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Micellization and Micellar Aggregation of Poly(ethylene-*alt*-propylene)-*b*-poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide) Triblock Terpolymers in Water

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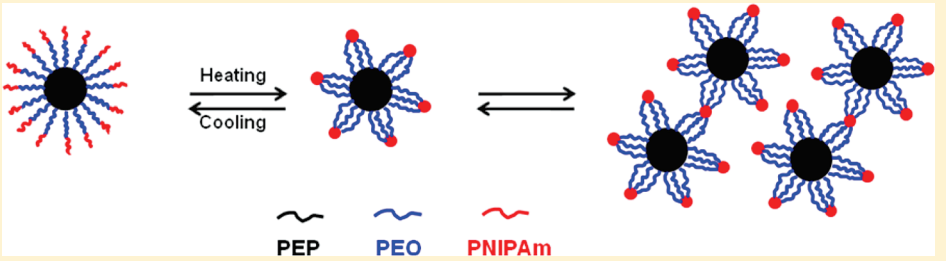
Supporting Information

ABSTRACT:



Three poly(ethylene-*alt*-propylene)-*b*-poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide) (PEP−PEO−PNIPAm, "PON") triblock terpolymers were synthesized using a combination of anionic and reversible addition−fragmentation chain transfer polymerization, and their micellization and micellar aggregation properties in dilute aqueous solution were studied by dynamic light scattering (DLS) and cryo-TEM. The PEP and PEO blocks had molecular weights of 3000 and 25 000, respectively, while the PNIPAm block was varied with molecular weights equal to 4000, 10 000, and 21 000. In dilute aqueous solution the terpolymers formed well-defined micelles with hydrophobic PEP cores surrounded by hydrophilic PEO−PNIPAm coronas at temperatures below the lower critical solution temperature (LCST) of PNIPAm. DLS revealed that the PON micelles prepared by a dialysis technique were significantly smaller than those prepared by a thin-film hydration technique. In either case, at temperatures above the LCST of PNIPAm, the micelles associated to form larger aggregated structures. The critical micellar aggregation temperature for these PON triblock terpolymers was higher than the typical LCST for a PNIPAm homopolymer and depended on the PNIPAm block length and polymer concentration. As the molecular weight of PNIPAm decreased from 21 000 to 4000, the critical micellar aggregation temperature increased from 36 °C to above 60 °C. The critical micellar aggregation temperature was also higher at lower polymer concentrations. These results demonstrate how the inclusion of a temperature-sensitive endblock in a linear ABC triblock terpolymer with a strongly hydrophobic component can lead to tunable and reversible micellar aggregation behavior.

INTRODUCTION

Block copolymers in which at least one block is a thermoresponsive polymer have attracted considerable interest in the area of self-assembled soft materials. They can show interesting properties such as thermoreversible aggregation and gelation and have found use as biomaterials for drug delivery and tissue engineering applications.[1−4] Poly(*N*-isopropylacrylamide) (PNIPAm), exhibiting a lower critical solution temperature (LCST) in water at ca. 32 °C, has been extensively employed as a thermoresponsive block since its LCST is both close to body temperature and tunable by copolymerization with other monomers.[5−8] There are typically two classes of PNIPAm-containing block copolymers reported in the literature. First, double hydrophilic block copolymers, in which PNIPAm is coupled to a hydrophilic block, can be dissolved in aqueous solution at low temperatures and form micelles with PNIPAm cores above the LCST of PNIPAm.[9−19] For example, using poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide) (PEO-*b*-PNIPAm) AB diblock copolymers, Zhang et al. reported the formation of spherical micelles at high PEO volume fractions,[15] and Qin et al. demonstrated that vesicles can be prepared using block copolymers with high PNIPAm volume fractions.[16] The other class is amphiphilic block copolymers in which PNIPAm is coupled to a hydrophobic block such as polystyrene (PS), poly(*n*-butyl methacrylate) (PBMA), poly(D,L-lactide) (PLA), or poly(ε-caprolactone) (PCL).[20−28] These block copolymers

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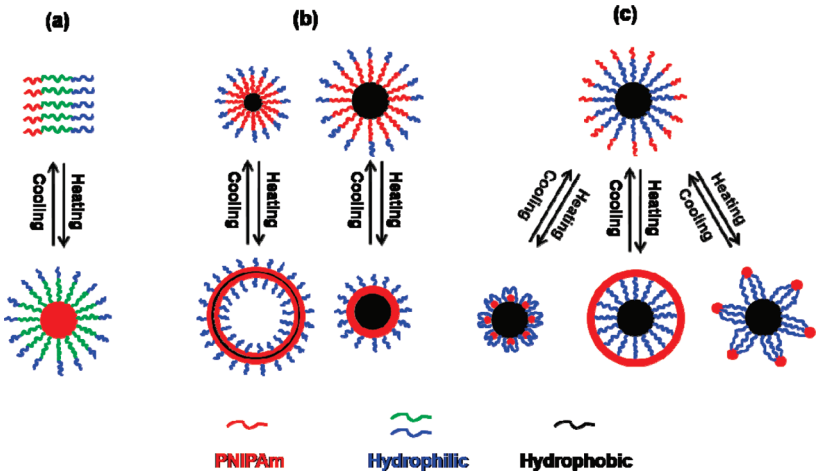


Figure 1. Schematic illustration of the possible thermo-induced structure changes of PNIPAm-containing triblock terpolymer micelles with (a) PNIPAm as the core, (b) PNIPAm as the shell, and (c) PNIPAm as the corona.

can form micelles with hydrophobic cores and hydrophilic PNIPAm coronas below the LCST of PNIPAm. At higher temperatures the PNIPAm coronas collapse around the hydrophobic cores, and this can induce micellar aggregation.

There have been a few reports on the incorporation of PNIPAm into ABC triblock terpolymers.[29−42] In these studies, PNIPAm has been used as the core, shell, or corona block for micelle formation, and the possible thermo-induced structure changes are summarized in Figure 1. As shown in Figure 1a, triblock terpolymers with PNIPAm as the core block form micelles above the LCST of PNIPAm. For example, McCormick et al. showed that poly(ethylene oxide)-*b*-poly[(*N*,*N*-dimethylacrylamide)-*stat*-(*N*-acryloxysuccinimide)]-*b*-poly(*N*-isopropylacrylamide) (PEO-*b*-P(DMA-*stat*-NAS)-*b*-PNIPAm) formed micelles with PNIPAm cores above 37 °C. In this particular case, the shell of the micelle could be reversibly cross-linked to control subsequent drug delivery.[30] When PNIPAm is used as the shell block, the micelles can change into a different morphology such as cylindrical micelles or vesicles at higher temperatures when the hydrophobic core is very short, allowing for structural rearrangement (Figure 1b). Grubbs and co-workers reported that poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide)-*b*-polyisoprene (PEO-*b*-PNIPAm-*b*-PI) formed spherical micelles with hydrophobic PI cores, PNIPAm shells, and PEO coronas, and they transformed into large vesicles above the LCST due to the change in the hydrophobic/hydrophilic volume ratio.[36] It is also possible that the PNIPAm shell will collapse around the hydrophobic core above the LCST (Figure 1b). Shi et al. prepared core−shell−corona micelles with PNIPAm shells from poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide)-*b*-polystyrene (PEO-*b*-PNIPAm-*b*-PS) and observed the collapse of PNIPAm chains above the LCST.[38]

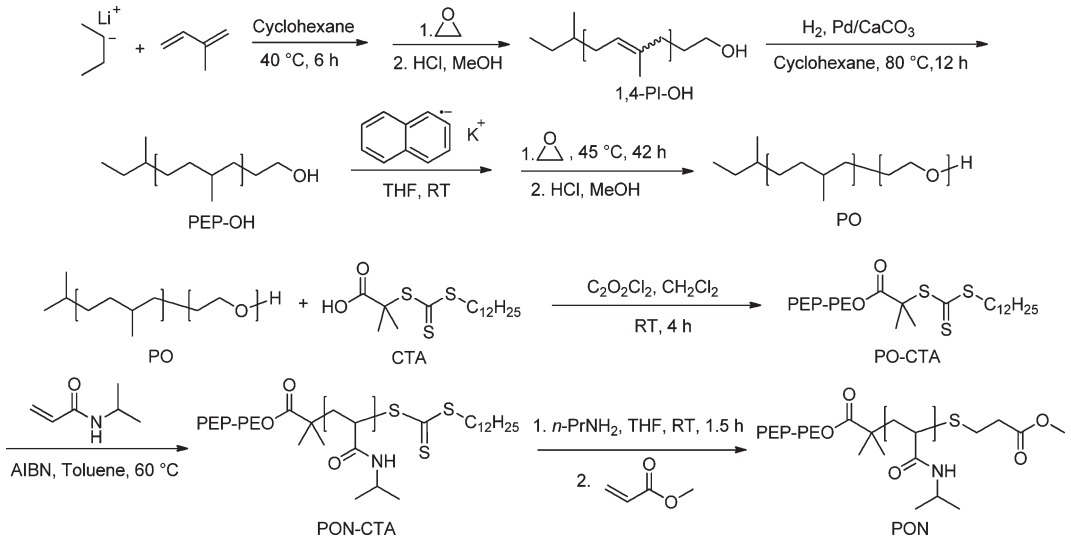
When PNIPAm is used as the corona block with PEO (or other hydrophilic) midblocks, the PNIPAm blocks might collapse around the hydrophobic core above the LCST to form "flowerlike micelles" with the PEO on the exterior, or they could collapse around the hydrophilic shell to form a thin layer or sticky patches, resulting in a decrease of micelle size in very dilute solution (Figure 1c). For example, micelles with thermoresponsive PNIPAm coronas have been prepared from poly(2-(diethylamino)ethyl methacrylate)-*b*-poly(2-(dimethylamino)ethyl methacrylate)-*b*-poly(*N*-isopropylacrylamide) and poly(ε-caprolactone)-*b*-PEO-*b*-PNIPAm (PCL-*b*-PEO-*b*-PNIPAm).[40,41] The collapse of PNIPAm coronas at temperatures above the LCST resulted in a decrease in micelle size. At higher concentrations, micelles with a thin layer or sticky patches of PNIPAm on the exterior can associate to form larger aggregated structures; however, micellar aggregation has not been studied in ABC triblock terpolymers with a PNIPAm corona block. In addition, such micellar aggregation can lead to hydrogel formation in more concentrated solutions, and these ABC hydrogels are multicompartment networks with two types of domains capable of performing different functions.[43,44] Therefore, it is interesting to investigate the micellization and micellar aggregation of triblock terpolymers with PNIPAm coronas.

In this work, we investigated the micellization and micellar aggregation behavior of poly(ethylene-*alt*-propylene)-*b*-poly(ethylene oxide)-*b*-poly(*N*-isopropylacrylamide) (PON) triblock terpolymers in water. The poly(ethylene-*alt*-propylene) (PEP) block, with a glass transition well below room temperature, high hydrophobicity, and a low molecular weight, was chosen as the hydrophobic core to mitigate kinetic complications of the micellization behavior associated with a glassy core. Poly(ethylene oxide) (PEO) was chosen as the hydrophilic midblock due to its compatibility with water at the temperatures of interest. This paper describes the synthesis and aqueous self-assembly of PON triblock terpolymers with different block lengths of PNIPAm and focuses on the effect of a PNIPAm endblock on the micellization and micellar aggregation properties. The gelation behavior at higher concentrations will be the subject of a future report.

EXPERIMENTAL SECTION

Chemical and Materials. Three PON triblock terpolymers were prepared using a combination of anionic and reversible addition−fragmentation chain transfer (RAFT) polymerizations (Scheme 1). All reagents were used as received unless otherwise noted. 2,2′-Azobis(isobutyronitrile) (AIBN) and *N*-isopropylacrylamide (NIPAm) were purchased from Aldrich and purified by recrystallization from methanol and benzene/*n*-hexane (65/35 v/v), respectively. Toluene and THF were purified by passing through an activated alumina column and a supported copper catalyst. The chain transfer agent (CTA) *S*-1-dodecyl-*S*′-(α,α′-dimethyl-α″-acetic acid) trithiocarbonate was synthesized following a reported procedure.[45]

Scheme 1. Synthesis of PON Triblock Terpolymers



Synthesis of PON Triblock Terpolymers. A PEP−PEO (PO) diblock copolymer was synthesized by anionic polymerization following a procedure described in detail elsewhere.[46,47] Briefly, hydroxyl-terminated 1,4-polyisoprene (1,4-PI-OH) was prepared by anionic polymerization of isoprene followed by end-capping with ethylene oxide. The polymer was found to contain 91% 1,4-units and 9% 3,4-units by ^{1}H NMR spectroscopy. 1,4-PI-OH was hydrogenated to give the corresponding hydroxyl-terminated poly(ethylene-*alt*-propylene) (PEP-OH). Next, the potassium alkoxide version of PEP-OH was used to initiate the anionic polymerization of ethylene oxide to afford hydroxyl-terminated poly(ethylene-*alt*-propylene)-*b*-poly(ethylene oxide) (PO) diblock copolymer.

The PON triblock terpolymers (PON-CTAs) were synthesized by RAFT polymerization from PO diblock copolymer.[48] The first step was the preparation of PO-CTA macroinitiator. CTA (1.3 g, 3.6 mmol) was mixed with excess oxalyl chloride (3.2 mL, 37 mmol) in dry CH_2Cl_2 (20 mL) under a nitrogen atmosphere and stirred at room temperature for 4 h. CH_2Cl_2 and excess oxalyl chloride were removed under vacuum. PO (10.1 g in 80 mL of CH_2Cl_2, 0.36 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The polymer was precipitated in acetone at −78 °C once and in pentane twice and dried in a vacuum oven at 50 °C overnight. In a representative synthesis toward PON-CTA, PO-CTA macroinitiator (3.0 g, 0.11 mmol), NIPAm (3.2 g, 0.028 mol), and AIBN (2 mg, 0.011 mmol) were dissolved in toluene (30 mL), degassed by three freeze−pump−thaw cycles, and reacted at 60 °C for 4 h. After that the reaction was quenched by cooling to 0 °C. The reaction mixture was diluted with CH_2Cl_2 and precipitated in pentane three times. Products with different PNIPAm block lengths were achieved by controlling the reaction time and the amount of NIPAm added.

The trithiocarbonate end groups of PON-CTAs were removed by aminolysis and Michael addition.[49] PON-CTA (1.5 g, 0.04 mmol), *n*-propylamine (0.1 g, 2 mmol), and tris(2-carboxyethyl)phosphine hydrochloride (11 mg, 0.04 mmol) were dissolved in THF (15 mL). The reaction mixture was stirred for 1.5 h at room temperature under a nitrogen atmosphere. Methyl acrylate (0.6 mL, 7 mmol) was added to the reaction mixture and stirred at room temperature for 36 h. Most of the THF was removed under vacuum. The residual mixture was diluted with CH_2Cl_2 (15 mL) and precipitated three times in pentane.

The product of each reaction step was confirmed by ^{1}H NMR spectroscopy and characterized by size exclusion chromatography (SEC) (Figures S1 and S2 in the Supporting Information). Samples investigated in this work are listed in Table 1 along with the molecular characteristics.

Table 1. Molecular Parameters of PO and PON Block Polymers

sample[a]	N_{PEP}[b]	N_{PEO}[b]	N_{PNIPAm}[b]	f_{PEP}[c]	f_{PEO}[c]	f_{PNIPAm}[c]	PDI[d]
PO(3−25)	45	565		0.14	0.86		1.02
PON(3−25−4)	45	565	33	0.13	0.76	0.12	1.05
PON(3−25−10)	45	565	83	0.11	0.63	0.26	1.05
PON(3−25−21)	45	565	187	0.08	0.49	0.43	1.05

[a] The numbers in parentheses correspond to the molecular weight of PEP, PEO, and PNIPAm, respectively, in kg/mol as determined by ^{1}H NMR spectroscopy. [b] Number-average degree of polymerization as determined by ^{1}H NMR spectroscopy end-group analysis. [c] The volume fraction was calculated using the molecular weight and the RT densities: ρ(PEP) = 0.856 g/cm^3,[50] ρ(PEO) = 1.12 g/cm^3,[51] and ρ(PNIPAm) = 1.07 g/cm^3.[52] [d] The PDI was measured by SEC with THF/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine as the eluting solvent.

Solution Preparation. The 0.5 wt % PON micelle solutions were prepared by two different protocols: thin-film hydration (TF) and dialysis (DI). In the thin-film hydration protocol, appropriate amounts of bulk polymer were dissolved in CH_2Cl_2, followed by evaporation of the solvent to yield a thin film on the walls of the vial. The thin film was then hydrated, and the resulting mixture was stirred at room temperature for at least 2 weeks before further characterization. In the dialysis procedure, the bulk polymer was dissolved in THF and then dialyzed against water. Water was changed twice a day for 5 days. After dialysis, the micelle solution was stirred at room temperature for at least 1 week prior to further analysis. The concentration of PON micelle solutions was varied from 0.005 to 0.5 wt %. The lower concentration samples were made by dilution of a 0.5 wt % solution prepared through the above-mentioned TF or DI procedure.

Dynamic Light Scattering. The micellization and micellar aggregation of the PO diblock and PON triblock terpolymers were investigated by dynamic light scattering (DLS). The solutions were passed through 0.45 μm filters into glass tubes with a diameter of 0.25 in. DLS measurements were carried out using a home-built photometer equipped with an electrically heated silicon oil bath, a Lexel 75 Ar^+ laser operating at 488 nm, a Brookhaven BI-DS photomultiplier, and a

Brookhaven BI-9000 correlator. Experiments were performed at various temperatures from 25 to 60 °C, and the intensity correlation functions $g^2(t)$ were recorded at three scattering angles between 60° and 120°. The hydrodynamic radius R_h was extracted using the cumulant method following the procedure described in the Supporting Information.[53] The angular dependence indicated that the relaxation in these samples is diffusive (Figure S3).

Cryo-TEM. Cryo-TEM samples were prepared in a controlled environment vitrification system (CEVS) at room temperature.[54] A micropipet was used to load a drop of micelle solution (ca. 5 μL) onto a lacey Formvar carbon-supported TEM grid. The excess solution was blotted with a piece of filter paper, resulting in the formation of thin films with thicknesses of ca. 100−300 nm in the mesh holes. After at least 20 s was allowed for relaxation of any stresses induced during the blotting, the samples were quickly plunged into a reservoir of liquid ethane cooled by liquid nitrogen. The vitrified samples were then stored in liquid nitrogen until they were transferred to a cryogenic sample holder (Gatan 626) and examined with a JEOL 1210 TEM instrument operated at an acceleration voltage of 120 kV at about −178 °C. The phase contrast was enhanced by acquiring images at a nominal underfocus of 6−15 μm. Images were recorded on a Gatan 724 multiscan CCD camera and processed with DigitalMicrograph, version 3.3.1. More than 50 micelles were measured to obtain the average diameter. The mean aggregation number was calculated using the following equation

$$p = \rho_{PEP} \times \frac{\frac{4}{3}\pi(d/2)^3 \times N_A}{M_{PEP}} \quad (1)$$

where ρ is the polymer density, d is the diameter of the micelle core, N_A is Avogadro's number, and M is the polymer molecular weight.

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic route for PON triblock terpolymers by a combination of anionic and RAFT polymerizations. It should be noted that the trithiocarbonate end group of the resulting PON-CTA was removed by aminolysis and Michael addition to afford PON triblock terpolymers free of the hydrophobic dodecyl chains associated with the CTA. The absence of methylene protons next to the trithiocarbonate unit (δ = 3.3 ppm) and the presence of methylene protons of the added acrylate (δ = 2.6, 2.8 ppm) (Figure S2), along with the disappearance of the absorption band of the trithiocarbonate group centered at ca. 310 nm (Figure S4), indicated the complete removal of the dodecyl end groups.

We recognized the importance of removal of the dodecyl end groups stemming from the RAFT agent as this hydrophobic moiety impeded the micellization behavior of the PON triblock terpolymers. For example, PON-CTA samples are not fully dispersible in water using the TF technique even after several months. PON samples, on the other hand, can be dispersed in less than 1 h. Using DI, PON-CTAs can be dispersed in water, but the hydrophobic end group was still a concern since it has been shown that alkyl-terminated PNIPAm could form micelles with alkyl end groups as the hydrophobic cores when the alkyl end groups contain 12 carbons or more.[55]

The PON(3−25−10) micelle solutions were characterized by dynamic light scattering (DLS). The measured correlation functions were analyzed by the cumulant method. This analysis yielded the average hydrodynamic radius R_h and the width of the size distribution (the reduced second cumulant μ_2/Γ^2). Micelles prepared by the DI method gave a R_h value of ca. 30 nm, and those prepared by the TF method gave R_h = 51−62 nm (Table S1). A comparison of the hydrodynamic radius distribution between the two preparation procedures, obtained by the application of inverse Laplace transformation (REPES) directly to the correlation functions,[56] is shown in Figures 2 and Figure S5. This difference is consistent with the recent reports from Meli and Lodge, who studied how the size of the PB−PEO micelles in ionic liquids depends on the preparation procedure.[57,58] At room temperature we expect that PON triblock copolymers form micelles with an insoluble PEP core and a solvated PEO−PNIPAm corona. Using the DI technique, we anticipate that as the THF is exchanged with water the interfacial tension between the PEP block and the solvent increases gradually, and micelles were formed at a relatively low interfacial energy between the PEP and the THF/H_2O solvent mixture. This results in a lower aggregation number and thus smaller micelles. On the other hand, the high incompatibility between the PEP and pure water in the TF technique leads to structures with larger hydrodynamic radii due to the high interfacial tension. This is also true for PO(3−25) diblock copolymer micelles with the size of DI-prepared micelles being much smaller than the TF-prepared micelles (Table S1 and Figure S6).

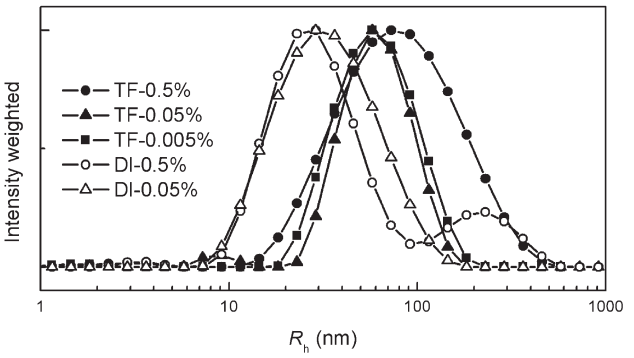


Figure 2. Hydrodynamic radius distributions for PON(3−25−10) triblock terpolymer micelles at 25 °C (θ = 60°). TF-0.5%, TF-0.05%, and TF-0.005% denote the samples prepared by thin-film hydration with the concentration of 0.5, 0.05, and 0.005 wt %, respectively. DI-0.5% and DI-0.05% denote the samples prepared by dialysis with the concentration of 0.5 and 0.05 wt %, respectively.

The size of the TF-prepared PON(3−25−10) micelles exhibits a strong concentration dependence. At a concentration of 0.5 wt %, large micelles (R_h = 62 nm) with a very broad size distribution (μ_2/Γ^2 = 0.49) were formed. As shown in Figure 2 and Figure S5, decreasing the concentration to 0.05 and 0.005 wt % resulted in the formation of micelles with smaller hydrodynamic radii ($R_h \approx$ 50 nm) and much narrower size distributions ($\mu_2/\Gamma^2 \approx$ 0.2). The decrease in R_h and size polydispersity upon dilution can be achieved by an increase in the number of micelles through either fission of the large aggregates or nucleation and growth of new micelles. However, theoretical studies suggest that fusion and fission mechanisms are inefficient kinetic pathways to micelle equilibration,[59] and nucleation and growth of new micelles require expulsion of unimers from a given aggregate, which should be very slow due to the extremely low critical micellar concentration (cmc) of block copolymer solutions.[60,61] Therefore, both processes are highly unlikely in this case. Cryo-TEM observations of these TF-prepared micelles at 0.5 and 0.05 wt % are shown in Figure 3. At both concentrations, the micelles showed the same spherical morphology with similar core radii ($R_c \approx 8 \pm 2$ nm) and thus similar mean aggregation number ($p \approx 350$). In contrast, we observed no significant concentration

dependence of TF-prepared PO(3−25) diblock copolymer micelles (Figure S6).

This concentration dependence seen in the PON samples at room temperature could be explained by the formation of a small number of micelle aggregates. Several groups have reported that PNIPAm-containing block copolymers can form "abnormal aggregates" at low temperature where all the blocks are ostensibly soluble in water. Topp et al. first reported that PEO-*b*-PNIPAm showed aggregation in water below the LCST of PNIPAm,[9] and Annaka et al. reported the formation of disordered micelles from PEO-*b*-PNIPAm at about 17 °C and attributed it to the asymmetric swelling of PEO and PNIPAm chains: PNIPAm chains are less well-dissolved than are the PEO chains.[14] Recently, Liang and Du studied the chain conformations of PEO-*b*-PNIPAm and PNIPAm-*b*-PEO-*b*-PPO-*b*-PEO-*b*-PNIPAm in water, respectively, and found that loose associates were also formed at low temperature.[17,18] They suggested the incompatibility between PEO and PNIPAm was the driving force for the associate structures containing PEO-rich domains and PNIPAm-rich domains. It is likely that these aggregated structures were also formed in PON micelles at a concentration of 0.5 wt % resulting from the formation of PNIPAm-rich domains. However, the PNIPAm chains are still hydrophilic, so the aggregation should be weak, and only a slight increase in R_h was observed upon increasing concentration. The PNIPAm chains are solvated by a large amount of water and should adopt a loose or extended conformation, and we suggest micelle aggregates with a broad size distribution were formed.

In contrast to the TF prepared micelles, the DI-prepared PON(3−25−10) micelles do not exhibit such dependence of size on concentration (Table S1). However, the hydrodynamic radius distribution gave a small peak centered at around 200 nm for DI-prepared micelles at 0.5 wt % that was not apparent at 0.05 wt % (Figure 2). These larger micelles can also be attributed to micelle aggregates as discussed above.

DLS experiments were also performed above room temperature on PO and PON micelle solutions. Figure 4 compares the temperature-dependent hydrodynamic radii and relative scattering intensity of TF-prepared PO(3−25) and PON micelles (Table S2). Both R_h and scattering intensity for PO(3−25) and PON(3−25−4) micelles were nearly constant up to 60 °C. On the other hand, R_h and scattering intensity for PON(3−25−10) and PON(3−25−21) micelles both increased around 42 and 36 °C, respectively. This was also confirmed by a comparison of the hydrodynamic radius distribution of these micelles at different temperatures (Figure S7) and cloud point measurements (Figure S8). In addition, we observed a hysteresis loop where the critical aggregation temperature is lower by 3−4 °C during cooling than upon heating (Figure S9). This is also consistent with the transmittance measurement (Figure S8). The increase of R_h and scattering intensity upon heating can be explained in terms of micellar aggregation. On increasing the temperature above the LCST, the PNIPAm chains can minimize their contact with water by forming larger multimicellar aggregates. On the basis of the micelle aggregation number and hydrodynamic radius, the effective volume fraction of micelles can be calculated; the effective micelle volume fraction of 0.5 wt % PON(3.2−25−10) micelle is 22%. Such a high micelle volume fraction clearly indicates that some micelle aggregation will occur above the LCST of PNIPAm.

We observed a strong molecular weight dependence of the critical micellar aggregation temperature in the PON triblock terpolymers. The critical micellar aggregation temperatures for PON(3−25−21) and PON(3−25−10) were determined from Figure 4 to be 36 and 42 °C, respectively. For PON(3−25−4) no such micellar aggregation was observed up to 60 °C. The commonly reported value of the LCST of PNIPAm is 32 °C.[5,6] The relatively high critical micellar aggregation temperatures for

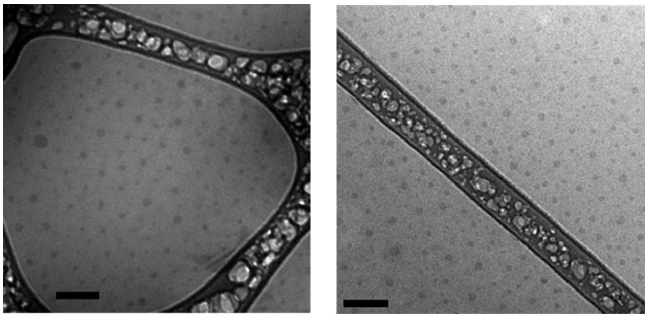


Figure 3. Cryo-TEM images of PON(3−25−10) triblock terpolymer micelles prepared by thin-film hydration at room temperature: left, 0.5 wt %; right, 0.05 wt %. Scale bars: 100 nm.

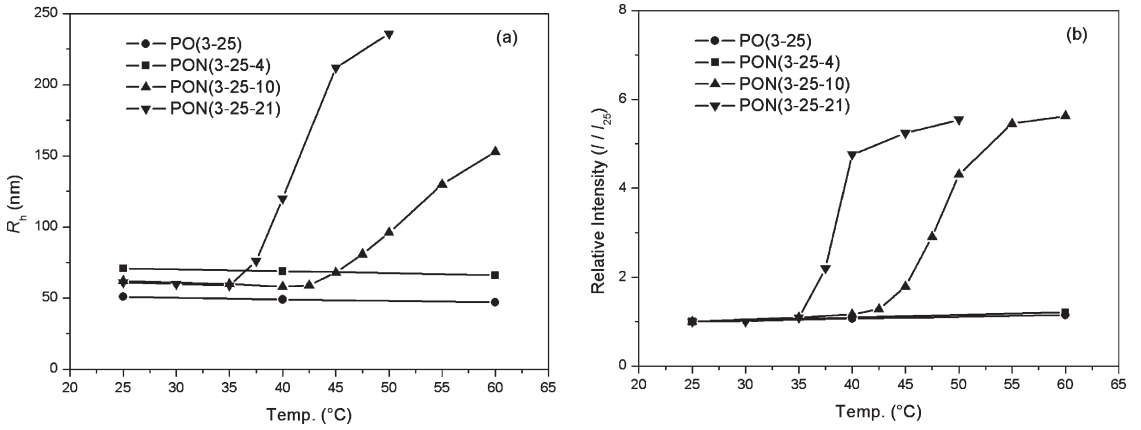


Figure 4. Temperature dependence of hydrodynamic radius (a) and intensity (b) for PO and PON micelles prepared by thin-film hydration with a concentration of 0.5 wt %. R_h was calculated from three different angles (60°, 90°, 120°) by the cumulant method. Intensity is measured at a 90° scattering angle, and the vertical axis is the relative intensity (I/I_{25}) where I_{25} is the intensity recorded at 25 °C.

the PON micelles is attributable to two factors. First, the low molecular weight of PNIPAm leads to a higher LCST. Stover et al. studied the molecular weight dependence of the LCST for PNIPAm prepared by atom transfer radical polymerization (ATRP). They reported a strong decrease of the phase transition temperature with increasing molecular weights (when the molecular weight increased from 2.8 to 26.5 kg/mol, the cloud point dropped from 43.0 to 33.3 °C).[62] Second, it has been shown that the incorporation of hydrophilic groups into PNIPAm raised the LCST of PNIPAm.[21] Tenhu et al. observed a very slight increase of the LCST (from 32 to 34 °C) with increasing PEO content in PEO-*b*-PNIPAm samples,[13] and Yang et al. reported a very strong LCST dependence on PEO content in similar PEO-*b*-PNIPAm systems. They found that the LCST of PNIPAm in these diblock copolymers were around 37 °C with 7.6 wt % PEO and a 24 kg/mol PNIPAm, while it was higher than 90 °C with 27 wt % PEO and a 5 kg/mol PNIPAm.[16] Both the relatively low molar mass of the PNIPAm blocks and the presence of PEO in the PON samples should lead to critical micelle aggregation temperatures that are higher than the LCST of higher molar mass PNIPAm, consistent with our results.

The critical micellar aggregation temperature of PON triblock terpolymers was also dependent on concentration. We found that the critical micellar aggregation temperature of TF-prepared PON(3−25−10) micelles increased from 42 to 47 °C as the polymer concentration decreased from 0.5 to 0.05 wt % (Table S3, Figure S10 and Figure S11). This was also true for the DI-prepared PON(3−25−10) micelles, where 0.5 and 0.05 wt % PON solutions had a critical micellar aggregation temperature of 45 and 47 °C, respectively (Table S3, Figure S12 and Figure S13). The higher critical micellar aggregation temperature of PON micelles at lower polymer concentration is consistent with the concentration dependence of the LCST of PNIPAm in homopolymer and PEO-*b*-PNIPAm below 1 wt %.[5,10,11,15]

As we have discussed in the Introduction, there are three possible thermo-induced structured changes of triblock terpolymer micelles with PNIPAm coronas: PNIPAm collapse around the hydrophobic core to form flowerlike micelles or collapse around the hydrophilic shell to form thin layers or sticky patches above the LCST of PNIPAm (see Figure 1). These changes could lead to a decrease in micelle size in very dilute solution. However, we are not able to resolve any micelle shrinkage even at a concentration of 0.005 wt % (Figure S14). Instead, only the aggregation of micelles was observed in the investigated concentration range (0.5−0.005 wt %). It is possible that micelle shrinkage is overshadowed by micelle aggregation. The observed micelle aggregation suggests that the formation of flowerlike micelles above the LCST of PNIPAm is unlikely because the collapsed PNIPAM is surrounded by the hydrophilic shell and thus cannot aggregate around the PEP core at higher temperatures. Although we do not know the detailed structure of micelle aggregates above the LCST of PNIPAm, we speculate that PNIPAm is likely to collapse into sticky patches instead of a thin layer. This would be entropically favored for the PEO midblocks.

SUMMARY

We have synthesized well-defined PON triblock terpolymers using a combination of anionic and RAFT polymerization and studied the micellization and micellar aggregation of these polymers in dilute aqueous solution by DLS and cryo-TEM. At room temperature, micelles with hydrophobic PEP cores, hydrophilic PEO shells, and PNIPAm coronas were formed. We found that the DI-prepared PON micelles were much smaller than the TF-prepared PON micelles due to the lower interfacial energy between the hydrophobic PEP block and the solvent in the course of micelle formation. In addition, the PON micelles formed some aggregated species at a concentration of 0.5 wt % even below the LCST. At temperatures higher than the LCST of PNIPAm, micellar aggregation occurred, resulting in an increase in R_h and scattering intensity. The critical micellar aggregation temperature depended on both the molecular weight of PNIPAm and polymer concentration. The longer PNIPAm block length and higher polymer concentration resulted in a lower critical micellar aggregation temperature. The micellar aggregation can lead to the formation of multicompartment hydrogels in the concentrated solution. The morphological and rheological properties of these hydrogels are currently under investigation.

ASSOCIATED CONTENT

Supporting Information. Table giving DLS results for PO and PON micelles at room temperature and elevated temperature; ^{1}H NMR and UV−vis spectra of PON-CTA and PON triblock terpolymers; SEC results of the synthesized polymers; DLS results of PO and PON micelles at 0.5, 0.05, and 0.005 wt % and a temperature range between 25 and 60 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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