이학석사 학위논문

황을 포함하는 새로운 온도 감응성 폴리 아크릴아마이드의 합성

Thermoresponsive sulfur-containing polyacrylamides with tunable LCST by oxygen and chain length

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이 논문을 이학석사학위 논문으로 제출함

2021년 02월

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2021년 02월

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Abstract

Thermoresponsive polyacrylamides substituted with sulfide, sulfone or sulfoxide was successfully prepared. The solubility of sulfur-containing polyacrylamides in water can be easily controlled by changing the number of oxygen atoms in sulfur atom or the chain length of the end of polyacrylamide. Moreover, an N-(2-(ethylsulfonyl)ethyl)- acrylamide (P1SO2) was polymerized from poly[N-(2-(propylthio)ethyl)acrylamide (P2S) macroCTA via reversible addition-fragmentation chain transfer (RAFT) polymerization, resulting in the formation of a well-defined block copolymer of P2S-*b*-P1SO2. The resulting block copolymer, P2S-*b*-P1SO2, was assembled in water to yield micelles that consist of a P1SO2 block forming a hydrophilic shell and a P2S block forming a hydrophobic core. P2S block was ultimately synthesized *via* post-polymerization modification using H_2O_2, which caused the conversion of the sulfide of P2S to sulfoxide that is hydrophilic in water, leading to the transformation of micelles to unmers.

Keywords: Thermoresponsive; polyacrylamide; RAFT; LCST; sulfide; sulfone; sulfoxide; amphiphilic block copolymer

1. Introduction

Stimuli-responsive polymers have attracted considerable interest over the past few decades in the fields of drug and gene delivery, imaging, sensors and so on.[ref] They respond to their environment by changing their physical and/or chemical properties. These polymers have been synthesized to be responsive to a variety of stimuli, *e.g.*, pH, temperature, redox and light.[1-5] Thermoresponsive polymers show a sharp change in properties upon a small or modest change in temperature. A lower critical solution temperature (LCST) which can be defined as a critical temperature at which the polymeric solution shows a phase separation is the important feature of thermoresponsive polymers. The polymers with LCST behavior undergo phase separation upon heating above their LCST.[6] These polymers are soluble in water through hydrogen bonding, but only below their LCST. When heated above the LCST, the polymers precipitate, leading to fast phase transitions. In fact, most of N-substituted polyacrylamides are thermoresponsive. Furthermore, poly(N-isopropyl- acrylamide) (NIPAm) is especially very promising polymer for extensive applications due to its LCST and it has found its way into new applications like drug delivery, sensors and other advanced materials.[7, 8] Therefore, we synthesized the new polyacrylamide containing sulfide, sulfone or sulfoxide.

Sulfur is the eighth most abundant chemical in the human body and is essential for life. The element is also found in many foods, such as garlic, onions, beef and dairy products. Of the 20 common amino acids, cysteine and methionine are organosulfur compounds, and the antibiotics penicillin and sulfa drugs both contain sulfur.[10] Organosulfur compounds, especially containing sulfone or sulfoxide, attract the special interest in medicinal chemistry and give the importance to many kinds of biological activity[11, 12], perhaps the SO group is a hydrogen bond receptor.

Amphiphilic block copolymers can self-asssemble into polymeric micelles in aqueous solutions.[13, 14] For AB di-block copolymers, however, where one block is hydrophilic and the other is hydrophobic, the amphiphilic character can be converted to doubly hydrophilic character by H_2O_2.[15]

Here we report that the thermosensitivity of sulfur-containing polyacrylamides can be easily controlled by changing the number of oxygen atoms in sulfur atom and the chain length in the terminal alkyl group of monomers (Scheme 1). Sulfur-containing polyacrylamides which have sulfide group with ethyl, propyl or butyl moiety in the end of the chain length are water-insoluble. Sulfoxide substituted poly[N-(2-(ethyl sulfinyl)-ethyl)acrylamide] (P2SO) is water-soluble while sulfone substituted poly[N-(2-(propyl-

sulfonyl)ethyl)acrylamide] (P2SO2) is water-insoluble. In this regard, sulfinyl group is more hydrophilic than sulfonyl group, however, sulfone has two oxygen in a sulfur atom which can make a hydrogen bonding with water. Poly[N-(2-(ethylsulfonyl)-ethyl)acrylamide] (P1SO2) which has shorter length of the terminal chain than water-insoluble P2SO2 exhibits a LCST in water of around 25-26 °C. Likewise, poly[N-(2-(butylsulfinyl)ethyl)acrylamide] (P3SO) containing more alkyl groups in the chain end than P2SO also exhibits a LCST in water around 24-25 °C. Thus, we can conclude that hydrophobicity will be increase according to length increment of the terminal alky groups.

2. Experimental

2.1 Materials.

N-(3-(dimethylamino)propyl)-N′-ethylcarbodiimide hydrochloride (EDC), Cysteamine (95%), bromoethane (99%) and 4-(dimethylamino)-pyridine (DMAP) were purchased form TCI and used as received. 2,2′-Azobis(isobutyronitrile) (AIBN, Aldrich, 98%) was recrystallized from ethanol prior to use. 1-Bromopropane (99%), 1-bromobutane (99%), N,N-Dimethylformamide (DMF, 99.8%), methanol (99.8%), acrylic acid (99%), 2-(Dodecylthiocarbonothioylthio)-2- methylpropionic acid (DMP, 98%) and 1,3,5-Trioxane (99%) were purchased from Aldrich and used as received. Oxone® monosulfate was purchased from alfa aesar and used as received. Hydrogen peroxide (H2O2, 30%) and sodium hydroxide (98%) and Acetic acid (99.5%) were purchased from general suppliers and used without further purification.

2.2 Characterization. ^{1}H NMR spectroscopy (Bruker Advance 300 MHz, Varian) was employed with CDCl3 as solvents. The apparent molecular weight and molecular weight distribution was measured by gel permeation chromatography (GPC, Agilent technologies 1200 series) using a poly(methyl methacrylate) (PMMA) standard, with DMF as the eluent at 30 °C and a flowrate of 1.00 mL/min. The UV–Vis spectra were recorded using a Varian Cary-100 UV–Vis spectrophotometer equipped with a digital temperature controller. A 650 nm wavelength was used to determine LCST. The temperature range was from 0 to 70 °C with a heating and cooling rate of 1 °C/min. The cloud point was defined as the middle point of the transmittance change. The hydrodynamic diameter was measured by dynamic light scattering (DLS, Nano ZS 90, Malvern, UK) with zetasizer software 7.01.

2.3 Synthesis.

2-(ethylthio)ethanamine (1S). Bromoethane (3 ml, 40.5 mmol), cysteamine (4.6 g, 40.5 mmol) and sodium hydroxide (3.29 g, 91 mmol) were dissolved in 50 ml of methanol. The solution was stirred for 24 h at room temperature and then extracted with dichloromethane. The resulting solution was dried over $MgSO_4$ and concentrated to give colorless oil (3.4 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 2.84-2.55 (4H, t, NH_2–$(CH_2)_2$–S–), 2.51–2.44 (2H, q, –S–CH_2–CH_3), 1.22–1.17 (3H, t, –CH_2–CH_3).

N-(2-(ethylthio)ethyl)acrylamide (M1S). 1S was added to round-bottom flask in the

presence of acrylic acid (1.9 ml, 27.7 mmol) and 150 ml of dry dichloromethane. The resulting suspension was cooled to 0 ℃, and 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (5.8 g, 30.5 mmol) followed by 4-dimethylamino- pyridine (0.34 g, 2.77 mmol) was added. The reaction was stirred for overnight at room temperature. The reaction mixture was washed with water and brine. The organic layer was dried with MgSO4, concentrated under reduced pressure, and then the product was purified by column chromatography using Hexane-EA (7:8) as an eluent to give M1S as pale yellow liquid (3.5 g, 66%). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.53–3.45 (2H, q, –NH–CH_2–CH_2–), 2.70–2.65 (2H, t, –CH_2–CH_2–S–), 2.55–2.49 (2H, q, –S–CH_2–CH_3), 1.25–1.21 (3H, t, –CH_2–CH_3).

N-(2-(ethylsulfonyl)ethyl)acrylamide (M1SO2). M1S (0.5 g, 3.1 mmol), diethylamine (0.065ml, 0.63mmol) and 3ml of acetonitrile were added to round-bottomed flask. Oxone (3.9 g, 2.2 mmol) in 20 ml of distilled water was added into the mixture. The reaction mixture was stirred for 3h at room temperature, and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was removed in *vacuo*. The product was purified by column chromatography using EA to give **M1SO2** as white powder (0.2 g, 32%). %). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.89–3.83 (2H, q, –NH–CH_2–CH_2–), 3.21–3.18 (2H, t, –CH_2–CH_2–(O=S=O)–), 3.05–2.99 (2H, q, –(O=S=O)–CH_2–CH_3), 1.42–1.37 (3H, t, –CH_2–CH_3).

N-(2-(ethylsulfinyl)ethyl)acrylamide (M1SO). M1S (0.5 g, 3.1 mmol) and 3ml of acetonitrile were added to round-bottomed flask. Oxone (3.9 g, 2.2 mmol) in 20 ml of distilled water was added into the mixture. The reaction mixture was stirred for 10min at room temperature, and then extracted with ethyl acetate. The organic layer was dried using over $MgSO_4$ and the solvent was removed in *vacuo*. The product was purified by column chromatography using Methanol-EA (1:4) as an eluent to give **M1SO** as white solid (0.13 g, 23%). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.97–3.78 (2H, m, –NH–CH_2–CH_2–), 3.08–2.73 (4H, m, –CH_2–CH_2–(S=O)–CH_2–CH_3), 1.35–1.31 (3H, t, –CH_2–CH_3)

2-(propylthio)ethanamine (2S). 1-bromopropane (4.79 ml, 52.6 mmol), cysteamine (6 g, 52.8 mmol) and sodium hydroxide (4.21 g, 105 mmol) were dissolved in 50 ml of methanol. The solution was stirred for 24 h at room temperature and then extracted with dichloromethane. The resulting solution was dried over $MgSO_4$ and concentrated to give colorless oil (4.87 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 2.84–2.54 (4H, t, NH_3–$(CH_2)_2$–S–), 2.44–2.41 (2H, t, –S–CH_2–CH_2–), 1.62-1.50 (2H, m, –CH2-CH2-CH3), 0.95-0.91 (3H, –CH_3)).

N-(2-(propylthio)ethyl)acrylamide (M2S). M2S was obtained as the same way to **M1S** (4.22 g, 55%). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.51–3.45 (2H, q, –NH–CH_2–CH_2–), 2.67–2.63 (2H, t, –CH_2–CH_2–S–), 2.40-2.44 (2H, t, –S–CH_2–CH_2–), 1.63–1.51 (2H, m, –CH_2–CH_2-CH_3), 0.97–0.92 (3H, t, –CH_2–CH_3).

N-(2-(propylsulfonyl)ethyl)acrylamide (M2SO2). M2SO2 was obtained as the same way to **M1SO2**. (0.3 g, 51%) ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.88–3.82 (2H, q, –NH–CH_2– CH_2–), 3.21–3.17 (2H, t, –CH_2–CH_2–(O=S=O)–), 2.99–2.94 (2H, t, –(O=S=O) –CH_2–CH_2–), 1.93–1.80 (2H, m, –CH_2–CH_2-CH_3), 1.09–1.05 (3H, t, –CH_2–CH_3).

N-(2-(ethylsulfinyl)ethyl)acrylamide (M2SO). M2SO was obtained as the same way to **M1SO**. (0.12 g, 22%) ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.93–3.80 (2H, m, –NH–CH_2– CH_2–), 3.07–2.58 (4H, m, –CH_2–CH_2–(S=O)–CH_2–CH_2–), 1.96–1.73 (2H, m, –CH_2 –CH_2-CH_3), 1.10–1.05 (3H, t, –CH_2–CH_3).

2-(butylthio)ethanamine (3S). 1-bromobutane (3 ml, 27.8 mmol), cysteamine (3.16 g, 27.8 mmol) and sodium hydroxide (2.22 g, 55.6 mmol) were dissolved in 30 ml of methanol. The solution was stirred for 24 h at room temperature and then extracted with dichloromethane. The resulting solution was dried over $MgSO_4$ and concentrated to give colorless oil. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): (2.689 g, 73%). 2.85–2.55 (4H, t, NH_2–$(CH_2)_2$–S–), 2.50–2.44 (2H, t, –S–CH_2–CH_2–), 1.55–1.30 (4H, m, –CH_2–$(CH_2)_2$–CH_3), 0.90-0.85 (3H, t, –CH_2–CH_3).

N-(2-(butylthio)ethyl)acrylamide (M3S). M3S was obtained as the same way to **M1SO2** (2.06 g, 54%). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.53–3.47 (2H, q, –NH–CH_2–CH_2–), 2.69–2.65 (2H, t, –CH_2–CH_2–S–), 2.53–2.48 (2H, t, –S–CH_2–CH_2–), 1.59–1.31 (4H, m, –CH_2–$(CH_2)_2$–CH3), 0.91–0.85 (3H, t, –CH_2–CH_3).

N-(2-(butylsulfonyl)ethyl)acrylamide (M3SO2). M3SO2 was obtained as the same way to **M1SO2** (0.7 g, 60%). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.89–3.83 (2H, q, –NH–CH_2–CH_2–), 3.21–3.17 (2H, t, –CH_2–CH_2–O=S=O)–), 3.01–2.95 (2H, t, –S–CH_2–CH_2–), 1.85–1.75 (4H, m, –CH_2–$(CH_2)_2$–CH3), 0.97–0.92 (3H, t, –CH_2–CH_3).

N-(2-(butylsulfinyl)ethyl)acrylamide (M3SO). M3SO was obtained as the same way to **M1SO** (0.6g, 55%). ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.97–9.78 (2H, m, –NH–CH_2–CH_2–), 3.07–2.62 (4H, m, –CH_2–CH_2–(S=O)–CH_2–CH_2–), 1.78–1.40 (4H, m, –CH_2–$(CH_2)_2$–CH3), 0.97–0.92 (3H, t, –CH_2–CH_3).

Poly-[N-(2-(ethylsulfonyl)ethyl)acrylamide] (P1SO2). M1SO2 (1.00g, 5.23 mmol), DMP (9.53 mg, 0.026 mmol), AIBN (0.21 mg, 0.001 mmol) and 1,3,5-trioxane (1.17 mg, 0.026 mmol) were added to a Schlenk flask with 6 mL of anhydrous DMF. The

solution was purged with argon for 20 min, and the reaction flask was placed in a preheated oil bath at 70 °C. Samples were removed periodically by syringe to determine molecular weight and polydispersity index (PDI) by gel permeation chromatography (GPC) and monomer conversion by ^{1}H NMR spectroscopy. Polymerization was quenched by exposing the mixture to air. The product was then precipitated in diethyl ether, filtered and dried in a vacuum oven at 30 °C for 24 h. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.65–3.16 (6H, broad, –NH–$(CH_2)_2$–(O=S=O)–CH_2–CH_3), 2.10–1.50 (3H, broad, polymer backbone part), 1.47–1.31 (3H, broad, –CH_2–CH_3).

Poly-[N-(2-(butylsulfinyl)ethyl)acrylamide] (P3SO). P3OS was obtained as the same way to **P1SO2**. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 4.00–3.33 (2H, broad, –NH–CH_2–CH_2 –), 3.15–2.67 (4H, broad, –CH_2–CH_2–(S=O)–CH_2–CH_2–), 2.38–1.95 (3H, broad, polymer backbone part), 1.87–1.31 (4H, broad, –CH_2–$(CH_2)_2$–CH3), 1.07–0.88 (3H, broad, –CH_2–CH_3).

Poly-{[N-(2-(propylsulfonyl)ethyl)acrylamide]-*co*-[N-(2-(ethylsulfinyl)ethyl)acrylamide]} (P2SO2-*co*-P2SO). P2SO2-*co*-P2SO was obtained as the same way to **P1SO2**. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 4.14–2.60 (12H, broad, –NH–$(CH_2)_2$–(O=S=O)–CH_2–CH_2– and –NH-$(CH_2)_2$-(S=O) –CH_2–CH_2–), 2.33–1.29 (3H, broad, polymer backbone part), 1.94–1.65 (4H, broad, –CH_2–CH_2–CH_3), 1.20–0.91 (6H, broad, –CH_2–CH_3).

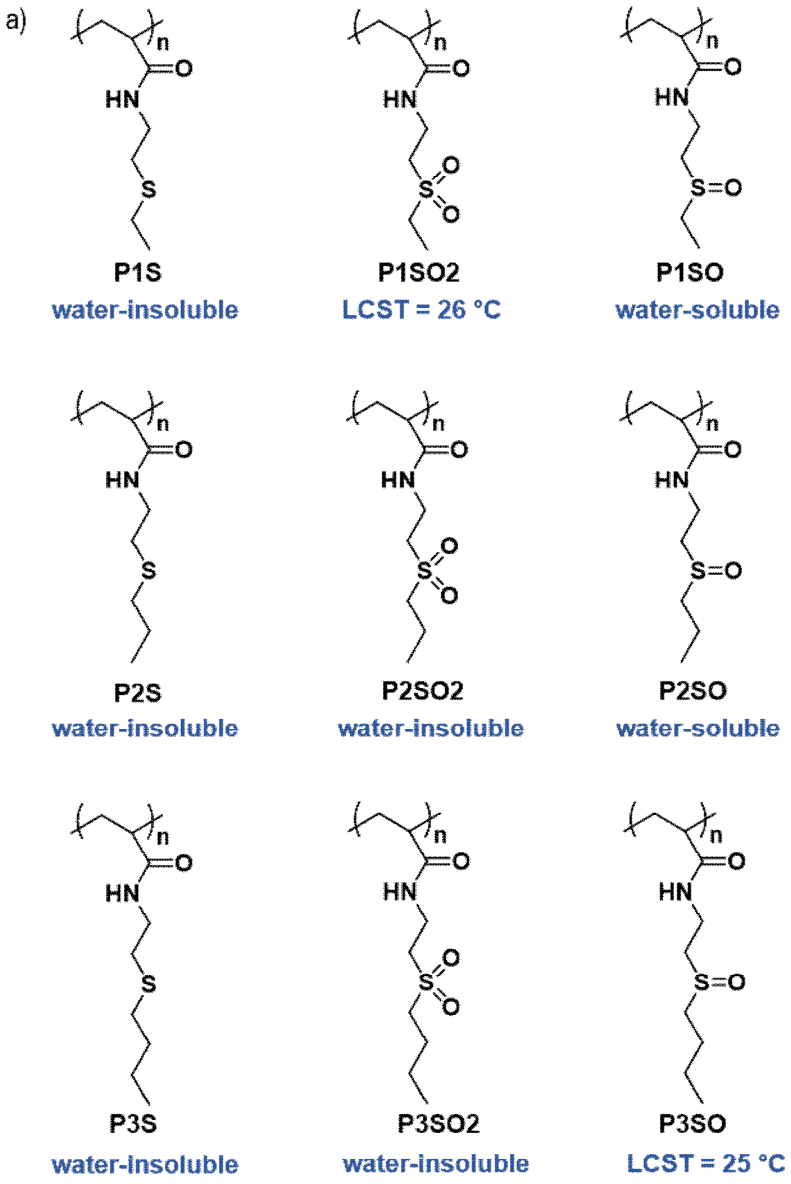
Poly-[N-(2-(propylthio)ethyl)acrylamide] monofunctional macroCTA (P2S-CTA). P2S-CTA was obtained as the same way to **P1SO2**. M_n = 31100 g/mol, M_w/M_n = 1.12. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 3.73–3.04 (2H, broad, –NH–CH_2–CH_2), 2.83–2.38 (4H, broad, –CH_2–CH_2–S–CH_2–CH_2–), 2.34–1.27 (3H, broad, polymer backbone part), 1.70–1.46 (2H, broad, –CH_2–CH_2–CH_3), 1.06–0.88 (3H, broad, –CH_2–CH_3).

Poly-[N-(2-(propylthio)ethyl)acrylamide-b-N-(2-(ethylsulfonyl)ethyl)acrylamide] (P2S-b-P1SO2). P2S-b-P1SO2 was obtained as the same way to **P1SO2**. M_n = 59900 g/mol, M_w/M_n = 1.20. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 4.11–2.99 (8H, broad, –NH–CH_2–S– and –NH–CH_2–CH_2–(O=S=O) –CH_2–CH_2–), 2.83–2.39 (4H, broad, –CH_2–CH_2–S–CH_2–CH_2–), 2.37–1.13 (3H, broad, polymer backbone part), 1.71–1.48 (2H, broad, –CH_2–CH_2–CH_3), 1.49–1.27 (6H, broad, –CH_2–CH_3).

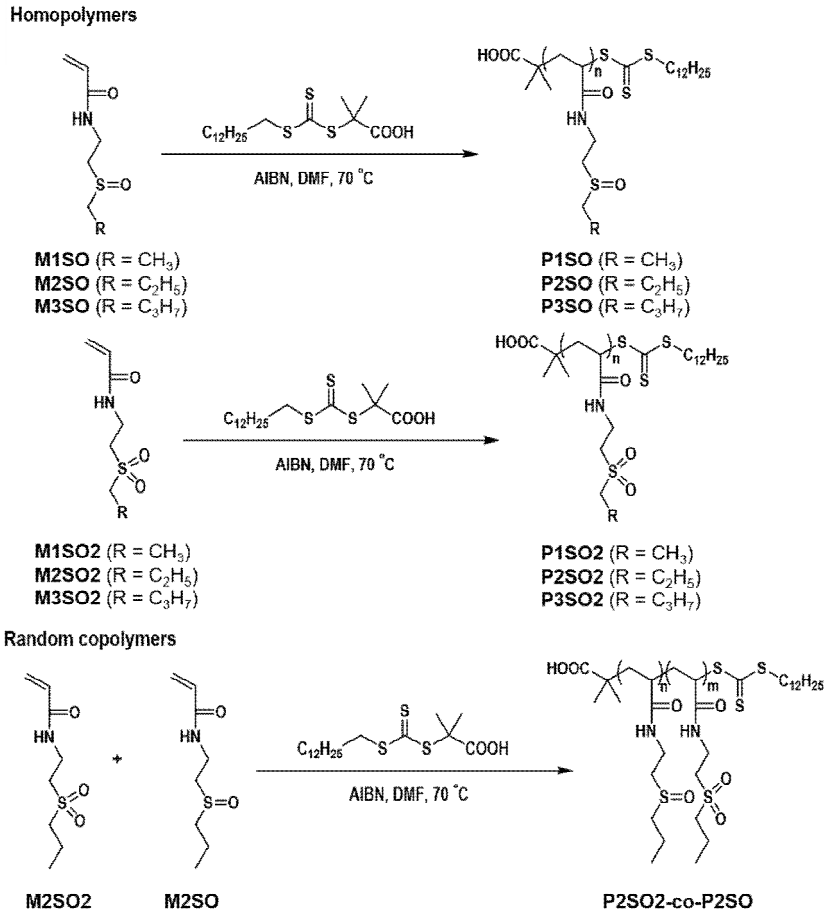
Oxidation of P2S-*b*-P1SO2 to give poly-[N-(2-(propylthio)ethyl)acrylamide-b-N-(2-(ethyl-sulfinyl)ethyl)acrylamide] (P2SO-*b*-P1SO2). P2S-*b*-P1SO2 micelle was suspended in 30% H2O2 and 1% AcOH in water and stirred at 0 °C. When the mixture of polymer was fully dissolved to yield a transparent homogeneous solution, the reaction was quenched with a few drops of 1M sodium thiosulfate in water. The resulting solution was transferred to a 2000 MWCO dialysis bag and dialyzed against DI water for 48 h with

water changes twice per day. The solution of dialysis bag was then lyophilized to dryness to give **P2SO-*b*-P1SO2**. M_n = 60400 g/mol, M_w/M_n = 1.40. ^{1}H NMR (300MHz, $CDCl_3$, δ in ppm): 4.08–2.55 (12H, broad, –NH–$(CH_2)_2$–(S=O)–CH_2–CH_2– and –NH–$(CH_2)_2$–(O=S=O) –CH_2–CH_2–), 2.39–2.07 (2H, broad, – (S=O) –CH_2–CH_2–), 2.31–1.19 (3H, broad, polymer backbone part), 1.49–0.97 (6H, broad, –CH_2–CH_3).

3. Results and Discussion



Scheme 1. Chemical structures of sulfur-containing polyacrylamides.



Scheme 2. Synthesis of thermoresponsive sulfur-containing homopolymers and random copolymers by RAFT polymerization.

Table 1 Results from synthesis of homopolymers (P1SO2 and P3SO) and random copolymers (P2SO2 : P2SO) by RAFT polymerization

Feed ratio	a : b	Incorporation ratio[a]	Polymer	conv of a[a] (%)	conv of b[a] (%)	$M_{n,theory}$[c] (g mol^{-1})	$M_{n,^1H\ NMR}$[b] (g mol^{-1})	$M_{n,app}$[d] (g mol^{-1})	PDI	LCST (°C)
M1SO2	—	—	P1SO2-FRP	—	—	—	—	46028	1.78	26
M2SO2	—	—	P2SO2-FRP	—	—	—	—	39230	2.11	—
M2SO	—	—	P2SO-FRP	—	—	—	—	22508	1.91	—
M3SO	—	—	P3SO-FRP	—	—	—	—	33832	2.09	25
M1SO2	—	—	$P1SO2_{60}$	33	—	12400	10100	31535	1.10	26
			$P1SO2_{100}$	47	—	17900	14500	35600	1.13	26
			$P1SO2_{200}$	69	—	39900	24400	69800	1.21	24
M3SO	—	—	$P3SO_{50}$	24	—	9868	6778	14700	1.18	25
			$P3SO_{120}$	59	—	23908	21694	23200	1.29	25
			$P3SO_{200}$	69	—	42465	31475	40400	1.34	24
M2SO2:M2SO	75:25	—	$P2SO2_{150}$-co-$P2SO_{46}$	—	—	—	—	40900	1.21	10
	50:50	—	$P2SO2_{55}$-co-$P2SO_{60}$	—	—	—	—	20188	1.20	35
	25:75	—	$P2SO2_{41}$-co-$P2SO_{121}$	—	—	—	—	30200	1.19	62

[a] Determined by ^{1}H NMR spectroscopy. [b] Calculated from 1H NMR spectroscopy using end group analysis. [c] Theoretical molecular weight determined from monomer conversions. [d] Apparent number-average molecular weight and PDI determined by DMF GPC with PMMA calibration.

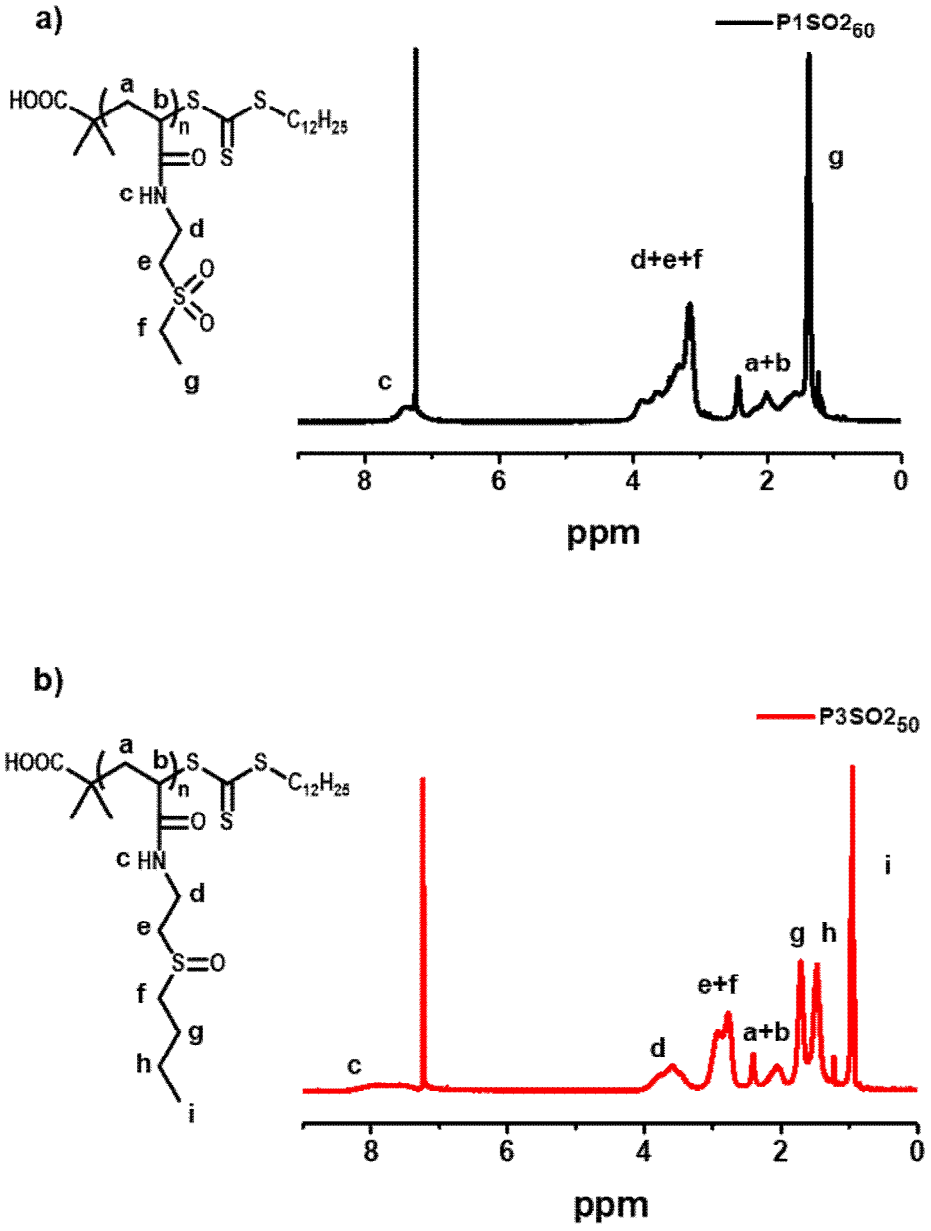


Figure 1. ^{1}H NMR spectra of (a) P1SO2 and (b) P3SO.

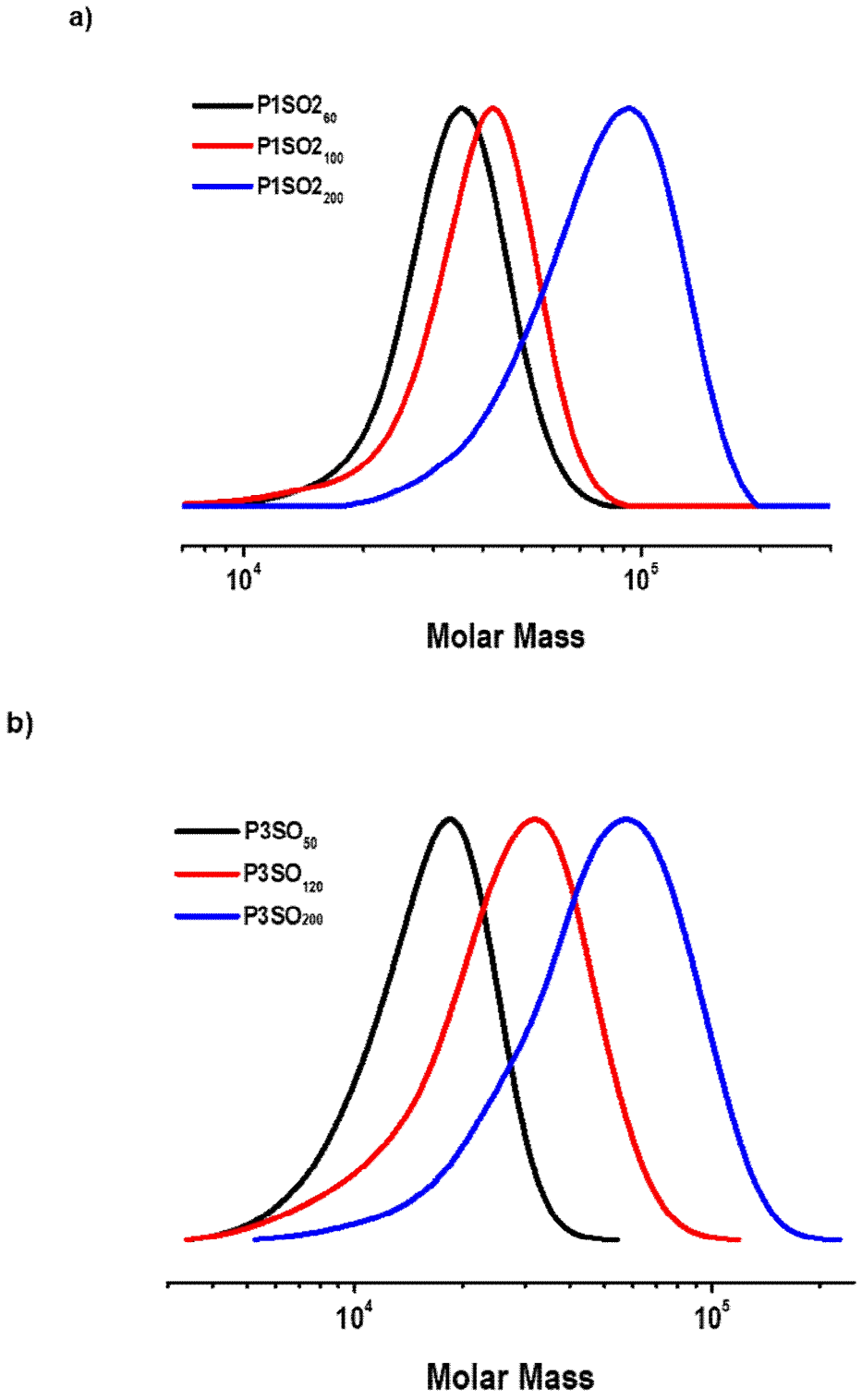


Figure 2. Overlaid GPC traces of (a) $P1SO_{60}$, $P1SO_{100}$ and $P1SO_{200}$ and (b) $P3SO_{50}$, $P3SO_{120}$ and $P3SO_{200}$.

A schematic of the strategy employed in this study is illustrated in Scheme 2. A series of homopolymers (P1SO2 and P3SO) and random copolymers (P2SO2-*co*-P2SO) were synthesized *via* reversible addition-fragmentation chain transfer (RAFT) polymerization[16] from sulfur- containing acrylamide monomers (M1SO2, M2SO2, M2SO and M3SO), using 2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl- propiionic acid (DMP) as the chain transfer agent (CTA) and 2,2′-azobisisobutyronitrile (AIBN) as the initiator. All cases of RAFT polymerization under the molar ratio of [monomer] : [DMP] : [AIBN] : [trioxane] at 200 : 1 : 0.1 : 10 with the total monomer concentration at 0.2 g mL^{-1} was fixed. The formation of these polymers was confirmed by ^{1}H-NMR spectroscopy and the number average molecular weights (Mn) was determined by gel permeation chromatography (GPC) (Table. 1, Fig. 1 and 2). However, the apparent molecular weight obtained by GPC was higher than the theoretical molecular weight calculated from the monomer conversion due to the differences in hydrodynamic volumes of sulfur-containing polyacrylamides and PMMA standards.

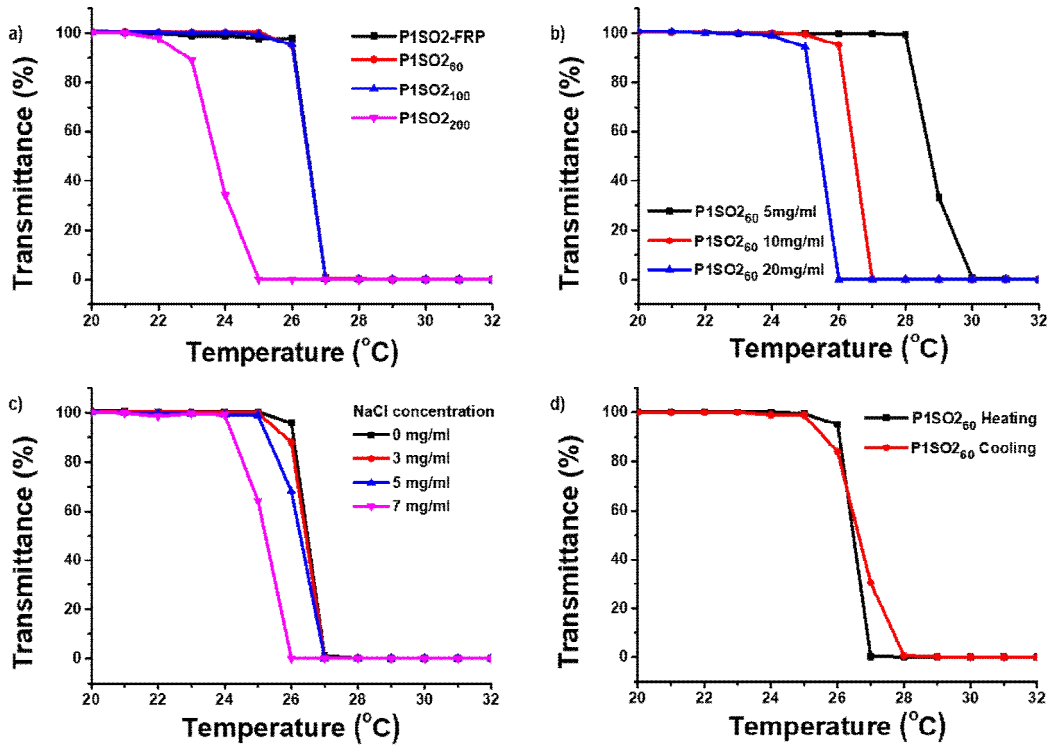


Figure 3. Plots of transmittance as a function of temperature measured for (a) 10 mg mL^{-1} aqueous solutions of P1SO2 homopolymers with different MWs and MWDs, (b) different concentrations of $P1SO2_{60}$ in water (c) 10 mg mL^{-1} aqueous solutions of $P1SO2_{100}$ with NaCl concentrations, and (d) 10 mg mL^{-1} aqueous solutions of $P1SO2_{60}$ homopolymer with a heating and a cooling cycle.

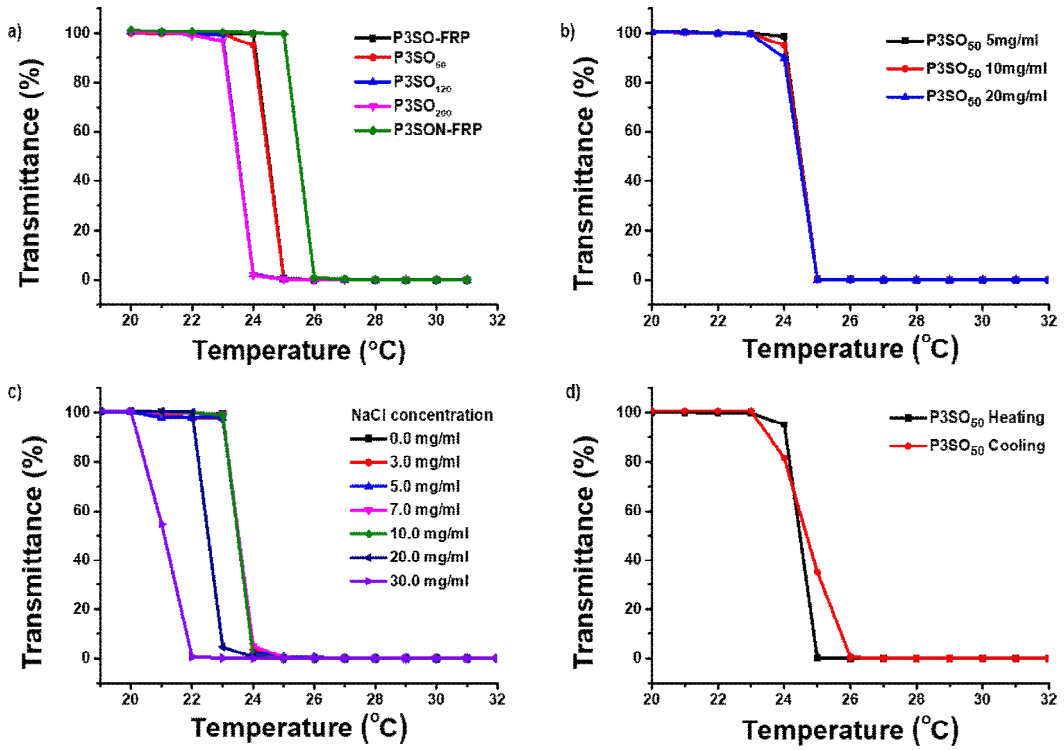


Figure 4. Plots of transmittance as a function of temperature measured for (a) 10 mg mL^{-1} aqueous solutions of P3SO homopolymers with different MWs and MWDs and P3SON homopolymer, (b) different concentrations of $P3SO_{200}$ in water (c) 10 mg mL^{-1} aqueous solutions of $P3SO_{200}$ with NaCl concentrations, and (d) 10 mg mL^{-1} aqueous solutions of $P3SO_{200}$ homopolymer with a heating and a cooling cycle.

At first, we focused on homopolymers (P1SO2 and P3SO) since they have thermosensitive property. The general trend observed for previous reports is that the LCST is lower for the higher molecular weight (MW) polymers.[17] Additionally, the LCST transition became extensive with broad molecular weight (MWD).[18] Fig. 3a and Fig. 4a appear that the transmittance of the 1 wt% P1SO2 and P3SO solution synthesized by RAFT polymerization with different chain lengths and P3SON solution synthesized by FRP polymerization decrease sharply at a certain temperature owing to the turbidity of the solutions when precipitation occurred. The cloud point of thermoresponsive polymers in water were determined at 50% transmittance point in the heating curve. We determined the LCST values of the polymer solutions at different concentrations. We found that MW had little effect on the thermal property of the P1SO2 and P3SO. We also investigated the cloud points of polydisperse P1SO2 (M_n = 46028, PDI = 1.78) and P3SO (M_n = 33832, PDI = 2.09) synthesized by free radical polymerization (FRP). Interestingly, the phase transition of P1SO2-FRP and P3SO-FRP occurs at the similar temperature compared to that of P1SO2 and P3SO synthesized by RAFT. It can notice that no significant differences on the LCST are observed for molecular weight and molecular weight distribution. The LCST of aqueous $P1SO2_{50}$ solution was 25 °C at a concentration of 0.5 mg mL^{-1}. It decreased a few degrees on increasing the polymer concentration. The cloud point of $P3SO_{60}$ solution had no change at 0.5, 1 and 2 mg mL^{-1} (Fig. 3b and Fig. 4b). Likewise, the concentration of P1SO2 and P3SO solution was not related on the LCST value. Note that, salt content can influence the LCST of thermoresponsive polymer in addition to the MW, MWD and concentration. For this reason, the concentration of NaCl on the thermoresponsiveness of aqueous solution of $P1SO2_{100}$ and $P3SO_{200}$ was investigated. Fig 3c demonstrates that the cloud point of an aqueous $P1SO2_{100}$ solution at a concentration of 10 mg mL^{-1} were found to decrease with the salt concentration due to a typical salting out effect, as reported previously.[19, 20] However, the LCST of aqueous $P1SO2_{100}$ solution did not measure after increasing the salt concentration at 10.0 mg mL^{-1} since the turbid $P1SO2_{100}$ solution became clear because of precipitation of $P1SO2_{100}$. Fig 4c also shows the cloud point of an aqueous $P3SO_{200}$ solution dropped slowly after the salt is added. We have also investigated the reversibility of thermoresponsive behavior. Fig 1d and Fig 2d showed $P1SO2_{100}$ and $P3SO_{200}$ had a very sharp transition when heated but a broad hysteresis was observed when cooled.

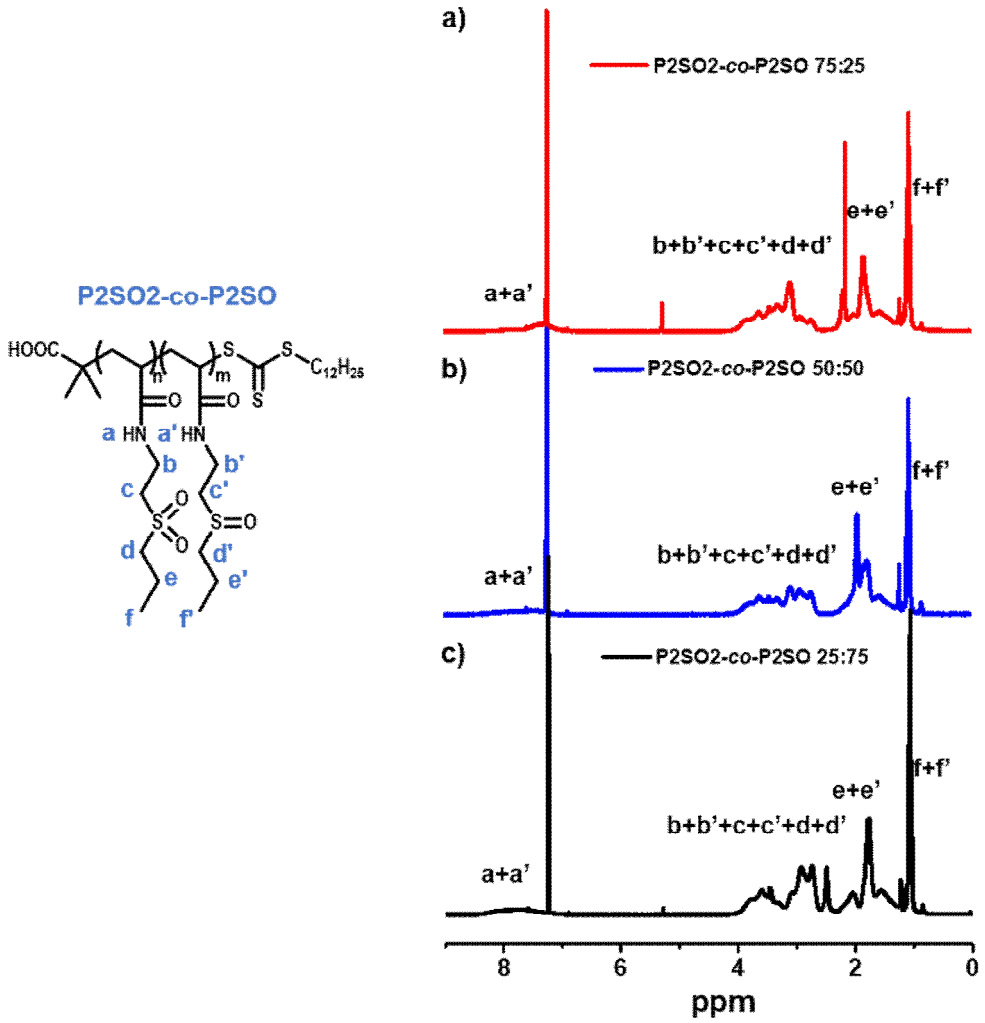


Figure 5. ^{1}H NMR spectra of P2SO2-*co*-P2SO with initial feed ratio of (a) 75:25, (b) 50:50 and (c) 25:75.

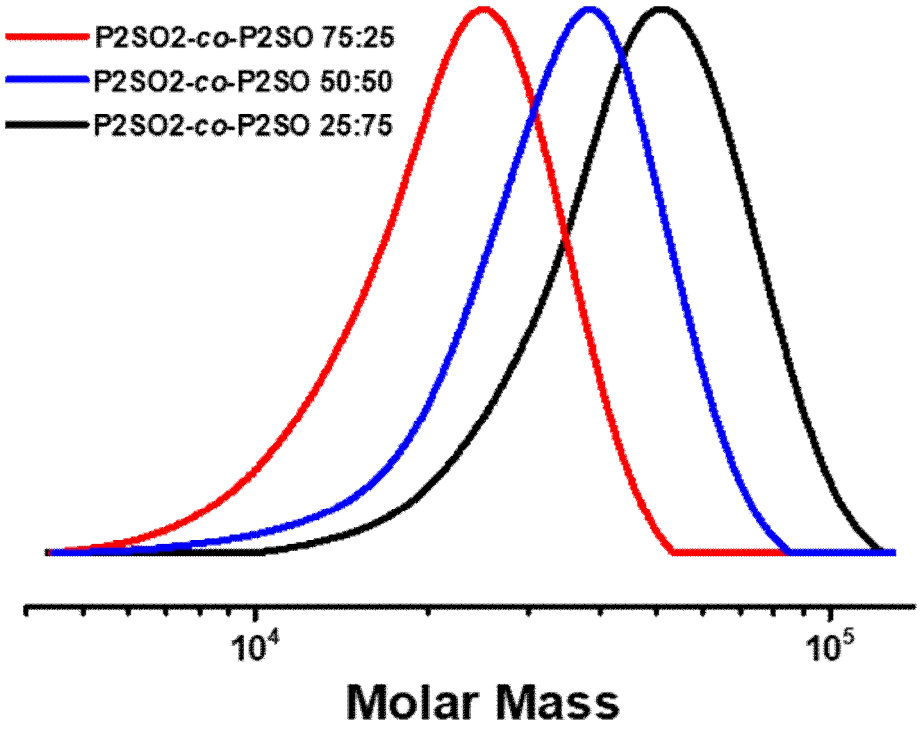


Figure 6. Overlaid GPC traces of P2OS2-*co*-P2SO with three different initial feed ratios.

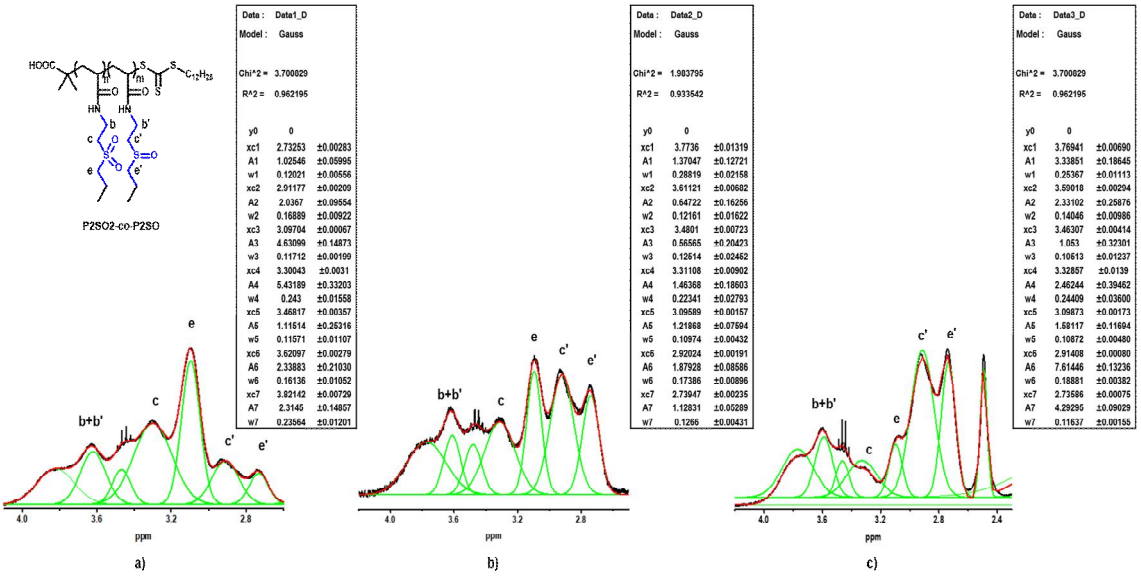


Figure 7. The deconvoluted ^{1}H NMR spectrum of P2SO2-*co*-P2SO with initial feed ratio of (a) 75:25, (b) 50:50 and (c) 25:75 for the quantification of the similar final structure.

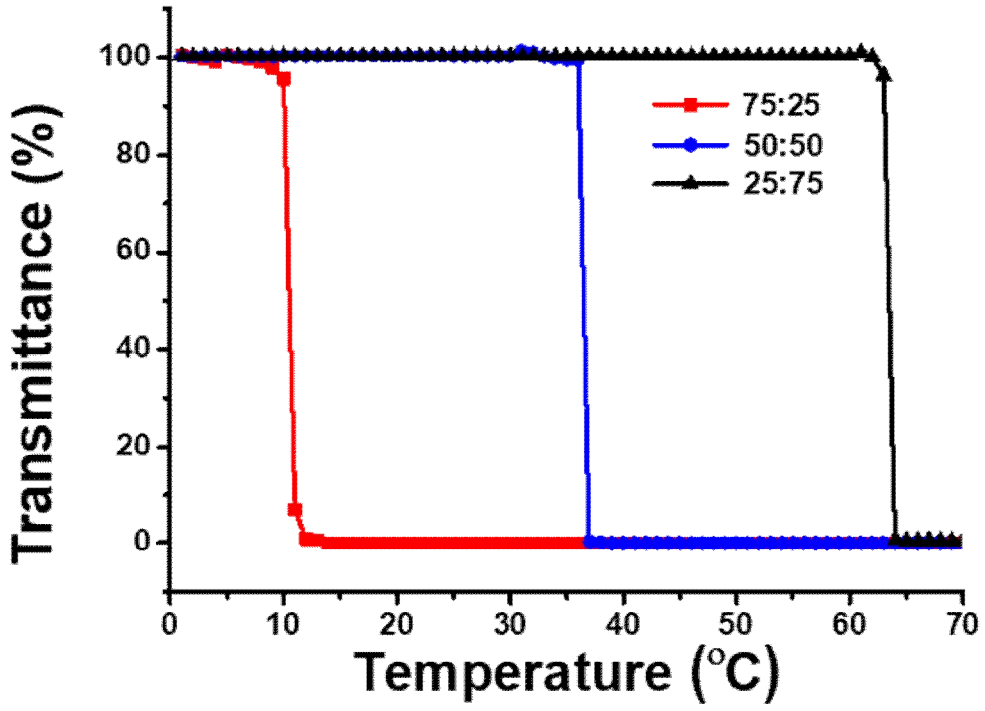
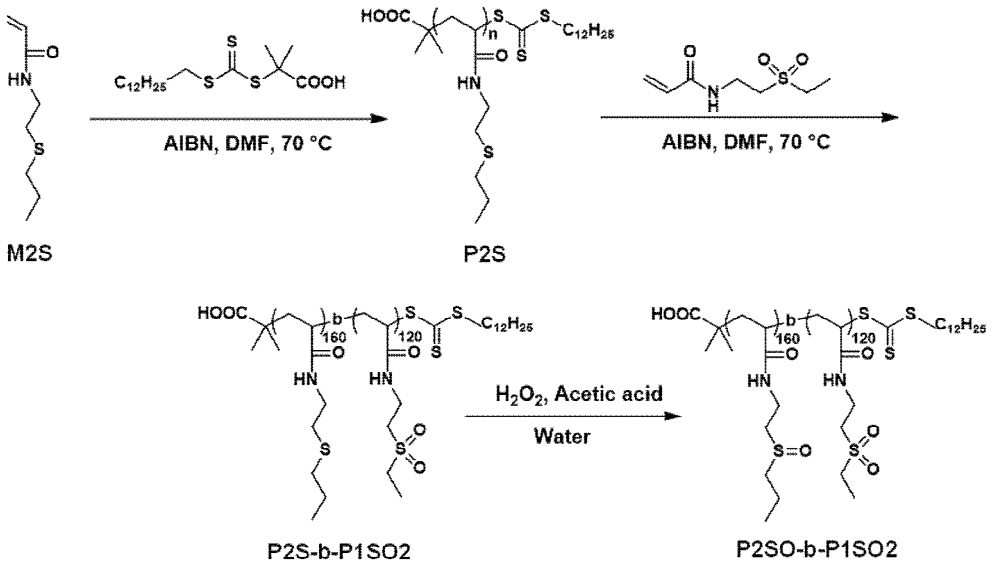


Figure 8. The cloud point for 10 mg mL^{-1} aqueous solutions of P2SO2-*co*-P2SO with three different initial feed ratios.

We evaluated the thermal behaviors of a series of random copolymers after we have demonstrated the sharp thermal transitions and relative insensitivity of P1SO2 and P3SO homopolymers to environmental conditions. In general, the LCST values depend on the introduction of comonomers that influence the hydrophilic/hydrophobic balance of the copolymer. P2SO2 is a hydrophobic homopolymer while P2SO is a hydrophilic homopolymer. Therefore, it is expected that the cloud point of the random copolymers can be tuned by adjusting the fraction of each monomer component in the copolymer chains. By controlling the initial feed ratio of M2SO2 and M2SO (75:25, 50:50 and 25:75), a series of P2SO2-*co*-P2SO random copolymers with three different compositions were prepared. The successful formation of these polymers was characterized by gel permeation chromatography (GPC) and ^{1}H-NMR spectroscopy (Fig 5 and 6). From the ratio of these peak areas, the final incorporation ratio of P2SO2/P2SO was similar with the initial feed ratio (Fig 7). The cloud point temperatures of the polymer samples were determined in aqueous solution at a concentration of 10 mg mL^{-1} (Fig 8). The three copolymers which have initial monomer feed ratio of 75:25, 50:50 and 25:75 were found to have transition temperatures of 9.8, 35.5, 62.1 ℃, respectively. This indicated that the incorporation of P2SO2 had caused an increase in hydrophobicity of the resulting copolymers. Compared to copolymer which has initial feed ratio of 75:25, a lower LCST was observed for its of 25:75 since it contained more hydrophobic P2SO2 comonomer.



Scheme 3. Synthesis of an amphiphilic block copolymer P2S-*b*-P1SO2, subsequent post-polymerization modification to yield P2SO-*b*-P1SO2.

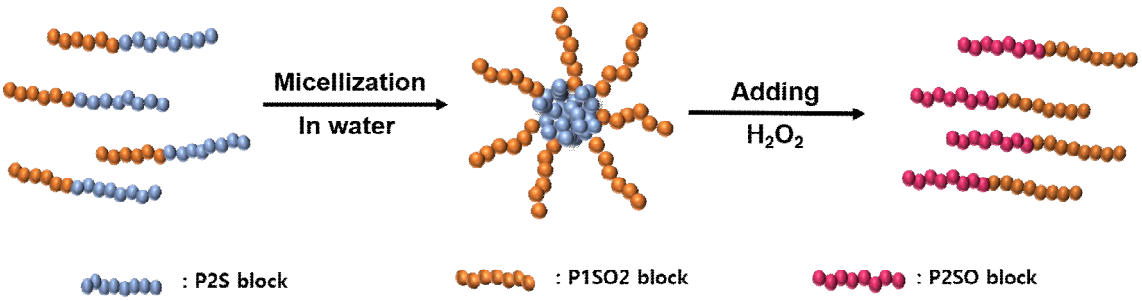


Figure 9. Schematic diagram of the formation/disruption of micelles for adding H_2O_2.

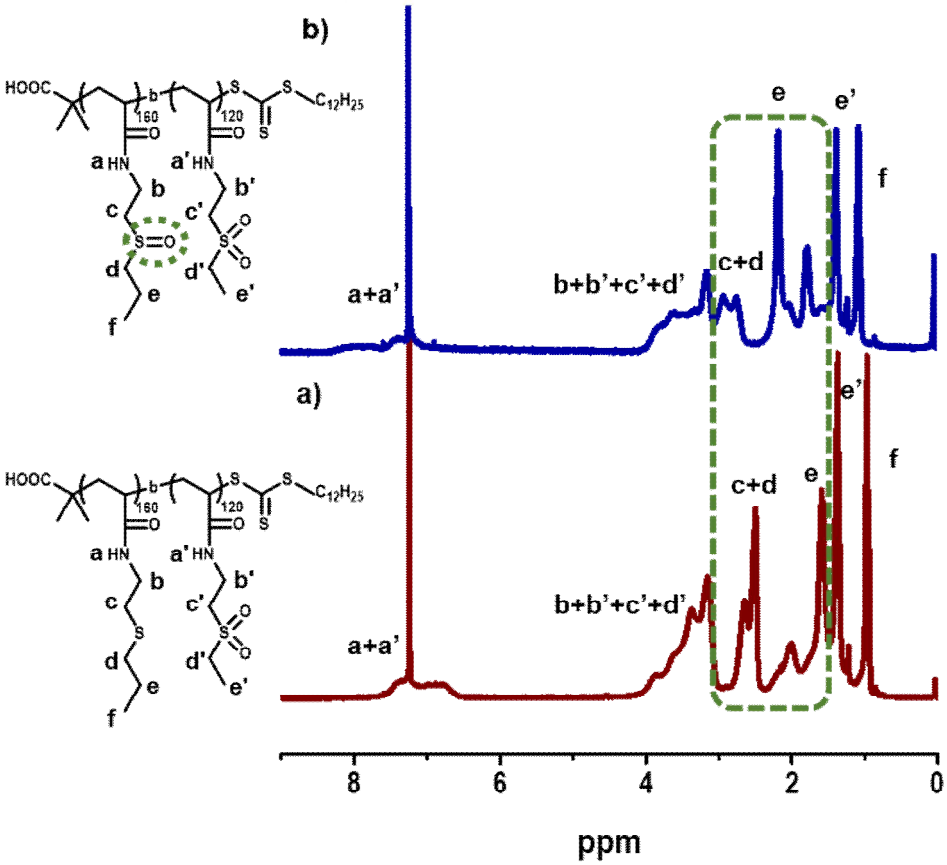


Figure 10. ^{1}H-NMR spectra of (a) P2S-*b*-P1SO2 and (b) P2SO-*b*-P1SO2.

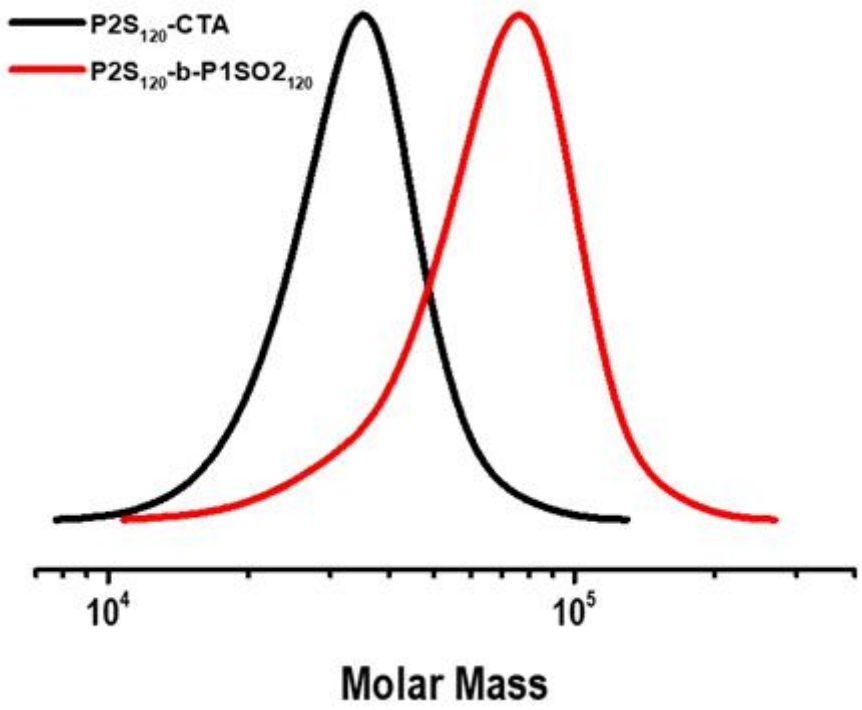


Figure 11. Overlaid GPC traces of P2S macro-CTA and $P2S_{120}$-*b*-$P1SO2_{120}$.

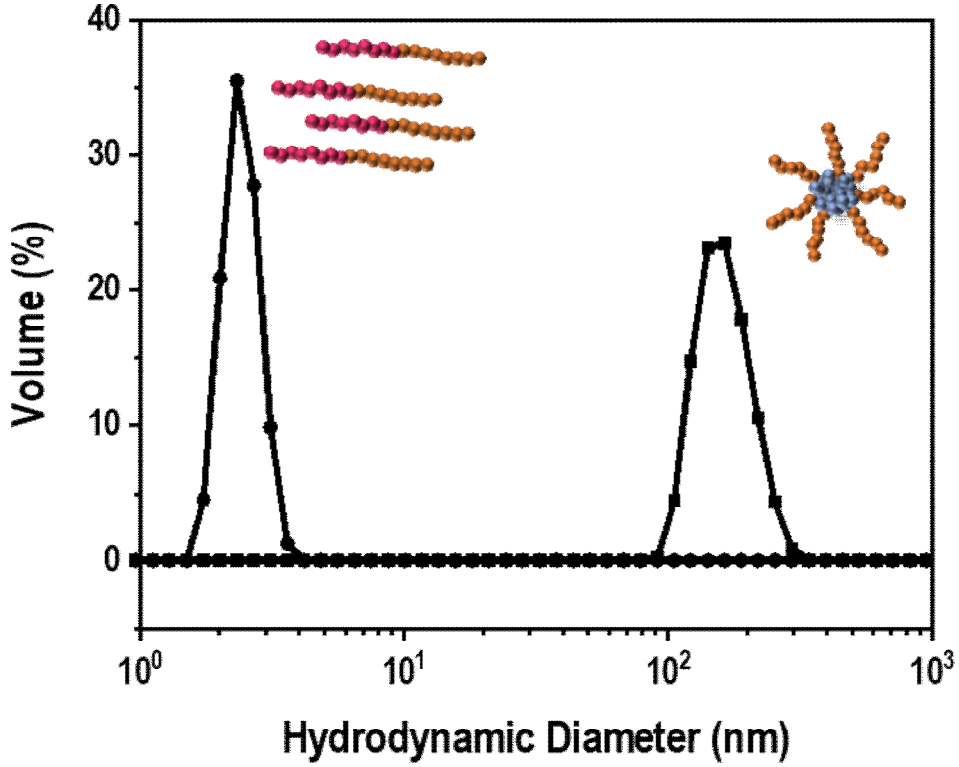


Figure 12. Hydrodynamic size distributions of a 0.025 wt% aqueous solution of P2S-*b*-P1SO2 before and after adding H_2O_2.

Scheme 3 shows the synthetic strategy used in this study. The thermoresponsive copolymer block of P1SO2 was extended from hydrophobic P2S macro-CTA via RAFT with a feed ratio 200:1 (P1SO2:P2S macro-CTA). The appearance of –(O=S=O)–CH_2– protons of P1SO2 at 3.01–3.25 ppm and –NH–CH_2– protons of P1SO2 at 3.76–4.04 ppm confirmed the successful synthesis of P2S-*b*-P1SO2 by ^{1}H-NMR spectroscopy (Fig 10a). The molecular weight and molecular weight distribution of P2S-b-P1SO2 were determined on a GPC DMF line using PMMA standards (Mn = 59 900 g/mol, M_w/M_n = 1.20) (Fig 11), showing a clear shift to a high molecular weight region. P2S is hydrophobic block and P1SO2 has thermoresponsive nature. Thus, P2S-*b*-P1SO2 is expected to exhibit an amphiphilic self-assembly behavior and forms micelles below the LCST of P1SO2. Here, a hydrophobic P2S block forms the inner core of the aggregates, whereas the outer shell consists of hydrophilic P1SO2 (at 20 °C). We investigated the transformation of P2S-*b*-P1SO2 micelles and conducted under the mild oxidation conditions (hydrogen peroxide, acetic acid, 30 min, 0 °C) to oxidize all sulfides in sulfoxides.[ref] Hydrogen peroxide convert hydrophobic P2S into hydrophilic P2SO. Therefore, after adding hydrogen peroxide, P2SO-b-P1SO2 micelles became unimers and eventually would not aggregate at 20 °C. ^{1}H-NMR spectroscopy provided evidence for post-polymerization modification of P2SO-*b*-P1SO2. The peak (c, d, e) representing the –CH_2–(S=O)–CH_2–CH_2– protons shifted to downfield in the spectrum (Fig 10b). DLS was used to obtain the size distributions before and after adding H_2O_2 for P2S-*b*-P1SO2. The average hydrodynamic diameter of the original micelles was 165 nm, which decreased to 1.38 nm after adding H_2O_2 (Fig 12). This confirmed the successful transformation of polymeric micelles to unimers.

4. Conclusion

A well-defined thermoresponsive substituted sulfide, sulfone and sulfoxide (co, block) polyacrylamide were successfully synthesized *via* RAFT polymerization. The number of the alkyl group in the chain length of the polymer and the oxygen in a sulfur atom led to significantly adjust the solubility in water. The thermoresponsive properties of P1SO2 and P3SO homopolymers were comparable to those of PNIPAM in terms of sharp thermosensitivity independence of MW, MWD, and inactivity of environmental conditions such as concentration and salt addition. Three different initial feed ratios of hydrophilic and hydrophobic monomers controlled the LCST values of copolymers. In addition, P2S-*b*-P1SO2 self-assembled into micelles aggregated in water at 20 °C. However, after adding H_2O_2, sulfide of P2S block changed to sulfoxide and the micelles became unimers. Indeed, by taking similar property of PNIPAM, sulfur-containing polyacrylamide are promising for a variety of applications in biomedicine and biotechnology because organosulfur compound has the importance to many kinds of bioactivity.

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국문 요약

자극 감응형 고분자들은 생물 의학적 분야에서 다양한 적용이 가능하여 지난 몇 년 동안 널리 연구되고 있습니다. 이러한 고분자들은 온도, 압력, pH, 산화 환원 그리고 빛 같은 환경적 조건 아래에서 작은 변화에 반응하여 화학적으로나 물리적인 변화를 겪게 됩니다. 그중 본 연구에서는 온도에 감응하는 고분자들을 합성하여 온도의 작은 변화에도 뚜렷한 변화가 있는지 확인하였습니다. 온도 감응성 고분자의 일부는 임계 하한 온도를 가지는데, 임계 하한 온도는 고분자만이 가질 수 있는 특성입니다. 임계 하한 온도란 고분자 수용액이 이 임계 온도 아래에서는 균일상이다가 임계 온도 이상으로 온도를 올려주게 되면 고분자가 더 이상 용액 안에 녹지 않는 온도를 말합니다. 대부분의 폴리 아크릴아마이드는 온도 감응성 고분자입니다. 더 나아가서, poly(N-isopropylacrylamide) (NIPAM)은 생체의 온도와 비슷한 LCST를 갖고 있기 때문에 약물 전달, 센서 그리고 진화된 물질로 응용이 가능한 전망 높은 고분자입니다. 그래서 저희는 새로운 폴리 아크릴아마이드를 합성하였습니다.

황은 저희 몸에서 여덟 번째로 풍부하고 삶에 필요한 물질입니다. 그리고 황은 마늘, 양파, 고기 같은 다양한 음식에서 찾아볼 수 있습니다. 20가지 아미노산 중 시스테인과 메타이오닌이 황을 포함한 유기물질입니다. 특히 설폭사이드 또는 설폰을 포함하는 유기물질은 의료 화학에서 흥미를 끌고 있습니다. 이런 이유로 본 연구에서 황을 포함하는 온도 감응형 고분자를 합성하였습니다.

양친매성 블락 공중합체는 수용액에서 마이셀 형태로 자기 조립이 가능합니다. 한쪽 블락은 친수성 그리도 다른 한쪽은 소수성을 가지는 AB 블락 공중합체에서, 양친매성 성질이 과산화수소수에 의해 두 블락 모두 친수성을 가지도록 바뀔 수 있습니다.

본 연구에서는 황을 포함한 아크릴아마이드계 고분자를 합성하여 설파이드, 설폰 또는 설폭사이드로 바꾸면서 그리고 사슬 말단의 탄소 수를 바꾸면서 물에서의 용해도를 쉽게 조절할 수 있었습니다. 설파이드를 가지는 아크릴아마이드계 고분자들은 사슬 말단의 길이가 짧든 길든 상관없이 물에 녹지 않았습니다. 설폰을 가지는 아크릴아마이드계 고분자 중 사슬 말단의 탄소 수가 2개인 경우 임계 하한 온도를 띄었고 사슬 말단의 탄소 수가 3개, 4개인 경우는 물에 녹지 않았습니다. 마지막으로 설폭사이드를 가지는 아크릴아마이드계 고분자들은 사슬 말단의 탄소 수가 2개, 3개인 경우는 물에 잘 녹았지만, 사슬 말단의 탄소 수가 4개인 경우는 임계 하한 온도를 가지는 것을 확인하였습니다. 따라서 물과 수소 결합을 할 수 있는 산소의 개수가 2개인 설폰보다 산소의 개수가 1개인 설폭사이드가 물과의 친화력이 더 높다는 것을 알 수 있었습니다. 설폰을 가지며 사슬 말단의 탄소 수가 2개인 Poly[N-(2-(ethylsulfonyl)ethyl)acrylamide] (P1SO2)는 임계 하한 온도가 25-26 °C였고,

설폭사이드를 가지며 사슬 말단의 탄소 수가 4개인 poly[N-(2-(butylsulfinyl)ethyl) acrylamide] (P3SO) 경우의 임계 하한 온도는 24-25 °C였습니다. 그리고 물에 잘 녹는 poly[N-(2-(ethylsulfinyl)ethyl)acrylamide] (P2SO)와 물에 잘 녹지 않는 poly[N-(2-(propylsulfonyl)ethyl)acrylamide] (P2SO2)의 초기 비율을 75:25, 50:50 그리고 25:75를 넣어주어 총 3가지의 랜덤 공중합체를 합성하였습니다. 물과의 친화력이 작은 P2SO2의 비율이 큰 75:25의 경우 10 °C부근의 아주 낮은 임계 하한 온도를 가졌고 물과의 친화력이 큰 P2SO의 비율이 큰 25:75의 경우 65 °C 부근의 아주 높은 임계 하한 온도를 가졌습니다. 하지만 P2SO2와 P2SO의 비율이 같은 50:50의 경우 앞서 합성한 두 가지 고분자의 임계 하한 온도 사이인 36 °C 부근으로 나타났습니다. 수소성과 친수성 단량체의 초기에 넣어준 비율로 랜덤 공중합체의 임계 하한 온도를 쉽게 조절할 수 있었습니다. 마지막으로 물에 잘 녹지 않는 poly[N-(2-(propylthio) ethyl)acrylamide (P2S)와 임계 하한 온도가 25 °C인 P1SO2의 블락 공중합체를 만들었습니다. 20 °C에서 이 블락 공중합체는 마이셀 형태로 응집하였습니다. 과산화수소수를 마이셀에 넣어준 후, 물에 잘 녹지 않는 P2S 블락의 설파이드가 과산화수소수를 만나 설폭사이드로 산화되어 블락 공중합체의 두 블락 모두 물에 잘 녹게 되었습니다. 따라서 마이셀의 형태가 깨지며 유니머 형태를 가지게 되었습니다.