Synthesis and Micellar Characterization of Amphiphilic Diblock Copolymers Based on Poly(2-ethyl-2-oxazoline) and Aliphatic Polyesters[1]

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ABSTRACT: Amphiphilic diblock copolymers were synthesized based on poly(2-ethyl-2-oxazoline) (PEtOz) as a hydrophilic block and aliphatic polyesters such as poly(L-lactide) (PLA) or poly(ϵ-caprolactone) (PCL) as a hydrophobic block. Their micellar characteristics in an aqueous phase were investigated by using dynamic light scattering and fluorescence techniques. The block copolymers formed micelles in the aqueous phase with critical micelle concentrations (cmcs) in the range of 1.0−8.1 mg/L. The cmc values become lower upon increasing the length of the hydrophobic block. The mean diameters of the micelles were in the range of 108−192 nm, with a narrow distribution. In general, the micelle size increased as the hydrophobic PLA or PCL block became larger. The partition equilibrium constants, K_v, of pyrene in the micellar solutions of the block copolymers were from 1.79×10^5 to 5.88×10^5. For each block copolymer system of PEtOz−PLA or PEtOz−PCL, 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) were 0.265−0.284 in PEtOz−PLA solution and 0.189−0.196 in PEtOz−PCL solution. The anisotropy values of PEtOz−PLAs were higher than those of PEtOz−PCLs. The anisotropy values were independent of the length of the hydrophobic block when the chemical structures of the hydrophobic blocks were identical. The micelles underwent hydrogen bonding at pH <3.5 with poly(acrylic acid), which produced polymer complex precipitates that could be reversibly dispersed as micelles at pH >3.8.

Introduction

Recently, polymeric micelles derived from block copolymers in an aqueous phase have attracted much attention, not only because of their unique morphological behavior, but also because of their potential application in separation technologies and the area of drug delivery.[2−12] Block copolymer micelles have several characteristics such as nanosize and thermodynamic stability. In addition, their hydrophobic core is surrounded by a hydrophilic outer shell so that the inner core can serve as a microcontainer for various substances. On the other hand, the solubility of micelles and the interactions of micelles with the external environment are determined by the chemical or physical nature of the hydrophilic outer shell.[9] Therefore, it is important to systematically diversify the structure of amphiphilic block copolymers so that their micellar characteristics can be tailored for specific applications. However, the range of amphiphilic block copolymers which form micelles in an aqueous phase is limited. Most micelle-forming amphiphilic block copolymers are based on hydrophilic poly(ethylene oxide) and the structural variations have been made mainly with hydrophobic blocks such as polyesters, polystyrene, poly(amino acids), poly(propylene oxide), and polyalkanes.[3−6,13−16] In this study, we describe the synthesis and micellar characterization of the amphiphilic block copolymers based on hydrophilic poly(2-ethyl-2-oxazoline) (PEtOz), for which only a few amphiphilic oxazoline block copolymers have been reported.[17−19] In addition, PEtOz in an acidic aqueous phase has the capability to form hydrogen bonding with carboxyl H-donor functionality, i.e., poly(methacrylic acid).[20] This may give us a route to further structural modification of the hydrophilic outer shell of PEtOz−based micelles. In this work, therefore, poly(2-ethyl-2-oxazoline), PEtOz, was employed as a hydrophilic block and a biodegradable aliphatic polyester, such as poly(L-lactide) (PLA) or poly(ϵ-caprolactone) (PCL), was selected as a hydrophobic block. The living cationic ring-opening polymerization of 2-ethyl-2-oxazoline provides a facile synthetic route for the preparation of hydroxyl-terminated PEtOz, which then initiates the ring-opening polymerization of L-lactide or ϵ-caprolactone in the presence of a Lewis acid catalyst to provide amphiphilic AB block copolymers of PEtOz−PLA or PEtOz−PCL. The micellar characteristics of these AB block copolymers in an aqueous phase were investigated by fluorescence techniques and dynamic light scattering.

Experimental Section

Materials and Equipment. 2-Ethyl-2-oxazoline (Aldrich) and ϵ-caprolactone (Aldrich) were dried and vacuum distilled over calcium hydride. Methyl p-toluenesulfonate (Aldrich) was vacuum distilled. L-Lactide (Aldrich) was recrystallized twice from ethyl acetate and then sublimed under reduced pressure. 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), 1,6-diphenyl-1,3,5-hexatriene (DPH) (Aldrich), and 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP) (Aldrich) were used as received. ^{1}H NMR spectra were obtained on a Bruker AC 250 spectrometer. Molecular weights and molecular weight 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 poly-

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styrene standards. UV−vis spectra were obtained using a Hewlett-Packard 8452A spectrophotometer. The pyrene fluorescence spectra, steady-state fluorescence anisotropy values, and fluorescence lifetimes of DPH were recorded on an ISS K2 spectrofluorometer. The hydrodynamic diameters of micellar particles were obtained using a He−Ne laser (Research Electrooptics 35 mW) and a BI-200SM Brookhaven apparatus.

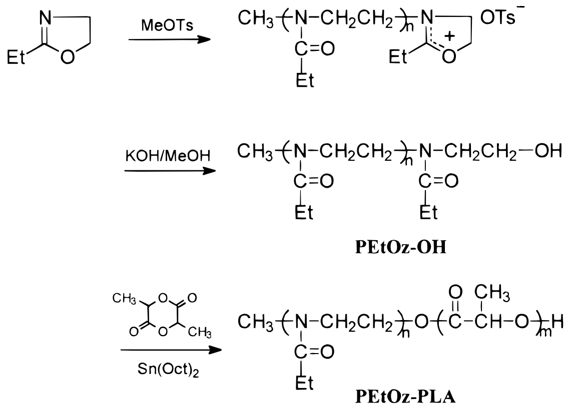
Preparation of Amphiphilic AB Diblock Copolymers. The diblock copolymers of 2-ethyl-2-oxazoline/L-lactide (PEtOz−PLA) and 2-ethyl-2-oxazoline/ϵ-caprolactone (PEtOz−PCL) were prepared by the modification of a literature procedure.[21] For example, the block copolymer, PEtOz−PLA-0.66, which has 0.66 mole ratio of L-lactide to 2-ethyl-2-oxazoline, was prepared by the following procedure: A solution of 2-ethyl-2-oxazoline (60.00 g, 605 mmol) and methyl *p*-toluenesulfonate (2.25 g, 12 mmol) in acetonitrile (200 mL) was stirred at reflux for 30 h under nitrogen. After cooling to room temperature, 0.1 N methanolic KOH was added to introduce hydroxyl groups at the end of the PEtOz chain. The polymer was filtered through the silica gel. The product, PEtOz−OH, was then isolated by precipitation into diethyl ether and then vacuum-dried before use. A solution of PEtOz−OH (2.00 g) in dry chlorobenzene (15 mL) was heated at reflux using a Dean−Stark apparatus. Approximately 10 mL of chlorobenzene was evaporated and the Dean−Stark apparatus was replaced by a condenser. At room temperature, L-lactide (1.02 g, 7 mmol) was added under nitrogen. The temperature was raised at reflux and stannous octoate (4 mg) was added under nitrogen. The reaction was maintained for 30 h. The block copolymer was isolated by precipitation into diethyl ether. Other block copolymers, which have different chain lengths of hydrophobic PLA or PCL block, PEtOz−PLA-0.27, PEtOz−PCL-0.19, PEtOz−PCL-0.49, and PEtOz−PCL-0.66, were synthesized in an identical manner except that different feed molar ratios of L-lactide or ϵ-caprolactone to the oxazoline unit of PEtOz−OH were employed.

Sample Preparation. To prepare micellar solutions, doubly distilled water (20 mL) was added dropwise to a mildly stirred THF solution of block copolymer. Then, THF was removed on a rotary evaporator at 30 °C for 2 h. The micellar solution in doubly distilled water was diluted to obtain a concentration range from 10 to 1×10^{-4} g/L. For the measurement of fluorescence spectra, pyrene solution in THF (1.2×10^{-3} M) was added to doubly distilled water to give a pyrene concentration of 12×10^{-7} M, and THF was removed using a rotary evaporator at 30 °C for 2 h. The pyrene solution was mixed with block copolymer solutions to obtain copolymer concentrations from 5 to 5×10^{-5} g/L. The pyrene concentration of the samples was 6.0×10^{-7} M. All the samples were sonicated for 10 min and were allowed to stand for 1 day before fluorescence measurements. For the measurements of steady-state fluorescence anisotropy and fluorescence lifetime, samples were prepared by adding 4 μL of DPH solution (2.1×10^{-3} M in THF) to the 5 mL block copolymer solutions in water. The DPH concentration of the samples was 1.7×10^{-6} M. The samples were degassed by gentle bubbling of nitrogen for 30 min.

Fluorescence Measurements. All the fluorescence measurements were performed using an ISS K2 spectrofluorometer with a thermostat cell unit. Pyrene and DPH were used as fluorescence probes to analyze the block copolymers in the doubly distilled water. For the measurement of pyrene excitation spectra, emission and excitation slit widths were set at 2 and 0.5 mm, respectively. For the excitation spectra, $\lambda_{em} = 393$ nm and the spectra were accumulated with an integration of 3 s/nm. Steady-state fluorescence anisotropy values of DPH were determined in the L-format geometry of detection. The excitation wavelength was 360 nm and the emission was measured at 430 nm. The anisotropy value (r) was calculated from the following relationship:

$$r = \frac{(I_{VV} - I_{VV}^{S}) - G(I_{VH} - I_{VH}^{S})}{(I_{VV} - I_{VV}^{S}) + 2G(I_{VH} - I_{VH}^{S})} \qquad (1)$$

Scheme 1



where I^S is the contribution of scattered light from a sample solution without DPH, G ($=I_{HV}/I_{HH}$) is an instrumental correction factor, and I_{VV}, I_{VH}, I_{HV}, and I_{HH} refer to the resultant emission intensities polarized in the vertical or the horizontal detection planes (second subindex) when excited with vertically or horizontally polarized light (first subindex).[22] Fluorescence lifetimes of DPH were measured using an ISS K2 fluorometer equipped with a frequency synthesizer (Marconi Instruments, Alendale, NJ) and an ISS-ADC interface for data collection and analysis. The phase-shift and demodulation ratios, using POPOP in ethanol as the reference ($\tau = 1.35$ ns),[23] were recorded at 10 different modulation frequencies, logarithmically spaced (5.0, 7.5, 11.4, 17.1, 25.8, 38.8, 58.5, 88.1, 132.8, and 200.0 MHz). The excitation was operated at 360 nm. The emission was collected through a 408 nm cut-on filter. Fluorescence lifetimes were determined using a nonlinear least-squares program (ISS187) that minimized the reduced χ^2 for an exponentially good fit.

Light Scattering Measurements. Dynamic light scattering measurements were performed using a Brookhaven BI-200SM goniometer and BI-9000AT autocorrelator. All the measurements were carried out at 25 °C. The sample solutions were purified by passing through a Millipore 0.45 μm filter. The scattered light of a vertically polarized He−Ne laser (632.8 nm) was measured at an angle of 90° and was collected on an autocorrelator. The hydrodynamic diameters (d) of micelles were calculated by using the Stokes−Einstein equation $d = k_B T/3\pi\eta D$ where k_B is the Boltzmann constant, T is the absolute temperature, η is the solvent viscosity, and D is the diffusion coefficient. The polydispersity factor of micelles, represented as μ_2/Γ^2, where μ_2 is the second cumulant of the decay function and Γ is the average characteristic line width, was calculated from the cumulant method.[24,25] CONTIN algorithms were used in the Laplace inversion of the autocorrelation function to obtain micelle size distribution.[4]

Results and Discussion

Synthesis and Characterization of Block Copolymers. The synthesis of amphiphilic PEtOz−PLA and PEtOz−PCL block copolymers is illustrated in Scheme 1.

The hydroxyl-terminated poly(2-ethyl-2-oxazoline) (PEtOz−OH) was prepared by the modication of a literature procedure.[21] 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. The hydroxyl groups of PEtOz−OH ($M_n = 4400$) were used as the initiation sites for the ring-opening polymerization of L-lactide or ϵ-caprolactone with a catalyst of stannous octoate to produce the block copolymers, PEtOz−PLA or PEtOz−PCL. The

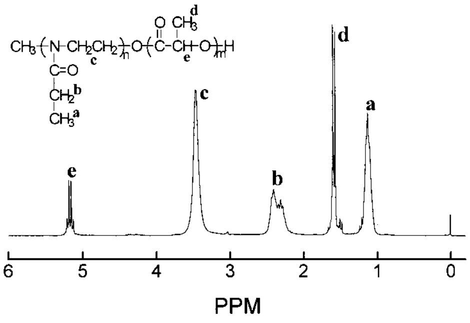


Figure 1. ^{1}H NMR spectrum of PEtOz−PLA-0.66.

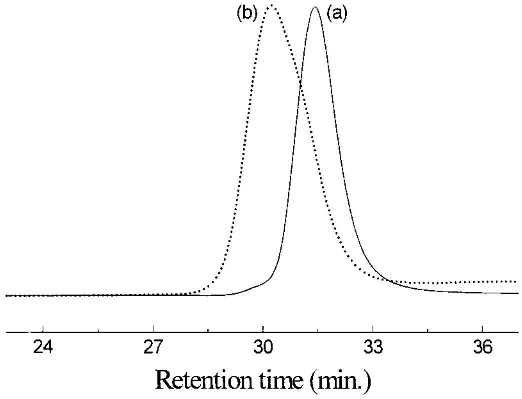


Figure 2. Gel permeation chromatograms of (a) PEtOz−OH and (b) PEtOz−PLA-0.66.

Table 1. Molecular Weights and Compositions of the Block Copolymers

block copolymers[a]	feed ratio[b] [LA]/[EtOz] or [CL]/[EtOz]	M_n[c]	composition ratio[d]	wt % of[e] hydrophobic block	M_w/M_n[f]
PEtOz−PLA-0.27	0.3	5300	0.27	17	1.11
PEtOz−PLA-0.66	0.7	6500	0.66	32	1.16
PEtOz−PCL-0.19	0.2	5400	0.19	19	1.11
PEtOz−PCL-0.49	0.5	6900	0.49	36	1.16
PEtOz−PCL-0.66	0.7	7700	0.66	43	1.39

[a] All the samples were prepared by using PEtOz−OH with M_n of 4400. [b] Molar feed ratio of L-lactide or ϵ-caprolactone to the repeating unit of PEtOz−OH. [c] Estimated by ^{1}H NMR. [d] Molar composition ratio of the repeating units of PLA or PCL to that of PEtOz by ^{1}H NMR analysis. [e] Weight percentage of the hydrophobic PLA or PCL block in the block copolymers. [f] Estimated by GPC.

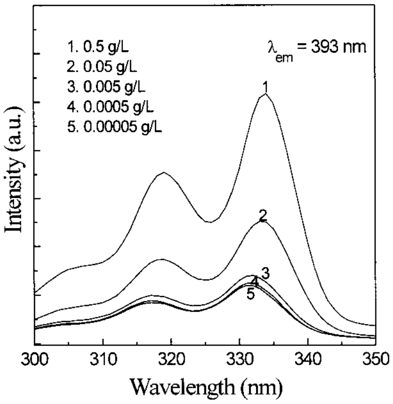


Figure 3. Excitation spectra of pyrene as a function of PEtOz−PLA-0.66 concentration in water.

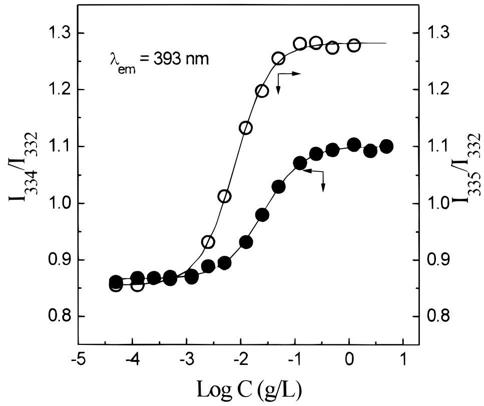


Figure 4. Plot of I_{334}/I_{332} and I_{335}/I_{332} (from pyrene excitation spectra) vs log C for PEtOz−PLA-0.66 (●) and PEtOz−PCL-0.49 (○), respectively.

block copolymers were prepared by varying the length of the hydrophobic PLA or PCL block, while that of the hydrophilic PEtOz block (M_n = 4400) 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−PLA-0.66 in Figure 1, as a representative example, shows the characteristic resonance peaks of a PEtOz−PLA block copolymer.

The molar ratios of repeating units in PEtOz and PLA blocks were determined by the peak integration ratios of methyl protons in each block. The PEtOz−PCL block copolymers were characterized in an identical manner. All the copolymers have identical PEtOz blocks with M_n = 4400 and M_w/M_n = 1.10 and showed narrow gel permeation chromatograms as typified in Figure 2. The high purity of the block copolymers was confirmed by the solubility test. The block copolymers did not form any precipitation in a selective solvent for PEtOz, such as water, reflecting the absence of the hydrophobic polyester homopolymers. On the other hand, when we attempted to dissolve the block copolymers in toluene or benzene, which is a selective solvent for polyester block, the block copolymers with longer polyester block such as PEtOz−PLA-0.66 and PEtOz−PCL-0.66 were only dispersed but did not form precipitates, which excludes the presence of PEtOz homopolymer. The block compositions and molecular weights of PEtOz−PLA and PEtOz−PCL are summarized in Table 1.

Micelles of Block Copolymers. The amphiphilic nature of the block copolymers, consisting of hydrophilic PEtOz and hydrophobic PLA or PCL blocks, provides an opportunity to form micelles in water. The characteristics of the block copolymer micelles in an aqueous phase were investigated by fluorescence techniques and dynamic light scattering. The critical micelle concentrations (cmcs) of the block copolymers in an aqueous phase were determined by a fluorescence technique using pyrene as a probe.[4,13−15,26]

In Figure 3, the excitation spectra of pyrene are shown at various concentrations of PEtOz−PLA-0.66. The characteristic feature of pyrene excitation spectra, (0,0) band shift from 332 to 334 nm upon pyrene partition into micellar hydrophobic core, was utilized to determine the cmc values of PEtOz−PLA block copolymers. For PEtOz−PCL block copolymers, a red shift of (0,0) band from 332 to 335 nm was observed and was considered to determine the cmc values. Figure 4 shows the intensity ratios (I_{334}/I_{332} and I_{335}/I_{332}) of pyrene excitation spectra versus the logarithm of PEtOz−PLA-0.66 and PEtOz−PCL-0.49 block copolymer

Table 2. Properties of PEtOz−PLA and PEtOz−PCL Micelles

block copolymers	cmc[a] (mg/L)	d[b] (nm)	μ_2/Γ^2 [c]	K_v ($\times 10^{-5}$)	r[d]
PEtOz−PLA-0.27	8.1	108	0.14	1.79	0.265
PEtOz−PLA-0.66	4.7	134	0.21	2.63	0.284
PEtOz−PCL-0.19	6.2	149	0.36	2.43	0.196
PEtOz−PCL-0.49	1.2	168	0.13	5.47	0.192
PEtOz−PCL-0.66	1.0	192	0.21	5.88	0.189

[a] Measured at 25 °C. [b] Mean diameters by dynamic light scattering at 25 °C. [c] Polydispersity factor. [d] Steady-state fluorescence anisotropy of DPH.

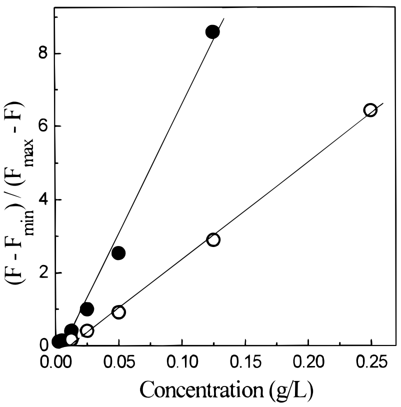


Figure 5. Plots of $(F - F_{\min})/(F_{\max} - F)$ vs concentration of PEtOz−PLA-0.27 (○) and PEtOz−PLA-0.66 (●) in water.

concentration. A negligible change of intensity ratios (I_{334}/I_{332} and I_{335}/I_{332}) was detected at a low concentration range, but at a certain concentration the intensity ratios exhibited a substantial increase, reflecting the incorporation of pyrene into the hydrophobic core region of the micelles. Therefore, the cmc was determined from the crossover point at the low concentration range in Figure 4. The cmc values of the block copolymers were, depending on the block composition, in the range of 1.0−8.1 mg/L (Table 2), 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 other polymeric amphiphiles.[4,13−15,27] As the composition of hydrophobic PLA or PCL 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 of 108−192 nm (Table 2). It is noteworthy that the micelle size increased as the hydrophobic PLA or PCL block became larger, while the length of the hydrophilic PEtOz block was identical ($M_n = 4400$). The polydispersity factors (μ_2/Γ^2) of the micelles, estimated by the cumulant method, were fairly low (0.14−0.36) suggesting narrow size distribution.[13,24,25]

Partitioning of Pyrene in a Micellar Solution. 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−PLAs and PEtOz−PCLs. In this work, the equilibrium constant K_v is calculated by the method of Wilhelm et al.[4] In this method, pyrene binding to the micelles was considered as a simple equilibrium between a micellar phase and a water phase. The ratio of pyrene in the micellar phase to water phase ($[\mathrm{Py}]_m/[\mathrm{Py}]_w$) can be correlated to the ratio of volume of each phase as expressed in eq 2.

$$[\mathrm{Py}]_m/[\mathrm{Py}]_w = K_v V_m/V_w \tag{2}$$

Equation 2 can be rewritten as

$$[\mathrm{Py}]_m/[\mathrm{Py}]_w = K_v xc/1000\rho \tag{3}$$

where *x* is the weight fraction of hydrophobic PLA or PCL block in the block copolymer and ρ is the density of the PLA or PCL core of micelles, which is assumed as the value of bulk polylactide (=1.248) or polycaprolactone (=1.146). In the intermediate range of polymer concentration with substantial increases of intensity ratios (I_{334}/I_{332} for PEtOz−PLA or I_{335}/I_{332} for PEtOz−PCL), $[\mathrm{Py}]_m/[\mathrm{Py}]_w$ can be written as

$$[\mathrm{Py}]_m/[\mathrm{Py}]_w = (F - F_{\min})/(F_{\max} - F) \tag{4}$$

where $F_{\max}$ and $F_{\min}$ correspond to the average magnitude of I_{334}/I_{332} and I_{335}/I_{332}, respectively, in the flat region of high and low concentration ranges in Figure 4, and *F* is the intensity ratio (I_{334}/I_{332} or I_{335}/I_{332}) in the intermediate concentration range of the block copolymers. By combining eqs 3 and 4, K_v values of pyrene are determined by using a plot $(F - F_{\min})/(F_{\max} - F)$ versus polymer concentration in Figure 5.

The K_v values, as summarized in Table 2, were in the range from 1.79×10^5 to 5.88×10^5. For each PEtOz−PLA or PEtOz−PCL system, as the length of the hydrophobic block of the copolymers increases, the K_v value increases, suggesting that the hydrophobicities of the micelles also increase.[15] 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.[4,28]

Microviscosity of Micellar Core. The microviscosity of the micellar core region was estimated by the measurement of the steady-state fluorescence anisotropy originated from the depolarization of DPH fluorescence due to the rotational diffusion of DPH. The anisotropy value increases upon increasing the microviscosity of the micellar core because the rotational diffusion of DPH is increasingly hindered. The anisotropy values, *r*, measured for PEtOz−PLA and PEtOz−PCL block copolymer micelles, are listed in Table 2. It is interesting to note that the anisotropy values of PEtOz−PLAs are higher than those of PEtOz−PCLs. In addition, the anisotropy values were not very dependent on the length of the hydrophobic blocks as long as the hydrophobic polyester blocks were identical. It is worth comparing *r* values in Table 2 with those of SDS (0.070), poly(ethylene-*co*-maleic acid) (0.187), poly(1-decene-*co*-maleic acid) (0.225), and poly(1-octadecene-*co*-maleic acid) (0.273).[29]

Fluorescence Lifetime. Although characteristic features of pyrene fluorescence spectra depending on the environmental polarity are very informative, the site-specific information on the polarity for hydrophobic microdomain cannot be obtained if the location of pyrene is not defined.[22] The site-specific information of polarity was obtained from the measurement of the fluorescence lifetime of DPH using a phase and modulation method.[30] The phase and modulation data at logarithmically spaced frequencies for DPH in the presence of PEtOz−PLA-0.27 are plotted in Figure 6. By using discrete biexponential functions, the goodness of fit (χ^2) was obtained more satisfactorily than with any other exponential function, as judged by the χ^2 values.

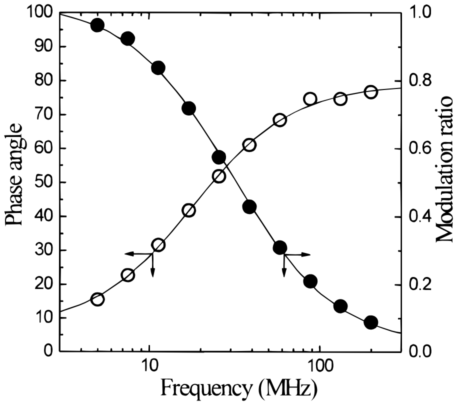


Figure 6. Frequency-dependent phase (○) and modulation (●) data for DPH in PEtOz−PLA-0.27 solution (polymer concentration = 2.5 g/L).

Table 3. Lifetime Data for DPH in Block Copolymer Solutions

block copolymers	τ_1 (ns)	$f_1{}^a$	τ_2 (ns)	$f_2{}^a$	χ^2	$\langle\tau\rangle^b$ (ns)
PEtOz−PLA-0.27	8.75	0.98	0.58	0.02	3.23	8.59
PEtOz−PLA-0.66	9.05	0.98	0.42	0.02	4.95	8.88
PEtOz−PCL-0.19	6.87	0.99	1.00	0.01	3.46	6.81
PEtOz−PCL-0.49	6.90	0.99	0.86	0.01	3.46	6.84
PEtOz−PCL-0.66	7.01	0.99	0.20	0.01	3.91	6.96

[a] Fractional intensity, $f_i = \alpha_i\tau_i/\Sigma\alpha_i\tau_i$, where α_i is preexponential factor representing the fractional contribution to the time-resolved decay of the component with a lifetime τ_i. [b] Average lifetime, $\langle\tau\rangle = \tau_1 f_1 + \tau_2 f_2$.

The single decay function or the three discrete exponential functions did not contribute to the reduction of χ^2 values. Lifetime data for DPH in the block copolymer solutions are summarized in Table 3. The micellar core may have two different hydrophobic domains. The microdomains with longer lifetime are the less polar regions. The fraction values (f_1 and f_2) in Table 3 suggest that the more hydrophobic microdomain out of two different hydrophobic domains occupies the majority of the micellar inner core.

For SDS micelles, the DPH lifetime of the main fraction was reported as 5.52 ns, indicating a relatively polar microdomain.[29] For block copolymers such as poly(1-decene-*co*-maleic acid) and poly(1-octadecene-*co*-maleic acid), the DPH lifetime values of the main domain were reported as 10.62 and 11.58 ns, respectively.[29]

Hydrogen Bonding of the PEtOz Block. Poly(2-ethyl-2-oxazoline) is known to undergo pH-sensitive hydrogen bonding with poly(methacrylic acid) in water.[20] At low pH (<5.0), they form hydrogen bonds to produce precipitates of the polymer complex, which then redissolve at high pH (>5.4) due to the disappearance of the hydrogen bonding. The block copolymer micelles have a hydrophilic outer shell of PEtOz blocks, which form a polymer complex with poly(acrylic acid) through hydrogen bonding. Our preliminary experiment showed that the micelles of PEtOz-based diblock copolymers could be quantitatively recovered as precipitates of polymer complex by the addition of poly(acrylic acid) at pH below 3.5. The precipitates could be shaped as a pellet and stored for several months. These pellets could be redispersed as micelles in water at pH >3.8. This interesting pH-sensitive behavior could find a novel applicability in the area of drug delivery. The details of this behavior will be reported elsewhere.

Conclusion

Amphiphilic diblock copolymers were synthesized with poly(2-ethyl-2-oxazoline) as a hydrophilic block and poly(L-lactide) or poly(ϵ-caprolactone) as a hydrophobic block. These block copolymers formed micelles in water solution. Critical micelle concentrations were in the range of 1.0−8.1 mg/L and were highly dependent on the length of the hydrophobic polyester block. The mean diameters of micelles were in the range of 108−192 nm with a narrow unimodal distribution. The hydrophobic character of the micellar core was estimated by measuring the partition equilibrium constant, K_v, of pyrene in the micellar solutions of the block copolymers. The K_v values were in the range from 1.79×10^5 to 5.88×10^5. For each block copolymer system (PEtOz−PLAs or PEtOz−PCLs), the K_v value increased as the length of hydrophobic block of the copolymers increased. The microviscosity of the micellar core was estimated from the steady-state fluorescence anisotropy value (r) of DPH in a block copolymer solution. The anisotropy values of PEtOz−PLAs were higher than those of PEtOz−PCLs. If the block copolymers have identical structures of hydrophobic polyester, the anisotropy values were independent of the length of the hydrophobic blocks. The pH-sensitive hydrogen-bonding ability of the 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 again be redispersed in an aqueous medium at high pH.

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References and Notes

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