Synthesis and Micellar Behavior of Amphiphilic Polystyrene−Poly[bis(methoxyethoxyethoxy)phosphazene] Block Copolymers

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ABSTRACT: Amphiphilic diblock copolymers with varying compositions of hydrophilic poly[bis(methoxyethoxyethoxy)phosphazene] and hydrophobic polystyrene were synthesized via the living, cationic polymerization of $Cl_3P=NSiMe_3$, using a polystyrenyl−phosphoranimine as a macroterminator. The self-association behavior of the block copolymers in aqueous media was investigated using fluorescence spectroscopy, transmission electron microscopy, and dynamic light scattering. The critical micelle concentrations of PS−MEEP block copolymers with molar block ratios of 1:0.37, 1:0.58, 1:0.70, and 1:0.86 were determined to be 1.8, 2.3, 10.0, and 13.6 mg/L, respectively. The mean diameters of micelles of these block copolymers were measured as 167, 168, 179, and 173 nm through dynamic light scattering. The equilibrium constants of pyrene in these micelles ranged from 5.75×10^5 to 7.31×10^4.

Introduction

Block copolymers that contain both hydrophobic and hydrophilic segments self-assemble in aqueous media to form aggregates.[1−3] Much research has been focused on the development of amphiphilic block copolymers and the study of micelles formed from these materials for use as drug and dye carriers, surfactants, or rheological modifiers.[4−7] We recently reported that various amphiphilic phosphazene block copolymers, such as poly[bis(trifluoroethoxy)phosphazene]−poly(ethylene oxide), poly[bis(ethyl glycinat-*N*-yl)phosphazene]−poly(ethylene oxide), and poly[bis(methoxyethoxyethoxy)phosphazene]−poly[phenyl(methoxyethoxyethoxy)phosphazene] formed micelles in aqueous media, where the inner cores were composed of the hydrophobic poly[bis(trifluoroethoxy)phosphazene], poly[bis(ethyl glycinat-*N*-yl)phosphazene], and poly[phenyl(methoxyethoxyethoxy)phosphazene] blocks.[8−10]

In this work we report the synthesis of novel polystyrene−poly[bis(methoxyethoxyethoxy)phosphazene] (PS−MEEP) block copolymers that contain varying lengths of hydrophilic poly[bis(methoxyethoxyethoxy)phosphazene] (MEEP) blocks covalently bound to hydrophobic polystyrene (PS) segments of constant length. The block copolymers were synthesized via controlled termination of the living, cationic polymerization of $Cl_3P=NSiMe_3$ with a polystyrenyl−phosphoranimine (**1**) (Scheme 1).[11,12] The amphiphilic PS−MEEP block copolymers are potentially useful for encapsulation of hydrophobic materials in an aqueous phase. Amphiphilic block copolymers that contain MEEP also have potential in drug delivery systems due to the biocompatibility of MEEP homopolymer.[13] The micellar characteristics of these block copolymers in aqueous media

Scheme 1. Synthesis of PS−MEEP Block Copolymers

were investigated using fluorescence spectroscopy, dynamic light scattering (DLS), and transmission electron microscopy (TEM).

Experimental Section

General. Lithium bis(trimethylsilyl)amide, phosphorus trichloride (PCl₃), and 95% sodium hydride were obtained from Aldrich and used without further purification. Phosphorus pentachloride (PCl₅) was obtained from Aldrich and was purified by sublimation prior to use. 2-(2-Methoxyethoxy)ethanol was dried over calcium hydride (CaH₂) and distilled under reduced pressure before use. $Cl_3P=NSiMe_3$, $(CF_3CH_2O)_3P=NSiMe_3$, and phosphoranimine-terminated polystyrene ($M_n = 5000$) were synthesized and purified by literature procedures.[11,14,15] Tetrahydrofuran (THF) was obtained from EM Science and distilled into the reaction flask from sodium−

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benzophenone ketyl under an atmosphere of dry argon. Dichloromethane (CH_2Cl_2) was obtained from EM Science, dried over $CaSO_4$, and distilled from CaH_2 into the reaction flask.

All glassware was dried overnight in an oven at 125 °C or flame-dried under reduced pressure before use. Reactions were carried out using standard Schlenck techniques or an inert atmosphere glovebox (MBraun) under an atmosphere of dry argon or nitrogen.

Equipment. [1]H, ^{13}C, and ^{31}P spectra were obtained using a Bruker AMX-360 NMR spectrometer, operated at 360, 90.27, and 146 MHz. ^{1}H and ^{13}C NMR spectra are referenced to solvent signals while ^{31}P NMR chemical shifts are relative to 85% phosphoric acid as an external reference, with positive shift values downfield from the reference. All chemical shifts are reported in ppm. Molecular weights were estimated using a Hewlett-Packard HP 1090 gel permeation chromatograph equipped with an HP-1047A refractive index detector, Phenomenex Phenogel 10 μm mixed MXL and linear (2) analytical columns, and calibrated against polystyrene standards (Polysciences). The samples were eluted at 40 °C in a 0.1 wt % solution of tetra-*n*-butylammonium nitrate (Aldrich) in THF (EM Science).

Typical Synthesis of a PS–MEEP Block Copolymer. PCl_5 (110 mg, 2 equiv) was dissolved in 25 mL of distilled CH_2Cl_2 at 25 °C. $(CF_3CH_2O)_3P=NSiMe_3$ (110 mg, 1 equiv) was added to the PCl_5, and the solution was stirred for 2 h. $Cl_3P=NSiMe_3$ (2.44 g, 40 equiv) was then added, and the solution was stirred for 4 h to generate living poly(dichlorophosphazene) chains. A polystyrenyl–phosphoranimine (5000 g/mol, 1.42 g, 1 equiv) was added, and the reaction mixture was stirred for 18–24 h to terminate the polymerization.[15] The CH_2Cl_2 was removed from the reaction mixture under reduced pressure, and the product was redissolved in 25 mL of distilled THF. Replacement of the labile chlorine atoms by sodium methoxyethoxyethoxide in THF yielded the hydrolytically stable polystyrene–poly[bis(methoxyethoxyethoxy)phosphazene] (PS–MEEP) block copolymer. The product was dialyzed (MWCO: 2000 g/mol) against deionized water for 24 h and THF for 24 h. The block copolymer was isolated as an off-white solid by precipitation into hexanes from THF. Typical chemical shifts are as follows, but integrations varied with the differing block copolymer compositions. ^{1}H NMR ($CDCl_3$): δ = 7.37–6.95 (br, −P−Ph (*o*)), 6.91−6.61 (br, −P−Ph (*m, p*)), 4.25 (s, −POC*H*$_2$CH$_2$O−), 3.78 (s, −POCH$_2$C*H*$_2$O−), 3.62 (s, −OC*H*$_2$CH$_2$O−), 3.47 (s, −OC*H*$_3$), 2.19−1.89 (br, −C*H*CH$_2$−), 1.72−1.52 (br, −CHC*H*$_2$−). ^{31}P NMR ($CDCl_3$): δ = −6.78 (br s).

Preparation of Micellar Solutions. Micellar solutions were prepared by the dispersion of PS–MEEP 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 according to literature procedures and ranged in concentration from 5 × 10^{-5} to 1 g/L.[8−10]

Fluorescence Measurements.[8−10] Fluorescence spectra were obtained using a Yobin Yvon Fluromax 2 spectrometer. Pyrene was used as a fluorescence probe to analyze PS–MEEP 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 an emission wavelength of 390 nm was used.

Light Scattering Measurements. Dynamic light scattering measurements were performed using a Brookhaven BI-200SM goniometer and a BI-9000AT autocorrelator. All measurements were carried out at 25 °C following literature procedures. 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 using the Stokes–Einstein equation, $d = k_BT/3\pi\eta D$, where k_B is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the solvent, and D is the diffusion coefficient. The polydispersity factor of the 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.

Table 1. Characterization of PS−MEEP Block Copolymers

polymer	weight ratio (PS:MEEP)	mole ratio (PS:MEEP)	$M_n{}^a$ (^{1}H NMR)	M_n (GPC)	$M_w/M_n{}^b$
5	1:0.17	1:0.06	5 900	8 000	1.7
6	1:0.45	1:0.17	7 300	8 200	1.7
7	1:1.0	1:0.37	10 000	12 600	1.6
8	1:1.57	1:0.58	13 000	14 700	1.8
9	1:1.89	1:0.70	14 400	17 900	2.0
10	1:2.33	1:0.86	16 600	18 300	1.8

^{a} Calculated from ^{1}H NMR spectra by comparing aromatic protons (6.6−6.9 and 7.0−7.4 ppm) on PS block ($M_n \sim$ 5000, PDI = 1.2) to methoxy protons (3.5 ppm) on MEEP block. ^{b} Measured by GPC vs polystyrene standards.

CONTIN algorithms were used in the Laplace inversion of the autocorrelation function to obtain micelle size distributions.[16]

Transmission Electron Microscopy. Transmission electron microscopy was performed using a JEOL JEM 1200 EXII unit, operated at an acceleration voltage of 80 kV. For observation of the size and distribution of micellar particles, a drop of a sample solution (concentration = 0.5 g/L) was placed on a 200 mesh copper grid coated with carbon. Approximately 2 min after deposition, any excess water on the surface of the grid was removed and the sample was air-dried. Negative staining was performed using a 2.5 wt % uranyl acetate solution.[17]
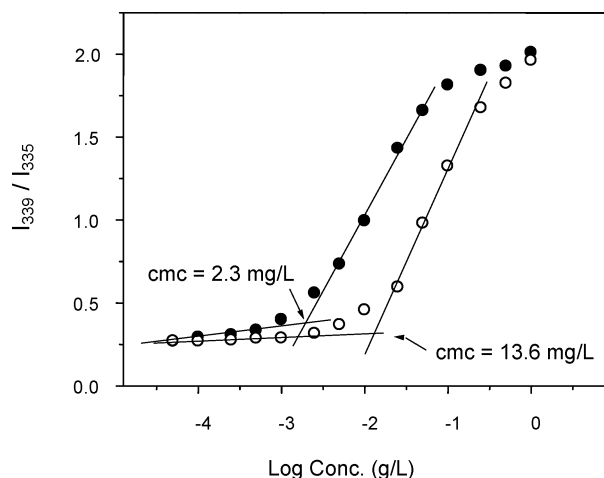
Results and Discussion

Synthesis of Block Copolymers. Amphiphilic PS–MEEP block copolymers were synthesized via the controlled, cationic polymerization of $Cl_3P=NSiMe_3$ at ambient temperature, using a polystyrenyl–phosphoranimine as a macroterminator (Scheme 1). Polystyrene with a terminal phosphine unit was prepared by quenching living polystyrene with Ph_2PCl. The phosphine-terminated polystyrene was treated with N_3SiMe_3 to yield the polystyrenyl–phosphoranimine **1**, which serves as a macromolecular terminator for the controlled, cationic polymerization of $Cl_3P=NSiMe_3$. Addition of **1** to solutions of $[(CF_3CH_2O)_3P=N-(Cl_2P=N)_n-PCl_3]^+-[PCl_6]^-$ (**2**), with varied chain lengths, yielded PS–poly-(dichlorophosphazene) block copolymers (**3**) with controlled phosphazene block lengths.[15,18] Macromolecular replacement of the labile chlorine atoms on the phosphazene block with an excess of sodium methoxyethoxyethoxide gave PS–MEEP block copolymers (**4**). A series of copolymers were prepared by varying the length of the MEEP block, while the length of the PS block remained constant ($M_n \sim$ 5000, DP = 50, PDI = 1.2). The molar composition ratios of the block copolymers, based on the number of repeating units of PS and MEEP, varied from 1:0.06 to 1:0.86. Gel permeation chromatography was used to measure average molecular weights and polydispersities, and these data were compared to values calculated using ^{1}H NMR (Table 1). All the block copolymers gave monomodal GPC traces, with retention times indicating molecular weights higher than the polystyrene starting block. M_n values obtained from GPC measurements were consistently higher than those calculated from ^{1}H NMR. This is probably an overestimation of the molecular weights by GPC due to differences in hydrodynamic radii between polystyrene standards used for calibration and the PS−MEEP block copolymers. PDI values for the final block copolymers were higher than expected, but the addition of one polydisperse polymer solution to another can account for this.

Self-Association in Aqueous Phase. The combination of a hydrophilic and a hydrophobic polymer in the
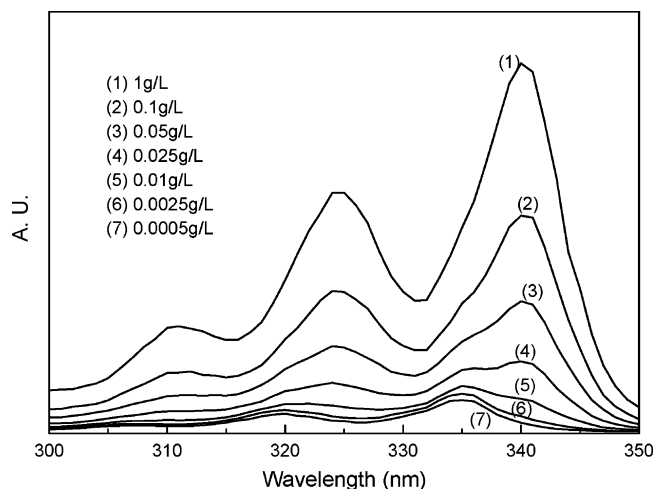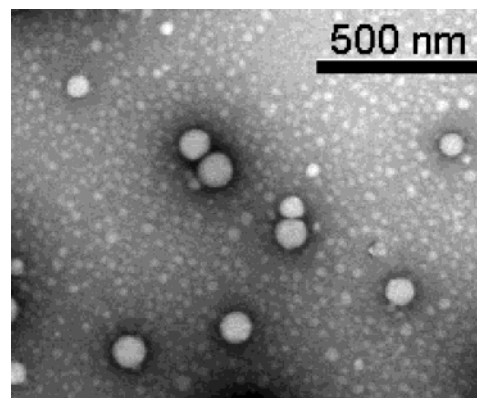
Figure 1. Excitation spectra of pyrene measured in aqueous solutions of polymer **8**, with concentrations from 0.0005 to 1 g/L.

Figure 2. Plot of I_{339}/I_{335} (from pyrene excitation spectra) vs log C for **8** (●) and **10** (○).

Figure 3. TEM image of micelles formed from a 0.5 g/L solution of **9**.

Table 2. Properties of PS−MEEP Micelles

polymer	cmc[a] (mg/L)	K_v	size[b] (nm)	μ_2/Γ^2 [c]
7	1.8	5.75×10^5	167	0.084
8	2.3	3.38×10^5	168	0.153
9	10.0	8.60×10^4	179	0.106
10	13.6	7.31×10^4	173	0.057

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

form of a block copolymer creates possibilities for unique micellar behavior in aqueous media. The aqueous phase characteristics of amphiphilic PS−MEEP block copolymers were studied using fluorescence techniques, DLS, and TEM. Critical micelle concentrations (cmc) of the block copolymers were determined from the excitation spectra of pyrene in aqueous solutions of the PS−MEEP copolymers.[19] The excitation spectra of pyrene in micellar solutions of PS−MEEP copolymers exhibit a shift from 335 to 339 nm, characteristic of the partitioning of pyrene into the hydrophobic core of a micelle (Figure 1). The critical micelle concentrations of the PS−MEEP block copolymers in aqueous media were determined from the ratio of the intensities of these two wavelengths (I_{339}/I_{335}) over a range of PS−MEEP concentrations (Figure 2). At low concentrations, a negligible change in the intensity ratios was detected. However, at some higher concentration, the intensity ratio increases sharply, indicating that the pyrene is transitioning from the aqueous media into the hydrophobic cores of micelles as they are formed. Thus, cmc values were taken as the concentration at which a sharp increase in the I_{339}/I_{335} ratio was seen in Figure 2.[20] The cmc values of PS−MEEP block copolymers were between 1.8 and 13.6 mg/L (Table 2). These values are much lower than those of low molecular weight surfactants (e.g., 2.3 g/L for sodium dodecyl sulfate) but

comparable with those of other polymeric amphiphiles.[21,22] As the ratio of MEEP to PS in the block copolymers increased, larger cmc values were found (Table 2). The aqueous phase behaviors of the block copolymers with the smallest ratios of MEEP to PS (polymers **5** and **6**) could not be investigated. The small hydrophilic portions of these polymers, relative to the size of the hydrophobic PS block, prevented self-association in aqueous media.

The mean diameters (d) of micelles formed from polymers **7**, **8**, **9**, and **10**, measured by dynamic light scattering, were determined to be 167, 168, 179, and 173 nm, respectively (Table 2). A previous study found that the size of a micelle formed from a block copolymer is highly dependent on the size of that copolymer's hydrophobic block.[20] Each of the PS−MEEP block copolymers studied contains a PS block of 50 repeating units, which is a probable cause for the similarity in the measured micellar diameters. The cumulant method was used to estimate the polydispersity factors (μ_2/Γ^2) of the micelles. These values were between 0.057 and 0.153. The size and shape of micelles formed from PS−MEEP block copolymers were also examined by TEM. Figure 3 shows micelles formed from a 0.5 g/L solution of polymer **9**. The micelles show a spherical shape, and the observed diameters are in good agreement with the mean diameters measured using DLS. The observed size distribution of the micelles in the TEM image is also narrow.

Formation of micelles from the PS−MEEP block copolymers was also confirmed by comparing ^{1}H NMR spectra in $CDCl_3$ and D_2O (Figure 4). In $CDCl_3$, which is a good solvent for both polystyrene and MEEP, all the protons from the PS block (1.40−2.25, 6.72, and 7.15 ppm) and the MEEP block (3.45, 3.62, 3.65−3.85, and 4.15 ppm) can be detected clearly. However, a micellar solution of polymer **9** in D_2O shows only signals from the hydrophilic MEEP block. Signals from the hydrophobic PS block (aromatic and aliphatic) were suppressed due to its transition to the interior of the micelle in aqueous media.[23]
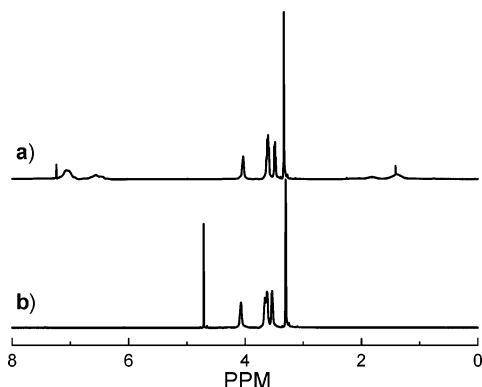
Figure 4. ^{1}H NMR spectra of **9** (a) in CDCl$_3$ and (b) in D$_2$O.
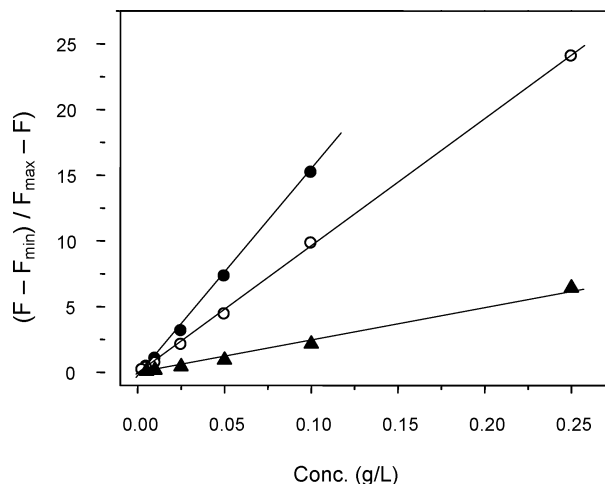
Figure 5. Plot of $(F - F_{min})/(F_{max} - F)$ vs concentration of **7** (●), **8** (○), and **9** (▲) in water.

The Binding Equilibrium. The hydrophobicity of the micellar core was estimated by measuring the equilibrium constant, K_v, for the partitioning of pyrene between the micellar core and the aqueous media.[24] In this work, K_v was calculated following the method suggested by Winnik et al.[16] Assuming a simple equilibrium of pyrene binding to the micelles, the ratio of pyrene concentration in the micellar phase to water phase ($[Py]_m/[Py]_w$) can be correlated to the ratio of volumes of each phase, as expressed in eq 1.

$$[Py]_m/[Py]_w = K_v V_m/V_w \qquad \text{(eq 1)}$$

Equation 1 can be rewritten as

$$[Py]_m/[Py]_w = K_v xc/1000\rho \qquad \text{(eq 2)}$$

where x is the weight fraction of polystyrene, c is the concentration of the amphiphile, and ρ is the density of the polystyrene core of micelles (1.04 g/mL). In the intermediate range of polymer concentration where substantial increases of I_{339}/I_{335} values occur, $[Py]_m/[Py]_w$ can be written as

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

where F_{max} and F_{min} correspond to the average magnitude of I_{339}/I_{335} in the flat regions of the high and low concentration ranges in Figure 2, and F is the intensity ratio (I_{339}/I_{335}) in the intermediate concentration range of the conjugates. Combining eqs 2 and 3, K_v values of pyrene are determined by using a plot ($F - F_{min}$)/

$(F_{max} - F)$ vs PS–MEEP concentration (Figure 5). The K_v values of polymers **7**, **8**, **9**, and **10** were 5.75×10^5, 3.38×10^5, 8.60×10^4, and 7.31×10^4, respectively. This indicates that the partition coefficient of pyrene decreases with increasing lengths of hydrophilic MEEP blocks. K_v values in the range of 2.0×10^5–3.8×10^5 were reported for micelles formed from a PEO–PS block copolymer.[16] In that study, the wt % of PEO ranged from 61 to 91%, and the PS molecular weights varied from 1700 to 11 200 g/mol. The wt % of MEEP in the PS–MEEP block copolymers ranged from 50 to 70%, and the molecular weight of the PS block remained constant at 5000 g/mol. K_v values in the range of 1.79×10^5–5.88×10^5 were reported for poly(2-ethyl-2-oxazoline)–poly(ϵ-caprolactone) and poly(2-ethyl-2-oxazoline)–poly(L-lactide), also similar to those obtained for PS–MEEP block copolymers.[20,25]

Conclusions

Block copolymers that contain a hydrophilic poly[bis-(methoxyethoxyethoxy)phosphazene] segment and a hydrophobic polystyrene segment were synthesized using the living, cationic polymerization of phosphoranimines. The amphiphilic PS–MEEP block copolymers self-associated with form micelles in aqueous media, in which the hydrophobic PS segments were incorporated into the micellar core. The cmc values of 1.8, 2.3, 10.0, and 13.6 mg/L were found for polymers **7**, **8**, **9**, and **10**, respectively, demonstrating the high dependence of micellar characteristics on the ratio of the hydrophilic polyphosphazene and hydrophobic polystyrene blocks. The mean diameters of micelles formed from the PS–MEEP block copolymers were in the range of 167–179 nm, with narrow distributions. The hydrophobic character of the micellar cores was evaluated by measuring the equilibrium constant, K_v, of pyrene in micellar solutions. The K_v values increased with decreasing hydrophilic block lengths.

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