Macromolecules **2006,** *39,* 3476−3479

Temperature-Induced Self-Association of Doubly Thermosensitive Diblock Copolymers with Pendant Methoxytris(oxyethylene) Groups in Dilute Aqueous Solutions

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Received March 15, 2006
Revised Manuscript Received April 9, 2006

Thermosensitive water-soluble polymers undergo phase transition in water from a soluble to an insoluble state when the temperature is above a critical point (lower critical solution temperature, LCST) or below a certain temperature (upper critical solution temperature, UCST).[1,2] These polymers, especially those exhibiting the LCST behavior,[1−3] have been intensively studied from both scientific and technological points of view. A variety of applications have been reported ranging from drug delivery,[4] to smart surfaces,[5] to microfluidic (microchemical) systems,[6] to catalysis,[7] and environmentally responsive Pickering emulsions.[8,9] Block copolymers consisting of two or more different thermosensitive blocks exhibit intriguing temperature-induced self-assembly behavior in water.[10−18] However, there were only a few reports in the literature.[10−18] Most notably, normal and reverse micellar aggregates were observed in aqueous solutions of diblock copolymers composed of one LCST and one UCST block at different temperatures.[10−13] Multistage transitions, from clear liquid, to transparent gel, to hot clear liquid, and opaque mixture, were found in concentrated aqueous solutions of block copolymers of oligo(ethylene glycol) vinyl ethers in which each block exhibited a LCST transition in water.[14−16] In addition to block copolymers, doubly thermoresponsive core−shell microgels[19,20] and unimolecular micelles[21] were reported and two-stage collapse processes were observed. We have recently developed a series of thermosensitive polystyrenics and polyacrylates with short pendant oligo(ethylene glycol) groups by nitroxide-mediated radical polymerization (NMRP) using 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (TPPA),[22,23] a α-hydrido alkoxyamine, as initiator.[24,25] The high level of alkoxyamine chain end retention allowed the synthesis of diblock copolymers composed of two LCST blocks with relatively low polydispersities ($<$1.25). In this Communication, we report an interesting thermoinduced self-association behavior of doubly thermosensitive diblock copolymers in water; dilute aqueous solutions of poly(methoxytri(ethylene glycol) acrylate)-*b*-poly(4-vinylbenzyl methoxytris(oxyethylene) ether) (PTEGMA-*b*-PTEGSt) underwent multiple transitions, from transparent, to cloudy, to clear bluish, and turbid, with the increase of temperature. The association/disassociation processes were reversible upon cooling.

Diblock copolymers of TEGMA and TEGSt were prepared by chain extension of alkoxyamine-terminated PTEGMA with TEGSt.[26a] Alkoxyamine-terminated PTEGMAs were synthesized by NMRP using TPPA as initiator with addition of free nitroxide 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TPA-NO). As reported before,[24,25] kinetics and gel permeation chromatography (GPC) analysis showed that the homopolymerizations of TEGSt and TEGMA with TPPA and TPANO as initiator system were "living" processes, yielding polymers with controlled molecular weights and relatively low polydispersities (for PTEGSt, polydispersity index (PDI) $\leq$ 1.10; PTEGMA, PDI $<$ 1.20). In the present work, four diblock copolymers with different molecular weights were prepared, and the characterization data are summarized in Table 1. All four samples have relatively narrow molecular weight distributions (PDI: ∼1.20).

These diblock copolymers dissolved in cold water forming transparent solutions and underwent phase transitions at elevated temperatures. Figure 1 shows the optical transmittance of a 1 wt % aqueous solution of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ recorded at the wavelength of 490 nm as a function of temperature for both heating and cooling processes. The solution was clear at low temperature and suddenly turned cloudy at 24 °C (T_1) upon heating. With further increasing the temperature, the solution became clear and bluish, a color suggesting the formation of micellar aggregates. The clearing point T_2 for this diblock copolymer was ∼32 °C, and the solution remained bluish until it became turbid at ∼51 °C (T_3). If the cloudy mixture was kept at the first cloud point T_1 for a long time ($>$24 h), the polymer precipitated. Raising the temperature to above 32 °C but below 50 °C dissolved the polymer yielding a bluish solution. The clear and bluish solution was very stable (no change was observed at 42 °C for $>$10 days). This thermoinduced process was reversible (little hysteresis was observed between heating and cooling, Figure 1A), and for a particular solution, temperature was found to be the only factor determining the state of the solution. For comparison, aqueous solutions of a homopolymer of TEGSt, a homopolymer of TEGMA, and a mixture of the two homopolymers were made, and the transmittances were measured with respect to temperature (Figure 1). The cloud points of PTEGSt and PTEGMA were ∼13 and ∼58 °C, respectively.[24,25] The solution of the mixture of the two homopolymers turned cloudy at a temperature essentially the same as that of pure PTEGSt and remained cloudy thereafter. It should be emphasized that the self-association behavior of our copolymer is different from those reported for the diblock copolymers of oligo(ethylene glycol) vinyl ethers, where the solutions did not turn cloudy in the first transition (irrespective of whether they were concentrated or dilute).[14] Very recently, Mertoglu et al. reported the synthesis of poly(*N*-acryloylpyrrolidine)-*b*-poly(*N*-isopropylacrylamide) among many amphiphilic block copolymers by reversible addition fragmentation chain transfer process.[18] This diblock copolymer exhibited a two-step aggregation process in water upon heating. However, only one disassociation step was detected by turbidimetry in the cooling process; i.e., the thermoinduced process was not reversible.[18]

The other three samples exhibited similar multiple transitions in water at a concentration of 1 wt %.[26b] The first cloud point T_1, clearing point T_2, and second cloud point T_3 for each copolymer are summarized in Table 1. With the increase of PTEGSt block length, T_1 decreased from 32, to 24, to 23, and 15 °C, and T_3 shifted from 55, to 51, to 49, and 44 °C. For all four samples, T_1 is higher than the LCST of PTEGSt (∼13 °C) and T_3 is lower than that of PTEGMA (∼58 °C). Because of the covalent bond between the two blocks, the cloud point of PTEGSt was raised by the more hydrophilic PTEGMA, and the LCST of PTEGMA block was lowered. The first clouding

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10.1021/ma060586v CCC: $33.50

Table 1. Characterization Data for Four Diblock Copolymers of Methoxytri(ethylene glycol) Acrylate (TEGMA) and 4-Vinylbenzyl Methoxytris(oxyethylene) Ether (TEGSt) Synthesized by Nitroxide-Mediated Radical Polymerization

diblock copolymer[a]	$M_{n,GPC}$[b]	PDI[c]	T_1[d]	T_2[e]	T_3[f]
PTEGMA$_{66}$-*b*-PTEGSt$_{45}$	16 300	1.20	32	39	55
PTEGMA$_{66}$-*b*-PTEGSt$_{72}$	26 800	1.21	24	32	51
PTEGMA$_{66}$-*b*-PTEGSt$_{87}$	32 200	1.22	23	34	49
PTEGMA$_{62}$-*b*-PTEGSt$_{98}$	34 400	1.16	15	25	44

[a] The subscript represents the degree of polymerization (DP) of the corresponding block. The DPs of macroinitiator PTEGMA were calculated from the monomer conversions determined by ^{1}H NMR spectroscopy and the monomer-to-initiator ratios. The DPs of PTEGSt were determined from ^{1}H NMR spectra of copolymers in CDCl$_3$ using the peaks located at 4.45 ppm, from $-CH_2-$ of the benzyl group of PTEGSt, and 4.17 ppm, from $-CH_2OOC-$ of PTEGMA. [b] Number-average molecular weights ($M_{n,GPC}$) were obtained from gel permeation chromatography (GPC) analysis relative to polystyrene standards. [c] PDI = polydispersity index. [d] T_1: the first cloud point of copolymer in water (1 wt %) during heating. [e] T_2: the clearing point in the beginning of the micelle formation zone during heating. [f] T_3: the second cloud point, defined as the temperature at which the optical transmittance was in the midpoint of the highest and lowest transmittances when the solution turned from clear bluish to turbid upon heating.

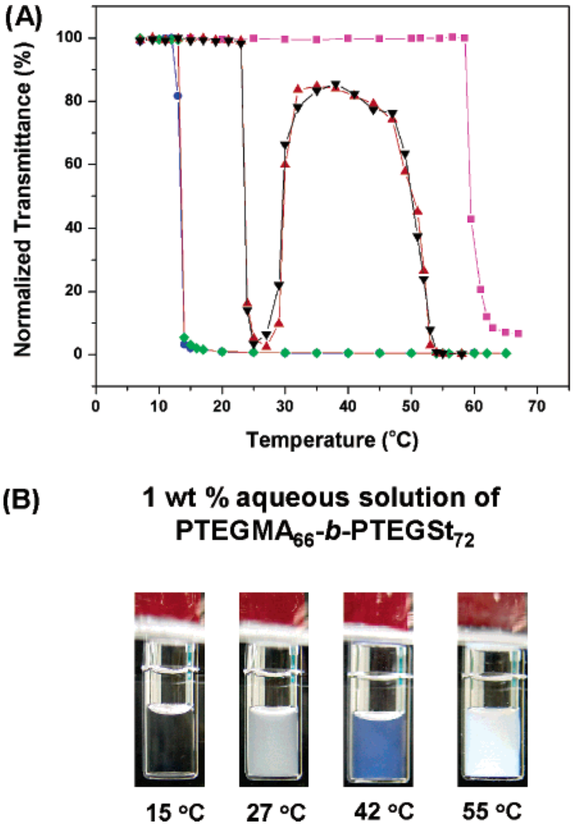

Figure 1. (A) Optical transmittances of aqueous solutions of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ ($M_{n,GPC}$ = 26 800 g/mol, PDI = 1.21, 1 wt %) upon heating (▲) and cooling (▼), PTEGSt (●, $M_{n,GPC}$ = 10 400 g/mol, PDI = 1.10, DP = 44, 0.5 wt %), PTEGMA (■, $M_{n,GPC}$ = 9500 g/mol, DP = 66, PDI = 1.19, 0.5 wt %), and a mixture (◆) of PTEGSt (M_n = 10 400 g/mol, DP = 44, PDI = 1.10, 0.5 wt %) and PTEGMA ($M_{n,GPC}$ = 9500 g/mol, DP = 66, PDI = 1.19, 0.5 wt %) at various temperatures. At each temperature, the solutions were equilibrated for 10 min. (B) Digital photographs of a 1 wt % aqueous solution of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ at 15, 27, 42, and 55 °C.

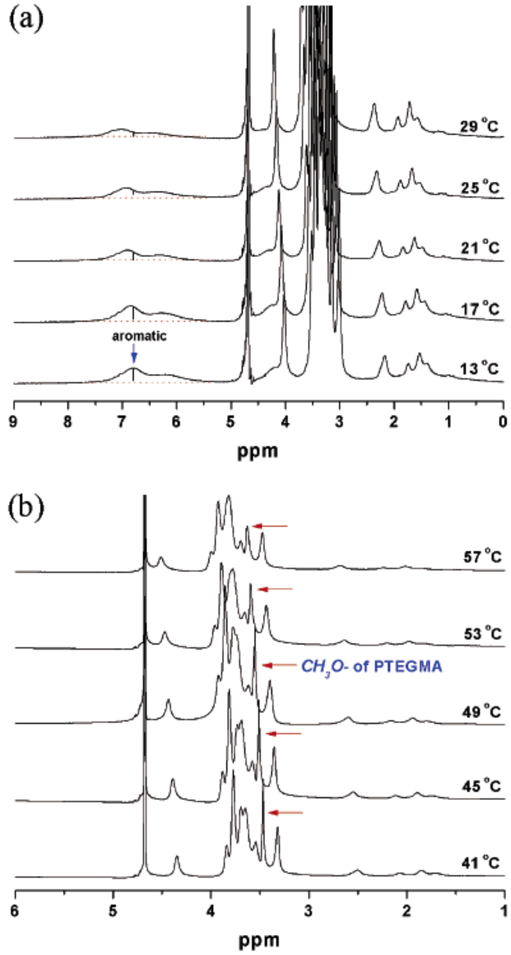

Figure 2. ^{1}H NMR spectra of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ ($M_{n,GPC}$ = 26 800 g/mol, polydispersity index = 1.21) in D$_2$O (1 wt %) at temperatures (a) from 13 to 29 °C and (b) from 41 to 57 °C.

is presumably due to the phase separation that resulted from the dehydration of PTEGSt block, followed closely by micellization (clearing point T_2), as suggested by Booth et al. for a similar clouding−micellization transition.[27] They observed that a 1 wt % aqueous solution of a poly(ethylene oxide)-*b*-poly(butylene oxide)-*b*-poly(ethylene oxide) prepared at low temperature (ca. 10 °C) clouded at 23 °C and cleared at 34 °C, remaining clear up to the limit of test (95 °C).[27] The transition from bluish to turbid in Figure 1 was attributed to the collapse of PTEGMA.

The dehydration of the two blocks of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ at different temperatures was supported by variable temperature ^{1}H NMR spectroscopy study (Figure 2). At each temperature, the solution was equilibrated for 20 min before data acquisition. The height and position of water peak were used as references. It is clear from Figure 2a that with the temperature increasing from 17 to 29 °C the aromatic peaks of PTEGSt at 6.0−7.5 ppm decreased appreciably, implying that the PTEGSt block underwent transition in this temperature range. On the other hand, when the temperature was raised from 45 to 53 °C, the pendant methoxy peak of PTEGMA decreased in intensity and broadened noticeably (Figure 2b), corresponding to T_3.

The phase transitions of these diblock copolymers were further studied by dynamic light scattering (DLS). The hydrodynamic diameters (D_h) of diblock copolymers at various temperatures were calculated from time-correlation functions by the CONTIN method, and the polydispersity indices of the aggregates were estimated by use of μ_2/Γ^2 from cumulants analysis. Figure 3 shows the DLS results for PTEGMA$_{66}$-*b*-PTEGSt$_{72}$. Below 23 °C, the values of D_h were <8 nm, suggesting that the polymer molecules were dissolved molecularly. When the temperature was raised to 24 °C, the D_h increased dramatically to >200 nm and the size distribution was broad, indicating that the polymer solution underwent phase

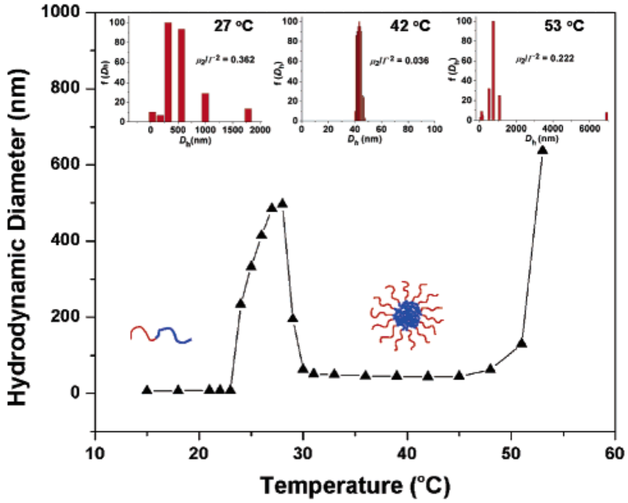

Figure 3. Temperature dependence of hydrodynamic diameter for a 1 wt % aqueous solution of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ ($M_{n,GPC}$ = 26 800 g/mol, PDI = 1.21). Hydrodynamic diameters were calculated by use of the CONTIN analysis method at scattering angle of 90°. At each temperature, the solution was equilibrated for 20 min before data recording. The insets are hydrodynamic size distributions at 27, 42, and 53 °C.

separation forming large and irregular aggregates. In the range 32−45 °C, the solution was bluish and only one size distribution was observed. For instance, at 42 °C, the D_h was 42.9 nm and the polydispersity index (μ_2/Γ^2) was as low as 0.036. Clearly, micellization occurred with dehydrated PTEGSt associating into the core and PTEGMA blocks remaining solvated in the corona. The values of D_h of the micelles obtained at scattering angles of 60° and 135° were 40.7 nm (μ_2/Γ^2: 0.044) and 40.2 nm (μ_2/Γ^2: 0.070), respectively (Figure S9), close to the D_h at scattering angle of 90°, suggesting that the micelles were nearly spherical.[28−30] Moreover, the micellization was found to be nearly independent of heating/cooling pathways (Figure 4). When the solution was quickly heated from 8 to 42 °C or the turbid mixture was quenched from 65 to 42 °C, and subsequently equilibrated for 20 min, the values of D_h were 43.2 nm (μ_2/Γ^2: 0.036) and 41.2 nm (μ_2/Γ^2: 0.062), respectively. Above 51 °C, large and polydisperse aggregates were observed, which resulted from the dehydration of PTEGMA.

For the three samples synthesized from the same macroinitiator PTEGMA$_{66}$, the smallest D_h of the micelles increased from 27, to 43, and 58 nm with the increase of PTEGSt block length. For PTEGMA$_{62}$-*b*-PTEGSt$_{98}$ in a 1 wt % aqueous solution, micellization occurred at room temperature with the D_h of 51.5 nm at 27 °C. Further study on the micelle formation and micelle structures by cryo-TEM is underway.

In summary, we observed that PTEGMA-*b*-PTEGSt exhibited multiple transitions in 1 wt % aqueous solutions, from transparent, to cloudy, to clear and bluish, and turbid, with the increase of temperature. This thermoinduced process was reversible. DLS results indicated the formation of monodisperse, nearly spherical micelles in the intermediate temperature range with dehydrated PTEGSt blocks associating into the core and PTEGMA blocks forming the corona.

Acknowledgment. The authors are grateful to the University of Tennessee and the National Science Foundation (DMR-0605663) for supporting this research.

Supporting Information Available: Experimental section; GPC and ^{1}H NMR spectroscopy analysis of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$; turbidimetry and DLS data. This material is available free of charge via the Internet at http://pubs.acs.org.

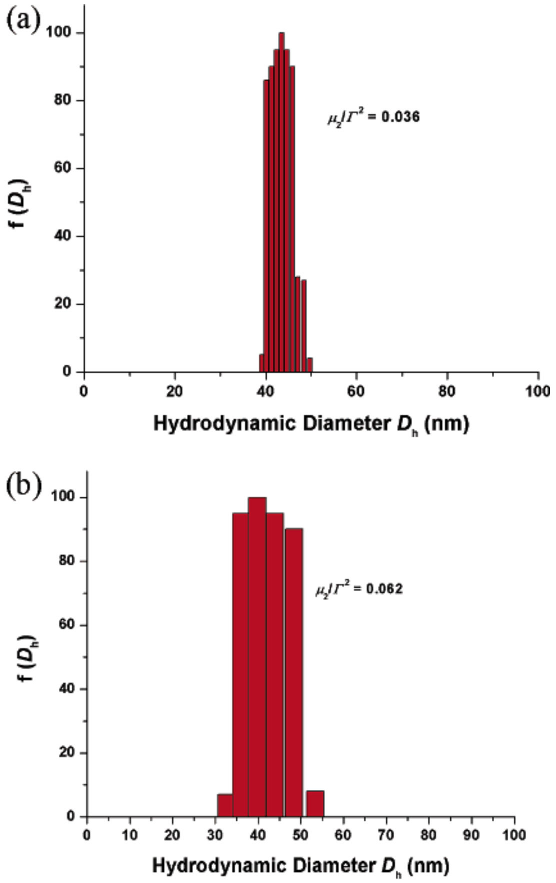

Figure 4. Hydrodynamic diameter distribution functions of aggregates formed from a 1 wt % aqueous solution of PTEGMA$_{66}$-*b*-PTEGSt$_{72}$ ($M_{n,GPC}$ = 26 800 g/mol, polydispersity index = 1.21) at 42 °C. (a) The solution was quickly heated from 8 to 42 °C (the solution in a tube was equilibrated at 8 °C and then loaded into the sample cell holder with a preset temperature of 42 °C). (b) The turbid mixture was quenched from 65 to 42 °C (the turbid mixture formed at 65 °C was loaded into the sample cell holder with a preset temperature of 42 °C). The solution was equilibrated for 20 min prior to data recording. Hydrodynamic diameters were calculated by use of the CONTIN analysis method at scattering angle of 90°.

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(26) (a) A typical example for the synthesis and characterization of diblock copolymers can be found in the Supporting Information. (b) Optical transmittances and DLS data at various temperatures can be found in the Supporting Information.

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MA060586V