Design of Biodegradable Amphiphilic Polymers: Well-Defined Amphiphilic Polyphosphates with Hydrophilic Graft Chains via ATRP

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ABSTRACT: Novel biodegradable amphiphilic polymers composed of hydrophobic polyphosphate grafted with well-defined hydrophilic poly[2-methacryloyloxyethyl phosphorylcholine (MPC)] were newly synthesized. 2-Isopropyl-2-oxo-1,3,2-dioxaphospholane and 2-(2-oxo-1,3,2-dioxaphosphoroyloxyethyl-2-bromoisobutylate) (OPBB) were copolymerized by ring-opening polymerization using triisobutylaluminum as an initiator. Polyphosphates (PIBr) whose molecular weights were 3.4×10^4 g/mol with 3.0 units of OPBB and 3.7×10^4 g/mol with 10.5 units of OPBB were obtained. MPC was grafted from the OPBB sites in PIBr via atom transfer radical polymerization (ATRP). The molecular weights of the graft copolymers [PIBr-*g*-poly(MPC) (PMPC)] and the amphiphilicity of the graft copolymers were well controllable with polymerization time. The solution properties of various amphiphilic PIBr-*g*-PMPCs were investigated by the methods of surface tension measurement, light scattering, and fluorescence probe. PIBr-*g*-PMPC showed high surface activity. The critical micelle concentration (cmc) of the surface tension of the PIBr-*g*-PMPCs increased with an increase in the molecular weight and density of the PMPC chain. Above the cmc of PIBr-*g*-PMPC with 3.0 units of PMPC per PIBr, the polymer associated and formed nanosize-hydrogels (nanogels) ($R_g = 26.2$ nm) observed by a light scattering method and a fluorescence probe method. Degradation of the PIBr-*g*-PMPC was also investigated under various pH conditions. In a basic condition, the rate of hydrolysis of the graft copolymer was quite large. The polyphosphate of PIBr-*g*-PMPC completely degraded after only 3 days. PIBr-*g*-PMPCs were novel biodegradable amphiphilic polymers.

Introduction

Controlled/"living" radical polymerization has been explored as a means of producing well-defined polymers.[1] Atom transfer radical polymerization (ATRP) is one of the best methods to accomplish this because it can be applied to the polymerization of a wide variety of monomers.[2−5] ATRP has great synthetic power to control the molecular architecture of polymers and is an exceptionally robust method of producing block or graft copolymers.[1,2,6−12]

Amphiphilic block and graft copolymers consisting of hydrophilic and hydrophobic segments are self-assembling materials, which are capable of forming polymeric associates in aqueous solutions, and have been used extensively in both research and technology. Various amphiphilic polymers have been synthesized via ATRP,[3,13−20] and their amphiphilic properties can be well controlled. However, extensive design of biodegradable amphiphilic polymers has not yet been performed via ATRP.

There has been a great deal of interest in polyphosphates, which are biodegradable through hydrolysis and possibly through enzymatic digestion of phosphate linkages under physiological conditions.[21] Biodegradable polyphosphates appear interesting for biological and pharmaceutical applications because of their biocompatibility and structural similarities to naturally occurring nucleic and teichoic acids. Recently, polyphosphates have been proposed for use in the field of tissue engineering as scaffolds and as gene carriers.[22−24] A variety of synthetic routes for polyphosphates has been reported, including ring-opening polymerization,[25,26] polycondensation,[27] transesterfication,[28,29] and enzymatic polymerization.[30] Novel biodegradable amphiphilic polymers with polyphosphates can be then obtained because the solubility of polyphosphates can be controlled with the structures of their side chains.

Recently, we have synthesized polyphosphates bearing isopropyl and methacryloyl groups.[31] These polyphosphates are soluble in ethanol, tetrahydrofuran (THF), and chloroform, but not in water. In the synthesis of amphiphilic polymers in this study, polyphosphates were used as hydrophobic polymers and water-soluble poly[2-methacryloyloxyethyl phosphorylcholine (MPC)] was selected as the hydrophilic graft chain.

We have been studying MPC polymers synthesized as biomimetics in biomembrane structures.[32−35] The MPC polymers exhibit a property that resists nonspecific interaction with plasma proteins and cells.[36,37] Further, it has been shown that the activation and inflammatory response of cells in contact with MPC polymers are not induced.[38,39]

Here, we report the synthesis of a novel biodegradable amphiphilic polymer consisting of polyphosphates prepared by ring-opening polymerization and the well-defined PMPC graft chain. In addition, solution properties of the amphiphilic graft copolymers are investigated.

Materials and Method

Materials. 2-Propanol, THF, acetnitrile, and diisopropylamine (DIPA) were purified by conventional distillation. 2-Chloro-2-oxo-1,3,2-dioxaphospholane (COP) was synthesized according to the method of Edmunson, purified by distillation under reduced pressure, and the fraction of bp 98 °C (1 mmHg) [lit.: bp 79 °C (0.4 mmHg)] was used.[40] 2-Isopropyl-2-oxo-1,3,2-

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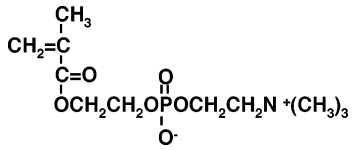
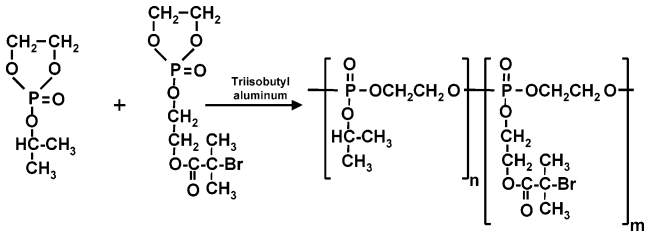


Figure 1. Chemical structure of MPC.

Scheme 1. Synthetic Route of Polyphosphate Bearing Bromoisobutylate (PIBr)



dioxaphospholane (IPP) was synthesized as previously reported,[40] purified by vacuum distillation, and stored under argon at −30 °C until use**.** MPC (Figure 1) was synthesized by the method previously described and purified by recrystallization from acetonitrile.[41] Ethylene glycol was purchased from Kanto Chemical Co., Ltd., Japan. Copper(I) bromide, 2,2′-bipyridine (bpy), and 2-bromoisobutyryl bromide were all purchased from Aldrich and used without further purification. 8-Anilino-1-naphthalene sulfonic acid sodium salt (ANS) was purchased from Tokyo Kasei Co., Ltd., Japan, and used without further purification. Distilled water was obtained by purification using a Millipore Milli-Q system that involves reverse osmosis, ion exchange, and filtration (18.2 MΩ).

Synthesis of Cyclic Phosphate for ATRP Initiator. 2-Hydroxyethyl-2′-bromoisobutylate (HEBB) was synthesized from the reaction of ethylene glycol and 2-bromoisobutyryl bromide and purified by vacuum distillation.[42] COP (0.047 mol) was added dropwise to a THF solution (300 mL) of DIPA (0.047 mol) and HEBB (0.047 mol) at −30 °C for a period of 1 h. The reaction was allowed to continue at −30 °C for another 2 h. The reaction mixture was filtered to correct the precipitate including the diisopropylammonium chloride. The solvent was then reduced by half, and the remaining THF solution was cooled to 0 °C. 2-(2-Oxo,1,3,2-dioxaphospholoyloxy) ethyl-2′-bromoisobutylate (OPBB) was obtained by recrystallization in 67.1% yield. The structure of OPBB was confirmed by ^{1}H NMR (α-500, JEOL, Tokyo, Japan) and FT-IR spectroscopy (FT-500, Jasco, Tokyo, Japan).

^{1}H NMR (500 MHz, $CDCl_3$), δ = OPBB: 1.97 (s; $-CH_3$, 6H), 4.43 (m; $-OCH_2CH_2O-$, 4H), 4.35−4.48 (m; $-OCH_2CH_2O-$ in cyclic phosphate, 4H).

IR: 2910 ($-CH_2-$), 1235 ($-OPO-$), 1089 ($-OPO-CH_2-$) cm^{-1}.

Synthesis of Polyphosphates. Given amounts of IPP and OPBB were placed into a thoroughly dried 50-mL round-bottomed flask equipped with a three-way stopcock. After the mixture was dried under reduced pressure for 2 h, triisobutyl aluminum was added under an argon gas atmosphere. The reaction was continued until the magnetic stirrer was stopped. Dry THF was then added to dilute the reaction mixture. The polyphosphate (PIBr) was purified by reprecipitation from diethyl ether. Scheme 1 and Table 1 show the chemical structure and the synthetic results of the PIBr reaction, respectively.

The weight-averaged molecular weights of the PIBrs were measured using gel-permeation chromatography (GPC) through a Shodex KF-803 column using a calibration curve based on linear polystyrene standards. THF was the GPC solvent. The absolute molecular weight (M_w) of the PIBr was determined by multiangle laser light scattering (MALLS) analysis in batch mode using a Wyatt Dawn DSP−F detector at a flow rate of 1 mL/min in ethanol. The refractive index increment (dn/dc) for the PIBr was measured using a Wyatt OPTILAB DSP detector with a 690 nm light. The absolute M_w was determined by Zimm extrapolation to zero angle and concentration for a series of measurements for five solutions at angles ranging from 50 to 130°.

The absolute M_w, the root-mean-square of gyration (R_g), and the second virial coefficient (A_2) for graft copolymer associates were determined from MALLS analysis using the following equation:

$$\frac{K_c}{R_\lambda} = \frac{1}{M_w}\left(1 + \frac{16\pi^2}{3\lambda^2}R_g{}^2 \sin^2\frac{\theta}{2}\right) + A_2 c \qquad (1)$$

where c denotes the weight concentration of polymer, R_λ is the Rayleigh ratio, θ is the scattering angle, λ is the wavelength of light in the medium, and K is given as

$$K = (4\lambda^2/\lambda_0{}^4 N_A) n_0{}^2 (\mathrm{d}n/\mathrm{d}c)^2 \qquad (2)$$

where λ_0 is the wavelength of light in a vacuum, N_A is Avogadro's number, n_0 is the refractive index of the medium, and dn/dc is the change in refractive index with the concentration of polymers. The mole fraction of the OPBB unit in the PIBr was calculated from ^{1}H NMR data.

ATRP of MPC from Polyphosphate. Because of the sensitivity of the Cu(I) complex to air, all reactions were performed under an argon gas atmosphere. The ethanol used as solvent was first heated to its boiling point and then stored with an argon bubble at room temperature. A given amount of the PIBr (OPBB unit: 0.067 mmol) was desorbed in the ethanol and argon gas was passed through the solution for 30 min to eliminate oxygen. Cu^IBr (9.5 mg, 0.067 mmol) and bpy ligand (21.0 mg, 0.135 mmol) were added to the stirred solution under argon. MPC (2.00 g, 6.73 mmol) was then added to the reaction mixture under argon. The solution was stirred at room temperature for 12 h. After polymerization, the graft copolymer [PIBr-*g*-poly(MPC) (PMPC)] was precipitated into THF, then dissolved in water, and passed through a silica gel column to remove any residual ATRP catalyst. In addition, the elution product was dialyzed for 1 day to remove unpolymerized MPC.

The absolute M_w of the graft copolymers was calculated from the ^{1}H NMR data and the M_w of PIBr determined by the MALLS analysis.

Amphiphilic Properties of PIBr-*g*-PMPC. The surface tension of the PIBr-*g*-PMPC aqueous solutions at various concentrations was measured by the Wilhelmy method with a dynamic contact angle meter (DCA-100, ORIENTEC, Co., Ltd., Tokyo, Japan). The critical micelle concentration (cmc) of the surface tension of the PIBr-*g*-PMPC aqueous solution was obtained from the middle point of the transition state, as summarized in Table 2.

The absolute molecular weight (M_w) of the PIBr-*g*-PMPCs was measured by the MALLS method at the higher concentration of the cmc of the surface tension. To determine the absolute M_w for polymeric associates, the cmc subtracted from the total concentration, c of eq 1. Distilled water was used as the solvent.

Interaction of ANS with a polymer associate was studied to estimate the polarity of the hydrophobic domain inside the polymeric associate. A fixed amount of PIBr-*g*-PMPC was dissolved in 1.0×10^{-5} M ANS aqueous solution. The PIBr-*g*-PMPC solution was further diluted with ANS aqueous solution (1.0×10^{-5}) to a desired concentration of polymer. The internal polarity of the polymer aggregates was evaluated by maximum wavelength from the fluorescence spectra of ANS (λ_{ex} = 350 nm, measurement range 420−650 nm).

The size of the polymeric associate of PIBr3-*g*-PMPC12, which was synthesized 12 h after ATRP of the MPC from the PIBr3, was determined by dynamic light scattering (DLS; Otsuka Electronics, Co., Ltd., Tokyo, Japan). The scattering was performed with a vertically polarized incident beam at a wavelength of 488 nm supplied by an argon ion laser. The measurements were carried out with a scattering angle of 90°, the measurement temperature was 25 °C, and the concentration of the PIBr3-*g*-PMPC12 was 0.5 g/dL.

Table 1. Synthetic Result of Polyphosphate

polyphospate	OPBB/IPP 9 mol %) in feed	OPBB/IPP 9 mol %) in copolymer[a]	yield (%)	M_w ($\times 10^{-4}$)	M_w/M_n[b]	no. of OPBB per PlBr molecule[d]	solubility H_2O	EtOH	THF	CH_3Cl
PIBr3	2.0/98.0	1.5/98/5	76.1	3.9[b] 3.4[b]	1.4	3.0	−	+	+	+
PIBr11	6.0/94.0	5.0/95.0	49.2	3.1[b] 3.7[c]	1.4	10.5	−	+	+	+

[a] Determined by ^{1}H NMR. [b] Apparent molecular weight: determined by GPC. [c] Absolute molecular weight: determined by MALLS with batch mode [d] Calculated from MALLS and ^{1}H−NMR analyses.

Table 2. Transition Point of Surface Tension for PIBr-*g*-PMPC Aqueous Solution

graft copolymer	mol wt[a] ($\times 10^{-4}$)	cmc (g/dL)
PIBr3-*g*-PMPC4	8.4	3.5×10^{-3}
PIBr3-*g*-PMPC6	9.8	3.9×10^{-3}
PIBr3-*g*-PMPC12	13.6	8.6×10^{-3}
PIBr11-*g*-PMPC4	14.8	1.1×10^{-2}
PIBr11-*g*-PMPC6	18.5	2.2×10^{-2}
PIBr11-*g*-PMPC12	25.8	2.3×10^{-1}

[a] Absolute molecular weight: determined by MALLS and ^{1}H NMR analyses.

Hydrolysis of PIBr-*g*-PMPC. Hydrolysis of the PIBr3-*g*-PMPC12 was evaluated by soaking the polymers (0.02 g) in an aqueous media (10 mL) at 37 °C. The pH of the media was adjusted to 4.0 (citric acid/NaH_2PO_4), 7.4 (phosphate buffer solution), or 11.0 (NaOH/NaH_2PO_4). After the polymer was soaked in water for the given time period, the molecular weights were measured and recorded with GPC under aqueous conditions. The chemical structures of the degradation products were confirmed by ^{1}H NMR analyses (α-500, JEOL, Tokyo, Japan).

The weight-averaged molecular weights and molecular weight distribution of PIBr3-*g*-PMPC and degradation products were measured with a Tosoh GPC system with a refractive index detector and size-exclusion columns, Shodex, SB-804 HQ with a poly(ethylene glycol) (PEG, Tosoh standard sample) standard in distilled water containing 10 mM LiBr.

Results and Discussion

Synthesis of Polyphosphates. The chemical structure and synthetic results of polyphosphates are shown in Scheme 1 and Table 1, respectively. Polymerization was homogeneously performed by a solvent-free reaction. As indicated in Table 1, the composition of each monomer unit could be controlled by the feed. The polyphosphates synthesized in this study were soluble in ethanol, THF, and chloroform, but not in water and diethyl ether. The polymer was stored in dry ethanol solution at −80 °C until use. The molecular weights of the polyphosphates were 3.9×10^4 and 3.1×10^4 g/mol by GPC and 3.4×10^4 and 3.7×10^4 by multiangle laser light scattering (MALLS). PIBr3 and PIBr11 contain 3.0 and 10.5 initiator sites per macromolecule, respectively. The PIBrs were novel biodegradable multimacroinitiators for ATRP.

Synthesis of Graft Copolymers via ATRP. ATRP of the MPC from polyphosphate was carried out in an ethanol solution. Figure 2 shows the average number of MPC units in a graft chain of PIBr3-*g*-PMPC and PIBr11-*g*-PMPC as determined by ^{1}H NMR. The numbers increased linearly with an increase in the duration of polymerization. The increment in the number (y) of MPC units in a graft chain with polymerization time (x) (dy/dx) for PIBr3-*g*-PMPC and PIBr11-*g*-PMPC were 7.4 and 4.8, respectively. The rate of polymerization decreased with graft density. This might be due to the steric effect of the bulky MPC. To obtain further information about graft polymerization of PIBr, the molecular weights of PMPC were evaluated by hydrolysis experiments on PIBr-*g*-PMPC. PIBr of PIBr-*g*-PMPC degraded in a basic buffer after 3 days (Table 3). From the results of MALLS and ^{1}H NMR analyses, the M_w of the PMPCs grafted from PIBr3 and PIBr11 were 3.4×10^4 and 2.1×10^4, respectively. The molecular weights of the graft chains cleaved from PIBr3 and PIBr11 determined by GPC were calculated to be 3.1×10^4 and 2.4×10^4, respectively, and coincident to the calculated values of PMPC, as shown in Table 3. Moreover, the molecular distribution of PMPC grafted from PIBr was quite narrow ($M_w/M_n = 1.2$). The polymerization proceeded homogeneously in every initiator site in PIBr. Figure 3 is a schematic representation of PIBr and PIBr-*g*-PMPC synthesized in this study. A wide variety of polymer architectures can be well controlled.

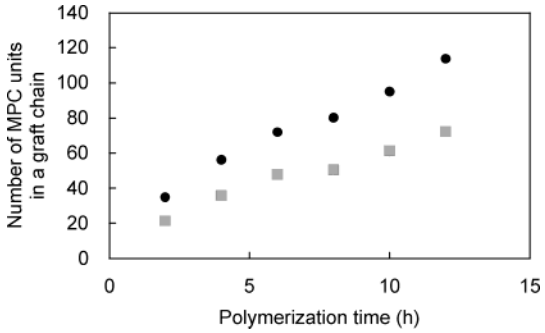


Figure 2. Change in number of units of MPC in a graft chain during ATRP: (circle) PIBr3-*g*-PMPC; (square) PIBr11-*g*-PMPC.

Table 3. Molecular Weight of PIBr-*g*-PMPC before and after Hydrolysis

graft copolymer	mol wt ($\times 10^{-4}$) synthesized polymer[a]	mol wt ($\times 10^{-4}$) polymer after soaking in basic buffer for 3 days
PIBr3-*g*-PMPC12	13.6	3.4[a] 3.1 (1.2)[b]
PIBr11-*g*-PMPC12	25.8	2.1[a] 2.4 (1.2)[b]

[a] Absolute molecular weight: determined by MALLS and ^{1}H NMR analyses. [b] Apparent molecular weight: determined by GPC. Molecular weight distribution is given in parentheses.

Surface Activity of Graft Copolymers. Figure 4 shows the surface tension of graft copolymers in water as a function of polymer concentration. As the polymer concentration increased, the surface tension decreased from 72 to about 40 dyn/cm. Changes in the surface tension are typically observed in the micelle formation of polymer amphiphiles. The cmc of the graft copolymers was evaluated from the change in the surface tension. The cmc increased with an increase in the M_w of the graft copolymer and the density of PMPC, as shown in Table 2. Typical examples of the concentrations of PIBr3-*g*-PMPC12 and PIBr11-*g*-PMPC12 are 8.6×10^{-3} and 2.3×10^{-1} g/dL, respectively. Although the density

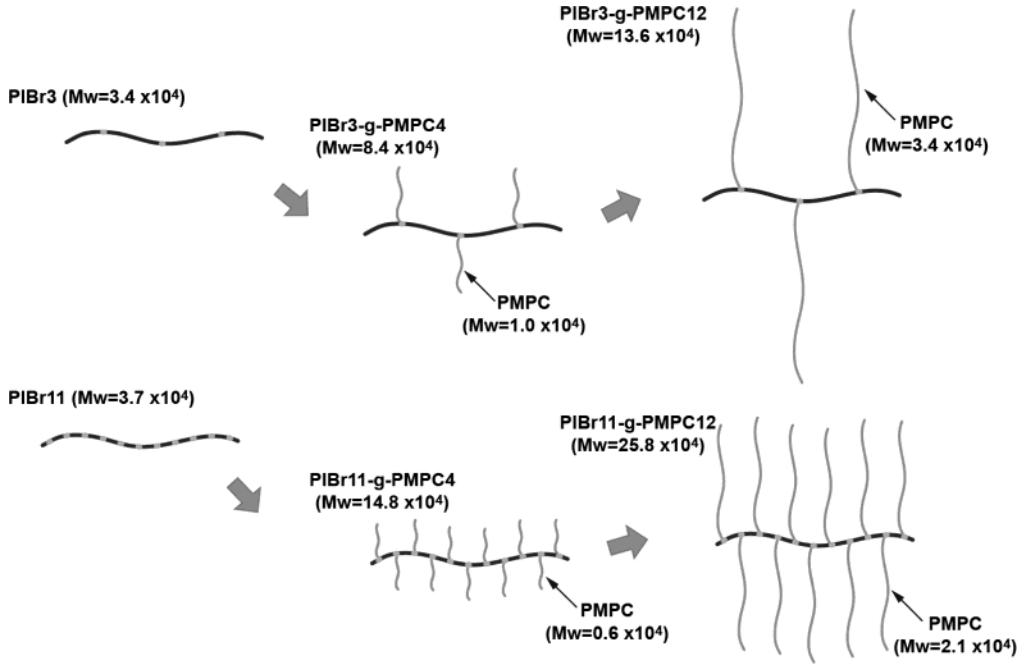


Figure 3. Schematic representation of PIBr and PIBr-*g*-PMPC.

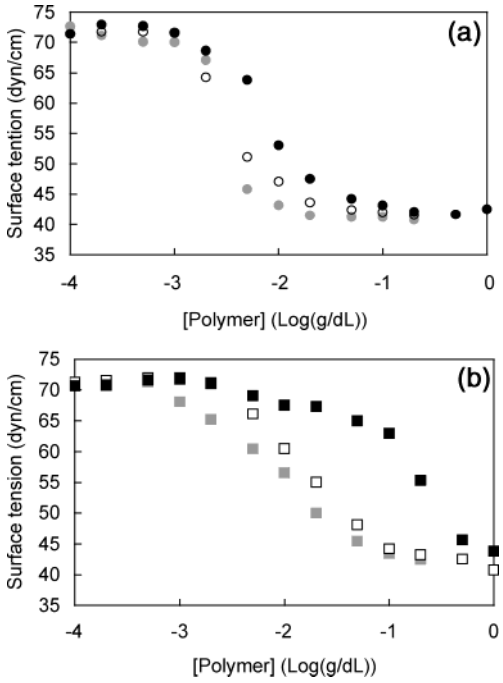


Figure 4. (a) Surface tension of PIBr3-*g*-PMPC in aqueous solution: (gray) PIBr3-*g*-PMPC4; (white) PIBr3-*g*-PMPC6; (black) PIBr3-*g*-PMPC12. (b) Surface tension of PIBr11-*g*-PMPC in aqueous solution: (gray) PIBr11-*g*-PMPC4; (white) PIBr11-*g*-PMPC6; (black) PIBr11-*g*-PMPC12.

and molecular weight of the PMPC affected the cmc of the PIBr-*g*-PMPC, the equilibrium surface tension reached 40 dyn/cm in every graft polymer. The polyphosphates of the graft copolymers act as hydrophobic polymers of the polymer surfactants. The cmc can be controlled with retaining high surface activity by their well-controlled molecular architectures.

Solution Property of Graft Copolymers in Water. Micelle formations were also investigated by the fluorescence probe method. Figure 5 shows typical fluorescence spectra of ANS in an aqueous solution of the PIBr3-*g*-PMPC12 at different concentrations. Weak fluorescence was observed in the ANS aqueous solution without the PIBr3-*g*-PMPC12. However, the fluorescence intensity of the ANS solution increased as the polymer concentration increased, and the peak shifted to a shorter wavelength. Figure 6 shows the dependence of the maximum fluorescence peak wavelength of ANS in the PIBr3-*g*-PMPC12 and PIBr11-*g*-PMPC12 aqueous solutions on its concentration. The behavior change in the wavelength of ANS in the polymer solutions was similar to that of their surface tensions.

The maximum fluorescence wavelength of ANS is influenced by the polarity of the microenvironment[43] and is lower with the lower polarity. The results in Figure 6 suggest the formation of hydrophobic domains upon the association of hydrophobic polyphosphates of both graft copolymers. The relationship between polarity and the maximum fluorescence peak wavelength of ANS is known.[44] From these data, the polarity of the hydrophobic domain is similar to the polarity of methanol.

The hydrodynamic radii (R_h) of the solution of PIBr3-*g*-PMPC12 and PIBr11-*g*-PMPC12 above cmc were measured by DLS. R_h of PIBr11-*g*-PMPC12 was not determined due to the low intensity of light scattering. PIBr11-*g*-PMPC12 probably exists as a monomer as does the unimer micelle because of the brush-type structures with long hydrophilic PMPC chains. In contrast, R_h in PIBr3-*g*-PMPC12 was 16.4 nm although the molecular weight of PIBr3-*g*-PMPC12 ($M_w = 13.6 \times 10^4$) is less than that of PIBr11-*g*-PMPC12 ($M_w = 25.8 \times 10^4$). PIBr3-*g*-PMPC12 may form nanoparticles by the intermolecular association. To obtain further information on the nanoparticles, static light scattering (MALLS) was performed.

Figure 7 shows the Zimm plot of PIBr3-*g*-PMPC12 at a concentration of 0.1−0.5 g/dL. The d*n*/d*c* of PIBr3-*g*-PMPC12 in aqueous solution was 0.119 and the effect of molecular weight PMPC on d*n*/d*c* was not observed. On the basis of this plot, M_w and R_g of the polymeric associate were 94.1×10^4 and 26.2 nm, respectively. The molecular weight of PIBr3-*g*-PMPC12 can be estimated at 13.6×10^4 from the absolute molecular weight of PIBr3 and ^{1}H NMR analysis. Thus, the association

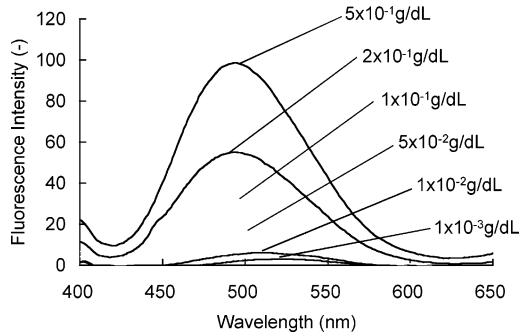


Figure 5. Fluorescence spectra of ANS incorporated in PIBr3-*g*-PMPC12 in aqueous solution.

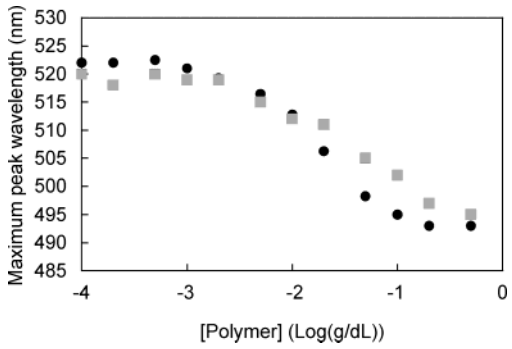


Figure 6. Concentration dependence of maximum fluorescence wavelength of incorporated ANS: (circle) PIBr3-*g*-PMPC12; (square) PIBr11-*g*-PMPC12.

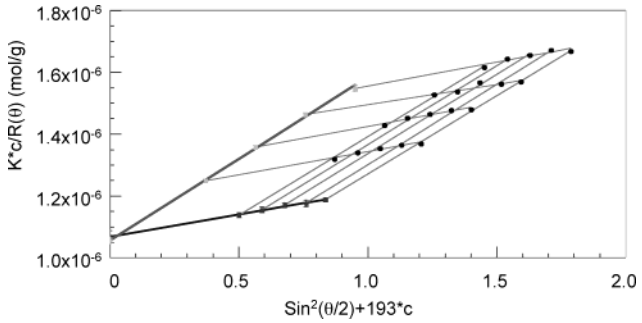


Figure 7. Zimm plot of associated PIBr3-*g*-PMPC12.

number of the PIBr3-*g*-PMPC12 was 6.9. It is well-known that the R_g/R_h ratio changes from infinity to 0.775 when the polymer structure changes from rod to sphere, with values from 1.3 to 1.5 for random coils.[45] The R_g/R_h ratio of the PIBr3-*g*-PMPC12 associate was 1.59, suggesting a slightly extended conformation of the polymer chain.

The average polymer density (ϕ_g) was calculated by R_h and M_w of the polymer by the following equation:

$$\phi_g = \frac{M_w}{N_A\left(\frac{4}{3}\pi {R_h}^3\right)^{-1}} \quad (3)$$

The density was estimated to be 8.4 wt %. The nanoparticles can be considered nanosized hydrogels (nanogels) containing 8.4 wt % polymers and 91.6 wt % water. The associate domains of the hydrophobic polyphosphates are cross-linking points of hydrogels although the detailed structure is not yet clear.

Considerable study has been given to the synthesis and structures of micelles from amphiphilic block copolymers.[46−50] In particular, there are interests in biomedical applications,[51,52] and novel block copolymers

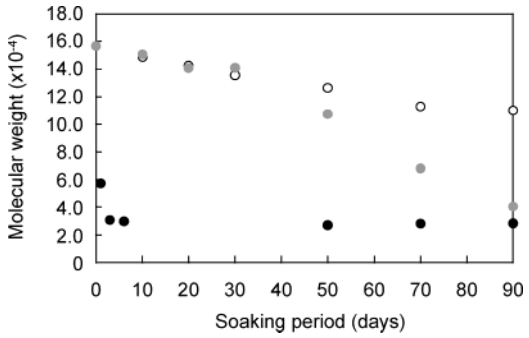


Figure 8. Degradation of profiles of PIBr3-*g*-PMPC12 in various pH aqueous media: (gray) pH 4.0; (white) pH 7.4; (black) pH 11.0.

containing PMPC moieties have been synthesized.[53,54] However, a few graft copolymers have been reported to form micelles.[43,55−57] Moreover, most graft copolymers reported in micelle formation have hydrophilic backbones. This is probably due to difficulties in synthesizing amphiphilic graft copolymers with controlled structures. Graft copolymers with hydrophobic backbones are rarely reported.[58−60] PIBr-*g*-PMPCs form polymer micelles by hydrophobic interaction of hydrophobic polyphosphates. The hydrophobicity of the polyphosphate may be controllable by changing the chemical structure of the side chain instead of the 2-isopropyl groups. The present synthetic procedure for PIBr-*g*-PMPCs is very suitable for synthesizing well-defined amphiphilic graft copolymers. PIBr3-*g*-PMPC12 formed novel nanogels of graft copolymers with biodegradable hydrophobic backbones. In biotechnology and medicine, nanogels with the characteristics of both nanoparticles and hydrogels have attracted growing interest as nanobiomaterials.[61,62]

Hydrolysis of Nanogels of Graft Copolymers. A degradation profile of nanogels of PIBr3-*g*-PMPC12 was investigated in aqueous media with various pH values, as shown in Figure 8. In an acidic medium, the loss of molecular weight of the graft copolymer was observed as being less and degradation occurred markedly after 50 days of soaking. Under physiological pH conditions, the weight-averaged molecular weight of the PIBr-*g*-PMPC decreased from 15.6×10^4 to 11.0×10^4 after 90 days. Under basic conditions, the polymers degraded nearly completely within 3 days. Although the basic condition used (pH 11.0) is not a physiological condition, we chose the optimal pH to characterize the degradation behavior of polyphosphates in a relatively short period. Under acidic conditions (pH 4.0), hydrolysis of the PIBr was slow. In contrast, under basic conditions (pH 11.0), the PIBr was completely degraded in only 3 days. Penczek et al. reported the hydrolysis of poly(methyl ethylene phosphate) in the range from pH 1 to pH 12.[63] Under basic conditions, the rate of hydrolysis of the main chain (k_m) was dramatically faster (1.32×10^{-5} s^{-1} at pH 11.16) than that under acidic conditions (1.14×10^{-8} s^{-1} at pH 3.78). The nanogel structure may be significant in the hydrolyzation of hydrophobic polyphosphates. Nanogels of PIBr3-*g*-PMPC12 are novel biodegradable nanoparticles.

Conclusions

PIBrs were synthesized as novel biodegradable multimacroinitiators for ATRP. The novel biodegradable amphiphilic graft copolymers, which consist of a hydrophobic polyphosphate backbone and hydrophilic PMPC graft chains, were synthesized via ATRP. The graft

copolymers with varied densities of PMPC could be obtained and the molecular weight of PMPC was monodisperse and well controllable. The polymers associate in aqueous solutions and form polymer micelle or nanogels. The associative properties were controlled by the architecture of the graft copolymer. PIBr-*g*-PMPCs are novel biodegradable building blocks for constructing polymer self-assembly. The polymer is hydrolyzable in aqueous solutions and PMPC could be obtained as a degradation product. We have reported that the PMPC has excellent biocompatibility.[64] The graft copolymers synthesized might be novel functional polymeric biomaterials, which could be used for diagnostic and drug delivery applications.

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