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Polycarbonates Derived from Glucose via an Organocatalytic Approach

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Supporting Information

ABSTRACT: An organocatalyzed ring-opening polymerization methodology was developed for the preparation of polycarbonates derived from glucose as a natural product starting material. The cyclic 4,6-carbonate monomer of glucose having the 1, 2, and 3 positions methyl-protected was prepared in three steps from a commercially available glucose derivative, and the structure was confirmed by means of NMR and IR spectroscopies, electrospray ionization mass spectrometry (MS), and single-crystal X-ray analysis. Polymerization of the monomer, initiated by 4-methylbenzyl alcohol in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene as the organocatalyst, proceeded effectively in a controlled fashion to afford the polycarbonate with a tunable degree of polymerization, narrow molecular weight distribution, and well-defined end groups, as confirmed by a combination of NMR spectroscopy, gel-permeation chromatography, and MALDI-TOF MS. A distribution of head-to-head, head-to-tail, and tail-to-tail regiochemistries was determined by NMR spectroscopy and tandem MS analysis by electron transfer dissociation. These polycarbonates are of interest as engineering materials because of their origination from renewable resources combined with their amorphous character and relatively high glass transition temperatures as determined by X-ray diffraction and differential scanning calorimetry studies.

Engineering plastics play significant technological roles,[1] and in particular, polycarbonate is a material of importance because of not only its high mechanical strength, transparency, and impact resistance but also its potential for degradability and biocompatibility.[2] On the other hand, as fossil fuels that are often used to produce these materials dwindle, much attention has been paid to the development of novel renewable feedstocks, such as readily available monosaccharides,[3−7] menthides,[8] and terpenes.[9] Among these, glucose would potentially be an ideal feedstock because of its abundance in nature in monomeric and polymeric forms.[9b]

We had anticipated that a controlled ring-opening polymerization (ROP) of glucose-based bicyclic carbonate monomers ideally would lead to renewable polycarbonates having well-defined structures and amorphous or crystalline phases with high thermal stabilities based on the cyclic saccharide repeat unit. Moreover, with the advances that have been made in controlled ROP via organocatalysis over the past decade, allowing metal catalysts to be replaced with less toxic and more environmentally acceptable alternatives,[10] we hypothesized that polycarbonates could be produced facilely and with potentially broad applications. ROP for the synthesis of polycarbonates, however, has been applied mainly with monocyclic six-membered ring structures, such as trimethylenecarbonate (TMC) derivatives, to afford aliphatic polycarbonates having relatively low glass transition temperatures (T_g).[10a,11] Although polycarbonates derived from various monosaccharides have been prepared by ROP[3−5,12] and polycondensation,[13] the organocatalyzed polymerization of a five-membered cyclic carbonate having a glucopyranoside structure was reported only recently.[6,14] Endo and co-workers conducted detailed studies of anionic- versus organobase-initiated and -catalyzed ROPs of 4,6-*O*-benzylidene-2,3-*O*-carbonyl-α-D-glucopyranoside, for which they postulated that a zwitterionic mechanism was involved with the use of an organobase and observed relatively broad molecular weight distributions with significant macrocyclic products.[14] In contrast, our interest is in the organocatalyzed ROP of six-membered bicyclic carbonate monomers derived from glucose by using initiating species to achieve high degrees of control, with detailed analysis of the regiochemical outcomes and the physicochemical properties of the materials.

Herein we report the synthesis of a glucose-based bicyclic carbonate monomer, **1**, and its controlled ROP with an organocatalyst. The monomer was prepared in three steps, and the polymerization proceeded in a controlled fashion, yielding amorphous polycarbonates with interesting physical properties.

As shown in Scheme 1, **1** was synthesized with methyl ether protection of the hydroxyl groups at the 1, 2, and 3 positions to suppress undesired side reactions during the polymerization. Commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was methylated by reaction with methyl iodide for 19 h in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF) at room temperature to afford **2** in 95% yield. Hydrogenolysis of **2** using H_2, Pd on carbon, and a catalytic amount of hydrochloric acid in dioxane over several days at room temperature gave **3** in 93% yield.[15] The cyclic carbonylation of **3** was attempted initially by using ethyl or 4-nitrophenyl

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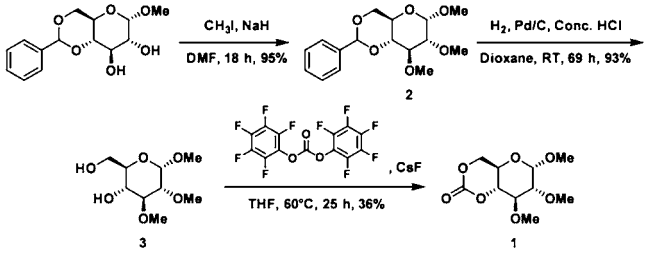
Scheme 1. Synthesis of Bicyclic Glucose-Based Carbonate Monomer 1



chloroformate, but only monosubstituted compounds were obtained.[16] The cyclization reaction was then performed successfully using bis(pentafluorophenyl) carbonate and CsF in tetrahydrofuran (THF)[17,18] at 60 °C over 25 h to afford **1** in 67% yield after column chromatography and 36% yield after subsequent recrystallization in chloroform/hexanes. The structure was confirmed by ^{1}H NMR (see Figure 3), ^{13}C NMR, and FT-IR spectroscopies combined with COSY, HMQC, HMBC, DEPT 90, and DEPT 135 NMR and electrospray ionization mass spectrometry (ESI-MS) analyses [Figures S1−S6 in the Supporting Information (SI)]. A single crystal of **1** was analyzed by X-ray diffraction, which further confirmed the structure (Figures 1 and S21 and Tables S12−S16). It was expected that the ROP would proceed efficiently, judging from the strained six-membered ring revealed by the X-ray analysis.

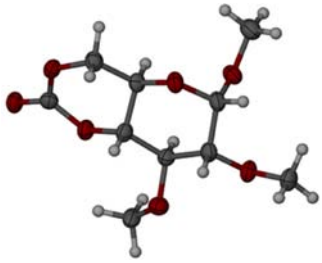


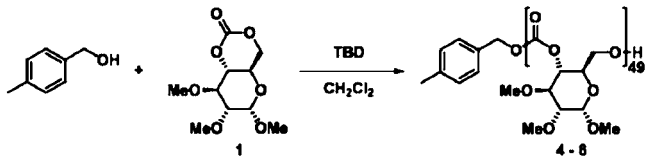
Figure 1. Single-crystal X-ray structure of **1**.

Despite having first been reported in 1970,[16] **1** had not been utilized in ROP. Similar bicyclic sugar-based carbonates have also been synthesized and investigated for ROP, although they typically did not present difficulties with their preparation as was observed for **1**. For instance, in the case of the synthesis of a xylofuranose-based monomer having a structure similar to that of **1**, the cyclic carbonylation proceeded using ethyl chloroformate.[4] In contrast, the more reactive and symmetrical carbonylation agent bis(pentafluorophenyl) carbonate was needed to form **1** (vide supra). Recently, Suzuki et al.[19] also reported difficulty in forming the cyclic carbonate of 2′-deoxyadenosine and resorted to condensation polymerization by a silicon-assisted alkoxy/carbonylimidazolide coupling reaction. The differences among these three cyclic carbonylations could arise from the configuration of the two hydroxyl groups involved with cyclization: the hydroxyl groups of the xylofuranose have a cis configuration and those of 2′-deoxyadenosine and **2** have a trans configuration. The moderate reproducibility of the cyclic carbonylation method may have contributed to the limited development of **1** and its lack of study as a monomer for ROP.[16]

The ROP of **1** was conducted via an initiator/chain-end activation mechanism under organocatalysis and studied first as a function of time and conversion at a constant monomer/initiator stoichiometry and then at various monomer/initiator ratios. Initially, the ROP kinetics were studied using a monomer/initiator feed ratio ($[M]_0/[I]_0$) of 51 in CH_2Cl_2 with 4-methylbenzyl alcohol as the initiator and commercially available 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as the organocatalyst (Table 1, entry 3) to allow for monitoring of the monomer conversion and the growth of the polymer chain as functions of time.[10a] The number-average molecular weights (M_n) were estimated by gel-permeation chromatography (GPC) and calculated using ^{1}H NMR spectroscopy by comparing the resonance for the methyl protons of the initiator with that for the proton at the 1-position of the repeat unit. The conversion of **1** reached 44% after 1 h and >98% after 6 h (Figure 2A). The GPC traces showed unimodal peaks during the reaction, which shifted toward shorter elution times as polymerization progressed while maintaining narrow polydispersity index (PDI) values (Figure 2A inset). Kinetic plots of $\ln([M]_0/[M])$ versus time were linear (Figure 2B), indicating first-order kinetics, which is characteristic of ROP.[20] Furthermore, when the $[M]_0/[I]_0$ feed ratio was varied to afford the series of polymers **4**−**6**, the value of M_n increased in proportion to the feed ratio while the PDI remained narrow (Table 1), indicating that the polymerizations proceeded in a controlled fashion.

The structure of the polycarbonate was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopies. The assignments of the ^{1}H and ^{13}C NMR spectra were carried out by COSY, HMQC, HMBC, DEPT 90, and DEPT 135 NMR analyses (Figures S7−S11). The characteristic carbonyl vibration of the carbonate linkage was observed at 1751 cm^{-1} in the IR spectra. As

Table 1. ROP of Glucose-Based Monomer 1 (M) via Organocatalysis by TBD with Initiation by 4-Methylbenzyl Alcohol (I)[a]



entry	polymer	cat. mol %	$[M]^b$	$[M]_0/[I]_0{}^c$	time (h)	conv. (%)[d]	M_n (g/mol)[e]	M_n (g/mol)[f]	M_n (g/mol)[g]	PDI[h]
1	**4**	2	1	15	2	>99	3850	2320	4140	1.11
2	**5**	2	1	27	2	>99	6780	5390	7600	1.16
3	**6**	1	1	51	7	>98	12800	14700	13000	1.15

[a]The polymerization of **1** was carried out with TBD in the presence of 4-methylbenzyl alcohol as the initiator at room temperature in CH_2Cl_2. [b]Concentration of **1** in mol/L. [c]monomer/initiator feed ratio. [d]Estimated by ^{1}H NMR analysis in benzene-d_6. [e]Calculated as (formula weight of initiator) + (formula weight of monomer) × ($[M]_0/[I]_0$) × (conversion/100 %). [f]Calculated by GPC (THF eluent) with a static laser detector. [g]Estimated using ^{1}H NMR spectra in CD_2Cl_2. [h]Estimated by GPC (THF eluent) using polystyrene standards.

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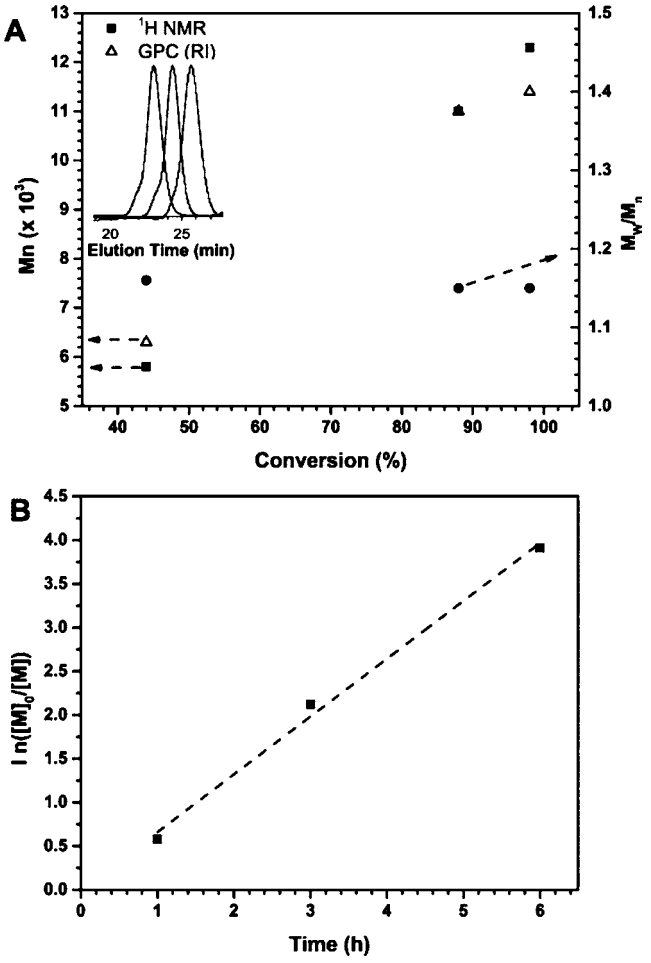

Figure 2. (A) Plots of M_n (■, △; left axis) and M_w/M_n (●, right axis) vs monomer conversion for ROP of **1** using TBD as the catalyst and 4-methylbenzyl alcohol as the initiator at a **1**/initiator/TBD ratio of 51/1/0.5, as obtained from NMR and GPC analyses of aliquots collected for evaluation after 1, 3, and 6 h of reaction. The inset shows GPC elution curves for monitoring of the polymerization of **1**. (B) Kinetic plot of $\ln([M]_0/[M])$ vs time using data obtained by GPC [refractive index (RI) detector].

illustrated by the ^{1}H NMR spectra of **1** and **5** (Figure 3), the most significant proton resonance differences between the monomer and the polymer occurred for the pyranoside methine proton (labeled as 4), the methoxy protons (7−9), and the methylene protons α to the carbonate linkage (4). Compared with the monomer, the polycarbonate proton 4 resonance was shifted downfield from ca. 4.0 to 4.6 ppm, whereas the methoxy proton signals (7−9) were shifted upfield from ca. 3.6 to 3.5 ppm. These shifts could arise from an electronic effect of the adjacent carbonyl group and the geometric conformational changes upon opening of the six-membered cyclic carbonate of the monomer to give the linear polycarbonate. The value of M_n estimated by ^{1}H NMR analysis [based on the ratio of the integral for the anomeric proton at position 1 in the repeat unit (4.8 ppm) to that for the methyl protons of the initiator at the α-chain end (2.4 ppm)] was 7600 g/mol, which is in agreement with the theoretical value of 6780 g/mol and the GPC-estimated value of 5390 g/mol.

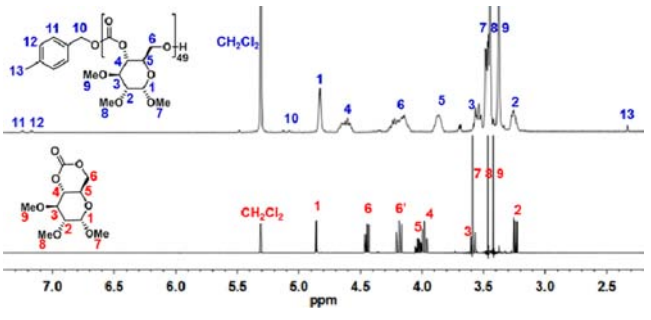

Figure 3. ^{1}H NMR spectra of the monomer **1** and the polymer **5** in CD_2Cl_2.

The ^{13}C NMR spectra showed the characteristic resonance for a carbonate linkage at 155.0−154.4 ppm (Figure S12), with three sets of observed signals. Multiple carbonyl resonance frequencies could arise from regiorandom ordering, as Gross and co-workers observed during their study of ROP of a xylofuranose-based monomer,[4] suggesting that the organocatalytic ROP of glucose-based monomer **1** propagated nonselectively to give a distribution of head-to-head (HH), head-to-tail (HT) and tail-to-tail (TT) regiochemistries.

The regiorandom nature of the polymerization was further supported through ESI tandem MS analysis by electron transfer dissociation (ETD) of the trisodiated polymer species of **5**. Ion assignments were made by determining all of the potential cross-ring cleavages for both the HT and tail-to-head (TH) orientations of the polymer subunit, and a table associated with each orientation was formulated (Figure S14a,b). Each orientation produces unique cross-ring cleavage fragment ions that were used as diagnostic ions to determine the regiochemistry for a particular subunit. The product ion spectrum (Figure S14c) shows loss of full subunits as well as product ions with cross-ring cleavages between each full subunit loss. The diagnostic ions for both the HT and TH orientations were observed for each subunit in the product ion spectrum, which indicates that all three regiochemistries (HH, HT, and TT) were present in roughly equivalent quantities (see the SI for a detailed discussion).

Furthermore, the polymer end groups were analyzed by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Figure S13) to confirm the controlled nature of the polymerization. The spectrum of **5** contains only one series of peaks corresponding to K^+ adducts of the polymers having chain ends of the 4-methylbenzyl alcohol initiator and a hydroxyl terminating group. The mass differences between the peaks (m/z 248.5 ± 1.3) were also in agreement with the average mass of the polycarbonate repeat units (248.2 g/mol). For example, the 21-mer of this distribution would be expected to give a chemical formula of $C_{10}H_{16}O_7 \times 21$ (repeat unit) + $C_8H_9O_1$ (initiating group) + H + K = $C_{218}H_{346}O_{148}K$, for which the calculated average mass is 5374.2 g/mol, and indeed, a signal was observed at m/z 5373.8. These data confirm not only the efficient incorporation of the initiator at the α chain end, which is consistent with the chain-end analysis by ^{1}H NMR spectroscopy, but also the fact that the MALDI-derived M_n value is in close agreement with the M_n values estimated by GPC and ^{1}H NMR analysis. These results indicate that the polycarbonates had well-defined end groups and were prepared by controlled polymerizations without significant side reactions.

The thermal properties of the glucose polycarbonates were evaluated by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) under inert atmosphere (Table S1 and Figures S15 and S16). Thermal degradation proceeded at relatively low temperatures (250−320 °C for initial to complete mass loss; Figure S16). One possible mechanism of the thermal

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degradation could be abstraction of a proton from C3 or C5 of the saccharide ring by the carbonyl O atom to afford CO_2 (Figure S17). The mass spectrometer coupled to the TGA detected peaks in increments of m/z 28 and 44, which could be attributed to the loss of CO^+ and CO_2^+, respectively. The DSC analysis of these polycarbonates (Figure S15) revealed high glass transition temperatures: even the lowest-molecular-weight polycarbonate, **4**, showed T_g = 106 °C, which is significantly higher than those of common aliphatic polycarbonates such as poly(1,3-trimethylene carbonate) ($T_g \approx -18$ °C).[11h] The elevated T_g of these glucose-based polycarbonates over aliphatic equivalents could arise from the cyclic structure in the main chain, making these materials attractive for various applications, such as for hard segments of novel biodegradable elastomers.[4]

Since DSC analysis did not reveal a melting point below the thermal degradation temperature, X-ray diffraction (XRD) measurements were made. Bulk and annealed samples of **6** were subjected to XRD and showed a broad halo rather than a sharp reflection peak (Figure S18), indicating an amorphous character. The lack of crystallinity could be explained by the regiorandom sequence of the polymer, although this is in sharp contrast to the case of the xylofuranose-based polycarbonate,[4] which exhibited a semicrystalline nature even though it also had a distribution of HH, HT, and TT regiochemistries.

In conclusion, we have demonstrated the synthesis of a glucose-based cyclic carbonate monomer and its controlled ROP via organobase catalysis to afford a polycarbonate having regiorandom order and well-defined end groups. In contrast to the recently reported ROP of a five-membered cyclic carbonate, our monomer contains smaller protecting groups, and the use of an initiator here affords polymers having narrower molecular weight distributions. These synthetic methodology developments are important steps toward the use of glucose as an effective and innovative feedstock for polycarbonate-based engineering materials. Furthermore, evaluation by XRD and thermal analysis revealed that this new glucose polycarbonate exhibits amorphous character and a significantly higher T_g than common aliphatic polycarbonates, making it attractive for a broad range of potential applications. In particular, such materials may impact numerous fields ranging from degradable plastics to tissue engineering and nanotherapeutic delivery vehicles. Moreover, simple modifications to the monomer protection chemistry that may influence the polymer properties and the incorporation of a glucose polycarbonate as part of a block-copolymer system with amphiphilic properties are being explored to expand beyond this current homopolymer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section and additional data. 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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