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Thermosensitive copolymer synthesized by controlled living radical polymerization: Phase behavior of diblock copolymers of poly(*N*-isopropyl acrylamide) families

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ABSTRACT: In this study, we prepared a series of thermosensitive polymers with low polydispersity index (PDI) values by nitroxide-mediated controlled radical polymerization (NMRP) with 2,2,6,6-tetramethyl-1-piperdinyloxy nitroxide (TEMPO) as a stable nitroxide-free radical. Poly(*N*-isopropyl acrylamide) (PNIPAAm)-*block*-poly(*N*-*tert*-butyl acrylamide) (PNTBA) was successfully synthesized, first, through polymerization with *N*-isopropyl acrylamide to obtain the reactive polymer PNIPAAm-TEMPO and, second, through polymerization by the addition of *N*-*tert*-butyl acrylamide (NTBA). The added molar fraction of NTBA during the second polymerization was adjusted accordingly to obtain the final polymerization product, a thermosensitive polymer (PNIPAAm-*block*-PNTBA), which had a targeted lower critical solution temperature (LCST). The result shows that the synthesis method used in this study effectively controlled the formation of the polymer to obtain a low PDI. The thermosensitive block copolymer, PNIPAAm-*b*-PNTBA (molar ratio = 9:1), with LCSTs in the range 27.7–39.8°C, was obtained through controlled living radical polymerization with PNIPAAm–TEMPO. Specifically, the 5 wt % aqueous solution of PNIPAAm-*b*-PNTBA (molar ratio = 9:1) had an LCST of 37.4°C; this was close to body temperature, 37°C. The 5 wt % aqueous solution of PNIPAAm-*b*-PNTBA (molar ratio = 9:1) showed potential for use in biomedical applications. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43224.

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INTRODUCTION

Thermosensitive polymers, a class of smart polymers,[1–3] respond to changes in temperature by swelling or deswelling; they are used extensively in nanobiotechnology and biomedical applications.[4–12] Poly(*N*-isopropyl acrylamide) (PNIPAAm) is a well-known representative thermosensitive polymer with a good thermal sensitivity and favorable biocompatibility. The *lower critical solution temperature* (LCST) is defined as the critical temperature below which the components of a mixture are miscible. PNIPAAm has an LCST of 32°C, which is close to body temperature. PNIPAAm swells when the temperature is lower than the LCST and deswells when the temperature is higher than LCST. The LCST of the *N*-isopropyl acrylamide (NIPAAm) copolymer can be lowered by the copolymerization of NIPAAm with a hydrophobic monomer,[13] such as *N*-*tert*-butyl acrylamide (NTBA). However, the phase behavior varies; it depends not only on the composition of the polymer but also on the interaction between the solvent and the polymer or other factors.[14] The LCST also varies with the concentration in water.

The polydispersity index (PDI) of a polymer synthesized by general radical polymerization cannot be controlled. Ionic (or chain-growth) polymerization and group-transfer polymerization can synthesize a polymer with a controlled molecular weight and PDI, but the reaction conditions are strict.[15–19] For example, a small amount of impurities may affect the reaction to have chain transfer or reaction termination, and the selection of monomers is also limited. In addition, the sequence of using monomers during block copolymerization needs to meet certain requirements. For example, the monomer used in the second polymerization should have an electron affinity that larger than or equal to the monomer used in the first polymerization.[18] On the other hand, controlled living radical polymerization can improve the previous limitations.[17]

The swelling behavior of PNIPAAm-*co*-poly(*N*-*tert*-butyl acrylamide) (PNTBA) random copolymers by radical polymerization was studied with particle diameters in the range 200–315 nm and LCSTs in the range 24–32°C for various molar ratios of NIPAAm to NTBA,[20] but the PDI values were not reported. In

addition, the nitroxide-mediated copolymerization of NIPAAm and NTBA with *N*-*tert*-butyl-*N*-[1-diethylphosphono(2,2-dimethyl propyl)] nitroxide (SG1)/2,2′-azobisisobutyronitrile (AIBN) was reported, and the PDIs of the synthesized poly(-PNIPAAm-*co*-PNTBA)–SG1 were within 1.2–1.3. The subsequent copolymerization of poly(PNIPAAm-*co*-PNTBA)–SG1 with styrene produced poly(PNIPAAm-*co*-PNTBA)-*block*-polystyrene–SG1 with PDIs in the range 1.3–1.4.[13] Furthermore, the synthesis of poly(*N*,*N*-dimethyl acrylamide) via nitroxide-mediated radical polymerization[21] was conducted with 2,2,6,6-tetramethyl-1-piperdinyloxy nitroxide (TEMPO)/AIBN, and the resulting PDI was reported to be in the range 1.5–2.5.

On the other hand, an amphiphilic block copolymer has both hydrophobic and hydrophilic segments and can formed into a micelle and, thus, was studied and has been reported extensively,[22,23] especially in the field of pharmaceutical applications, such as drug delivery and gene delivery. It is possible for a thermosensitive block copolymer having both hydrophobic and hydrophilic segments to form into a micelle through the control of the molecular weight and PDI of the hydrophobic and hydrophilic segments to obtain optimal properties of the micelles, including the LCST. An adjustable LCST can broaden the possible applications of a copolymer.

Therefore, in this study, we used controlled living radical polymerization, specifically nitroxide-mediated controlled radical polymerization (NMRP) with TEMPO as the stable nitroxide free radical, to synthesize a PNIPAAm-*b*-PNTBA block copolymer and not only graft a more hydrophobic unit, PNTBA, to PNIPAAm but also investigate the effect of a low PDI by comparing the results with the results of PNIPAAm-*co*-PNTBA random copolymers generated via general radical polymerization. We believed it would be advantageous to study a synthesized block copolymer with a low PDI because distinct properties, such as the LCST, particle diameter, and spectra, could be measured. Moreover, because the more hydrophobic segment, PNTBA, was grafted to PNIPAAm to form PNIPAAm-*b*-PNTBA diblock copolymers in this study, the micelle formation of the diblock copolymers was discovered.

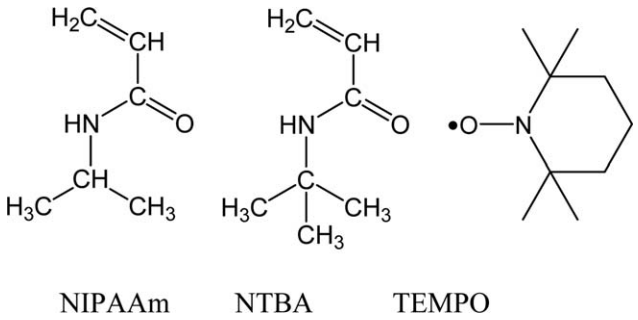
EXPERIMENTAL

Materials

The monomers, NIPAAm (97%; see Scheme 1) and NTBA (see Scheme 1), were purchased from SIGMA-Aldrich. AIBN (Uni-Region Bio-Tech). TEMPO (98%; see Scheme 1) was purchased from Alfa Aesar. Toluene, *p*-xylene (Echo Chemical Co. Ltd., 99.7%), methanol (100%), ethanol (99.8%), ether (99.8%), hexane, and tetrahydrofuran (99.8%) were all purchased from J. T. Baker. Chloroform-d (99.8 atom % deuterium) and hexadeuterated dimethyl sulfoxide (DMSO-d_6; C_2D_6OS; 99.9 atom % deuterium) were purchased from Aldrich.

Synthesis of the PNTBA Homopolymer

NTBA (20 mmol) as a monomer and AIBN (0.24 mmol) as an initiator were weighed and placed in a reaction flask. Toluene (10 mL) was added to the reaction flask. The reaction flask was purged with nitrogen for 10 min. In a nitrogen environment at 85°C, the reaction took place for 12 or 24 h (different reaction times). The reaction mixture was cooled, and a small amount of ether was added to dilute it. Then, the reaction mixture was added to an excess amount of hexane to generate precipitates. The reaction product (the precipitates) was then filtered and dried to obtain white solids (PNTBA). PNTBA was identified and characterized by ^{1}H-NMR, as shown in Figure 1(a), and its structure is shown in the upper portion of Figure 1(a).



Scheme 1. Chemical structures of NIPAAm, NTBA, and TEMPO.

Synthesis of PNTBA–TEMPO

NTBA (20 mmol), AIBN (0.24 mmol), and TEMPO (0.216 mmol) were weighed and placed in a reaction flask. *p*-Xylene (10 mL) was added to the reaction flask. The reaction flask was purged with nitrogen for 10 min. In a nitrogen environment at 125°C, the reaction took place for 12 or 24 h (different reaction times). The reaction mixture was cooled, and a small amount of ether was added to dilute it. Then, the reaction mixture was added to an excess amount of hexane to generate precipitates. The reaction product (the precipitates) was then filtered and dried to obtain white solids (PNTBA–TEMPO). PNTBA–TEMPO was identified and characterized by ^{1}H-NMR, as shown in Figure 1(b), and its structure is shown in the upper portion of Figure 1(b).

Synthesis of PNIPAAm–TEMPO

NIPAAm (20 mmol), AIBN (0.24 mmol), and TEMPO (0.216 mmol) were weighed and placed in a reaction flask. *p*-Xylene (10 mL) was added to the reaction flask. The reaction flask was purged with nitrogen for 10 min. In a nitrogen environment at 125°C, the reaction took place for 24 h. The reaction mixture was cooled, and a small amount of methanol was added to dilute it. Then, the reaction mixture was added to an excess amount of ether to generate precipitates. The reaction product (the precipitates) was then filtered and dried to obtain white solids (PNIPAAm–TEMPO). PNIPAAm–TEMPO was identified and characterized by ^{1}H-NMR, as shown in Figure 1(c), and its structure is shown in the upper portion of Figure 1(c).

Synthesis of Random PNIPAAm-*co*-PNTBA

The random PNIPAAm-*co*-PNTBA was synthesized by free-radical polymerization.[20] NIPAAm (20 mmol), NTBA (2.22 mmol), and AIBN (0.24 mmol) were weighed and placed in a reaction flask. Toluene (10 mL) was added to the reaction flask. The reaction flask was purged with nitrogen for 10 min. In a nitrogen environment at 85°C, the reaction took place for 24 h. The reaction mixture was cooled, and a small amount of

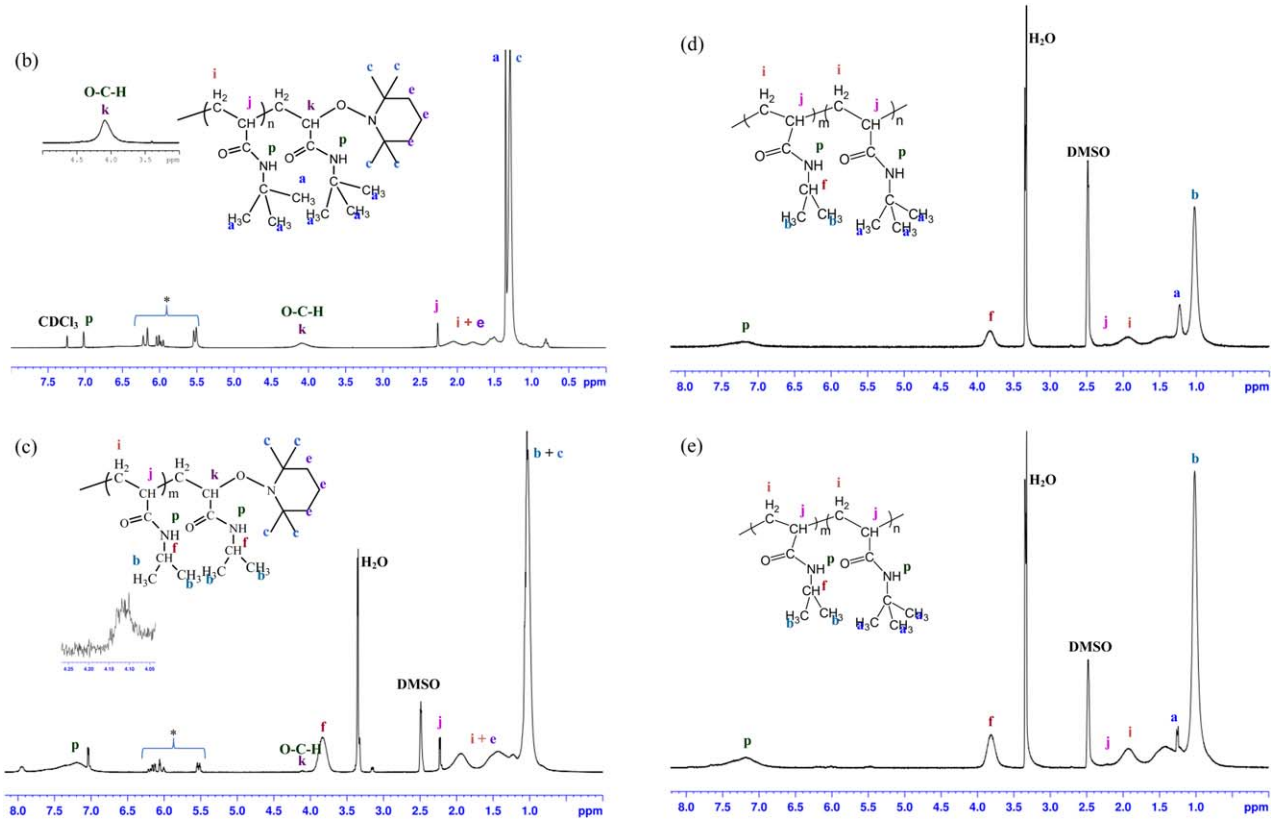


Figure 1. ^{1}H-NMR spectra of the (a) PNTBA homopolymer, (b) PNTBA–TEMPO, (c) PNIPAAm–TEMPO, (d) random PNIPAAm-*co*-PNTBA, and (e) PNIPAAm-*b*-PNTBA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

methanol was added to dilute it. Then, the reaction mixture was added to an excess amount of ether to generate precipitates. The reaction product (the precipitates) was then filtered and dried to obtain white solids (random PNIPAAm-*co*-PNTBA). The random PNIPAAm-*co*-PNTBA was identified and characterized by ^{1}H-NMR, as shown in Figure 1(d), and its structure is shown in the upper portion of Figure 1(d).

Synthesis of PNIPAAm-*block*-PNTBA

PNIPAAm-*block*-PNTBA was synthesized by NMRP through PNIPAAm–TEMPO as a reactive polymer. NIPAAm (20 mmol), AIBN (0.24 mmol), and TEMPO (0.216 mmol) were weighed and placed in a reaction flask. *p*-Xylene (10 mL) was added to the reaction flask. The reaction flask was purged with nitrogen for 10 min. In a nitrogen environment at 125°C, the reaction took place for 24 h. The reaction mixture was cooled. NTBA (2.22 mmol or 20 mmol) was added to the reaction mixture, and the temperature was raised to 135°C for the mixture to react for 24 h. Then, it was cooled, and a small amount of methanol was added to dilute it. Then, the reaction mixture was slowly added to an excess amount of ether to generate precipitates. The reaction product (the precipitates) was then filtered and dried to obtain white solids (PNIPAAm-*block*-PNTBA). The random PNIPAAm-*b*-PNTBA was identified and characterized by ^{1}H-NMR, as shown in Figure 1(e), and its structure is shown in the upper portion of Figure 1(e).

Identification and Characterization

We obtained the NMR spectra with a Bruker Advance 300-MHz NMR spectrometer by weighing 10 mg of a test sample and dissolving it in 1 mL of $CDCl_3$ and/or DMSO-d_6. The solvent signals were used as internal standards [DMSO-d_6: δ (^{1}H) = 2.47 ppm and $CDCl_3$: δ (^{1}H) = 7.24 ppm].

Fourier transform infrared (FTIR) spectra were obtained with a PerkinElmer RXI FTIR spectrometer with a resolution of 4.00 cm^{-1} within 4000–450 cm^{-1} at room temperature. A test sample (0.005 g) and KBr (0.1000 g, Aldrich, FTIR grade) was mixed and ground to a powder in an agate mortar. The powder was pressed with a subjected pressure of 10.0 tons into a pellet with a diameter of 20 mm.

A dimethylformamide solution containing 10 mg/L LiBr was used as an eluent at a flow rate of 0.20 mL/min at 50°C. Monodispersed polystyrene standards were used to obtain a calibration curve. A test sample containing the polymer to be tested was dissolved in dimethylformamide and filtered through a 0.45-μm Teflon filter. The weight-average molecular weight (M_w), number-average molecular weight (M_n), and PDI (M_w/M_n) of the test polymers were determined by a Viscotek 270max Advanced gel permeation chromatography (GPC) system from Malvern, Ltd. The temperature of the column was set to 50°C, the temperature of the detector was set to 50°C, and the injection quantities of the test sample and the standard were each 50 μL.

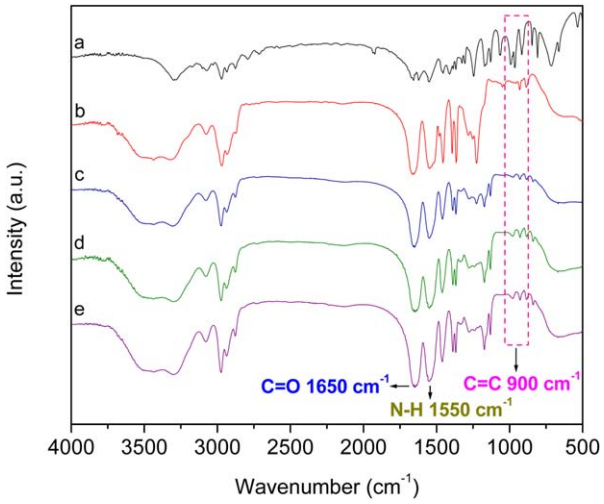


Figure 2. FTIR spectra of the (a) NIPAAm monomer, (b) PNIPAAm–TEMPO, (c) random PNIPAAm-*co*-PNTBA (molar ratio = 9:1), (d) PNIPAAm-*b*-PNTBA (molar ratio = 1:1), and (e) PNIPAAm-*b*-PNTBA (molar ratio = 9:1). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The particle diameter analysis was performed with a dynamic light scattering analyzer (90 plus, Brookhaven). A dilute aqueous test solution (≤0.01 wt %) containing the polymer was prepared, and the particle diameter of the polymer was measured with a dynamic light scattering analyzer.

The phase behavior of the test sample containing a specific polymer was measured with a laser transmittance meter (LASOS LGK 7628) with transmittance change as a function of the temperature or the concentration of the specific polymer in the test sample. Each of the LCSTs was determined from the transmittance of the test sample as a function of the temperature with the laser transmittance meter (LASOS LGK 7628); that is, the LCST was the temperature when the transmittance was 50%.

RESULTS AND DISCUSSION

NMR Results

PNTBA and PNIPAAm homopolymers and random PNIPAAm-*co*-PNTBA were prepared by free-radical polymerization and were used as references to compare with PNIPAAm-*block*-PNTBA synthesized by NMRP.

Figure 1(a–e) shows the ^{1}H-NMR spectra of the PNTBA homopolymer, PNTBA–TEMPO, PNIPAAm–TEMPO, random PNIPAAm-*co*-PNTBA, and PNIPAAm-*b*-PNTBA, respectively. The assignments of the spectra are also shown in Figure 1. For example, as shown in Figure 1(e) of the PNIPAAm-*b*-PNTBA block copolymer, the peaks at δs of 0.8–2.3 ppm were assigned as bands a, b, i, and j of PNIPAAm-*b*-PNTBA, and the peaks at δs of 3.7–4.0 ppm were attributed to the NIPAAm composition unit, which was also shown in the spectrum of the PNIPAAm-*co*-PNTBA random copolymer.[13]

The ^{1}H-NMR spectrum of the random copolymer (PNIPAAm-*co*-PNTBA) shown in Figure 1(d) confirmed that the positions of the characteristic peaks were the same as those for the block copolymer (PNIPAAm-*b*-PNTBA). Therefore, the ^{1}H-NMR spectra indicated the successful synthesis of PNIPAAm-*b*-PNTBA through NMRP.

GPC Analysis

The GPC spectra of random PNIPAAm-*co*-PNTBA and PNIPAAm-*b*-PNTBA are shown in Figure 2, and the M_w, M_n, and PDI (M_w/M_n) values calculated from GPC are shown in Table I.

The GPC spectra shown in Figure 3 confirmed that the PNIPAAm-*b*-PNTBA prepared by NMRP had a lower PDI (M_w/M_n) than the random PNIPAAm-*co*-PNTBA prepared by free-radical polymerization.

Table I shows the synthesis conditions and the physical properties of the various polymers synthesized in this study. PNIPAAm, PNTBA, and random PNIPAAm-*co*-PNTBA were synthesized with free-radical polymerization, whereas PNTBA–TEMPO, PNIPAAm–TEMPO, and PNIPAAm-*b*-PNTBA were synthesized with NMRP. This indicated that the NMRP method effectively controlled the PDI. The NTBA and NIPAAm monomers reacted with TEMPO in the preparation of PNTBA–TEMPO and PNIPAAm–TEMPO, respectively, to function as a reactive polymer. PNIPAAm–TEMPO had a PDI of 1.47 and reacted further with NTBA to form PNIPAAm-*b*-PNTBA with a lower PDI (1.26). The result indicates that the living free-radical polymerization further narrowed the PDI for the final polymerized product.

Table I. Synthesis Conditions and Physical Properties of Various Polymers

	Molar ratio				
Sample	NIPAAm	NTBA	$M_w/10^5$	$M_n/10^5$	PDI (M_w/M_n)
PNIPAAm homopolymer	100	—	1.15	0.41	2.80
PNTBA homopolymer	—	100	1.06	0.29	3.66
PNTBA homopolymer	—	100	1.35	0.53	2.53
Random PNIPAAm-co-PNTBA	90	10	2.27	1.02	2.25
PNTBA–TEMPO	—	100	0.31	0.25	1.29
PNIPAAm–TEMPO	100	—	0.32	0.21	1.48
PNIPAAm-*b*-PNTBA (9:1)	90	10	0.49	0.39	1.26
PNIPAAm-*b*-PNTBA (1:1)	50	50	0.52	0.42	1.27

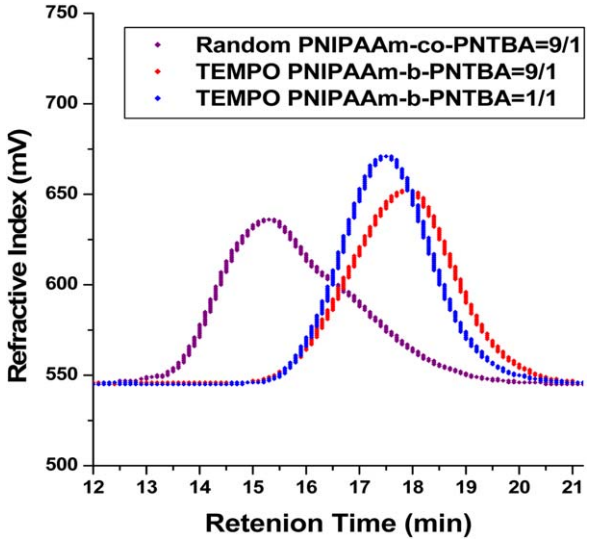


Figure 3. GPC spectra of the copolymers: random PNIPAAm-*co*-PNTBA and PNIPAAm-*block*-PNTBA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Phase Behavior

The phase behavior of the polymer solutions containing PNIPAAm–TEMPO and PNTBA–TEMPO in water and in a mixture of water and methanol (volume ratio = 9:1), respectively, are shown in Figure 4(a,b) by the plots of the transmittance versus the temperature for different concentrations with the laser transmittance meter (LASOS LGK 7628). The solution of PNTBA–TEMPO had an upper critical solution temperature (UCST), whereas the solution of PNIPAAm–TEMPO had an LCST. Figure 4(c) shows the temperature at a transmittance of 50% for each concentration of PNIPAAm–TEMPO and PNTBA–TEMPO; that is, the UCST and LCST are shown for each concentration of PNIPAAm–TEMPO and PNTBA–TEMPO. The LCSTs of PNIPAAm–TEMPO decreased as the concentration increased, whereas the UCSTs of PNTBA–TEMPO increased as the concentration increased.

In addition, the UCST and LCST of the polymer mixtures in general depended on the monomer ratios of the copolymer, the hydrophilic and hydrophobic natures of the polymer, the polydispersity, and so forth. Figure 5(a–c) shows the phase behavior of the polymer solutions containing random PNIPAAm-*co*-PNTBA, PNIPAAm-*b*-PNTBA (molar ratio = 9:1), and PNIPAAm-*b*-PNTBA (molar ratio = 1:1), respectively, through the plots of the transmittance versus the temperature for different concentrations. Figure 5(d) shows the LCSTs of PNIPAAm-*b*-PNTBA (molar ratio = 9:1), PNIPAAm-*b*-PNTBA (molar ratio = 1:1), random PNIPAAm-*co*-PNTBA, and PNIPAAm–

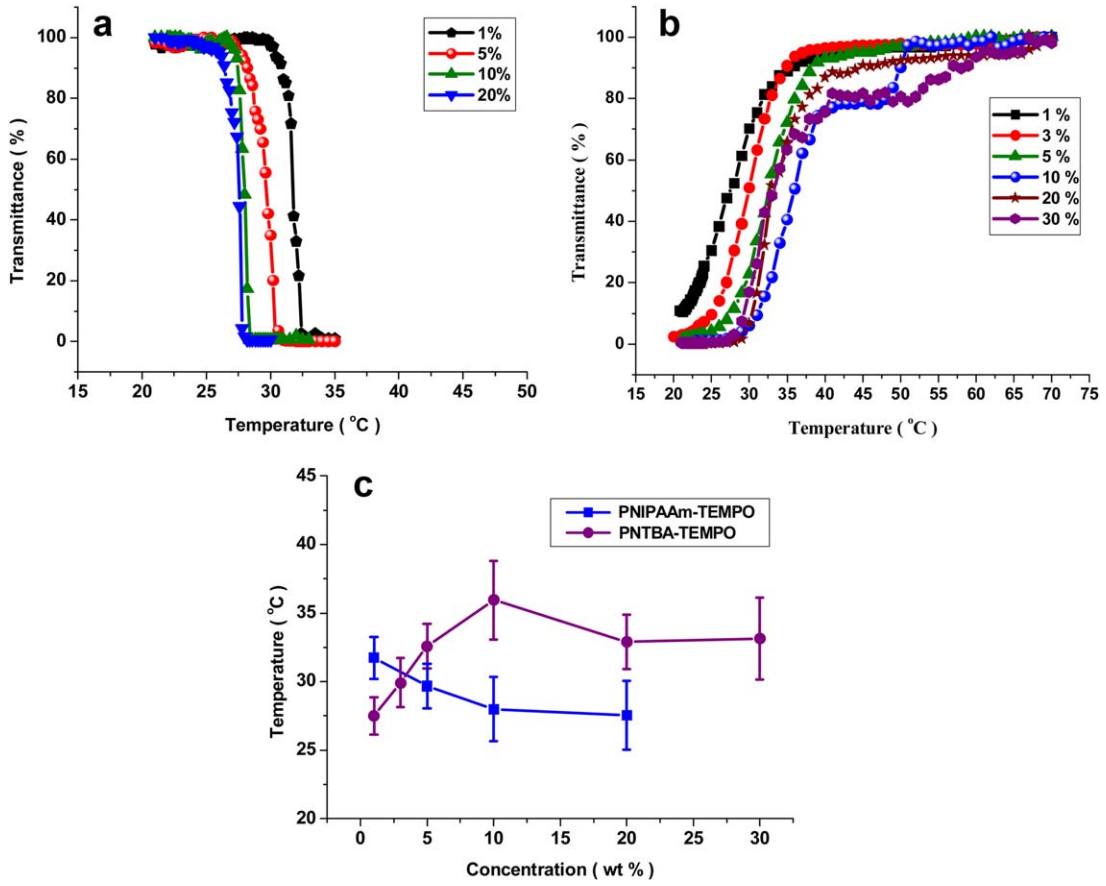


Figure 4. (a) Plot of the transmittance versus the temperature for a solution of PNIPAAm–TEMPO in H_2O, (b) plot of the transmittance versus the temperature for a solution of PNTBA–TEMPO in methanol/H_2O (9:1), and (c) temperature at the transmittance of 50% for each concentration of PNIPAAm–TEMPO and PNTBA–TEMPO. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

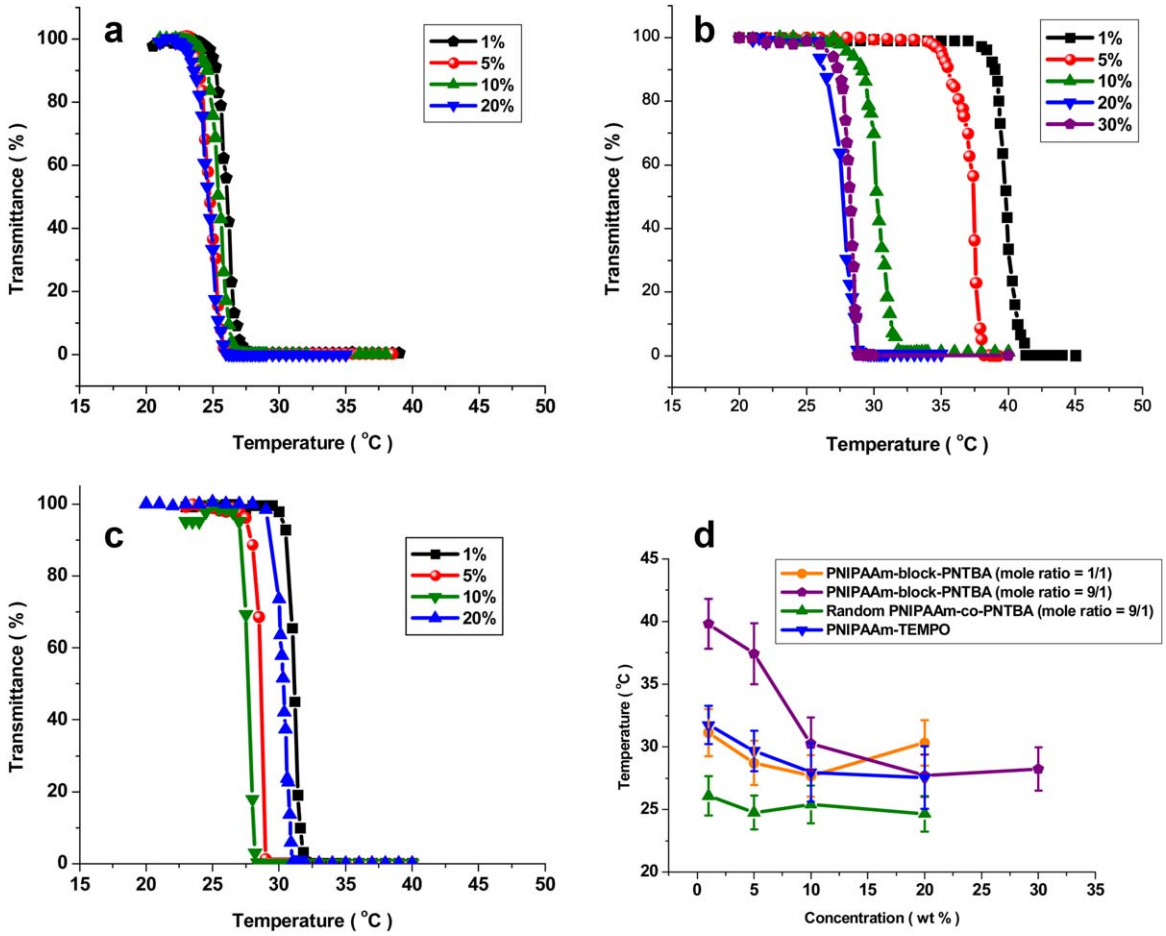


Figure 5. (a) Plot of the transmittance versus the temperature for a solution of random PNIPAAm-*co*-PNTBA in water, (b) plot of the transmittance versus the temperature for a solution of PNIPAAm-*b*-PNTBA (molar ratio = 9:1) in water, (c) plot of the transmittance versus the temperature for a solution of PNIPAAm-*b*-PNTBA (molar ratio = 1:1) in water, and (d) LCSTs of PNIPAAm-*b*-PNTBA (molar ratio = 9:1), PNIPAAm-*b*-PNTBA (molar ratio = 1:1), random PNIPAAm-*co*-PNTBA, and PNIPAAm–TEMPO as a function of the concentration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TEMPO as a function of the concentration. The UCSTs and LCSTs of various polymers were determined and are shown in Table II. The LCSTs of PNIPAAm-*b*-PNTBA (molar ratio = 9:1), random PNIPAAm-*co*-PNTBA, and PNIPAAm–TEMPO all showed a decreasing trend as the concentration increased. However, PNIPAAm-*co*-PNTBA, which had a large PDI (2.23), showed only a slight change in LCST when the concentration changed from 1 to 20%. PNIPAAm-*b*-PNTBA (molar ratio = 9:1) showed a significant change in LCST when the concentration changes from 1 to 10%, but PNIPAAm-*b*-PNTBA (molar ratio = 1:1) showed no similar trend. The LCSTs of the PNIPAAm homopolymer and PNIPAAm–TEMPO generally had no significant change with respect to changes in the concentration. Because the NTBA chain was hydrophobic and the NIPAAm chain was hydrophilic, PNIPAAm-*b*-PNTBA was amphiphilic, and the relatively high LCST of PNIPAAm-*b*-PNTBA (molar ratio = 9:1) at the low concentration shown in Figure 5(d) may have been due to micelle formation. When the steric hindrance effect during micelle formation was taken into account, the block copolymer with the smaller molar fraction of NTBA had a more significant impact on LCST, as shown in Figure 5(d). PNIPAAm-*b*-PNTBA (molar ratio = 9:1) had the smaller molar fraction of hydrophobic chains (NTBA), and thus, micelle formation was easier. Therefore, PNIPAAm-*b*-PNTBA (molar ratio = 9:1) had a high solubility, and its LCST increased significantly at the low concentration. To further confirm whether micelle formation occurred, particle diameter analysis of the block copolymers was conducted, and the result

Table II. UCSTs and LCSTs of Various Polymers

Sample	LCST (°C)	UCST (°C)
PNIPAAm	32.4–34.5	
PNIPAAm–TEMPO	27.6–31.7	
PNTBA–TEMPO		27.5–33.1
Random PNIPAAm-*co*-PNTBA	24.7–26.1	
PNIPAAm-*b*-PNTBA (molar ratio = 9:1)	27.7–39.8	
PNIPAAm-*b*-PNTBA (molar ratio = 1:1)	27.7–31.0	

Table III. Average Particle Diameters of Various Copolymers at Different Temperatures

Sample	25°C (±5% nm)	40°C (±5% nm)
PNIPAAm–TEMPO	233	156
Random PNIPAAm-*co*-PNTBA (molar ratio = 9:1)	291	190
PNIPAAm-*b*-PNTBA (molar ratio = 9:1)	493	88
PNIPAAm-*b*-PNTBA (molar ratio = 1:1)	554	115

is shown in Table III. The particle diameters at the two temperatures, 25 and 40°C, which were above and below the LCST, respectively, were measured. At the temperature below LCST, the self-assembly of the amphiphilic polymers occurred to form a micelle, and the polymers conformed into a spherical shape. Thus, the PNIPAAm-*b*-PNTBA block copolymers had a sphere-like structure and had larger diameters than the PNIPAAm-*co*-PNTBA random copolymers. The amphiphilic PNIPAAm-*b*-PNTBA formed into a micelle, which had the hydrophobic PNTBA at the center and the hydrophilic PNIPAAm facing outside in water. At 40°C, which was above the LCST, the particle diameter significantly decreased compared to the diameter at 25°C. This may have been because the hydrogen bonds between N—H/C=O groups and water broke at temperatures higher than the phase-transition temperature, and the intermolecular cohesive forces became larger than the interaction forces with water to cause the deswelling of the molecular chains and lower the particle diameter.

Cao *et al.*[9] reported amphiphilic triblock copolymers in aqueous solutions form stable nanovesicles, and the references therein also reported the use of AB, ABA, and ABC block copolymers to improve the properties of drug delivery through the introduction of a thermoresponsive block to a drug-delivery candidate. Cao *et al.*[9] used ring-opening polymerization and reversible addition–fragmentation chain-transfer polymerization techniques to synthesize the triblock copolymers, which had PDIs of 1.42–1.48, and the diblock copolymers, which had PDIs of 1.33–1.36. In this study, diblock copolymers, PNIPAAm-*b*-PNTBA, were synthesized with controlled living radical polymerization, and they had narrow PDIs within the range 1.26–1.27. PNIPAAm-*b*-PNTBA diblock copolymers formed micelles of more uniform sizes. We expected to see sharp changes in the phase transition, as shown in Figure 5(b,c), compared to a copolymer with larger PDI. In addition, our earlier study using radical polymerization[6] to synthesize poly(N-isopropylacrylamide-co-itaconamic acid) showed a PDI of about 1.8, and another study using atomic transfer radical polymerization[5] to synthesize hyperbranched copolymers hyper-*g*-(N-isopropylacrylamide-co-itaconamic acid) showed PDI values of about 1.34–1.36. This indicated that the advantage of using controlled living radical polymerization was a low PDI. Consequently, the phase behavior and sizes of the copolymer with a lower PDI were expected to be more distinct because the copolymer with a low PDI had a narrow molecular weight distribution; that is, it was more uniform in size, shape, and mass distribution.

PNIPAAm homopolymer is a thermally responsive or thermosensitive polymer and has an LCST-type phase transition, but the PNTBA homopolymer had a UCST-type phase transition. The LCST of PNIPAAm-*b*-PNTBA (molar ratio = 9:1) was higher than that of the PNIPAAm homopolymer. The LCST of PNIPAAm-*b*-PNTBA (molar ratio = 1:1), as the molar fraction of NTBA, which formed a UCST-type polymer, increased in the copolymer. PNIPAAm-*b*-PNTBA (molar ratio = 1:1) showed a less significant increase in the LCST than PNIPAAm-*b*-PNTBA (molar ratio = 9:1). For the purpose of forming a thermally responsive or thermosensitive polymer in this study, the molar fraction of NTBA was chosen to be as narrow as possible, as long as the LCST could be adjusted to the targeted range. Thus, PNIPAAm–TEMPO instead of PNTBA–TEMPO was used as a reactive polymer in the first polymerization because the molar fraction of NTBA was set to be low (the molar ratio of NIPAAm/NTBA was set to be higher than 1) and at least lower than that of NIPAAm.

CONCLUSIONS

In this study, we used controlled living radical polymerization to synthesize PNIPAAm-*b*-PNTBA block copolymers, and the study showed that PNTBA–TEMPO and PNIPAAm–TEMPO had reactivity and could be used as intermediates for the subsequent polymerization. The thermosensitive block copolymer, PNIPAAm-*b*-PNTBA (molar ratio = 9:1), with LCSTs in the range 27.7–39.8°C, was obtained through controlled living radical polymerization with PNIPAAm–TEMPO. Specifically, the 5 wt % aqueous solution of PNIPAAm-*b*-PNTBA (molar ratio = 9:1) had an LCST at 37.4°C; this was close to body temperature (37°C). In addition, PNIPAAm-*b*-PNTBA in a dilute solution showed an amphiphilic nature and, thus, had a high solubility and high LCST at low concentrations in water. The block copolymer, PNIPAAm-*b*-PNTBA (molar ratio = 9:1), with a smaller molar fraction of NTBA had more significant impact on the LCST, as shown in Figure 5(d). Because thermosensitive amphiphilic block copolymers are useful in drug delivery,[9,10] the properties of PNIPAAm-*b*-PNTBA in this study show potential uses in biomedical applications. In addition, it is advantageous to have a block copolymer having a low PDI through controlled living radical polymerization, as obtained in this study. For example, the size of the micelles (particle size) is more uniform, and the phase-transition change is sharper.

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