Amphiphilic Diblock Copolymers Based on Poly(2-ethyl-2-oxazoline) and Poly(1,3-trimethylene carbonate): Synthesis and Micellar Characteristics

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Received March 22, 2000; Revised Manuscript Received August 3, 2000

ABSTRACT: Amphiphilic diblock copolymers with various block compositions were synthesized on the basis of poly(2-ethyl-2-oxazoline) (PEtOz) as a hydrophilic block and poly(1,3-trimethylene carbonate) (PTMC) as a hydrophobic block. Their aqueous solutions were characterized using fluorescence techniques and dynamic light scattering. The block copolymers formed micelles with critical micelle concentrations (cmc's) in the range 2.8−25 mg/L in an aqueous phase. As the length of the hydrophobic PTMC block became longer, lower cmc values were generated. The mean diameters of the micelles were in the range 199−210 nm, with a narrow distribution. The partition equilibrium constants (K_v) of pyrene in the micellar solutions of the block copolymers were 0.91×10^5−1.61×10^5. The K_v value increased as the length of the hydrophobic block increased. The steady-state fluorescence anisotropy values (r) of 1,6-diphenyl-1,3,5-hexatriene (DPH) in PEtOz−PTMC solutions were 0.292−0.302. The anisotropy values were not significantly influenced by the length of the hydrophobic block. The micelles underwent hydrogen bonding at pH < 3.6 with poly(acrylic acid) resulting in polymer complex precipitates, which could be reversibly dispersed as micelles at pH > 3.9.

Introduction

Amphiphilic block copolymers in selective solvents for one of the blocks undergo macromolecular assembly to generate polymeric micelles and micelle-like aggregates on which recent intensive studies have been carried out.[1−17] Especially, the unique characteristics of polymeric micelles in an aqueous phase such as nanosize, thermodynamic stability due to low critical micelle concentration, and the core−shell structure have found numerous application fields, including separation technology and the area of drug delivery.[1−11] The hydrophilic block constructing the micellar outer shell in an aqueous media plays a critical role in the interaction with the surrounding environment and hence determines the solution properties and stability of the micelles.[8] Most micelle-forming block copolymers prepared so far are based on hydrophilic poly(ethylene oxide) (PEO), and the structural variations have been made mainly with the hydrophobic block such as polyesters, polystyrene, poly(amino acids), poly(propylene oxide), and polyalkanes.[2−5,18−21] Therefore, there exists a need to systematically diversify the hydrophilic block of amphiphilic block copolymers, thereby widening the class of micelle-forming block copolymers and expecting unique properties of their micelles in an aqueous media. In this study, we describe the synthesis and the micellar characterization of novel amphiphilic block copolymers, based on hydrophilic poly(2-ethyl-2-oxazoline) (PEtOz), for which only a few amphiphilic block copolymers have been reported.[22−25] In addition, PEtOz in an acidic aqueous phase has the capability to undergo hydrogen bonding with carboxyl H-donor functionality, i.e., poly(methacrylic acid) (PMAA) or poly(acrylic acid) (PAA).[26,27] Therefore, the introduction of PEtOz as a hydrophilic block to amphiphilic block copolymers may provide us with a route to the further structural modification of the hydrophilic outer shell of polymeric micelles. In a recent report, we described the micellar characteristics of amphiphilic diblock copolymers in an aqueous phase based on PEtOz as a hydrophilic block and aliphatic polyester such as poly(L-lactide) (PLA) or poly(ϵ-caprolactone) (PCL) as a hydrophobic block.[25] These block copolymers formed micelles, in which hydrophobic PLA or PCL constructed an inner core of micelles. In this work, poly(2-ethyl-2-oxazoline), PEtOz, was employed as a hydrophilic block, and poly(1,3-trimethylene carbonate) (PTMC) was selected as a hydrophobic block. The living cationic ring-opening polymerization of 2-ethyl-2-oxazoline provides a facile route for the preparation of hydroxyl-terminated PEtOz, which then initiates the ring-opening polymerization of 1,3-trimethylene carbonate in the presence of a Lewis acid catalyst to provide amphiphilic AB block copolymers, PEtOz−PTMCs. Micellar characteristics of these AB block copolymers in an aqueous phase were investigated by fluorescence techniques and dynamic light scattering. In addition, a detailed study was performed on the hydrogen-bonding behavior of micellar shell-forming PEtOz with PAA.

Experimental Section

Materials and Equipment. 2-Ethyl-2-oxazoline (Aldrich) was dried and distilled over calcium hydride. Methyl *p*-toluenesulfonate (Aldrich) was vacuum distilled. 1,3-Trimethylene carbonate was synthesized and purified following a reference method.[28] Acetonitrile and chlorobenzene were distilled under calcium hydride and calcium chloride, respectively. Other solvents, such as THF and diethyl ether, were used without further purification. Stannous octoate (Sigma), pyrene (Aldrich), and 1,6-diphenyl-1,3,5-hexatriene (DPH) (Aldrich) were used as received. ^{1}H NMR spectra were obtained on a Bruker AC 250 spectrometer at 250 MHz. Molecular weight

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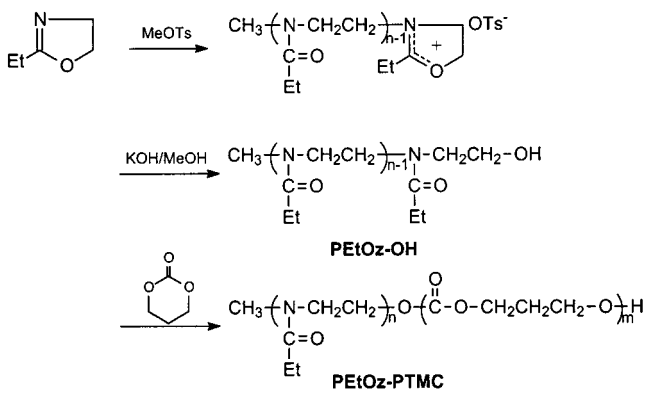
10.1021/ma000517v CCC: $19.00
Published on Web 09/14/2000

Scheme 1



distributions were determined using a GPC equipped with a Waters Associates 410 RI detector, 510 HPLC pump, and μ-Styragel columns with pore sizes of 10^2, 500, 10^3, and 10^4 Å. The eluent was THF, and the molecular weights were calibrated with polystyrene standards. UV−vis spectra were obtained using a Hewlett-Packard 8452A spectrophotometer. Pyrene fluorescence spectra and steady-state fluorescence anisotropy values of DPH were recorded on an ISS K2 spectrofluorometer. The hydrodynamic diameters of micellar particles were obtained using a He−Ne laser (Research Electro-Optics 35 mW) and a BI-200SM Brookhaven apparatus. Transmission electron microscopy (TEM) was performed on a Philips CM 200, operating at an acceleration voltage of 80 kV.

Preparation of Amphiphilic AB Diblock Copolymers. The diblock copolymers of 2-ethyl-2-oxazoline/1,3-trimethylene carbonate (PEtOz−PTMC) were prepared following a procedure reported previously.[27] As a representative example, the block copolymer, PEtOz−PTMC-0.46, which has 0.46 mole ratio of 1,3-trimethylene carbonate to 2-ethyl-2-oxazoline, was synthesized by the following procedure: At room temperature, 1,3-trimethylene carbonate (2.57 g, 25 mmol) was added under nitrogen to an azeotropically dried chlorobenzene solution of PEtOz−OH (5.00 g), which has a hydroxyl group at the end of PEtOz chain. The temperature was raised at reflux, and stannous octoate (7 mg) was added under nitrogen. The reaction was maintained for 30 h. The block copolymer was isolated by precipitation into diethyl ether twice. Other block copolymers, which have different chain lengths of hydrophobic PTMC block, PEtOz−PTMC-0.15 and PEtOz−PTMC-0.71, were synthesized in an identical manner except that different feed molar ratios of 1,3-trimethylene carbonate to the oxazoline unit of PEtOz−OH were employed.

Fluorescence and Light Scattering Measurements. The samples for fluorescence and light scattering measurements were prepared according to a reference method.[25] For the measurement of pyrene excitation spectra, emission and excitation slit widths were set at 2 and 0.5 mm, respectively. For excitation spectra, λ_{em} = 393 nm. A steady-state fluorescence anisotropy value (r) was determined in the L-format geometry of detection.[29] The excitation wavelength was 360 nm, and the emission was measured at 430 nm. Dynamic light scattering measurements were performed following a literature procedure.[25]

Transmission Electron Microscopy. For the observation of size and distribution of micellar particles, a drop of sample solution (concentration = 1 g/L) was placed onto a 200 mesh copper grid coated with carbon. About 2 min after deposition, the grid was tapped with a filter paper to remove surface water, followed by air-drying. Negative staining was performed by using a droplet of a 5 wt % uranyl acetate solution. The samples were air-dried before measurement.

Hydrogen Bonding of PEtOz Shell of Micelles with PAA. The aqueous block copolymer solutions (10 mL), with concentrations of 5 g/L, were mixed with PAA (M_n = 5000). The repeating unit of PAA was equimolar with respect to that of the block copolymers. The pH of the solutions was then adjusted in the range of 1.8−3.9. The pH, where complex formation of micelles and PAA occurred, was determined by detecting the formation of white precipitates. The precipitated complex of micelles and PAA was recovered, shaped as a pellet, and vacuum-dried at 50 °C for 48 h. The yields were calculated by the ratio of the weight of the recovered complex to the total weight of the initial block copolymer and PAA. The redispersion of the complex was performed in a phosphate-buffered saline (PBS) solution (pH 7.4). The redispersed aqueous solutions were characterized by dynamic light scattering.

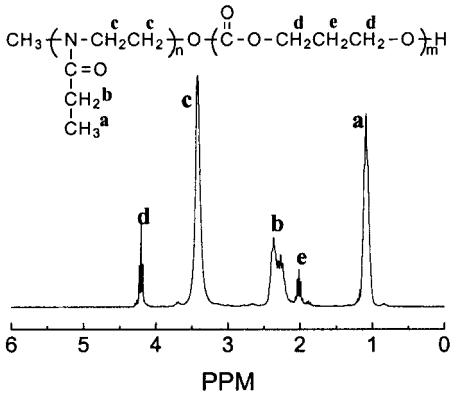


Figure 1. ^{1}H NMR spectrum of PEtOz−PTMC-0.15.

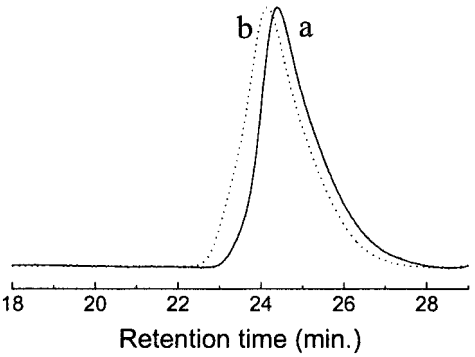


Figure 2. Gel permeation chromatograms of (a) PEtOz−OH and (b) PEtOz−PTMC-0.71.

Results and Discussion

Synthesis and Characterization of Block Copolymers. The synthesis of amphiphilic PEtOz−PTMC block copolymers is illustrated in Scheme 1. The polymerization of 2-ethyl-2-oxazoline was carried out with methyl tosylate as the initiator to produce poly(2-ethyl-2-oxazoline) with oxazolinium living end groups, which were then terminated by methanolic KOH to introduce hydroxyl groups at the chain end.[25] The hydroxyl groups of PEtOz-OH (M_n = 5400) were used as initiation sites for the ring-opening polymerization of 1,3-trimethylene carbonate with stannous octoate as a catalyst to produce the block copolymers, PEtOz−PTMCs. The block copolymers were prepared by varying the length of the hydrophobic PTMC block, while that of the hydrophilic PEtOz block (M_n = 5400) was fixed. The molecular weights and block compositions of the block copolymers were determined by the analysis of ^{1}H NMR spectra. The ^{1}H NMR spectrum of PEtOz−PTMC-0.15 in Figure 1, as a representative example, shows the characteristic resonance peaks of PEtOz−PTMC block copolymers.

The molar ratios of repeating units in PEtOz and PTMC blocks were determined by the peak integration ratios of methyl protons in PEtOz block and trimethylene protons in PTMC block. All the copolymers have

Table 1. Molecular Weights and Compositions of Block Copolymers

block copolymers[a]	feed ratio[b] ([TMC]/[EtOz])	M_n[c]	composition ratio[d]	mole fraction of TMC units[e] (%)	M_w/M_n[f]
PEtOz−PTMC-0.15	0.2	6200	0.15	13	1.21
PEtOz−PTMC-0.46	0.5	8000	0.46	32	1.23
PEtOz−PTMC-0.71	0.8	9200	0.71	42	1.29

[a] All the samples were prepared by using PEtOz−OH with M_n of 5400. [b] Molar feed ratio of 1,3-trimethylene carbonate to the repeating unit of PEtOz−OH. [c] Estimated by ^{1}H NMR. [d] Molar composition ratio of the repeating units of PTMC to that of PEtOz by ^{1}H NMR analysis. [e] Mole fraction of TMC repeating units in the block copolymers by ^{1}H NMR analysis. [f] Estimated by GPC.

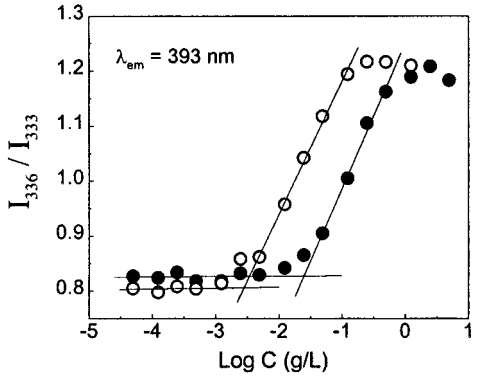


Figure 3. Plot of I_{336}/I_{333} (from pyrene excitation spectra) vs log C for PEtOz−PTMC-0.15 (●) and PEtOz−PTMC-0.71 (○).

identical PEtOz blocks with M_n = 5400 and M_w/M_n = 1.19 and showed molecular weight distributions in the range of 1.21−1.29, as shown in Figure 2.

The block compositions and molecular weights of PEtOz−PTMCs are summarized in Table 1.

Micellar Characteristics of Block Copolymers. The amphiphilic PEtOz−PTMC block copolymers can undergo self-association by a hydrophobic PTMC block, leading to the formation of a micellar structure in an aqueous phase. The characteristics of the block copolymer micelles in an aqueous phase were investigated using fluorescence techniques and dynamic light scattering. The critical micelle concentrations (cmcs) of the block copolymers in an aqueous phase were determined by the characteristic feature of pyrene excitation spectra.[3,18−20,30] Upon micellization, the pyrene molecules preferably locate inside or close to the hydrophobic inner core of micelles, resulting in the change of their photophysical characteristics. The characteristic feature of pyrene excitation spectra, (0,0) band shift from 333 to 336 nm upon pyrene partition into micellar inner core, was utilized to determine the cmc values of PEtOz−PTMCs. Figure 3 shows the intensity ratios (I_{336}/I_{333}) of pyrene excitation spectra versus the logarithm of PEtOz−PTMC-0.15 and PEtOz−PTMC-0.71 block copolymer concentration.

The cmc was determined from the concentration of the interception of two straight lines at the low concentration range in Figure 3.

As summarized in Table 2, the cmc values of the block copolymers, depending on the block composition, were in the range 2.8−25.0 mg/L, which were much lower than those of low molecular weight surfactants, e.g., 2.3 g/L for sodium dodecyl sulfate (SDS) in water, and were comparable with those of other polymeric amphiphiles.[3,16−20,31] As the content of hydrophobic PTMC became higher, lower cmc values were generated. The mean diameters (d) of the block copolymer micelles, measured by dynamic light scattering, were in the range 199−210 nm (Table 2). In general, the size of individual core−shell type micelles from amphiphilic diblock copolymers is in the range of several tens of nanometers.[3,19] However, the micelles with a size range of several hundreds of nanometers are often observed due to the intermicellar aggregation in amphiphilic block copolymer systems.[32,33] Therefore, it might be a possible suggestion that the micelles of PEtOz−PTMC would be a multicore structure formed by the association of individual micelles, rather than a simple core−shell structure. In previous reports, micelles with a PEO outer shell are frequently found to form large aggregates in an aqueous phase.[32,33] In particular, Eisenberg et al. recently reported that the formation of large aggregates of individual micelles was more pronounced in the case of micelles with a shell from a relatively short PEO block (M_n = ca. 2000), which could not outweigh the hydrophobic interactions between the exposed hydrophobic cores of micelles.[33] This explanation might also be applied to the case of PEtOz−PTMC block copolymer systems which generate the micelles with the multicore structure. The polydispersity factors (μ_2/Γ^2) of the micelles, estimated by the cumulant method, were fairly low (0.04−0.17), suggesting a narrow size distribution.[19,34,35] The micelles of PEtOz−PTMC block copolymers were observed by TEM as shown in Figure 4. The micelles of PEtOz−PTMC block copolymers were generally spherical.

The hydrophobicity of the micellar core was estimated by measuring the partition equilibrium constant K_v of pyrene, a hydrophobic probe, in the micellar solutions of the block copolymers PEtOz−PTMCs. The K_v value was calculated by the method of Wilhelm et al., where pyrene binding to the micelles was considered as a simple equilibrium between a micellar phase and a water phase.[3] In this approach, the ratio of pyrene concentration in the micellar phase to the water phase ($[Py]_m/[Py]_w$) can be correlated to the ratio of the volume of each phase, as expressed in eq 1.

$$[Py]_m/[Py]_w = K_v V_m/V_w \quad (1)$$

Equation 1 can be rewritten as

$$[Py]_m/[Py]_w = K_v x(c - \mathrm{cmc})/1000\rho \quad (2)$$

where x is the weight fraction of hydrophobic PTMC block, c is the concentration of the block copolymer, and ρ is the density of the PTMC core of micelles, which is assumed to be the value of bulk PTMC (=1.01 g/mL). In the intermediate range of polymer concentration with substantial increases of intensity ratios (I_{336}/I_{333}), $[Py]_m/[Py]_w$ can be written as

$$[Py]_m/[Py]_w = (F - F_{min})/(F_{max} - F) \quad (3)$$

where F_{max} and F_{min} correspond to the average magnitude of I_{336}/I_{333} in the flat region of high and low concentration ranges in Figure 3, and F is the intensity ratio (I_{336}/I_{333}) in the intermediate concentration range of the conjugates. Combining eqs 2 and 3, K_v values of

Table 2. Properties of PEtOz−PTMC Micelles

block copolymers	cmc[a] (mg/L)	d^b (nm)	$\mu_2/\Gamma^{2\,c}$	K_v ($\times 10^{-5}$)	r^d	d^e (nm)	d^f (nm)
PEtOz−PTMC-0.15	25.0	199	0.17	0.91	0.292	247	253
PEtOz−PTMC-0.46	5.6	203	0.14	1.12	0.304	265	224
PEtOz−PTMC-0.71	2.8	210	0.04	1.61	0.302	230	208

[a] Measured at 25 °C. [b] Mean diameters in distilled water at 25 °C. [c] Polydispersity factor. [d] Steady-state fluorescence anisotropy of DPH. [e] Mean diameters in PBS solution at 25 °C. [f] Mean diameters of redispersed micelles in PBS solution at 25 °C.

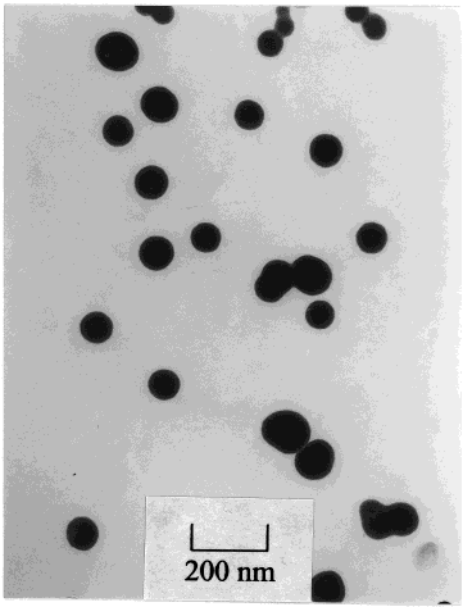


Figure 4. Transmission electron micrograph of PEtOz−PTMC-0.46 micelles.

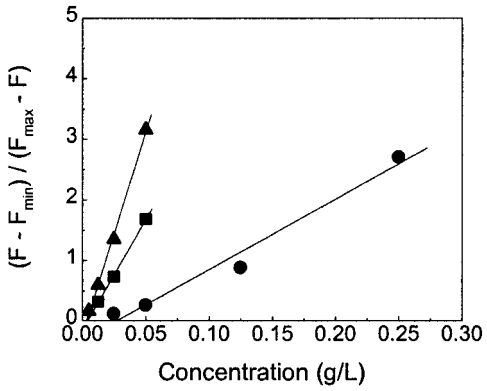


Figure 5. Plots of $(F - F_{min})/(F_{max} - F)$ vs concentration of PEtOz−PTMC-0.15 (●), PEtOz−PTMC-0.46 (■), and PEtOz−PTMC-0.71 (▲) in water.

pyrene are determined by using a plot $(F - F_{min})/(F_{max} - F)$ versus PEtOz−PTMC concentration as shown in Figure 5.

The K_v values, as summarized in Table 2, were in the range 0.91×10^5−1.61×10^5. As the length of the hydrophobic block of the copolymers increases, K_v value increases, suggesting that the hydrophobicities of the micellar core increase. The micelles of poly(2-ethyl-2-oxazoline)-*b*-poly(L-lactide) (PEtOz−PLA) and poly(2-ethyl-2-oxazoline)-*b*-poly(ϵ-caprolactone) (PEtOz−PCL) exhibited K_v values in the range 1.79×10^5−5.88×10^5.[25] Therefore, the inner core of PEtOz−PTMC micelles is less hydrophobic than those of PEtOz−PLA and PEtOz−PCL block copolymers in our experimental range of block composition. For SDS micelles and PEO−polystyrene block copolymer micelles, K_v values were reported as 1.2×10^5 and 3.0×10^5, respectively.[3,36]

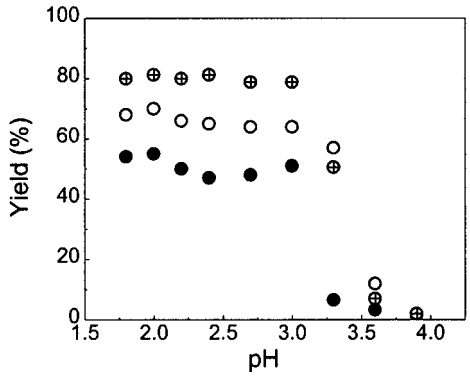


Figure 6. Yield of recovered complex precipitates of block copolymer micelles and PAA as a function of pH: PEtOz−PTMC-0.15 micelles−PAA (●); PEtOz−PTMC-0.46 micelles−PAA (○); PEtOz−PTMC-0.71 micelles−PAA (⊕).

The microviscosity of the micellar core region was estimated by the measurement of the steady-state fluorescence anisotropy of DPH. The anisotropy value increases with increasing the microviscosity of the micellar core because the rotational diffusion of DPH is increasingly hindered.[37] The anisotropy values of DPH, *r*, measured for PEtOz−PTMC micelles, are listed in Table 2. The anisotropy values were not very dependent on the length of the hydrophobic PTMC block, when that of hydrophilic PEtOz block was fixed. In contrast to the micelles from low molecular surfactants such as SDS ($r = 0.070$), PEtOz−PTMC micelles have a hydrophobic core with a fair degree of rigidity.[38] It is noteworthy that the rigidity of the hydrophobic core of PEtOz−PTMC micelles is somewhat higher than that of PEtOz−PLA micelles (ca. 0.270) and poly(1-octadecene-*co*-maleic acid) (0.273) and much higher than that of PEtOz−PCL micelles (ca. 0.190), poly(ethylene-*co*-maleic acid) (0.187), poly(1-decene-*co*-maleic acid) (0.225), and poly(1-octadecene-*co*-maleic acid) (0.273).[25,38]

Hydrogen Bonding of the PEtOz Block of Micelles. Poly(2-ethyl-2-oxazoline) is known to undergo pH-sensitive hydrogen bonding with poly(methacrylic acid) (PMAA) or poly(acrylic acid) (PAA) in acidic water.[26,27] At a low pH (< 5.0), PEtOz was reported to form hydrogen bonding with PMAA to produce precipitates of the polymer complex, which then redissolves at a high pH (> 5.4) due to the disappearance of hydrogen bonding. In a previous study, we have demonstrated that the micelles of PEtOz−PLA and PEtOz−PCL diblock copolymers could form complex precipitates with poly(acrylic acid) at pH below 3.5.[25] These precipitates could be redispersed as micelles in water at pH above 3.8. The PEtOz−PTMC block copolymer micelles have a hydrophilic outer shell of PEtOz blocks, which can form a polymer complex with poly(acrylic acid) through hydrogen bonding. Figure 6 shows the yields of recovered complex precipitates of PEtOz−PTMC micelles and PAA depending on a pH change of aqueous media.

It is obviously shown that the yield of complex precipitates is meaningless at pH above 3.9 but exhibits

an abrupt increase at pH below 3.6. Upon decreasing the pH, the equilibrium of the yield reached at pH of 3.0 for all PEtOz−PTMC block copolymers. As the content of hydrophobic PTMC became higher, the higher the yield of complex precipitates, probably because the micelles with higher hydrophobicity show a higher tendency toward precipitation with the enhanced loss of hydrophilicity, via hydrogen bonding with PAA. The precipitates could be shaped as pellets. When the pellet was placed on a phosphate-buffered saline (PBS) solution (pH 7.4), it was redispersed as micelles as a result of breakage of the hydrogen bonding between the PAA and PEtOz outer shell of the micelles. The redispersion of micelles was confirmed by measuring the hydrodynamic diameters of the micelles and comparing them with those of the micelles before hydrogen bonding with PAA in a PBS solution. As summarized in Table 2, the redispersed solution of complex precipitates contains micelles whose hydrodynamic diameters are comparable to those of micelles that are measured in a PBS solution, even though the diffusion of redispersed micelles in an aqueous phase might be affected by PAA chains. Therefore, in this study, we provide a method by which efficient recovery of a complex of PEtOz-based block copolymer micelles with PAA in a solid state and redispersion as micelles in an aqueous media could be accomplished. This interesting pH-sensitive behavior of PEtOz-based block copolymer micelles could find novel applicability in the area of drug delivery, in that the micelle−polymer complex can act as a matrix for the sustained release of drug-containing micelles at a physiological pH. This type of micelle−polymer complex could have an advantageous property over free micelles since it can act as an implantable matrix, providing an alternative route to the introduction of drug-loaded micelles other than the intravenous administration which has been employed for the introduction of free micelles.

Conclusions

Amphiphilic diblock copolymers were synthesized based on poly(2-ethyl-2-oxazoline) as a hydrophilic block and poly(1,3-trimethylene carbonate) as a hydrophobic block. Their micellar characteristics were investigated using fluorescence techniques and light scattering in an aqueous phase. These block copolymers formed micelles in an aqueous solution with critical micelle concentrations in the range 2.8−25.0 mg/L. As the length of the hydrophobic block increased, a lower cmc value was generated. The mean diameters of micelles were in the range 199−210 nm with a narrow distribution. The K_v values of pyrene estimating the hydrophobicity of the hydrophobic micellar core were in the range 0.91×10^5−1.61×10^5 and increased as the length of the hydrophobic block of copolymers increased. The steady-state fluorescence anisotropy values of DPH in block copolymer solutions were independent of the length of the hydrophobic blocks and reflected the highly limited mobility of the micellar hydrophobic core. The pH-sensitive hydrogen-bonding ability of PEtOz block with poly(acrylic acid) provides an efficient way of recovering micelles at low pH as a complex precipitates, which could then be formed into shapes such as pellets and could again be redispersed as micelles in an aqueous medium at high pH.

Acknowledgment. This work was supported by KIST. C.K. also thanks HOMRC for the support.

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MA000517V