A New, Crystalline High Melting Bis(hydroxymethyl)polycarbonate and Its Acetone Ketal for Biomaterial Applications

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ABSTRACT: Hydroxypolycarbonates **(HPC)** offer to the biomedical area hydroxyl functional polymers not now readily available to bind drugs, proteins, or carbohydrate polymers chemically or via hydrogen bonding to facilitate drug delivery and utility with subsequent biodegradibility to acceptable byproducts. The cyclic carbonate (**CC**) from the monoketal diol of pentaerythritol polymerized in $CHCl_3$ at 60 °C with Et_2Zn catalyst in $CHCl_3$ at 60 °C in 4 h to a quantitative yield of high molecular weight, crystalline polymer (**PCC**), melt peak 199 °C and T_g of 99 °C. **PCC** is readily hydrolyzed with 80% acetic acid to the water-insoluble but water-swollen **HPC**, poly[5,5-bis(hydroxymethyl)-1,3-dioxan-2-one], with $M_w = 3.1 \times 10^4$. **HPC** degrades completely in vitro in <16 h in PBS-1X buffer (pH 7.4, 37 °C) to pentaerythritol and presumably CO_2. This rapid degradation rate is decreased with random copolymers of **HPC** with **CC,** ϵ-caprolactone, or L-lactide. **HPC** and **PCC** may have important biomaterial applications as is and as the copolymers noted above or with ethylene oxide or other desirable comonomers. **PCC** and **CC** copolymers have properties attractive to the biomedical area as is or by conversion to the **HPC** product provided by hydrolysis or by in vivo enzymatic attack.

Introduction

Whereas aromatic polycarbonates have achieved wide application and great importance as polymeric materials since 1954,[1] aliphatic polycarbonates have been less interesting due to their poor thermal stability and easy hydrolysis. During the past decade, increasing attention has been paid to aliphatic polycarbonates for their potential in the medical field and in the environmental control of plastics.[2−8] Aliphatic polycarbonates derived from the five- and six-membered ring monomers have been thoroughly studied for their academic or biomedical value.[2−19] For example, poly(ethylene carbonate) (**PEC**) was reported to be totally eroded within 2 weeks in vivo.[2,3,6] However, introduction of a substituent methyl group, i.e., poly(1,2-propylene carbonate) (**PPC**), completely suppresses bioresorption.[2,3] The in vitro degradation of poly(trimethylene carbonate) (**PTMC**) in pH 7.4 buffer solution for 30 weeks at 37 °C only resulted in 9% weight loss and 7% molecular weight decrease, which was approximately 20 times less than that of poly(ϵ-caprolactone).[15] Pitt et al.[15] also reported that implantation of **PTMC** in rats over 26 weeks led to a weight loss and decrease in molecular weight of 21% and 55%, respectively. These results demonstrate the rate of enzymatic cleavage of **PTMC** is slower than that of **PEC** but much greater than that of **PPC**.

Controlled introduction of various functionalities into biopolymers has been sought for a variety of purposes including the attachment of drugs, promotion of bioadhesion, improvement of surface hydrophilicity, and regulation of cell activity.[20−26] However, very few papers report the introduction of functional groups into aliphatic polycarbonates.[18] Most aliphatic polycarbonates are amorphous, such as **PEC**, **PPC**, and poly[2,2-(2-pentene-1,5-diyl)trimethylene carbonate] (**PHTC**),[18] or semicrystalline with low melting temperature and melting enthalpy, such as **PTMC** ($T_m = 36$ °C, $\Delta H_m = 7$ J/g, $T_g = -19$ °C) and poly(2,2-dimethyltrimethylene carbonate) (**PDTC**: $T_m = 108$ °C, $\Delta H_m = 20$ J/g).[10,15,27] For better physical properties crystalline aliphatic polycarbonates with higher melting temperatures are desirable. A higher T_g could also be desirable for some applications.

In this paper, we report (1) the polymerization of the cyclic carbonate of 2,2-dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (**CC**) whose preparation and polymerization were previously disclosed in a U.S. patent[29] with little detail on the monomer (Ex 8B) and no specific details on the polymer synthesis or the polymer properties.[30] This initial polymer product is the acetone ketal of the desired hydroxy polycarbonate (**HPC**). This ketal-protected polymer has some rather interesting properties in its own right to be presented later in detail. (2) The complete deprotection of the ketal-protected polycarbonate to form the hydroxy polycarbonate (**HPC**), poly[5,5-bis(hydroxymethyl)-1,3-dioxan-2-one, is described in the Results and Discussion sections with detailed characterization including preliminary in vitro degradation tests.

The extensive work of Höcker and collaborators on a related hydroxypolycarbonate and on other polycarbonates[10a−l] is noteworthy, particularly for studies on synthesis with emphasis on catalysis, hydroxyl protection and deprotection characterization, copolymerization, and mechanism aspects of the polymerization. The related hydroxypolycarbonate, poly(2-ethyl-2-hydroxymethyltrimethylene carbonate) is, however, very different from our previously unreported **HPC** since it is of much lower functionality, has a much lower crystalline melting point, does not crystallize from the melt, and is of questionable biocompatibility.

Experimental Section

Materials. Aluminum tri-*sec*-butoxide (ATSB) was purchased from Aldrich and was dissolved in toluene (0.107 M)

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Table 1. Ring-Opening Polymerization of CC by Different Catalysts in Solution or in Bulk[a]

entry	catalyst	solvent	monomer concn (g/mL)	temp (°C)	time (h)	monomer conversion[b] (%)	η_{inh}[c] (dL/g)
1	IBAO	toluene	20	80	17	100	0.34
2	IBAO		bulk	180	3	83	0.19
3	IBAO-0.50AA[28]	toluene	20	80	42	59	0.06
4	IBAO-0.50AA[28]		bulk	180	3	73	0.20
5	$^{i}Bu_3Al$-0.5H_2O-6.0Et_2O	toluene	20	80	24	100	0.30
6	$^{i}Bu_3Al$-0.5H_2O-6.0Et_2O	$CHCl_3$	20	60	18	74	0.15
7	Et_3Al-0.6H_2O-0.5AA-2THF	$CHCl_3$	20	60	18	68	0.15
8	Et_2Zn	$CHCl_3$	20	60	4	100	0.95

[a] Monomer-to-catalyst ratio ($[M]_0/[C]_0$) was 76 mol/mol; $[C]_0$ was taken as the moles of [Al] or [Zn]. [b] Determined by ^1H NMR. [c] Inherent viscosity, η_{inh}, was determined in $CHCl_3$ at 30.0 °C.

before used. Isobutylalumoxane (IBAO, prepared by reacting $^{i}Bu_3Al$ with H_2O (molar ratio of 1:0.65), 0.93 M in heptane) and diethylzinc (0.91 M in *n*-hexane), were from Akzo Nobel Chemicals, Inc. Catalyst $iBu_3Al-0.5H_2O-6.0Et_2O$ (0.60 M Al in toluene) from Hercules, Inc., was the reaction product of 1 mol of triisobutylaluminum, 6 mol of diethyl ether, and 0.5 mol of water. Catalyst $Et_3Al-0.6H_2O-0.5$acetylacetone-2THF (1.40 M Al in toluene) from Hercules, Inc., was the reaction product of 1 mol of triethylaluminum, 0.6 mol of water, 0.5 mol of acetylacetone, and 2 mol of tetrahydrofuran. All other materials were commercially available and used as received unless otherwise noted. The pentaerythritol was the best commercial grade from Hercules Inc. The buffer type used for in vitro degradation tests at pH 7.4 and 37 °C was PBS-1X of Boehringer Mannheim.

Preparation of 2,2-Dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane. Pentaerythritol (50.0 g, 0.36 mol) and *p*-toluenesulfonic acid monohydrate (0.61 g) were dissolved in 500 mL of *N*,*N*-dimethylformamide at about 80 °C (DMF, dried by molecular sieve at room temperature), and then the mixture was allowed to cool undisturbed. When the solution cooled to about 40 °C, stirring was started and 55.4 mL of 2,2-dimethoxypropane (0.36 mol) was added. After stirring 24 h at room temperature, the solution was stirred at room temperature with 9.0 g of base-treated DOWEX 1XZ-100 ion-exchange resin for 1 h and filtered, and then the solvent was evaporated under reduced pressure below 85 °C. The base-treated DOWEX 1XZ-100 ion exchange was prepared by washing 30 g twice with 200 mL of deionized water, then washed with 300 mL of 4% aqueous NaOH, and then washed three times with 200 mL of water, filtered, and then air-dried in a hood. After the treatment with this resin as noted above, the dry product was ground and extracted (Soxhlet), first with light petroleum ether (bp 40−60 °C) for 6 h and then with diethyl ether for 12 h, collected, and dried. Yield: 40.0 g, white crystals (61.9% of theory); mp 124.5−125.5 °C. ^1H NMR (300 MHz, DMSO-d_6): 1.28 ppm (s, 6H), 3.34 ppm (d, $J = 5.7$ Hz, 4H), 3.58 ppm (s, 4H), 4.47 ppm (t, $J = 5.4$ Hz, 2H).

Preparation of the Cyclic Carbonate of 2,2-Dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (CC). This general carbonate synthesis has been described by Endo et al.[14] Triethylamine (70.6 mL, 0.501 mol) was added dropwise to a mixture of 2,2-dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (40.0 g, 0.227 mol) and ethyl chloroformate (47.0 mL, 0.477 mol) dissolved in 1310 mL of tetrahydrofuran (THF) at 0 °C over 30 min. The reaction mixture was stirred for 2 h at 0 °C, then the precipitated triethylammonium chloride was filtered out, and the filtrate was concentrated under reduced pressure below 55 °C. The residue was recrystallized from THF. Yield: 27.2 g of white crystals (59.3%); mp 155.5−156.5 °C. ^1H NMR (300 MHz, $CDCl_3$): 1.44 ppm (s, 6H), 3.80 ppm (s, 4H), 4.31 ppm (s, 4H).

Polymerization Procedure. Polymerizations were run under nitrogen in capped tubes with self-sealing, rubber-lined caps (Buna N or butyl rubber). Air was removed by nitrogen sparging of the closed vessel containing solid monomer for at least 20 min, and then solvent and catalyst solution were injected via syringe. The containers were tumbled in a constant-temperature bath. Runs were usually short-stopped with anhydrous ethanol (1 mL per 10 mL of solvent). Additional information on polymerization conditions, monomer-to-catalyst ratios, and monomer initial concentration are given in Table 1 for **CC**. The resulting polymer, **PCC**, was purified by precipitation from chloroform with methanol and dried under an oil pump vacuum at room temperature. **PCC** is crystalline, readily soluble in $CHCl_3$ at room temperature, partially soluble in CH_2Cl_2, soluble in THF, and soluble in DMSO at low concentration at about 80−90 °C.

Deketalization of Poly[cyclic carbonate of 2,2-dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane] (PCC). A 3.0 g sample of **PCC** dissolved in 300 mL of $CHCl_3$ and 100 mL of 80% acetic acid were mixed and stirred at room temperature overnight. Then, 200 mL of 80% acetic acid was added into the mixture and then refluxed in a 85 °C oil bath for 1 h. The resulting **HPC** was recovered by evaporation of the volatile components under reduced pressure below 70 °C. The product was further air-dried in a hood overnight, then washed with pH 6.0 buffer, water washed, and then dried in a vacuum at room temperature. This procedure completely deprotects **PCC** to give **HPC.** Lower degrees of deprotecion such as **HPC**-65 (65% deprotection) used in Table 5 are obtained by reducing the reflux time. **HPC** is soluble in DMSO, DMF, and DMAC at about 60−70 °C and insoluble in $CHCl_3$ and THF.

Characterization. ^1H NMR spectra of homopolymers or copolymers were obtained in $CDCl_3$ or DMSO-d_6 at 300 MHz for ^1H or at 400 or 500 MHz for ^{13}C with Varian Unity spectrometers. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using the described equipment operating at 75, 100, or 125 MHz. Chemical shift data for ^1H spectra were relative to TMS in $CDCl_3$ and to the isotope impurity peak for ^1H spectra in DMSO-d_6 (δ 2.49) and for ^{13}C spectra in $CDCl_3$ (δ 77.1). Copolymer composition was determined by ^1H NMR from the relative intensity of the methylene signal of **PCC** at 3.75 ppm and the methylene signal of **PCL** (poly(ϵ-caprolactone)) at 2.35 ppm. Inherent viscosities (η_{inh}) were measured at 0.3% in $CHCl_3$ for **PCC** or 0.2% in DMSO for **HPC** at 30.0 °C unless otherwise noted.

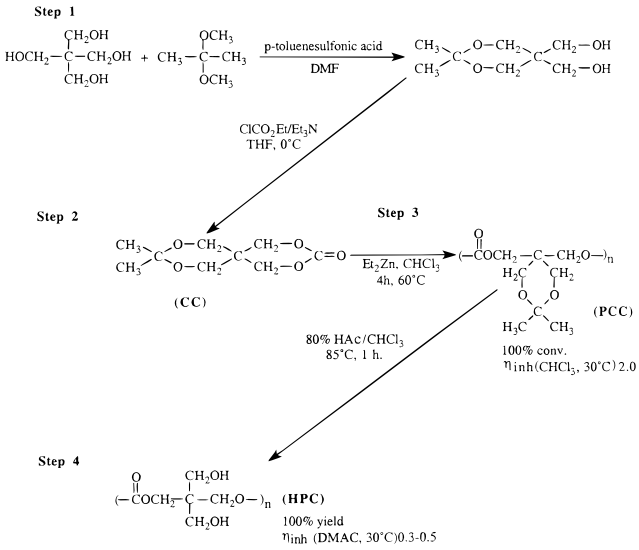
Differential scanning calorimetry (DSC) was carried out with a Perkin-Elmer DSC 7 thermal analyzer calibrated with indium and zinc. All the samples were heated at 20 °C/min heating rate from 25 to 200 °C under nitrogen for the first scan, then cooled at 50−100 °C/min to 25 °C, and immediately heated a second time. Peak melting temperatures (T_m) and melting enthalpy (ΔH_m) were measured on the first scan, and glass transition temperatures (T_g) were measured on the second scan.

The degree of hydrolysis of the polymer in vitro was measured by immersion of the powder samples in phosphate-buffered saline (pH = 7.4 PBS-1X buffer) with agitation at 37 °C under nitrogen. The samples were recovered periodically to determine weight loss, ^1H NMR spectra, and inherent viscosity.

Results and Discussion

Synthesis of the Cyclic Carbonate of 2,2-Dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (CC) (Scheme 1, Steps 1 and 2). The cyclic carbonate monomer, **CC**, was prepared by two-step reactions from pentaerythri-

Scheme 1. Synthesis of Poly[5,5-bis(hydroxymethyl)-1,3-dioxan-2-one] (HPC)



tol. The yield for the first step diol and the second step (**CC**) was 61.9% and 59.3%, respectively. The purity and structure of the first step diol as well as the final **CC** were confirmed by melting point and ^{1}H NMR analyses (see Experimental Section for more details).

Polymerization of CC with Different Catalysts in Solution or in Bulk to PCC (Scheme 1, Step 3). The best conditions for preparing **PCC** are given in step 3, Scheme 1. The work that led to this selection is summarized below (Tables 1−3).

As Table 1 shows, five different organometallic catalysts, including Al-based and Zn-based systems, were selected to investigate their abilities to catalyze **CC** ring-opening polymerization. Polymerizations were carried out in solution at 20% monomer concentration or in bulk with a initial monomer to catalyst molar ratio ($[M]_0/[C]_0$) of 76. IBAO catalyst (1, Table 1) gave 100% polymer yield at 80 °C in toluene in 17 h with η_{inh} of 0.34 dL/g. Using 0.5 acetylacetone as chelate with IBAO had a negative effect on polymerization, with a much longer polymerization time (42 h), and produced a lower polymer yield (59%) with very low inherent viscosity (0.06). Et_2Zn (8, Table 1) gave more promising results, with 100% polymer yield and η_{inh} of 0.95 in only 4 h at 60 °C in $CHCl_3$. The final polymer inherent viscosity was about 2.8 times higher than that of IBAO at the same polymerization condition (1, Table 1). Other modified Al catalysts in solution (5−7, Table 1) were less effective. IBAO and IBAO-0.5AA catalyst in bulk at 180 °C gave promising results with somewhat lower η_{inh} (2 and 4, Table 1), offering the potential of a lower cost process. The typical ^{1}H NMR spectrum of **PCC** is shown in Figure 1. The intensity ratios of protons Ha1, Hb1, and Hc are quite close to 2:2:3 within the limits of the NMR experimental errors, which is in good agreement with their theoretical ratio. Moreover, ^{1}H NMR spectra of **PCC** prepared by using Al-based or Zn-based catalysts showed no evidence for decarboxylation occurring during the polymerization as no methylene protons of ether-linked repeat units ($-CH_2-O-CH_2-$, δ = 3.5 ppm) could be detected.

Effect of Monomer Concentration, Polymerization Temperature, and Solvent on the Ring-Opening Polymerization of CC (Table 2). For IBAO-catalyzed polymerization (1−3), the initial monomer

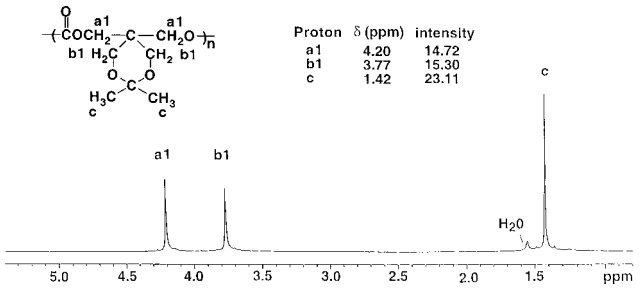


Figure 1. H NMR spectrum of **PCC** (in $CDCl_3$).

concentration has almost no effect on the final polymer inherent viscosity when the polymerization was conducted at 65 °C, but the polymer yield rapidly decreased at higher initial monomer concentration (40%), with the same 17 h polymerization time. Higher polymerization temperature increased the inherent viscosities from 0.29 to 0.34 and 0.80 when the polymerization temperature was increased from 65 to 80 and 90 °C, respectively (2, 4, and 5). Contrary to the lower polymerization temperature results, the inherent viscosity increased with the initial monomer concentration at 90 °C; e.g., η_{inh} increased from 0.80 to 1.03 when monomer concentration increased from 20% to 50% in toluene (5 and 6). Comparing 6 and 7 at the same polymerization conditions, 50% monomer concentration, and 90 °C, Et_2Zn increased η_{inh} from 1.03 to 1.61 compared to the case of IBAO. For Et_2Zn-catalyzed polymerization, η_{inh} increased with monomer concentration in 1,1,2,2-tetrachloroethane at 80 °C or in chloroform at 60 °C (8−11). Different solvents have a different effect on η_{inh} (7−11). These data indicate that chloroform is the best solvent with a higher inherent viscosity of 1.51, at a lower temperature (60 °C) and shorter reaction time (4 h) compared to the case of toluene (7) or 1,1,2,2-tetrachloroethane (9).

Effect of Polymerization Time on the Ring-Opening Polymerization of CC. Table 3 shows the effect of polymerization time on the polymerization of **CC** catalyzed by Et_2Zn at 60 °C in chloroform with a **CC** to Zn molar ratio of 76 and 50% (g/mL) initial CC/$CHCl_3$ concentration. The polymerization was fast, giving 87% monomer conversion at 2 h 10 min and 100% at 3 h 15 min. The inherent viscosity increased with monomer conversion. However, after monomer conversion was complete, the molecular weight decreased with time if the polymerization was not stopped. ^{1}H NMR analyses of these samples showed that no ether linkages can be detected, which indicates no decarboxylation reaction even after keeping the "active" polymerization for 17 h. Transesterification is only one reasonable explanation for the decrease of inherent viscosity after complete monomer conversion.

Deketalization of PCC. Removal of the hydroxyl ketal blocking groups has been carried out with 80% acetic acid in a chloroform medium, with a 100% yield. As an example, Figure 2 shows the ^{1}H NMR spectrum of **HPC** after the deketalization of **PCC**. The ketal protons at δ = 1.42 ppm have completely disappeared, whereas correspondingly the singlets at δ = 4.20 ppm (Ha1) and 3.77 ppm (Hb1) of the precursor **PCC** (Figure 1) have been shifted to higher fields (singlet at δ = 4.04 ppm (Ha2) and doublet at 3.36 ppm (Hb2), which is clear evidence for the completeness of the deketalization reaction. Furthermore, a triplet for the hydroxyl protons has appeared at δ 4.68 ppm (Hd), and the intensity ratio

Table 2. Effect of Monomer Concentration, Polymerization Temperature, and Solvent on the Ring-Opening Polymerization of CC[a]

entry	catalyst	solvent	monomer concn (g/mL)	temp (°C)	time (h)	monomer conversion[b] (%)	η_{inh}[c] (dL/g)
1	IBAO	toluene	10	65	17	100	0.26
2	IBAO	toluene	20	65	17	100	0.29
3	IBAO	toluene	40	65	17	30	0.22
4	IBAO	toluene	20	80	17	100	0.34
5	IBAO	toluene	20	90	17	100	0.80
6	IBAO	toluene	50	90	17	97	1.03
7	Et_2Zn	toluene	50	90	17	98	1.61
8	Et_2Zn	$Cl_2CHCHCl_2$	20	80	2	96	0.51
9	Et_2Zn	$Cl_2CHCHCl_2$	50	80	2	97	0.90
10	Et_2Zn	$CHCl_3$	20	60	4	100	0.95
11	Et_2Zn	$CHCl_3$	50	60	4	100	1.51

[a] See Table 1 for footnotes.

Table 3. Effect of Time on the Polymerization of CC at 50% Concentration Catalyzed by Et_2Zn at 60 °C in Chloroform[a]

entry	monomer concn (g/mL)	time (h)	monomer conversion[b] (%)	η_{inh}[c] (dL/g)
1	50	2.17	87	1.57
2	50	3.00	92	2.16
3	50	3.25	100	2.29
4	50	3.50	100	1.90
5	50	4.00	100	1.51
6	50	17.00	100	1.01

[a] See Table 1 for footnotes.

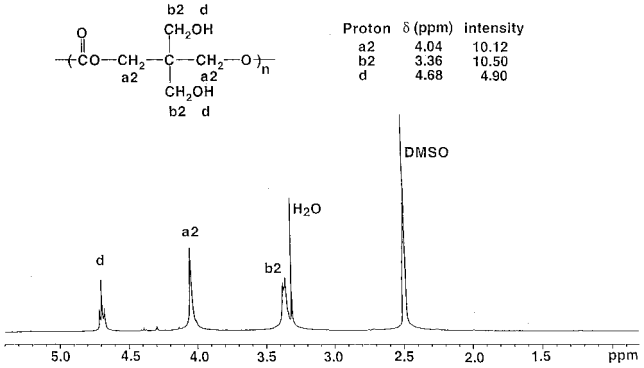


Figure 2. ^{1}H NMR spectrum of **HPC** (in DMSO-d_6).

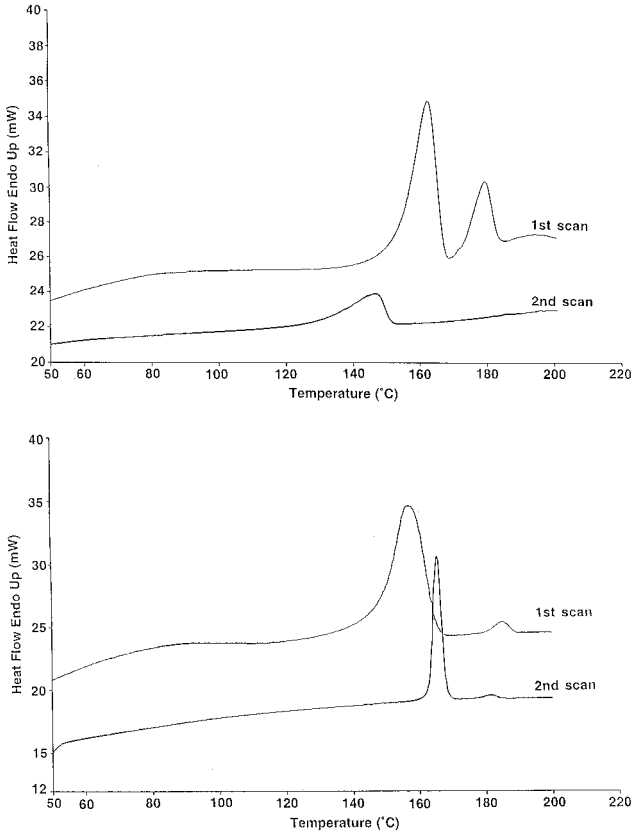


Figure 3. DSC curves: (A, top) **HPC** (η_{inh} = 0.19); (B, bottom) **HPC** containing 2% ketal protected groups (η_{inh} = 0.31).

of protons Ha2, Hb2, and Hd is very close to 2:2:1 with a good agreement with theoretical values within the limits of the NMR experimental error. Thus, aliphatic polycarbonates bearing hydroxyl pendant groups, poly-[5,5-bis(hydroxymethyl)-1,3-dioxan-2-one] (**HPC**, Scheme 1), have been successfully prepared, which opens new application prospects. This new functional aliphatic polycarbonate is not soluble in chloroform, THF, acetone, methanol, toluene, etc., but soluble in DMSO, DMF, and DMAC. It is completely dissolved in water only at higher temperature, i.e., above 70 °C, with complete degradation based on ^{1}H NMR and related data and text for Figure 3. The inherent viscosity is lower if compared with its precursor. For example, η_{inh} are between 0.12 and 0.35 in DMSO at 30.0 °C, corresponding to the precursor **PCC** with η_{inh} between 0.80 and 2.3 in $CHCl_3$ at 30.0 °C. Inherent viscosities are not directly comparable due to their different polymer structure and the different solvent systems for η_{inh} measurement. Laser light scattering Zimm analysis shows that the weight-average molecular weight (M_w) is 3.1×10^4 for **HPC** in molecular sieve dried DMF at ambient temperature when its η_{inh} is 0.31 in DMSO at 30.0 °C. It is very probable that the precursor **PCC** is of much higher molecular weight, based on the apparent ease with which HPC is hydrolyzed, although exact data are not available.

Crystalline Properties. The crystalline properties of **PCC** and **HPC** have been analyzed by differential scanning calorimetry (DSC). All the thermal properties are listed in Table 4, and a typical DSC thermogram for **HPC** is shown in Figure 3A with no ketal and in Figure 3B with 2% ketal, **HPC**-98. For **PCC**, the melting peak is quite sharp (T_m) and is quite high, i.e., 199 °C, and the melting enthalpy (ΔH_m) is high at 45.1 J/g. No crystallization from the melt occurs even when the cooldown from the melt is at a rate of 10 °C/min to room temperature, followed by a reheat cycle. The glass transition temperature (T_g) of **PCC** is also quite high, though it dropped from 99 °C for crystalline sample to 68 °C for amorphous sample. Clearly, high crystallinity with high melting temperature and glass transition temperature of **PCC** is a big improvement over the

Table 4. DSC Data for PCC and HPC

		first scan			second scan		
sample	η_{inh} (dL/g)	T_g (°C)	T_m[b] (°C)	ΔH_m (J/g)	T_g (°C)	T_m[b] (°C)	ΔH_m (J/g)
PCC	2.29	99	199	45.1	68		
HPC	0.19		163; 179	41.8; 12.4		147	12.8
HPC[a]	0.31		157; 185	55.7; 2.0		166; 182	15.2; 0.4

[a] This sample contains 2% ketal protecting groups. [b] Melt peak.

Table 5. In Vitro Degradation Test in PBS-1X Buffer[a]

		η_{inh} (dL/g)		
sample	time (h)	before test	after test	wt loss (%)
PCC	16	1.90	1.74	0
HPC	1	0.14	0.11	50.8
HPC	2	0.14	0.05	55.0
HPC	4	0.14		77.5
HPC	16	0.14		100
HPC-65[b]	16	0.19	0.17	42.9
HPC-CL[c]	16	0.35	0.16	58.3

[a] For **PCC**, η_{inh} was determined in $CHCl_3$ at 30.0 °C; all the other samples were determined in DMSO at 30.0 °C. [b] 65% deketalization of **PCC**. [c] **HPC-CL**: copolymer of **HPC** and ϵ-caprolactone (**CL**) containing 17.5% of **CL** repeat unit.

current aliphatic polycarbonates, such as **PTMC** (T_g = −20 °C, T_m = 36 °C, ΔH_m = 7 J/g) and **PDTC** (T_g = 27 °C, T_m = 108 °C, ΔH_m = 20 J/g), etc. After deketalization, the polymers still retain high crystallinity and a high melting temperature, but two melting endotherm peaks were found for the first heat of **HPC** (Figure 3A). The melting temperature of **HPC** is lower somewhat compared to that of **PCC**. After fast cooling of the **HPC** from meltdown to room temperature at a rate of 50−100 °C/min and heating again, a substantial melting endotherm was detected (24% of the total first heat melt peaks), which suggests a faster crystalline rate of **HPC** compared with that of its precursor **PCC**. For the second scan, both samples (HPC and HPC-98) showed one melting endotherm peak (Figure 3A,B), but the HPC-98 peak was sharper and at about 20 °C higher temperature compared to that of HPC. This difference might result from their different molecular weight and/or because one sample contained 2% protected groups (Table 4). No T_g could be detected for **HPC** at the experimental temperature range (50−200 °C) studied.

Polymer in Vitro Degradation Test. The in vitro degradation test was carried out by immersion of the powder form of the polymer in phosphate-buffered saline (PBS-1X), pH = 7.4 at 37 °C, with agitation under nitrogen. The samples were recovered periodically, and their η_{inh} and weight loss data are summarized in Table 5. For the protected polycarbonate, **PCC**, no gravimetric weight loss was detected after 16 h, while its η_{inh} decreased somewhat. For the completely deprotected polymer, **HPC**, the rate of hydrolytic polymer chain cleavage was very rapid, so that after 16 h there was no water-insoluble **HPC** left. ^{1}H NMR of the 16 h solution showed that only pentaerythritol was detectable. The expected coproduct, CO_2, was not checked for. After the 1 h degradation period, the inherent viscosity of **HPC** decreased 21.4%; meanwhile, its weight loss was 50.8%. These results confirmed that hydroxyl pendant groups improve the hydrophilicity of polycarbonates chains and enhance its hydrolytic degradability.

The partial (65%) deketalization of **PCC** (**HPC**-65 in Table 5), prepared by a milder deketalization treatment, decreased the hydrolysis rate compared with the case of **HPC**. As Table 5 shows, **HPC**-65 only lost 10.5% of η_{inh} and 42.9% of weight over the 16 h degradation period, but at the same conditions, the complete deketalization sample (**HPC**) was completely decomposed. ^{1}H NMR analysis indicated that, after immersion of **HPC**-65 in phosphate-buffered saline at 37 °C for 16 h, the ketal content increased from 35% (before test) to 68% (after test). This result indicates that the deketalization is not a random one; i.e., after one chain unit is deprotected, the adjacent ketal unit is deprotected next. Eventually, the **HPC** blocks break up by an unidentified process to give pentaerythritol and CO_2.

Aliphatic Carbonate and Ester Copolymers of CC and Their in Vitro Degradation. Copolymerization is known to provide new materials, whose properties are often the average of those of the parent homopolymers. This is a valuable method to finely tune one property to the value needed for a specific application. Preliminary copolymerizations of **CC** with ϵ-caprolactone (**CL**) or L-lactide (**LA**) were made using Et_2Zn catalyst in $CHCl_3$ at 60 °C (Table 6). For copolymerization of **CC** with **CL**, the copolymers yield a quite high inherent viscosity after 16 h reaction with a high comonomer conversion. Copolymerization of **CC** with **LA** was not complete after 48 h reaction, and the inherent viscosity of the copolymer is lower (3). The compositions of the copolymers totally depend on the comonomer feed ratio and were in a good agreement with their charge composition within the limits of NMR experiment errors, indicating very favorable copolymerization. Figure 4 shows ^{13}C NMR of the **CC**/**CL** copolymer at the carbonyl region in $CDCl_3$. The relative chemical shifts are summarized in Table 7. Clearly, ^{13}C NMR analysis confirmed copolymer formation.

Deacetalization of these copolymers has also been successfully performed with 80% acetic acid in a chloroform medium, with a 100% yield. The in vitro degradation test of **HPC**-*co*-**CL**) (F_{CL} = 0.17) was also carried out by immersion of powder form (2, Table 6) in phosphate-buffered saline (pH = 7.4) at 37 °C with stirring under nitrogen. This sample lost 54.3% η_{inh} and 58.3% weight over 16 h. As expected, the degradation rate of **HPC** can be adjusted by introducing ϵ-caprolactone units into the **HPC** polycarbonate chains via random copolymerization.

Conclusions

A ketal-protected aliphatic cyclic carbonate, **CC**, was synthesized from pentaerythritol. This new monomer has been successfully ring-opening polymerized in solution using various organometallic catalysts, such as isobutylalumoxane and Et_2Zn. Polymerization in chloroform at 60 °C catalyzed by Et_2Zn was preferred for the synthesis of high molecular weight **PCC**. After complete monomer conversion, increasing polymerization time decreases polycarbonate molecular weight, probably due to transesterfication reaction. This new monomer can copolymerize with ϵ-caprolactone or L-lactide. Deketalization of **PCC** or copolymers of **CC** has been achieved with 100% yield in 80% acetic acid and

Table 6. Ring-Opening Copolymerization of CC with ϵ-Caprolactone (CL) and with L-Lactide (LA) in Chloroform at 60 °C with Et_2Zn Catalyst[a]

				conversion[c]			F_{CC}[e]	
entry	comonomer	f_{CC}[b]	time (h)	CC	comonomer (%)	η_{inh}[d] (dL/g)	theor	exp
1	CL	0.83	16	91.1	100	2.57	0.820	0.826
2	CL	0.17	16	100	100	1.08	0.170	0.175
3	LA	0.83	48	92.6	72.9	0.12	0.864	0.892

[a] Monomer-to-catalyst ratio ($[M]_0/[C]_0$) was 76 mol/mol; initial total monomer concentration was 50%. [b] Molar fraction of **CC** in the feed. [c] Determined by ^1H NMR. [d] η_{inh} was determined in $CHCl_3$ at 30.0 °C. [e] Molar fraction of the **CC** repeating units in the copolymer.

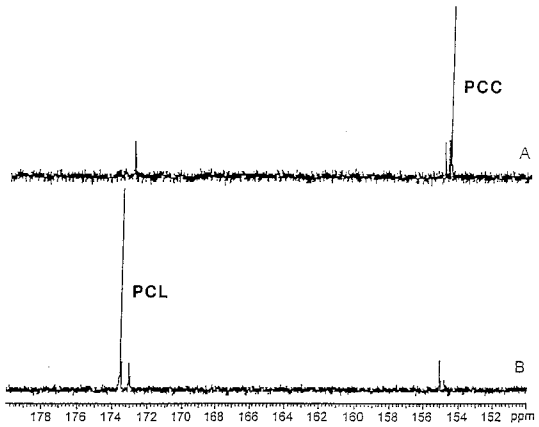


Figure 4. Carbonyl region of ^{13}C NMR of **CC**/**CL** copolymer (in $CDCl_3$): (A) $F_{CC} = 0.83$; (B) $F_{CC} = 0.17$.

Table 7. Chemical Shift of PCC, PCL, and CC/CL Copolymer at Carbonyl Region by ^{13}C NMR

polymer	F_{CC}[a]	F_{CL}[b]	δ (ppm)
PCC	1.0	0	154.7
P(CC-Co-CL)	0.826	0.174	154.7, 154.8, 155.0, 173.0
P(CC-Co-CL)	0.175	0.825	154.8, 155.1, 173.1, 173.5
PCL	0	1.0	173.5

[a] F_{CC}: molar fraction of the **CC** repeating units in the copolymer. [b] F_{CL}: molar fraction of the **CL** repeating units in the copolymer.

chloroform medium. Therefore, aliphatic polycarbonates bearing hydroxyl pendant groups (**HPC**) can be easily prepared. The ketal-protected aliphatic polycarbonates (**PCC**) and the new hydroxy polycarbonate (**HPC**) are high crystallinity polymers with high melting temperature, i.e., 199 °C for **PCC** and 163−179 °C for **HPC**. This is a unique property compared with current aliphatic polycarbonates. The advantage of the novel hydroxy aliphatic polycarbonate, **HPC**, is that its hydroxyl pendant groups permit attachment of desirable entities to the biodegradable main chain, such as therapeutic agents, proteins, or carbohydrate polymers, to enhance biomedical activity. In vitro degradation tests showed that the degradation rate of **HPC** is fast, and this rate can be decreased by the partial deketalization of **PCC** or copolymerization with ϵ-caprolactone or L-lactide. On the other hand, **PCC** was very stable in the same in vitro degradation test. We had not expected that **HPC** with its neopentylcarbon would degrade so readily. Although this anomaly needs further study, it may relate to hydrogen bonding of the hydroxyls to the carbonate ester oxygen or carbonyl. The unusual hydrolytic stability and the interesting physical properties of **PCC** may permit a variety of biomedical applications. Also, **PCC** or **CC** copolymers may be hydrolyzed in vivo by enzymatic attack to confer some of the possible advantages of **HPC** and its copolymers.

An intriguing possibility is that **CC** copolymers with ethylene oxide (EO) may be especially useful products before or after deprotection to provide copolymers varying from water-insoluble but swellable to water-soluble depending on composition and with increasing hydrolytic stability. Such products should be biocompatible, at least in the deprotected form, since PEO is currently approved as biocompatible by the FDA. Previously, EO was found by one of us (E.J.V.) to give a unique epichlorohydrin copolymer for elastomer applications and may be unique here, partly because of its low molecular weight and water solubility of its polymers.[31]

Other **CC** copolymers with monomers that form biocompatible homopolymers such as ϵ-caprolactone, L-lactide, glycolide, trimethylene carbonate, β-hydroxy butyrate, etc., need extensive study on synthesis, properties, biocompatibility, and biomedical utility.

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