Tuning Micellization and Dissociation Transitions of Thermo- and pH-Sensitive Poly(ethylene oxide)-*b*-poly(methoxydi(ethylene glycol) methacrylate-*co*-methacrylic acid) in Aqueous Solution by Combining Temperature and pH Triggers

Xueguang Jiang and Bin Zhao*

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996

Received August 8, 2008; Revised Manuscript Received October 5, 2008

ABSTRACT: We report in this article on the active control of multiple micellization and dissociation transitions of thermo- and pH-sensitive water-soluble block copolymers, poly(ethylene oxide)-*b*-poly(methoxydi(ethylene glycol) methacrylate-*co*-methacrylic acid) (PEO-*b*-P(DEGMMA-*co*-MAA)), in aqueous solutions by combining temperature and pH triggers. Two block copolymers and one random copolymer P(DEGMMA-*co*-MAA) were prepared by atom transfer radical polymerization of a mixture of methoxydi(ethylene glycol) methacrylate (DEGMMA) and *tert*-butyl methacrylate (*t*-BMA) with a molar ratio of 100: 13 from a PEO macroinitiator and a small molecule initiator, respectively, and subsequent removal of *t*-butyl group. PDEGMMA is a thermosensitive water-soluble polymer exhibiting a lower critical solution temperature in water at 25 °C. The cloud point of P(DEGMMA-*co*-MAA) in water can be readily tuned from 24 to 60 °C by changing the solution pH. The block copolymers dissolved molecularly in cold aqueous buffer solutions with a pH of 4.0 and underwent micellization when the temperature was raised to a critical point. Upon judiciously changing the solution pH by injection of a predetermined amount of a KOH solution, the block copolymer micelles were dissociated into the unimers, which subsequently reformed micelles at the same temperature in response to the addition of a predetermined amount of a HCl solution or heating to a higher temperature. These temperature- and pH-induced micellization/dissociation transitions were reversible. By continuously increasing temperature from 20 to 57 °C and simultaneously controlling the pH, three cycles of micellization and disassembly transitions of these block copolymers in aqueous solutions were realized, demonstrating the possibility of achieving on-demand micellization and dissociation transitions by combining temperature and pH triggers. Fluorescence spectroscopy studies showed that a hydrophobic fluorescence dye, Nile Red, can be repeatedly encapsulated by block copolymer molecules upon micellization and released upon dissociation of micelles under different combinations of pH and temperature.

Introduction

Block copolymer micelles that can dissociate into the molecularly dissolved unimers upon application of an external stimulus are of great interest for controlled encapsulation and triggered release of substances in many technological applications including targeted drug delivery and cosmetics.[1−45] A common principle for destabilizing micellar assemblies involves the modification of the polarity or hydrophobicity/hydrophilicity balance of the core-forming component by the use of an external trigger.[1] When the core-forming block becomes soluble in the medium, the driving force for the micellization is eliminated and the micellar assemblies are dissociated into the unimers. The dissociation process can be reversible or irreversible depending on the response mechanism. In many applications, reversible dissociation/micellization transitions induced by external stimuli can be advantageous or are desired because the reformation of micelles allows the re-encapsulation of the released substance.[38,39]

Various chemical and physical stimuli including pH,[1−23] temperature,[1−3,24−35] light,[36−41] specific molecules,[1,41−43] redox,[1,44,45] or their combinations[7,8,21,22,40] have been employed to induce the formation and dissociation of block copolymer micelles or vesicles. Among them, pH and temperature are the most commonly used external triggers.[1−3] In general, there are two types of pH-sensitive block copolymer micelles: (i) those in which the core-forming blocks contain weak acid or base moieties (e.g., carboxylic acid, tertiary amine, etc.),[4−15] and (ii) those in which the core-forming blocks contain hydrolyzable pendant groups.[16−23] In the first type, deprotonation or protonation of weak acid or base groups modifies the polarity of the core-forming block upon pH changes, triggering the formation/dissociation of micellar assemblies. For example, Armes et al. reported a series of schizophrenic diblock copolymers that formed conventional and inverted micelles by varying the solution pH.[4−7] In the second type of pH-sensitive micelles, pH change-induced hydrolysis of pendant groups converts the core-forming hydrophobic block into hydrophilic. For example, Frétchet et al. developed block copolymers with one block functionalized with acid-labile cyclic benzylidene acetal groups.[16−18] The micelles were stable at physiological pH, but once the pH was lowered to 5, hydrolysis of acetal bonds occurred and the micelles disassembled. Lee et al. recently reported a diblock copolymer containing citraconic amide side groups, which were stable at pH ≥ 7 but became unstable at acidic pH.[21] They observed that the micelles underwent fast dissociation at pH = 5.5.

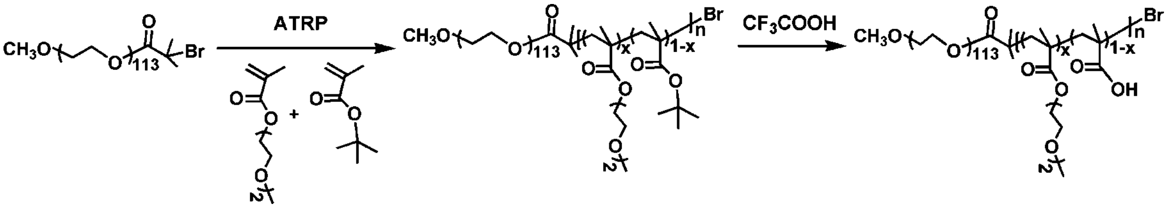
Temperature is a very attractive physical stimulus for the formation and dissociation of micelles.[1−3,24−35] Thermosensitive water-soluble polymers undergo a transition from a hydrated to a dehydrated state when the temperature is above a critical point, known as lower critical solution temperature (LCST).[1−3,46−49] Water-soluble block copolymers with one or more blocks exhibiting thermoresponsive properties in water have attracted growing interest in recent years.[24−35] These block copolymers undergo reversible micellization and dissociation in water in response to temperature changes. Note that one advantage of stimuli-responsive water-soluble block copolymers for the preparation of micelles is the elimination of the use of organic solvents. It is known that the LCST of a thermosensitive

---

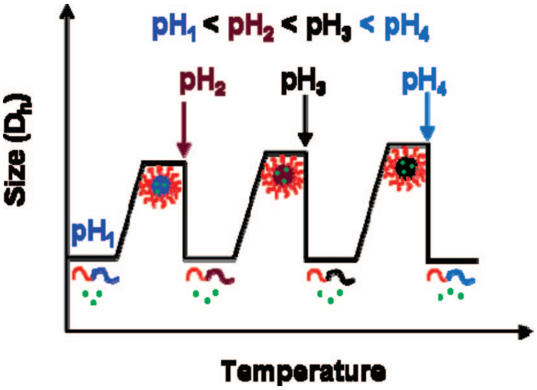
* Corresponding author. E-mail: zhao@ion.chem.utk.edu.

10.1021/ma8018238 CCC: $40.75

Scheme 1. Synthesis of Thermo- and pH-Sensitive Water-Soluble Poly(ethylene oxide)-*b*-poly(methoxydi(ethylene glycol) methacrylate-*co*-methacrylic acid) (PEO-*b*-P(DEGMMA-*co*-MAA))



Scheme 2. Multiple Micellization and Dissociation Transitions of Thermo- and pH-Sensitive Block Copolymer PEO-*b*-P(DEGMMA-*co*-MAA) by Controlling Temperature and pH



polymer can be modified by copolymerization with a second monomer,[1−3,48−57] which has been utilized to design block copolymer micelles with controlled instability.[1,50−53] Hennink et al. developed a series of block copolymers composed of poly(ethylene oxide) (PEO) and thermosensitive polymers that contained lactate side chains.[1,50−53] Hydrolysis of lactate side groups caused an increase of the LCST of the thermosensitive block. When the polymer became soluble in water, dissociation of micelles occurred and the encapsulated molecules were released. The LCST of a thermosensitive water-soluble polymer can also be tuned by changing the solution pH if the polymer contains a small amount of weak acid or base groups.[58−66] The transition temperature is higher if more charges reside on the polymer chain, which is in turn controlled by the solution pH. For example, Yin et al. recently reported that the LCST of poly(*N*-isopropylacrylamide-*co*-propylacrylic acid) copolymers can be tuned from 4.8 to 63.8 °C by varying the acid content in the copolymer and the solution pH.[58] The pH dependence of the LCST has been exploited by Lokitz et al. to control the critical micellization temperature (CMT) of a thermosensitive block copolymer in aqueous solution.[66]

We have been interested in developing multiresponsive water-soluble block copolymers that can undergo multiple micellization and dissociation transitions by combining two external stimuli. In a previous publication,[40] we reported a thermo- and light-sensitive block copolymer, which dissolved molecularly in cold water but formed micelles when the temperature was above the CMT. Upon UV irradiation, the micelles were dissociated into the unimers, which on further increasing temperature formed micelles again. Although the thermo-induced micellization/dissociation transitions were reversible, the UV-triggered disassembly of micelles of this block copolymer was irreversible.[40] For many applications, it is more desired if stimuli-induced dissociation transitions are reversible. In the present work, two stimuli, pH and temperature, are employed to achieve multiple reversible micellization and dissociation transitions of thermo- and pH-sensitive poly(ethylene oxide)-*b*-poly(methoxydi(ethylene glycol) methacrylate-*co*-methacrylic acid) (PEO-*b*-P(DEGMMA-*co*-MAA), Scheme 1). PDEGMMA is a thermosensitive water-soluble polymer with a LCST reportedly at 25 °C in water.[67,68] We show that by continuously increasing temperature and simultaneously controlling the pH, three complete cycles of micellization and dissociation transitions of PEO-*b*-P(DEGMMA-*co*-MAA) were realized (Scheme 2), demonstrating the possibility of achieving on-demand reversible micellization/dissociation transitions by combining two external triggers.

Results and Discussion

Synthesis and Hydrolysis of Random Copolymer P(DEGMMA-*co*-*t*BMA) and Block Copolymer PEO-*b*-P(DEGMMA-*co*-*t*BMA). Poly(methoxydi(ethylene glycol) methacrylate) (PDEGMMA) belongs to a new family of thermosensitive water-soluble polymers in which short oligo(ethylene glycol) groups are covalently bonded to the polymer backbone as a pendant group from each repeating unit.[24−30,40,56,57,67−80] The cloud point can be readily tuned by varying the type of polymer backbone, the length and end group of oligo(ethylene glycol) pendant, or the chain end group, or by copolymerizing with a second monomer. One advantage of these thermosensitive water-soluble polymers is that the short oligo(ethylene glycol) pendant groups render the polymers a property of biocompatibility.[81] In this work, thermo- and pH-sensitive water-soluble block copolymers, PEO-*b*-P(DEGMMA-*co*-MAA), with controlled molecular weights and narrow polydispersities were prepared and used to pursue multiple reversible micellization and dissociation transitions by controlling both temperature and pH. We chose PDEGMMA because its reported cloud point in water is 25 °C, which is located in a convenient temperature range.

The macroinitiator, PEO with a molecular weight of 5000 Da and one end functionalized with an ATRP initiator (PEO-Br), was prepared by following a procedure in the literature.[40] Block copolymers PEO-*b*-P(DEGMMA-*co*-*tert*-butyl methacrylate) (PEO-*b*-P(DEGMMA-*co*-*t*BMA, **BR3** and **BR4** in Table 1) were synthesized from macroinitiator PEO-Br by ATRP of a mixture of DEGMMA and *t*BMA with a molar ratio of 100:13 at 60 °C in anisole using CuBr/*N,N,N′,N′,N″*-pentamethyldiethylenetriamine as catalyst. The polymers were purified by repeated precipitation in a mixture of hexanes and diethyl ether (v/v, 80: 20). Gel permeation chromatography (GPC) analysis showed that the peaks of block copolymers shifted to the high molecular weight side compared with that of the macroinitiator PEO-Br and were narrow.[82] For the study of pH effect on cloud point, one homopolymer PDEGMMA (**H1**) and one random copolymer P(DEGMMA-*co*-*t*BMA) (**R2**) were prepared by the use of ethyl 2-bromoisobutyrate as initiator. The degrees of polymerization (DPs) of **H1** and **R2** were calculated from the monomer conversion and the monomer-to-initiator ratio, assuming that the initiator efficiency was 100%. The numbers of DEGMMA and *t*BMA units in the two samples of PEO-*b*-P(DEGMMA-*co*-*t*BMA) (**BR3** and **BR4**) were determined from ^{1}H NMR spectra. The molar ratios of DEGMMA to *t*BMA units in the two block copolymers were essentially identical (∼ 100:18), and were also close to that in the random copolymer **R2**

Table 1. Characterization Data for PDEGMMA, P(DEGMMA-*co*-*t*BMA) and the Corresponding P(DEGMMA-*co*-MAA), Two Samples of PEO-*b*-P(DEGMMA-*co*-*t*BMA) and the Corresponding PEO-*b*-P(DEGMMA-*co*-MAA) Used in this Work

no.	polymers	$M_{n,GPC}$ (Da)[a]	PDI[a]	n_{EO}:n_{DEGMMA}:n_{tBMA}[b]
H1	PDEGMMA	16200	1.11	0:85:0[c]
R2	P(DEGMMA-*co*-*t*BMA)	15000	1.14	0:71:11[c,d]
R2-H	P(DEGMMA-*co*-MAA)	NA	NA	0:71:11
BR3	PEO-*b*-P(DEGMMA-*co*-*t*BMA)	21800	1.06	113:100:18
BR3-H	PEO-*b*-P(DEGMMA-*co*-MAA)	NA	NA	113:100:18
BR4	PEO-*b*-P(DEGMMA-*co*-*t*BMA)	30200	1.07	113:144:25
BR4-H	PEO-*b*-P(DEGMMA-*co*-MAA)	NA	NA	113:144:25

[a] The number average molecular weight ($M_{n,GPC}$) and polydispersity index (PDI) were determined by gel permeation chromatography using polystyrene calibration. [b] n_{EO}, n_{DEGMMA}, and n_{tBMA} (or n_{MAA}) are the numbers of EO (in the PEO block), DEGMMA, and *t*BMA units (or the corresponding MAA units) in the polymers, respectively. The values of n_{DEGMMA} and n_{tBMA} in the block copolymers were determined from ^{1}H NMR spectra. [c] The degrees of polymerization of PDEGMMA and P(DEGMMA-*co*-*t*BMA) were calculated from the monomer conversion and the monomer-to-initiator ratio assuming that the initiator efficiencies were 100% in the polymerizations. [d] The molar ratio of DEGMMA and *t*BMA in the random copolymer was determined from ^{1}H NMR spectrum.

(~100:16). The molecular characteristics of the polymers used in this work are summarized in Table 1. The polydispersities of all these polymers, determined from GPC using PS standards, were <1.15.

The *tert*-butyl groups of P(DEGMMA-*co*-*t*BMA) and PEO-*b*-P(DEGMMA-*co*-*t*BMA) were removed by the use of CF_3COOH, which has been shown to selectively cleave the *tert*-butyl ester group without affecting other types of esters.[73] ^{1}H NMR spectroscopy analysis of **BR3** and **BR4** before and after treatment with CF_3COOH revealed that the peak located at 1.40 ppm, which is characteristic for the *tert*-butyl group, disappeared, indicating that the hydrolysis was essentially complete. To confirm that the ester group of PDEGMMA was not affected by CF_3COOH, we carried out a control experiment by treating PDEGMMA (**H1**) with CF_3COOH under the same condition. No changes were observed from ^{1}H NMR spectra and GPC analysis.[82]

Thermosensitive Properties of P(DEGMMA-*co*-MAA) and PDEGMMA. Our hypothesis of achieving multiple reversible micellization and dissociation transitions as shown in Scheme 2 is based on that the LCST transition temperature of the thermosensitive block that contains a small amount of carboxylic acid groups can be tuned in a large temperature range by changing the solution pH. Thus, we first studied the thermoresponsive properties of P(DEGMMA-*co*-MAA) (**R2-H**) in 10 mM aqueous potassium hydrogen phthalate (KHP) buffer solutions with pH ranging from 4.0−7.0. The pH was adjusted by addition of an aqueous KOH solution and was measured by a pH meter. We used KHP buffers instead of pure water to make polymer solutions because the pH can be readily tuned and precisely controlled.

Figure 1a shows the optical transmittances of 0.2 wt % aqueous buffer solutions of **R2-H** with pH values of 4.0, 5.5, 6.0, and 6.5 at wavelength of 550 nm as a function of temperature. At pH values of 4.0, 5.5, and 6.0, the thermo-induced phase transitions were sharp and there were essentially no hystereses between heating and cooling processes. Apparently, the cloud point (CP) increases with the increase of pH (Figure 1b, the CP is defined as the temperature at which the optical transmittance drops by 50%). A higher pH results in a higher degree of ionization of carboxylic acid groups, which shifts the hydrophobic/hydrophilic balance of the thermosensitive block, making the transition occur at a higher temperature. The LCST transition of **R2-H** in the buffer with pH = 6.5 is noticeably broader than in other three buffers, indicating that the transition at this pH is weaker, which is likely because more charges residing on the polymer chains at a higher pH result in less structured or “frozen” water being released from hydrated polymer chains during the transition as discussed by Urry.[83] At pH = 7.0, no LCST transition was observed up to 70 °C. From Figure 1, we can conclude that the CP of **R2-H** can be tuned in a temperature range from 24 to 60 °C, providing great flexibility in controlling the micellization and dissociation transitions of the corresponding block copolymers in water. In contrast, the pH has little effect on the CP of PDEGMMA (CP of **H1** = 27.5 °C at pH = 4.1, 27 °C at pH = 5.3, and 26.5 °C at pH = 6.1).[82]

Temperature-Induced Reversible Micellization and Dissociation Transitions of PEO-*b*-P(DEGMMA-*co*-MAA) in Aqueous Buffer Solutions. Two samples of PEO-*b*-P(DEGMMA-*co*-MAA) with different molecular weights but essentially the same compositions for the thermosensitive blocks (**BR3-H** and **BR4-H**) were used for the study of thermo- and pH-induced multiple reversible micellization and dissociation transitions in aqueous KHP buffer solutions. We first studied their reversible micellization in response to temperature changes at pH = 4.0 by dynamic light scattering (DLS) and fluorescence spectroscopy (FS).

Figure 2 shows the intensity of scattered light at scattering angle of 90° and the hydrodynamic size as a function of temperature for a 0.2 wt % aqueous buffer solution of **BR3-H** with a pH of 4.0. When the temperature was ≤29 °C, the scattering intensity was very low and the apparent hydrodynamic size was <8 nm, indicating that the block copolymer was dissolved molecularly in water. With the increase of temperature, the scattering intensity gradually increased, and two size distributions, one ascribed to the unimers and one to the micelles, were observed at 30 °C with an average apparent hydrodynamic size of 26.1 nm, indicating that the thermosensitive block was undergoing a hydration-to-dehydration transition at 30 °C. The critical micellization temperature ($CMT_{4.0\text{-}I}$), determined from the plot of intensity of scattered light versus temperature in the heating process (Figure 2a), was 30 °C, which was 6 °C higher than the CP of P(DEGMMA-*co*-MAA) at the same pH. This observation is similar to that of thermo- and light-sensitive block copolymer PEO-*b*-poly(ethoxytri(ethylene glycol) acrylate-*co*-*o*-nitrobenzyl acrylate) in our previous work.[40] It is known that the LCST transition temperature is slightly higher when a thermosensitive polymer is attached to a hydrophilic block.[1−3] When the temperature reached 32 °C, only micelles with apparent hydrodynamic diameter (D_h) of 33.4 nm were observed. The micelle size eventually became stabilized around 36 nm. The polydispersity of micelles at 50 °C was 0.018, indicating that the micelles were uniform in size.[82] Moreover, we found that the value of Γ/q^2 was essentially independent of scattering angle,[82] suggesting that the micelles were of a spherical shape. The thermo-induced micellization was reversible; decreasing the temperature caused the micelles to dissociate into the unimers (Figure 2).

The thermo-induced reversible micellization of **BR4-H** in a 10 mM KHP buffer with a pH of 4.0 was also studied by DLS[82] and the results are summarized in Table 2 along with those from **BR3-H**. The $CMT_{4.0\text{-}I}$ of **BR4-H** at the same concentration (0.2 wt %) and same pH (4.0) was 26 °C, which was 4 °C lower than that of **BR3-H** but 2 °C higher than the CP of **R2-H**. This is understandable because the molecular weight of the thermosensitive block in **BR4-H** is higher than that in **BR3-H** and a higher molecular weight thermosensitive polymer tends to undergo a LCST transition at a lower temperature.[72] The hydrodynamic diameter of micelles of **BR4-H** at 50 °C was

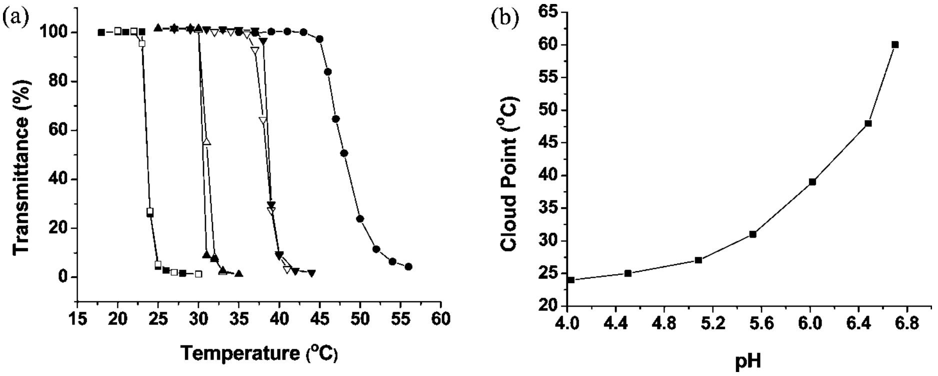


Figure 1. (a) Optical transmittances at wavelength of 550 nm of 0.2 wt % aqueous solutions of P(DEGMMA-*co*-MAA) (**R2-H**) in 10 mM potassium hydrogen phthalate buffers with pH values of 4.0 (■ heating; □ cooling), 5.5 (▲ heating; △ cooling), 6.0 (▼ heating; ▽ cooling), and 6.5 (● heating) as a function of temperature. The transmittances were recorded with a UV−visible spectrometer. (b) Dependence of the cloud point of **R2-H** on the solution pH.

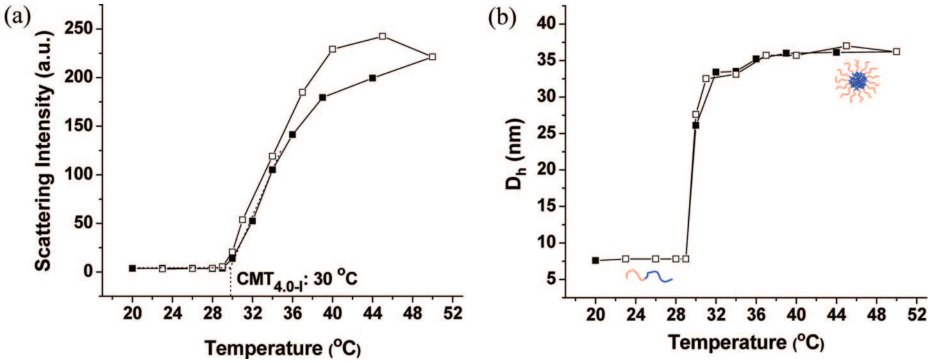


Figure 2. Intensity of scattered light at scattering angle of 90° (a) and the hydrodynamic diameter (b) as a function of temperature (■ heating; □ cooling) in a DLS study of a 0.2 wt % aqueous buffer solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) at pH = 4.0. In part b, at 30 °C in both heating and cooling processes, two size distributions, one ascribed to the unimers and one to the micelles, were observed and the reported hydrodynamic diameters for this temperature were the average values over two hydrodynamic size distributions.

Table 2. Critical Micellization Temperatures of Block Copolymer PEO-*b*-P(DEGMMA-*co*-MAA) (BR3-H and BR4-H) and the Hydrodynamic Sizes and Polydispersities of Their Micelles under Various Conditions

buffer pH	description	BR3-H	BR4-H
pH = 4.0	CMT$_{4.0\text{-I}}$	30 °C, [a] 30 °C [b]	26 °C,[a] 26 °C[b]
	size[c] and PD[d] of micelles at 50 °C	36.2 nm, 0.018	45.8 nm, 0.004
pH = 5.4 (the buffer pH after addition of KOH)	CMT$_{5.4}$	37 °C,[a] 36 °C[b]	33 °C,[a] 33 °C[b]
	size and PD of micelles at 50 °C	38.3 nm, 0.055	65.3 nm, 0.034
pH = 4.0 (the buffer pH after addition of HCl)	CMT$_{4.0\text{-II}}$	29 °C,[a] 29 °C[b]	25 °C,[a] 25 °C[b]
	size and PD of micelles at 50 °C	36.2 nm, 0.004	46.6 nm, 0.003

[a] Critical micellization temperature (CMT) determined by DLS. [b] CMT determined by FS. [c] The hydrodynamic diameter of micelles at a specific temperature was obtained by the use of the CONTIN method. [d] The polydispersity (PD) of micelles at a specific temperature obtained by the use of the CONTIN method. The concentration of block copolymers in the buffer was 0.2 wt %.

~46 nm, which was ~10 nm larger than that of **BR3-H** under the same condition (Table 2). The micelles of **BR4-H** also had narrow polydispersities, and a spherical shape (as suggested by the independence of Γ/q^2 on scattering angle).[82]

The thermo-induced reversible formation and dissociation of micelles of **BR3-H** and **BR4-H** were further studied by FS.[82] Nile Red was used as the fluorescence probe because its fluorescence is known to increase substantially in a hydrophobic environment such as the core of micelles.[16,17,37,40] The fluorescence emission spectra of Nile Red in a 0.2 wt % aqueous buffer solution of **BR3-H** with a pH of 4.0 at various temperatures upon heating were recorded (Figure S9 in the Supporting Information).[82] The noticeable fluorescence intensity at temperatures <30 °C might be due to the enhanced solubilization of Nile Red by the polymer in water.[37,40] When the temperature was raised above 30 °C, the fluorescence emission intensity increased significantly, indicating that the molecularly dissolved polymer chains began to associate into micelles and the dye molecules were sequestered into the core. The maximum peak underwent a blueshift with the increase of temperature, from 623.5 nm at 20 °C to 615.5 nm at 50 °C, which further supported that the dye molecules moved from a hydrophilic to a hydrophobic environment and thus the micelles formed in the solution.[16,17,37,40] The CMT$_{4.0\text{-I}}$, determined from the plot of maximum fluorescence intensity versus temperature, was 30 °C, same as that obtained from DLS study. When the temperature was decreased to 22 °C, the fluorescence emission intensity decreased and the λ_{max} underwent a redshift from 615.5 nm at 50 °C to 623 nm at 22 °C,[82] indicating that the micelles were dissociated into the unimers and the dye molecules were released into water. Thus, consistent with DLS study, the thermo-induced micellization was reversible. Similarly, we studied the thermo-induced reversible micellization of **BR4-H** under the same conditions by FS and determined the CMT$_{4.0\text{-I}}$,[82] which was found at 26 °C, consistent with the result obtained from DLS study (Table 2).

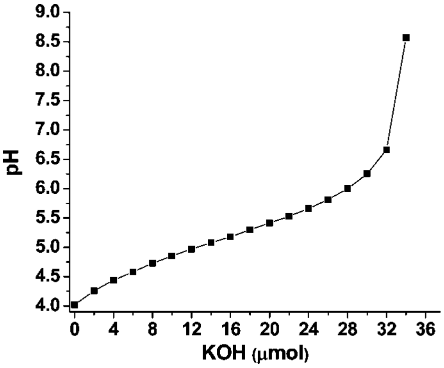


Figure 3. Plot of solution pH versus number of μmols of KOH injected into a 0.2 wt % solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) in 10 mM KHP buffer (2.50 g). The KOH solution was added stepwise; each time, 10 μL of a 0.20 M aqueous KOH solution was injected via a microsyringe, followed by the measurement of pH with a pH meter.

KOH-Triggered Dissociation of Micelles and Subsequent Temperature-Induced Formation and Disassembly of Micelles. As shown in the preceding section, when the temperature was above CMT$_{4.0\text{-I}}$, the thermosensitive block of **BR3-H** or **BR4-H** underwent a hydration-to-dehydration transition and the block copolymer molecules self-assembled into the micelles. If a condition is chosen under which the LCST of the thermosensitive block becomes higher than the solution temperature, dissociation of micelles will occur. Since we were especially interested in disassembling micelles in situ by changing the solution pH and it was not practical and convenient to measure the pH of a solution in a DLS tube or a fluorescence quartz cuvette, we investigated how the solution pH varied with the addition of KOH and used it as a guide for determining how much KOH needs to be added to achieve a particular pH. We conducted titration of a 0.2 wt % aqueous solution of **BR3-H** in 10 mM KHP buffer (2.50 g) by injecting 10 μL of a 0.20 M KOH solution each time and subsequently measuring the pH with a pH meter. A plot of solution pH versus number of μmols of added KOH was obtained, and is shown in Figure 3. Note that after the completion of titration, the volume increased by only 6.8%, which had a negligible effect on the concentrations of KHP and the polymer. We also conducted the titration of a 0.2 wt % aqueous solution of **BR4-H** in 10 mM KHP buffer; the titration curve is identical to the one shown in Figure 3.[82] Figures 1b and 3 were used as a guide for effecting dissociation of micelles in situ in the DLS and FS experiments.

In Figure 2b, at 34 °C, the micelles of **BR3-H** were well developed and only one size distribution was observed from DLS. Thus, this temperature was well suited for effecting dissociation of micelles by injection of an aqueous KOH solution. We have seen from Figure 2 that at pH = 4.0 the CMT$_{4.0\text{-I}}$ of **BR3-H** is 6 °C higher than the CP of **R2-H**. If we assume that the difference between the CP of **R2-H** and the CMT of **BR3-H** at a higher pH is the same as that at pH = 4.0, to disrupt the micelles at 34 °C, a pH value must be chosen at which the CP of **R2-H** is at least 28 °C. From Figure 1b, a CP of 28 °C corresponds to a pH value of 5.2, and from Figure 3, 16 μmol of KOH needs to be added to bring the pH to 5.2. To ensure that the micelles were disrupted, we injected 19 μmol of KOH via a microsyringe into the DLS tube that contained 2.50 g of the polymer solution. The KOH aqueous solution was prefiltered through a 0.2 μm filter. Note that from Figure 3 the pH increased to 5.4. Figure 4 shows the DLS data. The scattering intensity dropped immediately to the level before the micellization of the polymer solution at pH = 4.0 and the hydrodynamic size decreased from 33.5 to 7.8 nm, clearly indicating that the micelles disassembled into the individually dissolved block copolymer molecules in the solution.

The solution was then gradually heated from 34 to 50 °C. When the temperature was above 37 °C, the scattering intensity began to increase, and the average hydrodynamic size jumped from 7.8 nm at 37 °C to 31.5 nm at 38 °C and eventually became stabilized around 38 nm with the increase of temperature. These observations indicate that when the temperature was >37 °C, the thermosensitive block of **BR3-H** became dehydrated again and the micelles reformed. The CMT of **BR3-H** at the new pH (CMT$_{5.4}$), determined from the heating curve in Figure 4a, was 37 °C. Note that at pH = 5.4, the CP of **R2-H** is 30 °C. Thus, the predicted CMT of **BR3-H** at this pH would be 36 °C (30 + 6 °C), only 1 °C different from the experimentally observed value, 37 °C. The hydrodynamic size of the micelles at 50 °C was 38.3 nm, which was slightly larger than that of the micelles of **BR3-H** at pH = 4.0 and T = 50 °C (36.2 nm), likely because more carboxylic acid groups on the thermosensitive block were ionized at pH = 5.4, resulting in charge−charge repulsive interactions in the core and/or more molecules being assembled in each micelle. The micelles at 50 °C had narrow polydispersities, and a spherical shape.[82] As shown in Figure 4, upon cooling, both the scattering intensity and the hydrodynamic size decreased, and at 34 °C, the observed hydrodynamic size was <8 nm, indicating that the micelles were completely dissociated. However, unlike the transitions in Figure 2b where the cooling and heating curves superimposed each other, there was a hysteresis between heating and cooling in Figure 4 (∼ 3 °C difference). Similar results were obtained from **BR4-H** (Table 2 and Supporting Information, KOH was injected at 30 °C), and there was also a hysteresis of 3 °C between the heating and cooling curves.[82] However, the average hydrodynamic diameter of micelles of **BR4-H** at T = 50 °C and pH = 5.4 (65.3 nm) was ∼ 20 nm larger than that of **BR4-H** at the same temperature but a pH of 4.0 (45.8 nm). This is in contrast to a difference of only 2 nm for the micelles of **BR3-H** at the two different pH values (Table 2). Likely, the chain length of the thermosensitive block plays an important role here; the longer chain of **BR4-H** contained more carboxylic acid groups and thus had more charges per chain at the same pH, resulting in larger micelles.

FS studies showed that after the injection of KOH at 34 °C to increase the pH of the **BR3-H** solution to 5.4, the fluorescence emission intensity of Nile Red decreased dramatically (Figure 5a) and the maximum peak position shifted from 618 to 623 nm, indicating that the micelles were dissociated into the unimers. Further increasing temperature resulted in the reformation of micelles, as evidenced by the increase of fluorescence emission intensity and the blueshift of $\lambda_{\max}$ (from 623 nm at 34 °C to 615 nm at 50 °C). The transition is reversible; cooling from 50 to 32 °C triggered the disassembly of micelles. The CMT (CMT$_{5.4}$) determined from the plot of maximum emission intensity versus temperature was 36 °C, very close to that from DLS (37 °C). Unlike the observations from DLS, there was no hysteresis between cooling and heating curves in Figure 5a. Since the fluorescence property of Nile Red is very sensitive to the microenvironment, this observation suggests that the micelles in the range of 35−37 °C in the cooling curve of Figure 4 were in a metastable state. For **BR4-H**, KOH was added at 30 °C and the CMT at pH = 5.4 (CMT$_{5.4}$) from FS studies was 33 °C, identical to that from the DLS experiment (Table 2).

HCl-Triggered Formation of Micelles and Subsequent Temperature-Induced Dissociation and Reformation of Micelles. To find out whether the KOH-triggered dissociation of micelles was a reversible process, we injected the same amount of HCl as that of KOH into the solution of **BR3-H** at

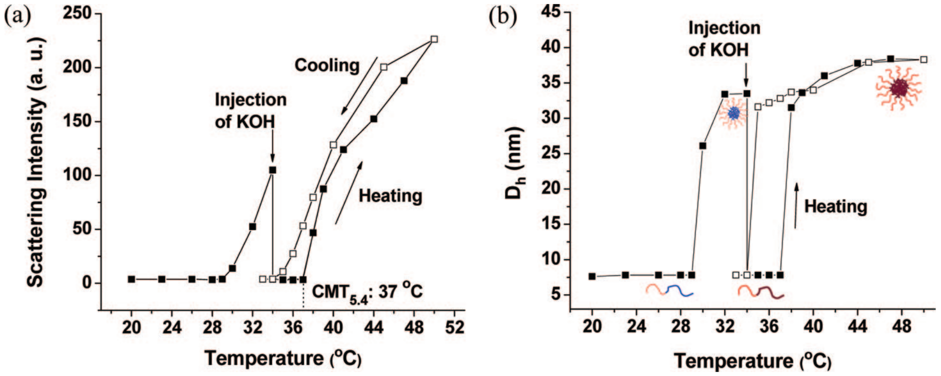


Figure 4. Intensity of scattered light at scattering angle of 90° (a) and the apparent hydrodynamic diameter (b) as a function of temperature (■ heating; □ cooling) in a DLS study of multiple micellization and dissociation transitions of a 0.2 wt % solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) in 10 mM KHP buffer solution (2.50 g, the same solution used in Figure 2) in response to addition of KOH (19 μL of 1.00 M KOH at 34 °C) and subsequent temperature changes. The data points from 20 to 34 °C were from the heating process in Figure 2. In part b, at 30 and 38 °C in the heating process, two size distributions were observed and the reported hydrodynamic diameters for these temperatures were the average values over two hydrodynamic size distributions.

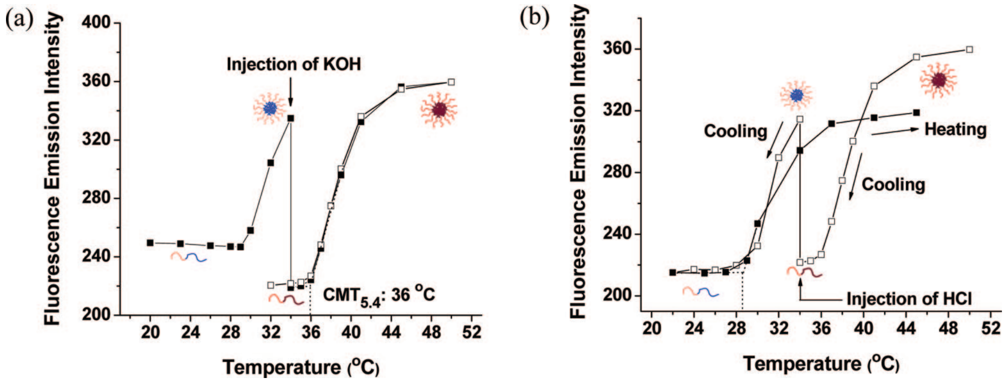


Figure 5. Maximum fluorescence emission intensity of Nile Red in a 0.2 wt % solution of **BR3-H** (PEO-*b*-P(DEGMMA-*co*-MAA)) in 10 mM KHP buffer in response to pH and subsequent temperature changes (■ heating; □ cooling). In part a, at 34 °C, 7.5 μmol of KOH was injected into the fluorescence quartz cuvette that contained 1.00 g of a 0.2 wt % polymer buffer solution (the pH increased from 4.0 to 5.4). In part b, the data points from 50 to 34 °C were from the cooling process in part a. At 34 °C, 7.5 μmol of HCl was injected into the solution (1.00 g) to change the pH from 5.4 to 4.0.

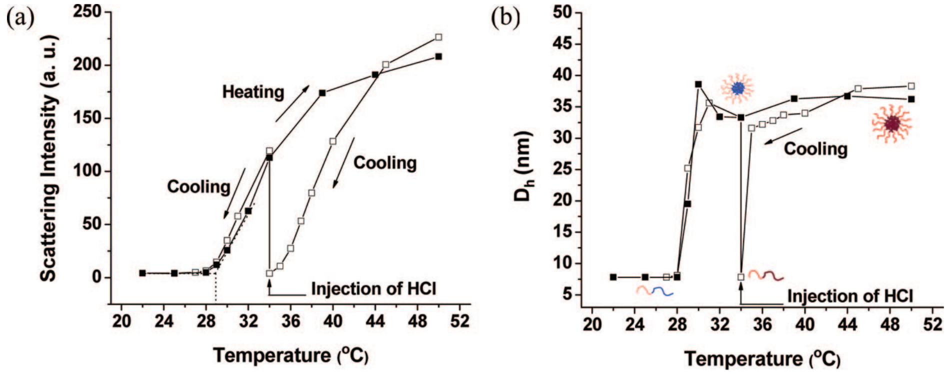


Figure 6. Intensity of scattered light at a scattering angle of 90° (a) and the hydrodynamic diameter (b) as a function of temperature (□ cooling; ■ heating) in a DLS study of multiple micellization/dissociation transitions of a 0.2 wt % solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) in 10 mM KHP buffer solution (2.50 g, the same solution used in Figure 4) in response to addition of HCl (19 μL of 1.00 M HCl solution at 34 °C) and subsequent temperature changes. The data points in the cooling curve from 50 to 34 °C were from the cooling process in Figure 4. In part b, at 30 °C in both cooling and heating processes, two size distributions were observed and the reported hydrodynamic diameters for this temperature were the average values over two hydrodynamic size distributions.

34 °C, in which the block copolymer was molecularly dissolved. The pH changed back to 4.0 from 5.4. The intensity of scattered light at scattering angle of 90° jumped up immediately and micelles with a hydrodynamic size of 33.3 nm were observed (Figure 6). The micelle size and the scattering intensity were essentially identical to those obtained by heating the 0.2 wt % polymer solution with a pH of 4.0 from 20 to 34 °C in Figure 2, which conclusively demonstrated the reversibility of pH-induced transition of **BR3-H**. Furthermore, the micelles were dissociated when the temperature was decreased below 28 °C; the apparent D_h decreased from 33.3 nm at 34 °C to 7.8 nm at 27 °C. Subsequent heating induced micellization and the hydrodynamic size and the scattering intensity at 34 °C were essentially identical to those observed right after the addition of HCl. From the plot of scattering intensity versus temperature in the heating curve, the CMT ($CMT_{4.0\text{-II}}$) was found at 29 °C,

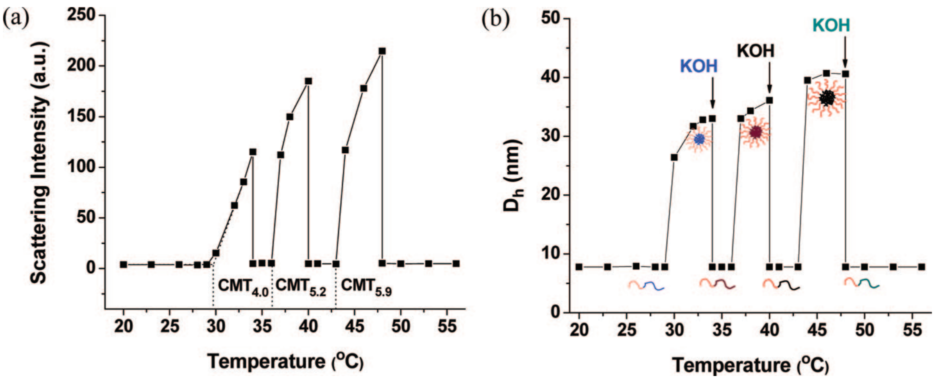


Figure 7. Intensity of scattered light at a scattering angle of 90° (a) and the hydrodynamic diameter (b) as a function of temperature in a DLS study of multiple micellization and dissociation transitions of a 0.2 wt % solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) in 10 mM KHP buffer solution (2.50 g) in response to temperature and pH changes. At 34 °C, 16 μL of a 1.00 M KOH solution was injected into the solution (the pH changed to 5.2). At 40 °C, 11 μL of a 1.00 M KOH solution was injected (the pH changed to 5.9). At 48 °C, 7.0 μL of a 1.00 M KOH solution was injected (the pH changed to ~ 8.6). In part b, at 30 °C, two size distributions were observed, and the reported hydrodynamic diameter for this temperature was the average value over two hydrodynamic size distributions.

which was only 1 °C different from $CMT_{4.0\text{-I}}$ in Figure 2 (Table 2). The size of the micelles at 50 °C was 36.2 nm. Also, the micelles had narrow polydispersities, and a spherical shape.[82] The pH- and temperature-induced reversible micellization processes were also supported by the results from FS studies (Figure 5b). After the addition of HCl at 34 °C, the fluorescence emission intensity of Nile Red jumped from the level for the unimers to the level for the micelles, and the maximum peak shifted from 622.5 to 617 nm and to 622 nm upon cooling to 22 °C, which indicated the formation and the subsequent dissociation of micelles. Upon heating, the fluorescence emission intensity gradually increased and the λ_{max} underwent a blueshift from 622 nm at 22 °C to 617.5 nm at 34 °C, to 614.5 nm at 45 °C, indicating the formation of micelles.

Similar results were obtained from the study of **BR4-H** by DLS and FS[82] and are summarized in Table 2. Note that the CMT values of **BR3-H** and **BR4-H** ($CMT_{4.0\text{-I}}$, $CMT_{5.4}$, and $CMT_{4.0\text{-II}}$) were consistently higher than the CPs of **R2-H** at the corresponding pH values by 5−7 °C and 2−3 °C, respectively. These observations support our assumption that the difference between the CMT of PEO-*b*-P(DEGMMA-*co*-MAA) and CP of **R2-H** was largely the same in the studied pH range.

Three Cycles of Micellization and Dissociation Transitions of Thermo- and pH-Responsive Block Copolymer PEO-*b*-P(DEGMMA-*co*-MAA) Achieved by Judiciously Controlling Temperature and pH. Having observed that PEO-*b*-P(DEGMMA-*co*-MAA) underwent reversible micellization/dissociation transitions in response to temperature and pH changes, we then proceeded to pursue multiple micellization/dissociation transitions by gradually increasing the temperature and simultaneously controlling the pH. We started with 0.2 wt % solutions of **BR3-H** in 10 mM KHP buffer with a pH value of 4.0 (Figures 7 and 8). With the increase of temperature, the block copolymer underwent micellization and the CMT at pH = 4.0 ($CMT_{4.0}$) was 30 °C, same as that found in Figure 2. The micelle size at 34 °C (33.0 nm) was essentially identical to that of micelles in Figures 2 (33.5 nm) and 6 (33.3 nm). As discussed earlier, to disassemble the micelles at 34 °C, the pH needs to be increased to at least 5.2 if we assume that the difference between the CP of **R2-H** and the CMT of **BR3-H** at pH = 5.2 is the same as that at pH = 4.0 (6 °C). After the injection of the calculated amounts of KOH into the solutions at 34 °C to increase the pH to 5.2, the DLS results (the intensity of scattered light at scattering angle of 90° and the hydrodynamic size) and the FS data (fluorescence emission intensity and the maximum peak position) showed that the micelles were dissociated into the molecularly dissolved unimers.

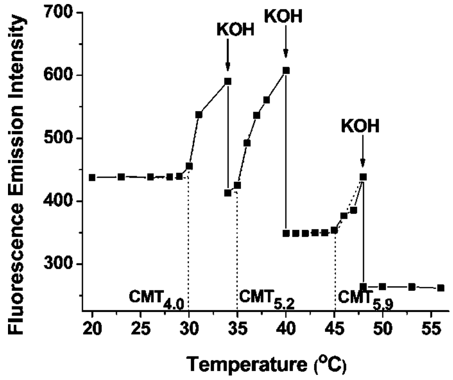


Figure 8. Maximum fluorescence emission intensity of Nile Red in a 0.2 wt % solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) in 10 mM KHP buffer solution in response to the temperature and pH changes. At 34 °C, 6.3 μmol of KOH was injected into the solution (the pH changed to 5.2); the λ_{max} shifted from 617 to 621.5 nm. At 40 °C, 4.5 μL of 1.00 M KOH was added (the pH changed to 5.9); the λ_{max} changed from 615.5 to 623 nm. At 48 °C: 2.7 μL of 1.00 M KOH was injected (the pH changed to ~8.6); the λ_{max} shifted from 616.5 to 625 nm.

We then gradually heated the solutions from 34 °C, and found from DLS and FS that the micelles reformed when the temperature was above a critical point ($CMT_{5.2}$ = 36 °C from DLS and 35 °C from FS). The size of the micelles at 40 °C was 36.1 nm, virtually identical to that of the micelles of **BR3-H** at pH = 4.0 and T = 39 °C (36.0 nm in Figure 2b), which implied that the increase of pH from 4.0 to 5.2 had little effect on the micelle size. To dissociate the micelles at 40 °C, the pH needs to be increased to a value at which the CP of **R2-H** is 34 °C assuming that the difference between the CP of **R2-H** and the CMT of **BR3-H** at the new pH is the same as that at pH = 4.0. From Figure 1b, a CP of 34 °C for **R2-H** corresponds to a pH value of 5.7, which means that a minimal amount of 25 μmol of KOH needs to be injected into 2.50 g of the solution (see Figure 3). To ensure that the micelles were disrupted, we injected 11 μmol of KOH (a total of 27 μmol of KOH including the amount of KOH added at T = 34 °C and pH = 4.0) into the DLS tube that contained 2.50 g of the polymer solution to increase the pH to 5.9, or 4.5 μmol of KOH into 1.00 g of the polymer solution for FS study. The DLS and FS data showed that the micelles were completely disrupted. Further increasing the temperature induced the micellization again ($CMT_{5.9}$ is 43 °C from DLS and 45 °C from FS, Figures 7 and 8). The size of micelles at pH = 5.9 and T = 44−48 °C (~ 40 nm) was noticeably larger than those at the lower pH

Table 3. Critical Micellization Temperatures (CMT) and Micelle Characteristics of PEO-*b*-P(DEGMMA-*co*-MAA) Obtained from Three Cycles of Micellization and Dissociation Transitions as Well as Critical Micelle Concentrations (CMC) at Different pH Values

	BH3-H	BH4-H
CMT$_{4.0}$ at pH = 4.0 (DLS, FS)	30 °C,[a] 30 °C[b]	26 °C,[a] 26 °C[b]
micelle size [c] and PD[d] at pH = 4.0	33.0 nm, 0.034 (34 °C)	41.0 nm and 0.006 (30 °C)
CMC$_{4.0}$ at pH = 4.0 and T = 50 °C [e]	0.031 mg/mL	0.023 mg/mL
CMT$_{5.2}$ at pH = 5.2 (DLS, FS)	36 °C,[a] 35 °C [b]	31 °C,[a] 31 °C[b]
micelle size [c] and PD[d] at pH = 5.2	36.1 nm, 0.015 (40 °C)	47.9 nm and 0.035 (37 °C)
CMC$_{5.2}$ at pH = 5.2 and T = 50 °C	0.032 mg/mL	0.024 mg/mL
CMT$_{5.9}$ at pH = 5.9 (DLS, FS)	43 °C,[a] 45 °C[b]	40 °C,[a] 42 °C[b]
micelle size[c] and PD[d] at pH = 5.9	40.6 nm, 0.008 (48 °C)	84.6 nm and 0.046 (45 °C)
CMC$_{5.9}$ at pH = 5.9 and T = 50 °C	0.039 mg/mL	0.037 mg/mL

[a] CMT determined by dynamic light scattering (DLS). [b] CMT determined by fluorescence spectroscopy (FS). [c] the average hydrodynamic diameter of micelles at a specific temperature was obtained by the use of the CONTIN method. [d] The polydispersity (PD) of micelles at a specific temperature obtained by the use of the CONTIN method. [e] CMC: critical micelle concentration at a particular pH and temperature, determined by FS using Nile Red as fluorescence probe. The polymer concentration in the buffer was 0.2 wt %. Note that the CP of **R2-H** is 24 °C at pH = 4.0, 28 °C at pH = 5.2, and 37 °C at pH = 5.9 (from Figure 1b).

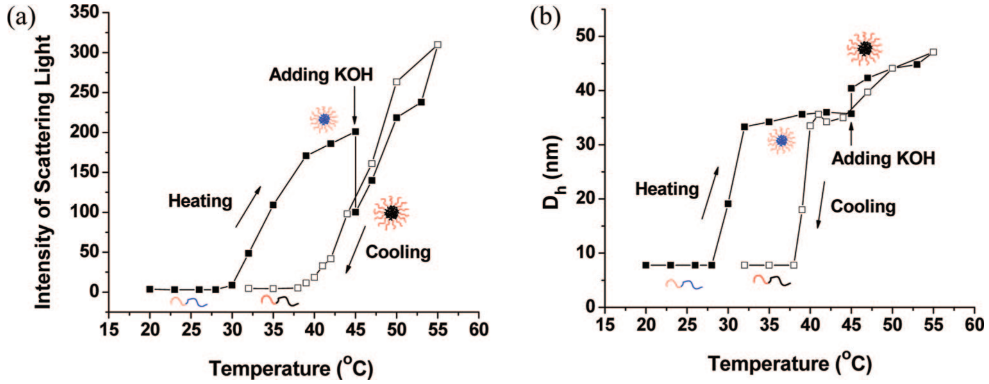


Figure 9. Intensity of scattered light at a scattering angle of 90° (a) and the hydrodynamic diameter (b) as a function of temperature in a DLS study of a 0.2 wt % solution of PEO-*b*-P(DEGMMA-*co*-MAA) (**BR3-H**) in 10 mM KHP buffer solution (2.50 g) in response to temperature and pH changes. At 45 °C, 25 μL of 1.00 M KOH solution was injected to bring the pH to 5.7 from 4.0. In part b, at 30 °C in the heating process and at 39 and 40 °C during the cooling process, two size distributions were observed, and the reported hydrodynamic diameters for these temperatures were the average values over two hydrodynamic size distributions.

values, which is believed to result from the higher degree of ionization of carboxylic acid groups at pH = 5.9 than at pH = 5.2 and 4.0.

To break the micelles at 48 °C, a similar consideration showed that the pH needs to be increased from 5.9 to at least 6.2, which from Figure 3 corresponds to the addition of 30 μmol of KOH into 2.50 g of a polymer solution with pH = 4.0. We injected 7 μmol of KOH into the solution, bringing the total amount of KOH to 34 μmol that made the solution pH = ~8.6. Similarly, a calculated amount of KOH was injected into the FS quartz cuvette to increase the pH to ~8.6. The DLS and FS data showed that the micelles were dissociated into the unimers (Figures 7 and 8). In a similar way, we achieved three cycles of micellization and dissociation transitions of **BR4-H** by using the same pH values but different temperatures for micelle dissociation.[82] Table 3 summarizes the results for both **BR3-H** and **BR4-H** obtained from three micellization and dissociation cycles, including the CMT and micelle characteristics at representative temperature at each pH. It is worth noting here that the values of CMT of **BR3-H** and **BR4-H** obtained by DLS and FS at each pH were consistently higher than the CP of **R2-H** by 6−8 °C and 2−5 °C, respectively. Although for both block copolymers the values of CMT at pH 4.0 and 5.2 determined by DLS and FS were essentially identical, the CMT from FS at pH 5.9 was 2 °C higher than that from DLS for both polymers. Since the core of the micelles contained more ionized carboxylic acid groups at pH = 5.9 and the fluorescence intensity of Nile Red is sensitive to the polarity of the microenvironment, a higher temperature is believed to be required for the fluorescence emission intensity of the dye to begin to increase.

With the increase of pH, the LCST transition temperature of the thermosensitive block of PEO-*b*-P(DEGMMA-*co*-MAA) increases and the polymer becomes more hydrophilic, which is expected to result in a higher critical micelle concentration (CMC). By the use of FS with Nile Red as fluorescence probe, we determined the CMCs of **BR3-H** and **BR4-H** at pH = 4.0, 5.2, and 5.9, same pH values as in the experiments of three cycles of micellization and dissociation transitions of the two block copolymers. The results are included in Table 3. Although the CMCs at pH = 4.0 and 5.2 were very close for both **BR3-H** (0.031 and 0.032 mg/mL, respectively) and **BR4-H** (0.023 and 0.024 mg/mL, respectively), the CMCs at pH 5.9 were appreciably higher (0.039 mg/mL for **BR3-H** and 0.037 mg/mL for **BR4-H**, all at 50 °C), consistent with the anticipated trend. Note that at any of the three pH values, the CMC of **BR4-H** was consistently lower than that of **BR3-H**, which can be attributed to the longer chain length of the thermosensitive block of **BR4-H** compared with that of **BR3-H**.

Control Experiment. In the preceding section, three cycles of micellization and dissociation transitions of PEO-*b*-P(DEGMMA-*co*-MAA) were achieved by gradually heating the polymer solution from 20 to 57 °C and rationally changing the pH. It should be emphasized here that it is important to judiciously choose both temperature and pH using Figures 1b and 3 as a guide for designing micellization/dissociation transitions. To further demonstrate this point, we carried out a control experiment. First, 2.50 g of a 0.2 wt % buffer solution of **BR3-H** with a pH of 4.0 was gradually heated to 45 °C (Figure 9). The micellization occurred as expected, and the size of the micelles at 45 °C was 35.7 nm, which was essentially identical to the result shown in Figure 2 (36.1 nm at pH = 4.0 and T = 44 °C). We then injected 25 μL of 1.00 M KOH solution into the DLS tube, which was then taken out, shaken for a few seconds, and placed back into the tube holder of the instrument. The micelles did not disassemble into the unimers, but were swelled from 35.7 to 40.4 nm at the same temperature (Figure 9). Interestingly, the scattering intensity decreased by 50%, indicating that the micelles were not as tight as those before the injection of KOH. Apparently, the amount of added KOH was not enough to break the micelles, but the increase in pH caused more carboxylic acid groups to ionize and hence introduced more charge−charge interactions in the micelle core. From Figure 3, one can find out that the pH of the polymer solution increased to 5.7 after the addition of 25 μmol of KOH, which is expected to be able to break the micelles at 40 °C but not at 45 °C (to break the micelles at 45 °C, the CP of **R2-H** needs to be 39 °C, corresponding to a pH value of 6.0 and 28 μmol of KOH). When the temperature was further increased from 45 to 50 °C, the scattering intensity increased significantly, suggesting that the thermosensitive block in the core underwent continuous dehydration with the increase of temperature. When the solution was cooled from 50 to 44 °C, the size of the micelles became smaller (35 nm at 44 °C), similar to that of the micelles at the original pH value (35.7 nm at 45 °C and pH = 4.0). This is probably due to rearrangement of the micelles and the change in the number of association of molecules in each micelle.

Conclusion

In summary, we demonstrated in this work that thermo- and pH-sensitive block copolymers PEO-*b*-P(DEGMMA-*co*-MAA) can undergo multiple, reversible micellization and dissociation in response to temperature and pH changes. A random copolymer P(DEGMMA-*co*-*t*BMA) and two samples of PEO-*b*-P(DEGMMA-*co*-*t*BMA) with controlled molecular weights and narrow polydispersities were synthesized by ATRP; hydrolysis with CF_3COOH produced the corresponding P(DEGMMA-*co*-MAA) and PEO-*b*-P(DEGMMA-*co*-MAA). The cloud point of P(DEGMMA-*co*-MAA) in aqueous KHP buffer solutions can be tuned from 24 to 60 °C by changing the pH from 4.0 to 6.7. The block copolymers underwent reversible thermo-induced micellization and dissociation transitions in 10 mM KHP buffer solutions at relatively low pH values, and the micelles had narrow polydispersities and a spherical shape. For the micelles formed at pH = 4.0, we observed that by injection of a predetermined amount of KOH the micelles were rapidly dissociated into the unimers, which reformed micelles by injection of the same amount of HCl at the same temperature or by heating to a higher temperature. We further showed that by gradually raising temperature and simultaneously controlling the pH, three cycles of micellization and dissociation transitions were realized, demonstrating the possibility of achieving on-demand micellization and dissociation transition in the studied pH and temperature ranges. Fluorescence spectroscopy studies showed that Nile Red can be repeatedly encapsulated and released by the block copolymers. Note that we can also obtain a plot of CMT of **BR3-H** or **BR4-H** versus pH and use it as a guide along with Figure 3 for designing micellization and dissociation transitions. The method reported in this article for tuning multiple micellziation and dissociation transitions may find applications in controlled encapsulation and triggered release of substances.

Acknowledgment. This work is supported by a grant from National Science Foundation (DMR-0605663).

Supporting Information Available: Text giving experimental details including materials, general characterization, DLS and FS experiments, synthesis of PDEGMMA, P(DEGMMA-*co*-*t*BMA), PEO-*b*-P(DEGMMA-*co*-tBMA), hydrolysis of P(DEGMMA-*co*-*t*BMA) and PEO-*b*-P(DEGMMA-*co*-tBMA), and treatment of PDEGMMA with CF_3COOH and figures showing characterization data including GPC analysis of PEO-Br and **BR3**, ^1H NMR spectra of **BR3** and **BR3-H**, GPC traces of **H1** before and after treatment with CF_3COOH, ^1H NMR spectra of **H1** before and after treatment with CF_3COOH, optical transmittances at wavelength of 550 nm of 0.2 wt % aqueous solutions of **H1** with pH of 4.1, 5.3, and 6.1 as a function of temperature, hydrodynamic diameter (D_h) distribution of micelles of **BR3-H** and plot of Γ/q^2 of micelles of **BR3-H** vs q^2 at pH = 4.0 and $T = 50$ °C, scattering intensity and D_h as a function of temperature in a DLS study of a 0.2 wt % solution of **BR4-H** at pH = 4.0; D_h distribution of micelles of **BR4-H** and plot of Γ/q^2 of micelles of **BR4-H** vs q^2 at pH = 4.0 and $T = 50$ °C, fluorescence spectra of Nile Red in a 0.2 wt % solution of **BR3-H** at various temperatures in both heating and cooling, fluorescence spectra of Nile Red in a 0.2 wt % solution of **BR4-H** at various temperatures in both heating and cooling processes, the plot of pH versus number of μmol of KOH injected into a 0.2 wt % solution of **BR4-H** (2.50 g), D_h distribution of micelles of **BR3-H** and plot of Γ/q^2 of micelles of **BR3-H** vs q^2 at pH = 5.4 and $T = 50$ °C, scattering intensity and D_h as a function of temperature in a DLS study of a 0.2 wt % solution **BR4-H** in response to addition of KOH and subsequent temperature changes, fluorescence intensity of Nile Red in a 0.2 wt % solution of **BR4-H** in response to addition of KOH and subsequent temperature changes, D_h distribution of micelles of **BR3-H** at pH = 4.0 and $T = 50$ °C and plot of Γ/q^2 of micelles of **BR3-H** vs q^2 at pH = 4.0 and $T = 34$ °C, scattering intensity and D_h as a function of temperature in a DLS of a 0.2 wt % solution of **BR4-H** in response to addition of HCl and subsequent temperature changes, fluorescence intensity of Nile Red in a 0.2 wt % solution of **BR4-H** in response to addition of HCl and subsequent temperature changes, scattering intensity and D_h as a function of temperature in a DLS study of a 0.2 wt % solution of **BR4-H** (2.50 g) in response to temperature and pH changes, fluorescence intensity of Nile Red in a 0.2 wt % solution of **BR4-H** in response to the temperature and pH changes, determination of CMCs of **BR3-H** and **BR4-H** at different pH values but the same temperature (50 °C). This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Rijcken, C. J. F.; Soga, O.; Hennink, W. E.; van Nostrum, C. F. *J. Controlled Release* **2007**, *120*, 131–148.
(2) Dimitrov, I.; Trzebicka, B.; Müller, A. H. E.; Dworak, A.; Tsvetanov, C. B. *Prog. Polym. Sci.* **2007**, *32*, 1275–1343.
(3) Gil, E. S.; Hudson, S. M. *Prog. Polym. Sci.* **2004**, *29*, 1173–1222.
(4) Bütün, V.; Billingham, N. C.; Armes, S. P. *J. Am. Chem. Soc.* **1998**, *120*, 11818–11819.
(5) Bütün, V.; Armes, S. P.; Billingham, N. C.; Tuzar, Z.; Rankin, A.; Eastoe, J.; Heenan, R. K. *Macromolecules* **2001**, *34*, 1503–1511.
(6) Liu, S. Y.; Armes, S. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1413–1416.
(7) Liu, S. Y.; Billingham, N. C.; Armes, S. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2328–2331.
(8) Gohy, J. F.; Antoun, S.; Jérome, R. *Macromolecules* **2001**, *34*, 7435–7440.
(9) Schilli, C. M.; Zhang, M. F.; Rizzardo, E.; Thang, S. H.; Chong, Y. K.; Edwards, K.; Karlsson, G.; Müller, A. H. E. *Macromolecules* **2004**, *37*, 7861–7866.
(10) André, X.; Zhang, M. F.; Müller, A. H. *Macromol. Rapid Commun.* **2005**, *26*, 558–563.
(11) Bellomo, E. G.; Wyrsta, M. D.; Pakstis, L.; Pochan, D. J.; Deming, T. J. *Nat. Mater.* **2004**, *3*, 244–248.
(12) Borchert, U.; Lipprandt, U.; Bilang, M.; Kimpfler, A.; Rank, A.; Peschka, R.; Schubert, R.; Lindner, P.; Forster, S. *Langmuir* **2006**, *22*, 5843–5847.
(13) Xu, J.; Ge, Z. S.; Zhu, Z. Y.; Luo, S. Z.; Liu, H. W.; Liu, S. Y. *Macromolecules* **2006**, *39*, 8178–8185.
(14) Wang, D.; Yin, J.; Zhu, Z.; Ge, Z.; Liu, H.; Armes, S. P.; Liu, S. Y. *Macromolecules* **2006**, *39*, 7378–7385.
(15) Zhang, W.; Shi, L.; Ma, R. An. Y.; Xu, Y.; Wu, K. *Macromolecules* **2005**, *38*, 8850–8852.
(16) Gillies, E. R.; Fréchet, J. M. J. *Chem. Commun.* **2003**, *14*, 1640–1641.

(17) Gillies, E. R.; Jonsson, T. B.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11936–11943.

(18) Gillies, E. R.; Fréchet, J. M. J. *Bioconjugate Chem.* **2005**, *16*, 361–368.

(19) Bae, Y.; Fukushima, S.; Harada, A.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4640–4643.

(20) Bae, Y.; Nishiyama, N.; Fukushima, S.; Hoyama, H.; Yasuhori, M.; Kataoka, K. *Bioconjugate Chem.* **2005**, *16*, 122–130.

(21) Lee, Y.; Fukushima, S.; Bae, Y.; Hiki, S.; Ishii, T.; Kataoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 5362–5363.

(22) Zhang, L.; Bernard, J.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. *Macromol. Rapid Commun.* **2008**, *29*, 123–129.

(23) Chan, Y.; Wong, T.; Byrne, F.; Kavallaris, M.; Bulmus, V. *Biomacromolecules* **2008**, *9*, 1826–1836.

(24) Aoshima, S.; Sugihara, S. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 3962–3965.

(25) Sugihara, S.; Kanaoka, S.; Aoshima, S. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 2601–2611.

(26) Sugihara, S.; Kanaoka, S.; Aoshima, S. *Macromolecules* **2005**, *38*, 1919–1927.

(27) Arotcarena, M.; Heise, B.; Ishaya, S.; Laschewsky, A. *J. Am. Chem. Soc.* **2002**, *124*, 3787–3793.

(28) Mertoglu, M.; Garnier, S.; Laschewsky, A.; Skrabania, K.; Sorsberg, J. *Polymer* **2005**, *46*, 7726–7740.

(29) Skrabania, K.; Juliane, K.; Laschewsky, A.; Akdemir, O.; Hoth, A.; Lutz, J.-F. *Langmuir* **2007**, *23*, 84–93.

(30) Hua, F. J.; Jiang, X. G.; Zhao, B. *Macromolecules* **2006**, *39*, 3476–3479.

(31) Qin, S. H.; Geng, Y.; Discher, D. E.; Yang, S. *Adv. Mater.* **2006**, *18*, 2905–2909.

(32) Zhang, W. Q.; Shi, L. Q.; Wu, K. An. Y. G. *Macromolecules* **2005**, *38*, 5743–5747.

(33) Dimitrov, P.; Rangelov, S.; Dworak, A.; Tsvetanov, C. B. *Macromolecules* **2004**, *37*, 1000–1008.

(34) Convertine, A. J.; Lokitz, B. S.; Vasileva, Y.; Myrick, L. J.; Scales, C. W.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2006**, *39*, 1724–1730.

(35) Li, Y. T.; Lokitz, B. S.; McCormick, C. L. *Macromolecules* **2006**, *39*, 81–89.

(36) Jiang, J. Q.; Tong, X.; Zhao, Y. *J. Am. Chem. Soc.* **2005**, *127*, 8290–8291.

(37) Jiang, J. Q.; Tong, X.; Morris, D.; Zhao, Y. *Macromolecules* **2006**, *39*, 4633–4640.

(38) Jiang, Y.; Wang, Y.; Ma, N.; Wang, Z.; Smet, M.; Zhang, X. *Langmuir* **2007**, *23*, 4029–4034.

(39) Lee, H.-I.; Wu, W.; Oh, J. K.; Mueller, L.; Sherwood, G.; Peteanu, L.; Kowalewski, T.; Matyjaszewski, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2453–2457.

(40) Jiang, X. G.; Lavender, C. A.; Woodcock, J. W.; Zhao, B. *Macromolecules* **2008**, *41*, 2632–2643.

(41) Katayama, Y.; Sonoda, T.; Maeda, M. *Macromolecules* **2001**, *34*, 8569–8573.

(42) Ishihara, Y.; Bazzi, H. S.; Toader, V.; Godin, F.; Sleiman, H. F. *Chem. Eur. J.* **2007**, *13*, 4560–4570.

(43) Joseph, J.; Dreiss, C. A.; Cosgrove, T. *Langmuir* **2007**, *23*, 460–466.

(44) Napoli, A.; Valentini, M.; Tirelli, N.; Muller, M.; Hubbell, J. A. *Nat. Mater.* **2004**, *3*, 183–189.

(45) Napoli, A.; Boerakker, M. J.; Tirelli, N.; Muller, M.; Sommerdijk, N. A.; Hubbell, J. A. *Langmuir* **2004**, *20*, 3487–3491.

(46) Wu, C.; Wang, X. H. *Phys. Rev. Lett.* **1998**, *80*, 4092–4094.

(47) Plamper, F. A.; Schmalz, A.; Ballauff, M.; Müller, A. H. E. *J. Am. Chem. Soc.* **2007**, *129*, 14538–14539.

(48) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163–249.

(49) Huang, X. N.; Du, F. S.; Ju, R.; Li, Z. C. *Macromol. Rapid Commun.* **2007**, *28*, 597–603.

(50) Neradovic, D.; van Nostrum, C. F.; Hennink, W. E. *Macromolecules* **2001**, *34*, 7589–7591.

(51) Neradovic, D.; van Steenbergen, M. J.; Vansteelant, L.; Meijer, Y. J.; van Nostrum, C. F.; Hennink, W. E. *Macromolecules* **2003**, *36*, 7491–7498.

(52) Soga, O.; van Nostrum, C. F.; Ramzi, A.; Visser, T.; Soulimani, F.; Frederik, P. M.; Bomans, P. H. H.; Hennink, W. E. *Langmuir* **2004**, *20*, 9388–9395.

(53) Rijcken, C. J. F.; Veldhuis, T. F. J.; Ramzi, A.; Meeldijk, J. D.; van Nostrum, C. F.; Hennink, W. E. *Biomacromolecules* **2005**, *6*, 2343–2351.

(54) Kohori, F.; Sakai, K.; Aoyagi, T.; Yokoyama, M.; Yamato, M.; Sakurai, Y.; Okano, T. *Colloids Surf. B: Biointerfaces* **1999**, *16*, 195–205.

(55) Gotzamanis, G.; Tsitsilianis, C. *Polymer* **2007**, *48*, 6226–6233.

(56) Lutz, J.-F.; Hoth, A. *Macromolecules* **2006**, *39*, 893–896.

(57) Lutz, J. F.; Weichenhan, K.; Akdemir, O.; Hoth, A. *Macromolecules* **2007**, *40*, 2503–2508.

(58) Yin, X.; Hoffman, A. S.; Stayton, P. S. *Biomacromolecules* **2006**, *7*, 1381–1385.

(59) Chen, G.; Hoffman, A. S. *Nature* **1995**, *373*, 49–52.

(60) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *Macromolecules* **1992**, *25*, 5528–5530.

(61) Bulmus, V.; Ding, Z.; Long, C. J.; Stayton, P. S.; Hoffman, A. S. *Bioconjugate Chem.* **2000**, *11*, 78–83.

(62) Zhou, S. Q.; Chu, B. *J. Phys. Chem. B.* **1998**, *102*, 1364–1371.

(63) Olea, A. F.; Thomas, J. K. *Macromolecules* **1989**, *22*, 1165–1169.

(64) Murthy, N.; Robichaud, J. R.; Tirrell, D. A.; Stayton, P. S.; Hoffman, A. S. *J. Controlled Release* **1999**, *61*, 137–143.

(65) Reference deleted in proof.

(66) Lokitz, B. S.; York, A. W.; Stempka, J. E.; Treat, N. D.; Li, Y.; Jarrett, W. L.; McCormick, C. L. *Macromolecules* **2007**, *40*, 6473–6480.

(67) Han, S.; Hagiwara, M.; Ishizone, T. *Macromolecules* **2003**, *36*, 8312–8319.

(68) Li, D. J.; Jones, G. J.; Dunlap, J. R.; Hua, F. J.; Zhao, B. *Langmuir* **2006**, *22*, 3344–3351.

(69) Li, D. J.; Zhao, B. *Langmuir* **2007**, *23*, 2208–2217.

(70) Zhao, B.; Li, D. J.; Hua, F. J.; Green, D. R. *Macromolecules* **2005**, *38*, 9509–9517.

(71) Hua, F. J.; Jiang, X. G.; Li, D. J.; Zhao, B. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 2454–2467.

(72) Jiang, X. G.; Zhao, B. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 3707–3721.

(73) Li, D. J.; Zhao, B. *Langmuir* **2008**, *24*, 5911–5918.

(74) Lutz, J.-F.; Andrieu, J.; Uzgun, S.; Rudolph, C.; Agarwal, S. *Macromolecules* **2007**, *40*, 8540–8543.

(75) Aathimanikandan, S. V.; Savariar, E. N.; Thayumanavan, S. *J. Am. Chem. Soc.* **2005**, *127*, 14922–14929.

(76) Chang, Y.; Powell, E. S.; Allcock, H. R.; Park, S. M.; Kim, C. *Macromolecules* **2003**, *36*, 2568–2570.

(77) Allcock, H. R.; Dudley, G. K. *Macromolecules* **1996**, *29*, 1313–1319.

(78) Yamamoto, S.-I.; Pietrasik, J.; Matyjaszewski, K. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 194–202.

(79) Jiang, X. W.; Smith, M. R.; Baker, G. L. *Macromolecules* **2008**, *41*, 318–324.

(80) Wang, N.; Dong, A.; Radosz, M.; Shen, Y. Q. *J. Biomed. Mater. Res. Part A* **2008**, *84A*, 148–157.

(81) Andruzzi, L.; Senaratne, W.; Hexemer, A.; Sheets, E. D.; Ilic, B.; Kramer, E. J.; Baird, B.; Ober, C. J. *Langmuir* **2005**, *21*, 2495–2504.

(82) Details can be found in the Supporting Information.

(83) Urry, D. W. *J. Phys. Chem. B* **1997**, *101*, 11007–11028.

MA8018238