Polycarbonate and Poly(carbonate−ester)s Synthesized from Biocompatible Building Blocks of Glycerol and Lactic Acid

William C. Ray, III and Mark W. Grinstaff*

Departments of Chemistry, Ophthalmology, and Biomedical Engineering, Duke University and Duke University Medical Center, Durham, North Carolina 27708

Received November 25, 2002; Revised Manuscript Received March 4, 2003

ABSTRACT: The synthesis and characterization of a polycarbonate of glycerol and poly(carbonate−ester)s of glycerol and L-lactic acid are reported. These new polymers possess a hydrolyzable backbone, tunable hydrophobic/hydrophilic properties, and functionalizable pendant groups. The free hydroxyl groups on the poly(glycerol-*co*-L-lactic acid) were derivatized with 4-isobutylmethylphenylacetic acid, a common nonsteroidal antiinflammatory drug.

Introduction

Polymers find extensive use as medical materials, ranging from simple nylon sutures to the first tissue-engineered device, an artificial skin construct composed of living cells.[1−7] Since the 1960s, biodegradable synthetic polymers, such as poly(L-lactide) (PLLA), have been increasingly used in applications, such as drug delivery, where long-term stability is not required.[8−13] Copolymerization and blending of biodegradable polymers can lead to a wide range of physical properties and degradation rates, but functionalization of these polymers is relatively limited. Few polymers with biocompatible and hydrolyzable backbones possess functional or reactive pendant groups. This impedes the development of advanced biomaterials with tailored chemical functionality and optimized physical, mechanical, and biological properties.

Several notable examples of functionalizable or biologically inspired polymers are reported in the literature. These include linear polyesters such as poly(*β*-malic acid),[14,15] poly(L-serine ester),[16,17] poly(glycolic acid-*co*-malic acid),[18] poly(5-hydroxy-*ϵ*-caprolactone),[19−26] poly(lactic acid-*co*-xylofuranose),[27] and poly(lactic acid-*co*-pentofuranose)[28] as well as polyester−amides such as poly(lactic acid-*co*-lysine),[29,30] poly(lactic acid-*co*-aspartic acid),[31] and poly(depsipeptide)s.[32,33] Two linear polycarbonates are known, including poly(2-ethyl-2-hydroxymethyltrimethylene carbonate)[34] and poly(tyrosine carbonate).[35,36] Recently, poly(ether−ester) and polyester dendrimers composed of glycerol−lactic acid and glycerol−succinic acid, respectively, are also described.[37−40] New biocompatible polymers are needed to expand the current repertoire of customized biomaterials. Polymers are highly sought after that possess functionalizable side chains (OH, NH_2, CO_2H, etc.), alternative main-chain linkages, tunable degradation rates, or other architectures such as comb, ladder, or dendritic, while composed of building blocks that are natural metabolites or known to be biocompatible. Herein, we report the synthesis and characterization of a polycarbonate of glycerol and poly(carbonate−ester)s of glycerol and L-lactic acid. These polymers possess a hydrolyzable backbone, tunable hydrophobic/hydrophilic properties, and functionalizable heteroatom pendant groups.

* Corresponding author: e-mail mark.grinstaff@duke.edu.

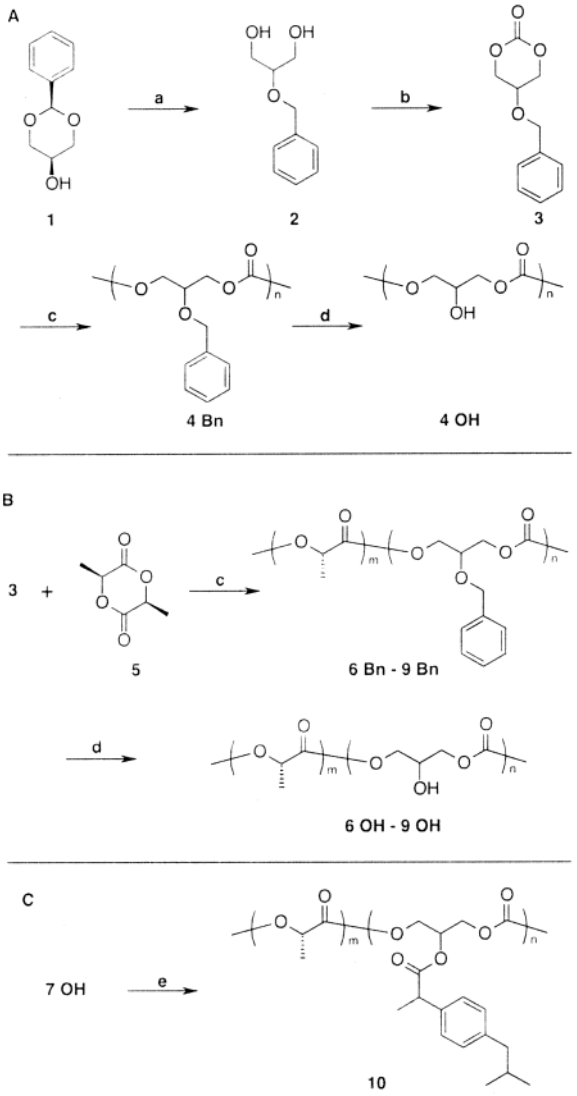
Results and Discussion

As shown in Scheme 1, the polycarbonate of glycerol was synthesized via ring-opening polymerization of a cyclic glycerol carbonate using tin(II) 2-ethylhexanoate ($Sn(oct)_2$) followed by Pd catalyzed hydrogenation to remove the benzyl (Bn) protecting group attached to the secondary hydroxyl of glycerol.[41,42] The monomer, 5-benzyloxy-1,3-dioxan-2-one, **3**, was prepared in two steps starting from *cis*-1,3-*O*-benzylideneglycerol (5-hydroxy-2-phenyl-1,3-dioxane), **1**.[43] *cis*-1,3-*O*-Benzylideneglycerol was treated with NaH and benzyl bromide in THF to afford the doubly protected intermediate, which was not isolated. The benzylidene group was subsequently removed by acid hydroylsis (10% aqueous HCl) to give 2-benzyloxy-1,3-propanediol, **2**, in 98% yield. The diol was then converted to the cyclic carbonate, **3**, in 67% yield using ethyl chloroformate and TEA in THF. Polymerization of neat 5-benzyloxy-1,3-dioxan-2-one at 140 °C with $Sn(oct)_2$ as catalyst (monomer-to-catalyst ratio was 500:1) led to a modest molecular weight polymer, **4 Bn**. Under these polymerization conditions, longer reaction times neither increased the molecular weight nor altered the polydispersity.

Poly(carbonate−ester)s of varying mole ratios of L-lactic acid and glycerol were prepared in an analogous manner (**6** to **9**), except using a higher reaction temperature (180 °C). The benzyl-protected polymers (**4 Bn**, **6 Bn** to **9 Bn**) were subsequently deprotected using $Pd(OH)_2/C$ and H_2 to afford the polycarbonate of glycerol, **4 OH**, and poly(carbonate−ester)s of glycerol and L-lactic acid (**6 OH** to **9 OH**). The molecular weight dependence as a function of mol % L-lactic acid monomer for the poly(glycerol-*co*-L-lactic acid) is shown in Table 1. Under these polymerization conditions, L-lactide did not undergo racemization; the specific optical rotation for a sample of PLLA was −158°. This value agreed with the reported value[44] as well as a commercial sample (Polysciences). This result is expected as the racemization of lactide by $Sn(oct)_2$-catalyzed polymerization does not occur up to temperatures of 200 °C.[45] Both NMR and IR spectroscopy also provide additional evidence for polymer formation. Polymerization of 5-benzyloxy-1,3-dioxan-2-one, **3**, leads to an IR carbonyl stretching frequency shift from 1737 to 1746 cm^{-1} (Δ +9 cm^{-1}) and a ^{13}C NMR carbonyl resonance shift from 148.1 to 155.1 ppm (Δ +7.0 ppm; see Table 2). By comparison,

10.1021/ma025872v CCC: $25.00
Published on Web 04/24/2003

Scheme 1. Synthesis of a Polycarbonate of Glycerol (A) and Poly(carbonate−ester)s of Glycerol and Lactic Acid (B) and a Poly(carbonate−ester) of Glycerol and Lactic Acid Derivatized with an NSAID (C)[a]



[a] Reagents and conditions: a. i. NaH, THF, ii. BnBr, iii. 10% aq HCl; b. i. EtOCOCl, THF, ii. Et_3N; c. $Sn(Oct)_2$; d. H_2, $Pd(OH)_2/C$; e. 4-isobutylmethylphenylacetyl chloride, Et_3N, CH_2Cl_2.

polymerization of trimethylene carbonate leads to an IR carbonyl frequency shift from 1724 to 1738 cm^{-1} (Δ +14 cm^{-1}) and a ^{13}C NMR carbonyl resonance shift from 148.2 to 154.9 ppm (Δ +6.7 ppm). Removal of the **Bn** group of the secondary hydroxyl of **4 Bn** and **6 Bn** to **9 Bn** afforded a new IR OH stretch at 3400 cm^{-1}. The similarities in the IR and NMR shifts between poly(trimethylene carbonate) and poly(glycerol carbonate) and their corresponding monomers support the formation of the polycarbonate. NMR analysis of the copolymers shows that the ratio of L-lactic acid to glycerol in the copolymer correlated reasonably well with the starting monomer ratio. For example, a mol % starting ratio of 1:1 for monomers **3** and **5** affords a copolymer composed of 60% lactic acid and 40% glycerol.

In the poly(carbonate−ester)s the ^{13}C NMR resonances of the monomers vary with the copolymer sequence, each monomer unit being sensitive to its nearest neighbor.[20,46,47] Thus, information on the sequence arrangement (e.g., random, block, alternating) can be obtained by analyzing the ^{13}C NMR spectrum of the copolymer. Analysis of the copolymer in terms of monomer triads is a common method. We modeled[48] the ^{13}C NMR spectrum for the eight triads possible for the two repeating units, L-lactic acid, L, and glycerol, G (i.e., LLL, LLG, GLL, GLG, LGL, LGG, GGL, GGG). The ^{13}C NMR resonances for the LLL and GGG triads were assigned from the respective homopolymers (i.e., PLLA and **4 Bn**); the remainder were predicted using NMR simulation software (see Figure 1).[48] As expected, a single resonance is found for the carbonyls of the homopolymers. However as seen in Figure 1, four resonances are found in the carbonyl region for the 30% carbonate copolymer (**8Bn**). The resonance at 169.7 ppm is assigned to the LLL triad, which is the most prevalent sequence in the copolymer. In addition, there is a resonance just downfield at 169.9 ppm. This signal is attributed to the central carbonyl in the LLG triad. For the carbonate carbonyl, the resonance appears at 154.4 ppm, slightly upfield from its position in the homopolymer (154.8 ppm). This resonance is assigned to the central carbonyl in the LGL triad. Similar data are observed with the 10% carbonate copolymer (**9Bn**), except that the signal at 154.8 ppm for the GGG triad is absent. These data indicate that the copolymers are statistical copolymers.

Table 1. Molecular Weight and T_g Data for the Polycarbonate and Poly(carbonate−ester)s[a]

polymer	mol % lactic acid	M_w[b]	PDI	% yield	T_g
4 Bn	0	12 000	1.76	70	6
4 OH	0	8 600	1.43		
6 Bn	25	12 800	1.65	70	18
6 OH	25	10 900	1.62		
7 Bn	50	11 500	1.46	78	30
7 OH	50	9 700	1.67		20
8 Bn	70	18 200	1.48	70	34
8 OH	70	17 400	1.57		24
9 Bn	90	30 800	1.21	84	53
9 OH	90	16 700	1.58		33
PLLA	100	44 900	1.79	85	60
10	50	8 400	1.42	90	38

[a] All polymers were obtained by bulk polymerization for 2 h, at 140 °C (**4**) or 180 °C (**6**−**9** and **PLLA**). [b] Determined by size-exclusion chromatography.

Table 2. Spectroscopic Data for Monomers and Polycarbonates

monomer or polymer	carbonyl stretch (IR, neat)	carbonyl shift (^{13}C NMR, $CDCl_3$)
5-benzyloxy-1,3-dioxan-2-one	1737	148.1
poly(5-benzyloxy-1,3-dioxan-2-one)	1746	155.1
trimethylene carbonate	1724	148.2
poly(trimethylene carbonate)	1738	154.9

Polymers **4** and **6** through **9** displayed a range of physical properties consistent with their chemical composition. The benzyl-protected polycarbonate and poly(carbonate−ester)s were soluble in halogenated solvents, aromatic solvents, THF, and ethyl acetate. The free-hydroxy polycarbonate and poly(carbonate−ester)s were soluble in hydrophilic solvents such as DMF and MeOH. Polymer **4 OH** was soluble in water, and copolymers **6 OH** to **9 OH** become more hydrophobic with increasing mol % L-lactic acid in the polymer. Thermal analysis of the copolymers by differential scanning calorimetry revealed two trends. First, the

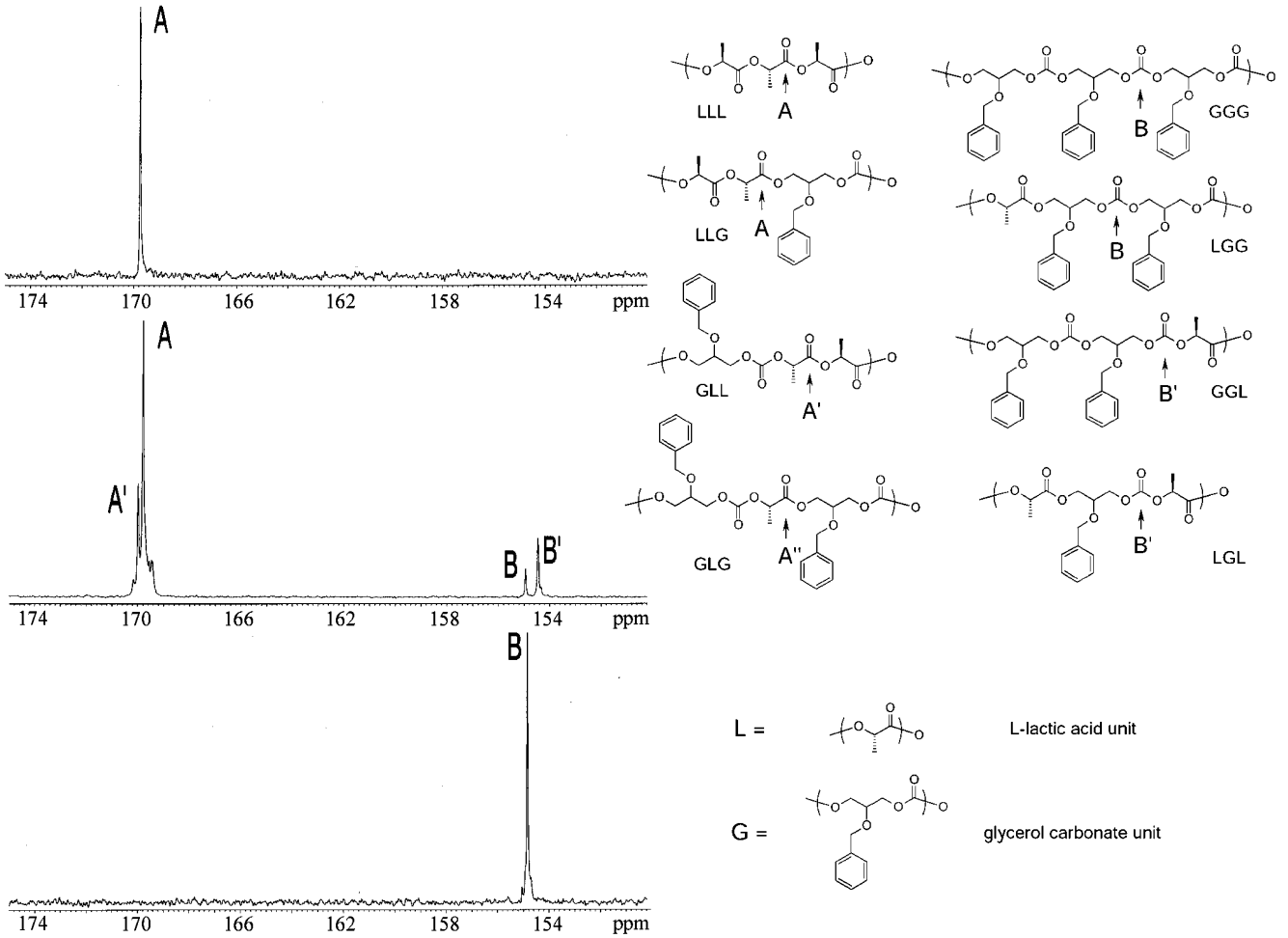


Figure 1. ^{13}C NMR spectra of **PLLA**, **8Bn**, and **4Bn** and the chemical structures of the eight triads possible with the respective carbonyls noted.

copolymer glass transition temperature (T_g) increased with decreasing glycerol content, from 6 °C for **4Bn** to 60 °C for PLLA. These data are given in Table 1. Second, introduction of glycerol−carbonate linkages to the poly(L-lactide) chain led to a significant reduction of the crystallinity of the polymer. For a sample of PLLA a crystallization was observed at approximately 109 °C, followed by a melt (T_m) at 171 °C (ΔH_f = 32 J/g). A sample of **9Bn** crystallized at 130 °C, followed by a T_m of 151 °C (ΔH_f = 1.5 J/g). Analysis of the copolymers with higher glycerol content indicated no crystallinity.

The degradation of the poly(carbonate−ester)s was next investigated at neutral pH (pH = 7.4), at acidic pH (pH = 4.4), and in the presence of an esterase. Samples of 1 cm^2 films of **8 OH**, **9 OH**, and PLLA were submerged in a 0.1 molar buffered phosphate solution of the appropriate condition at 37 °C. Samples were then measured at 1, 2, 4, 7, 10, and 14 day intervals, and the molecular weight of the polymer was determined by size-exclusion chromatography. Under neutral and mild acidic conditions the poly(carbonate−ester)s, **8 OH** and **9 OH**, degraded while PLLA remained essentially unchanged. After 14 days, the molecular weight had decreased by approximately 35% for both copolymers. Degradation was slightly greater at pH = 4.4. Data for copolymer **9 OH**, for example, are shown in Figure 2. The presence of porcine liver esterase also does not effect significantly the degradation of the polymers. The physical appearance of the polymer samples did not appreciably change. The poly(carbonate−ester)s were more susceptible to hydrolytic degradation than PLLA consistent with the decreased crystallinity present in the copolymers. A similar conclusion was reported for poly(lactic acid-*co*-lysine).[30]

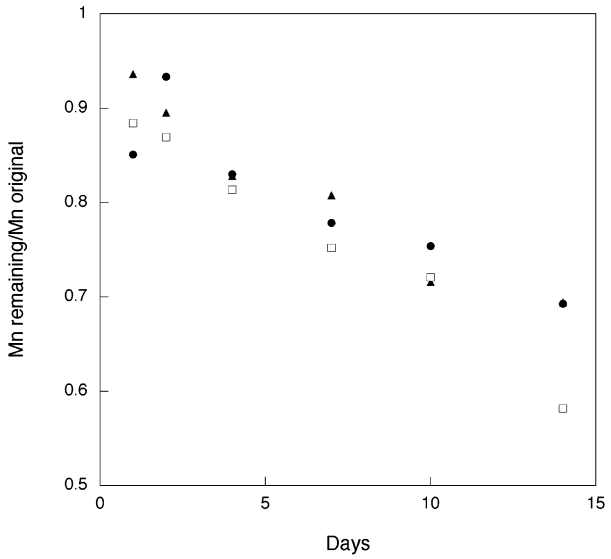


Figure 2. Degradation of copolymer **9 OH** at pH = 7.4 (solid triangle), at pH = 4.4 (open squares), and in the presence of an esterase (solid circles).

The free hydroxyl group on the glycerol−lactic acid copolymer is amenable to functionalization, and this provides opportunities for covalent attachment of biological epitopes for cell recognition, photo-cross-linkable moieties for 3D-gel formation, or pharmaceutical agents for drug delivery. Nonsteroidal antiinflammatory drugs (NSAIDs) represent a large class of pharmaceuticals widely used as antiinflammatories, analgesics, or antipyretics.[49] The therapeutic actions of NSAIDS arise from altering prostaglandin production by inhibiting the cyclo-oxygenase (COX) enzyme.[50] One common NSAID used to treat rheumatoid arthritis and osteoarthritis is 4-isobutylmethylphenylacetic acid. Derivatization of the poly(glycerol-*co*-L-lactic acid), **7 OH**, with an excess of 4-isobutylmethylphenylacetyl chloride afforded the NSAID functionalized copolymer **10**. Size exclusion chromatography revealed the weight-average molecular weight to be 8400. The unique aromatic protons of 4-isobutylmethylphenylacetate at 7 ppm were observed in the NMR spectrum of **10**, and integration of the proton resonances of the copolymer indicated that ∼90% of the hydroxyls were modified with this NSAID.

Conclusion

In summary, aliphatic polycarbonates with glycerol repeating units are synthesized by ring-opening polymerization of 5-benzyloxy-1,3-dioxan-2-one followed by catalytic hydrogenolysis. Copolymers with L-lactide can be prepared suggesting that other cyclic carbonates and lactones are likely monomers for tailored copolymers. These polymers offer several advantages including functionalizable side chains for modification, known biocompatible units of glycerol and lactic acid, and a tunable hydrophilic structure. Optimization of the chemical, physical, and mechanical properties of such polymers through judicious choice of the monomer(s) is likely to facilitate the synthesis of new polymers designed for specific drug delivery and tissue engineering applications.

Experimental Section

General Procedures. All solvents were dried and freshly distilled prior to use. THF and toluene were distilled under N_2 from sodium; methanol and CH_2Cl_2 were distilled under N_2 from calcium hydride. All other reagents were used as received, without further purification. Glycerol, benzaldehyde, sodium hydride (60% in mineral oil), benzyl bromide, ethyl chloroformate, triethylamine, and palladium on carbon were purchased from Acros. Stannous 2-ethylhexanoate (stannous octoate), LL-lactide, and α-methyl-4-(isobutyl)phenylacetic acid were purchased from Aldrich. *cis*-1,3-*O*-Benzylideneglycerol was either purchased from Aldrich or prepared according to the literature,[51] and α-methyl-4-(isobutyl)phenylacetyl chloride was also prepared according to the literature.[52] All reactions were performed under a nitrogen atmosphere unless otherwise noted. NMR spectra were recorded on a Varian INOVA spectrometer (for ^{1}H and ^{13}C at 400 and 100.6 MHz, respectively). FT-IR spectra were recorded on a Nicolet Smart MIRacle Avatar 360 using a zinc selenide crystal. Chemical ionization mass spectra were obtained on a Hewlett-Packard HP 5988A spectrometer using NH_3. Fast atom bombardment mass spectra (FABMS) were obtained on a JEOL JMS-SX102A spectrometer using a 3-nitrobenzyl alcohol matrix. Elemental analysis was obtained from Atlantic Microlab, Inc. Size exclusion chromatography was performed using THF as the eluent on a Polymer Laboratories PLgel 3 μm MIXED-E column (3 μm bead size) and a Rainin HPLC system (temperature = 25 °C; flow rate = 1.0 mL/min). Polystyrene standards (Polysciences, Inc.) were used for calibration. A TA Instruments DSC 2920 modulated DSC was used to collect T_g data (ramp 10 °C/min to 125 °C, cool 10 °C/min to −25 °C, ramp 10 °C/min to 125 °C); thermal transitions were measured on the second heating cycle. The optical rotation of the polymers was measured in dichloromethane at a concentration of 0.025 g/mL at 26 °C using a Rudolph Autopol IV automatic polarimeter at a wavelength of 589 nm. THF = tetrahydrofuran, EtOAc = ethyl acetate, Pd/C = 10% palladium on activated carbon, PLLA = poly(L-lactide), PCG = polycarbonate of glycerol.

Synthesis of 2-Benzyloxy-1,3-propanediol. Sodium hydride (5.0 g 60% in mineral oil, 0.125 mol) was suspended in freshly distilled THF (400 mL), and the mixture was cooled in an ice/H_2O bath. 5-Hydroxy-2-phenyl-1,3-dioxane (18.2 g, 0.100 mol) was added in portions, and the mixture was stirred for 15 min. Benzyl bromide (14.4 mL, 0.120 mol) was added via a syringe, and the reaction was stirred at 0 °C to room temperature (RT) overnight. Approximately half of the THF was evaporated under reduced pressure, and 100 mL of H_2O and 300 mL of 10% aqueous HCl were added. The mixture was refluxed for 2 h, cooled to room temperature, and poured into 50 mL of saturated aqueous Na_2CO_3. The solution was extracted with ethyl acetate (3 × 50 mL). The extracts were dried over Na_2SO_4 and evaporated to yield 18.0 g (98% yield) of a viscous residue. The product was used without further purification. A small portion, purified by vacuum distillation (149 °C/0.2 mmHg), solidified upon freezing; mp = 35−37 °C (lit. 38.5−40 °C). ^{1}H NMR ($CDCl_3$): 2.02 (s, 2H, CH_2OH), 3.56 (m, 1H, OC*H*), 3.67−3.78 (m, 4H, CH_2OH), 4.67 (s, 2H, PhCH_2), 7.23−7.34 (m, 5H, aromatic). IR (neat) 2881, 2927, 3375 cm^{-1}.

Synthesis of 5-Benzyloxy-1,3-dioxan-2-one. 5-Benzyloxy-1,3-dioxan-2-one was previously reported in 1983 by Schaeffer as an intermediate in the synthesis of several antiviral compounds.[43] 5-Benzyloxy-1,3-propanediol (10.5 g) and ethyl chloroformate (20.3 mL, 0.21 mol) were dissolved in freshly distilled THF (250 mL). The solution was stirred at 0 °C under N_2 for 15 min. Triethylamine (31.0 mL, 0.22 mol) was added via a dropping funnel over 30 min. The reaction was then stirred at 0 °C to RT for 3 h. The solid precipitate was removed by filtration, and the solvent was evaporated to yield 12 g (67% yield). The residue was recrystallized from THF/diethyl ether to yield 4.0 g white crystals; mp = 120−121 °C. ^{1}H NMR ($CDCl_3$): 3.89 (p, J = 2.7 Hz, 1H, OC*H*), 4.41−4.51 (m, 4H, OCH_2CH), 4.65 (s, 2H, PhCH_2), 7.33−7.40 (m, 5H, aromatic). ^{13}C NMR: 66.35, 69.93, 71.06, 128.08, 128.63, 129.03, 136.91, 148.12. IR (neat): 1737 (C=O)cm^{-1}. HR FAB MS: M/Z^+: 209.0811 (209.0815 calculated). Elemental analysis: C, 63.64; H, 5.97 (calculated: C, 63.45; H, 5.81).

Polymerization of 5-Benzyloxy-1,3-dioxan-2-one. 5-Benzyloxy-1,3-dioxan-2-one (520.5 mg, 5.00 mmol) was placed in a 10 mL Schlenk flask. The reaction vessel was evacuated and flushed with N_2 three times. Next, the reaction vessel was partially immersed in a thermostated oil bath, preheated to 140 °C. After 5 min, the catalyst (0.10 M solution of Sn(Oct)$_2$ in toluene, 500/1 monomer/catalyst ratio) was added via a syringe. The reaction was cooled to room temperature after 2 h. The polymer was dissolved in dichloromethane (10 mL) and precipitated into cold methanol (25 mL). The polymer was then isolated by filtration (362 mg, 70% yield). ^{1}H NMR ($CDCl_3$): 3.84 (broad p, J = 5.0 Hz, 1H, OC*H*), 4.19−4.31 (m, 4H, OCH_2-CH), 4.64 (s, 2H, PhCH_2), 7.27−7.35 (m, 5H, aromatic). ^{13}C NMR: 66.82, 72.63, 74.31, 128.18, 128.37, 128.80, 137.84, 155.10. IR (neat): 1746 (C=O) cm^{-1}.

Copolymerization of 5-Benzyloxy-1,3-dioxan-2-one and L-Lactide. L-Lactide and 5-benzyloxy-1,3-dioxan-2-one (combined total of 10 mmol) were placed in a 10 mL Schlenck flask. The reaction vessel was sealed, evacuated, and purged with N_2 three times. Next, the reaction vessel was partially immersed in a thermostated oil bath, preheated to 180 °C. After 5 min, a 50 μL solution of 0.50 M solution Sn(Oct)$_2$ in toluene (monomer/catalyst ratio = 200:1) was added via a syringe. The reaction was stirred at 180 °C for 2 h and then cooled to room temperature. The cooled copolymer was dissolved in minimal CH_2Cl_2 and precipitated into cold MeOH. The copolymer was then isolated by filtration and dried under vacuum. The yields for **6 Bn**−**9 Bn** ranged from 60 to 75%. The NMR and IR

spectra were similar for all the copolymers. For example, the characterization data for compound **6 Bn** include the following: ^{1}H NMR ($CDCl_3$): 1.46−1.56 (broad m, PLLA CH_3), 3.81 (broad, PCG CH), 4.20−4.23 (broad, PCG CH_2), 4.61 (broad, PCG benzyl CH_2), 4.97−5.15 (broad, PLLA CH), 7.23−7.29 (broad, PCG aromatic). IR (neat): 1748 cm^{-1} (lactide and carbonate C═O).

Hydrogenolysis of Benzylated Polymers. The homopolymer (poly(5-benzyloxy-1,3-dioxan-2-one) (300 mg) or copolymer (poly(5-benzyloxy-1,3-dioxan-2-one-*co*-L-lactide) (300 mg) was dissolved in 25 mL of dry THF. 10% Pd/C (50 mg) and 20% $Pd(OH)_2$/C (50 mg) was then added to this solution. The reaction mixture, in a Parr bottle, was evacuated and purged with H_2 three times. The flask was then pressurized to 60 psi with hydrogen and shaken for 24 h. The reaction mixture was filtered through Celite and the filter cake washed with 50 mL of THF. The solvents were then evaporated to yield the final polymer (quantitative yield). The NMR and IR spectra were similar for all the copolymers. For example, the characterization data for compound **6 OH** include the following: ^{1}H NMR ($CDCl_3$): 1.55−1.58 (broad m, PLLA CH_3), 4.13−4.22 (broad, PCG CH, CH_2), 5.12−5.15 (broad, PLLA CH). IR (neat): 1747 cm^{-1} (lactide and carbonate C═O), 3503 cm^{-1} (OH).

Esterification of Free-Hydroxy Groups with of 4-Isobutylmethylphenylacetic Acid (Ibuprofen). The free-OH copolymer (**7 OH**, 20 mg) was dissolved in 5 mL of dry CH_2Cl_2. Triethylamine (46 mg in 1 mL of CH_2Cl_2, 3 equiv) was added, and the solution was cooled in an ice/H_2O bath. Next, 4-isobutylmethylphenylacetyl chloride (34 mg in 1 mL of CH_2Cl_2, 1 equiv) was added dropwise. The reaction was stirred at 0 °C for 5 min and quenched by the addition of H_2O. The organic layer was washed twice with 1% (w/v) Na_2CO_3(aq), dried by Na_2SO_4, and evaporated to yield the functionalized polymer. ^{1}H NMR: 0.86 (d, J = 6.5 Hz, 6H, ibuprofen isobutyl CH_3), 1.45 (d, J = 5.6 Hz, 3H, ibuprofen CH_3), 1.55−1.57 (broad, 6H, PLLA CH_3), 1.81 (m, 1H, ibuprofen isobutyl CH), 2.41 (d, J = 7.0 Hz, 2H, ibuprofen CH2), 3.69 (broad, 1H, ibuprofen CH), 4.10−4.40 (broad, 5H, PCG CH, CH_2), 5.10−5.25 (broad, 1H, PLLA CH), 7.05 (m, 2H, ibuprofen aromatic), 7.15 (m, 2H, ibuprofen aromatic).

Degradation Studies. Polymers were either pressed into 1−2 mm thick pellets (PLLA) or cast into 1−2 mm thick films (10% carbonate and 30% carbonate) which were cut into 1 cm^2 squares. The polymer samples were then submerged in 0.1 molar buffered phosphate or phosphate/citrate solutions; neutral solution (pH = 7.4), enzyme solution (pH = 7.4, plus 2 IU/mL porcine liver esterase), acidic solution (pH = 4.4). The immersed samples were incubated at 37 °C, and three samples of each polymer/solution combination were isolated at intervals of 1, 2, 4, 7, 10, and 14 days. The molecular weight of the polymer samples was determined by size-exclusion chromatography.

Acknowledgment. This research was supported in part by the Pew Scholars Program in the Biomedical Sciences and the NIH (R01-EY13881). W.C.R. gratefully acknowledges the NIH Pharmacology Training Grant Program at Duke University. M.W.G. also thanks the Dreyfus Foundation for a Camille Dreyfus Teacher-Scholar, the 3M Corporation for a Non-Tenured Faculty Award, the Johnson and Johnson Foundation, and the Alfred P. Sloan Foundation for a Research Fellowship.

Supporting Information Available: SEC graphs. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Lanza, R. P.; Langer, R.; Chick, W. L. *Principles of Tissue Engineering*; R.G. Landes/Academic Press: San Diego, CA, 1997.
(2) *Sci. Am.* **1999** (*April*).
(3) Christenson, L.; Mikos, A. G.; Gibbons, D. F.; Picciolo, G. L. *Tissue Eng.* **1997**, *3*, 71−76.
(4) Langer, R.; Vacanti, J. P. *Science* **1993**, *260*, 920−926.
(5) Peppas, N. A.; Langer, R. *Science* **1994**, *263*, 1715−1720.
(6) Ratner, B. D.; Hoffman, A. S.; Schoen, F. J.; Lemons, J. E. *Biomaterials Science: An Introduction to Material in Medicine*; Academic Press: San Diego, 2000.
(7) Griffith, L. G.; Naughton, G. *Science* **2002**, *295*, 1009−1014.
(8) Frazza, E. J.; Schmitt, E. E. *J. Biomed. Mater. Res. Symp.* **1971**, *1*, 43−58.
(9) Shalaby, S. W.; Johnson, R. A. *Biomed. Polym.* **1994**, 2−34.
(10) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181−3198.
(11) Vert, M.; Li, S. M. *J. Mater. Sci.: Mater. Med.* **1992**, *3*, 432−446.
(12) Vert, M.; Feijen, J.; Albertsson, A. C.; Scott, G.; Chiellini, E. In *Biodegradable Polymers and Plastics*; Royal Society: London, 1992.
(13) Hench, L. L.; Polak, J. M. *Science* **2002**, *295*, 1014−1017.
(14) Guérin, P.; Vert, M.; Braud, C.; Lenz, R. W. *Polym. Bull. (Berlin)* **1985**, *14*, 187−192.
(15) Cammas-Marion, S.; Guérin, P. *Macrmol. Symp.* **2000**, *153*, 167−186.
(16) Zhou, Q. J.; Kohn, K. *Macromolecules* **1990**, *23*, 3399−3406.
(17) Gelbin, M. E.; Kohn, J. *J. Am. Chem. Soc.* **1992**, *114*, 3962−3965.
(18) Kimura, Y.; Shirotani, K.; Yamane, H.; Kitao, T. *Macromolecules* **1998**, *21*, 3338−3340.
(19) Tian, D.; Dubois, P.; Grandfils, C.; Jérôme, R. *Macromolecules* **1997**, *30*, 406−409.
(20) Tian, D.; Dubois, P.; Grandfils, C.; Jérôme, R. *Macromolecules* **1997**, *30*, 2575−2581.
(21) Mecerreyes, D.; Atthoff, B.; Boduch, K. A.; Trollsas, M.; Hedrick, J. L. *Macromolecules* **1999**, *32*, 5175−5182.
(22) Detrembleur, C.; Mazza, M.; Lou, X.; Halleux, O.; Lecomte, P.; Mecerreyes, D.; Hendrick, J. L.; Jérôme, R. *Macromolecules* **2000**, *33*, 7751−7760.
(23) Detrembleur, C.; Mazza, M.; Halleux, O.; Lecomte, P.; Mecerreyes, D.; Hendrick, J. L.; Jérôme, R. *Macromolecules* **2000**, *33*, 14−18.
(24) Stassin, F.; Halleux, O.; Dubois, P.; Detrembleur, C.; Lecomte, P.; Jérôme, R. *Macromol. Symp.* **2000**, *153*, 27−39.
(25) Trollsas, M.; Lee, V. Y.; Mecerreyes, D.; Löwenhielm, P.; Möller, M.; Miller, R. D.; Hendrick, J. L. *Macromolecules* **2000**, *33*, 4619−4627.
(26) Latere, J. P.; Lecomte, P.; Dubois, P.; Jérôme, R. *Macromolecules* **2002**, *35*, 7857−7858.
(27) Chen, X.; Gross, R. H. *Macromolecules* **1999**, *32*, 308−314.
(28) Kumar, R.; Gao, W.; Gross, R. H. *Macromolecules* **2002**, *35*, 6835−6844.
(29) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *J. Am. Chem. Soc.* **1993**, *115*, 11010−11011.
(30) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *Macromolecules* **1995**, *28*, 425−432.
(31) Elisseeff, J.; Anseth, K.; Langer, R.; Hrkach, J. S. *Macromolecules* **1997**, *30*, 2182−2184.
(32) Helder, J.; Kohn, F. E.; Sato, S.; van den Berg, J. W.; Feijen, J. *Makromol. Chem., Rapid Commun.* **1985**, *6*, 9−14.
(33) Helder, J.; Lee, S. J.; Kim, S. W.; Feijen, J. *Makromol. Chem., Rapid Commun.* **1986**, *7*, 193−198.
(34) Kuhling, S.; Keul, H.; Höcker, H. *Makromol. Chem.* **1991**, *192*, 1193−1205.
(35) Pulapura, S.; Kohn, J. *Biopolymers* **1992**, *32*, 411−417.
(36) Ertel, S. I.; Kohn, J. *J. Biomed. Mater. Res.* **1994**, *28*, 919−930.
(37) Carnahan, M. A.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2001**, *123*, 2905−2906.
(38) Carnahan, M. A.; Grinstaff, M. W. *Macromolecules* **2001**, *34*, 7648−7655.
(39) Carnahan, M. A.; Middleton, C.; Kim, J.; Kim, T.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2002**, *124*, 5291−5293.
(40) Grinstaff, M. W. *Chem.—Eur. J.* **2002**, *8*, 2838−2846.
(41) Ray, W. C.; Grinstaff, M. W. *Polym. Prepr.* **2001**, *42*, 123−124.

(42) Wang, X. L.; Zhuo, R.; Liu, J.; He, F.; Liu, G. *J. Polym. Sci., Part A* **2001**, *40*, 70−75.
(43) Schaeffer, H. J. European Patent 82-107247, 1983.
(44) Tsuji, H.; Ikada, Y. *Macromolecules* **1992**, *25*, 5719−5723.
(45) Kricheldorf, H. R. *Macromol. Symp.* **2000**, *153*, 55−65.
(46) Kricheldorf, H. R.; Jonté, J. M.; Berl, M. *Makromol. Chem. Suppl.* **1985**, *12*, 25.
(47) Schmidt, P.; Keul, H.; Höcker, H. *Macromolecules* **1996**, *29*, 3674−3680.
(48) CDSLABS INC 13 NMR software.
(49) Lewis, A. J.; Furst, D. E. *Nonsteroidal Anti-infammatory Drugs: Mechanisms and Clinical Uses*; Dekker: New York, 1994.
(50) Smith, W. L.; DeWitt, D. L.; Garavito, R. M. *Annu. Rev. Biochem.* **2000**, *69*, 145−182.
(51) Carlsen, P. H. J.; Sorbye, K.; Ulven, T.; Aasbo, K. *Acta Chim. Scand.* **1996**, *50*, 185−187.
(52) Saavfedra, J. E.; Booth, M. N.; Hrabie, J. A.; Davies, K. M.; Keefer, L. K. *J. Org. Chem.* **1999**, *64*, 5124.

MA025872V