Amphiphilic Triblock Copolycarbonates with Poly(glycerol carbonate) as Hydrophilic Blocks

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Received October 18, 2008; Revised Manuscript Received December 14, 2008

ABSTRACT: Amphiphilic triblock copolycarbonates poly(glycerol carbonate-*b*-DTC-*b*-glycerol carbonate) with poly(glycerol carbonate) chains as the hydrophilic blocks were designed and synthesized. In the first step, the PDTC diol macroinitiators were synthesized via bulk polymerization of DTC with 1,6-hexanediol as an initiator and $Sn(Oct)_2$ as a catalyst. Then the amphiphilic triblock copolycarbonates were synthesized via cationic ring-opening polymerization of 2-benzyloxytrimethylene carbonate (BTMC) with PDTC diol as a macroinitiator and fumaric acid as a catalyst, followed by a hydrogenolytic deprotection reaction with Pd−C as a catalyst in an autoclave. The amphiphilic triblock copolymers were characterized by ^{1}H NMR, ^{13}C NMR, GPC, DSC, and water contact angle. The self-assemble behavior of the amphiphilic triblock copolycarbonate in deuterated solvents monitored by ^{1}H NMR showed a strong incompatibility of the two segments. Stable micelle solution of the amphiphilic triblock copolycarbonate in water was prepared by adding water to a THF solution of the polymer followed by removal of the organic solvent by rota-evaporation. Dynamic light scattering measurement showed that the micelle had a narrow unimodal size distribution. Drug-loading properties of the copolycarbonate micelles were tested with prednisone acetate as a model drug.

Introduction

Aliphatic polycarbonates, such as poly(trimethylene carbonate) (PTMC) and poly(2,2-dimethyltrimethylene carbonate) (PDTC), have been extensively studied as biomedical materials because of their excellent biocompatibility and biodegradability.[1,2] Ring-opening polymerization (ROP) of six-membered cyclic carbonate monomers is so far the most effective method for the preparation of aliphatic polycarbonates for its low heat effect, rapid velocity, and capability to achieve higher molecular weight.[3] To meet the requirements in different biomedical fields, polycarbonates are enabled to possess versatile properties, such as hydrophilicity, biodegradability, and mechanical properties, through tailoring the main-chain structures or incorporating functional pendant groups, such as OH, NH_2, COOH, etc.[4−9]

We[6,9] and others[7c] have reported two types of glycerol-derived polycarbonates bearing pendant hydroxyl groups: poly(glycerol carbonate) or poly(2-hydroxytrimethylene carbonate) (PHTMC) and poly[2-(2-hydroxyethoxy)trimethylene carbonate] (PHETC) and their copolymers. The presence of pendant hydroxyl groups results in increased hydrophilicity of the polycarbonate, thus leading to an increased degradation rate. The hydrophilicity and degradability of the copolymers are tunable by adjusting the feed ratio of the different monomers.

By now, a lot of the amphiphilic block copolymers composed of poly(ethylene glycol) (PEG) as the hydrophilic block and polycarbonate as the hydrophobic block were reported. ABA-type triblock copolymers PTMC-*b*-PEG-*b*-PTMC[10] and PDTC-*b*-PEG-*b*-PDTC[11] were synthesized via ROP of cyclic carbonate initiated by dihydroxyl PEG. AB-type diblock copolymer PEG-PTMC[12] was prepared by ROP of trimethylene carbonate (TMC) with poly(ethylene glycol) monomethyl ether (mPEG) as the macroinitiator.

It would be attractive to use hydroxyl-bearing poly(glycol carbonate) chains instead of PEG as the hydrophilic blocks in the amphiphilic block copolycarbonates because a hydroxyl-bearing polycarbonate block is biodegradable and the hydroxyl pendant groups provide great potential for further functionalization. In this paper, we reported the synthesis and characterization of novel amphiphilic triblock copolycarbonates (PHTMC-*b*-PDTC-*b*-PHTMC)s. By means of NMR, GPC, DSC, and water contact angle, the polymeric structure and physical properties were characterized. The self-assemble behavior of the amphiphilic copolycarbonate in aqueous medium was investigated. The drug-loading content and entrapment efficiency of the amphiphilic triblock copolycarbonates were determined.

Experimental Section

Materials. THF was distilled over Na−K alloy in the presence of benzophenone before use. Toluene was dried over Na before use. $Sn(Oct)_2$ (95%) was purchased from Aldrich and purified by distillation under reduced pressure and then dissolved in dry toluene prior to use. Other reagents purchased from Shanghai Chemical Reagent Co., China, were of analytical grade and used as received. DTC[2] and 2-benzyloxytrimethylene carbonate[9] were synthesized as described in the literature.

Characterization. ^{1}H NMR analyses were performed on a Mercury VX-300 spectrometer using tetramethylsilane (TMS) as internal reference and $CDCl_3$ or DMSO-d_6 as a solvent. ^{13}C NMR spectra were recorded on a Unity-Inova 600 spectrometer at 150 MHz using $CDCl_3$ as a solvent.

Molecular weight was determined by GPC using a Waters high-pressure liquid chromatographic system equipped with a model 2690D separation module, a model 2410 refractive index detector, and Styragel HR1 THF and HR4 THF columns. THF was used as the eluent at a flow rate of 0.3 mL min^{-1}. Polystyrene standards with narrow distribution were used to generate a calibration curve.

The thermal property of the polymers was measured by a differential scanning calorimeter (DSC) (Perkin-Elmer Pyris-1). The polymers were heated at a heating rate of 20 °C min^{-1} (first scan) and 10 °C min^{-1} (second scan). Water contact angle was determined on Contact Angle System OCA20 in air using a sessile droplet technique.

Synthesis of PDTC Diol Macroinitiators. For the synthesis of PDTC diols with molecular weights of 10 and 3 kDa, the molar feed ratios of DTC and 1,6-hexanediol were 76 and 22, respectively. Taking the synthesis of $PDTC_{22}$ diol (M_w = 3 kDa) as an example, a round-bottom flask pretreated with trimethylchlorosilane was

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10.1021/ma802350g CCC: $40.75
Published on Web 01/26/2009

Table 1. Synthetic Results of PDTC Diol Macroinitiators and the Triblock Copolycarbonates PBTMC-*b*-PDTC-*b*-PBTMC

			^{1}H NMR		GPC	
sample	feed ratio *f* (mol/mol)	yield (%)	*F* (mol/mol)	M_n	M_n	M_w/M_n
$PDTC_{22}$ diol[a]	22[c]	>87	21[c]	2900	5600	1.52
$PDTC_{76}$ diol[a]	76[c]	90	63[c]	8300	20700	1.58
$PBTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{14}$[b]	1.3[d]	89	1.2[d]	8200	11800	1.54
$PBTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{29}$[b]	2.6[d]	91	2.4[d]	13800	15500	1.75
$PBTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PBTMC_{48}$[b]	1.3[d]	41	1.2[d]	27200	54200	1.86

[a] Polymerization conditions: [monomer]/[$Sn(Oct)_2$] = 1000, 120 °C, 24 h, in bulk. [b] Polymerization conditions: 2.0 wt % fumaric acid, 150 °C, 24 h, in bulk. [c] DTC/1,6-hexanediol. [d] BTMC/DTC.

charged with 0.1508 g (1.28 mmol) of 1,6-hexanediol, 3.828 g (29.4 mmol) of DTC, and 294 μL of 0.1 M $Sn(Oct)_2$ solution in dry toluene. The flask was evacuated and charged with argon three times and then sealed under vacuum with a magnetic stirring bar inside. After the mixture was stirred at 120 °C for 24 h, the polymerization was quenched by immersing the flask in a cool water bath. The product was purified by precipitation from dichloromethane with cold methanol and hexane, respectively, and dried under vacuum at 35 °C for 24 h to give 3.458 g of white solid in 87% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS), main peaks: δ 3.97 (CCH_2OCO_2), 0.97 (CH_3); minor peaks for the terminal groups and initiator unit: δ 4.15−4.10 ($OCH_2CH_2CH_2$), 3.37−3.35 (CCH_2OH), 1.71−1.66 ($OCH_2CH_2CH_2$), 1.42−1.39 ($OCH_2CH_2CH_2$), 0.94 (CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.7, 72.8, 35.5, 21.8.

Synthesis of the Triblock Copolycarbonates PBTMC-*b*-PDTC-*b*-PBTMC. Taking the synthesis of $PBTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{14}$ (M_w = 9 kDa) as an example, a round-bottom flask pretreated with trimethylchlorosilane was charged with 0.255 g of $PDTC_{22}$ diol, 0.510 g of BTMC, and 10.2 mg of fumaric acid. The flask was evacuated and charged with argon three times and then sealed under vacuum with a magnetic stirring bar inside. After the mixture was stirred at 150 °C for 24 h, the polymerization was quenched by immersing the flask in a cool water bath. The product was purified by precipitation from dichloromethane with cold methanol and hexane, respectively, and dried under vacuum at 35 °C for 24 h to give 0.681 g of white solid in 89% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 7.32 (aromatic), 4.64 (CH_2Ph), 4.38−4.28 ($CHCH_2O$), 3.96 (CCH_2O), 3.86−3.84 (CH_2CHCH_2), 0.99 (CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.6, 155.1, 137.8, 128.8, 74.3, 72.8, 72.6, 66.8, 35.5, 21.7.

Synthesis of the BTMC-DTC Non-Triblock Copolymer with $Sn(Oct)_2$ as a Catalyst. A round-bottom flask pretreated with trimethylchlorosilane was charged with 0.104 g of $PDTC_{22}$ diol, 0.208 g of BTMC, and 10 μL of 0.1 M $Sn(Oct)_2$ solution in dry toluene. The flask was evacuated and charged with argon three times and then sealed under vacuum with a magnetic stirring bar inside. After the mixture was stirred at 120 °C for 24 h, the polymerization was quenched by immersing the flask in a cool water bath. The product was purified by precipitation from dichloromethane with cold methanol and hexane, respectively, and dried under vacuum at 35 °C for 24 h to give 0.257 g of white solid. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 7.32 (aromatic), 4.64 (CH_2Ph), 4.37−4.27 ($CHCH_2O$), 3.96 (CCH_2O), 3.86−3.83 (CH_2CHCH_2), 0.99 (CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.6, 155.1, 154.9, 137.7, 128.6, 74.3, 72.6, 72.5, 66.7, 35.4, 21.6.

Synthesis of the Triblock Copolycarbonates PHTMC-*b*-PDTC-*b*-PHTMC. Taking the synthesis of $PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$ (M_w = 6 kDa) as an example, a flask was charged with 0.631 g of $PBTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{14}$ (M_w = 9 kDa), 99.3 mg of Pd−C (10% Pd), and 10 mL of dry THF. The flask was placed in an autoclave. The system was evacuated and charged with hydrogen three times. After the mixture was magnetically stirred at room temperature for 48 h under 30 atm of hydrogen pressure, the Pd−C catalyst was removed by filtration. The filtrate was evaporated to give $PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$ (M_w = 6 kDa). The product was dried under vacuum at 35 °C for 24 h to give 0.403 g of white solid in 95% yield. ^{1}H NMR (DMSO-d_6, 300 MHz, TMS): δ 5.48−5.47 (O*H*, disappeared after D_2O exchange), 4.07−4.05 ($CHCH_2O$), 3.91 (CCH_2O, CH_2CHCH_2), 0.92 (CH_3).

Table 2. Synthesis of PHTMC-*b*-PDTC-*b*-PHTMC by Debenzylation of PBTMC-*b*-PDTC-*b*-PBTMC[a]

		^{1}H NMR	GPC		
sample	yield (%)	debenzylation degree (%)	M_n	M_n	M_w/M_n
$PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$	95	100	6100	9000	1.50
$PBTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{29}$	96	100	9200	13800	1.72
$PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$	100	100	19000	43800	1.80

[a] Debenzylation conditions: 10% Pd−C, THF, 30 atm H_2, 48 h.

Water Contact Angle Measurements. Polymer films of $PDTC_{76}$ diol and $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$ about 10 μm thick were prepared by casting polymer solutions in $CHCl_3$ on glass carriers. The concentration of the solution was 10 mg mL^{-1}. The films were first dried in a circulating air oven at room temperature and then in vacuum at room temperature. Water contact angle was determined on Contact Angle System OCA20 in air using a sessile droplet technique. The drop size was 4 μL. Readings were taken at 30 s. Four measurements were made on each sample.

^{1}H NMR Study on Self-Assemble Behavior of the Amphiphilic Copolycarbonates. In an NMR tube, 5 mg of PHTMC-*b*-PDTC-*b*-PHTMC was dissolved in 0.4 mL of DMSO-d_6, and then the ^{1}H NMR spectrum was recorded. Whereafter, the composition of the solvent was adjusted by adding designed amounts of D_2O, and ^{1}H NMR spectra were recorded after each addition to monitor the aggregation of the hydrophobic block.

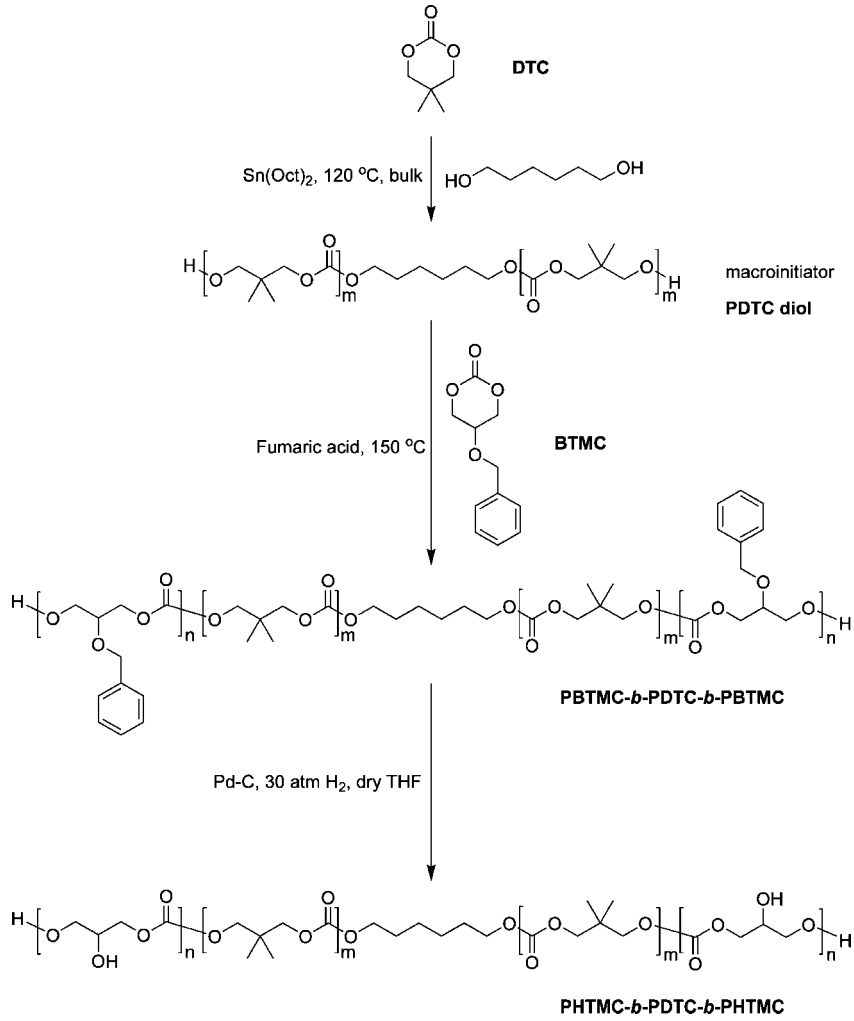
Preparation and Characterization of the Amphiphilic Copolycarbonate Micelles and Drug-Loaded Micelles. To a solution of PHTMC-*b*-PDTC-*b*-PHTMC copolymer (15 mg) or a mixture of the copolymer (15 mg) and prednisone acetate (3.0 mg) in THF (2.0 mL), deionized water (20 mL) was added dropwise under vigorous shaking. The solution was concentrated to a volume of 5 mL by rotary evaporation under reduced pressure to remove the organic solvent. The micelle solution was filtered through a 0.45 μm syringe filter. The micelle size and size distribution were determined by dynamic light scattering (DLS) at an angle of 90° in a quartz cuvette on a Beckman Coulter N4 Plus submicron particle sizer at 25 °C.

Determination of Drug-Loading Content (DLC) and Entrapment Efficiency (EE). Drug-loaded micelle solutions of known volume were rotary evaporated to dryness. The residue was dissolved in acetonitrile. UV absorbance at 235 nm was measured to determine the drug concentration with a Perkin-Elmer Lambda Bio 40 UV−vis spectrophotometer.

Results and Discussion

The amphiphilic triblock copolycabonates were synthesized as shown in Scheme 1. First, a linear PDTC diol with two terminal hydroxy groups was synthesized by the ROP of DTC using 1,6-hexanediol as an initiator and $Sn(Oct)_2$ as a catalyst. Then, the PDTC diol was used as a macroinitiator for the ROP of PBTMC with fumaric acid as a catalyst, affording a triblock copolycarbonate PBTMC-*b*-PDTC-*b*-PBTMC. Finally, benzyl protection groups on PBTMC-*b*-PDTC-*b*-PBTMC were removed by Pd-catalyzed hydrogenolysis to give the final amphiphilic triblock copolycarbonate PHTMC-*b*-PDTC-*b*-PHTMC.

Scheme 1. Synthesis of the Amphiphilic Triblock Copolycarbonate PHTMC-*b*-PDTC-*b*-PHTMC



The molecular weights were controlled by the monomer/initiator feed ratios, and the results are listed in Tables 1 and 2.

For the synthesis of PDTC diols $PDTC_{22}$ and $PDTC_{76}$ (the subscript numbers 22 and 76 refer to theoretical polymerization degrees) with molecular weights of 10 and 3 kDa, the molar feed ratios of DTC and 1,6-hexanediol were 76 and 22, respectively. The ^{1}H NMR spectrum of $PDTC_{22}$ diol macroinitiator (M_n = 3 kDa) is shown in Figure 1. The actual polymerization degrees and molecular weights of the PDTC diols were calculated from ^{1}H NMR spectra by comparing the integration of signals at 3.97 ppm for the main chain and 3.37−3.35 ppm for the end groups. The results are shown in Table 1. The actual compositions of polymers were close to the feed ratios. So, the amount of the monomer in the polymer

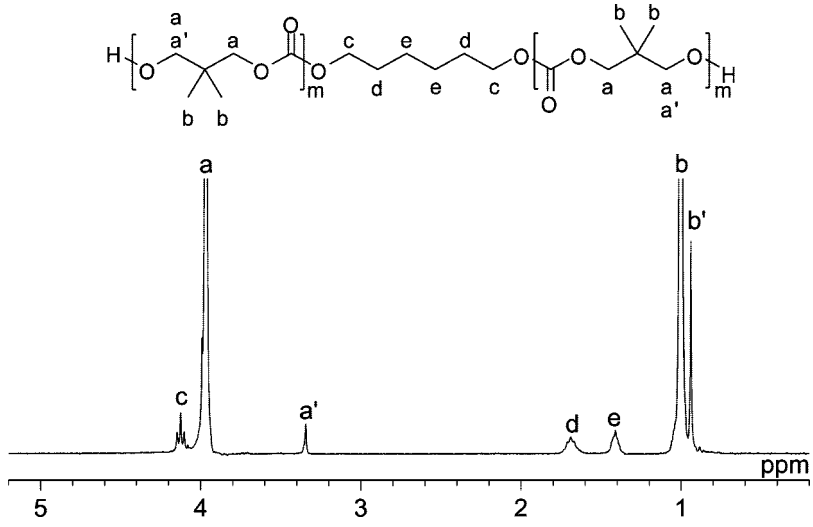


Figure 1. ^{1}H NMR spectrum of $PDTC_{22}$ diol macroinitiator (300 MHz, $CDCl_3$).

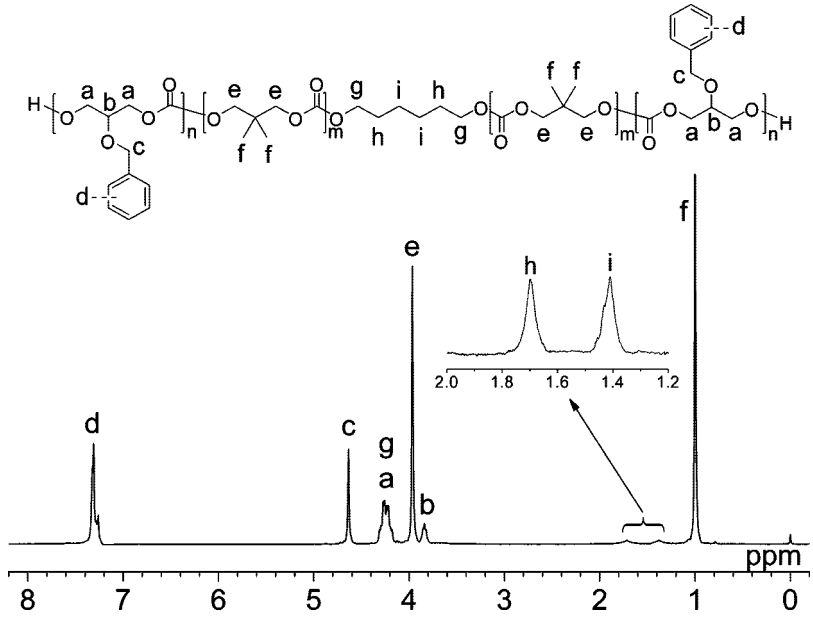


Figure 2. ^{1}H NMR spectrum of the triblock copolycarbonate PBTMC$_{14}$-*b*-PDTC$_{22}$-*b*-PBTMC$_{14}$ (300 MHz, $CDCl_3$).

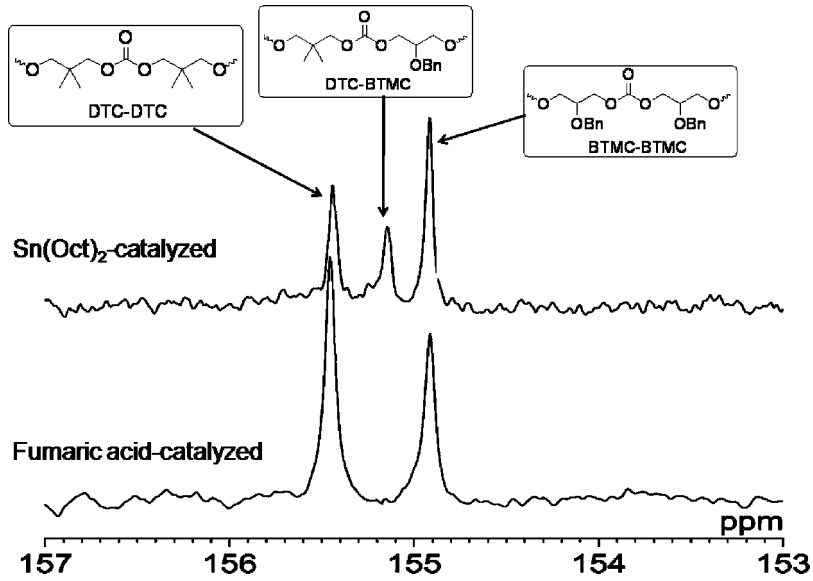


Figure 3. Partial ^{13}C NMR spectrum for the carbonyl groups of triblock copolycarbonate PBTMC$_{14}$-*b*-PDTC$_{22}$-*b*-PBTMC$_{14}$ prepared by fumaric acid-catalyzed polymerization. For comparison, the spectrum of non-triblock BTMC-DTC copolymer prepared by Sn(Oct)$_2$-catalyzed polymerization is also shown (125 MHz, $CDCl_3$).

chains can be adjusted through changing the molar ratio of the monomer and initiator.

The ^{1}H NMR spectrum of triblock copolycarbonate PBTMC$_{14}$-*b*-PDTC$_{22}$-*b*-PBTMC$_{14}$ is shown in Figure 2. Compared with the ^{1}H NMR spectra of PDTC$_{22}$ diol, the signals at 3.37−3.35 and 0.94 ppm for the end DTC unit disappeared, indicating that the copolycarbonates were synthesized successfully through polymerization of BTMC monomer with PDTC diol as the initiator. The actual composition and molecular weights of the triblock copolycarbonates PBTMC-*b*-PDTC-*b*-PBTMC can be calculated from the ^{1}H NMR spectra by comparing the integration of signals at 4.64 ppm ($PhCH_2O$ in BTMC) and 0.99 ppm (methyl groups in DTC). The results are shown in Table 1. They were close to those predicted on the basis of the feed ratios. No signal around 3.1 ppm[13] for ether unit ($-CH_2OCH_2-$) protons was observed, revealing no detectable decarboxylation occurs during the cationic polymerization with fumaric acid as the catalyst.

The triblock structure of the copolycarbonates was proved by ^{13}C NMR spectra. As shown in Figure 3, the copolycarbonate PBTMC$_{14}$-*b*-PDTC$_{22}$-*b*-PBTMC$_{14}$ prepared by fumaric acid-catalyzed ROP of BTMC with PDTC diol as a macroinitiator shows only two carbonyl signals 155.6 and 154.9 ppm, for the PDTC block and PBTMC block, respectively. This indicated that chain exchange reaction is negligible during the fumaric acid-catalyzed polymerization, resulting in a triblock structure. For comparison, a BTMC−DTC copolymer was prepared by Sn(Oct)$_2$-catalyzed ROP of BTMC with PDTC diol as a macroinitiator. In contrast, this copolycarbonate shows three carbonyl signals at 155.6, 154.9, and 155.1 ppm (Figure 3). In addition to the two signals for DTC−DTC and BTMC−BTMC sequences, the newly appeared signal at 155.1 ppm is assignable to DTC−BTMC sequences, which were formed by chain-exchanging byreactions during the polymerization. These results indicated that using fumaric acid instead of Sn(Oct)$_2$ as a catalyst is essential for preparation of the block copolycarbonates.

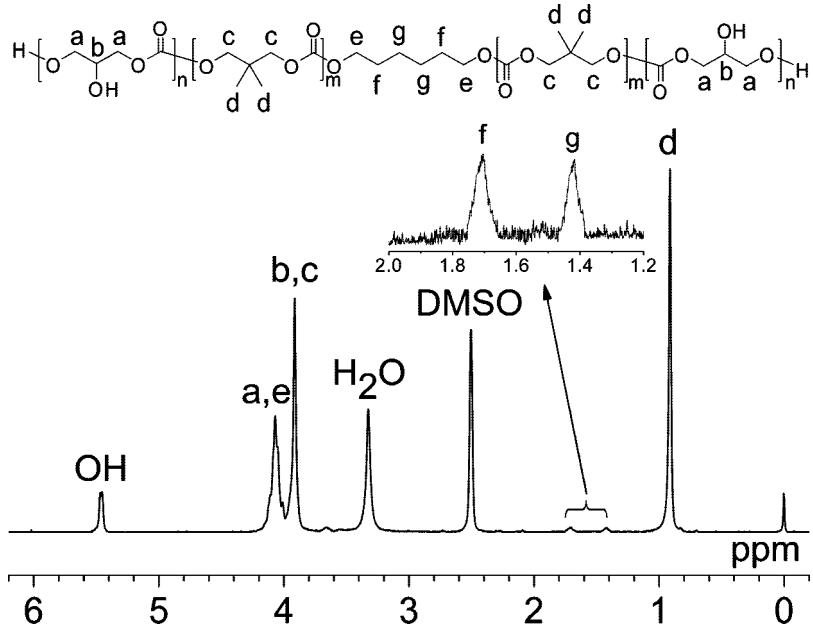


Figure 4. ^{1}H NMR spectrum of the amphiphilic triblock copolycarbonate $PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$ (300 MHz, DMSO-d_6).

The molecular weights of the polymers were also determined by GPC analyses with results listed in Table 1. The polymers PDTC and PBTMC-*b*-PDTC-*b*-PBTMC had unimodal molecular weight distributions and moderate polydispersities. The molecular weights measured by GPC were well correlated to the predicted and ^{1}H NMR-calculated molecular weights though the values are about 1-fold higher. This difference was in the reasonable range since the GPC value was calibrated with a different type of polymer.

The protecting benzyl groups of the triblock copolycarbonates PBTMC-*b*-PDTC-*b*-PBTMC were effectively removed by 10% Pd−C-catalyzed hydrogenation at room temperature at 30 atm of hydrogen pressure (Scheme 1). The ^{1}H NMR spectrum of the amphiphilic triblock copolycarbonate $PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$ is shown in Figure 4. Disappearance of the signals for the benzyl groups at 7.3 and 4.6 ppm indicated that the benzyl protecting groups of copolymers were nearly completely removed within 48 h under the reaction conditions. The appearance of the signal for OH group at 5.5 ppm further proved the successful debenzylation. GPC analysis results revealed that the effectively deprotecting reaction did not result in remarkable decrease in molecular weight or wider molecular weight distribution. The GPC curves of $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$ series are shown in Figure 5. The three polymers were in unimodal molecular weight distributions, and the elution times shortened with molecular weight increasing. This once again proves the successful synthesis of the amphiphilic triblock copolycarbonates.

The thermal properties of the polymers were investigated by DSC. The DSC curves of polymers are shown in Figure 6. PDTC is a semicrystalline polymer. There were two peaks of T_m in $PDTC_{76}$ diol macroinitiator, one of which (91.2 °C) was a little lower than that in $PDTC_{22}$ (93.7 °C). The crystallinity of the triblock copolymers came down sharply, and the peak of T_m was feeble in $PBTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{14}$ and disappeared in $PBTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PBTMC_{48}$. The triblock copolycarbonates PBTMC-*b*-PDTC-*b*-PBTMC were amorphous polymers. But the peaks of T_m came forth again in the deprotected hydroxyl copolycarbonates PHTMC-*b*-PDTC-*b*-PHTMC.

The hydrophilicity can be evaluated by static water contact angles (Figure 7). The correlation of the static contact angle and time of $PDTC_{76}$ and $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$ are shown in Figure 7. The water contact angle of $PDTC_{76}$ was about 114° and independent of contact time. In contrast, the

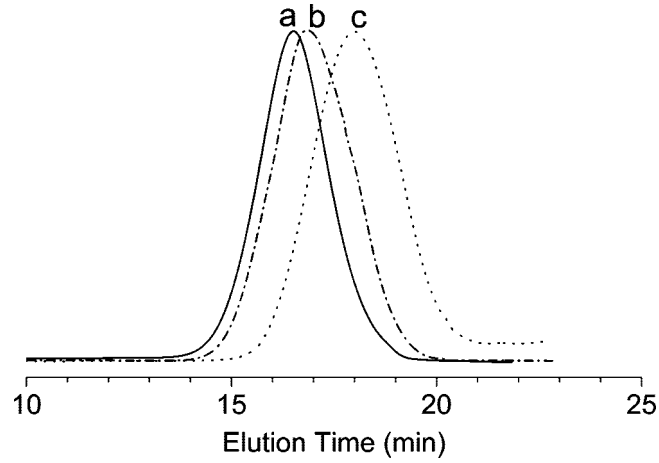


Figure 5. Normalized GPC curves of $PBTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PBTMC_{48}$ (a), $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$ (b), and $PDTC_{76}$ diol (c).

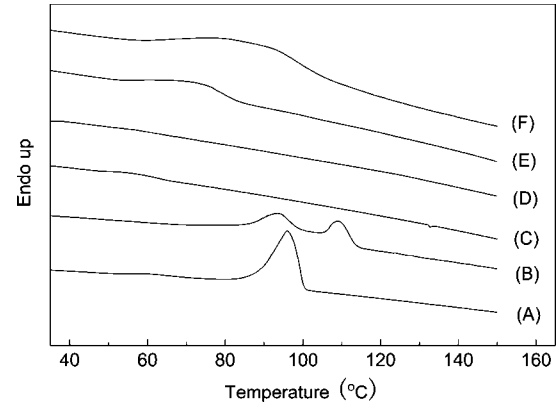


Figure 6. DSC curves of polymer: (A) $PDTC_{22}$, (B) $PDTC_{76}$, (C) $PBTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PBTMC_{14}$, (D) $PBTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PBTMC_{48}$, (E) $PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$, (F) $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$.

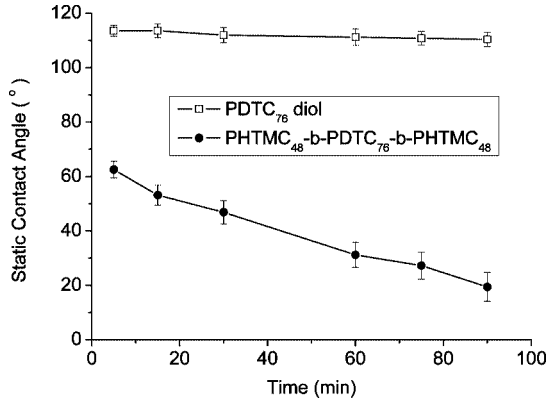


Figure 7. Static water contact angles of $PDTC_{76}$ diol (at top) and $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$ (at bottom) at various contact time (average of four readings).

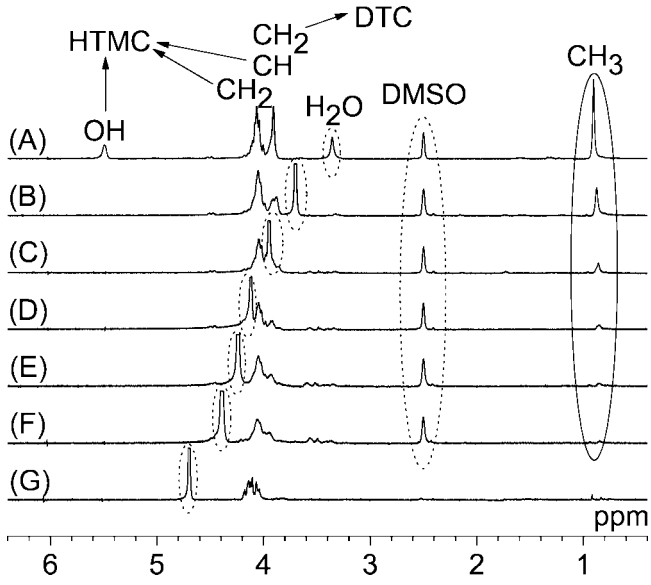


Figure 8. ^{1}H NMR spectra of the amphiphilic triblock copolycarbonate $PHTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{29}$ in (A) 0.4 mL DMSO-d_6, (B) 0.4 mL of DMSO-d_6 and 0.05 mL of D_2O; (C) 0.4 mL of DMSO-d_6 and 0.1 mL of D_2O; (D) 0.4 mL of DMSO-d_6 and 0.15 mL of D_2O; (E) 0.4 mL of DMSO-d_6 and 0.2 mL of D_2O; (F) 0.4 mL of DMSO-d_6 and 0.3 mL of D_2O, and (G) 0.5 mL of D_2O (300 MHz).

water contact angle of the triblock polymer $PHTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PHTMC_{48}$ was much lower and became even lower with the contact time prolonging. This is understandable because the surface of the triblock copolymer film prepared in air should be hydrophobic block-rich at the initial. Upon contact with water, the hydrophilic block immigrates gradually from the inner part to the outer surface, leading to a decreasing water contact angle.

The self-assemble behaviors of the amphiphilic triblock copolycarbonate $PHTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{29}$ in deuterated solvents were monitored by ^{1}H NMR through stepping up the proportion of D_2O to change the hydrophobic environment. Figure 8 presents the ^{1}H NMR spectra of the amphiphilic triblock copolycarbonate $PHTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{29}$ in deuterated solvents. The proportion of PDTC signals, most notably around 0.9 ppm for methyl groups, stepped down drastically with the increase of D_2O content in the solvent. In high D_2O content solvents or pure D_2O, only the signals of PHTMC block were observable at around 4.0 ppm. These results revealed the formation of core−shell micelle structure. The hydrophobic PDTC block aggregated to a core and became undetectable by NMR in hydrophilic solvent, while the hydrophilic PHTMC block in the shell remained highly solvated and NMR detectable.

Table 3. Drug-Free and Drug-Loaded Micelles of the Triblock Copolymers[a]

	drug-free micelle		drug-loaded micelle			
copolymers	size (nm)	PDI	size (nm)	PDI	DLC[b] (%)	EE[c] (%)
$PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$	73	0.07	83	0.13	8.8	42
$PHTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{29}$	61	0.10	79	0.15	11.7	57

[a] Measured with 15 mg of the polymers and 3.0 mg of prednisone acetate as a model drug. [b] Drug-loading content (DLC). [c] Entrapment efficiency (EE).

Micelle dispersions of the amphiphilic triblock copolycarbonates were prepared by gradually adding water to a THF solution of the polymers followed by removal of the organic solvent by rota-evaporation. The particle size was measured by dynamic light scattering (DLS) and shown in Table 3. Micelles prepared with $PHTMC_{14}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{14}$ and $PHTMC_{29}$-*b*-$PDTC_{22}$-*b*-$PHTMC_{29}$ had a narrow monomodal size distribution and a mean diameter below 100 nm. The size and size distribution had no significant change after the micelle solution was placed at room temperature for 1 week or exposed to ultrasound for 5 min, showing a good stability of the micelle in water. In contrast, the copolymer $PBTMC_{48}$-*b*-$PDTC_{76}$-*b*-$PBTMC_{48}$ with a higher molecular weight formed dispersion with particle size of several hundred of nanometers, wide size distribution, and poor reproducibility (data not shown).

Prednisone acetate was used as a model drug to test the drug-loading properties of the copolycarbonate micelles. The drug-loaded micelles were prepared by adding water to a THF solution of the polymer/drug mixture, followed by removal of the organic solvent by rota-evaporation. The particle size and drug content were determined by DLS and UV absorbance, respectively. As shown in Table 3, the drug-loaded particles are slightly bigger than the drug-free ones. The drug-loading content of around 10% and entrapment efficiency of around 50% were in a reasonable range. The copolymer with longer hydrophilic PHTMC block formed smaller micelle particles and showed slightly higher entrapment efficiency.

Conclusions

A novel amphiphilic triblock copolycarbonate (PHTMC-*b*-PDTC-*b*-PHTMC) was successfully synthesized through polymerization and deprotection reaction of BTMC with PDTC diol as an initiator and fumaric acid as a catalyst. The composition and molecular weight were in good accordance with the values predicted based on the feed ratio. ^{13}C NMR spectra showed the copolycarbonates have triblock structure. The amphiphilic triblock copolycarbonates can form stable micelle solutions upon addition of water to an organic solution. Primary experiments showed a potential of the micelles as drug carriers.

Acknowledgment. This research was financially supported by National Natural Science Foundation of China (20574054), National Basic Research Program of China (2005CB623903 and 2009CB930300), and Program for New Century Excellent Talents in University (NCET) of the Ministry of Education of China.

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MA802350G