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Thermoresponsive Sulfone and Sulfoxide-Containing Polyacrylamides

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A series of thermoresponsive polyacrylamides containing sulfide, sulfone, or sulfoxide was successfully prepared by reversible addition-fragmentation chain transfer (RAFT) polymerization. The thermal properties of polyacrylamides with sulfone or sulfoxide, which have not been studied before, were investigated for the first time. While poly[*N*-(2-(propylsulfonyl)ethyl)acrylamide] (P2SO2) with sulfone groups was water insoluble, poly[*N*-(2-(propylsulfinyl)ethyl)acrylamide] (P2SO) with sulfoxide groups was water soluble, indicating that the sulfoxide moiety is more hydrophilic than sulfone. By controlling the end of the polymer chain, we synthesized poly[*N*-(2-(ethylsulfonyl)ethyl)acrylamide] (P1SO2) and poly[*N*-(2-(butylsulfinyl)ethyl)acrylamide] (P3SO), which exhibit an lower critical solution temperature (LCST) in water around 24–26°C. For adjusting a wide range of LCST, we synthesized the random copolymers by controlling the initial feed ratio of hydrophobic M2SO2 and hydrophilic M2SO. The amphiphilic block copolymers were also synthesized and assembled in water to yield the micelles. After adding H_2O_2 to this micellar solution, the hydrophobic block was oxidized and converted to a hydrophilic block, leading to the transformation of micelles to unimers.

Keywords: Sulfide, Sulfone, Sulfoxide, Thermoresponsive, Polyacrylamide, RAFT, LCST

Introduction

Stimuli-responsive polymers have been widely investigated over the past few decades because of their numerous applications in the biomedical field. They undergo physical or chemical changes in response to small variations under environmental conditions, such as temperature, pressure, pH, chemicals, redox, light, and so on.[1–4] 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 a LCST have one phase below a critical temperature, but they become insoluble upon heating above their LCST.[5–7] Common LCST-type polymers show rapid, sharp, and reversible phase transitions in response to temperature changes. These types of polymers have become more important in recent years as they have a wide range of applications in drug delivery, bio-engineering, sensors, and other advanced materials.[8]

There are many known examples of LCST-type thermoresponsive polymers. Poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA) has been reported to show an LCST transition at around 50°C. Moreover, derivatives of 2-oxazoline (POx) are also widely used as thermoresponsive polymers. The POx family has an LCST ranging from 23 to 75°C, which depends on the side chain.[9] A combination of poly(ethylene glycol) (PEG) or oligo(ethylene glycol) (OEG) with other structural motifs will afford water-soluble thermoresponsive (co) polymers with the LCSTs lower than 100°C if an appropriate hydrophilic/hydrophobic balance is achieved.[10] The most well-known and extensively researched thermoresponsive polymers are poly(*N*-isopropylacrylamide) (PNIPAm) and its derivatives. PNIPAm has a LCST in the range of 30–35°C in water. The most interesting feature of PNIPAm is that its LCST is very close to that of the human physiological temperature, which could be very advantageous.[11] However, changing the N-substituent group of PNIPAM results in the largest and most documented thermoresponsive polymers of the polyacrylamide family. Our previous study on thermo-sensitive fluorinated polyacrylamide has indicated that their thermal properties can be controlled.[12] Therefore, we try to control the LCST behavior, by sulfonation of thermoresponsive polyacrylamide. A study on the comparison of the thermoresponsive behavior of sulfone and sulfoxide in polyacrylamide has not been systematically conducted before.

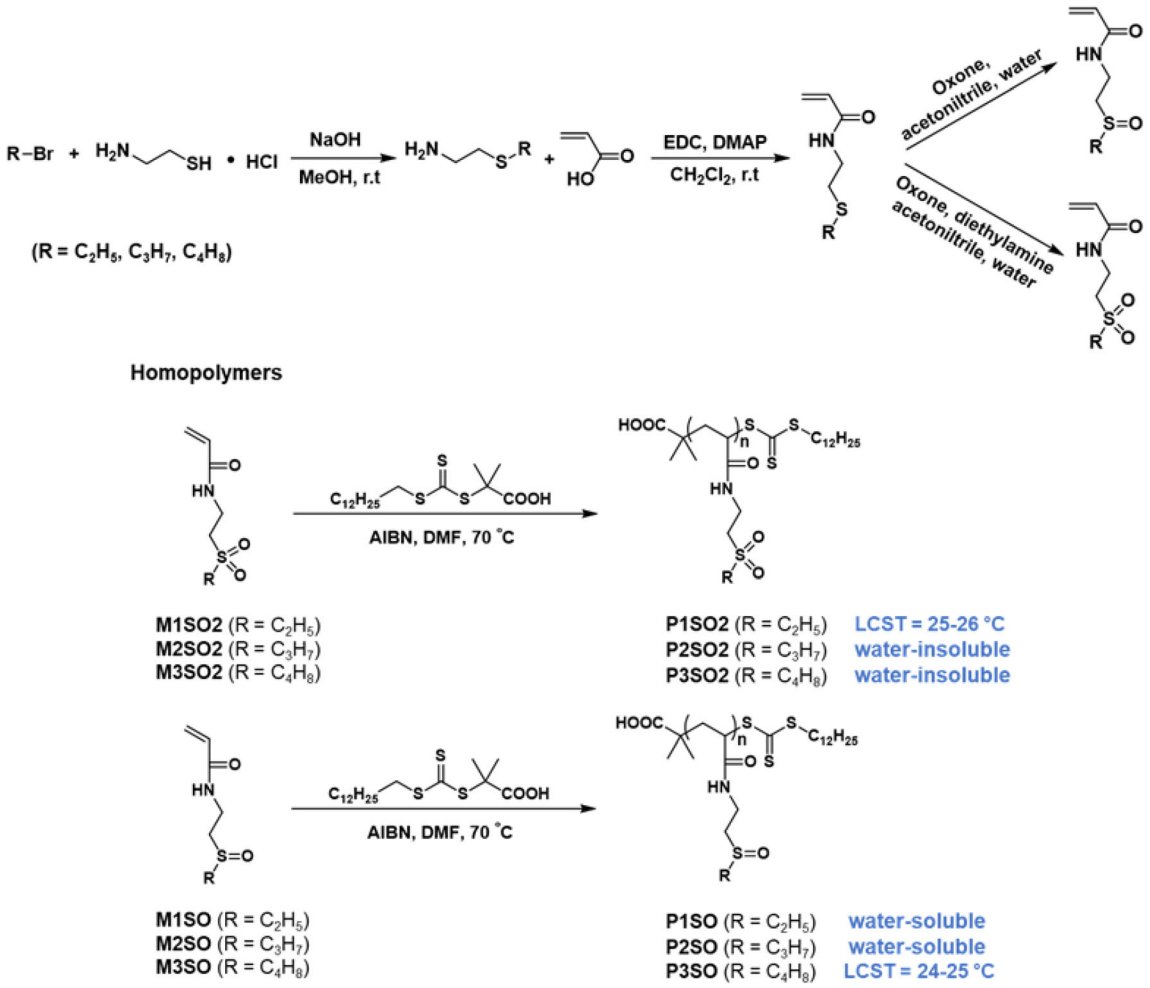
Organosulfur compounds, especially those containing sulfone or sulfoxide, attract special interest in medicinal chemistry and gives significance to many kinds of biological activity, meaning that the SO group could be a hydrogen bond receptor.[13–15] For example, sulfoxide-containing polymer showed no cytotoxicity toward human embryonic kidney cells (HEK 293).[16] Furthermore, the oxidation-responsive thioethers have been investigated as platforms for reactive oxygen species (ROS).[17,18] Sulfone-containing poly(NIPAm) could be used in electrodeposition and cell adhesion/detachment of human umbilical vein endothelial cells (HUVECs).[19] Considering this potential, we adjusted the LCST by changing the structure of the acrylamide

polymer with sulfone and sulfoxide. Theoretically, sulfone would be more hydrophilic than sulfoxide because sulfone has two oxygens, which can make hydrogen bonding with water molecules, while sulfoxide has only one oxygen. However, this study showed that sulfoxide moiety is more water-soluble than sulfone moiety. This could be due to the partial negative charge on the oxygen atom of sulfoxide groups, which favors the formation of the hydrogen bonds with water molecules, giving rise to the hydrophilicity of the sulfoxide.

Herein, we synthesized the series of sulfur-containing polyacrylamide, controlling the degree of sulfonation. The thermal behavior was tuned by adjusting the degree of polymerization (DP), molecular weight distribution (MWD), and environmental conditions such as concentration and the addition of salt. In addition, to give a wide range of LCST, random copolymers were synthesized with different initial ratios. We also synthesized amphiphilic block copolymers that formed micelles in water. Subsequently, H_2O_2 was added into the polymer aqueous solution causing the micelles to become unimers.

Results and Discussion

P1SO2 and P3SO exhibit an LCST in water around 24–26°C, which is comparable to body temperature. A schematic of the strategy employed in this study is illustrated in Scheme 1. A series of homopolymers (P1SO2 and P3SO) and random copolymers (P2SO2-*co*-P2SO) were synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization[20] from sulfur-containing acrylamide monomers (M1SO2, M2SO2, M2SO, and M3SO), using 2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropiionic 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, 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; Supporting Information Figures. S2 and S3). However, the apparent molecular weight obtained by GPC was higher than the theoretical molecular weight calculated from



Scheme 1. Synthesis of thermo-responsive sulfur-containing monomers and homopolymers by RAFT polymerization.

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

Monomer (M)	a:b	Polymer	Conv of M[a] (%)	$M_{n,theory}$[b] (g/mol)	$M_{n,\ ^1HNMR}$[c] (g/mol)	$M_{n,app}$[d] (g/mol)	PDI	LCST (°C)
M1SO2	—	P1SO2-FRP	—	—	—	46 000	1.78	26
M2SO2	—	P2SO2-FRP	—	—	—	39 200	2.11	—
M2SO	—	P2SO-FRP	—	—	—	22 500	1.91	—
M3SO	—	P3SO-FRP	—	—	—	33 800	2.09	25
M1SO2	—	$P1SO2_{60}$	33	12 400	10 100	31 500	1.10	26
		$P1SO2_{100}$	47	17 900	14 500	35 600	1.13	26
		$P1SO2_{200}$	69	39 900	24 400	69 800	1.21	24
M3SO	—	$P3SO_{50}$	24	9870	6780	14 700	1.18	25
		$P3SO_{120}$	59	23 900	21 700	23 200	1.29	25
		$P3SO_{200}$	69	42 500	31 500	40 400	1.34	24
M2SO2:M2SO	75:25	$P2SO2_{77}$-*co*-$P2SO_{23}$	—	—	—	40 900	1.21	10
	50:50	$P2SO2_{43}$-*co*-$P2SO_{47}$	—	—	—	20 200	1.20	35
	25:75	$P2SO2_{24}$-*co*-$P2SO_{76}$	—	—	—	30 200	1.19	62

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

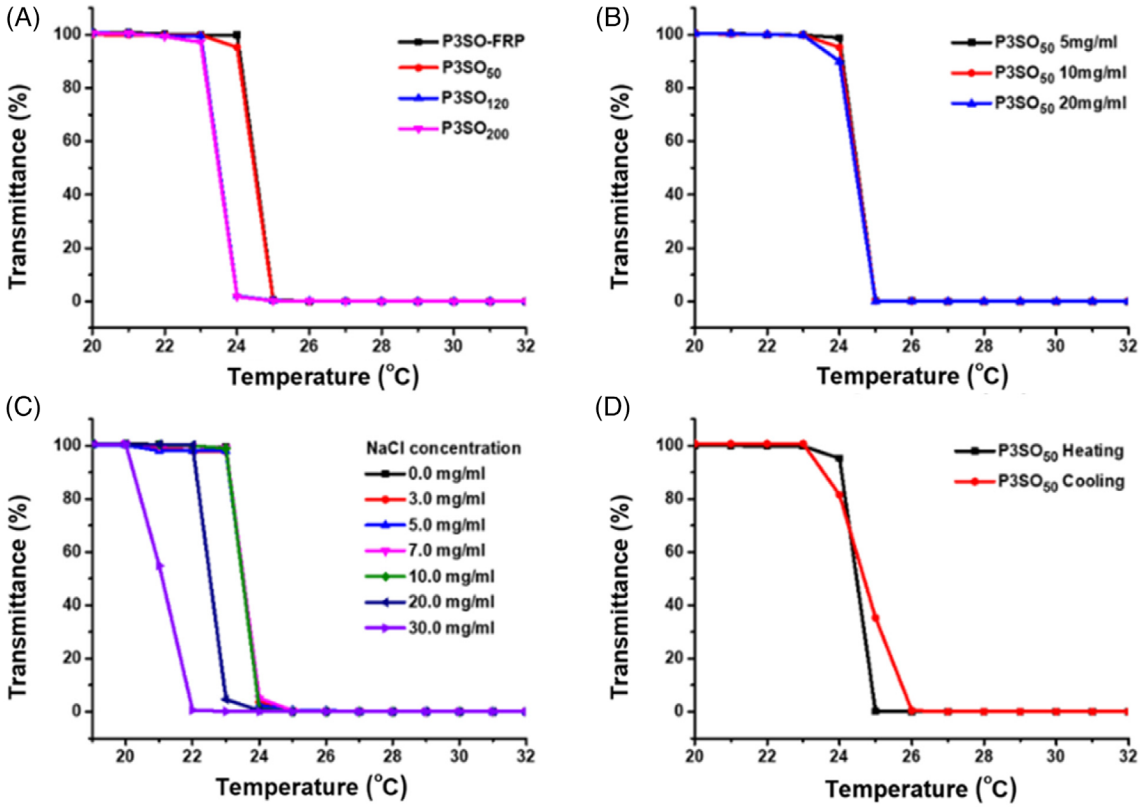
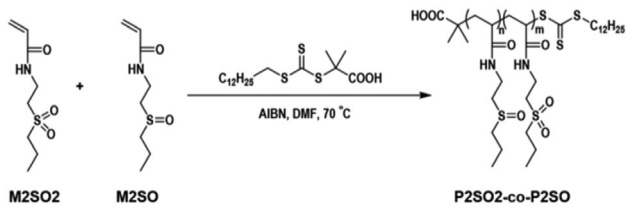


Figure 1. Plots of transmittance as a function of temperature measured for (a) 10 mg/mL aqueous solutions of P3SO homopolymers with different MWs and MWDs, (b) different concentrations of $P3SO_{200}$ in water (c) 10 mg/mL aqueous solutions of $P3SO_{200}$ with NaCl concentrations, and (d) 10 mg/mL aqueous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

the monomer conversion, due to the differences in hydrodynamic volumes of sulfur-containing polyacrylamides, and PMMA standards.

At first, we focused on the homopolymer (P3SO) since it has thermosensitive properties. The general trend observed from previous reports is that the LCST is lower for the

higher molecular weight (MW) polymers.[21] Additionally, the LCST transition became extensive with broad molecular weight distribution (MWD).[22] Figure 1(a) indicates that the transmittance of the 1 wt % P3SO solution, with different chain lengths, synthesized by RAFT polymerization decreases sharply at a certain temperature, owing to the turbidity of the solutions when precipitation occurred. The cloud point of thermoresponsive polymers in water was determined at 50% transmittance point in the heating curve. We found that MW had little effect on the thermal property of the P3SO. We also investigated the cloud point of polydisperse P3SO (Mn = 33 800, PDI = 2.09) synthesized by free-radical polymerization (FRP). Interestingly, the phase transition of P3SO-FRP occurs at a similar temperature compared to that of P3SO, synthesized by RAFT. Moreover, no significant differences in the LCST are observed for molecular weight and molecular weight distribution. We determined the LCST values of the polymer solutions at different concentrations. The cloud point of the $P3SO_{60}$ solution had no change at 0.5, 1, and 2 mg/mL (Figure 1 (b)). Similarly, the concentration of the P3SO solution was not related to the LCST value. Note that, salt content can influence the LCST of a thermoresponsive polymer in addition to the MW, MWD, and concentration. For this reason, the concentration of NaCl on the thermoresponsiveness of an aqueous solution of $P3SO_{200}$ was investigated. The addition of salt generally results in a decrease of the cloud point temperature ("salting out" effect), as a function of the salt concentration.[23,24] However, Figure 1(c) shows the cloud point of an aqueous $P3SO_{200}$ solution had no difference after the salt was added. We have also investigated the reversibility of thermoresponsive behavior. Figure 1(d) showed $P3SO_{200}$ had a very sharp transition when heated, but a broad hysteresis was observed when cooled. However, there are no differences in the heating and cooling cycle of P3SO homopolymer. The P1SO2 homopolymer was also investigated in the same way as the P3SO homopolymer (Supporting Information Figure S4). Moreover, there are no significant differences in the thermal properties of the P1SO2 homopolymer. The major disadvantage of PNIPAm is the strong hysteresis of the thermal solubility transition, which is due to the formation of intramolecular hydrogen bonds in the collapsed state.[25] Therefore, we can overcome this weakness of PNIPAm with P1SO2 and P3SO homopolymers.



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

First, we have to synthesize the sulfur-containing polyacrylamide, which has a wide range of LCSTs because P1SO and P3SO have limited LCSTs. In general, the LCST values depend on the introduction of comonomers that influence the hydrophilic/hydrophobic balance of the

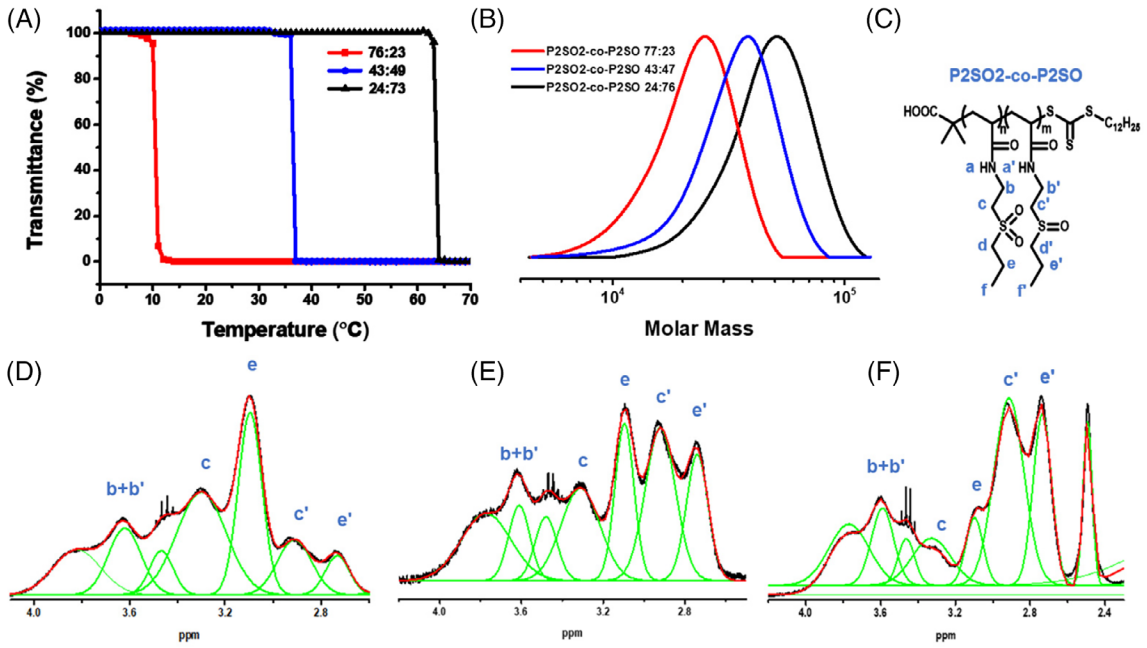
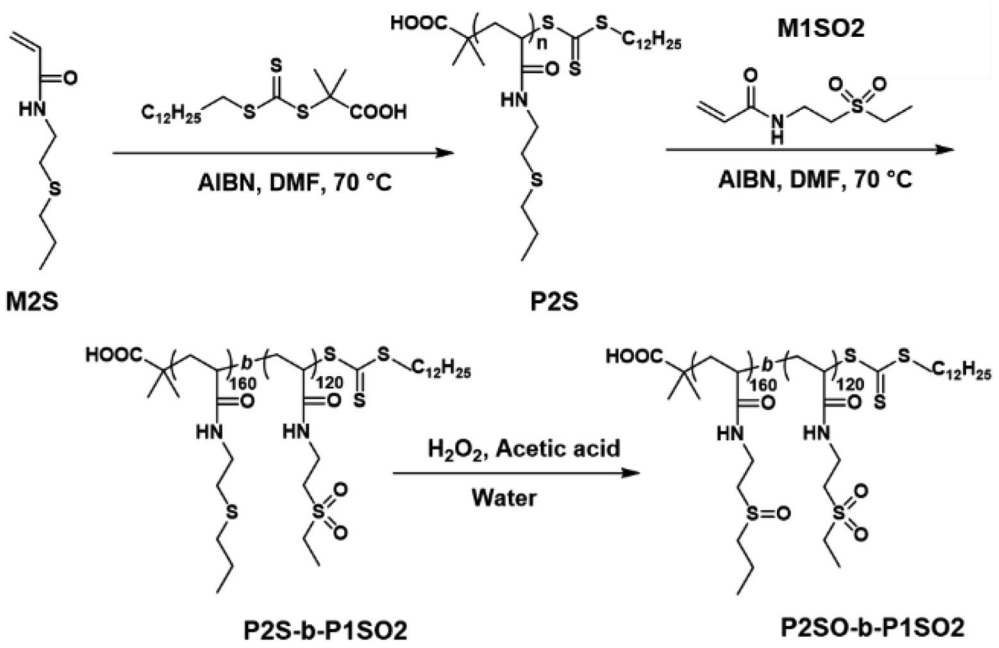


Figure 2. (a)The cloud point for 10 mg/mL aqueous solutions of P2SO2-*co*-P2SO with three different initial feed ratios, (b) GPC traces of series of P2SO2-co-P2SO, and the deconvoluted ^{1}H NMR spectrum of P2SO2-*co*-P2SO with initial feed ratio of (c) 75:25, (d) 50:50, and (e) 25:75 for the quantification of the similar final structure.



Scheme 3. Synthesis of an amphiphilic block copolymer $P2SO_{120}$-*b*-$P1SO2_{120}$, subsequent postpolymerization modification to yield $P2SO_{120}$-*b*-$P1SO2_{120}$.

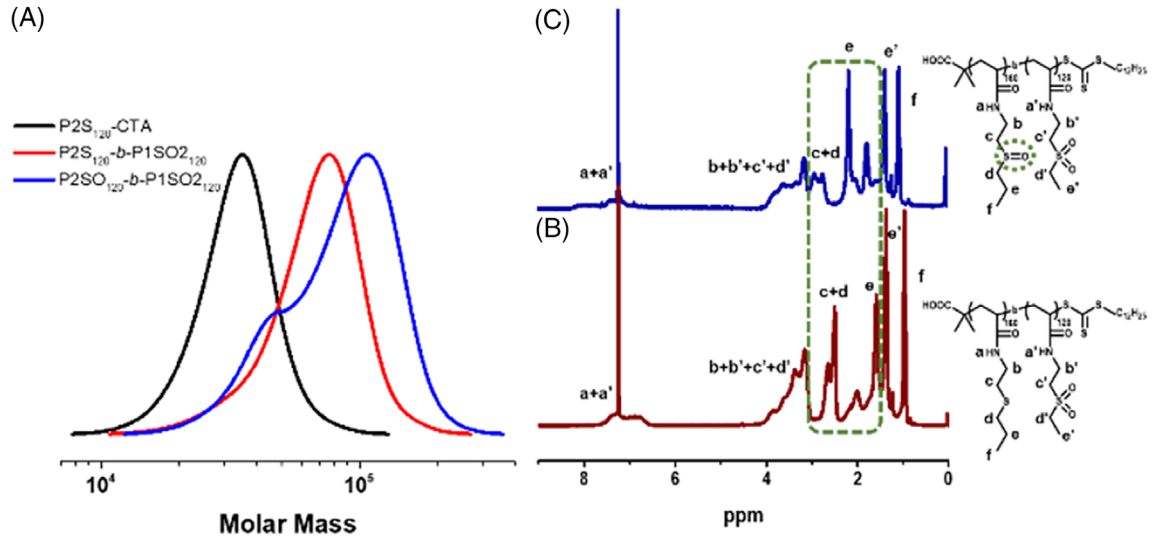


Figure 3. (a) Overlaid GPC traces of $P2S_{120}$-CTA, $P2SO_{120}$-*b*-$P1SO2_{120}$, and P2SO120-*b*-P1SO2120, ^{1}H NMR spectra of (b) $P2SO_{120}$-*b*-$P1SO2_{120}$, (c) $P2SO_{120}$-*b*-$P1SO2_{120}$.

copolymer. P2SO2 is a hydrophobic homopolymer and 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 (Scheme 2). The successful formation of these polymers was characterized by gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy (Figure 2(b) and Supporting Information S5). From the ratio of these peak areas, the final incorporation ratio of P2SO2/P2SO was similar to the initial feed ratio (Figure 2(c)–(e)). The cloud point

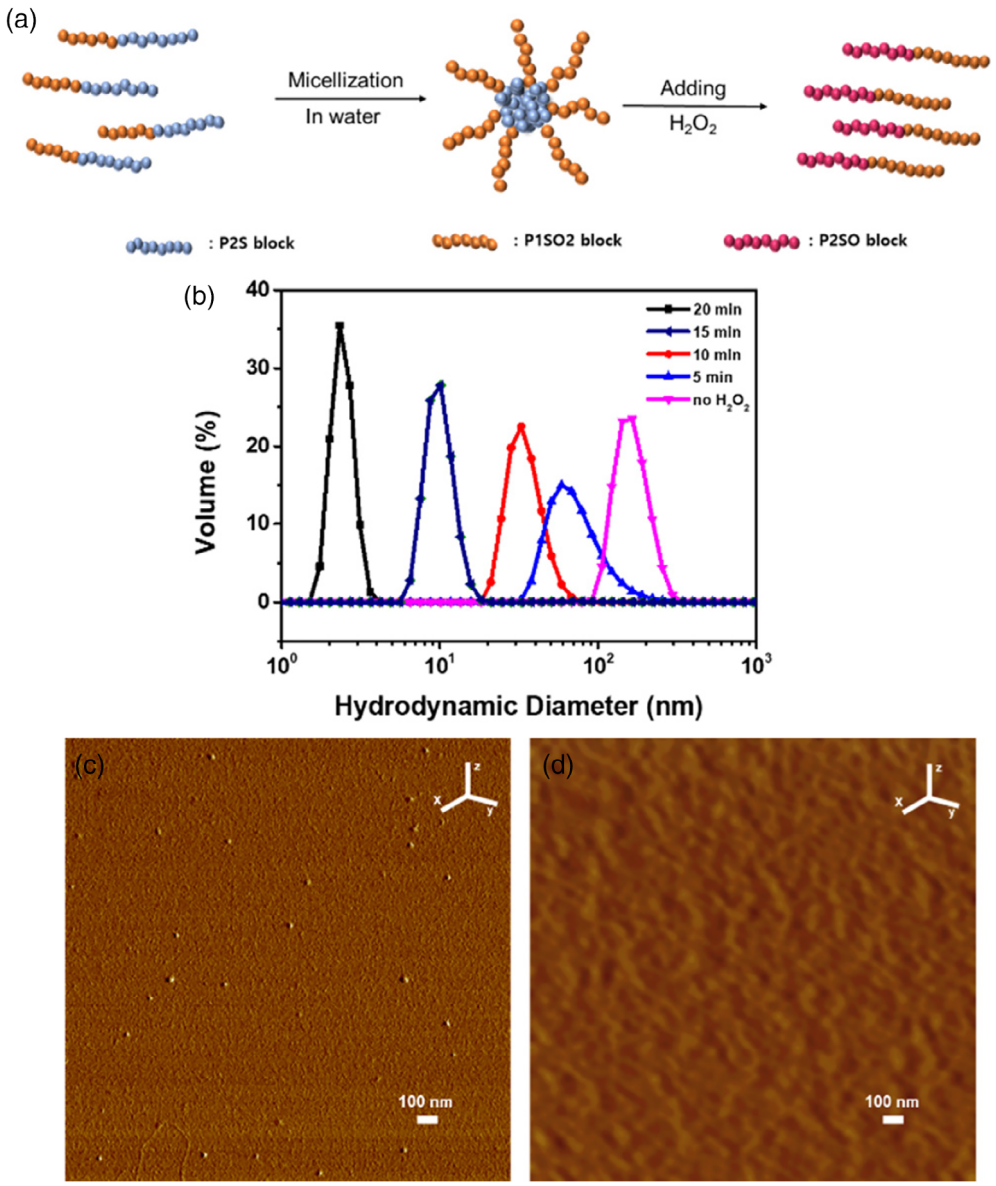


Figure 4. (a) Schematic diagram of the formation/disruption of micelles for adding H_2O_2, (b) hydrodynamic size distributions of a 0.025 wt % aqueous solution of $P2SO_{120}$-*b*-$P1SO2_{120}$ after adding H_2O_2 depending on the time, and representative AFM phase images of 0.005 wt % of $P2SO_{120}$-*b*-$P1SO2_{120}$ micellar solutions spin-coated on mica (c) before and (d) after adding H_2O_2.

temperatures of the polymer samples were determined in an aqueous solution at a concentration of 10 mg/mL (Figure 2 (a)). These three copolymers which have an initial monomer feed ratio of 75:25, 50:50, and 25:75 were found to have transition temperatures of 9.8, 35.5, and 62.1 °C, respectively. This indicated that the incorporation of P2SO2 had caused an increase in the hydrophobicity of the resulting copolymers. Also, the LCST increased with increasing P2SO composition because P2SO is water soluble. In other words, by tuning the initial ratio of random copolymers, sulfur-containing polyacrylamide with a wide range of LCSTs, even similar to body temperature, could be obtained.

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 of 200:1 (P1SO2:P2S macro-CTA). The molecular weight and molecular weight distribution of $P2SO_{120}$-*b*-$P1SO2_{120}$ were determined on a GPC DMF line, using PMMA standards (Mn = 59 900 g/mol, Mw/Mn = 1.20) (Figure 3(a)), showing a clear shift to a high-molecular weight region. 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 $P2SO_{120}$-*b*-$P1SO2_{120}$

by ^{1}H NMR spectroscopy (Figure 3(b)). After polymerization, the sulfide groups of $P2SO_{120}$-*b*-$P1SO2_{120}$ were converted to sulfoxide groups, by reacting with H_2O_2, leading to the formation of $P2SO_{120}$-*b*-$P1SO2_{120}$. ^{1}H NMR spectroscopy provided evidence for the post-polymerization modification of $P2SO_{120}$-*b*-$P1SO2_{120}$. The peak (c, d, e) representing the $-CH_2-(S=O)-CH_2-CH_2-$ protons shifted downfield in the spectrum (Figure 3(b)). The GPC traces in Figure 3(a) also showed that a small change in the apparent molecular weight occurred after the post-polymerization modification had been performed.

P2S is a hydrophobic block and P1SO2 exhibits an LCST in water at 25°C. Thus, $P2SO_{120}$-*b*-$P1SO2_{120}$ is expected to exhibit an amphiphilic self-assembly behavior and forms micelles below the LCST of P1SO2. Here, the 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 $P2SO_{120}$-*b*-$P1SO2_{120}$ micelles which were prepared under mild oxidation conditions (hydrogen peroxide, acetic acid, 20 min, 0 °C) to oxidize all sulfides to sulfoxides.[26,27] Hydrogen peroxide converted hydrophobic P2S into hydrophilic P2SO.

Therefore, after adding hydrogen peroxide, the $P2SO_{120}$-*b*-$P1SO2_{120}$ micelles became unimers which eventually would not aggregate at 20°C. The overall process is schematically depicted in Figure 4(a). DLS was used to obtain the size distributions for $P2SO_{120}$-*b*-$P1SO2_{120}$ before and after the addition of H_2O_2. The average hydrodynamic diameter of the original micelles was 165 nm, which decreased to 120.4, 67.45, 34.90, and 1.38 nm after H_2O_2 addition, depending on the time (Figure 4(b)). The formation and subsequent disruption of micelles by H_2O_2 were confirmed by atomic force microscopy (AFM) measurements, which showed the morphological changes of micelles. These microscopy experiments were performed by preparing samples from an aqueous solution of $P2SO_{120}$-*b*-$P1SO2_{120}$. AFM images of the samples (0.005 wt %), deposited directly onto a mica substrate by way of spin-coating, were collected after micellization. The results revealed the presence of uniform, well-dispersed individual globular micelles, with a mean diameter of 60 nm (Figure 4(c)). H_2O_2 was added to the $P2SO_{120}$-*b*-$P1SO2_{120}$ micelle solution, and 20 min later the resulting solution was spin-coated onto a mica substrate for AFM analysis. The previous well-defined globular micelles gave way to molecularly resolved individual polymer chains (Figure 4(b)), indicating that the formation of sulfoxide groups induced micellar disruption. This confirmed the successful transformation of polymeric micelles to unimers. This study may provide a promising application of these block copolymers for drug delivery and sensing applications.

Conclusions

A well-defined thermoresponsive sulfur-containing (co, block) polyacrylamide was successfully synthesized via RAFT polymerization. Through the comparison of polyacrylamide with sulfone and sulfoxide, we can conclude that the sulfoxide moiety is more hydrophilic than the sulfone moiety. We also adjusted the solubility of the polyacrylamide, with sulfone and sulfoxide, in water by controlling the length of the polymer chain end. We also indicated that PNIPAm, with a strong hysteresis for the thermal solubility transition, can be overcome with P1SO2 and P3SO homopolymers. To tailor a wide LCST range, including an LSCT similar to body temperature, random copolymers with three different initial feed ratios of hydrophilic and hydrophobic monomers were synthesized. In addition, P2S-*b*-P1SO2 self-assembled into micelles in water at 20°C. However, after adding H_2O_2, the sulfide of the P2S block changed to sulfoxide and the micelles became unimers. Indeed, sulfur-containing polyacrylamides are promising for a variety of applications in biomedicine and biotechnology, because the organosulfur compound has the potential for bioactivity.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

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