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Organocatalyzed ROP of a Glucopyranoside Derived Five-Membered Cyclic Carbonate

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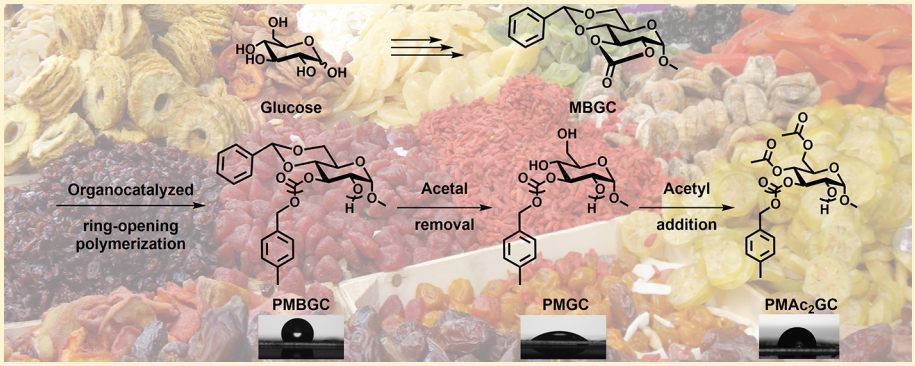
Supporting Information



ABSTRACT: Saccharides, based on their wide bioavailability, high chemical functionality and stereochemical diversity, are attractive starting materials for the development of new synthetic polymers. Established carbonylation methodologies were used to synthesize a 5-membered cyclic carbonate monomer, 4,6-*O*-benzylidene-2,3-*O*-carbonyl-α-D-glucopyranoside (MBGC), in high yield (>95%) from a commercially available D-glucopyranoside derivative. The ability of this monomer to undergo ring-opening polymerization (ROP) with a range of organocatalysts, rather than the previously reported anionic initiators, was investigated. These new conditions were developed to widen the functional group tolerance in the polymerization, and achieve better control over the final properties of the polymers. The most promising of the catalysts examined, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), was used in a kinetic study to confirm the well-controlled nature of the ROP. Optimized conditions were then successfully applied to the synthesis of polymers of different molecular weights. Two post-polymerization modifications were completed via the removal of the benzylidene acetal protecting group to release a water-soluble poly(glucose carbonate), and then addition of acetyl groups to facilitate characterization studies. MALDI-TOF MS analysis was performed to further probe the chemistry of the polymerization and deprotection. A wide range of thermal decomposition temperatures (233−347 °C), glass transition temperatures (87−233 °C), and water contact angles (38−128°) was achieved by this series of polymers. The hydrolytic degradability of these polymers was also examined, demonstrating differing degradation mechanisms based on the acidic vs. basic conditions used. Consequently, this single monomer was successfully employed in the straightforward synthesis of a polymeric system with tunable properties based on the molecular weight and repeat unit composition.

INTRODUCTION

Polycarbonates, predominantly composed of phenolic-type monomers, e.g. bisphenol A, are fundamental mainstay materials that serve broad purposes in technically demanding conditions, for instance automotive components and commodity materials. However, aliphatic polycarbonates are also of significant value. Over the past decade, aliphatic polycarbonates have garnered increasing interest for use in biomedical applications, primarily because of their tissue compatibility, potential degradation *in vivo*, and benign degradation products.[1−3] The wide range of stereochemical diversity and high degree of functionality of carbohydrates, as well as the ability to perform functional group transformations and combine different carbohydrates, make them attractive starting materials in the synthesis of monomers that can be converted into polymer materials with a diversity of structures and properties. Moreover, due to the extensive bioavailability of carbohydrates, their use as feedstocks for the synthesis of polycarbonates can reduce the dependence on petrochemical starting materials and offers a high potential of hydrolytic

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degradation into easily metabolized byproducts. Significant work has been done to produce poly(saccharide carbonate)s from various carbohydrates and their derivatives, including xylose,[4−6] deoxyadenosine,[7] isosorbide,[8] and pyranosides.[9−20]

Polycarbonates are most commonly synthesized by condensation polymerizations (such as those with phosgene analogues and a diol),[6,17,18] transesterification of a carbonate comonomer with a diol monomer,[8] copolymerization of carbon dioxide with ring-opening of an epoxide,[21−23] or ring-opening of cyclic carbonate monomers.[12,16,19,20,24−26] Among these methods, ring-opening polymerization (ROP) provides the greatest control over the molecular weight, selectivity of the reaction, and, ultimately, the properties of the final materials. In recent years, a large variety of catalysts has been developed for the ROP of cyclic carbonates.[24,27] Organocatalysts are becoming competitive with inorganic catalysts, in both price and reactivity, overcoming the toxicity and difficulties with the availability of metal-based catalysts.[24,25,28] However, their applications in certain ROPs are still limited by monomer reactivity. For instance, the polymerization of five-membered cyclic carbonate monomers is challenging under common catalytic conditions. Monomers of this ring size, for esters or carbonates, generally do not undergo polymerization[29] or even ring-opening to produce acyclic molecules under common catalytic conditions.[30−34] In cases where polymerization was achieved, side reactions, such as the elimination of CO_2 during the polymerization leading to a poly(carbonate-*co*-ether) rather than the desired polycarbonate, were also a main issue.[35−37] One of the early examples of an efficient five-membered ROP leading to a polycarbonate was the anionic polymerization of methyl 4,6-*O*-benzylidene-2,3-*O*-carbonyl-α-D-glucopyranoside (MBGC), a fused *trans*-cyclic carbonate.[9] In this anionic ROP, the effects of solvent, monomer concentration, and initiator were studied thoroughly by the Endo and Haba groups.[9,13,14,38] The selective ROP of other *trans*-fused ring carbonate monomers has been investigated further by Guillame and Carpentier et al., using several catalysts, including an organocatalyst.[39−41] The additional strain from the cyclic carbonates being in a *trans*-fused bicyclic conformation was likely the driving force for these polymerizations. These interesting results guided us to examine the ability of MBGC to undergo organocatalyzed ROP.

Herein, we report a study of the organocatalytic scope and a kinetic analysis of the MBGC polymerization to confirm its controlled nature. Optimized experimental conditions were then applied to the synthesis of several molecular weights of PMBGC to explore the thermophysical properties. The acid sensitivity of the benzylidene protecting group was then used to generate the deprotected, polyhydroxyl-presenting polycarbonates, which were further functionalized. Finally, the physical properties and hydrolytic stabilities of the synthesized polymers were analyzed and compared in terms of molecular weight and side chains (benzylidene acetal, hydroxyl, or acetyl), which revealed interesting mechanistic differences under acidic vs basic aqueous conditions.

EXPERIMENTAL SECTION

Instrumentation. ^{1}H, ^{13}C, COSY, and HMBC NMR spectra were recorded on an Inova500 spectrometer; chemical shifts were referenced to the resonance signals of the deuterated solvent.

IR spectra were recorded on a Shimadzu IR Prestige attenuated total reflectance Fourier-transform infrared spectrophotometer and analyzed using IR solution v. 1.40 software.

Size exclusion chromatography was performed with (1) $CHCl_3$ as eluent on a Tosoh EcoSEC for the organocatalytic scope and kinetic studies and (2) DMF as eluent on a Waters chromatography system for the molecular weight determinations across the polymer samples having challenging solubilities due to the different side chain groups.

Instrumental details: (1) Tosoh Co. (Tokyo, Japan) model HLC-8320 EcoSEC system with a two-column set of TOSOH bioscience TSKgel columns (Super HM-M 6.0 mm i.d × 15 cm columns) and a guard column (Super H-H 4 μm) with chloroform as the eluent (0.300 mL/min) at 30 °C. Polymer solutions were prepared at ca. 3 mg/mL and an injection volume of 200 μL was used. The system was calibrated with Polymer Laboratories, Inc. (Amherst, MA) polystyrene standards (580−271 800 Da). (2) A Waters Chromatography, Inc. (Milford, MA) system with an isocratic pump model 1515, a differential refractometer model 2414, and a four-column set of 5 μm Guard (50 × 7.5 mm), Styragel HR 4 5 μm DMF (300 × 7.5 mm), Styragel HR 4E 5 μm DMF (300 × 7.5 mm), and Styragel HR 2 5 μm DMF (300 × 7.5 mm) with DMF (0.05 M LiBr) as the eluent (1.00 mL/min) at 70 °C. Polymer solutions were prepared at ca. 5 mg/mL, with toluene as a flow marker, and an injection volume of 200 μL was used. The system was calibrated with Polymer Laboratories, Inc. (Amherst, MA) polystyrene standards (580−1 233 000 Da).

Mass spectral data were collected using a Bruker-Daltonics matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) Autoflex III mass spectrometer in reflector mode with positive ion detection. Typical sample preparation for MALDI-TOF MS data acquisition was performed by making stock solutions in THF of matrix (20 mg/mL), polymer analyte (2 mg/mL), and an appropriate cation source (2 mg/mL). The stock solutions were mixed in a 25/5/1 ratio (matrix/analyte/cation), deposited onto the MALDI target plate and allowed to evaporate via the dried droplet method. *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) and α-cyano-4-hydroxycinnamic acid (α-cyano) were used as matrices for PMBGC and PMGC, respectively. Sodium trifluoroacetate was used as the primary cation. Lithium iodide and potassium trifluoroacetate were used as cations for additional ionization studies. MALDI-TOF MS data were calibrated against SpheriCal dendritic calibrants from Polymer Factory (Stockholm, Sweden).

Glass transition temperatures were measured by differential scanning calorimetry with a Mettler-Toledo DSC822^e under N_2, as the midpoint of the inflection tangent on the third heating scan, with a 10 °C/min heating and cooling rate. Melting points were measured as the onset of the inflection tangent of the first heating scan with a heating rate of 10 °C/min. Measurements were analyzed using Mettler-Toledo Star^e v.10.00 software.

Thermogravimetric analysis (TGA) was performed under an Ar atmosphere using a Mettler-Toledo model TGA/DSC 1, with a heating rate of 10 °C/min. Measurements were analyzed using Mettler-Toledo Star^e v.10.00 software.

Contact angles were measured as static contact angles with an Attension Theta optical tensiometer (Biolin Scientific). The static contact angle was calculated with the Theta software (Biolin Scientific), using a Young−Laplace fit to the drops of liquid (water).

Materials. All materials were purchased from VWR or Sigma-Aldrich. Unless noted; all reagents were used as received. Dichloromethane (DCM) was purified and dried by a solvent purification system (J. C. Meyer Solvent System). 4-Methylbenzyl alcohol (MBA) and TBD were dried over CaH_2, dried under vacuum, and stored under an argon atmosphere. DBU was dried over CaH_2, distilled, and stored under an argon atmosphere. TU and MBGC were dried under reduced pressure over P_2O_5 and stored under an atmosphere of argon. *Caution: When working with phosgene precursors, including triphosgene, special precautions should be taken as they are highly toxic by inhalation or ingestion.*

Synthesis of Methyl 4,6-O-Benzylidene-2,3-O-carbonyl-α-D-glucopyranoside (MBGC). To a solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (6.0677 g, 21.5 mmol) in DCM (100 mL), pyridine was added (8.7 mL, 110 mmol). A solution of triphosgene (2.3130 g, 7.79 mmol, 23.4 mmol of carbonylation agent generated *in situ*) in DCM (75 mL) was added dropwise to the glucopyranoside solution.

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The reaction was monitored using TLC and was stirred at RT until no starting material was present; a stain of 5% HCl in methanol was used for visualization. Any remaining triphosgene was quenched by the addition of a saturated solution of sodium bicarbonate; this mixture was stirred until no bubbles were visible in the reaction vessel. The organic layer was then collected and washed with saturated sodium bicarbonate, a 5% HCl solution, and finally a sodium chloride brine solution. The organic layer was then dried over sodium sulfate, filtered, and concentrated to yield 6.6102 g (99.8% yield) of a white powder. FTIR (ATR): 3000−2800, 1807, 1454, 1385, 1275, 1213, 1169, 1097, 1065, 1038, 976, 951, 924, 785, 762, 698, 648 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.43 (overlapping, 2 H), 7.39 (overlapping, 3 H), 5.76 (s, 1 H), 5.36 (d, J = 3 Hz, 1 H), 4.84 (t, J = 11 Hz, 1 H), 4.66 (dd, J = 3 Hz, 11 Hz, 1 H), 4.31 (t, J = 9.5 Hz, 1 H), 4.24 (dd, J = 4.6 Hz, J = 10 Hz, 1 H), 3.90 (t, J = 10 Hz, 1 H), 3.67 (td, J = 4.6 Hz, J = 9.5 Hz, 1 H), 3.46 (s, 3 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.2, 136.9, 129.1, 128.1, 126.2, 100.3, 95.9, 78.2, 77.0, 76.0, 67.4, 64.7, 55.3 ppm. MS (ESI^+): calculated $[M + H]^+$ for $C_{15}H_{17}O_7$ 309.0974; found 309.0973; m_p = 110 °C.

Synthesis of Poly(methyl 4,6-O-benzylidene-2,3-O-carbonyl-α-D-glucopyranoside) (PMBGC). In a glovebox, MBGC (1.00 g, 3.24 mmol) was dissolved in 4.8 mL of DCM. A solution of MBA (9.3 mg, 0.076 mmol) in 668 μL of DCM was added, followed by a solution of TBD (9.5 mg, 0.068 mmol) in 1.0 mL of DCM. The reaction was monitored by SEC ($CHCl_3$ eluent) and was quenched when there was no visible monomer signal or change in MW of the polymer signal in the trace (2−9 h, for **1**−**7** depending on the polymerization), by adding Amberlyst 15 H-form resin. The reaction mixture was purified by precipitation into methanol from DCM (three times) to give **3** as a white powder. FTIR (ATR): 3100−2750, 1759, 1454, 1373, 1277, 1234, 1215, 1092, 1049, 988, 752, 698, 656 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.50−7.26 (br), 5.73−5.53 (br), 5.22−5.03 (br), 5.08−4.87 (br), 4.78−4.66 (br), 4.41−4.13 (br), 3.91−3.61 (br), 3.41−3.19 (br) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.0, 137.0, 130.1−127.3, 127.0−125.2, 101.4−99.5, 97.3−95.4, 78.0−76.3, 75.1−72.1, 68.0−66.9, 62.9−61.3, 56.8−54.3 ppm.

During MALDI-TOF MS analysis of these materials, it was determined that an undesired side reaction occurred between the polymer backbone and methanol during the precipitation, which was estimated to occur in approximately 10% of the polymer chains, primarily caused by free TBD present during the first precipitation. This reaction could be avoided by changing the precipitation procedure to use a non-nucleophilic solvent, such as ether, followed by a final precipitation into methanol. Mechanistic explanation and MALDI-TOF MS data are given in the Supporting Information on pages S9−S14.

2: 79% yield, M_n(DMF SEC) = 8600 g/mol, $Đ$(DMF SEC) = 1.32, T_g(midpoint) = 104 °C, TGA in Ar: 296−338 °C, 62% weight loss, 14% mass remaining at 500 °C.

3: 97% yield, M_n(DMF SEC) = 11 500 g/mol, $Đ$(DMF SEC) = 1.36, T_g(midpoint) = 134 °C, TGA in Ar: 307−346 °C, 71% weight loss, 0% mass remaining at 500 °C.

5: 75% yield, M_n(DMF SEC) = 13 700 g/mol, $Đ$(DMF SEC) = 1.27, T_g(midpoint) = 220 °C, TGA in Ar: 339−370 °C, 70% weight loss, 5% mass remaining at 500 °C.

Synthesis of Poly(methyl 2,3-O-carbonyl-α-D-glucopyranoside) (PMGC). Aqueous trifluoroacetic acid (200 μL, 88% v/v) was added to a solution of **3** (410.1 mg, 0.038 mmol) in DCM (5.0 mL); the reaction was stirred at RT for 16 h. The reaction mixture was then precipitated three times into cold ether to give **9** as a white powder. FTIR (ATR): 3600−3200, 3050−2850, 1763, 1450, 1281, 1234, 1161, 1038, 980, 910, 779 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 5.66−5.34 (br), 5.05−4.84 (br), 4.76−4.63 (br), 4.56−4.40 (br), 3.71−3.59 (br), 3.57−3.31 (br) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.8, 96.7−94.8, 77.9−75.3, 75.2−73.2, 73.0−71.8, 68.2−67.1, 60.6−59.4, 55.4−53.9 ppm.

8: 88% yield, M_n(DMF SEC) = 9600 g/mol, $Đ$(DMF SEC) = 1.34, T_g(midpoint) = 132 °C, TGA in Ar: 279−299 °C, 58% weight loss, 6% mass remaining at 500 °C.

9: 90% yield, M_n(DMF SEC) = 12 600 g/mol, $Đ$(DMF SEC) = 1.26, T_g(midpoint) = 148 °C, TGA in Ar: 248−277 °C, 57% weight loss, 17% mass remaining at 500 °C.

10: 78% yield, M_n(DMF SEC) = 16 400 g/mol, $Đ$(DMF SEC) = 1.23, T_g(midpoint) = 158 °C, TGA in Ar: 233−260 °C, 43% weight loss, 25% mass remaining at 500 °C.

Synthesis of Poly(methyl 4,6-di-O-acetyl-2,3-O-carbonyl-α-D-glucopyranoside) ($PMAc_2GC$). Acetic anhydride (69.0 μL, 0.730 mmol) was added to a mixture of DCM (1.0 mL) and PMGC (41.3 mg, 0.188 mmol with respect to monomeric repeat unit). After stirring for 10 min DMAP (91.8 mg, 0.751 mmol) was added, and the reaction was stirred at RT until all of the solids had dissolved. The reaction mixture was quenched and purified by precipitation into cold methanol from DCM (three times) to give **12** as a white powder. FTIR (ATR): 3030−2820, 1744, 1445, 1368, 1287, 1223, 1169, 1132, 1034, 976, 924, 773, 602 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 5.15−4.87 (br), 4.87−4.61 (br), 4.24−3.97 (br), 3.97−3.78 (br), 3.43−3.32 (br), 2.17−1.85 (br) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.8−169.1, 154.9−153.1, 97.1−95.0, 76.9−73.5, 68.4−65.9, 62.7−61.5, 55.9−54.6, 21.1−19.8 ppm.

11: 41% yield, M_n(DMF SEC) = 16 000 g/mol, $Đ$(DMF SEC) = 1.15 T_g(midpoint) = 140 °C, TGA in Ar: 264−330 °C, 74% weight loss, 5% mass remaining at 500 °C.

12: 56% yield, M_n(DMF SEC) = 17 400 g/mol, $Đ$(DMF SEC) = 1.16, T_g(midpoint) = 149 °C, TGA in Ar: 246−327 °C, 78% weight loss, 4% mass remaining at 500 °C.

13: 59% yield, M_n(DMF SEC) = 20 700 g/mol, $Đ$(DMF SEC) = 1.19, T_g(midpoint) = 156 °C, TGA in Ar: 290−327 °C, 70% weight loss, 4% mass remaining at 500 °C.

Production of Bulk Polymer Samples. Pellets were produced using a high-pressure hydraulic press heated to 120 °C. Between 13 and 18 mg of polymer was heated in a homemade mold for 15 min under 1/2 ton of pressure, giving cylindrical pellets with a diameter of 4 mm and a height of 2 mm.

Aqueous Degradation Studies. Preweighed pellets of PMBGC were individually submerged in 4 mL of phosphate-buffered saline (PBS, pH = 7), 1 M HCl (pH = 1), or 1 M NaOH (pH = 14) and placed in a heated shaker at 37 °C and 60 rpm. At designated time points, samples were removed from the shaker, and the aqueous solution was withdrawn using a syringe. The pellets were taken from their vials, any large droplets of aqueous solution were blotted with a kimwipe, and a "wet" pellet weight was measured. The pellets were then dried under vacuum at 40 °C for 7−8 h, and their weight was recorded as a "dry" weight. Fresh PBS, HCl(aq), or NaOH(aq) solution was then added to the pellets, and the samples were returned to the shaker. Swelling was measured by comparing the wet vs dry pellet weights, and the mass remaining was measured by comparing the dry pellet weight to the original dry pellet weight (eqs S1 and S2 of the Supporting Information).

NMR Degradation Studies. Pristine samples of PMBGC and PMGC were added to NMR tubes, and 1 M NaOD or 1 M DCl was added; the samples were stored in a heated shaker at 37 °C and 60 rpm. At designated time points, the samples were removed from the shaker and analyzed by ^1H NMR spectroscopy.

RESULTS AND DISCUSSION

On the basis of our interest in the production of well-defined poly(glucose carbonate)s,[11,12,17,26] and reported ROPs of five-membered cyclic carbonates,[9,13,14,31,38−40] we investigated the polymerization of a five-membered cyclic carbonate of glucose under a range of organocatalytic conditions, the post-polymerization modification of the polymers produced, and their thermophysical and degradation properties.

Monomer Synthesis. The methyl 4,6-*O*-benzylidene-2,3-*O*-carbonyl-α-D-glucopyranoside (MBGC) monomer may be synthesized from the commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside by establishment of a five-membered cyclic carbonate through the hydroxyl groups at

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positions 2 and 3. This carbonylation reaction has been reported to proceed by using excess (30 equiv) ethyl chloroformate[42] or 2 equiv of phosgene.[43] To overcome the safety hazards associated with gaseous phosgene, we chose to employ equivalent phosgene, generated *in situ* from triphosgene, as the carbonylation agent. Several other carbonylation agents were tested, and none was able to produce the cyclic product in an acceptable isolated yield (Table S1 and Scheme S1). Although, the use of triphosgene requires additional safety precautions, as it degrades into phosgene, the nearly quantitative yield and ease of purification made this route our favored method of synthesis. All relevant NMR and IR spectra for the monomer and polymers can be found in Figures S1, S2, and S9−S24.

Organocatalytic Scope of Polymerization and Kinetic Study. Literature precedent suggested the five-membered cyclic carbonate would require highly active catalyst regimes.[9,35,37,40] Consequently, the polymerization of MBGC (initiator:monomer, 1:50) was initially tested using a range of organocatalysts among the most active organobase catalysts (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a mixture of DBU and *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*′-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]thiourea (TU), a mixture of DBU and TBD, or TBD).[24,25] Surprisingly, all the conditions tested were able to polymerize MBGC with reasonable molecular weights (2.9−5.8 kDa, as measured by $CHCl_3$ SEC), narrow molecular weight distributions (*Đ*, 1.19−1.29), and good yields (63−78%, Table 1 and Figure S3). The *trans*-fused bicyclic configuration of the cyclic carbonate generates strain energy and was likely responsible for the feasibility of the ROPs. As expected, higher catalyst loadings (4 mol % vs 2 mol %) gave slightly higher molecular weights over the same reaction time, as did more active catalyst regimes (TBD vs. DBU). The highest M_ns and lowest *Đ* were achieved with TBD as the catalyst. The molecular weights and *Đ* were initially measured via SEC with $CHCl_3$ eluent (this was necessary to ensure separation between the SEC signals for the eluent injection and the lowest molecular weight polymers). While the M_ns determined by this SEC were lower than anticipated, the trend in MW is valid, indicating that TBD produced the largest polymers at the 5 h time point, relative to the other organobase catalyst systems. Therefore, the kinetics of the polymerization were studied using TBD.

Table 1. Effect of Organocatalyst System on the ROP of MBGC, Each Measured at a Time Point of 5 h[a]

catalyst	catalyst loading (mol %)	M_n[b] (kDa)	*Đ*[b]	yield[c] (%)
DBU	2	3.8	1.23	63
	4	5.0	1.25	70
DBU/TU	2	2.9	1.24	63
	4	3.1	1.23	78
TBD/DBU	2	4.8	1.29	74
	4	5.7	1.20	68
TBD	2	4.5	1.20	78
	4	5.8	1.19	65

[a]$[MBGC]_0$ = 0.50 M, MBGC:MBA = 50:1, 30 °C, 5 h, in DCM. [b]Measured with SEC ($CHCl_3$ eluent) calibrated with polystyrene standards. [c]After three precipitations into methanol, no monomer detected by SEC.

The kinetics of the ring-opening of MBGC were studied using 4-methylbenzyl alcohol (MBA) as an initiator (initiator:monomer, 1:50), and TBD as a catalyst (2 mol % to MBGC, Figure S4 and Table S2). The monomer conversion was monitored by SEC using an internal standard because significant overlap between monomer and polymer proton resonance frequencies was responsible for inaccurate conversion values by ^1H NMR. Naphthalene was chosen as an internal standard because of its compatibility with the reaction conditions and its unique signal in the SEC from monomer and oligomers. The polymerization had reached 50% conversion after 90 min and full conversion after 180 min. The SEC traces revealed monomodal signals during the polymerization, which progressed to lower elution times as the monomer was consumed. The polymer molecular weight grew linearly with the conversion of monomer, while maintaining relatively low *Đ*. As expected, a kinetic plot of $\ln\frac{[M]_0}{[M]}$ versus time confirmed the controlled nature of the polymerization and indicated the polymerization was pseudo-first-order with respect to the monomer (Figure 1). Comparing these data to the polymerizations described by our group of six-membered glucose carbonate monomers, the polymerization overall required significantly longer time to reach full conversion, supporting the lower reactivity of the five-membered glucose carbonate monomer.[11] As with the investigation of the organocatalytic scope, the molecular weight values determined are lower than expected; however, use of the SEC with $CHCl_3$ eluent was necessary as it was the only instrument accessible that provided separation between the retention volumes for the monomer, internal standard, and the growing polymer chain, without overlap with the eluent injection negative peak. The conversion values were determined independently and are not subject to potential errors from the artificially reduced MWs determined; therefore, the trends determined from these data are valid (Figure 1). Absolute molecular weight determination was attempted using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS, Figure 2); however, the data were not accurate because of the relatively high *Đ*s and the resulting non-Gaussian distributions observed in the MALDI-TOF spectra for several of the samples.

Polymer Synthesis and Post-Polymerization Modification. A series of PMBGCs with different degrees of polymerization were synthesized using MBA as initiator and TBD as catalyst (Table 2). The breadth of PMBGC molecular weights was then used to investigate the effect of the degree of polymerization on the thermophysical properties. Three of the PMBGC syntheses were conducted on a gram scale to allow for post-polymerization modification reactions and further investigations (Figure S25). For these large-scale reactions, each polymer was obtained in good yield (>75%), with *Đ* < 1.36 (**2**, **3**, and **5**).

Analysis of the PMBGC samples by MALDI-TOF MS provided further insight into the mechanism of the polymerization. The mass spectra of the PMBGC samples exhibited narrow polymer distributions with the expected monoisotopic repeating unit of 308.10 Da (RU_{theor} = 308.09),[44] confirming CO_2 was not eliminated during the polymerization, and the benzylidene protecting groups were retained throughout the polymerization and acidic work-up (Figure 2). Further examination of the data (Figure S5) revealed the presence of multiple distributions, each with a 308.1 Da repeat unit, resulting from different initiating and terminating events (Scheme 1, Schemes S2 and S3). The major distribution corresponded to the expected polymer species, with MBA as

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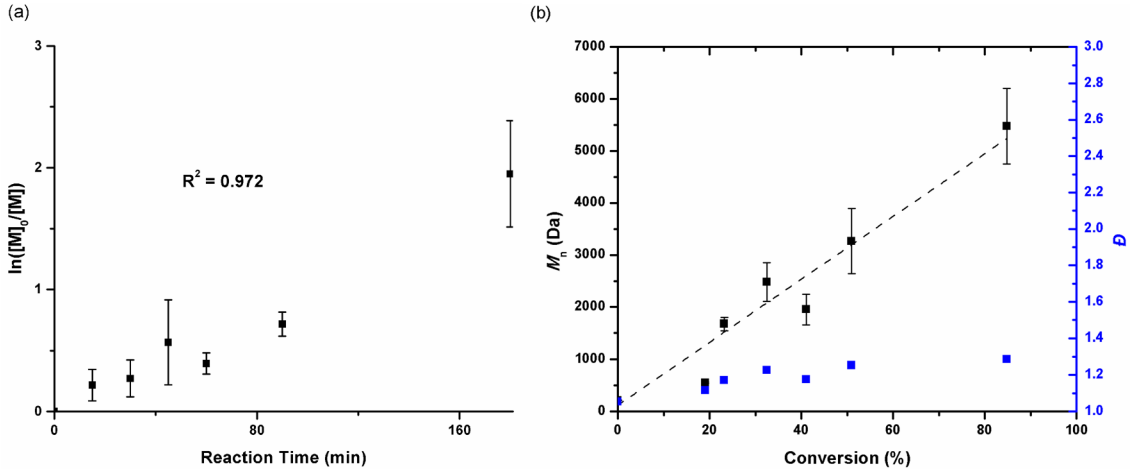

Figure 1. (a) Kinetic plot of $\ln\frac{[M]_0}{[M]}$ vs reaction time. (b) M_n (left axis, black) and $Đ$ (right axis, blue) vs monomer conversion of MBGC using TBD (catalyst), MBA (initiator), and naphthalene (internal standard). Data for both plots were obtained using SEC (UV detector, $CHCl_3$ eluent), $n = 3$.

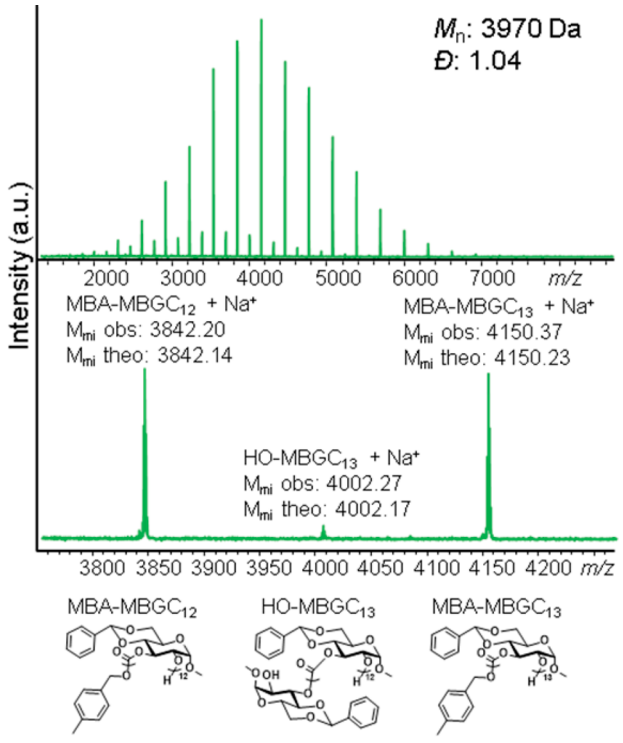

Figure 2. Entire MALDI-TOF mass spectrum of PMBGC (above) and expanded inset (below) showing the monoisotopic masses (M_{mi}) observed for PMBGC with the proposed chemical structures of each individual species identified.

the initiating end group and a free hydroxyl on either the 2- or 3-position of the glucopyranoside as the terminating functionality. The second series of signals was consistent with PMBGC polymers with water as the initiating group and an alcohol terminating group, resulting in a −147.9 Da mass shift with respect to the main distribution. Unlike the polymers initiated from MBA, this product undergoes a single decarboxylation to yield a free hydroxyl group on the initiating end (Scheme S2). This peak series represents ∼10% of the total peak area relative to that of the main distribution. While these MALDI-TOF MS data cannot be considered as accurate for quantification purposes, they do qualitatively suggest this species is a minor component. There are no ^{1}H NMR signals unique to this initiating species that would allow for a more accurate quantitation of this species. Finally, in some samples, a third series of signals was identified that was consistent with the MBA initiation, but termination with a methyl carbonate end group rather than the expected 2- or 3-free hydroxyl group. This distribution exhibited a +58.0 Da shift with respect to the main distribution and is proposed to have originated from a competing termination during the methanolic purification, wherein the TBD present would allow methanol to react with the carbonate backbone (Scheme 1 and Scheme S3). This side reaction is similar to the previously reported intentional organocatalytic depolymerizations in the presence of alcohols.[33,45−47] The use of dendritic calibrants in the mass range of interest enable sufficient mass accuracy (generally ±0.1 Da) to make these assignments with confidence.[48] Further confirmation of these proposed mass spectral assignments was gained by analyzing an alternative initiation with 4-*tert*-butylbenzyl alcohol (tBBA, Figure S5c,d). As expected, analogous series to the first and third distributions described in the MBA initiated polymers were observed, but shifted +42.0 Da, corresponding to the mass increase for the tBBA initiator. The distribution which was identified in the MBA initiated polymerization as the water initiated series, on the other hand, showed no shift in molecular weight, confirming that this species originated from adventitious initiation with water.

The presence of competing termination chemistry during the purification with methanol led to the investigation of alternative work-up procedures, and the products of these alternative protocols were subsequently analyzed by MALDI-TOF MS. The substitution of a non-nucleophilic solvent, diethyl ether, for methanol in the purification did cause the disappearance of the methyl carbonate chain ends; however, a new polymer species was identified as the major distribution with a −5.0 Da mass shift relative to the main polymer distribution observed as a result of the methanolic purification (Figure S6). A cation competition study, comparing the mass spectra of samples prepared with added lithium, sodium, and potassium salts, was explored to confirm the ionizing species for this distribution. During this study, regardless of the added cation, there was no shift in the distribution. It was therefore verified that the polymer species included a preionized cationic end group, which was determined to be the TBD cation (Figure S6). This

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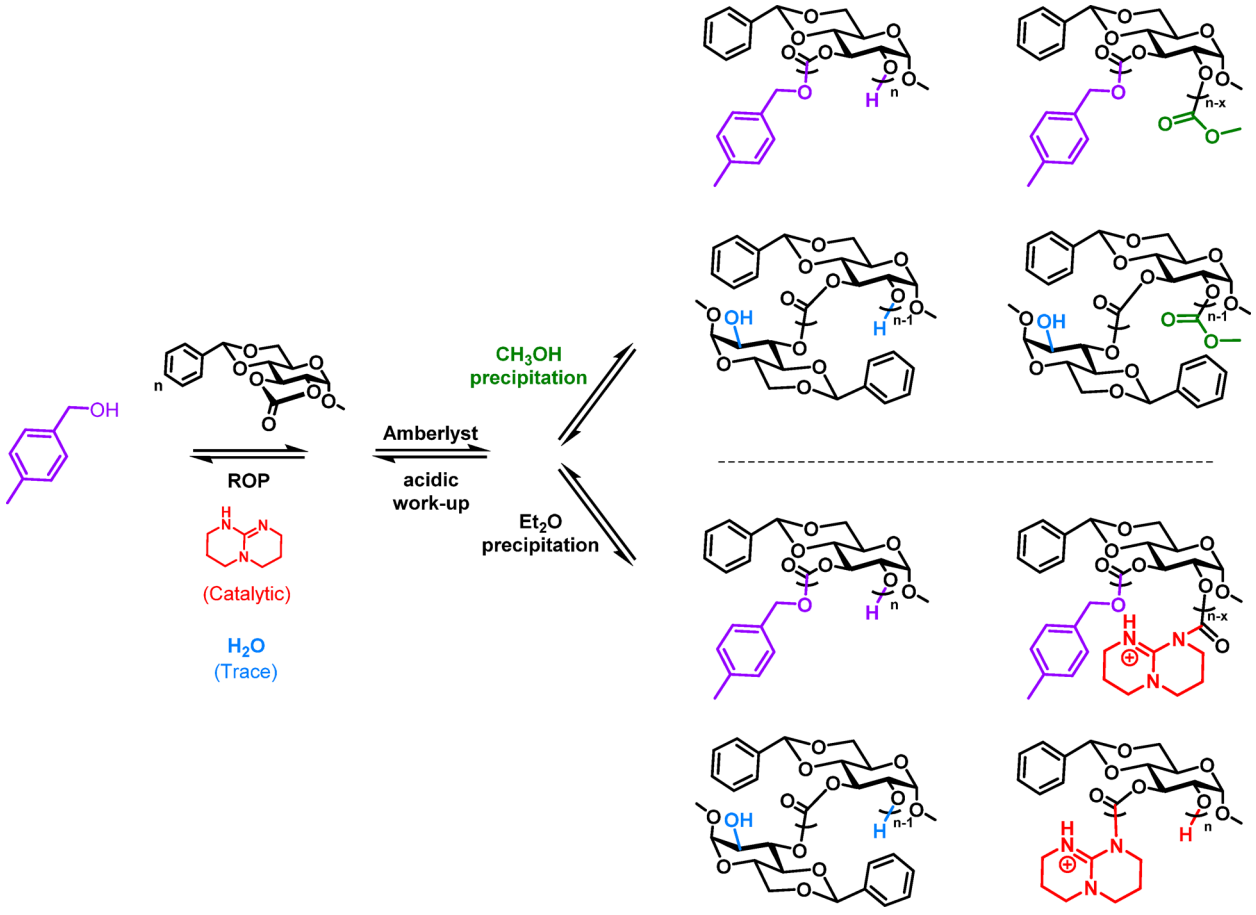
Table 2. Properties of PMBGC, PMGC, and $PMAc_2GC$

polymer	sample	M:I[a]	M_n[b] (kDa)	M_n[c] (kDa)	$Đ$[c]	T_d[d] onset (°C)	T_g[e] midpoint (°C)	water contact angle[f] (deg)
PMBGC	**1**	20	4.1	6.4	1.22		87	
	2	25	7.8	8.6	1.32	296	104	108 ± 13
	3	40	9.7	11.5	1.36	307	134	116 ± 7
	4	50	10.3	12.4	1.28		172	
	5	55	12.5	13.7	1.27	339	220	128 ± 9
	6	100	18.6	16.8	1.38	347	232	
	7	200		18.2	1.41	346	233	
PMGC	**8**			9.6	1.34	279	132	38 ± 3
	9			12.6	1.26	247	148	58 ± 10
	10			16.4	1.23	233	158	40 ± 8
$PMAc_2GC$	**11**			16.0	1.15	264	140	110 ± 4
	12			17.4	1.16	247	149	103 ± 11
	13			20.7	1.19	290	156	94 ± 5

[a]MBGC:MBA. [b]Measured by NMR comparing the aromatic signals of the polymer to the methyl signal of the initiator. [c]Measured with SEC (DMF eluent) calibrated with polystyrene standards. [d]Measured by TGA. [e]Measured by DSC. [f]Measured with a droplet of water, average of 4 droplets with measurements taken over 10 s. Polymers **8**, **9**, and **10** were synthesized from **2**, **3**, and **5** respectively, and **11**, **12**, and **13** were synthesized from **8**, **9**, and **10**, respectively.

Scheme 1. Synthesis and Purification via Precipitation of PMBGC with MBA as Intended Initiator and TBD Catalyst[a]



[a]Polymer structures shown are all supported by MALDI-TOF MS (Figures S5–S7) and are colored to match the initiating or terminating species (MBA = purple, water impurity = blue, TBD = red, methanol = green).

study showed two polymer populations: one with initiation by the TBD catalyst during the polymerization and a second with both a MBA chain end and a TBD cation chain end (Scheme 1). There was no presence of the expected MBA-initiated hydroxyl-terminated polymer by MALDI-TOF MS; however, ^{1}H NMR spectroscopy showed the expected signal of the MBA initiator. This observation may result from the amplification of mass spectral signals from the TBD-functionalized chains, owing to their inherent cationic nature and therefore increased ionization efficiency. To probe this inconsistency, an additional precipitation into methanol was performed after the ether precipitation (Figure S7). This final methanol precipitation

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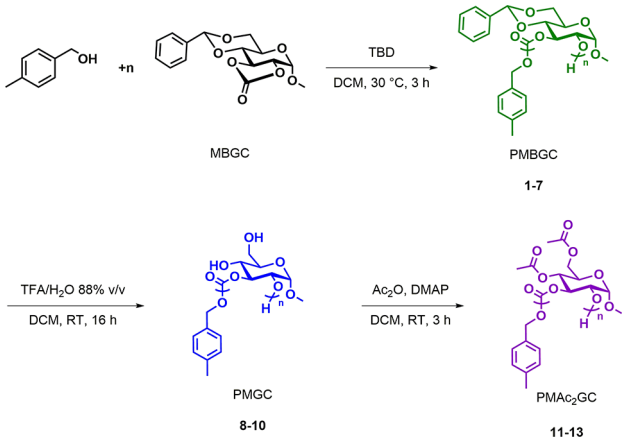
caused the MS signals of the TBD chain end populations to disappear, as the TBD cation is an excellent leaving group and would be removed upon exposure to nucleophilic methanol. The resultant PMBGC samples exhibited only two distributions in their mass spectra, the expected MBA initiated product, and a minor water-initiated distribution (Figure 2).

The benzylidene protecting group on MBGC was chosen specifically for its ease of removal in acidic conditions to produce free hydroxyl groups, allowing for a switching of the polymer chain character, from hydrophobic to hydrophilic, through a straightforward post-polymerization modification. The PMBGCs that were synthesized on a gram scale were therefore deprotected to generate polyhydroxyl polymers (**8**, **9**, and **10**, synthesized from **2**, **3**, and **5**, respectively; Scheme 2).

Scheme 2. Synthesis and Postpolymerization Modification of Poly(methyl 4,6-*O*-benzylidene-2,3-*O*-carbonyl-*α*-D-glucopyranoside)s (PMBGC)[a]



[a]Although preliminary data suggest that the polymerization is not regioregular (Figures S11–S19), only one repeat unit connectivity is shown for simplicity.

The deprotection was achieved under acidic conditions (trifluoroacetic acid/water in DCM). The completion of these reactions (>78% yield) was confirmed through the disappearance of ^{1}H and ^{13}C NMR signals corresponding to the benzylidene group (Figures S9, S10, S20, and S21) as well as the appearance of an IR signal at 3600–3200 cm^{-1} corresponding to the O–H stretch (Figure S24). Upon deprotection, the M_n of the precipitated polymer sample, measured by SEC (DMF), was larger than the protected precursor polymer (Table 2). Examination of the reaction supernatant suggested transcarbonation reactions between the deprotected hydroxyl groups and the carbonate units in the backbones may have contributed to the larger than expected M_n. Intra- and intermolecular transcarbonation reactions could explain the observation of cleaved chains appearing at longer retention times in the SEC of the reaction supernatant (Figure S25d) and could also produce the observed longer polymeric chains by intermolecular transcarbonations (Scheme S4). Alternatively, the shorter retention times for the deprotected polymer precipitant could also be attributed to a more flexible monocyclic repeat unit of PMGC vs the bicyclic repeats of PMBGC, with the PMGC being better solvated by DMF than were the PMBGC precursors, giving them larger hydrodynamic volumes, even at comparable degrees of polymerization. Examination of the ^{1}H NMR spectra of **3** and **8** also supports transcarbonation reactions occurring during the deprotection. In sample **3**, the DP value is calculated to be 30, whereas in sample **8**, the DP value calculated is 70, suggesting that not every polymer chain retained its initiator. The deprotected polymers were further analyzed by MALDI-TOF MS to probe the completeness of the deprotection as well as the presence of polymer species caused by transcarbonation (Figure S8). Although the protected PMBGC precursors exhibited a relatively narrow molecular weight distribution in their mass spectra, the PMGC product signal patterns were consistent with an increased dispersity, further supporting transcarbonation occurred under the acidic reaction conditions. Meaningful average molecular weight and dispersity data could not be gained from these samples; however, analyses of the distributions did give information about the repeat unit and end group structure. For example, at least four different distributions were observed in these samples, but all exhibited a 220.1 Da spacing, consistent with complete removal of the benzylidene protecting groups on each repeat unit. Furthermore, end group analysis confirmed the two major distributions corresponded to water initiated polymer chains with a hydroxyl end group and water initiated chains with a methyl carbonate end, from the PMBGC precursor. The expected product, the MBA-initiated polymer with a hydroxyl end group, was also observed, though the signals were less intense. The fact that the MBA distribution appeared to have been significantly attenuated relative to the protected starting material provides further evidence of transcarbonation reactions during the benzylidene removal. Finally, a fourth distribution is observed which is consistent with cyclic polymers having no end groups. Again, this observation is consistent with transcarbonation occurring during the deprotection reaction.

Further reaction of the hydroxyl side chains was also conducted to probe the SEC behaviors without the significant solubility difference. The PMGCs were functionalized with acetic anhydride to facilitate SEC characterization, confirming the apparent higher degree of polymerization after the deprotection reaction, and demonstrating the reactivity of the resulting hydroxyl groups (**11**, **12**, and **13** synthesized from **8**, **9**, and **10**, respectively). Additionally, this functionalization would allow for differentiation between the changes in the thermophysical properties of the polymers caused by the presentation of hydroxyl groups and those caused by the transcarbonation that may have occurred during the benzylidene removal. The success of the acetylation was confirmed through the disappearance of the OH stretch in the IR spectrum, the appearance of the methyl signals in both the ^{1}H (2.17–1.85 ppm) and ^{13}C (21.1–19.8 ppm) NMR spectra, and the appearance of the ^{13}C signal of the ester carbonyls (Figures S22 and S23). As expected, the SEC (DMF) traces for the PMAc$_2$GCs shifted to shorter elution times than their PMGC and PMBGC precursors.

Thermal and Physical Properties of the PMBGCs, PMGCs, and PMAc$_2$GCs. The thermal and physical properties were examined by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and contact angle measurements (Table 2). The analyses performed on the polymers highlighted the correlation between the repeat unit structure and thermal properties. For the protected polymers, PMBGCs and PMAc$_2$GCs, higher numbers of repeat units resulted in higher thermal decomposition temperatures (T_d, Figure S26); between the smallest polymer and the largest (8.6 to 18.2 kDa, as measured by SEC, DMF eluent), the T_d rose ca. 50 °C. The

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deprotected materials (PMGC), however, demonstrated the opposite trend: as the molecular weight increased, a ca. 50 °C decrease was observed in the T_d. We do not have an explanation for the observed dependence of T_d on molecular weight. However, contributions of the hydroxyls to these changes in T_d are supported by the general increase in T_d with molecular weight upon capping of those hydroxyl groups by two different protecting groups, as seen in the $PMAc_2GC$ and PMBGC series of polymers.

The polymers were then examined by DSC to determine their glass transition temperatures (T_gs). Inconsistencies in the T_g values determined from the polymers led us to the hypothesis that water was being absorbed by the polymer samples and having an effect on the glass transition. The effect of water on the polymers was confirmed by monitoring the changes in T_g for two polymer samples (**5** and **10**) as a function of added water (0, 5, and 10 wt %, Figures S31 and S32, Table S3). Therefore, because of the changes in T_g caused by water, all samples were dried under reduced pressure with mild heating prior to analysis by DSC. As expected, the T_gs of all the dried samples of polymers increased with the molecular weight. The observed changes in T_g with increasing MW were most pronounced in the PMBGC polymers with a ca. 150 °C change vs a change of 15−30 °C in the PMGCs and $PMAc_2GC$s (Figures S27, S29, and S30). This significant change in T_g for the PMBGC series over the 3-fold range of M_n, from below to above an expected entanglement molecular weight, is in accordance with the classical dependence of T_g on M_n of linear homopolymers, with an apparent $(T_g)_\infty$ of ca. 230 °C (Figure S28). In contrast, the PMGCs and $PMAc_2GC$s were each of higher and narrower ranges of molecular weights. The relatively high T_gs in the PMBGC series are likely due to the rigidity of the bicyclic backbone repeat unit. Upon deprotection, the changes in the T_gs are presumably caused by the removal of the benzylidene acetal to give a monocyclic repeat unit, rather than the transesterification that occurred during the deprotection. This hypothesis is supported by the similar T_g values observed in both PMGC and $PMAc_2GC$ (Figures S29 and S30).

Water contact angles, as expected, revealed significant differences in the wettabilities (Figure 3, Figure S33, and Table 2). The benzylidenated and acetylated polymers were hydrophobic (contact angles between 94° and 128°) while PMGC was hydrophilic (38°−58°). PMGC is, in fact, moderately water-soluble. This observation did not affect the contact angle measurements, as several hours were required for PMGC to dissolve in buffer or water, and intact films were observed after the measurement. In addition, the polymer length had little to no effect on the polymer hydrophilicity.

PMBGC Bulk Degradation and Identification of the Degradation Products. The bulk degradation of **2**, **3**, and **5** as polymer pellets was investigated under acidic, basic, and neutral aqueous conditions. When the polymer was exposed to physiological conditions (PBS, pH = 7, 37 °C), no significant bulk degradation or pellet swelling was observed over several months (Figures S35 and S36). More rigorous aqueous conditions (1 M HCl or 1 M NaOH) were then used to examine the bulk hydrolytic degradation, revealing differing degradation kinetics and profiles (Figure S34). Under acidic conditions, an incubation period was observed, between 0 and 40 days, where no significant degradation (≥90% mass remaining) or swelling occurred (≤5%). This initial period was followed by a rapid loss of pellet weight, increased swelling as the pellet degraded, and complete degradation within 4 months total for all samples. However, under basic conditions, no incubation period was observed; instead, a gradual weight loss occurred, with 0−10% of the pellet weight being lost in 2 days, followed by 10−20% in the first week, and complete degradation in 9 months. These differing degradation profiles and kinetics suggested that acidic and basic conditions proceeded via different degradation mechanisms, which was further investigated by NMR spectroscopy.

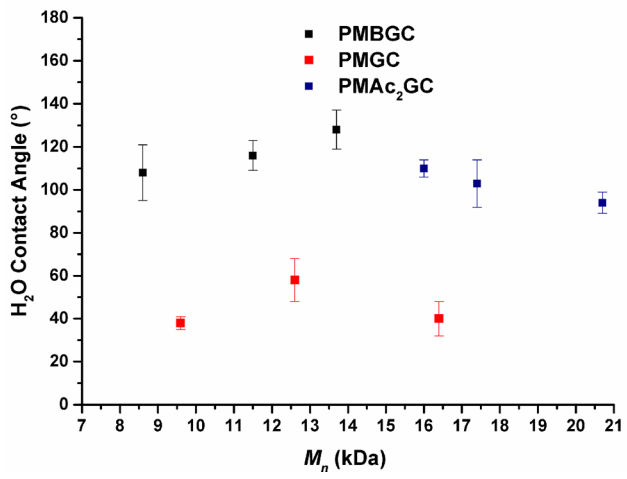

Figure 3. Static water contact angle vs M_n of the PMBGC (black), PMGC (red), and $PMAc_2GC$ (blue), where each sample was analyzed using four 5 μL drops of nanopure water and 20 images were collected per drop. M_n values were measured by SEC (DMF eluent) calibrated with polystyrene standards.

^{1}H NMR spectroscopy was used to identify the degradation products and, thereby, the likely degradation mechanisms, for PMBGC and PMGC. Pristine polymer samples were added to either 1 M DCl or 1 M NaOD in D_2O, and the portions of the materials that underwent dissolution into the aqueous solutions were, subsequently, examined over time. In basic solutions, both PMBGC and PMGC degraded into their monomeric repeat units, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl α-D-glucopyranoside, respectively (Figure 4, Figures S40 and S41). PMBGC showed sharp signals matching in chemical shift and integration with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside within 7 days, with solid remaining in the NMR tube, whereas PMGC degraded even more rapidly, undergoing full dissolution with the appearance of sharp ^{1}H resonance signals corresponding to methyl α-D-glucopyranoside within 1 day. However, in acidic conditions (Figure 4, Figures S37 and S38), no significant degradation of the polymer backbone appeared to occur over 30 weeks. The PMBGC sample released the benzylidene protecting group after 40 days. The presence of benzaldehyde was confirmed by the aldehyde ^{1}H resonance frequency at 9.89 ppm and the aromatic signals at 7.93, 7.72, and 7.60 ppm. After removal of the benzylidene, the resulting PMGC was soluble in the acidic aqueous solution; however, it did not appear to degrade further into methyl α-D-glucopyranoside (Figure S39), as no sharp signals appeared in the ^{1}H NMR spectrum consistent with saccharide chemical shifts (4.5−3.0 ppm).

Applying this knowledge of the degradation products to the bulk degradation of PMBGC, the incubation period in 1 M HCl is likely the acidic solution removing the benzylidene acetal, supported by a strong scent of almond in the degradation solution, and the pellet lost weight as the polymer

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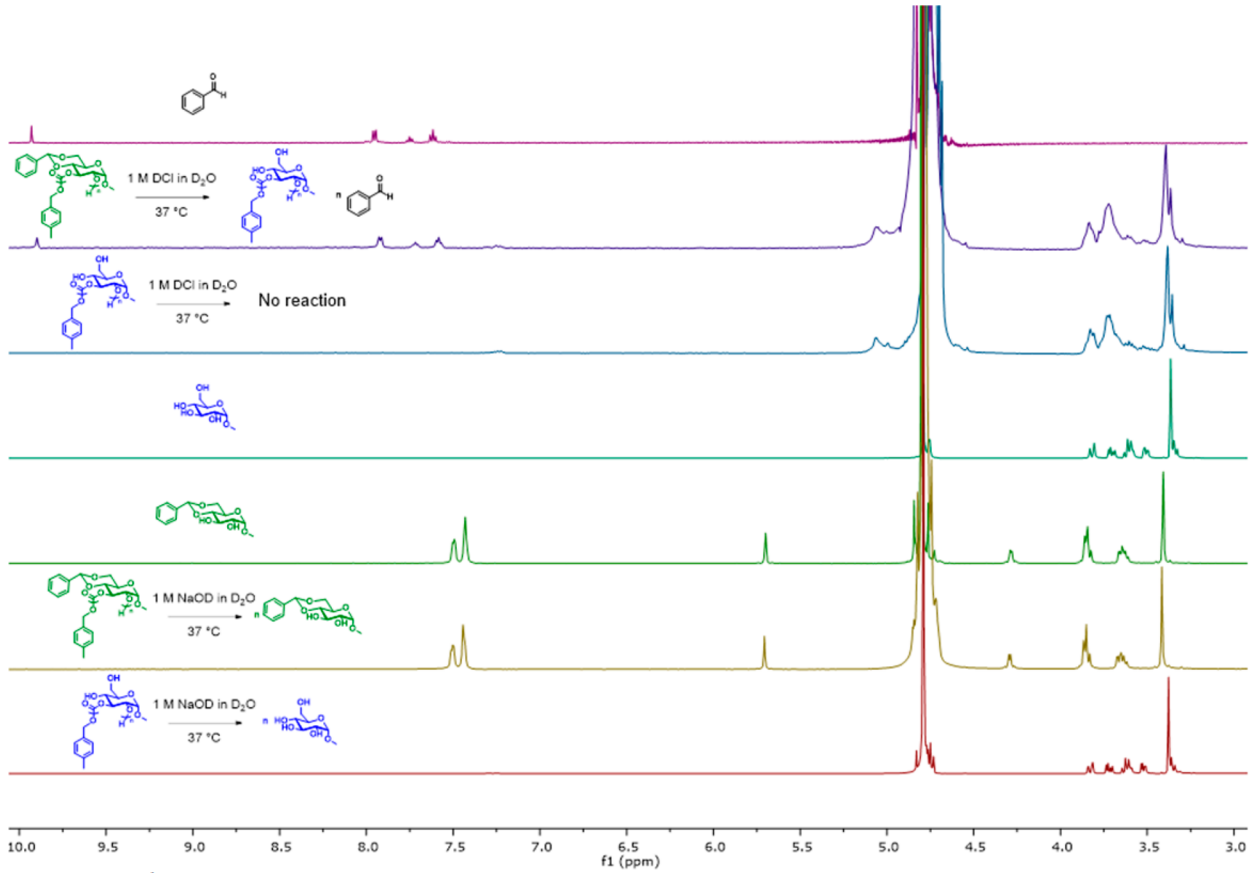

Figure 4. ^{1}H NMR spectra of PMBGC and PMGC, each collected as the latest time point from acidic (1 M DCl/D_2O) and basic (1 M NaOD/D_2O) degradation experiments (Figures S37−S41), and the identified small molecule degradation products. The reactions shown with each spectrum indicates the polymeric sample, reaction conditions, and degradation products.

became water-soluble as more hydroxyl groups were released. In 1 M NaOH, the carbonate backbone itself was cleaved and the small molecule diol was released, causing the pellet to lose weight. Taken together, these experiments support the hypothesis that the difference in kinetics observed in the bulk degradation is caused by a difference in degradation mechanisms occurring under acidic and basic conditions.

CONCLUSIONS

Our interest in functional polymer materials that lead to biologically benign byproducts upon degradation, whether or not they are meant to degrade, has guided us toward the development of synthetic methodologies that utilize carbohydrates as diverse building blocks. In this current work, we have expanded the scope of glucose as a monomer to generate a series of polymers having varied properties, which coincidentally advances ROP to simple conditions for five-membered cyclic carbonates that are accessible across laboratories. The five-membered cyclic carbonate monomer, methyl 4,6-*O*-benzylidene-2,3-*O*-carbonyl-α-D-glucopyranoside, was synthesized in high yields (99%) through well-established carbonylation techniques. The investigation of this monomer under various organocatalytic conditions revealed the high potential of this *trans*-fused bicyclic monomer to undergo controlled, pseudo-first-order ROP. The optimized polymerization conditions using TBD as the organocatalyst were applied toward the preparation of different molecular weights of the protected polymer, PMBGC, which were then deprotected under acidic conditions to give polyhydroxyl polymers (PMGCs). These deprotected polymers were then functionalized with acetyl groups to yield $PMAc_2GCs$. MALDI-TOF MS analysis gave significant insight into the chemistries of the polymerization and post-polymerization modification. For the synthesis of PMBGC, mass spectral analysis revealed the inclusion of the entire monomeric repeat unit during the polymerization with no elimination of CO_2 as well as an undesired transcarbonation reaction that occurred during purification with methanol. This better understanding of the polymerization chemistry allowed for the improvement of experimental procedures in future studies. Additionally, during the deprotection to generate PMGC, unexpected changes in the molecular weights were shown to be caused in part by transcarbonation during the acid-catalyzed reaction.

The effects of the polymer length and protecting group presence on the thermophysical properties were investigated. As expected, a significant change in the water contact angle was observed between the protected polymers (hydrophobic material) vs the deprotected polymer (hydrophilic material). The polymer length had a direct effect on the T_d; the benzylidenated and acetylated polymers had higher T_ds as the polymer length increased while the deprotected polymers had a decrease in the T_d with increasing molecular weight. The T_g of the benzylidenated materials rose as the polymer length increased, while for the deprotected and acetylated polymers, no significant changes were observed in the T_g with varying the molecular weight over a narrower range.

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Consequently, these natural product-derived versatile materials give access to a wide range of thermophysical properties through a robust polymerization technique and simple post-polymerization modifications. The potential optimization of the desired polymer properties to a specific target application makes these materials suitable for biomedical and engineering applications, such as orthopedic devices or drug delivery vehicles. Moreover, the ability of the polymers to degrade hydrolytically into methyl α-D-glucopyranoside and carbon dioxide, as benign small molecules, with the additional degradation product of benzaldehyde or acetic acid in the protected forms, creates possibilities in applications using engineering polymers, in general. The mechanical properties of these polymers as well as their biological interactions are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.7b01785.

Additional synthetic and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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