Comparison of Micelles Formed by Amphiphilic Poly(ethylene glycol)-*b*-Poly(trimethylene carbonate) Star Block Copolymers

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ABSTRACT: In this article, we describe the synthesis and solution properties of PEG-*b*-PTMC star block copolymers via ring-opening polymerization (ROP) of trimethylene carbonate (TMC) monomer initiated at the hydroxyl end group of the core PEG using HCl Et_2O as a monomer activator. The ROP of TMC was performed to synthesize PEG-*b*-PTMC star block copolymers with one, two, four, and eight arms. The PEG-*b*-PTMC star block copolymers with same ratio of between hydrophobic PTMC and hydrophilic PEG segments were obtained in quantitative yield and exhibited monomodal GPC curves. The amphiphilic PEG-*b*-PTMC star block copolymers formed spherical micelles with a core–shell structure in an aqueous phase. The mean hydrodynamic diameters of the micelles increased from 17 to 194 nm with increasing arm number. As arm number increased, the critical micelle concentration (CMC) of the PEG-*b*-PTMC star block copolymers increased from 3.1×10^{-3} to 21.1×10^{-3} mg/mL but the partition equilibrium constant, which is an indicator of the hydrophobicity of the micelles of the PEG-*b*-PTMC star block copolymers in aqueous media, decreased from 4.44×10^4 to 1.34×10^4. In conclusion, we confirmed that the PEG-*b*-PTMC star block copolymers form micelles and, hence, may be potential hydrophobic drug delivery vehicles. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 111: 1706–1712, 2009

Key words: poly(ethylene glycol); poly(trimethylene carbonate); star block copolymer; micelle

INTRODUCTION

Star polymers with well-defined structures are of considerable interest in the understanding of the fundamental question of how macromolecular architecture in comparison with linear polymers can affect polymer properties.[1–3] Amphiphilic block copolymers are well known to self-assemble into core–shell micelles when they are dissolved in selective solvents, which are thermodynamically favorable for one block but unfavorable for the other.[4–6] From the viewpoint of star polymers and amphiphilic block copolymers, amphiphilic star block copolymers with hydrophilic and hydrophobic block might induce much interest because of their useful rheological and mechanical properties and are expected to display diverse morphologies in comparison with linear amphiphilic block copolymers.[7,8] Amphiphilic star block copolymers can form micelles in aqueous phase and be utilized in various applications, such as in drug delivery and colloidal applications, depending upon the structure of their core and shell and their size and shape.[9,10] The structural properties of micelles such as the micelle size and the critical micelle concentration (CMC) can be mainly affected by the chemical composition and the structural architecture of the amphiphilic star block copolymer.[11,12]

Poly(ethylene glycol) (PEG) has nontoxicity and has been found to possess biocompatibility demanded when introducing synthetic materials into biomedical applications.[13] Poly(trimethylene carbonate) (PTMC) is an attractive material for biomedical application, such as drug delivery carrier, tissue engineering, surgical sutures, and etc., because of its good biodegradability and biocompatibility.[14–16] Recently, considerable effort has been devoted to creating biodegradable PEG-*b*-PTMC block copolymers.[17,18] In particular, PEG-*b*-PTMC star block copolymers consist of radially extended PTMC block

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arms attached to a central PEG core should have great influence on the properties of star polymers. One route for preparing PEG-*b*-PTMC star block copolymers is via the ring-opening polymerization (ROP) of trimethylene carbonate (TMC) by the hydroxyl end group of PEG. The usually utilized method in the preparation of PEG-*b*-PTMC star block copolymers by ROP of TMC for PEG as an initiator is using stannous or metal catalysts.[19,20] However, some problems have been found in the star block copolymers obtained by ROP using stannous or metal catalysts, including incomplete catalyst removal.[21]

Here, we describe the synthesis of PEG-*b*-PTMC star block copolymers via ROP of TMC from the one-, two-, four-, or eight-hydroxyl end group of core PEG in the presence of HCl Et_2O as a monomer activator, as we believe this method has a possibility of utilizing to a wide range of TMC monomers leading to PEG-*b*-PTMC star block copolymers with controlled characteristics. Then, we examine the micelle formation behavior of the star block copolymers to understand how the number of arms of PEG-*b*-PTMC star block copolymers influences the CMC and partitioning of the hydrophobic molecule pyrene.

RESULTS AND DISCUSSION

Preparation of PEG-*b*-PTMC star block copolymers

MPEG-OH and HO-PEG-OH (M_n, 2000 g/mol), and PEG molecules with four or eight terminal alcohols (M_n, 2000 g/mol) were used as the initiator to prepare one-, two-, four-, or eight-arm PEG-*b*-PTMC star block copolymers. All PEG-*b*-PTMC star block copolymers were designed to have a constant value of 2000 g/mol for the molecular weights of the hydrophobic and hydrophilic segments. Thus, the length of PTMC in the designed PEG-*b*-PTMC star block polymers is shorted as the arm number increased.

One-arm (1a-MPEG-*b*-PTMC), two-arm (2a-PTMC-*b*-PEG-*b*-PTMC), four-arm (4a-PEG-*b*-PTMC), and eight-arm (8a-PEG-*b*-PTMC) star block copolymers were synthesized via the ROP of TMC as the monomer using the terminal alcohol of PEG as an initiator in the presence of HCl Et_2O at room temperature. PEG-*b*-PTMC star block copolymers were prepared at quantitative yield by using HCl Et_2O as a monomer activator. The ^{1}H NMR spectra for 1a-MPEG-*b*-PTMC and 8a-PEG-*b*-PTMC are shown in Figure 1(a,b). The 1a-MPEG-*b*-PTMC exhibited characteristic peaks of PTMC and MPEG. Terminal methoxy protons (1) and methylene protons (2) of MPEG were observed at $\delta = 3.39$ and 3.69 ppm, respectively. The signals (4–6) assignable to the sequence of α, γ, and β-methylene protons of the carbonate carbonyl moiety of PTMC were also observed at = 4.2–4.3 and 2.08 ppm, respectively. The 8a-PEG-*b*-PTMC star block copolymer also exhibited characteristic peaks for methylene protons of the carbonate of PTMC as a shell and methylene protons of glycerol moiety and PEG as a core.

The molecular weights can be calculated by integration of the ^{1}H NMR spectra, that is, by calculating the ratio of the ethylene oxide protons of the PEG main chain to the characteristic methylene protons of the PTMC main chain (ethylene oxide units/TMC units). The molecular weight values calculated in this manner are in excellent agreement with the theoretical values ([2000]/[2000] g/mol) calculated from the PEG/PTMC ratio employed (Table I). The GPC curve completely shifted to longer retention

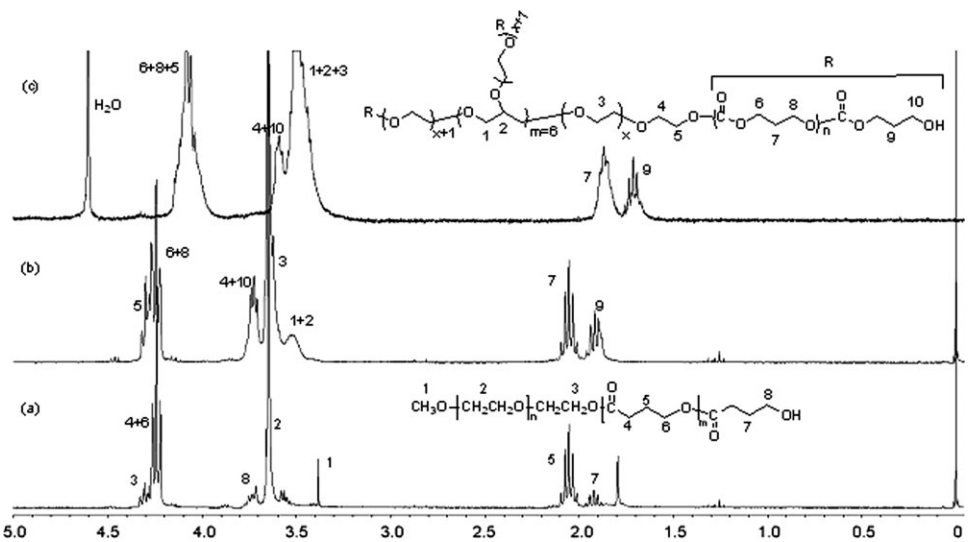

Figure 1 ^{1}H NMR spectra of (a) 1a-MPEG-*b*-PTMC, (b) 8a-PEG-*b*-PTMC in $CDCl_3$, and (c) 8a-PEG-*b*-PTMC in D_2O.

TABLE I
Synthesis of PEG-*b*-PTMC Star Block Copolymers

	[M]/[I]	$M_{n,\ calcd}$ PEG[a] – PTMC	Yield[b] (%)	$M_{n,\ NMR}$[c] PEG-PTMC	M_w/M_n[d]
1a-MPEG-*b*-PTMC	19.6	2000–2000	95	2000–2200	1.19
2a-PTMC-*b*-PEG-*b*-PTMC	19.6	2000–2000	93	2000–2100	1.21
4a-PEG-*b*-PTMC	19.6	2000–2000	97	2000–2100	1.28
8a-PEG-*b*-PTMC	19.6	2000–2000	99	2000–2200	1.41

[a] MPEG-OH = 2000 (M_w/M_n = 1.08), HO-PEG-OH = 2000 (M_w/M_n = 1.09), PEG-$(OH)_4$ = 2000 (M_w/M_n = 1.10), PEG-$(OH)_8$ = 2000 (M_w/M_n = 1.14).
[b] *n*-Hexane insoluble part.
[c] Determined by ^{1}H NMR.
[d] Measured by gel permeation chromatography (based on standard polystyrene).

times after the polymerization compared with the curve for the PEG precursor and exhibited a monomodal without any trace of dead polymer, indicates that the homopolymerization of PTMC occurred to a negligible degree. The molecular weight distribution (M_w/M_n) of the star polymers broadened slightly as the arm number increased. These findings indicate that the PTMC shell was incorporated into PEG core and, thus, all of the PEG hydroxyl groups acted as initiators to give the PEG-*b*-PTMC star block polymers.

Study of micelles

As described in the previous section, we successfully prepared PEG-*b*-PTMC star block copolymers of which hydrophobic and hydrophilic segments had almost same molecular weights. The amphiphilic nature of the segments of these PEG-*b*-PTMC star block copolymers means that they can form micelles with a core–shell structure in an aqueous phase. As one example, Figure 1(c) shows the ^{1}H NMR spectrum for 8a-PEG-*b*-PTMC star block copolymers at 1 wt % concentration in D_2O at room temperature. Compared with the spectrum of this star block copolymer in $CDCl_3$ [Fig. 1(b)], which showed clear peaks assignable to both the PEG and PTMC blocks, the peaks arising from the PTMC blocks are broader in the D_2O spectra. This indicates that PTMC blocks preferably locate inside the core of the micelles, and consequently, PTMC molecular motion are limited by PEG or water, compared with PEG blocks located at the outer shell of the micelles in an aqueous phase.

Figure 2 shows pictures of 1a-MPEG-*b*-PTMC, 2a-PTMC-*b*-PEG-*b*-PTMC, 4a-PEG-*b*-PTMC, and 8a-PEG-*b*-PTMC star block copolymers at 1 wt % concentration in deionized water at room temperature. The turbidity of the solution indicates the micelle formation of the star block copolymers. Inspection of the solutions reveals that the turbidity increases with increasing arm number. The mean hydrodynamic diameters of the micelles, as determined from dynamic light scattering (DLS) measurements, also increased from 17 to 194 nm with increasing arm number (Fig. 3). This change in mean hydrodynamic diameter might be due to the structural architecture of the block copolymer, where the decreasing length of the hydrophobic core forming block with increasing arm number restricts aggregation.

To explore the morphologies of the micelles, we used AFM to examine the micelles of the star block copolymers (Fig. 4). The AFM images revealed that most of the micelles were spherical, with nonspherical micelles being observed only rarely. The diameters of the micelles observed by AFM were in good agreement with the values determined from DLS observations.

Next, fluorescence measurements using pyrene as a probe were carried out to determine the CMCs of the PEG-*b*-PTMC star block copolymers in aqueous solution at room temperature. Fluorescence probe analysis constitutes a simple yet a very versatile technique for the study of properties of aggregated micelles. When a pyrene as hydrophobic probe is transferred to the micellar phase of PEG-*b*-PTMC star block copolymers, it is preferentially localized inside or close to the hydrophobic microdomain of micelles. Hence, the photophysical characteristics of

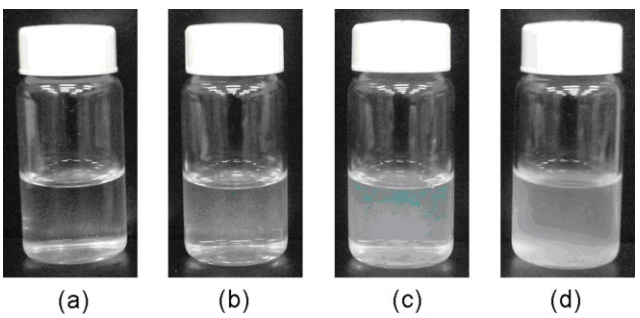

Figure 2 Images of the micelle solutions formed from PEG-*b*-PTMC star block copolymers, (a) 1a-MPEG-*b*-PTMC, (b) 2a-PTMC-*b*-PEG-*b*-PTMC, (c) 4a-PEG-*b*-PTMC, and (d) 8a-PEG-*b*-PTMC. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

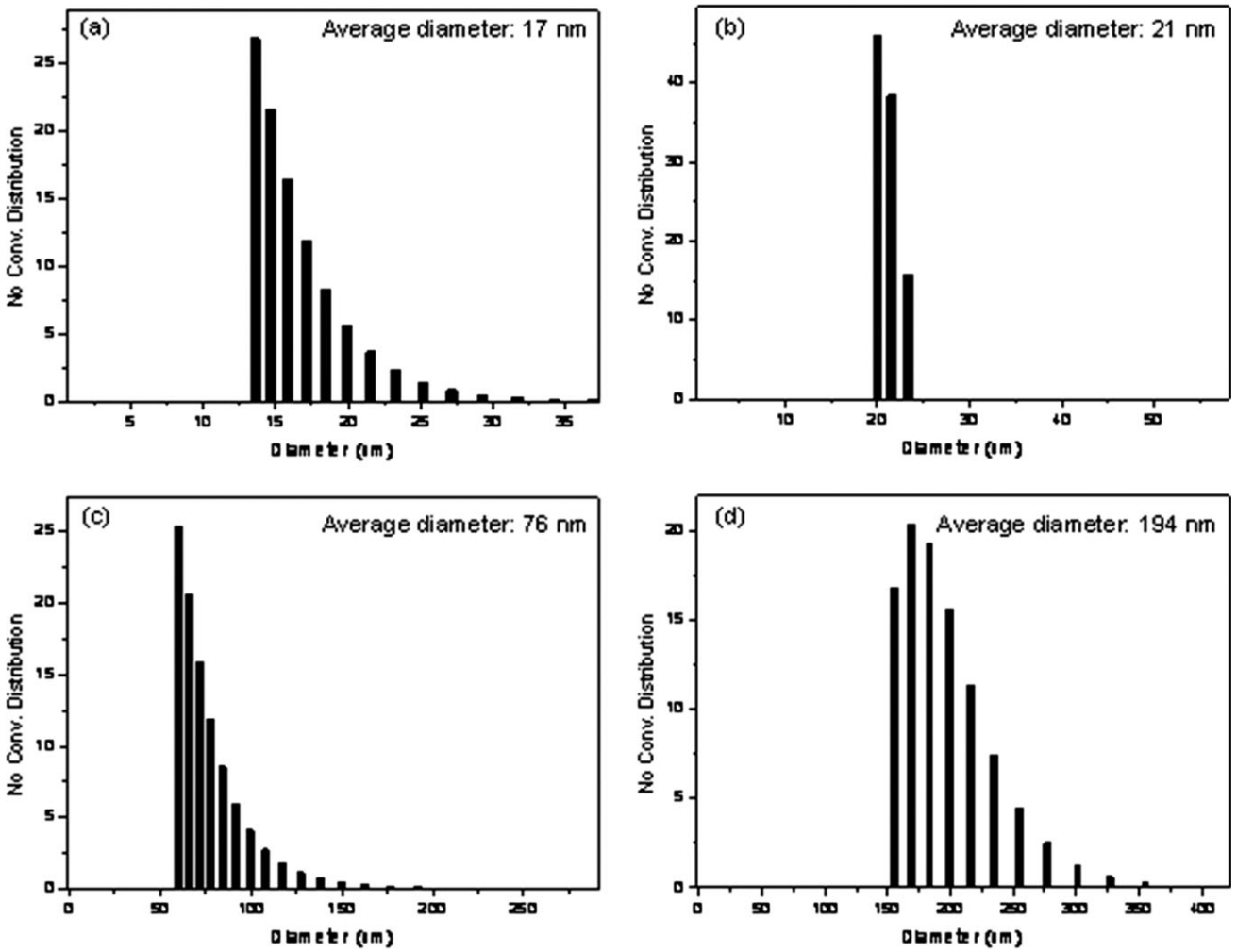

Figure 3 The micelle size distribution of PEG-*b*-PTMC star block copolymers, (a) 1a-MPEG-*b*-PTMC, (b) 2a-PTMC-*b*-PEG-*b*-PTMC, (c) 4a-PEG-*b*-PTMC, and (d) 8a-PEG-*b*-PTMC.

pyrene in micelles are different from those of free pyrene molecules in water. The pyrene excitation spectrum shifted from 335 nm for free pyrene to 338 nm for the micellar phase, indicating partitioning of pyrene into the hydrophobic micellar core. Thus, this change can be used in the calculation of CMCs of the PEG-*b*-PTMC star block copolymers. As shown in Figure 5, the fluorescence intensity ratio (I_{338}/I_{335}) of pyrene excitation spectra was plotted against the logarithm of the concentration of the PEG-*b*-PTMC star block copolymers. The fluorescence intensity ratio showed a substantial increase at a certain concentration, indicating the onset of micelle formation. The intercept of straight line fits of the intensity ratio data above and below this onset point is defined as the CMC.

Table II shows the CMC of the PEG-*b*-PTMC star block copolymers. The CMC values ranged from 3.1 $\times$ 10^{-3} to 21.1 $\times$ 10^{-3} mg/mL. As the arm number increased, the CMCs of PEG-*b*-PTMC star block copolymers increased, and the outer PTMC blocks with short length needs large concentration in PTMC blocks to form micelles. This might be attributed to decreased aggregation of the hydrophobic PTMC segments with increasing arm number. This decreasing of PTMC aggregation can be understood in terms of the translational entropic change associated with the formation of micellar aggregates, which increases with increasing arm number.

Partitioning of pyrene to the micellar core

The partition equilibrium constant (K_v) of pyrene can be used to display the hydrophobicity of the micellar core of PEG-*b*-PTMC star block copolymers. The Wilhelm et al.[22] proposed the method to calculate partition equilibrium constant by considering the incorporation of pyrene into the micelles as a simple equilibrium between the micellar phase ($[Py]_m$) and the aqueous phase ($[Py]_w$). The ratio of pyrene concentration in the micellar to the aqueous phase ($[Py]_m/[Py]_w$) can be correlated to the volume ratio of each phase according to the following equation.

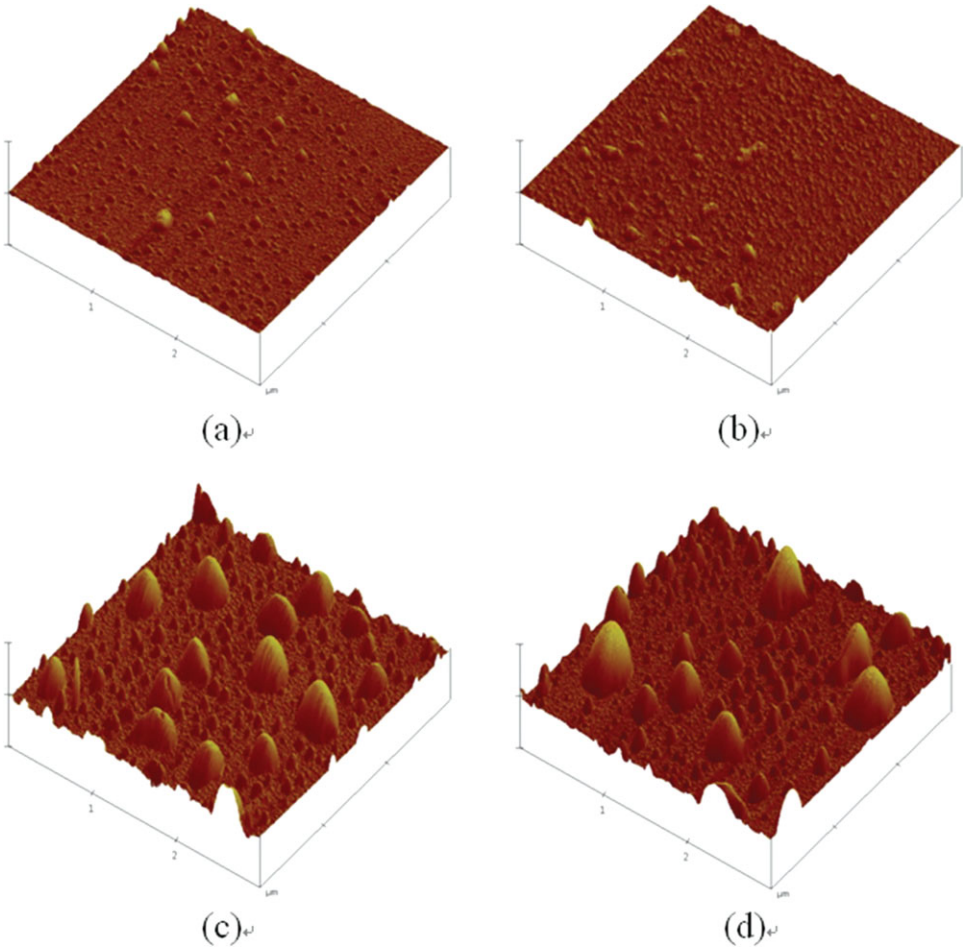

Figure 4 AFM three-dimensional images (3 × 3 μm) of micelles prepared from PEG-*b*-PTMC star block copolymers, (a) 1a-MPEG-*b*-PTMC, (b) 2a-PTMC-*b*-PEG-*b*-PTMC, (c) 4a-PEG-*b*-PTMC, and (d) 8a-PEG-*b*-PTMC. Z-scale is 60 nm. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

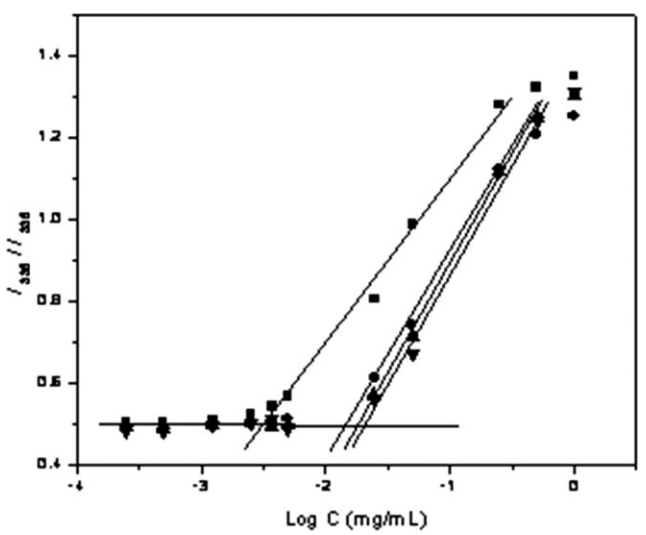

Figure 5 Plot of I_{338}/I_{335} (from pyrene excitation spectra) versus log *C* for concentration of (■) 1a-MPEG-*b*-PTMC, (●) 2a-PTMC-*b*-PEG-*b*-PTMC, (▲) 4a-PEG-*b*-PTMC, and (▼) 8a-PEG-*b*-PTMC at 25°C.

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

which can be rewritten as

$$[\mathrm{Py}]_m/[\mathrm{Py}]_w = K_v x(c - \mathrm{CMC})/1000\rho \quad (2)$$

where x is the weight fraction of hydrophobic PTMC block, c is the concentration of the PEG-*b*-PTMC star block copolymer, and ρ is the density of the PTMC micellar core, which is assumed to be equal to the value for bulk PTMC (1.01).[23] $[\mathrm{Py}]_m/[\mathrm{Py}]_w$ can be written as

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

TABLE II
Critical Micelle Concentration (CMC) and K_v Determined by PEG-*b*-PTMC Star Block Copolymers

	CMC × 10^3 (mg/mL)	$K_v \times 10^{-4}$
1a-MPEG-*b*-PTMC	3.1	4.44
2a-PTMC-*b*-PEG-*b*-PTMC	14.2	2.02
4a-PEG-*b*-PTMC	18.0	1.47
8a-PEG-*b*-PTMC	21.1	1.34

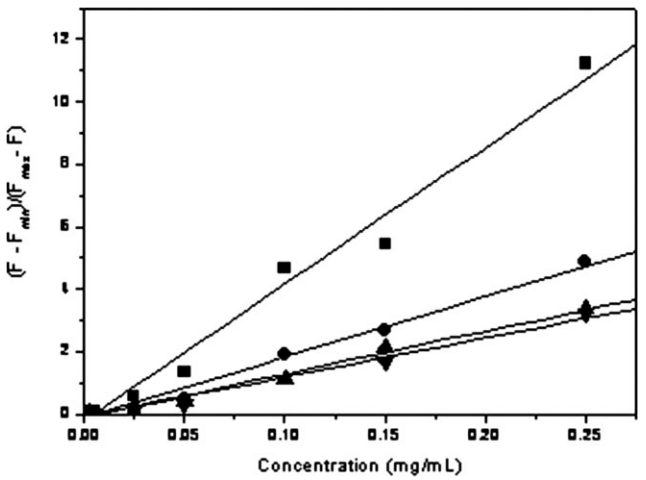

Figure 6 Plots of $(F - F_{min})/(F_{max} - F)$ versus concentration of PEG-*b*-PTMC star block copolymers at 25°C; (■) 1a-MPEG-*b*-PTMC, (●) 2a-PTMC-*b*-PEG-*b*-PTMC, (▲) 4a-PEG-*b*-PTMC, and (▼) 8a-PEG-*b*-PTMC.

where F_{min} and F_{max} correspond to the average magnitude of I_{338}/I_{335} in the flat region of low and high concentration ranges, and F is the I_{338}/I_{335} intensity ratio in the intermediate concentration range of the PEG-*b*-PTMC star block copolymers. Figure 6 illustrates the plot of $(F - F_{min})/(F_{max} - F)$ versus concentration of PEG-*b*-PTMC star block copolymer at concentrations above the CMC. The plots exhibited linear variations. From the slope of the plots, K_v was determined. Thus, K_v may be an indicator of the hydrophobicity of the PEG-*b*-PTMC star block copolymers.

The K_v values for the PEG-*b*-PTMC star block copolymers are summarized in Table II. The K_v values ranged from 4.44×10^4 to 1.34×10^4, in the opposite order to the CMCs. For PEG-*b*-PTMC star block copolymers with different arm numbers, K_v decreases in the order: 1a-MPEG-*b*-PTMC > 2a-PTMC-*b*-PEG-*b*-PTMC > 4a-PEG-*b*-PTMC > 8a-PEG-*b*-PTMC. Notably, the partition coefficient for pyrene in 1a-MPEG-*b*-PTMC micelles was approximately threefold higher than that of 8a-PEG-*b*-PTMC star block copolymers. The higher partition coefficient suggests that pyrene is more easily trapped in the hydrophobic PTMC regions, because the enhancement of the hydrophobicity for the cores of micelles can make the core a more attractive environment for pyrene. This finding indicates that the capacity of hydrophobic parts of the star block copolymers to be solubilized in micelles diminishes as the arm number increases.

CONCLUSIONS

We prepared amphiphilic PEG-*b*-PTMC star block copolymers in quantitative yield via ROP of TMC initiated at the hydroxyl end group of core PEG in the presence of HCl Et_2O as a monomer activator. In the aqueous, the amphiphilic nature of the segments of these PEG-*b*-PTMC star block copolymers gave micelles with a core–shell structure in an aqueous phase. Most of the micelles prepared from PEG-*b*-PTMC star block copolymers were spherical. With increasing arm number, the mean hydrodynamic diameters of micelles and CMC increased but partition equilibrium constant of pyrene decreased. In ongoing studies, we are investigating PEG-*b*-PTMC star block copolymers as potential hydrophobic drug carriers in the biomedical application.

EXPERIMENTAL

Materials

Methoxy polyethylene glycol (MPEG-OH, M_n 2000), PEG (HO-PEG-OH M_n 2000), and HCl (1.0*M* solution in diethyl ether) were purchased from Aldrich and used as received. Pentaerythritol, tetra-polyethylene glycol ether (PEG-$(OH)_4$ M_n 2000) and hexaglycerine, octa-polyethylene glycol ether (PEG-$(OH)_8$, M_n 2000) were purchased from Nippon oil and fats and used as received. Pure-grade TMC (Boehringer Ingelheim) was recrystallized in xylene. CH_2Cl_2 was distilled sequentially from $CaCl_2$ and CaH_2 under nitrogen before use.

Instrumentation

^1H NMR spectra were measured using Bruker 300 instrument with $CDCl_3$ in the presence of tetramethylsilane as internal standard or with D_2O. Molecular weights and molecular weight distribution of PEG-*b*-PTMC star block copolymers were estimated by gel permeation chromatography (GPC) on Futecs At-4000 GPC system (Shodex RI-101 detector) using three columns (Shodex K-802, K-803, K-804 polystyrene gel column) at 40°C, using $CHCl_3$ as an eluent with a flow rate of 0.8 mL/min by polystyrene calibration.

Synthesis of 8 arm-poly(ethylene glycol)-*block*-poly(trimethylene carbonate) star block copolymers (8a-PEG-*b*-PTMC)

All glasses were dried by heating in vacuum and handled under a dry nitrogen stream. The typical process for the polymerization to give 8a-PEG-*b*-PTMC is as follows. The 8a-PEG (M_n = 2000) (1.5 g, 0.75 mmol) and toluene (80 mL) were introduced into a flask. The 8a-PEG solution was distillated by azeotropic distillation to remove water. Toluene was then distilled off completely. To 8a-PEG, the CH_2Cl_2 (30 mL) was added followed by the addition of TMC (1.5 g, 14.7 mmol). The polymerization was

initiated by the addition of 1.0 *M* solution of HCl in diethyl ether (12 mL, 12 mmol) at 25°C. After 24 h, the reaction mixture was poured into *n*-hexane to precipitate a polymer, which was separated from the supernatant by decantation. The obtained polymer was redissolved in CH_2Cl_2 and then filtered. The polymer solution was concentrated by rotary evaporator and dried in vacuum to give a colorless polymer of quantitative yield. The TMC monomer conversion was determined by ^{1}H NMR spectroscopy before precipitation with *n*-hexane. The molecular weight of PTMC segment in the star block copolymers was determined by the intensity of methylene proton signal of 8a-PEG at $\delta = 3.64$ ppm and methylene proton signal of PTMC at $\delta = 4.24$, 2.05, 1.91 ppm in ^{1}H NMR spectroscopy.

Determination of critical micelle concentration

The CMC was determined using pyrene as a fluorescence probe. One milliliter of pyrene solution in THF (1.2 m*M*) was added to 1000 mL of distilled water. THF was removed by a rotary evaporator at 30°C for 2 h to give pyrene solution in water (1.2×10^{-6} *M*). Stock solutions of star block copolymer were prepared by dissolving the star block copolymer samples in distilled water under stirring. From the stock solution a series of concentration was prepared by dilution. The pyrene solution was added by the star block copolymer solution. The solutions after filtration using 0.45 μm membrane filter were allowed to stand overnight at room temperature to equilibrate. The formed micelle sizes were measured by DLS (ELS-8000, Photal, Otsuka Electronics, Tokyo, Japan). The micelle concentration in these experiments varied from 0.5×10^{-7} to 1.0 mg/mL. The pyrene concentration in star block copolymer solution was 6×10^{-7} *M*. For the measurements of pyrene excitation spectra scan speed was set at 240 nm/min and, emission and excitation slit widths were set at 2.5 nm. For the excitation spectra, the emission wavelength was 373 nm. Fluorescence intensities of the pyrene entrapped in the micelle core were determined by an F-4500 fluorescence spectrophotometer (*I*ex 338 nm, Hitachi Co. LTD, Japan) at room temperature.

Atomic force microscopy (AFM)

One drop of solutions of star block copolymer with different arm numbers at 1 wt % concentration in deionized water was transferred onto silicone wafer which washed with MeOH. The wafer was quickly placed in liquid nitrogen, followed by the freeze drying for 3 days. AFM measurements were carried out in the tapping mode with a Nanoscope IV instrument (Digital Instruments Inc.).

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