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Hydrophilic Polycarbonates: Promising Degradable Alternatives to Poly(ethylene glycol)-Based Stealth Materials

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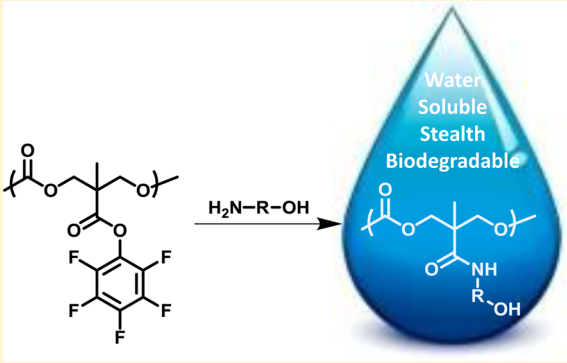
Supporting Information

ABSTRACT: Poly(ethylene glycol) (PEG) represents the gold standard for stealth polymers in polymer-based therapeutic delivery. Unfortunately, PEG has some limitations which warrant the examination of alternative polymers. High molecular weight PEG (>40 kDa) can accumulate in tissue, and in some patients, PEG can provoke an immunological response and/or an accelerated blood clearance upon repeated exposure. As an alternative to PEG, water-soluble, nonfouling polycarbonates have been developed. These hydrophilic polycarbonates, prepared by acid-catalyzed ring-opening polymerization, contain hydroxyl groups attached to the polymer side chain via an amide linkage. These materials offer an enzymatically and hydrolytically degradable alternative to PEG. The results of cell viability studies and LD_{50} studies indicate that these materials have minimal toxicity. Nonfouling behavior and the ability to resist/reduce aggregation with proteins were demonstrated. Diblock copolymers were also synthesized to demonstrate that these polymers can be utilized for micellar drug delivery systems.



INTRODUCTION

Poly(ethylene glycol) (PEG) is considered the gold standard for stealth polymers in polymer-based therapeutic delivery. PEG is synthesized from the ring-opening polymerization of ethylene oxide. In general, it can be polymerized at a wide variety of molecular weights with a narrow dispersity. It is soluble in a wide range of organic and aqueous solvents. Furthermore, reactive functionalities at the polymer endgroups can be introduced with ease, making it an excellent candidate for functionalization onto biologically relevant molecules. When PEG is in the bloodstream, water molecules form a neutral coating around the PEG, reducing adsorption of opsonins to the polymer surface and interaction of the polymer with the physiological environment.[1−3] PEGylated drugs and drug carriers have reduced enzymatic degradation, decreased uptake by the reticular endothelial system, and reduced renal filtration, resulting in increased circulation half-life and bioavailability.[4] Attaching PEG to therapeutics also significantly reduces toxicity of drugs and nanocarriers by decreasing the interaction with the body.[5]

PEGylated products have been on the market for 20 years, and there is a vast amount of clinical experience with this class polymers.[5] Despite the many advantages conferred by PEG, there also remain several drawbacks to its usage. The most obvious disadvantage of PEG is that it is not biodegradable, and at high molecular weights, it can accumulate in tissue. For example, PEGs with molecular weights below 40−60 kDa are required to prevent accumulation in the liver. Unfortunately, 40 kDa molecular weight PEG is commonly used for PEGylation of biologically active molecules.[5] In some patients, PEG can cause an immunological response and hypersensitivity as well as an accelerated blood clearance upon repeated exposure. Antibodies produced in response to PEG exposure have also been reported.[3]

The aforementioned disadvantages associated with PEG have motivated researchers to develop alternative polymers for therapeutic delivery, a topic which has been the subject of several review articles.[3,5] Although significant research has been performed in this area, there are few synthetic biodegradable polymer alternatives that offer the same stealth properties and can be prepared with the same level of synthetic control as PEG. One strategy is to synthesize polymers containing short PEG units within the polymer backbone, connected through a degradable linkage[6−9] or PEG units attached to the side chain

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of a polymer with degradable backbone.[10−13] Although both systems are degradable, undesirable toxicity can result if the PEG units have molecular weights lower than 400 Da.[5,14] Polycarbonates have the potential to be both water-soluble and biodegradable.[15,16] Recently, Chan et al. reported zwitterionic polycarbonates prepared by a well-controlled ring-opening polymerization. These polymers exhibited both degradability and nonfouling characteristics.[17] One common issue with zwitterionic polymers is that they exhibit minimal solubility in most organic solvents, thereby requiring subsequent synthetic transformations to be performed in aqueous media, which presents challenges if conjugation to a hydrophobic drug molecule is desired. Others have reported on hydroxyl-containing polycarbonates prepared from epoxides and CO_2 using a metal catalyst.[18,19] Poly(amino acid)-based polymers, such as poly(hydroxyethyl-L-asparagine) and poly(hydroxyethyl-L-glutamine), that have side groups containing hydroxyl groups attached through an amide linkage also show PEG-like characteristics (Figure 1).[20,21] These materials are

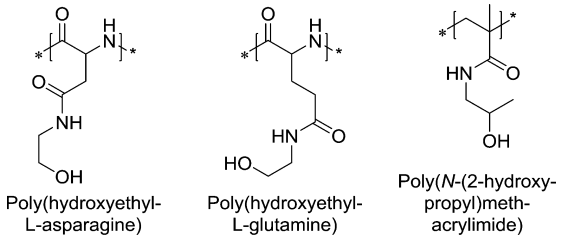
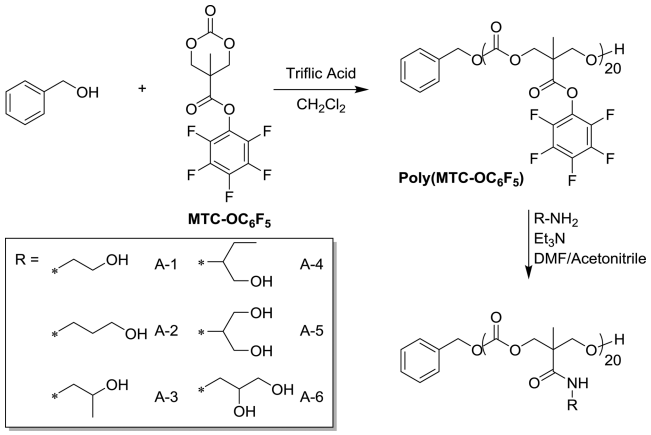


Figure 1. Polymers containing hydroxyl side groups attached through an amide linkage.

prepared by the ring-opening polymerization of *N*-carboxyanhydrides and degrade enzymatically *in vivo* into their corresponding amino acids.[17,18] A similar nonbiodegradable methacrylate-based polymer, poly(*N*-(2-hydroxypropyl)-methacrylamide) (Figure 1), reported by Duncan and others, has been evaluated in clinical trials with promising results.[5,22] In both of these polymer systems, the OH groups enhance water solubility and the amide groups facilitate hydrogen bonding with water molecules.[23] These polymers are also soluble in both aqueous and select organic solvents.

Herein we report a series of hydrophilic polycarbonates containing hydroxyl groups attached to the polymer side chain via an amide linkage. These materials have many of the positive characteristics of PEG including, access to a wide range of molecular weights, a narrow dispersity, solubility in both water and organic solvents, and minimal toxicity. Unlike PEG and the abovementioned polymers containing amide-linked alcohol side groups, polycarbonates are both hydrolytically and enzymatically degradable.[15,16] These new water-soluble polycarbonates are prepared by metal-free, acid-catalyzed ring-opening polymerization of a cyclic carbonate monomer containing an activated ester (MTC-OC_6F_5).[24] After polymerization, the activated ester polymer was functionalized with various amino alcohols, yielding a series of polycarbonates with pendent alcohol side chains attached by an amide linkage (Scheme 1). The pendant OH groups facilitate polymer side-chain hydration, and the resulting amide linkage was added to promote hydrogen bonding of the water molecules. The polymers were characterized by gel permeation chromatography and ^{1}H NMR spectroscopy to verify that the introduction of the desired OH group had no detrimental effects on the

Scheme 1. Synthesis of Water-Soluble Polycarbonates



sensitive polycarbonate backbone and to verify the chemoselectivity of the amines over hydroxyls. Polymer toxicity was determined using cell viability and LD_{50} studies. Nonfouling characteristics were determined using aggregation studies, which polymers were shown to resist nonspecific protein interactions. Diblock copolymers were also synthesized to determine if these polymers could be utilized for micellar drug delivery systems.

EXPERIMENTAL SECTION

Materials. MTC-OC_6F_5 was obtained from Central Glass and purified by crystallizing twice from a mixture of ethyl acetate and hexanes. MTC-OEt was prepared according to literature protocol.[25] Dichloromethane was dried using activated alumina columns and stored over molecular sieves (3 Å). All other materials were purchased from Sigma-Aldrich and used as received.

Methods. ^{1}H NMR spectra were obtained on a Bruker Avance 400 instrument at 400 MHz. Gel permeation chromatography (GPC) was performed in tetrahydrofuran (THF) using a Waters system equipped with four 5 μm Waters columns (300 mm × 7.7 mm) connected in series with an increasing pore size (100, 1000, 10^5, and 10^6 Å), a Waters 410 differential refractometer, and a 996 photodiode array detector. The system was calibrated with polystyrene standards. GPC analysis was also performed in *N*,*N*-dimethylformamide (DMF) spiked with 0.01 M LiBr using a Waters system equipped with two Agilent PolyPore columns (300 mm × 7.5 mm) connected in series and a Waters 410 differential refractometer. The system was calibrated with poly(methyl methacrylate) standards.

Poly(MTC-OC_6F_5). In a nitrogen-charged glovebox, benzyl alcohol (0.050 g, 0.46 mmol) and MTC-OC_6F_5 monomer (3.02 g, 9.25 mmol) were dissolved in dichloromethane (12 mL). The catalyst, triflic acid (0.069 g, 0.46 mmol), was added, and the reaction mixture was stirred at room temperature overnight. The crude polymer solution was precipitated into hexanes to yield a white solid (3.0 g, 97%). From GPC using THF as eluent, M_n = 6200 Da, PDI = 1.15, DP = 20 (m = 20 in the above reaction). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48 (s, 4H, CH_2), 1.51 (3H, CH_3).

Representative Synthesis of Poly(MTC-OC_6F_5)-*b*-Poly(MTC-OEt). In a nitrogen-charged glovebox, 3-butyn-1-ol initiator (0.085 g, 0.12 mmol) and MTC-OC_6F_5 monomer (1.98 g, 6.06 mmol) were dissolved in dichloromethane (8 mL). The catalyst, triflic acid (0.045 g, 0.30 mmol), was added, and the reaction mixture was stirred at room temperature overnight. The reaction progress was monitored by ^{1}H NMR, which showed near-complete conversion (93%) after 18 h. At this point, MTC-OEt monomer (0.57 g, 3.03 mmol) was added, and the reaction was allowed to stir at room temperature before being stopped at 73% conversion. The crude polymer was precipitated into hexanes to afford a white solid (2.36 g, 91.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48 (s, CH_2 poly(MTC-OC_6F_5), 4H), 4.26 (m, CH_2

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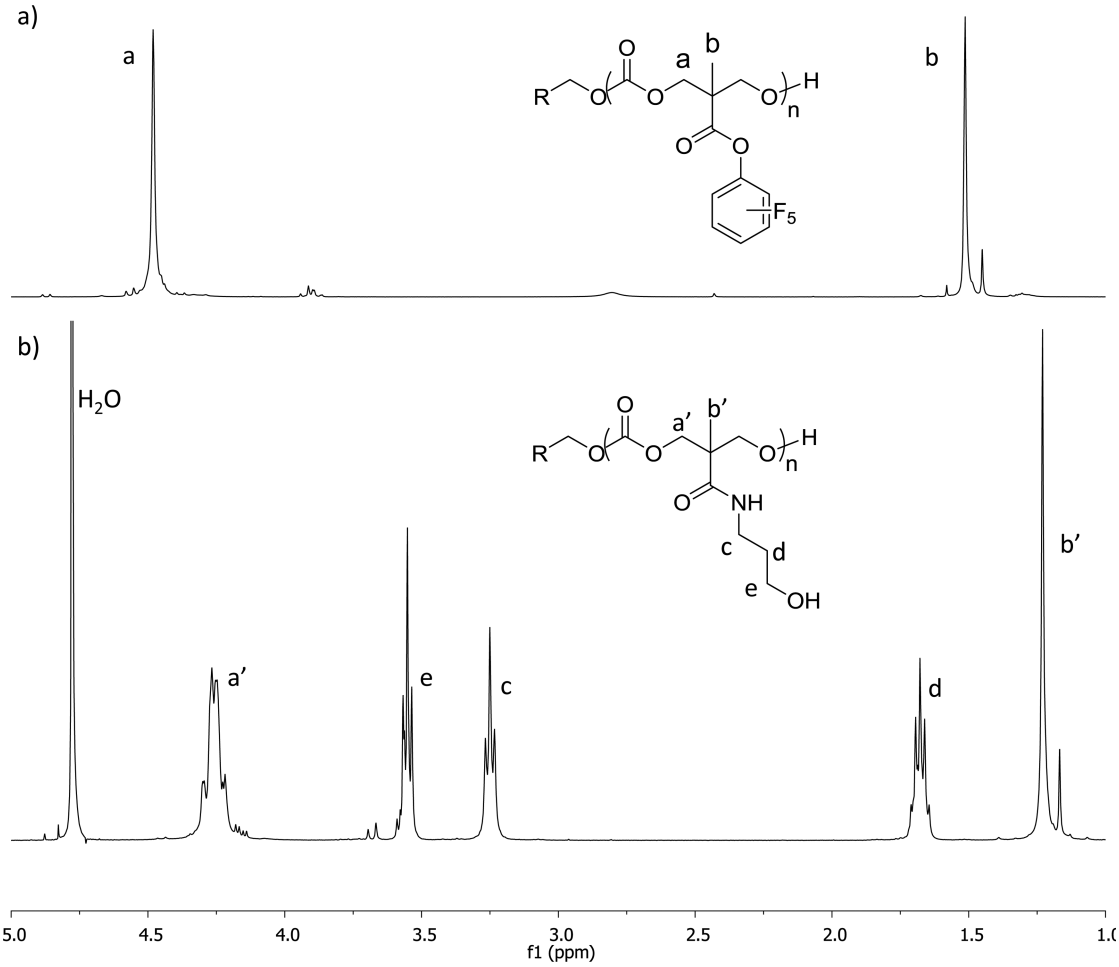

Figure 2. ^{1}H NMR in $CDCl_3$ of poly(MTC-OC_6F_5) and ^{1}H NMR in D_2O of polymer A-2. R = Phenyl.

poly(MTC-OEt), 4H), 4.20 (m, CH_2CH_3 poly(MTC-OEt), 2H), 1.51 (s, CH_3, 3H) poly(MTC-OC_6F_5), 1.26 (m, CH_3 poly(MTC-OEt), 3H), 1.26 (m, CH_2CH_3 poly(MTC-OEt), 3H).

Representative Postpolymerization Functionalization. Poly(MTC-OC_6F_5) (200 mg, 0.613 mmol repeat units) was dissolved in 1 mL of acetonitrile (MeCN). 2-Aminoethanol (0.039 g, 0.64 mmol) and triethylamine (0.065 g, 0.644 mmol) were dissolved in 1 mL of MeCN and added dropwise to the polymer solution, whereupon a white precipitate began to form. An additional 1 mL of DMF was added to produce a clear solution. The reaction was allowed to proceed for an additional 2 h, and then it was precipitated into ether. A white solid was recovered, dialyzed against water (pH 4, molecular weight cutoff of 1000 Da), freeze-dried, and analyzed by GPC (DMF) and ^{1}H NMR. Please note that the dialysis is performed at pH 4 after precipitation into ether. We found that if the dialysis was performed under basic aqueous conditions (pH > 7.5) after 12 h, polymer degradation was observed (i.e., no polymer was left in the 1000 Da cutoff dialysis bag).

Cell Viability. HEK293 cells were cultured in RPMI-1640 supplied with 10% fetal bovine serum (FBS) and 1% penicillin−streptomycin. HEK293 cells were seeded onto 96-well plates at a density of 10 000 cells/well. The cells were incubated at 37 °C, 5% CO_2. After 24 h, the medium was replaced with fresh medium containing polymer at various concentrations. After being incubated for 48 h, 100 μL of fresh medium and 20 μL of 5 mg/mL MTT solution were used to replace the sample medium. After 4 h of incubation, the medium was removed, and DMSO (150 μL) was added to each well to dissolve the formazan crystals. The absorbance of each well was measured as that at 550 nm deducted by that at 690 nm with a microplate reader (PowerWave X, Biotek Instruments). The results were presented as a percentage of absorbance of the blank control.

LD_{50} Studies. Female Balb/c mice (19−21 g) were randomly selected and kept in cages for at least 5 days to allow for acclimatization to the laboratory conditions. Before injection, mice were fasted for 12 h before testing. Polymer was dissolved in sterilized saline solution at a concentration of 50 mg/mL and administered via intravenous injection at a dose of 50 mg/kg. Polymer solution was initially given to one mouse, and if the first mouse survived after 48 h, two more mice were further used for the test. After injection, all the animals were observed every 30 min for the first 4 h and daily thereafter, for a total of 14 days.

Aggregation Study. Polymers were dissolved in PBS containing 10% FBS. The particle sizes within the polymer solutions were analyzed using a Zetasizer 3000 HAS (Malvern Instrument Ltd., Malvern, UK) equipped with a He−Ne laser beam at 658 nm (scattering angle: 90°) over 24 or 48 h. The concentration of the polymers was 500 mg/L. Each sample was measured three times, and an average particle size was obtained.

RESULTS AND DISCUSSION

Synthesis and Physical Characterization of Water-Soluble Polymers. The polymers described in this work (Scheme 1) are based on an aliphatic polycarbonate backbone and were designed to be degradable analogues of poly(*N*-(2-hydroxypropyl)methacrylamide. Briefly, poly(MTC-OC_6F_5) was prepared via triflic acid-catalyzed ring-opening polymerization of MTC-OC_6F_5 (degree of polymerization = 20, from GPC with THF as eluent: M_n = 6200 Da, PDI = 1.15). After

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Table 1. Summary of Functionalized Homopolymers Including Molecular Weight and Polydispersity by GPC (DMF), Water Solubility, and ^{1}H NMR Chemical Shifts

	amino alcohol used	water-soluble at 50 mg/mL?	GPC M_n	GPC M_w	GPC PDI	^{1}H NMR (400 MHz)
P-1	NA	no	5200	5500	1.05	$CDCl_3$, δ 4.48 (s, 4H, CH_2), 1.51 (s, 3H, CH_3)
A-1	2-aminoethanol	yes	6800	7400	1.09	D_2O, δ 4.23 (s, 4H, CH_2), 3.53 (t, 2H, CH_2OH), 3.26 (t, 2H, NHCH_2), 1.19 (s, 3H, CH_3)
A-2	3-amino-1-propanol	yes	6200	6600	1.07	D_2O, δ 4.20 (s, 4H, CH_2), 3.51 (t, 2H, CH_2OH), 3.20 (t, 2H, NHCH_2), 1.62 (t, 2H, $CH_2CH_2CH_2$), 1.18 (s, 3H, CH_3)
A-3	1-amino-2-propanol (racemic)	yes	5600	6000	1.07	D_2O, δ 4.22 (s, 4H, CH_2), 3.8 (q, 1H, CHOH), 3.15 (d, 2H, NHCH_2), 1.19 (s, 3H, CH_3), 1.03 (t, 2H, CHCH_3)
A-4	2-amino-1-butanol	insoluble[a]	6400	7000	1.08	DMSO-d_6, δ 4.57 (m, 1H, NHCH), 4.19 (s, 4H, CH_2), 3.64, 3.23 (m, 2H, CH_2OH), 1.58, 1.28 (m, 2H, CH_2CH_3), 1.19 (s, 3H, CH_3), 1.03 (t, 2H, CHCH_3)
A-5	serinol	yes	7100	7600	1.07	D_2O, δ 4.23 (s, 4H, CH_2), 3.94 (d, 1H, NHCH), 3.56 (t, 2H, CH_2OH), 1.21 (s, 3H, CH_3)
A-6	(±)-3-amino-1,2-propanediol	yes	5400	5700	1.06	D_2O, δ 4.22 (m, 4H, CH_2), 3.67 (m, 1H, CHOH), 3.38 (m, 1H, NHCH), 3.22 (m, 2H, CH_2OH), 1.17 (s, 3H, CH_3)

[a]When observed visually, polymer A-4 did not appear to dissolve in water at 50 mg/mL.

polymerization, the polymers were functionalized with amino alcohols such that each repeat unit contains an amide and one or more hydroxyl groups. Complete functionalization was observed with the amine selectively reacting with the activated ester instead of reacting with the hydroxyl, ensuring that there was no deleterious cross-linking or ester formation. This chemoselectivity was also verified by ^{1}H NMR and is shown in Figure 2 which contains ^{1}H NMR spectra of poly(MTC-OC_6F_5) and 3-aminopropanol postfunctionalization product (A-2). Quantitative reaction of the activated ester to an amide was verified by monitoring the shift in the polycarbonate backbone peaks (Figure 2, a and b to a′ and b′, respectively) and the appearance of new peaks associated with small molecule amine substitution. Furthermore, integration of the new signals against that of the polymer backbone was consistent with complete substitution (Figures S-1 to S-6).

During postpolymerization modification, degradation of the polymer backbone was a concern because of the basic condition required for the functionalization reaction and the abundance of free hydroxyl groups. The polymers were analyzed by GPC to determine if there was a significant drop in molecular weight or broadening in dispersity. As summarized in Table 1, no broadening in dispersity was observed, and in all cases similar molecular weights were observed, indicating that the polymer backbone remained intact after functionalization.

Polymer Stability Studies. One method of determining if a polymer system exhibit stealth characteristics is to look at polymer aggregation in serum. Using dynamic light scattering, the size of particles in serum can be measured. If the particle size remains consistent over time (i.e., the polymers are not causing aggregation), it indicates that the polymer is sufficiently hydrated such that it has nonfouling characteristics.[26,27] For these measurements, the water solubility of each of the new polymers was determined by placing purified polymer (50 mg) in a small vial and adding water (1 mL). If the solution was clear at a concentration of 50 mg/mL, the polymer was labeled as water-soluble (Table 1). Poly(MTC-OC_6F_5) substituted with 2-aminobutanol did not visually dissolve (A-4), but all other polymers were fully water-soluble. The fully water-soluble polymers were then dissolved in PBS containing 10% FBS at a concentration of 500 mg/L. Particle size was measured as a function of time using dynamic light scattering, with PEG (2 kDa) used for comparison. For all water-soluble polymers, the particle size remained constant, indicating that there is no observed aggregation caused by the polymers.

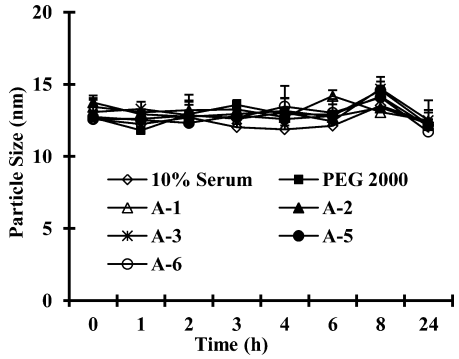

Figure 3. Particle size measured by DLS as a function of time for homopolymers dissolved in 10% serum.

Polymer Toxicity. Cell viability studies were performed using HEK293 cells. PEG (5000 and 10 000 Da) were used as controls. As shown in Figure 4, only the polymer substituted

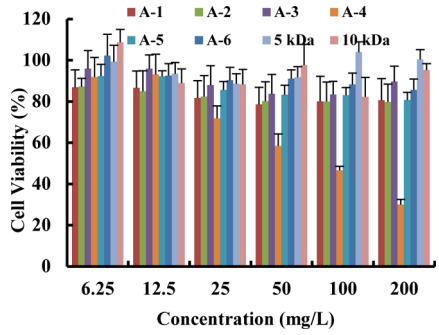

Figure 4. Cell viability studies of water-soluble polycarbonates compared to PEG (labeled as 5 kDa and 10 kDa).

with 2-amino-1-butanol exhibited cell viability that drops below 80%. This toxicity is most likely a result of the high hydrophobicity associated with this polymer. All other polymers show similar toxicity profiles to what is observed for the 5 and 10 kDa PEG. The more hydrophilic serinol-substituted polymer was selected for LD_{50} studies. Mice were intravenously injected with polymer at a dose of 500 mg/kg. The animals were observed every 30 min for the first 4 h and daily after, for a total of 14 days. All mice exhibited good health, with no observable toxicity at the dose of 500 mg/kg, indicating an LD_{50} > 500 mg/kg.

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Scheme 2. Synthesis of Diblock Copolymers Containing Water-Soluble Polycarbonate Block and the Hydrophobic Block Poly(MTC-OEt)

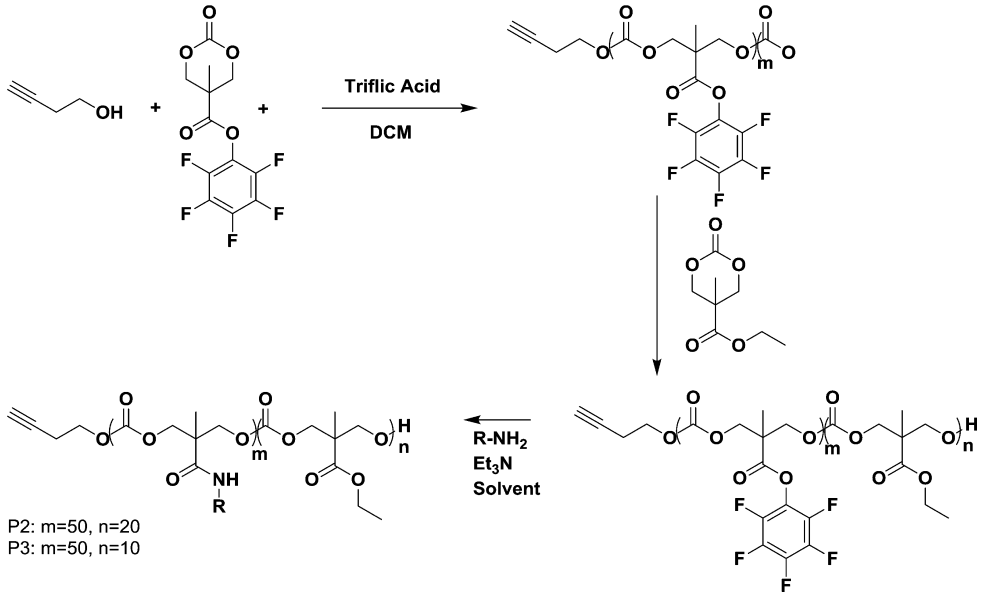

Table 2. Molecular Weight Characterization by NMR End-Group Analysis and GPC (THF)

			poly(MTC-OC_6F_5) GPC data			diblock GPC data		
	m by NMR	*n* by NMR	M_n	M_w	PDI	M_n	M_w	PDI
P-2	50	20	10100	11600	1.15	12800	15200	1.18
P-3	50	10	10500	11900	1.14	12600	14800	1.16

Micelle Formation. One strategy commonly explored for hydrophobic drug delivery is the use of diblock copolymers that self-assemble into micelles. PEG-based diblock copolymers are very common in the literature where water-soluble PEG stabilizes the micelles in water and serum. Diblock copolymers comprising water-soluble polycarbonates with a hydrophobic polycarbonate second block (poly(MTC-OEt)) were selected for this study. These polymers were synthesized by first polymerizing MTC-OC_6F_5 followed by the sequential addition of MTC-OEt (Scheme 2). Two different poly(MTC-OC_6F_5)-*b*-poly(MTC-OEt) polymers were made with varying lengths of poly(MTC-OEt), which were subsequently subjected to the postmodification protocol using various amino alcohols. As shown in Table 2, diblock copolymers with controlled structure and narrow molecular weight distributions were obtained. Representative ^{1}H NMR spectra of the diblock copolymers can be found in the Supporting Information. Quantitative substitution of poly(MTC-OC_6F_5) was also observed for these materials.

Light scattering was performed on these materials in water to determine micelle size (Table 3). Diblock copolymer wherein the hydrophilic block contained a single hydroxyl unit and propyl spacers between the amide and hydroxyl group (Table 3, entries B-2 and B-3) formed larger micelles than the diblock copolymers with more hydrophilic side groups. This result indicates that the materials in the former category are not hydrated enough to create small stable micelles suitable for drug delivery. The other, more hydrophilic diblock copolymers (entries B-1, B-4, and B-5) self-assembled into micelles on the order of 10−20 nm. Lastly, aggregation studies were performed on the serinol- and 3-aminopropanol-substituted diblock copolymers (Figure 5). The serinol-substituted micelles were

Table 3. Dynamic Light Scattering Data of Diblock Copolymer Micelles in Water

		backbone P-2 (*m* = 50, *n* = 20)		backbone P-3 (*m* = 50, *n* = 10)	
entry	amino alcohol	micelle size by DLS (nm)	PDI by DLS	micelle size by DLS (nm)	PDI by DLS
B-1	2-aminoethanol	15	0.26	15	0.40
B-2	3-amino-1-propanol	176	0.38	610	0.11
B-3	1-amino-2-propanol (racemic)	258	0.77	190	0.16
B-4	serinol	20	0.44	20	0.31
B-5	(±)-3-amino-1,2-propanediol	14	0.40	19	0.47

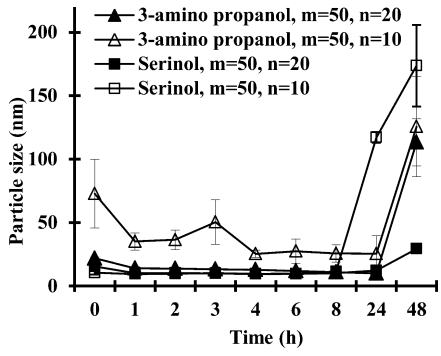

Figure 5. Particle size measured by DLS as a function of time for diblock copolymers substituted with serinol and 3-aminopropanol dissolved in 10% serum.

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stable in serum for at least 8 h. The micelles formed from the diblock copolymer with a longer hydrophobic block (P-2 backbone) demonstrated higher stability, and particle size remained below 50 nm even after 48 h. The 3-aminopropanol-substituted polymers with lower hydrophobicity (entry B-2, P-3 backbone) were less stable with the micelle size being less consistent over time. Similar to the serinol-substituted polymers, the more hydrophobic 3-aminopropanol-substituted polymers exhibited better stability. Changing the micelle media from water to 10% serum did cause a decrease in micelle size for the 3-aminopropanol-substituted polymers (series B-3). For backbone P-2, the micelle size decreased from 176 to 21 nm, and for backbone P-3 the micelle size decreased from 610 to 73 nm (Table 3 and Figure 5). The diblock stability studies indicate that select water-soluble polycarbonates can serve as the hydrophilic block of amphiphilic diblock copolymers for preparation of micellar drug delivery systems.

CONCLUSION

Hydrophilic polycarbonates containing hydroxyl groups attached to the polymer side chain via an amide linkage were prepared by the acid-catalyzed ring-opening polymerization of the cyclic carbonate MTC-OC_6F_5 and subsequent reaction with amino alcohols. Quantitative, chemoselective substitution of the activated ester groups to the corresponding amides was observed, and polymer dispersity was maintained after functionalization. These materials were designed with OH side groups and amide linkages to promote hydrogen bonding with water molecules to facilitate polymer hydration. These materials exhibited nonfouling properties similar to PEG with the added benefit of being both enzymatically and hydrolytically degradable. Cytotoxicity assays and LD_{50} evaluations indicate that these polymers have toxicity similar to that of the PEG controls. Preliminary micelle studies indicate that these materials are promising candidates for micellar drug delivery.

ASSOCIATED CONTENT

Supporting Information

Additional ^{1}H NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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