Novel Functional Polycarbonate by Lipase-Catalyzed Ring-Opening Polymerization of 5-Methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one

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ABSTRACT: Water-soluble polycarbonate having pendent carboxyl groups on the main-chain carbons is reported for the first time. This paper describes synthesis and enzyme-catalyzed ring-opening polymerization of a novel carbonate monomer, 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (**1**). Various commercially available lipases were screened for their ability to polymerize **1** in bulk at 80 °C. Monomer conversion and molecular weight of the polymer were significantly influenced by the source of the enzyme. For example, of the seven lipases screened, lipase AK (from *Pseudomonas fluorescens*) gave the highest monomer conversion (97%) and molecular weight (M_n = 6100). In reactions carried out under identical experimental conditions, no polymerization was observed when thermally deactivated lipase AK was used. Debenzylation of **2** by catalytic hydrogenation led to the corresponding linear polycarbonate, **3**, with pendent carboxyl groups. Presence of pendent carboxyl groups is expected to enhance the biodegradability of the polycarbonate and facilitate a variety of potential biomedical applications, e.g., as polymeric drug carriers in time-controlled drug delivery systems.

Introduction

Well-defined functional polymers are attractive materials not only for basic research but also in various industrial applications. The availability of strategically placed functional groups enables postpolymerization modifications for a wide variety of purposes such as immobilization of catalysts, biocompatibilization, etc.[1] Biodegradable/bioresorbable nontoxic materials having pendent functional groups are of particular importance in biomedical and surgical applications, e.g., as polymeric drug carriers in time-controlled drug delivery systems.[2] In recent years, polycarbonates have attracted attention as bioresorbable, biomedical materials[3] and are of interest in the design of drug delivery systems.[4] Aliphatic polycarbonates and their copolymers have been extensively investigated. Also, increasing efforts have been devoted to synthesis of polycarbonates having pendent functional groups.[1d,5,6] Recently, polycarbonates with pendent hydroxyl groups have been described.[1d,5,6] The presence of pendent hydroxyl groups has been demonstrated to enhance the biodegradability of polycarbonates.[1d,5] Thus far, pendent carboxyl-containing polycarbonates have not been reported.

Ring-opening polymerization of cyclic carbonates has been studied by both cationic and anionic polymerization.[7] The most commonly studied cyclic carbonates for ring-opening polymerization are five- and six-membered. Inherently, chemical synthesis of polycarbonates requires extremely pure monomers, inert atmosphere, and anhydrous conditions as well as an organometallic initiator, which must be completely removed, especially for biomedical applications. It is no wonder, therefore, that chemists have turned to the nature-evolved enzymes from which to learn and utilize these efficient catalysts in organic transformations.[8] In recent years, the benefits of enzyme catalysis have been realized for synthesis of nonnatural polymers.[8a,9] The ability of the enzymes to accept cyclic carbonates as substrates for ring-opening polymerizations has also been demonstrated in the lipase-catalyzed ring-opening polymerization of trimethylene carbonate (TMC).[9,10] High monomer conversion and polymer molecular weight were achieved under relatively mild conditions.[9] Interestingly, enzyme-catalyzed ring-opening polymerization of cyclic carbonates has not been investigated with the same vigor as that of lactones. To date, TMC is the only cyclic carbonate monomer studied for enzyme-catalyzed ring-opening polymerization.[9,10]

Water-soluble polycarbonates having pendent carboxyl substituents on the main-chain carbons have now been synthesized for the first time. In this work, we report the synthesis and enzymatic polymerization of a new carbonate monomer, 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (**1**). Various commercially available lipases were screened for their ability to polymerize **1** in bulk at 80 °C. Debenzylation under mild conditions led to the isolation of a novel pendent carboxylic acid group-containing polycarbonate. Detailed structural and end-group analysis of the polymer will be discussed.

Experimental Section

Lipases AYS, AS, AK, and PS-30 were generous gifts from Amano Enzyme Co. Novo Nordisk Bioindustrial, Inc., kindly provided Novozym-435 and lipase IM. Porcine pancreatic lipase (PPL) type II was purchased from Sigma Chemical Co. Benzyl 2,2-bis(hydroxymethyl)propionate was prepared according to the procedure described in the literature.[11] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-360 spectrometer at 360 and 90 MHz, respectively. Chemical shifts (ppm) are reported downfield from 0.00 ppm using tetramethylsilane (TMS) as internal standard. The concentrations used were ∼4% w/v in deuterated chloroform ($CDCl_3$) or DMSO-d_6. Monomer conversions were determined from the relative peak areas of signals corresponding to methyl (−CH_3) protons of the polymer and monomer at 1.21 and 1.34 ppm, respectively. Molecular weights were measured by GPC based on a calibration curve generated by narrow molecular weight distribution polystyrene standards. A Shimadzu HPLC system and Waters HR 4E, HR and 5E styragel columns connected

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in series were used. Chloroform (HPLC grade) was used as eluent at a flow rate of 1.0 mL/min. Molecular weights were also calculated from the ^{1}H NMR spectra. It is noteworthy to mention that molecular weights determined from the two techniques were comparable.

5-Methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (1). The monomer **1** was synthesized from ethyl chloroformate and benzyl 2,2-bis(hydroxymethyl)propionate. Triethylamine (28 g, 0.277 mol) was added dropwise to a mixture of benzyl 2,2-bis(hydroxymethyl)propionate (10 g, 0.0446 mol) and ethyl chloroformate (28.5 g, 0.2623) dissolved in (670 mL) tetrahydrofuran (THF) at 0 °C over a period of 30 min. The reaction mixture was stirred at room temperature for 2 h. Precipitated triethylamine hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from THF and ether. White crystal was obtained (yield 89%); mp 72−74 °C. ^{1}H NMR ($CDCl_3$): 1.34 (s, 3H, $-CH_3$), 4.22 (d, J = 10.8, 2H, $-CH_2O-$), 4.70 (d, J = 10.8, 2H, $-CH_2O-$), 5.22 (s, 2H, $-CH_2Ar$), and 7.35 ppm (m, 5H, *Ar*). ^{13}C NMR ($CDCl_3$): 17.52 (CH_3), 40.19 ($C(CH_3)$), 67.86 ($ArCH_2O-$), 72.89 ($-CH_2O-$), 128.17 (Ar*C*), 128.71 (Ar*C*), 134.72 (Ar*C*), 147.36 (O*C*=OO), 170.88 (O*C*=O).

Enzymatic Polymerization of 1. All reactions were carried out in bulk at 80 °C. The monomer **1** and lipase were dried (0.1 mmHg; 38 h; room temperature) separately. In a glovebag maintained under an argon atmosphere, the monomer was placed in 6 mL reaction vials, and then preweighed enzyme was added. The vials were capped with a rubber septum and placed in a constant temperature oil bath maintained at 80 °C for predetermined times. Control reactions with thermally deactivated lipase AK were also setup as described. Reactions were terminated by dissolution of the content of the reaction vial in chloroform and removal of enzyme (insoluble) by filtration (glass fritted filter, medium pore porosity). The filtered enzyme was washed with chloroform. The filtrates were combined, solvents were removed in vacuo, and the crude products were analyzed by proton (^{1}H) NMR and gel permeation chromatography (GPC). When specified, the polymer was purified by addition of its chloroform solution to methanol, which precipitated the polymer (**2**).

Removal of the Benzyl Ester Group. 36 Mg of Pd/C (5%) was added to a solution of 0.180 g (0.7 mmol) of **2** in 30 mL of anhydrous ethyl acetate. The apparatus for catalytic hydrogenation was evacuated from air and filled with H_2. After the theoretical quantity of hydrogen was absorbed, the Pd/C catalyst was filtered off and carefully washed with ethyl acetate and methanol. The combined filtrate was evaporated to give **3** as a white solid (0.112 g, 97%). The polymer was dissolved in DMSO-d_6 to acquire the NMR spectral data.

Results and Discussion

Polymers such as poly(β-malic acid) and poly(glutamic acid) have received much attention because of the presence of carboxylic acid pendent groups for drug attachment and for solubilization in water.[1b] However, thus far, polycarbonates having pendent carboxyl groups have not been reported. We studied enzyme-catalyzed ring-opening polymerization of a novel carbonate monomer for synthesis of pendent carboxyl-containing polycarbonates. The monomer **1** was synthesized in 89% yield (Scheme 1). The structure of **1** was confirmed from its ^{1}H NMR and ^{13}C NMR spectral data (see Experimental Section). In the ^{13}C NMR spectrum, the carbonate and benzyl ester carbon resonances were observed at 147.36 and 170.88 ppm, respectively.

Seven different lipases, all commercially available, were investigated for polymerization of **1**, carried out at 80 °C in bulk. Table 1 shows the data obtained for 24 and 72 h reactions at 80 °C. Interestingly, under the reaction conditions, a significant variation in the monomer conversion and molecular weight was observed for lipases from different origins. For example, for 24 h

Scheme 1

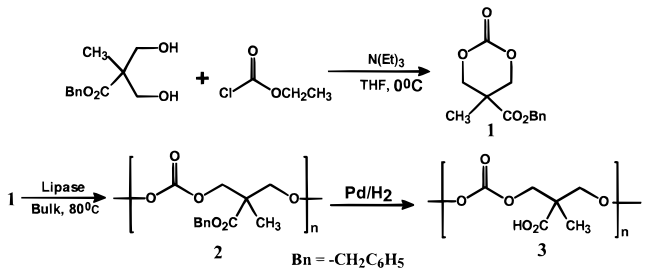

Table 1. Ring-Opening Polymerization of 5-Methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one in Bulk at 80 °C[a]

entry	lipase[b]	time (h)	conversion (%)[c]	DP[c]	M_n[d]	M_n/M_w[d]
1	AK	24	54	4.7	1500	1.076
2	AK	72	97	28.3	6100	1.647
3	PPL	24	54	4.7	1700	1.164
4	PPL	72	98	4.0	1300	1.380
5	PS-30	24	50	4.5	1450	1.079
6	NOVO-435	24	29	3.0	950	1.007
7	NOVO-435	72	86	13.4	4400	2.117
8	IM	24	13	N/A	N/A	N/A
9	AS	24	12	N/A	N/A	N/A
10	AYS	24	8	N/A	N/A	N/A
11	AK[e]	72	0	N/A	N/A	N/A

[a] Data shown is the statistical mean of duplicate experiments carried out using 2:1 monomer-to-enzyme ratio. [b] Enzyme (source): AYS (*Candida rugosa*), AS (*Aspergillus niger*), AK (*Pseudomonas fluorescens*), PS-30 (*Pseudomonas cepacia*), PPL (porcine pancreas), Novozym-435 (*Candida antarctica*), and IM (*Mucor miehei*). [c] Determined by ^{1}H NMR. [d] Determined by GPC. [e] Thermally deactivated lipase.[10] N/A = not determined due to low conversion and overlapped signals.

reactions, the lipases AS (from *Aspergillus niger*), AYS (from *Candida rugosa*), and IM (from *Mucor miehei*) showed poor conversion (12, 8, and 13%, respectively) whereas lipases PPL, AK, and PS (from porcine pancreas, *Pseudomonas fluorescens*, and *Pseudomonas cepacia*, respectively) showed considerably higher conversions (Table 1). The molecular weight of the polymer formed was also influenced by the source of the lipase. In reactions run for 72 h, at comparable conversions, much higher molecular weight polymer was obtained in lipase AK and Novozym-435 catalyzed polymerization (6100 g/mol, entry 2 and 4400 g/mol, entry 7, Table 1). Also, it is noteworthy to mention that, in a reaction carried out in the presence of deactivated lipase AK, no polymerization was observed even after 72 h, and the monomer was recovered quantitatively (Table 1, entry 11).[12]

Water in lipase-catalyzed ring-opening polymerization reactions is known to affect the monomer conversion and polymer molecular weight.[9b,13] In general, it has been established that decreasing water content in a reaction leads to higher molecular weight polymers.[9b,13] To prepare high molecular weight polymer **2,** we carried out bulk polymerization of **1** by lipase AK at lower water content. The lower water content was achieved by rigorous drying of the lipase AK in a drying pistol over P_2O_5, at 50 °C/0.1 mm of Hg, for 36 h. As expected, the lower water content in the reaction resulted in a much higher molecular weight polymer with M_w 59 000 g/mol, however, with a much higher polydispersity index of 7.5. The broad molecular weight of the polymer may be due to the increasing diffusion constraints in the reaction system. With increasing molecular weight, the diffusion

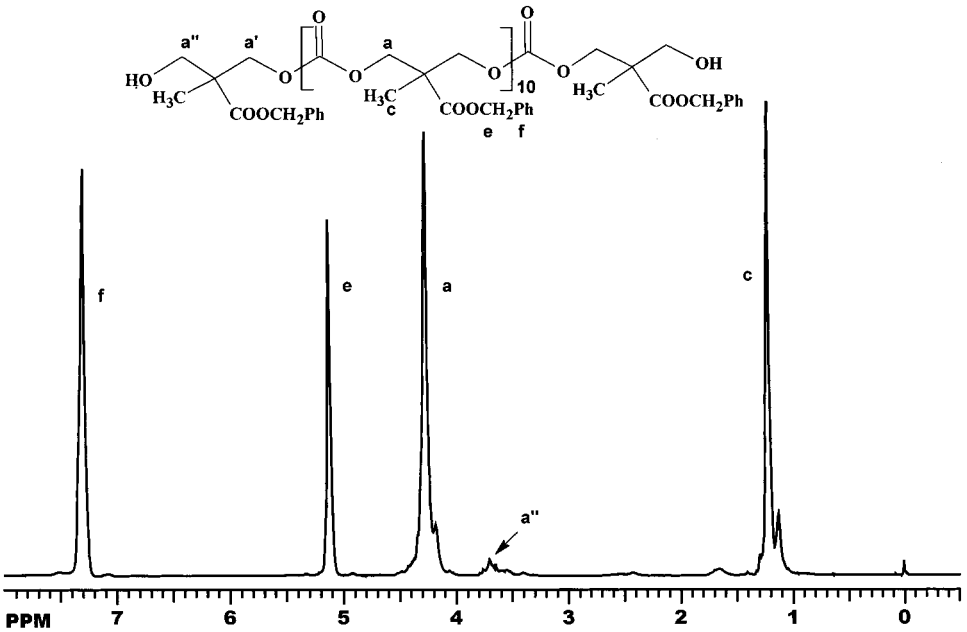

Figure 1. ^{1}H NMR spectrum of **2** obtained by lipase-catalyzed ring-opening polymerization (360 MHz, $CDCl_3$).

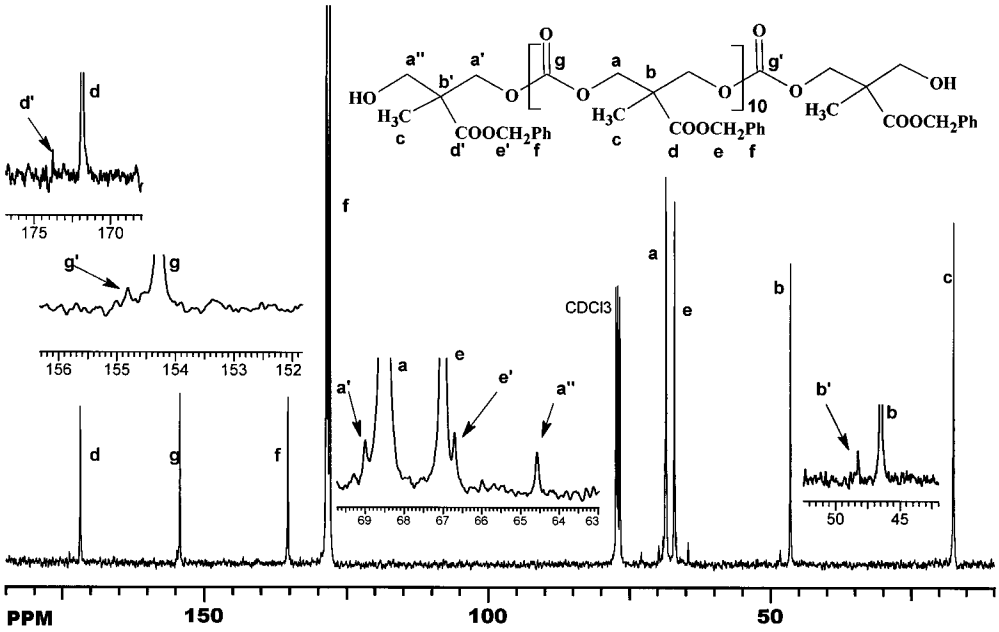

Figure 2. ^{13}C NMR spectrum of **2** obtained by lipase-catalyzed ring-opening polymerization (90 MHz, $CDCl_3$).

of polymer chains in a solvent less system may become severely limited. This may prevent further chain growth, and instead new polymer chains may be initiated leading to a broad molecular weight distribution. Efforts to overcome the diffusion limitation by carrying out the ring opening in different solvents, however, led to lower monomer conversion and molecular weight polymer.

The polymers obtained (Table 1) have been characterized by ^{1}H and ^{13}C NMR experiments. Figure 1 shows the ^{1}H NMR spectrum of the polymer obtained by lipase AK catalyzed polymerization (entry 2, Table 1) and precipitated in methanol. The assignments of protons resonances in Figure 1 were based upon model compounds and comparison with the ^{1}H NMR spectrum of the monomer. The signal at 3.69 ppm was assigned to the protons a″ in the end-group hydroxy methylenes, i.e., $-CH_2-OH$.[9b] This assignment was confirmed by derivatization with trifluoroacetic anhydride. Upon derivatization the resonance signal at 3.69 ppm was shifted downfield by about 0.8 ppm (see Supporting Information Available). Further proof of the end-group structure came from the ^{13}C NMR spectrum (Figure 2). The ^{13}C NMR spectrum, in addition to the resonances due to carbons a−g in the intrachain repeat unit, contained low-intensity resonances due the end-group carbons, i.e., a′, a″, b′, d′, e′, and g′ (see inserts in the Figure 2). The resonance at 64.51 ppm was assigned to the end-group hydroxymethylene carbons ($-CH_2OH$, a″) and confirmed by an observed downfield shift of 4.0 ppm upon derivitization with trifluoroacetic anhydride (see Supporting Information). Peak assignments in Figures 1 and 2 were further confirmed from corresponding cross-peaks in the ^{1}H−^{13}C HETCOR spectrum (not shown, see Supporting Information). In the absence of any other end group observed, we concluded that the polymer must have hydroxyl end groups at both termini. This conclusion is further supported by the fact the molecular weights calculated from the ^{1}H NMR spectra

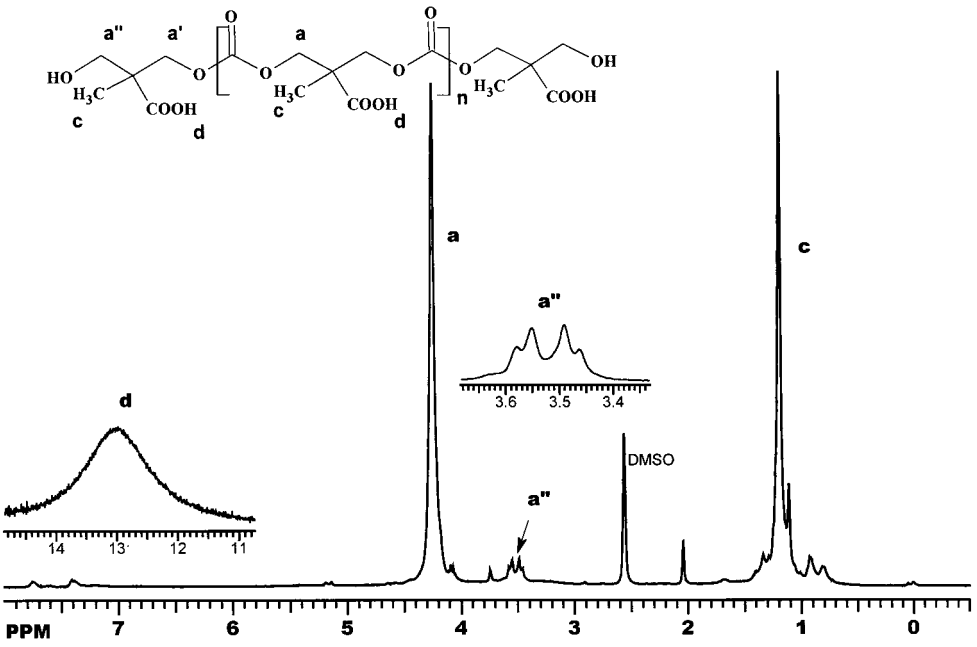

Figure 3. ^{1}H NMR spectrum of **3** obtained by lipase-catalyzed ring-opening polymerization (360 MHz, DMSO-d_6).

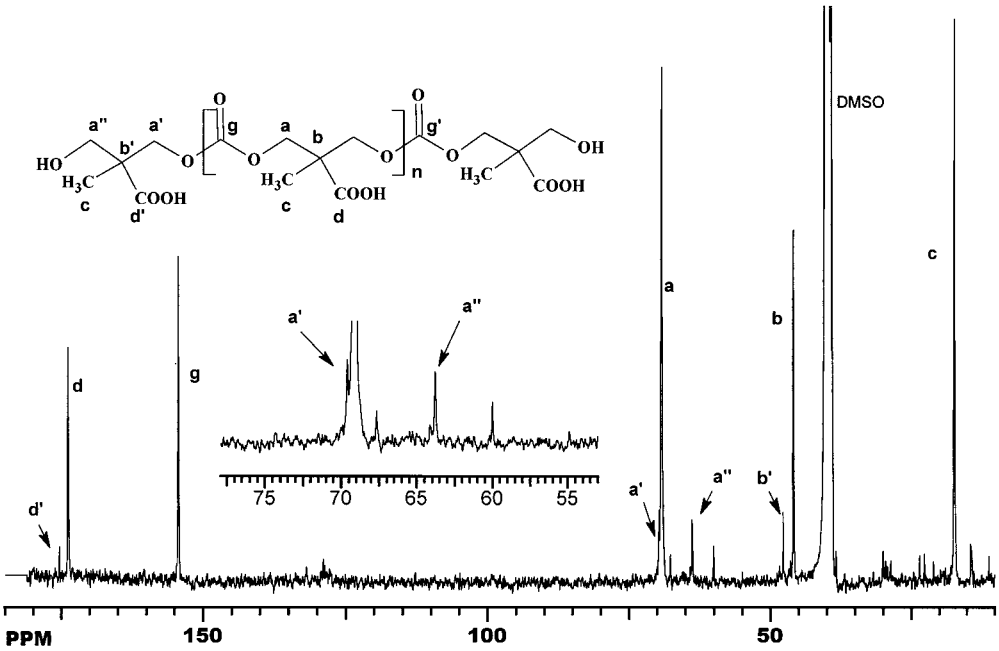

Figure 4. ^{13}C NMR spectrum of **3** obtained by lipase-catalyzed ring-opening polymerization (90 MHz, DMSO-d_6).

and the GPC were comparable within experimental error. Moreover, a carbonic acid end group would be too unstable to survive the reaction conditions.

An important consideration in our choice to protect the carboxylic acid groups in **2** as benzyl esters was the ease with which it can be removed, when desired. Though a number of different reagents allow easy removal of the benzyl group, hydrogenolysis by far remains the most useful and mild method for removal of the benzyl ester group.[14] The choice of the deprotecting reagent becomes more important in the presence of other sensitive linkages in the molecule, e.g., ester and carbonate linkages. Lenz and co-workers reported successful removal of the pendent benzyl ester groups in poly(benzyl malonate) by hydrogenolysis over Pd/C in quantitative yields.[1b,15] Importantly, these workers and others did not observe any degradation of the polyester backbone as a result of hydrogenolysis.[16] To our surprise, we did not find a prior report of debenzylation on a carbonate-containing molecule in the literature. We therefore, taking cue from successful application of hydrogenolysis using Pd/C catalyst for debenzylation in polyesters under mild reaction conditions, investigated it for removal of the benzyl protecting group in **2**. Polycarbonate **2** ($M_n = 2500$, $M_w/M_n = 1.4$) was, therefore, subjected to catalytic hydrogenation over palladium in charcoal in anhydrous ethyl acetate. Complete removal of the benzyl groups led to the corresponding linear polycarbonates (**3**) (Scheme 1) with pendent carboxyl groups. Polymer **3** was isolated in quantitative yield as a white solid. In addition to water, the polymer was soluble only in polar organic solvents, e.g., DMSO, DMF, methanol, ethanol, etc. The structure of the polymer was confirmed from its ^{1}H and ^{13}C NMR

spectra (Figures 3 and 4). The absence of resonances, in the ^{1}H NMR (DMSO-d_6), at ~5.15 and 7.30 ppm indicated complete removal of the benzyl groups. The intrachain methylene (−OCH_2−, a) and methyl proton (c) resonances were observed at 4.25 and 1.20 ppm, respectively (Figure 3). The carboxylic acid protons (d) were observed as a broad singlet centered at ~13.0 ppm (Figure 3 insert). Importantly, the ratio of the signal at 3.50 ppm (−CH_2OH, a″) to the one at 4.25 ppm (−OCH_2−, a) before and after catalytic hydrogenation did not change (see Supporting Information). This indicated that no degradation of the polycarbonate chain occurred during the debenzylation procedure. The ^{13}C NMR spectrum further supported the structure of the polymer and confirmed complete removal of the benzyl groups (Figure 4). Resonances due to the benzyl methylene and aromatic carbons were not observed. The resonances due to the methyl (c), the quaternary (b), methylene (a), carbonate carbonyl (g), and the carboxylic acid (d) carbons were observed at 17.19, 45.87, 69.10, 154.21, and 173.77 ppm, respectively (Figure 4). The end-group tertiary (−*C*(CH_3)(COOH)−, b′), methylene (−O*C*H_2−, a′), and the carboxyl (−*C*OOH, d′) carbons were at 47.69, 69.57, and 175.32 ppm, respectively. The hydroxymethylene carbons (−*C*H_2OH, a″) resonances were observed at 63.78 ppm.

Synthesis of substituted polycarbonates is important due to their potential in many biomedical and industrial applications as outlined in the introductory section. Accordingly, research has been conducted with efforts to identify suitable catalytic system(s) to enable synthesis of high molecular weight substituted polycarbonates.[6,17] It has been a general observation that with increasing bulk of the substituents the polymerizability of the monomer and polymer molecular weight decreases significantly. The explanation offered for the low polymerizability and molecular weight has been the steric constraints imposed by the bulk of the substituent(s). In a relevant study, Endo and co-workers studied effects of substituents on anionic ring-opening polymerizations of six-membered cyclic carbonates.[17a] These workers observed that, with increasing bulk of the substituent from a methyl to a phenyl group, the polymer yield and molecular weight decreased from 90 to 46% and 54 000 to 12 700 g/mol, respectively. Noticeably, in these reactions longer reaction time did not improve the polymer yield significantly but resulted in lower molecular weights. Enzyme-catalyzed ROPs of cyclic carbonates, as demonstrated, with high monomer conversion and molecular weights therefore has the potential to provide an environmentally friendly alternative for synthesis of substituted polycarbonates, when a suitable biocatalyst can be found.

Conclusions

Enzymatic polymerization of a novel carbonate monomer, 5-benzyloxycarbonyl-1,3-dioxan-2-one, is reported. No evidence of decarboxylation during propagation is observed. Catalytic hydrogenation to remove benzyl groups yields polycarbonate having pendent carboxyl substituents on the main chain. No degradation of the polycarbonate chain was detected under the hydrogenolysis condition employed. To the best of our knowledge, this is the first report of a polycarbonate containing a pendent carboxyl group. Synthesis of ester and amide derivatives of the carboxyl groups in polycarbonate **3** and their physical, chemical, and biodegradation evaluation are currently underway in our laboratories.

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Supporting Information Available: NMR spectra of polymer **3** and trifluoroacetyl derivative of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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