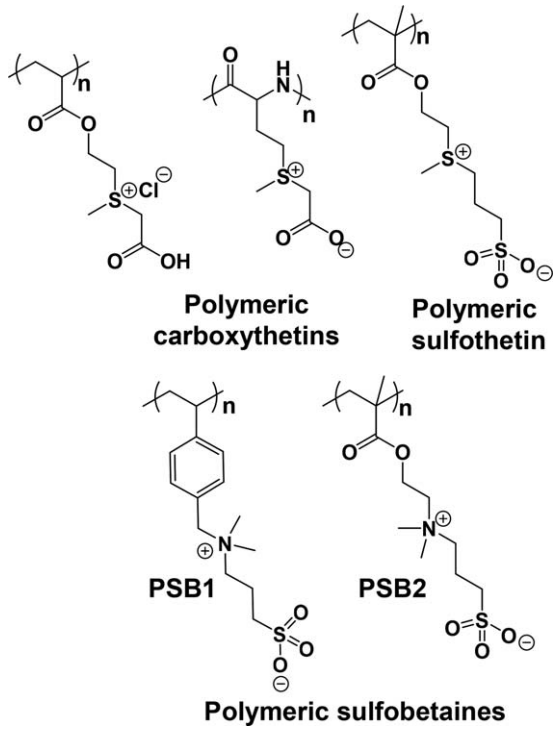


FIGURE 1 Examples of sulfonium- and ammonium-based polymer zwitterions.

Sulfothetin **2** was obtained by ring-opening of 1,3-propanesultone with 4-vinylbenzyl methyl sulfide **1** as shown in Figure 2. Specifically, 4-vinylbenzyl methyl sulfide **1** (4.5 g, 27 mmol) was dissolved in anhydrous acetonitrile (25 mL). BHT (0.25 g, 1.1 mmol) was added to this solution followed by 1,3-propanesultone (16.6 g, 136 mmol, 5 eq). The mixture was stirred at room temperature until a homogeneous solution formed, then immersed in a preheated oil bath (50 °C) and stirred for 67 h. Upon cooling to room temperature, **2** precipitated as a white solid, and was recovered by centrifugation, washing several times with THF and ether, and drying under vacuum (5.2 g, 67% yield). ^{1}H NMR [Fig. 3(a)] (500 MHz, D_2O, δ): 7.60 (d, J = 7.9 Hz, 2H, ArH), 7.49 (d, J = 7.9 Hz, 2H, ArH), 6.83 (dd, J = 17.6, 10.9 Hz, 1H, Ar—CH═), 5.96 (d, J = 17.6 Hz, 1H, CH_2═), 5.45 (d, J = 10.9 Hz, 1H, CH_2═), 4.70 (d, J = 13.2 Hz, 1H, H_a or H_b of Ar—CH_2—S^+), 4.63 (d, J = 13.2 Hz, 1H, H_a or H_b of Ar—CH_2—S^+), 3.47 (ddd, J = 13.1, 9.2, 6.6 Hz, 1H, H_a or H_b of CH_2—S^+), 3.37 (ddd, J = 13.0, 9.2, 6.2 Hz, 1H, H_a or H_b of CH_2—S^+), 3.12 (t, J = 7.4 Hz, 2H, —CH_2—SO_3^-), 2.84 (s, 3H, CH_3—S^+), 2.20 (m, 2H, —CH_2—). ^{13}C NMR (500 MHz, D_2O, δ): 139.2(C—CH═CH_2), 135.9(CH═CH_2), 131.2(ArC), 127.3(ArC), 125.8(ArC—CH_2),

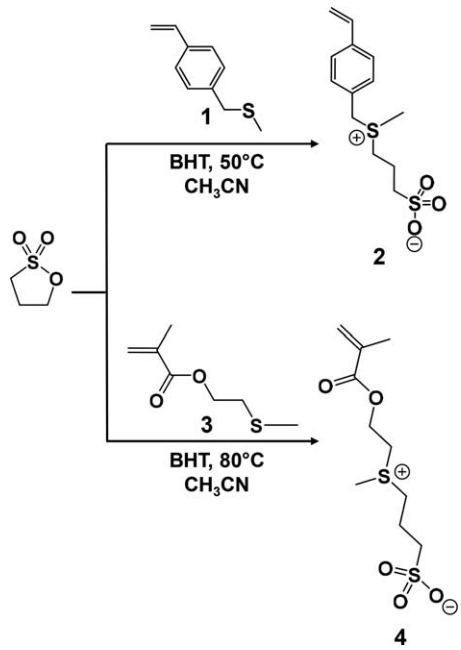


FIGURE 2 Synthesis of sulfothetin monomers **2** and **4**.

116.2(CH_2═), 48.8(CH_2—SO_3^-), 45.5(Ar—CH_2-S^+), 39.5(CH_2—S^+), 21.5(CH_3), 19.5(CH_2). ESI-MS (m/z): [M + H]+ calcd from $C_{13}H_{18}O_3S_2$, 287.0776; found, 287.0906.

3-(Methyl{2-[(2-Methylacryloyl)Oxyl]Ethyl} Sulfaniumyl) Propane-1-Sulfonate (4)

Sulfothetin **4** was synthesized by ring-opening of 1,3-propanesultone with 2-(methylthio)ethyl methacrylate **3**. Specifically, **3**(5.5 g, 33 mmol) was dissolved in anhydrous acetonitrile (33 mL) and BHT (0.22 g, 1 mmol) was added to this solution. Next 1,3-propanesultone (20.2 g, 165 mmol, 5 eq) was added to the mixture. The mixture was stirred at room temperature until a homogeneous solution formed, then refluxed under $N_{2(g)}$ for 24 h. Upon cooling to room temperature, sulfothetin methacrylate precipitated as a white solid, and was recovered by centrifugation and washed several times with THF and ether. After drying under vacuum overnight, **4** was obtained (7.9 g, 84% yield). ^{1}H NMR [Fig. 3(b)] (500 MHz, D_2O, δ): 6.13(s, 1H, CH_2═), 5.75 (s, 1H, CH_2═), 4.63 (m, 2H —C(O)O—CH_2) 3.78(m, 2H, CH_2—S^+), 3.54(m, 2H, CH_2—S^+), 3.04 (t, J = 7.42 Hz, 2H, CH_2—SO_3^-), 2.99(s, 3H, CH_3—S^+), 2.27 (m, 2H, CH_2), 1.90 (s, 3H, C—CH_3) . ^{13}C NMR (500 MHZ, D_2O, δ): 168.5(C═O), 135.0(C═CH_2), 127.9(CH_2═C), 58.8(C(O)O—CH_2), 48.5(CH_2—S^+), 41.1 (CH_3—S^+), 40.4(CH_2—S^+), 22.7(CH_2—SO_3^-), 19.4(CH_2), 17.2(CH_3). ESI-MS(m/z): [M + H]+ calcd from $C_{10}H_{18}O_5S_2$, 283.0674; found, 283.0800.

Polymer Synthesis

Preparation of Polymer 11 by RAFT Polymerization of 2

In a representative example, monomer **2** (500 mg, 1.70 mmol), CPTTC (17.7 mg, 4.40 × 10^{-2} mmol) and ACVA (2.5 mg, 8.8 × 10^{-3} mmol) were added to a 20 mL glass vial equipped with a septum and magnetic stir bar. The solids were dissolved in TFE (1 mL) to form a homogeneous yellow solution. This solution was degassed with $N_{2(g)}$ for greater than 30 min while immersed in an ice bath to prevent TFE evaporation. The degassed solution was immersed in an oil bath preheated to 70 °C; after 15 h the mixture was quenched by immersing the vial in liquid nitrogen while open to air. A monomer conversion of 95% was calculated from the ^{1}H-NMR spectrum of the crude mixture, using the vinylic and aromatic signals of the monomer [7.60, 7.49, 6.83, 5.96, and 5.45 ppm, Fig. 3(a)] and polymer (6.00–8.00 ppm, Fig. 7). The viscous polymer solution was diluted in 0.5 M $NaNO_{3(aq)}$ (15 mL), then dialyzed against 0.5 M $NaNO_{3(aq)}$ to remove unreacted monomer and TFE, then against water to remove salt. Polymer 11 was recovered as a yellow solid by lyophilization (430 mg, 86% yield, M_n = 8.8 kDa and $Đ$ = 1.20). ^{1}H NMR (Fig. 7) (500 MHz, TFE-d_3, δ): 7.24 (ArH), 6.62 (ArH), 4.57 (Ar—CH_2—S^+), 3.49 (CH_2—S^+), 3.05 (CH_3—SO_3^-), 2.73 (CH_3—S^+), 2.29 (CH_2), 0.8–2.00 (CH_2 and CH backbone), 1.32 and 0.9 ppm (CH_3 and CH_2 end group signals).

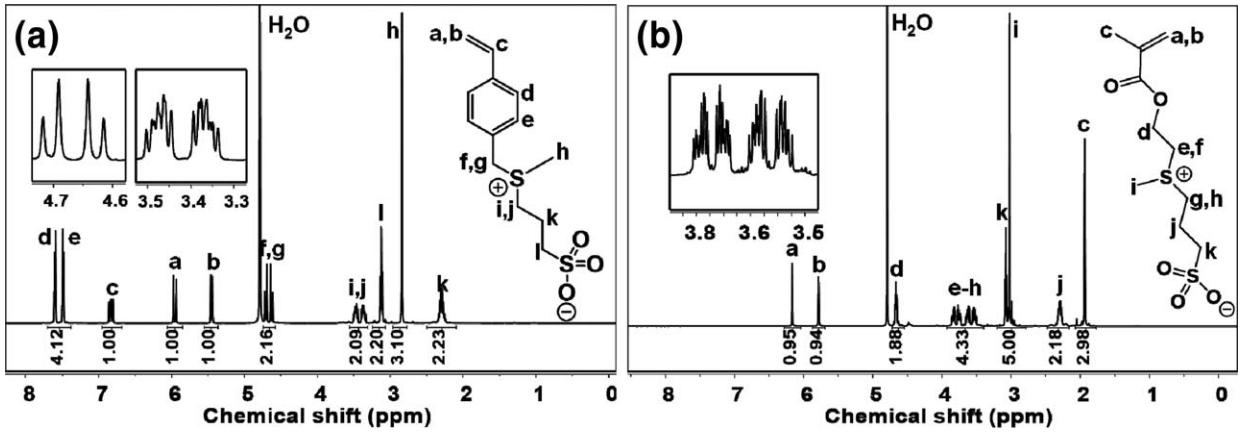


FIGURE 3 ^{1}H-NMR spectra of (a) sulfothetin styrene (**2**) and (b) sulfothetin methacrylate (**4**) in D_2O. Insets show splitting of methylene protons alpha to the sulfonium cation.

Preparation of Polymer 12 by RAFT Polymerization of 4

Sulfothetin **4** was polymerized in aqueous salt solution using 4-cyano-4-(phenylcarbonothioyl thio)pentanoic acid (CPDB) as CTA and ACVA as initiator. In a representative example, monomer **4** (500 mg, 1.80 mmol) was dissolved in 0.5 M $Na_2SO_{4(aq)}$ (2.5 mL) inside a 20 mL glass vial equipped with septum and magnetic stirring bar. CPDB (4.7 mg, 1.70 $\times$ 10^{-2} mmol) was added to this solution and stirred until dissolved. Then ACVA (0.94 mg, 3.4 $\times$ 10^{-3} mmol) was added. This solution was degassed by bubbling through with $N_{2(g)}$ for greater than 30 min. The vial was immersed in a preheated oil bath (70 °C) for 15 h. Nearly quantitative monomer conversion was calculated from the ^{1}H NMR spectrum of the crude mixture, using the signals from the alkene monomer protons [6.13 and 5.75 ppm, Fig. 3(b)] and the methylene polymer protons (0.8–1.5 ppm, Fig. 8). The pink colored polymer solution obtained was diluted with 0.5 M $NaCl_{(aq)}$ (10 mL) and dialyzed against 0.5 M $NaCl_{(aq)}$ to remove excess monomer, then against water to remove salt. Polymer 12 was recovered as a pink solid by lyophilization (252 mg, 51% yield $M_n = 28.8$ kDa and $Đ = 1.07$). ^{1}H NMR (Fig. 8) (500 MHz, 0.5 M NaCl in D_2O, δ): 4.61 (C(O)O—CH_2), 3.60–4.00 (CH2—S+), 3.17 (CH_3—S^+ and CH_2—SO_3^-), 2.41 (CH_2), 1.6–2.3(CH_2 backbone), 0.8–1.5 (CH_3 backbone).

Kinetics of RAFT Polymerization of 2 and 4

Polymerizations of monomer **2** and **4** were conducted as described previously to evaluate kinetics. Aliquots were removed under nitrogen periodically, and quenched immediately, by immersing them in $N_{2(l)}$. Monomer conversion was evaluated by ^{1}H NMR spectroscopy (0.5 M $NaNO_3$ in D_2O), and molecular weights were estimated by SEC relative to PMMA standards, eluting with TFE (containing 0.02 M CF_3COONa).

Nucleophilic Dealkylation of Sulfothetin Monomers and Polymers

The reactivity of monomers **2** and **4** toward nucleophiles was evaluated by ^{1}H NMR spectroscopy. Solutions of **2** and **4** (23 mM) were prepared in deuterated solvents (D_2O and DMSO-d_6) followed by addition NaBr, NaN_3, or 2-mercaptopyridine. The solutions were kept in the dark at room temperature, then ^{1}H NMR spectra were recorded at different times. In analogous fashion, the reactivity of polymers **11** and **12** was evaluated in D_2O in the presence of NaBr and 2-mercaptopyridine. In a representative example, 4 mg of polymer ($\sim$14 μmol of sulfothetin units) was dissolved in D_2O (0.6 mL) and NaBr (50 mg, 486 μmol) was added. The solution was transferred into an NMR tube and kept in the dark at room temperature over the course of evaluation by ^{1}H NMR spectroscopy.

Preparation of Hydrogels Incorporating Sulfothetins

Hydrogels containing polymer **11** were prepared by post-polymerization nucleophilic substitution using 4-arm PEG-thiol as a crosslinker. Polymer **11** (15 mg, 52 μmol of sulfothetin units, 3 wt %) was dissolved in 1 M $NaNO_{3(aq)}$ (0.6 mL). 4-arm PEG-thiol (50 mg, 40 μmol of SH, 9 wt %) was added to the solution and stirred until dissolved. Solution pH was adjusted to 11.8 using 1 M NaOH. The solution was allowed to stand at room temperature overnight. A control PEG only-gel sample (with no addition of **11**) was also prepared.

DTT-Induced Degradation of Sulfothetin Hydrogels

The prepared hydrogels were immersed in DTT solution (50 mM, pH 7, RO water). The gel incorporating polymer **11** remained stable for at least one week, while the PEG-gel dissolved completely after 5 min.

RESULTS AND DISCUSSION

Synthesis of Sulfothetin Monomers 2 and 4

Monomers **2** and **4** were synthesized by the reaction of styrenic or methacrylic dialkyl sulfides with 1,3-propanesultone (Fig. 2) in acetonitrile, using butylated hydroxytoluene (BHT) as a radical scavenger. Dialkyl sulfides are modestly nucleophilic and thus benefitted from fivefold excess of sultone to achieve high conversion. Sulfothetin **2** was prepared by reacting 4-vinylmethylsulfide **1** with 1,3-propanesultone in acetonitrile at 50 °C for 67 h (67% yield). Other reaction conditions, such as refluxing acetonitrile (85 °C), afforded an insoluble gel due to undesired polymerization. Sulfothetin **2** precipitated from acetonitrile as a white solid upon cooling to room temperature and was purified by washing with THF and ether, then drying under vacuum. Monomer **2** proved highly soluble in 2,2,2-trifluoroethanol (TFE, >1 g/mL), slightly soluble in MeOH (3 mg/mL), and sparingly soluble in aqueous NaBr and Na_2SO_4 solutions (<5 mg/mL in 0.5 M NaBr or Na_2SO_4).

Considering that its analogous sulfobetaine is highly soluble in 0.5 M NaBr (>200 mg/mL),[10] the suprinsingly low aqueous solubility of the novel styrenic sulfothetin **2** suggests that the sulfonium cation of the zwitterion impacts solubility significantly. However, monomer **2** is highly soluble in $NaClO_{4(aq)}$ (>200 mg/mL in 0.5 M $NaClO_4$). Sulfothetin methacrylate **4** was synthesized by refluxing a solution of commercially available 2-(methylthio)ethyl methacrylate **3** with excess 1,3-propanesultone in acetonitrile for 24 h. Upon cooling to room temperature, **4** precipitated as a fine white powder, and was purified in similar fashion to **2**. Monomer **4** proved highly soluble in TFE (>1 g/mL) and unlike **2** was soluble in aqueous salt solution (> 1 g/mL in 0.5 M Na_2SO_4 or NaBr) and slightly soluble in MeOH (40 mg/mL). ^{1}H NMR spectroscopy of **2** and **4** (Fig. 3) confirmed the desired structures and reflected the expected asymmetry of the tertiary sulfonium cation. In the spectrum of **2,** the benzylic protons [4.70 and 4.63 ppm signals f and g in Fig. 3(a)] appear as doublets, and the methylene protons positioned α and β to the sulfonium cation [3.47, 3.37, and 2.35 ppm signals i, j, and k in Fig. 3(a)] exhibit ABX_2 splitting due to the chirality of the neighboring sulfur. The ^{1}H NMR spectrum of **4** [Fig. 3(b)] revealed multiplets at 4.63, 3.78, and 3.54 ppm, with the splitting complexity again resulting from the asymmetry of the tertiary sulfonium. Mass spectral analysis of **2** and **4**

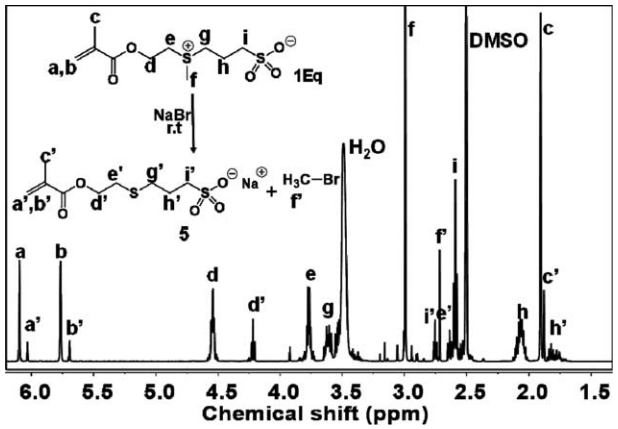


FIGURE 4 ^{1}H NMR spectrum of **4** after 113 h in the presence of NaBr in DMSO-d_6 at room temperature. [Br]:[S^+] = 5:1 [**4**] = 23 mM (the demethylation product (**5**) is shown in red).

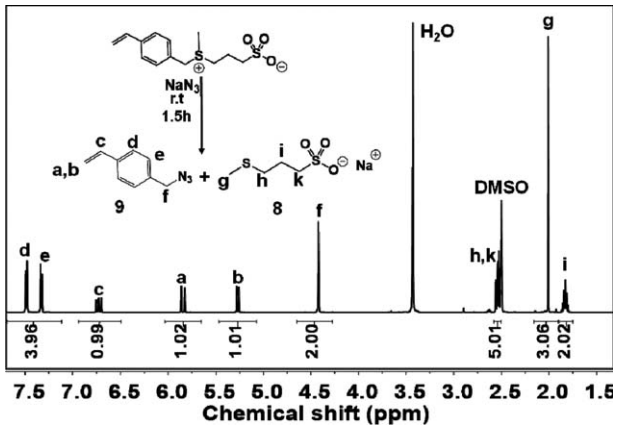


FIGURE 6 ^{1}H NMR spectrum of **2** after 1.5 h in the presence of NaN_3 in DMSO-d_6 at room temperature. [N_3]:[S^+] = 20:1 [**2**] = 23 mM (the debenzylation products (**8** and **9**) are shown in blue.

(Supporting Information Fig. S1) showed M^{+H} and M^{+Na} signals for both monomers (287.0906 and 309.0689 g/mole for **2** and 283.0800 and 305.0584 g/mole for **4**).

Nucleophilic Dealkylation of 2 and 4

Cationic tertiary sulfonium salts undergo dealkylation in the presence of nucleophiles,[20–23] the rate of which depends on the selection of nucleophile and solvent. Mackenzie et al. studied demethylation of acrylic sulfonium salts in sodium halide solution (both in D_2O and DMSO-d_6),[21] which proceeded more rapidly in DMSO than in water, and likewise faster with increasing halide concentration. Haryono et al. reported the demethylation of methyl-(4-methylthio)phenyl)-phenyl sulfonium trifluoromethanesulfonate with tetraethyl ammonium halides.[39] Demethylation rates were inversely proportional to solvent permittivity and followed the trend of $I^- > Br^- > Cl^-$.

The nucleophilic dealkylation of sulfothetin monomers **2** and **4** was studied to determine whether the reactivity of the sulfonium cation is maintained when incorporated into a zwitterion and to assist in establishing effective polymerization conditions for these monomers. Figure 4 shows the ^{1}H NMR spectrum of **4** in DMSO-d_6, after 113 h in the presence of NaBr ([Br^-]:[**4**] = 5:1, [**4**] = 23 mM). Demethylation is evident from the appearance of a CH_3Br signal at 2.7 ppm (f' in Fig. 4) and the alkene protons (6.03 and 5.7 ppm, signals a' and b' in Fig. 4) of demethylation product **5**. These demethylation reactions proceed slowly: after 113 h at room temperature and a fivefold-excess of the nucleophile, only approximately 18% demethylation had occurred (judged by integrating signals a and a' in Fig. 4). A similar experiment in D_2O led to no appreciable dealkylation of **4** after 144 h, suggesting its stability in aqueous sodium bromide even when presented with a 20-fold excess of nucleophile([Br^-]:[**4**] = 20, [**4**] = 23 mM). When using a stronger nucleophile, sodium azide, in DMSO ([N_3^-]:[S^+] = 20 [**4**] = 23 mM), 16% demethylation was observed in 17 h, and 69% after 160 h. In contrast, in D_2O only 10% conversion occurred after 160 h, likely due to greater solvation and lesser nucleophilicity in D_2O.

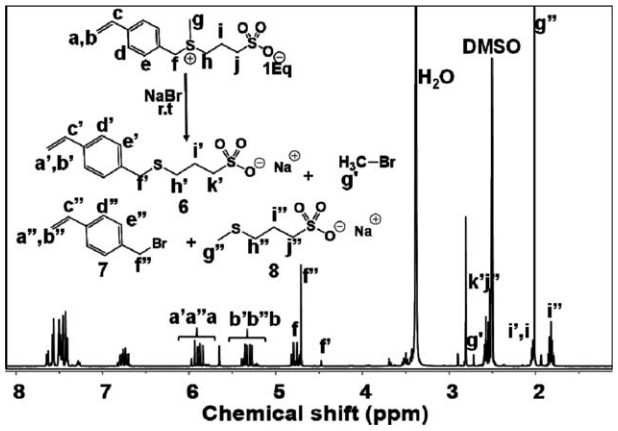
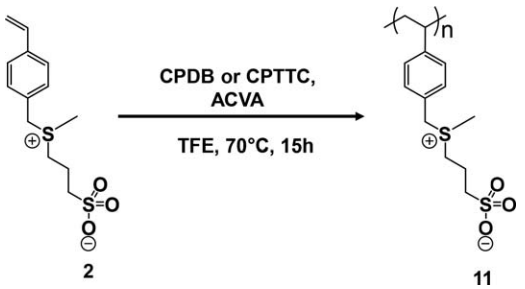


FIGURE 5 ^{1}H NMR spectrum of **2** after 113 h in the presence of NaBr in DMSO-d_6 at room temperature. [Br]:[S^+] = 5:1 [**2**] = 23 mM (the demethylation (**6**) and debenzylation products (**7** and **8**) are shown in red and blue, respectively.

Dealkylation of styrenic sulfothetin **2** with Br^- in DMSO was non-regiospecific, affording both demethylation (**6**) and debenzylation products (**7** and **8**) (Fig. 5). Demethylation was confirmed by the appearance of the CH_3Br resonance at 2.7 ppm (g', Fig. 5) and the benzylic methylene protons of **6** at 4.47 ppm (signal f', Fig. 5). Debenzylation was noted by the signals at 4.71 and 2.07 ppm (f" and g" in Fig. 5) corresponding to the CH_2 of 4-vinyl benzylbromide **7** and the CH_3 of **8**, respectively. A 1:2.5 demethylation-to-debenzylation ratio was obtained.

In contrast, sodium azide solutions gave highly regiospecific debenzylation of **2** after only 1.5 h at room temperature, affording 4-vinylbenzylazide **9** and sulfonate **8** (Fig. 6). The faster reaction of sulfothetin **2** over **4** is attributed to the electron-withdrawing benzyl group. This effect is also seen

TABLE 1 Representative Data for RAFT Polymerization of 2



Entry	CTA	$[M]_0$:[CTA]:[ACVA]	$[M]_0$ (M)	Mon Conv[a] (%)	M_n[b] (kDa)	$Đ$[b]
1	CPDB	196:1:0.2	1.8	69	52.6	1.89
2	CPDB	300:1:0.2	1.8	66	41.9	1.90
3	CPDB[c]	150:1:0.1	1.7	56	25.2	1.25
4	CPDB[c]	150:1:0.2	1.2	21	11.7	1.10
5	CPTTC	40:1:0.2	1.8	95	8.8	1.20
6	CPTTC	100:1:0.2	1.8	95	18.3	1.22
7	CPTTC	160:1:0.2	1.8	95	28.9	1.28

[a] Estimated using ^{1}H NMR.
[b] Estimated by SEC eluting in TFE relative to PMMA standards.
[c] Polymerization stopped at 6 h.

in sulfonium-based polyelectrolytes in which nucleophilic dealkylation hinges on the presence and type of nearby electron-withdrawing groups.[40]

The reaction of **2** with azide ions in D_2O ($[N_3^-]$:[**2**] = 20, [**2**] = 23 mM) was also regiospecific but slower than in DMSO (29% debenzylation at $t = 17$ h; 70% at $t = 160$ h). Dealkylation was also examined using 2-mercaptopyridine in order to increase reaction rate and conversion under aqueous conditions. To ensure monomer solubility, experiments were conducted in 0.5 M $NaClO_4$ D_2O solutions, where **2** is stable against debenzylation (Supporting Information Fig. S2). Sulfothetin **2** underwent complete dealkylation by reaction with 2-mercaptopyridine ([SH]:[S+] = 7.5, [**2**] = 23 mM, in 0.5 M $NaClO_4$ in D_2O) in 15 h [Supporting Information Fig. S3(a)]. Debenzylation product **10** was confirmed by ^{1}H-NMR spectroscopy [Supporting Information Fig. S3(b)]. Interestingly, sulfothetin **4** did not react with 2-mercaptopyridine under similar conditions, suggesting again that the higher reactivity of **2** rests on the influence of the benzyl group. Altogether, understanding the reactivity of monomers **2** and **4** toward nucleophiles is crucial for guiding selection of polymerization conditions, and for realizing opportunities to exploit the reactivity of polymeric sulfothetin zwitterions as starting materials.

RAFT Polymerization of Sulfothetin Monomers

The surprisingly low water solubility of sulfothetin **2** impeded its polymerization under aqueous RAFT conditions. Instead, **2** was polymerized in 2,2,2-trifluoroethanol (TFE), one of the few organic solvents suitable for polymer zwitterions,[4,5] and useful in the case of sulfothetins for its low nucleophilicity.[41] RAFT polymerization of **2** was conducted using 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (CPDB) and 4-cyano-4-[(dodecylsulfanylthio carbonyl) sulfanyl] pentanoic acid (CPTTC) as chain-transfer agents (CTAs) (Table 1).

Polymerization of **2** using the dithiobenzoate CPDB CTA presented challenges, since polymer **11** was obtained with relatively low conversion (~60%) and high dispersity at monomer concentrations of 1.8 M (Table 1, entries 1–3). Narrow dispersity polymer products were achieved using lower monomer concentrations (1.2 M) but only at very low monomer conversion (~20% Table 1, entry 4). In contrast, polymerization of **2** using the trithiocarbonate CPTTC CTA produced polymers with relatively narrow and monomodal molecular weight distributions ($Đ < 1.30$) and high monomer conversion (>90%) after 15 h. The superior performance of

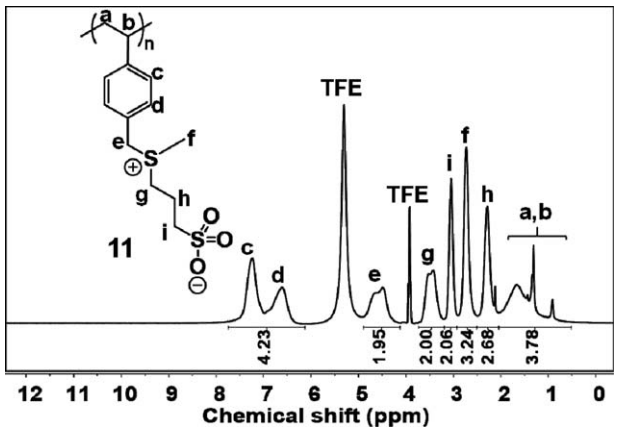
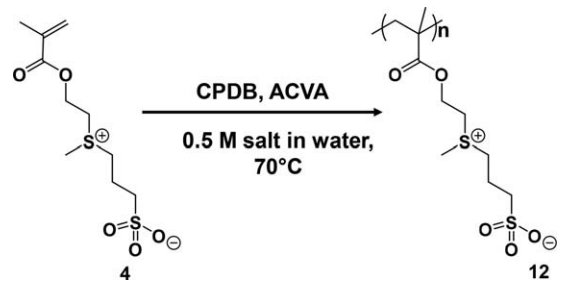


FIGURE 7 ^{1}H NMR spectrum of polymer **11** in TFE-d_3.

TABLE 2 Representative Data for Aqueous RAFT Polymerization of 4 at 70 °C and $[M]_0$ 0.7 M



Entry	Salt	$[M]_0$:[CPDB]:[ACVA]	Mon Conv[a] (%)	M_n[b] (kDa)	$Đ$[b]
1	NaBr	177:1:0.2	88	64.9	1.15
2	NaBr	70:1:0.2	49	23.7	1.22
3	NaBr	300:1:0.2	39	34.4	1.21
4	Na_2SO_4	177:1:0.2	94	50.6	1.08
5	Na_2SO_4	106:1:0.2	99	28.8	1.07
6	Na_2SO_4	300:1:0.2	98	55.4	2.61

[a] Determined by ^{1}H NMR spectroscopy.
[b] Estimated by SEC relative to PMMA standards, eluting in TFE.

CPTTC over CPDB is likely due to faster re-initiation of the R group in CPTTC, similar to that reported for trithiocarbonate-mediated RAFT of other styrenic monomers.[42]

The polymerization kinetics of 2 in TFE using CPTTC (Supporting Information Fig. S4) exhibited pseudo-linear kinetics up to about 80% conversion, beyond which the polymerization rate decreased, likely due to inefficient mixing caused by the high viscosity of the polymerization mixture. GPC traces revealed monomodal distributions and dispersity values remained less than 1.3 up to 90% conversion. A typical ^{1}H NMR spectrum of polymer **11** in TFE-d_3 is presented in Figure 7.

Sulfothetin methacrylate **4** exhibited excellent solubility in aqueous salt solutions (approaching 1 M) allowing for

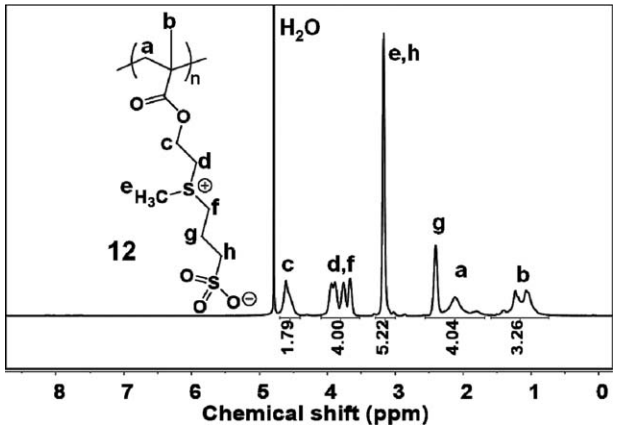


FIGURE 8 ^{1}H NMR spectra of polymer **12** in 0.5M NaCl in D_2O.

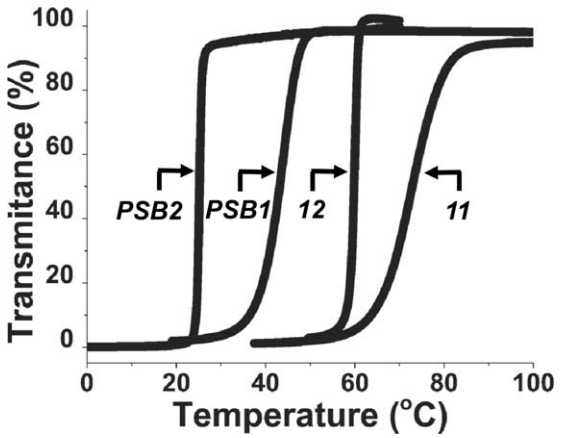


FIGURE 9 Turbidity curves in water for polymer **11** and **PSB1** at 0.5 mg/mL and polymer **12** and **PSB2** at 10 mg/mL (data collected during cooling).

aqueous RAFT polymerizations. Conditions tested included CPDB as CTA, ACVA as initiator, and 0.5 M $NaBr_{(aq)}$ or $Na_2SO_{4(aq)}$ solvent environments. These solvents proved suitable for polymerization of **4** and the obtained polymer zwitterions exhibited low dispersity (Table 2).

Limitations were reached when attempting to synthesize polymers with M_n greater than 50 kDa ($[M]_0$:[CTA] = 300), as only low monomer conversion (Table 2, entry 3) or uncontrolled polymerization (Table 2, entry 6) occurred. However, polymer **12** prepared in 0.5 M $Na_2SO_{4(aq)}$ exhibited remarkably low dispersity ($Đ < 1.1$). As such, this polymerization was examined further (Supporting Information Fig. S5) to reveal linear pseudo-first order kinetics. Molecular weight increased linearly with monomer conversion and dispersity values remained less than 1.1 during the entire course of the polymerization, indicating a well-controlled free radical polymerization. A representative ^{1}H NMR spectrum of sulfothetin polymer **12** in 0.5 M NaCl in D_2O is presented in Figure 8.

Solution Properties of Polymeric Sulfothetins

Obtaining sulfonium-based polymer zwitterions **11** and **12** allowed a comparative investigation of their solution properties relative to sulfobetaine analogues **PSB1** and **PSB2**. Samples were prepared for cloud point determination using CPDB as the CTA giving $Đ < 1.3$ (Table 3). Both **11** and **12** exhibited cloud point temperatures about 30 °C higher than the sulfobetaine versions (Fig. 9). In the presence of 50 mM $NaNO_{3(aq)}$, the UCST of **11** decreased by 22 °C, while all other samples became soluble over the entire temperature range (Table 3). Thus, polymeric sulfothetins exhibit an antipolyelectrolyte effect typical of polymer zwitterions. As expected, polymer **11** and **PSB1** with their hydrophobic styrenic backbones presented higher cloud points than the methacrylate structures. On the other hand, the higher cloud point temperatures of sulfothetin polymers **11** and **12** over **PSB1** and **PSB2** were unexpected, since sulfobetaines carry an additional hydrophobic methyl group in their cation segment. Interestingly, literature reports on ionic liquid (IL)

TABLE 3 Cloud Point of Polysulfothetins and Polysulfobetaines in Water and 50 mM $NaNO_{3(aq)}$

Polymer	DP[a]	Conc (mg/mL)	Cloud Point (°C) in Water	Cloud Point (°C) in 50 mM $NaNO_3$
11	86	0.5	80	58
PSB1	81	0.5	48	Soluble[b]
12	178	10	61	Soluble[b]
PSB2	144	10	26	Soluble[b]

[a] Degree of polymerization estimated by SEC eluting in TFE relative to PMMA standards.

[b] Soluble down to 0 °C.

miscibility in water show similar trends, where ammonium-based ILs have greater miscibility in water than the corresponding sulfonium-based ILs with fewer carbon atoms.[43] Greater hydrogen bonding affinity with water and larger charge distribution in the ammonium center are thought responsible for the greater miscibility of the IL based on these cations.[43] Thus, the presence of sulfonium cations in polymeric zwitterions decreases their solubility in water, allowing for the preparation of materials with high UCST values.

Nucleophilic Dealkylation of Polymeric Sulfothetins

The presence of sulfonium cations in novel polymer zwitterions **11** and **12** opens opportunities for reactive chemistries not available to conventional polymer zwitterions. The reactivities of **11** and **12** were examined in D_2O using excess Br^- ($[Br^-]:[S^+] = 35:1$, $[Br^-] = 0.8$ M) to drive dealkylation. Debenzylation of **11** was apparent from the sharp signals at 3.13(t), 2.77(t), 2.22(s), and 2.13(m) ppm(signals a, b, c, and d in Fig. 8, respectively) to **8** (Fig. 10), though the superposition of the polymer and product NMR resonances prevented quantitative determination of conversion. In contrast, the ^1H NMR spectrum of **12** remained unchanged over 88 h, suggesting its stability in aqueous salt at concentrations at and above physiological, a finding of potential importance in biomaterials research.

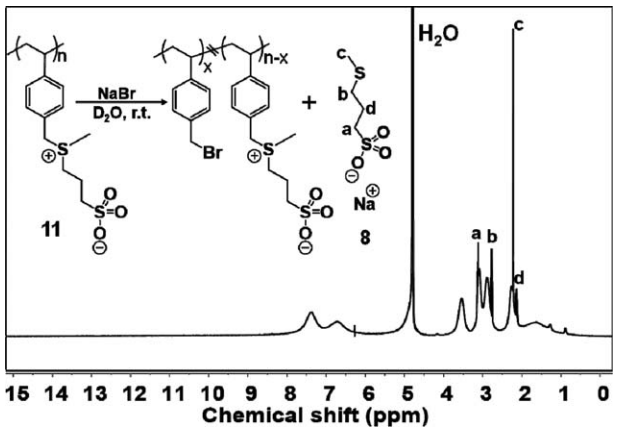


FIGURE 10 ^1H NMR spectrum recorded after reaction of **11** for 88 h in the presence of NaBr in D_2O at room temperature. $[Br^-] = 0.8$ M $[Br]:[S^+] = 35:1$ (the debenzylation products are shown in blue).

Reacting sulfothetin **11** with 2-mercaptopyridine ($[SH] = 0.18$ M $[SH]:[S^+] = 7.5:1$) afforded complete and regiospecific debenzylation to copolymer **13** in 15 h (Supporting Information Fig. S6). The precipitated product was washed with D_2O and characterized by ^1H NMR spectroscopy in DMSO-d_6 to confirm the composition of product **13** [Supporting Information Fig. S6(c)]. In contrast, in the presence of 2-mercaptopyridine, the ^1H NMR spectrum of polymer **12**

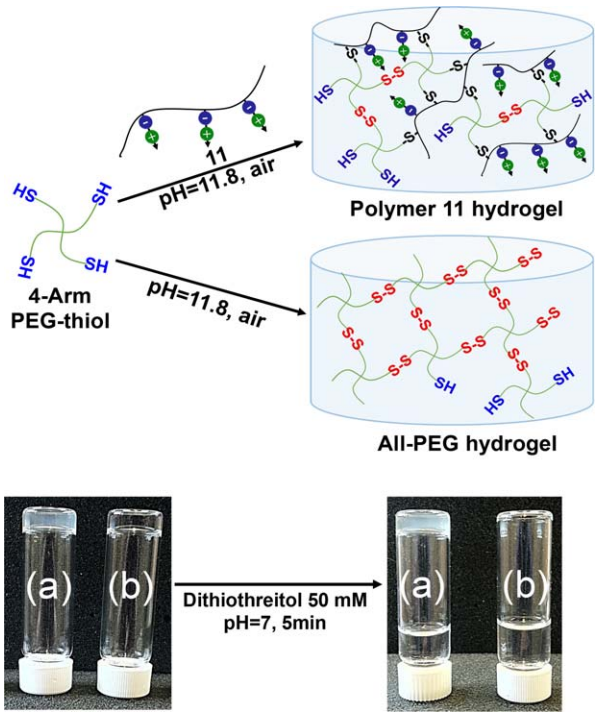


FIGURE 11 Preparation of hydrogels incorporating polymer **11** using 4-arm PEG-thiol as crosslinker. *Top*: schematic representation (disulfide bonds, thioether bonds and free thiols are displayed in red, black and blue, respectively). *Bottom*: photographs of (a) a hydrogel prepared using **11** as precursor and (b) an all-PEG control hydrogel; before and after treatment with dithiothreitol. [Color figure can be viewed at wileyonlinelibrary.com]

remained unchanged, suggesting its stability at room temperature even in the presence of this strong nucleophile.

Incorporation of Polymeric Sulfothetins into Hydrogels

The regiospecific nucleophilic dealkylation of polymer **11** by thiolates in water presents an opportunity to prepare a wide variety of functional materials by post-polymerization modification.

For hydrogel preparation we selected a 4-arm PEG-thiol as a tetrafunctional crosslinker (Fig. 11). Hydrogels were prepared by dissolving **11** and the PEG crosslinker in water at pH 12 at room temperature. An example of the free standing hydrogels obtained is given in Figure 11. As a comparative control sample, an all-PEG hydrogel was prepared without addition of **11** (in which gelation results from disulfide bond formation). Both gels were immersed in a solution of dithiothreitol: the all-PEG gel dissolved in 5 min due to disulfide cleavage, whereas the gel incorporating polymer **11** was stable for up to a week (Fig. 11, bottom).

This enhanced stability against reducing agents is attributed to the presence of thioethers (Fig. 11) formed by the nucleophilic dealkylation of **11** by the PEG-thiolate end groups, as opposed to the disulfide groups present in the all-PEG control gel (Fig. 11). Such incorporation of polymer **11** into hydrogels illustrates an example of exploiting the reactivity of these polymeric sulfothetins and the potential of this zwitterion family to serve as reagents without the need for additional functional groups or co-monomers into the polymer structure.

CONCLUSIONS

We have reported the synthesis, solution properties, and reactivity of novel sulfonium-based polymer zwitterions, or polymeric sulfothetins. Sulfothetin monomers were synthesized in multigram quantities and the corresponding polymers were prepared by RAFT polymerization using chain-transfer agents that afforded well-controlled kinetics. Polymeric sulfothetins exhibited UCST behavior and antipolyelectrolyte characteristics with cloud point temperatures higher than those of the ammonium-based polymer sulfobetaines, independent of their backbone chemical structures. The sulfothetin monomers and polymers are inherently reactive and the regioselectivity and rate of the nucleophilic dealkylation depends on the solvent, nucleophile and presence of electron-withdrawing groups nearby the sulfonium cation. The intrinsic reactivity of sulfothetins allows for the preparation of functional polymeric zwitterions without the need for copolymerization, end-group functionalization, or the inclusion of additional functional groups and allows for their post-polymerization modification into novel polymers and incorporation into hydrogel materials.

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