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Synthesis and Self-Association Behavior of Biodegradable Amphiphilic Poly[bis(ethyl glycinat-*N*-yl)phosphazene]−Poly(ethylene oxide) Block Copolymers

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Amphiphilic diblock copolymers with varying compositions of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly[bis(ethyl glycinat-*N*-yl)phosphazene] (PNgly) were synthesized via the controlled cationic-induced polymerization of a phosphoranimine ($Cl_3P{=}NSiMe_3$) at ambient temperature using a PEO−phosphoranimine macroinitiator. The aqueous-phase transition behavior of PEO−PNgly-3 (M_n = 10 000) and micelle formation of both PEO−PNgly-3 and PEO−PNgly-4 (M_n = 8500) were investigated using fluorescence techniques and dynamic light scattering. The critical micelle concentrations (cmc's) of PEO−PNgly-3 and PEO−PNgly-4 were determined to be 3 and 12 mg/L with the mean diameters of micelles being 120 and 130 nm, respectively. The hydrolytic degradation of these diblock copolymers was also studied in solution. These studies coupled with the biodegradability of the poly[bis(ethyl glycinat-*N*-yl)-phosphazene] block to give benign products make PEO−PNgly copolymers well-suited for a wide variety of biomedical applications including novel biodegradable drug-delivery systems.

Introduction

Recently, many researchers have focused on designing amphiphilic block copolymers composed of hydrophilic and hydrophobic segments because of their potential applications in drug delivery and separations technology.[1−3] In the field of biotechnology, polymeric self-aggregations, which form micelles in aqueous media, have become attractive biomaterials and have been the subject of much current research.[4−6] Poly(ethylene oxide) (PEO) has been widely used as a hydrophilic segment in many polymeric amphiphiles for a variety of biomedical applications because of its low toxicity and good biocompatibility.[7] The selection of hydrophobic segments in polymeric amphiphiles is important because micelle formation depends on both the nature of the hydrophobic block and an appropriate balance between the hydrophobic and hydrophilic regions. Various polyesters, polystyrene, poly(propylene oxide), and polyalkanes have been employed previously for structural variations of the hydrophobic segments in amphiphiles.[8−11] Our interest lies in the polymeric self-aggregation of copolymers comprised of a novel hydrophobic segment, poly[bis(ethyl glycinat-*N*-yl)phosphazene], which is known to hydrolyze slowly to a mixture of biologically benign products (amino acid, phosphate, and ammonia), which are much less acidic than the degradation products of polyesters such as poly(lactide-*co*-glycolide).[12,13] Polyphosphazenes, which contain a backbone of alternating nitrogen and phosphorus atoms, may exhibit many different chemical and physical properties depending on the structure of the R group attached to each phosphorus atom. In particular, polyphosphazenes that bear bioinert or biodegradable groups have attracted much attention as potential biomaterials.[14−16]

In a recent paper, we described the aqueous-phase behavior of amphiphilic block copolymers based on a hydrophilic block, poly[bis(methoxyethoxyethoxy)phosphazene] (MEEP), and poly[phenyl(methoxyethoxyethoxy)phosphazenes] (Ph/MEEP) as a hydrophobic block.[17] This block copolymer formed micelles in water in which the inner core was composed of the hydrophobic Ph/MEEP segments. In this work, we have synthesized novel poly(ethylene oxide)−poly-[bis(ethyl glycinat-*N*-yl)phosphazene] (PEO−PNgly) block copolymers that contain different ratios of hydrophilic PEO blocks and hydrophobic biodegradable poly[bis(ethyl glycinat-*N*-yl)phosphazene] segments via the ambient temperature cationic condensation polymerization of a phosphoranimine ($Cl_3P{=}NSiMe_3$) with a PEO−phosphoranimine macroinitiator (**2**) (Scheme 1).[18,19] This method has been used to synthesize well-defined polymers with narrow polydispersities and controlled molecular weights based on the monomer-to-initiator ratios and has allowed the synthesis of polyphosphazene block copolymers by the sequential polymerization of phosphoranimines that bear different organic side groups.[20] The combination of polyphosphazenes with organic polymers provides a facile synthetic route to unique hybrid materials with well-defined block copolymer structures for use in a wide variety of applications.[21] The micellar characteristics of these block copolymers in aqueous media were investigated by fluorescence techniques, dynamic light scattering (DLS), and transmission electron microscopy (TEM). In addition, a brief study on the hydrolytic stability

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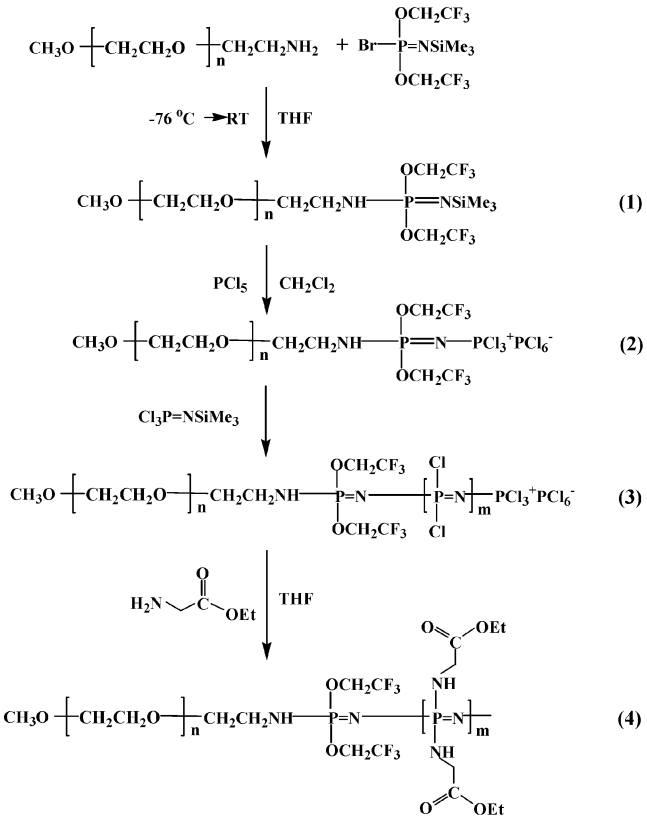
Scheme 1



of these diblock copolymers was performed through gel permeation chromatography (GPC).

Experimental Section

Materials. Amine-terminated monomethoxy PEO was obtained from Shearwater Polymer Inc. and used as received. Lithium bis(trimethylsilyl)amide and glycine ethyl ester hydrochloride were obtained from Aldrich and were used without further purification. Phosphorus pentachloride (Aldrich) was purified by sublimation under vacuum prior to use. $Cl_3P{=}NSiMe_3$ and $Br(OCH_2CF_3)_2P{=}NSiMe_3$ were synthesized and purified by literature procedures.[18,22] Tetrahydrofuran (THF) and hexane (Aldrich) were distilled into the reaction flask from sodium benzophenone ketyl under an atmosphere of dry argon. Dichloromethane and triethylamine (Aldrich) were dried and distilled from CaH_2.

Equipment. ^{1}H, ^{13}C, and ^{31}P spectra were recorded on a Bruker WM-360 NMR spectrometer operated at 360, 146, and 90.27 MHz, respectively. ^{1}H and ^{13}C NMR spectra are referenced to tetramethylsilane (TMS), while ^{31}P NMR chemical shifts are relative to 85% phosphoric acid as an external reference with positive shift values downfield from the reference. Molecular weights were estimated using a Hewlett-Packard HP 1090 gel permeation chromatograph equipped with an HP-1047A refractive index detector and two Phenogel linear 10 columns and calibrated versus polystyrene standards (Polysciences). The samples were eluted (flow rate = 1.0 mL/min) at 40 °C with a 0.1 wt % solution of tetra-*n*-butylammonium nitrate (Aldrich) in THF (OmniSolv).

Synthesis of $CH_3O-PEO-NH[(CF_3CH_2O)_2P{=}NSiMe_3]$ (1). The diblock copolymers of poly(ethylene oxide)−poly[bis(ethyl glycinat-*N*-yl)phosphazene] (PEO−PNgly) were prepared by the modification of a literature procedure.[18,19] For example, the block copolymer PEO−PNgly-1, which has a 1:1 feed ratio of phosphazene to ethylene oxide, was prepared by the following procedure: A mixture of $CH_3O-PEO-NH_2$ (M_n = 5400) (1.2 g, 0.2 mmol) and triethylamine (0.5 mL) in THF (20 mL) was cooled to −76 °C. To this solution, $(CF_3CH_2O)_2BrP{=}NSiMe_3$ (0.095 g, 0.24 mmol) was added dropwise over a 30 min period. The reaction mixture was stirred at −76 °C and then allowed to warm to room temperature. The salt (Et_3NHBr) was removed by filtration. All volatiles were removed under reduced pressure to produce a white solid, which was washed with hexanes and dried under vacuum. For **1**, ^{1}H NMR ($CDCl_3$) δ −0.03 (d, J = 4 Hz, $-Si(CH_3)_3$), 1.40 (br, $-NHCH_2CH_2-O-$), 2.50 (br, $-NHCH_2CH_2-O-$), 3.30 (s, PEO−O−CH_3), 3.51 (br, $-OCH_2CH_2O-$), 4.23 (q, J = 16 Hz, $-OCH_2CF_3$) and ^{31}P NMR ($CDCl_3$) δ −0.76.

Synthesis of $CH_3O-PEO-NH[(CF_3CH_2O)_2P{=}NPCl_3^+PCl_6^-]$ (2). To a stirred solution of PCl_5 (0.093 g, 0.48 mmol) in 10 mL of methylene chloride at −76 °C, **1** (0.24 mmol) in 25 mL of methylene chloride was added slowly. The reaction mixture was stirred at −76 °C for 1 h and then allowed to warm to room temperature. After removal of the solvent, the product was washed with hexane to produce a light yellow solid. For **2**, ^{1}H NMR ($CDCl_3$) δ 1.29 (m, $-NHCH_2CH_2-O-$), 3.04 (br, $-NHCH_2CH_2-O-$), 3.30 (s, PEO−O−CH_3), 3.51 (br, $-OCH_2CH_2O-$), 5.74 (br, $-OCH_2CF_3$) and ^{31}P NMR ($CDCl_3$) δ −2.97 (s), −6.8 (d, J = 51 Hz), 4.3 (d, J = 51 Hz).

Synthesis of $CH_3O-PEO-NH[(CF_3CH_2O)_2P-[N{=}P-[(NHCH_2COOCH_2CH_3)_2]]_m$ (4). A 10 mL methylene chloride solution of polymer **2** (0.24 mmol) was added to a solution of $Cl_3P{=}NSiMe_3$ (6.12 g, 27 mmol) in 20 mL of methylene chloride at room temperature. The reaction mixture was stirred under argon for 3 h and monitored by ^{31}P NMR spectroscopy until complete conversion of $Cl_3P{=}NSiMe_3$ to polymer **3** had occurred. After complete consumption of $Cl_3P{=}NSiMe_3$, all volatiles were removed under reduced pressure, and the remaining polymer **3** was dissolved in THF. Glycine ethyl ester hydrochloride (22.8 g, 163 mmol) was suspended in a THF (200 mL)/triethylamine (10 mL) solution. This suspension was refluxed for 4 h, cooled to room temperature, filtered, and added to the above polymer solution in THF. The reaction mixture was stirred for 2 h at room temperature and heated to 50 °C for 5 h at which time the reaction was complete by ^{31}P NMR. The reaction mixture was then filtered, concentrated under reduced pressure, purified by repeated precipitation into hexanes (3×), and dried under vacuum to yield a pale yellow powder. For polymer **4**, ^{1}H NMR ($CDCl_3$) $\boldsymbol{\delta}$ 1.02 (tri, $-OCH_2CH_3$), 3.42 (s, $-OCH_2CH_2O-$), 3.51 (s, $-NHCH_2COO-$), 3.86 (q, $-OCH_2CH_3$) and ^{31}P NMR ($CDCl_3$) $\boldsymbol{\delta}$ 1.88.

Sample Preparation. Micellar solutions were prepared by the dispersion of PEO−PNgly block copolymers in distilled water through gentle stirring for 3 h, followed by sonication for 30 min. Samples for fluorescence measurements of pyrene in micellar solutions were prepared accord-

ing to literature procedures[17,23] and ranged in concentration from 5×10^{-5} to 2 g/L.

Fluorescence Measurements. The fluorescence spectra were obtained using Shimadzu RF-5301 PC spectrofluorometer. Pyrene was used as a fluorescence probe to analyze PEO−PNgly block copolymers in doubly distilled water. For the measurement of pyrene excitation spectra, emission and excitation slit widths were set at 3 and 1.5 nm, respectively, and the emission wavelength was set at 390 nm.

Light Scattering Measurements. Dynamic light scattering measurements were performed using a Brookhaven BI-200SM goniometer and BI-9000AT autocorrelator. All of the measurements were carried out at 25 °C as described in the literature.[17,23] 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] CONTIN algorithms were used in the Laplace inversion of the autocorrelation function to obtain micelle size distribution.[17,23]

Transmission Electron Microscopy. Transmission electron microscopy (TEM) was performed using a JEOL JEM 1200 EXII unit operated at an acceleration voltage of 80 kV. 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 surface water was removed, and the sample was air-dried. Negative staining was performed using a droplet of a 2.5 wt % uranyl acetate solution.[25]

Hydrolysis Study. The hydrolysis studies of PEO−PNgly (**1**−**4**) were carried out via gel permeation chromatography according to a method developed by Pucher et al.[12] for the solution-state hydrolysis of poly(amino acid ester)phosphazenes. An initial gel permeation chromatogram of each polymer in THF was obtained. Deionized water (0.5 mL) was then added to each sample (polymer concentration 1.5 wt % in THF). The chromatogram of each polymer was then monitored after 1 week and then weekly over a 5-week period to follow the molecular weight change.[12]

Results and Discussion

Synthesis of Block Copolymers. The diblock copolymers used in this study consist of a hydrophobic biodegradable glycine ethyl ester substituted polyphosphazene block and a hydrophilic PEO chain (Scheme 1). The amphiphilic PEO−PNgly diblock copolymers were synthesized via the controlled cationic-induced polymerization of $Cl_3N{=}PSiMe_3$ at ambient temperature using a PEO−phosphoranimine macroinitiator (**2**) (Scheme 1). The PEO−phosphoranimine macroinitiator (**2**) was synthesized via the reaction of CH_3O−PEO−NH_2 (M_n = 5400) with $BrP(OCH_2CF_3)_2{=}NSiMe_3$ followed by the addition of 2 equiv of PCl_5 to obtain the cationic species CH_3O−PEO−NH−$P(OCH_2CF_3)_2{=}N$−PCl_3^+-PCl_6^- (**2**). Subsequent reaction of **2** with $Cl_3P{=}NSiMe_3$ resulted in the formation of the PEO−poly(dichlorophosphazene) block copolymer **3**. Treatment of this reaction mixture with the free amine, $H_2NCH_2COOCH_2CH_3$, in the presence of triethylamine yielded fully substituted PEO−PNgly block copolymers **4** as confirmed by ^{31}P NMR. These polymers were soluble in THF, acetone, methylene chloride, and DMF. The structural characterization was carried out by multinuclear NMR, and the molecular weights of the copolymers were determined by both ^1H NMR and gel permeation chromatography (GPC) as summarized in Table 1. The number average molecular weights of PEO−phosphazene block copolymers were determined by ^1H NMR through comparison of the integration ratio of the glycine ethyl ester protons at 1.02, 3.51, and 3.86 ppm and the methylene protons in PEO at 3.42 ppm. GPC chromatograms showed narrow, unimodal molecular weight distributions (M_w/M_n) that ranged from 1.3 to 1.6.

Table 1. Characterization of PEO−PNgly Block Copolymers

polymer	yield (%)	feed ratio (n/m)	composition ratio (n/m)[a]	M_n[a] (^1H NMR)	M_n (M_w/M_n)[b]
PEO− PNgly-1	72	1:1	1:0.77	28 600	20 000 (1.5)
PEO− PNgly-2	90	1:0.5	1:0.42	18 000	12 600 (1.6)
PEO− PNgly-3	75	1:0.25	1:0.23	11 400	10 000 (1.3)
PEO− PNgly-4	63	1:0.1	1:0.06	6700	8500 (1.5)

[a] Calculated by ^1H NMR spectra based on CH_3O−PEO−NH_2 (M_n = 5400). [b] Measured by GPC.

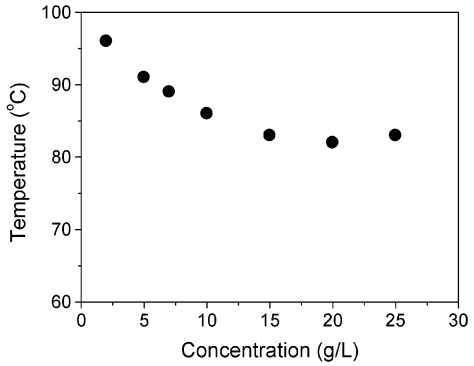


Figure 1. LCST of PEO−PNgly-3 in aqueous phase.

Aqueous-Phase Behavior. Amphiphilic block copolymers typically show unusual behavior in aqueous media, such as micelle formation, and lower critical solution temperatures (LCST).[1,8−11] Similar results have now been seen with PEO−PNgly copolymers. For example, heating of an aqueous solution of PEO−PNgly-3 above 80 °C resulted in the immediate precipitation of the copolymer. The precipitation temperature of PEO−PNgly-3 was influenced by the block copolymer concentration as depicted in Figure 1. Similar observations with block copolymers composed of PEO−poly(propylene oxide) and PEO−polyesters have been reported previously.[26,27] The precipitation of PEO-based amphiphiles at higher temperatures is attributed to dehydration of water molecules around the PEO segments. At room temperature, two or three water molecules are hydrogen-

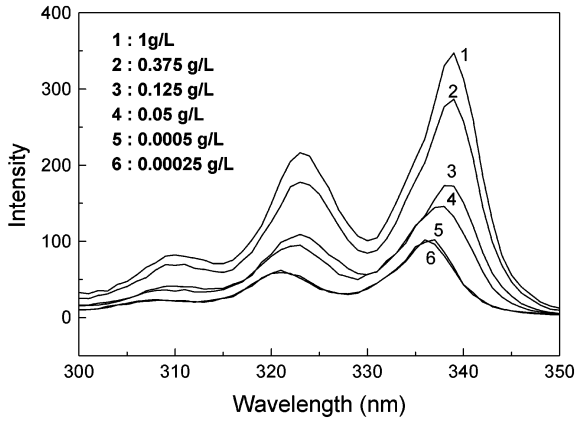


Figure 2. Excitation spectra of pyrene as a function of PEO−PNgly-3 concentration in water.

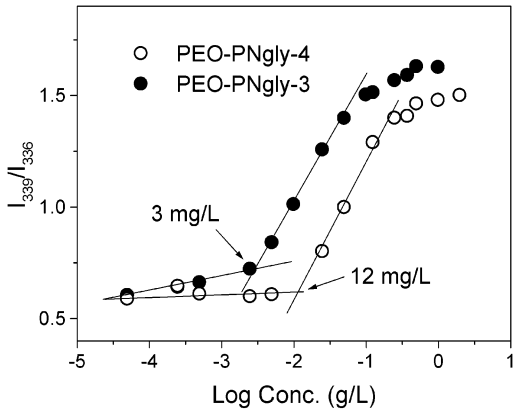


Figure 3. Plot of I_{339}/I_{336} (from pyrene excitation spectra) vs log C for (●) PEO−PNgly-3 and (○) PEO−PNgly-4.

bonded to each ethyleneoxy repeating unit in the PEO block. As the temperature increases, dehydration expels water molecules and induces precipitation.[26,27] For PEO−PNgly-3, the LCST in aqueous media ranged from 82 to 96 °C, depending on the block copolymer concentration, which is lower than that of PEO homopolymer solutions.[26,27] This result suggests that the hydrophobic poly[bis(ethyl glycinat-*N*-yl)phosphazene] block may facilitate the collapse of the PEO block, leading to a lowering of the precipitation temperature. However, PEO−PNgly-1 and PEO−PNgly-2 were not soluble in water because of their large hydrophobic poly[bis(ethyl glycinat-*N*-yl)phosphazene] blocks.

The amphiphilic PEO−PNgly block copolymers provide an opportunity for these polymers to disperse in aqueous media and form assembled aggregates. The amphiphilic aqueous-phase characteristics of these block copolymers were studied through fluorescence techniques, DLS, and TEM. The critical micelle concentrations (cmc's) were determined by the excitation spectra of pyrene, a fluorescence probe,[28] in various aqueous concentrations of PEO−PNgly-3 and PEO−PNgly-4. The characteristic shift of the pyrene excitation spectra, from 336 to 339 nm following pyrene partition into the hydrophobic core of the micelle, was utilized to determine the critical aggregation concentration of aqueous PEO−PNgly block copolymers (Figure 2). Figure 3 shows the intensity ratios (I_{339}/I_{336}) at 339 and 336 nm of pyrene excitation in the presence of different concentrations of PEO−PNgly-3 and PEO−PNgly-4. At low concentrations,

Table 2. Properties of PEO−PNgly Micelles

polymer	cmc[a] (mg/L)	R_h[b] (nm)	μ_2/Γ^2 [c]	K_v ($\times 10^{-5}$)
PEO−PNgly-3	3	130	0.134	1.70
PEO−PNgly-4	12	120	0.197	1.59

[a] Measured at 25 °C. [b] Hydrodynamic radius determined by dynamic light scattering at 25 °C. [c] Polydispersity factor.

a negligible change in the intensity ratios (I_{339}/I_{336}) was detected. However, at a certain concentration, the intensity ratios showed a substantial increase, which suggested that the pyrene molecules are incorporated into the hydrophobic core during micellar aggregation. Therefore, the critical micelle concentrations (cmc's) were determined from the crossover point at the low-concentration range in Figure 3. The cmc values of PEO−PNgly-3 and PEO−PNgly-4 were 3 and 12 mg/L, respectively (Table 2). These values are much lower than those of low molecular weight surfactants, for example, 2.3 g/L for sodium dodecyl sulfate (SDS), but comparable with those of other polymeric amphiphiles.[29−31] In comparing PEO−PNgly-3 and PEO−PNgly-4, the effect of the longer hydrophobic polyphosphazene block is evident in the lower cmc observed for PEO−PNgly-3. The aqueous behavior of the longer chain polyphosphazene-containing block copolymers, PEO−PNgly-1 and PEO−PNgly-2, was not be investigated because of their long hydrophobic blocks, which rendered them nondispersable in water. The mean diameters (d) of PEO−PNgly-3 and PEO−PNgly-4 micelles, measured by dynamic light scattering, were determined to be 130 and 120 nm, respectively (Table 2). Although the typical size of individual core−shell-type micelles formed from amphiphilic diblock copolymers is several tens of nanometers,[31,32] micelles with a size range of several hundreds of nanometers are often observed because of the intermicellar aggregation of amphiphilic block copolymer systems.[33,34] Therefore, it is possible that PEO−PNgly micelles form a multicore structure through 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 aqueous media.[33,34] The polydispersity factors (μ_2/Γ^2) of the micelles, estimated by the cumulant method, were fairly low (0.134 and 0.197), suggesting a narrow size distribution.[24,31] The shape and size of PEO−PNgly-3 and PEO−PNgly-4 were also measured by TEM, and the picture of PEO−PNgly-4 is depicted in Figure 4.[25]

The micellar core hydrophobicity was estimated by measurement of the partition equilibrium constant (K_v) using a hydrophobic probe, pyrene, in the micellar solutions of the amphiphilic block copolymers. The K_v values were calculated using the method of Wilhelm et al.,[32] in which pyrene binding to the micelles was considered as a simple equilibrium between a micellar phase and a water phase.[35] 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.

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

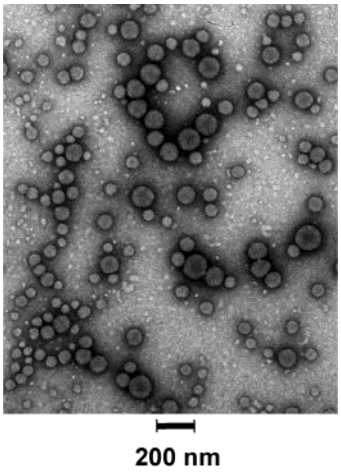


Figure 4. TEM image of PEO−PNgly-4.

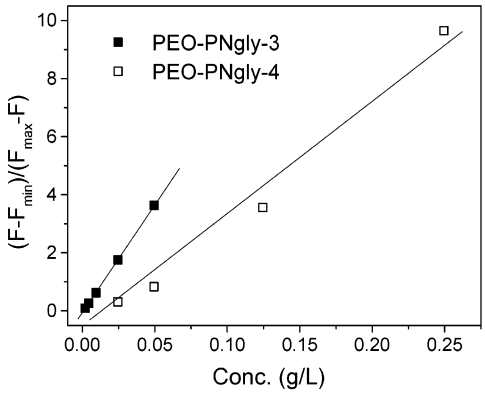


Figure 5. Plots of $(F - F_{min})/(F_{max} - F)$ vs concentration of (■) PEO−PNgly-3 and (□) PEO−PNgly-4 in water.

Equation 1 can be rewritten as

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

where x is the weight fraction of hydrophobic polyphosphazene block, c is the concentration of the block copolymer, and ρ is the density of the polyphosphazene micelle core, which is assumed to be the value of glycine ethyl ester (1.16 g/mL). In the intermediate range of polymer concentrations (Figure 3), $[\mathrm{Py}]_m/[\mathrm{Py}]_w$ can be written as

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

where F_{max} and F_{min} correspond to the average magnitude of I_{339}/I_{336} in the flat region of high and low concentration ranges, and F is the intensity ratio (I_{339}/I_{336}) in the intermediate concentration range of Figure 3. Combining eqs 2 and 3, we determine K_v values of pyrene by using a plot $(F - F_{min})/(F_{max} - F)$ versus PEO−PNgly concentration as shown in Figure 5.[22,32] The K_v values of PEO−PNgly-3 and PEO−PNgly-4 were determined to be 1.70×10^5 and 1.59×10^5, respectively, suggesting that the length of the hydrophobic polyphosphazene block has little effect on the hydrophobicity of the micellar core. It is interesting to note that the K_v values of PEO−PNgly 3 and PEO−PNgly 4 are similar to that of sodium dodecyl sulfate (SDS) micelles (1.2×10^5) even though the size of the hydrophobic blocks in the copolymer are larger than that of SDS. In comparison to other amphiphilic block copolymer systems, PEO−PNgly-3 and

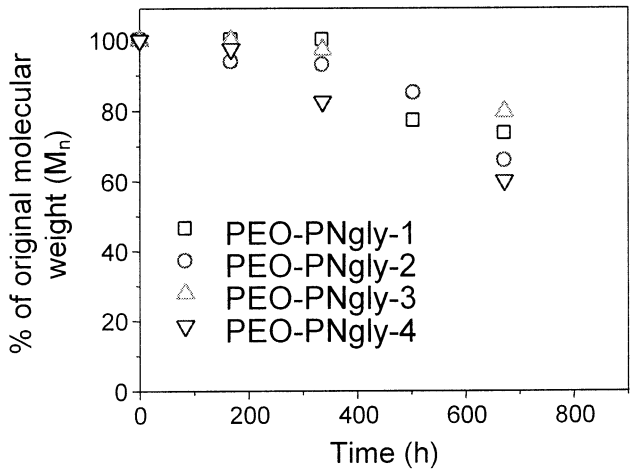


Figure 6. Percentage molecular weight decline during solution-state hydrolysis of PEO−PNgly block copolymers.

PEO−PNgly-4 displayed K_v values comparable to that reported for PEO−polystyrene block copolymers ($K_v = 3.0 \times 10^5$)[36] and much larger than those of other polyphosphazene amphiphilic systems such as poly[bis(methoxyethoxyethoxy)phosphazene]−poly[phenyl(methoxyethoxyethoxy) phosphazenes] (MEEP)−(Ph/MEEP), which exhibited a K_v value of 7.0×10^3.[17]

Hydrolysis Study. Polyphosphazenes that bear amino acid ester side groups have been shown previously to degrade slowly in aqueous solutions and as solid films.[12] For example, poly[bis(ethylglycinat-*N*-yl)phosphazene] hydrolyzes in aqueous media to yield ethanol, glycine, ammonia, and phosphate as byproducts.[12] Because of the hydrolytically sensitive nature of the hydrophobic polyphosphazene block, the degradation of PEO−PNgly block copolymers in aqueous THF (1 wt % of water in THF) was investigated by gel permeation chromatography over a 5 week period. All of the PEO−PNgly copolymers underwent molecular weight decline (Figure 6), as seen by the broad and bimodal GPC chromatograms, which are typical of polyphosphazene hydrolysis.[12]

Conclusions

Novel, amphiphilic diblock copolymers with varying ratios of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly(bis[ethyl glycinat-*N*-yl]phosphazene) (PNgly) blocks were synthesized via the controlled cationic-induced polymerization of $Cl_3N{=}PSiMe_3$ at ambient temperature using a PEO−phosphoranimine as a starting material. Aqueous solutions of PEO−PNgly-3 showed LCSTs, while both PEO−PNgly-3 and PEO−PNgly-4 displayed micelle formation in aqueous media as confirmed by fluorescence techniques and DLS. The critical micelle concentrations (cmc)'s of these micelles were shown to be dependent on the length of the hydrophobic polyphosphazene block and were found to be 3 and 12 mg/L, respectively, for PEO−PNgly-3 and PEO−PNgly-4. PEO−PNgly block copolymers were also shown to hydrolyze in aqueous solutions over a 5 week period. Amphiphilic PEO−PNgly block copolymers have similar aqueous phase behavior to other PEO-based amphiphiles, such as LCST and micelle formation. These

attributes coupled with the biodegradability of the poly[bis-(ethyl glycinat-*N*-yl)phosphazene] block to give benign products make PEO−PNgly copolymers well-suited for a wide variety of biomedical applications including novel biodegradable drug-delivery systems.

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