4484 *Macromolecules* **2009**, *42*, 4484–4490
DOI: 10.1021/ma900567n

Macromolecules
ARTICLE

Synthesis of Adamantyl Polyphosphazene−Polystyrene Block Copolymers, and β-Cyclodextrin-Adamantyl Side Group Complexation

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Received March 16, 2009; Revised Manuscript Received April 20, 2009

ABSTRACT: Hydrophobic block copolymers with adamantyl polyphosphazene and polystyrene blocks were synthesized via the controlled cationic living polymerization of a phosphoranimine at ambient temperature. β-Cyclodextrins (β-CDs) were then complexed with the adamantyl side groups in aqueous media to generate amphiphilic block copolymers. These underwent micelle formation in an aqueous environment. The micellar behavior of these complexes was monitored using fluorescence techniques, transmission electron microscopy (TEM), and dynamic light scattering. The critical micelle concentration of the adamantyl polyphosphazene-polystyrene block copolymer complexes was 0.925 mg/L. TEM imaging revealed spherically shaped micelles. A mean diameter of 193 nm was measured by dynamic light scattering. It was possible to control micelle formation by changing the amount of β-CD in the aqueous medium at constant block copolymer concentration.

Introduction

The ability of amphiphilic block copolymers to form micelles is well-known. It is also established that certain block copolymers such as acrylic copolymers modified with adamantane units can be switched from hydrophobic to amphiphilic if one of the blocks can form complexes with hydrophilic conjugate molecules such as cyclodextrins. Such a switching process allows a block copolymer that is insoluble in water to be converted to one that forms micelles. Such processes are of interest because they could form the basis of controlled drug delivery systems triggered by the presence or loss of conjugate molecules in specific regions of the body. An expansion of the portfolio of responsive micelles is clearly needed, especially to include macromolecules that are sensitive to hydrolytic bioerosion to harmless small molecules that can be metabolized or excreted, a property that is not accessible through existing responsive conjugate systems.

In this paper, we describe an initial step toward the synthesis of such a system. Specifically, we have developed a method to produce block copolymers of an adamantane-substituted polyphosphazene connected to polystyrene that can be solubilized to micelles in the presence of aqueous solutions of β-cyclodextrin (β-CD). This is *not* a bioerodible system, but it is a model for block copolymers that contain bioerodible polyphosphazenes that bear hydrophilic and hydrophobic amino acid ester side groups and adamantyl side units. Thus, our objective in this work was to develop a synthesis pathway to responsive micelles, and examine their behavior, as a prelude to use of a similar protocol to produce bioerodible counterparts.

The synthesis of block copolymers that contain polyphosphazene units via the use of a living cationic condensation polymerization has been reported in our earlier studies.[1−12] Specifically, block copolymers that contain two different phosphazene blocks with different side groups, and block copolymers with a phosphazene block and an organic polymer or polysiloxane block have been reported.[2,4−8] In this study, we describe a new block copolymer comprised of an organic hydrophobic polystyrene (PS) block connected to another hydrophobic polyphosphazene that bears adamantyl side groups (APN). β-Cyclodextrin was used to form inclusion complexes with the adamantyl side groups on the phosphazene blocks. The outside of β-CD molecules is hydrophilic because of the presence of numerous hydroxyl groups, while the inside is hydrophobic because of the alkyl moieties. It is well-known that adamantane units form strong complexes with β-CD[13] and that polyrotaxane-type inclusion complexes are formed between CDs and various polymers.[14−20] However, the micellar characteristics of a *polymer*−CD complex system have not been reported. Here we demonstrate that the formation of inclusion complexes between block copolymers and β-CDs does indeed change the micelle forming characteristics of a block copolymer in aqueous media.

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Experimental Section

Materials. Lithium bis(trimethylsilyl)amide, sodium hydride (60%, dispersed in mineral oil), phosphorus trichloride, and sulfuryl chloride were obtained from Aldrich and were used without further purification. Adamantaneethanol (TCI) was used without further purification. Ethanol was dried over calcium hydride (CaH_2) and was distilled before use. Phosphorus pentachloride (Aldrich) was purified by sublimation under reduced pressure before use. The compounds $Cl_3P{=}NSiMe_3$, $(CF_3CH_2O)_3P{=}NSiMe_3$, and $(CF_3CH_2O)_2BrP{=}NSiMe_3$ were synthesized and purified by literature procedures.[21−26] Tetrahydrofuran (THF) and *n*-hexane were distilled into the reaction flask from sodium-benzophenone ketyl under an atmosphere of dry argon. Dichloromethane (CH_2Cl_2) was obtained from Aldrich, 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 vacuum before use. Reactions were carried out using standard Schlenk techniques or an inert atmosphere glovebox (MBraun) under an atmosphere of dry argon or nitrogen.

Equipment. ^1H and ^{31}P NMR spectra were obtained using a Bruker AMX-360 NMR spectrometer, operated at 360 and 146 MHz respectively. ^1H NMR spectra were referenced to tetramethylsilane signals while ^{31}P NMR chemical shifts are relative to 85% phosphoric acid as an external reference, with

 Published on Web 05/13/2009

positive shift values downfield from the reference. All chemical shifts are reported in ppm. Molecular weight distribution data 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 with a 10 mM solution of tetra-*n*-butylammonium nitrate (Aldrich) in THF (OmniSolv).

Synthesis of Adamantyl Polyphosphazene−Polystyrene (APN−PS) Block Copolymer 4. A 25 mL portion of a methylene chloride solution of PCl_5 initiator (0.092 g, 0.44 mmol) and $(CF_3CH_2O)_3P{=}NSiMe_3$ (0.091 g, 0.22 mmol) was stirred at room temperature for 2 h. To this solution, was added $Cl_3P{=}NSiMe_3$ (1.679 g, 7.48 mmol), and the mixture was stirred at room temperature for 4 h. Progress of the reaction was monitored using ^{31}P NMR spectroscopy until complete conversion of the $Cl_3P{=}NSiMe_3$ to poly(dichlorophosphazene) had occurred. A solution of polystyrenyl-phosphoranimine (5000 g/mol, 1.00 g, 0.20 mmol) in methylene chloride was then added to the polyphosphazene solution, and the mixture was stirred for 24 h at room temperature to terminate the polyphosphazene. The CH_2Cl_2 was removed from the reaction mixture under vacuum, and the product was redissolved in distilled THF. An excess of sodium adamantaneethoxide in THF was added to the polymer solution and the mixture was stirred for 24 h at reflux to replace the labile chlorine atoms in the phosphazene blocks. To a solution of the partially substituted polyphosphazenes with adamantaneethoxy groups in THF, was added an excess of sodium ethoxide in THF to complete the replacement of the remaining chlorine atoms. The product was dialyzed against deionized water for 24 h and against water/THF (1/5) for 48 h (Spectra/Por Membrane, MWCO 3 500) to remove any additional impurities. After removal of the solvent, the polymer was redissolved in THF and precipitated into methanol. The block copolymer was isolated as a pale yellow powder (3.50 g, 96%). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, adamantane), 1.57−1.73 (br m, adamantane), 1.97 (s, adamantane), 4.03 (br s, −P−OCH_2−), 6.51−6.62 (brm, −P−Ph (*o*)), 7.01−7.12 (br m, −P−Ph (*m*, *p*)). ^{31}P NMR ($CDCl_3$): δ −7.80 (br s), 18.07 (s).

Preparation of APN−PS Block Copolymer/β-Cyclodextrin Complexes. To a stirred solution of APN−PS (0.02 g, 1.183 μmol) in THF (10 mL) was added dropwise β-cyclodextrin (0.080 g, 0.070 mmol) in D_2O (10 mL). The THF was removed on a rotary evaporator at 40 °C for 1 h. The polymer solution was sonicated for 30 min and stirred vigorously for 24 h.

Polymeric Micelle Sample Preparation. To prepare micellar solutions, the APN−PS block copolymer/β-cyclodextrin complex was dispersed in distilled water with gentle stirring for 3 h, followed by sonication for 30 min. For measurements of the fluorescence spectra of pyrene in the micellar solutions, samples were prepared following a literature procedure.[21−24] The concentrations of the sample solutions were varied from 5×10^{-5} to 1 g/L. To control the β-cyclodextrin concentration in the APN−PS 5 solution, a series of 1.4 mL of β-cyclodextrin solutions of the concentration range from 1.6 to 0.16 g/L was added to 1.4 mL of 0.4 g/L of the APN−PS polymer solutions. These solutions were sonicated for 30 min and stirred vigorously for 24 h. To these APN−PS block copolymer/β-cyclodextrin complex solutions 2.8 mL of 1.2×10^{-6} M of pyrene solution was added and the system was sonicated for 30 min for fluorescence measurements.

Fluorescence Measurements. [27] Fluorescence spectra were obtained using a Yobin Yvon Fluoromax 4 spectrometer. Pyrene was used as a fluorescence probe to analyze the APN−PS block copolymer/β-cyclodextrin complex in doubly distilled water. For the measurement of the pyrene excitation spectra, emission and excitation slit widths were set at 3 and 1.5 nm, respectively. For the excitation spectra, the emission wavelength was 390 nm.

Sizes and Size Distributions. The sizes and size distributions of the block copolymer micelles were evaluated by dynamic light scattering (DLS) using a particle size analyzer (Zetasizer Nano S, Malvern Instruments Ltd.) at room temperature (25 °C) with a scattering angle of 90°. Samples were filtered through a 0.45 μm syringe filter before measurement of particle size for each sample.

Transmission Electron Microscopy. Transmission electron microscopy (TEM) was performed using a JEOL 2010, operated at an acceleration voltage of 200 kV. For observation of the size and distribution of the micellar particles, a drop of sample solution (concentration = 0.1 g/L) was placed onto a 400-mesh copper grid coated with carbon. About 2 min after deposition, the grid was tapped with filter paper to remove surface water, followed by air-drying. Negative staining was performed by using a droplet of a 2.5 wt % uranyl acetate solution.[28] The samples were air-dried before measurements.

Results and Discussion

Synthesis of Block Copolymers. Adamantyl polyphosphazene−polystyrene (APN−PS) 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 amine unit was prepared by quenching living polystyrene with 2,2,5,5-tetramethyl-1-(3-chloropropyl)-1-aza-2,5-disilacyclopentane. The amine-terminated polystyrene was treated with $(CF_3CH_2O)_2BrP{=}NSiMe_3$ to yield the polystyrenyl-phosphoranimine **1**, which served as the macromolecular terminator for the controlled, cationic polymerization of $Cl_3P{=}NSiMe_3$. The addition of **1** to solutions of $[(CF_3CH_2O)_3P{=}N{-}(Cl_2P{=}N)_m{-}PCl_3]^+[PCl_6]^-$ (**2**), yielded polystyrene−poly(dichlorophosphazene) block copolymers (**3**) with controlled phosphazene block length.[9]

The macromolecular substitution reactions of poly(dichlorophosphazene) are known to be sensitive to the steric hindrance of the incoming nucleophile. For example, the replacement of the chlorine atoms in poly(dichlorophosphazene) by bulky aryloxy or arylamino groups often requires forcing experimental conditions and may in some circumstances lead to only incomplete halogen replacement.[29] It has also been reported that complete replacement of all the chlorine atoms in poly(dichlorophosphazene) by adamantanemethoxy groups is not possible under normal reaction conditions.[30] The presence of unreacted phosphorus-chlorine units is likely to lead to long-term hydrolytic instability. Thus, it is necessary to replace the residual chlorine atoms with the use of a less hindered and more reactive reagent.

The nucleophile chosen for this purpose was sodium ethoxide due to the amphiphilic character of the ethoxy group and its low steric profile. Moreover, adamantaneethoxy groups were used instead of adamantanemethoxy groups to achieve higher adamantyl substitution ratios by use of a longer spacer group. Thus, macromolecular replacement of chlorine atoms along the phosphazene block was performed first with sodium adamantaneethoxide followed by treatment with sodium ethoxide. The resultant substitution ratio on the phosphazene block was estimated by ^{1}H NMR to be 9:1 adamantaneethoxy:ethoxy groups (Table 1). This was a much higher adamantyl substitution ratio than the ratio of adamantanemethoxy units to trifluoroethoxy side groups (5:5) in a previous report.[30]

The molar composition ratio of the repeating units of polyphosphazene (PN) to polystyrene (PS) in **4** was 0.64:1.0. The number average molecular weight was estimated by comparing the ^{1}H NMR peak integration ratio of the

Scheme 1. Synthesis of Adamantyl Polyphosphazene−Polystyrene Block Copolymers

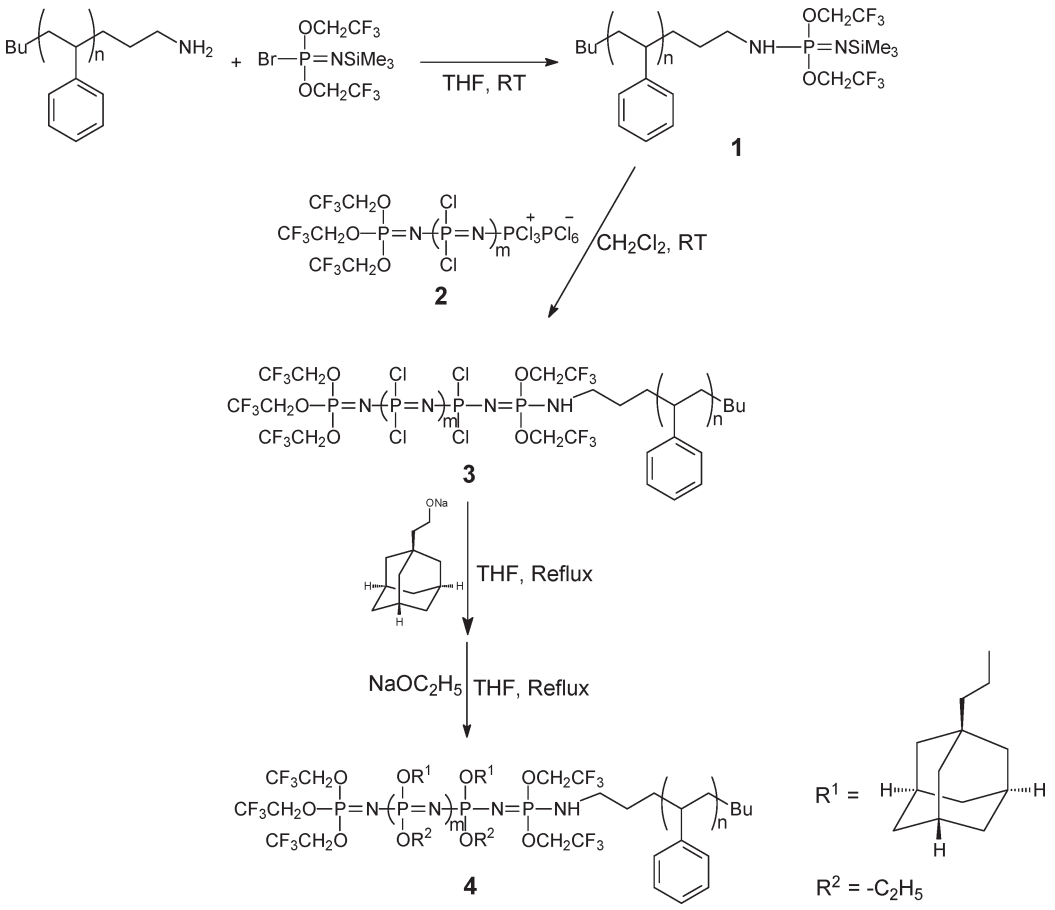


Table 1. Characterization of Adamantyl Polyphosphazene−Polystyrene Block Copolymers

			block ratio (APN:PS)[b]			
block copolymer	yield	M_n (^{1}H NMR)	feed	found	substitution ratio (adamantane ethoxy/ethoxy)[c]	M_n (M_w/M_n)[d]
APN−PS[a]	3.50 g (95%)	16 900	0.72:1.0	0.64:1.0	0.9:0.1	9400 (1.5)

[a] Prepared by using polystyrene with M_n of ~5000 (M_w/M_n = 1.2). [b] Calculated from ^{1}H NMR by comparing aromatic protons (6.51−6.62 ppm and 7.01−7.12 ppm) on PS block to adnamantaneethoxy and ethoxy protons (4.03 ppm) on PN block. [c] Calculated from ^{1}H NMR by comparing ethoxy protons (4.03 ppm) to adnamantantyl protons (1.97 ppm) [d] Measured by GPC.

ethoxy protons of the polyphosphazene at 4.03 ppm and the aromatic protons of the polystyrene at 6.51−6.62 and 7.01−7.12 ppm based on the molecular weight of polystyrene (Table 1 and Figure 1). Gel permeation chromatography was used to estimate average molecular weight and polydispersity values, and these data were compared to the value calculated using ^{1}H NMR (Table 1).

Complexation of Adamantyl Units on the Polyphosphazene Blocks with *β*-Cyclodextrin in an Aqueous Medium. The adamantyl polyphosphazene-polystyrene block copolymer was completely insoluble in water, but the solution became clear in the presence of *β*-cyclodextrin in an aqueous environment. This observation supports the host−guest interactions of the adamantyl groups with the hydrophobic inner cavity of *β*-cyclodextrin and is consistent with micelle formation via a change of the polyphosphazene blocks from hydrophobic to hydrophilic. This means that the overall hydrophobic character of the adamantyl polyphosphazene-polystyrene block copolymers was modified to amphiphilic by *β*-cyclodextrin complexation, which induces the formation of polymeric micelles (Scheme 2). ^{1}H NMR

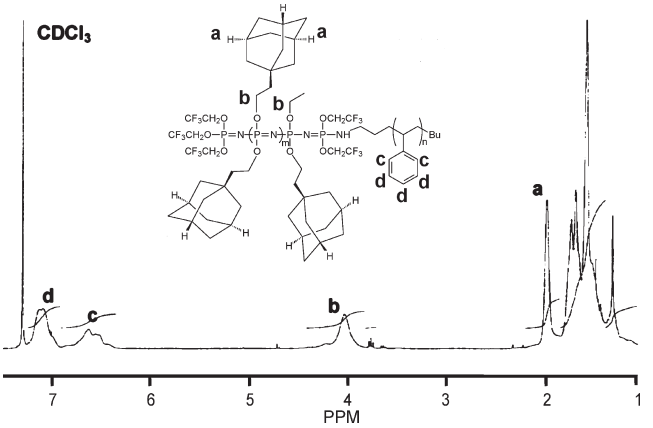
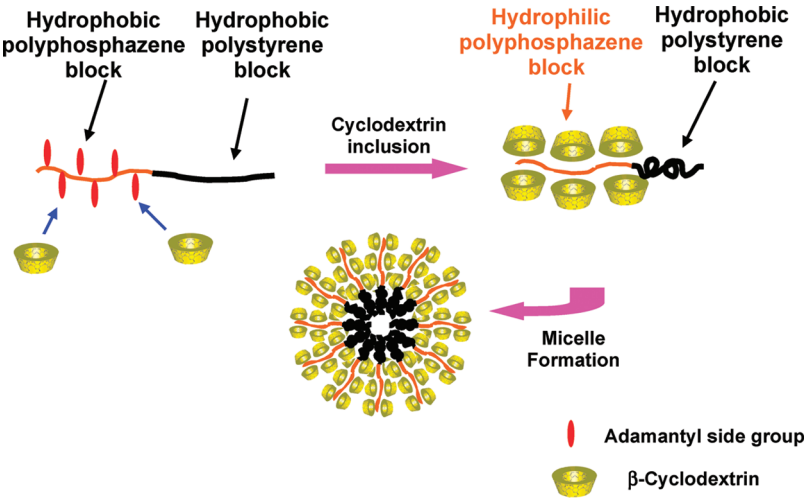


Figure 1. ^{1}H NMR spectrum of adamantyl polyphosphazene−polystyrene block copolymers.

studies were conducted with the block copolymers and *β*-cyclodextrin in D_2O to verify this complexation. The chemical shift of the H-3 proton (3.98 ppm, uncomplexed)

Scheme 2. Formation of Micelles via the Inclusion Complexes of β-Cyclodextrin and Adamantyl Polyphosphazene−Polystyrene Block Copolymers



located at the inner surface of the cyclodextrin cavity was monitored relative to the HDO internal reference (4.79 ppm). As shown in Figure 2, a prominent upfield shift of H-3 ($\Delta\delta$ = −0.0107) was detected for the block copolymer/β-cyclodextrin complex (APN−PS/β-CD) caused by magnetic perturbation due to the adamantane guest group, while the chemical shifts of H-2 and H-4, positioned outside the β-cyclodextrin cavity, were negligible. This observation is consistent with the interpretation that the adamantyl side groups on the polyphosphazene blocks have been encapsulated within the β-cyclodextrin cavity.

Self-association of Block Copolymers Complexed with β-Cyclodextrin in an Aqueous Phase. As discussed above, the adamantyl polyphosphazene-polystyrene block copolymers complexed with β-cyclodextrin switch the properties from hydrophobic to amphiphilic. This provided an opportunity for formation of a self-assembled micellar structure in the aqueous phase. The critical micelle concentration (cmc) was determined by using pyrene as a fluorescence probe, which partitioned into the hydrophobic PS core of the micelles when the system exceeded the critical micelle concentration (cmc).[27,31,32] Because the complexation ability of the adamantyl groups with β-cyclodextrin is much stronger than that of pyrene (the complex stability constant of pyrene at 25 °C is ~2.69[33] compared to the value of 5 for adamantane[34]), the adamantyl groups should not be displaced from the hydrophobic β-cyclodextrin cavity to the outside bulk aqueous solution by the addition of pyrene to the APN−PS/β-CD solutions. The addition of pyrene to an aqueous solution containing 6×10^{-6} M β-cyclodextrin ([pyrene] = 6×10^{-7} M) caused no increase in fluorescence emission. Thus, the complexation of pyrene with β-cyclodextrin should not occur even if it were ten times higher than the concentration of adamantyl groups. On the other hand, APN−PS/β-CD ([APN−PS] = 1.25 g/L, [β-CD] = 6×10^{-6} M and [pyrene] = 6×10^{-7} M) showed a dramatic increase in fluorescence emission by the partition of pyrene molecules into the hydrophobic micellar core. This result strongly suggests that the addition of pyrene to the APN−PS/β-CD solutions after the formation of the adamantyl−β-cyclodextrin complex has no influence on the structural stability of the polymer complexation. Furthermore, this means that APN−PS/β-CD complex should be stable even when more pyrene is added to the system.

The critical micelle concentration (cmc) is an important physical property of micelles which indicates the stability of

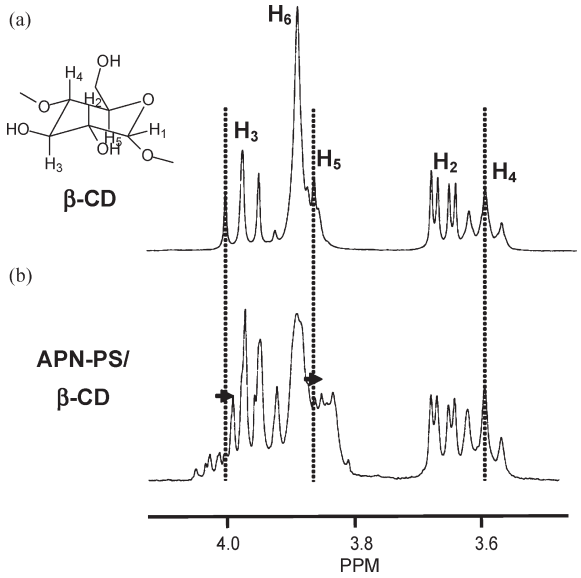


Figure 2. ^{1}H NMR spectra of (a) the uncomplexed β-cyclodextrin and (b) β-cyclodextrin in the block copolymer/β-CD complex in D_2O at 25 °C.

the micellar structure. The excitation and emission spectra of pyrene are shown at varying concentrations of APN−PS/β-CD in Figure 3. In the excitation spectra, increasing concentrations of APN−PS/β-CD caused greater fluorescence intensity at around 339 nm (Figure 3a). It is known that the excitation intensity of pyrene in an aqueous phase is very small at 339 nm, but it increases dramatically when pyrene is partitioned into a hydrophobic environment.[27,32,35] This suggests that the block copolymer complex with β-CD spontaneously forms micelles in aqueous solutions and that this enabled the pyrene to partition into the hydrophobic core of the micelles. Moreover, increasing the concentration of APN−PS/β-CD caused a red shift, a characteristic feature of pyrene excitation spectra. The (0,0) band of pyrene shifted from 334 to 339 nm following the partition of pyrene into the hydrophobic core of the micelles. The fluorescence intensity ratio at the two excitation wavelengths (I_{339}/I_{334}) as a function of the APN−PS/β-CD concentration was used to determine the cmc value of APN−PS/β-CD micelles according to previous reports.[27,32,35] The cmc value determined by this method was about 0.93 mg/L, as shown in Figure 4a.

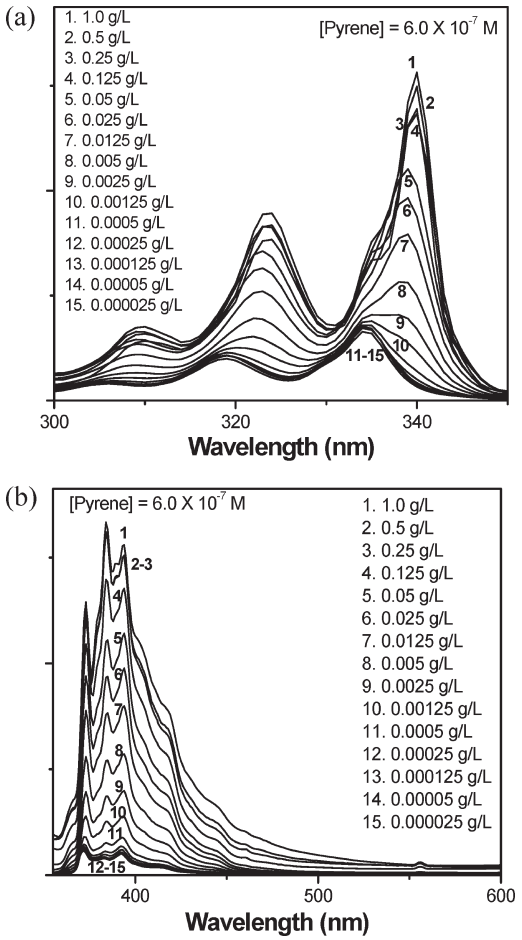


Figure 3. (a) Excitation spectra of pyrene in the presence of APN−PS/β-CD at a fixed emission wavelength of 390 nm, and (b) fluorescence emission spectra of pyrene in the presence of APN−PS/β-CD at a fixed excitation wavelength of 339 nm. The concentration of pyrene was 6×10^{-7} M. The concentration of APN−PS/β-CD was varied from 1 to 2.5×10^{-5} g/L. The concentration of β-CD complexed with APN−PS was varied from 4 to 1.0×10^{-4} g/L.

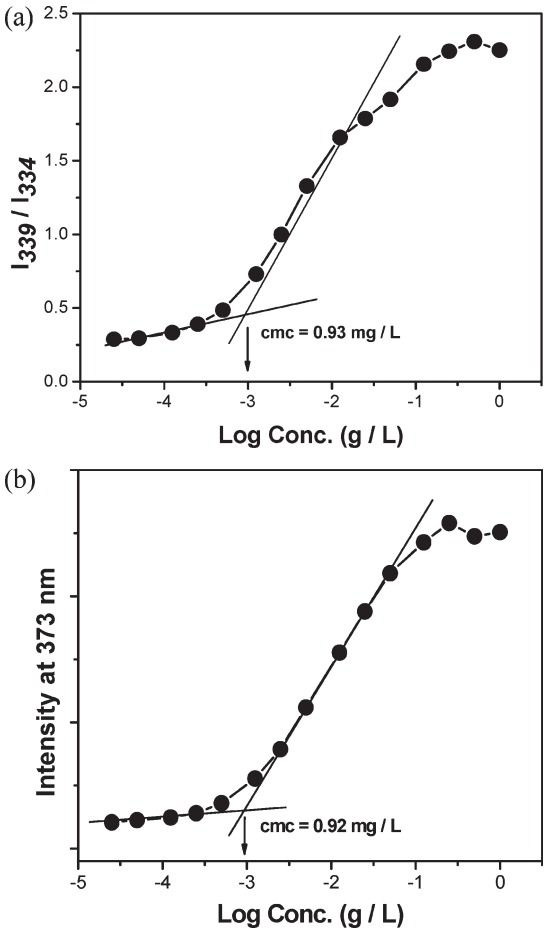


Figure 4. (a) Intensity ratio (339 nm/334 nm) of pyrene in the excitation spectra and the (b) emission intensity of pyrene at 373 nm as a function of logarithm of the APN−PS/β-CD concentration.

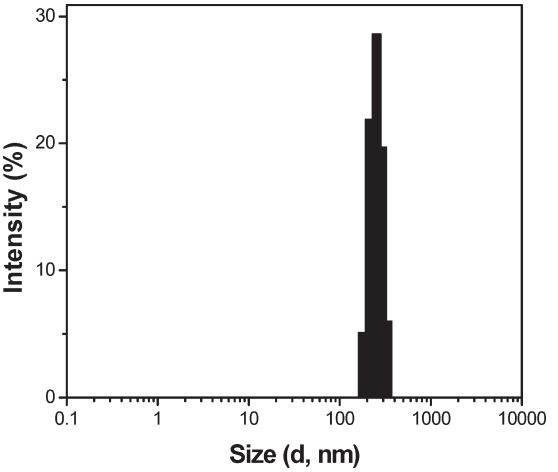
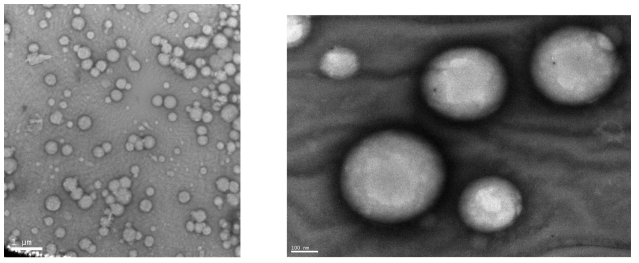


Figure 5. Effective hydrodynamic volume of APN−PS/β-CD micelles analyzed by dynamic light scattering (DLS).

Figure 4b presents another method for determining the cmc value of micelles based on a plot of the pyrene emission at 373 nm as a function of the APN−PS/β-CD concentration. The cmc value of the APN−PS/β-CD micelles by this method was 0.92 mg/L. The difference between the two cmc values obtained by the two methods is negligible. The cmc of the APN−PS/β-CD micelles is much lower than that of oligo(methyl methacrylate)−poly(acrylic acid) micelles (cmc = 100 mg/L) and is even lower than that of poly(ethylene glycol)−poly(lactide) diblock copolymer (cmc $<$ 2 mg/L).[35,36] It is conceivable that the highly hydrophilic character of the β-cyclodextrin outer surface in the shell layer surrounding the PS core provides a more stable corona structure in the micelles in a hydrophilic medium. This indicates that, even with a small concentration of block copolymer, a stable micelle structure can be formed.

Dynamic light scattering (DLS) was carried out to determine the hydrodynamic volume of the micelles, as shown in Figure 5. These experiments suggested an effective diameter of 193 nm with a narrow size distribution. A comparison of the length of the block copolymer chain and the micelle size suggests that the micelles are multicore structures formed by association of individual micelles rather than simple core−shell structures. TEM was also used for the direct visualization of the size and morphology of the micelles. In Figure 6, it can be seen that the micelles formed from a 0.1 g/L solution of APN−PS/β-CD have a spherical shape. 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.

Control of Micelle Formation via β-Cyclodextrin Concentration. The most interesting feature of this block copolymer/β-CD complex system is that the formation of the micelles can be controlled by changing the β-cyclodextrin concentration in an APS-PS block copolymer aqueous solution. As shown in Figure 7, the pyrene fluorescence emission



(a) (b)

Figure 6. TEM micrographs of APN−PS/β-CD micelles. The bars indicate 1 μm for (a) and 100 nm for (b).

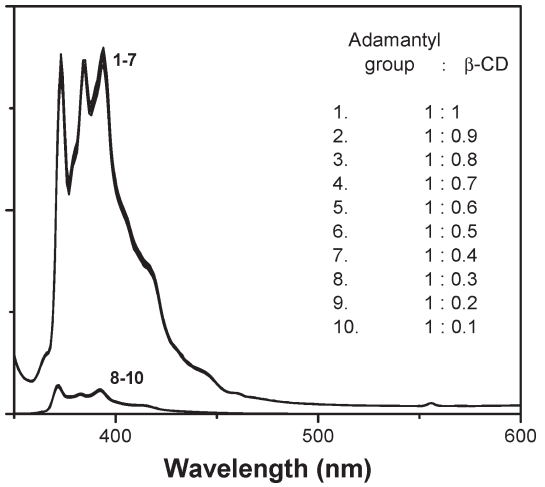


Figure 7. Fluorescence emission spectra of pyrene obtained by changing the β-CD concentration at constant APN−PS concentration at a fixed excitation wavelength of 339 nm. The concentration of pyrene was 6×10^{-7} M, and the concentration of APN−PS was 0.1 g/L.

intensity increased only when more than 40% of the adamantyl groups on the polyphosphazene blocks were complexed with β-cyclodextrin. On the other hand, a fluorescence emission increase was not detected when the β-cyclodextrin ratio to adamantyl group ratio was below 0.3. This observation strongly suggests that a critical concentration of β-cyclodextrin is needed to provide enough hydrophilicity for micelle formation. In this case, the critical ratio between adamantyl groups and β-cyclodextrin units for micelle formation was 1 to 0.4. The cmc values of APN−PS/β-CD complex were also determined by fluorescence excitation and emission of pyrene for the different adamantyl group and β-cyclodextrin ratios above the critical value of 1:0.3 (Figure 8). The measured cmc values were 0.645, 0.755, 0.881, and 0.925 mg/L for the ratios between adamantyl groups and β-cyclodextrin units of 1:0.4, 1:0.6, 1:0.8, and 1:1. As the proportion of the β-cyclodextrin components in the APN block became higher, larger cmc values were generated. This result further suggests that the hydrophilicity of the APN blocks created by β-cyclodextrin complexation is dependent on the amount of β-cyclodextrin in the system. Assuming that all the added β-cyclodextrin can complex with adamantyl groups on the APN blocks, as indicated by the ^{1}H NMR of β-cyclodextrin, this cmc behavior provides us with information that the hydrophilicity of the APN block has a linear relationship with the concentration of β-cyclodextrin. Such controlled micelle formation and critical micelle concentration provides a significant opportunity for the selective encapsulation of guest molecules into the micelle core simply by modifying the concentration of the secondary participant such as β-cyclodextrin.

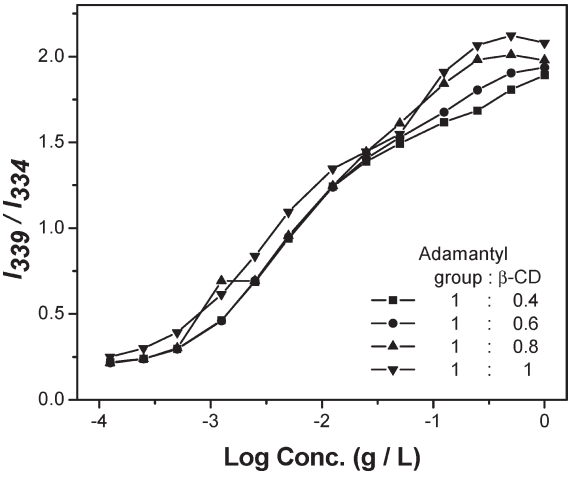


Figure 8. Intensity ratios (339 nm/334 nm) of pyrene in the excitation spectra as a function of the logarithm of APN−PS/β-CD. The concentration of pyrene was 6×10^{-7} M.

Conclusions

Novel block copolymers that contain adamantyl polyphosphazene segments and a polystyrene segment were synthesized using the living, cationic polymerization of phosphoranimines. Adamantyl groups on a phosphazene block are capable of forming inclusion complexes with β-cyclodextrin, and this complexation results in the significant change of block copolymer character from hydrophobic to amphiphilic. The resultant amphilphilic PN−PS block copolymers self-associate to form micelles in aqueous media, in a way that causes the hydrophobic PS segments to be incorporated into the micellar core. A lower cmc value of 0.925 mg/L was found for the block copolymer complex with β-cyclodextrin than for other synthetic amphiphilic block copolymers. This demonstrates that the highly hydrophilic shell of these micelles is due to the hydrophilic cyclodextrin outer surface. The mean diameter of the micelles formed from the APN−PS/β-CD complex was 193 nm with narrow distributions. Significantly, the micelle formation can be manipulated by changes to the β-cyclodextrin concentration in an aqueous medium. This can be used for controlled micelle formation even at higher polymer concentrations.

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