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Hydrophobic, Hydrophilic, and Amphiphilic Polyglycocarbonates with Linear and Macrocyclic Architectures from Bicyclic Glycocarbonates Derived from CO_2 and Glucoside

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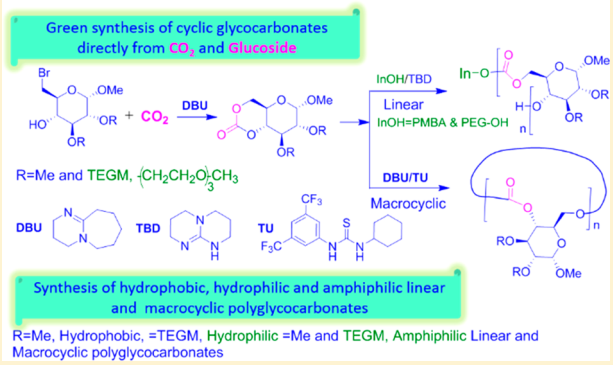
Supporting Information

ABSTRACT: Two bicyclic glycocarbonates were synthesized in five steps from α-methyl-D-glucoside without resorting to phosgene or to its derivatives for the first time. The 4- and 6-positions of glucose were modified to introduce a six-membered carbonate ring, using CO_2 as the carbonylating reagent; the 2- and 3-positions of the same glucoside substrate were first transformed into either methyl or triethylene glycol monomethyl ether groups to protect these positions from undesirable reactions and also to impart hydrophobicity in the first case and hydrophilicity in the second. The polymerization behavior of these bicyclic glycocarbonates was then investigated under different conditions. On the one hand, through ring-opening polymerization of the above monomers, linear polyglycocarbonate homopolymers and diblock copolymers were obtained initiated by *p*-methylbenzyl alcohol using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as catalyst; on the other hand, macrocyclic polyglycocarbonate homopolymers and diblock copolymers were grown using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) which served as zwitterionic initiator. The various architectures derived were all thoroughly characterized by NMR, GPC, and MALDI-tof and shown to exhibit the expected structure. Finally, the self-assembly of linear and macrocyclic amphiphilic copolyglycocarbonates in water was investigated and characterized by cryo-TEM.



INTRODUCTION

Glycopolymers are synthetic polymer scaffolds that carry dangling sugar moieties.[1−6] Such sugar-modified synthetic polymers find applications as clinical diagnostics, bioassays, affinity separation, etc.,[7,8] wherever different carbohydrates serving as multivalent ligands on the exterior of the membrane proteins and lipids can bring about biological activity through carbohydrate−protein interactions.[9,10] Polysaccharides are another family of polymers that also comprise sugars in their structure. In contrast to the glycopolymers, sugars in polysaccharides are part of the main chain and serve as repeating units or building blocks.[11−14] In natural polysaccharides that originate from different sources (plants, bacteria, and animals), sugars are bound one to another by glycosidic linkages.[15−19] But polysaccharides can also be synthetically produced, and besides glycosidic linkages other chemical functions have been contemplated to link sugars one to another.[20,21] Carbonates are one such linkage that have been used to generate polycarbonates featuring sugar moieties in the main chain.[22−28] Sugar-based polycarbonates are usually prepared through ring-opening polymerization (ROP) of either five- or six-membered, sugar-derived carbonate rings. For instance, Gross and collaborators[22,24] reported the synthesis of D-xylofuranose-based polycarbonates and its copolymers from the corresponding six-membered cyclic carbonate using for this purpose zinc or tin catalysts; Wooley and co-workers[27,28] described the synthesis of D-glucose-based six-membered cyclic carbonate that they successfully polymerized via an organocatalytic approach. Interestingly, the same sugar substrate, D-glucose, was modified by Endo and co-workers[25,26] into a five-membered cyclic carbonate that they anionically ring-opened under mild conditions to obtain well-defined D-glucose-based polycarbonates of different structure from that prepared by Wooley.[27,28] Polycondensation reactions involving sugar-based diols and phosgene were also tried as a means to generate sugar-containing linear polycarbonates.[18,23,29,30] Whether the monomers were meant for ROP or polycondensation all of the carbonylation reactions used so to date for the generation of carbonate functions in the above works involved either phosgene or its derivatives: ethyl chloroformates or bis(pentafluorophenyl)carbonate.[18,23−32]

The lack of studies on glucose-based polycarbonates or polyglycocarbonates and the limitations related to the use of phosgene and of its derivatives prompted us to explore new

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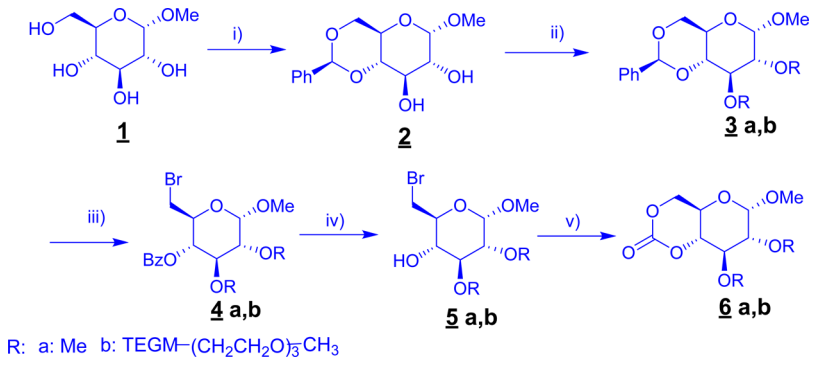
Scheme 1. General Scheme for the Synthesis of Six-Membered Bicyclic Glycocarbonate Monomers from α-Methyl D-Glucopyranoside[a]



[a]Reagents and conditions: (i) $PhCH(OMe)_2$, PTSA, DMF, 1 h (yield, 69%); (ii) DMF/NaH, CH_3I (**3a**)/TEGM-OTs (**3b**), 0 °C for 1 h and overnight at RT (yield, 72%); (iii) NBS, $CaCO_3$, CCl_4, 1 h (yield, 58%); (iv) 2% NaOH in MeOH, 2 h (yield, 60%); (v) CO_2 (10 bar), DBU, DMF, RT, 5 h for monomer **6a** (yield, 40%) and 22 h for monomer **6b** (yield, 40%).

Table 1. ROP of Hydrophobic and Hydrophilic Monomers 6a and 6b under Different Initiating Conditions

entry	polymer	initiator/Cat.	M	$[M]_0/[I]_0$	time (h)	conv[a] (%)	yield (%)	$M_{(theo)}$[b] (10^3 g/mol)	$M_{n(NMR)}$[c] (10^3 g/mol)	$M_{n(GPC)}$[d] (10^3 g/mol)
01	**LP_1-6a**	PMBA/TBD	**6a**	25	1	98	90	6.20	6.08	6.5/1.2
02	**LP_2-6a**	PMBA/DBU	**6a**	30	45	90	75	6.82	5.33	4.0/1.3
03	**LP-6b**	PMBA/TBD	**6b**	17	5	94	83	8.18	7.80	5.0/1.2
04	**CP-6a**	DBU	**6a**	30	45	91	65	6.78	ND[e]	5.0/1.2
05	**CP-6b**	DBU/TU	**6b**	12	60	90	60	6.14	ND[e]	3.8/1.2
06	**LP_3-6a**	PEG-OH/TBD	**6a**	20	1	99	80	9.91	9.00	8.6/1.2
07	**LP-6a-*b*-6b**	PMBA/TBD	**6a:6b**	18:9	11	>99 (**6a**), >92 (**6b**)	75	8.86	8.61	8.1/1.2
08	**CP-6a-*b*-6b**	DBU/TU	**6a:6b**	15:7	96	>99 (**6a**), >90 (**6b**)	75	6.90	ND[e]	4.0/1.2

[a]Aliquots of the reaction medium were analyzed by ^1H NMR to calculate the monomer conversion. [b]Expected molar mass deduced from monomer conversion (^1H NMR). [c]Molar mass was calculated from end-group analysis (^1H NMR) of the isolated polymer. [d]Calculated from GPC calibrated with narrow distributed polystyrene standard in THF as eluent (1 mL/min). [e]Not determined.

synthetic avenues. In this study, we demonstrate that CO_2 can be effectively resorted to for the carbonylation reaction of α-methyl-D-glucoside instead of toxic phosgene or its derivatives, opening up the access to two bicyclic six-membered carbonate monomers (Scheme 1)—the first hydrophobic and the second water-soluble. From these two monomers a wealth of well-defined polyglycocarbonate architectures could be obtained, including hydrophobic and hydrophilic homopolymers with either a linear or a macrocyclic structure as well as linear and macrocyclic amphiphilic diblock copolymers. The ring-opening polymerization of these glucoside-based bicyclic carbonates was triggered by an organocatalyst: the latter gave rise to macrocyclic architectures, and in the presence of an alcohol serving as initiator it brought about the formation of linear chains.

RESULTS AND DISCUSSION

Monomer Synthesis. There are only very few reports on the synthesis of polymers featuring sugar units in their main chain linked by carbonate groups. As previously indicated,[7,8] such polyglycocarbonates whether obtained either by polycondensation of sugar-based diols or by ring-opening polymerization of glycocarbonates required at one step of their synthesis the use of phosgene or its derivatives. In the course of this work Buchard and co-workers reported the synthesis of D-mannose-based six-membered glycocarbonate using CO_2 as carbonylation reagent.[33] Along the same line we show in this investigation (Scheme 1) that both hydrophobic (**6a**) and hydrophilic (**6b**) bicyclic glycocarbonates can be prepared from α-methyl-D-glucoside using CO_2 as carbonylation reagent. Both **6a** and **6b** monomers were synthesized in five steps starting from the commercially available α-methyl-D-glucoside: to the exception of step 2, all steps were carried out following the same experimental procedures for the two monomers. In step 1, the 4- and 6-dihydroxyl groups of α-methyl-D-glucoside were protected by the benzylidene group so as to obtain α-methyl-4,6-*O*-benzylidene D-glucopyranoside (**2**) (Supporting Information Figures S8 and S9), using for this purpose benzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-toluenesulfonic acid. The protection step of the two 2- and 3-dihydroxyls groups of α-methyl-4,6-*O*-benzylidene D-glucopyranoside (**2**), or step 2, served to eventually generate either a hydrophobic bicyclic glycocarbonate (**6a**) or its hydrophilic equivalent (**6b**). In the first case, **3a** (Figures S10 and S11), two methyl groups were introduced as protecting groups using methyl iodide and sodium hydride and in the second, **3b** (Figures S24–S26), two molecules of triethylene glycol monomethyl ether were grafted at the 2- and 3-positions of the glucopyranosyl rings using tosylated triethylene glycol methyl ether and sodium hydride. Step 3 was identical for the two monomers: α-methyl-6-bromo-4-benzyl ester-2,3-di-*O*-methyl-d-glucopyranoside (**4a**) and α-methyl-6-bromo-4-benzoate-2,3-di-*O*-TEGM-D-glucopyranoside (**4b**) were obtained by bromination of α-methyl-2,3-dimethyl-4,6-*O*-benzylidene-D-

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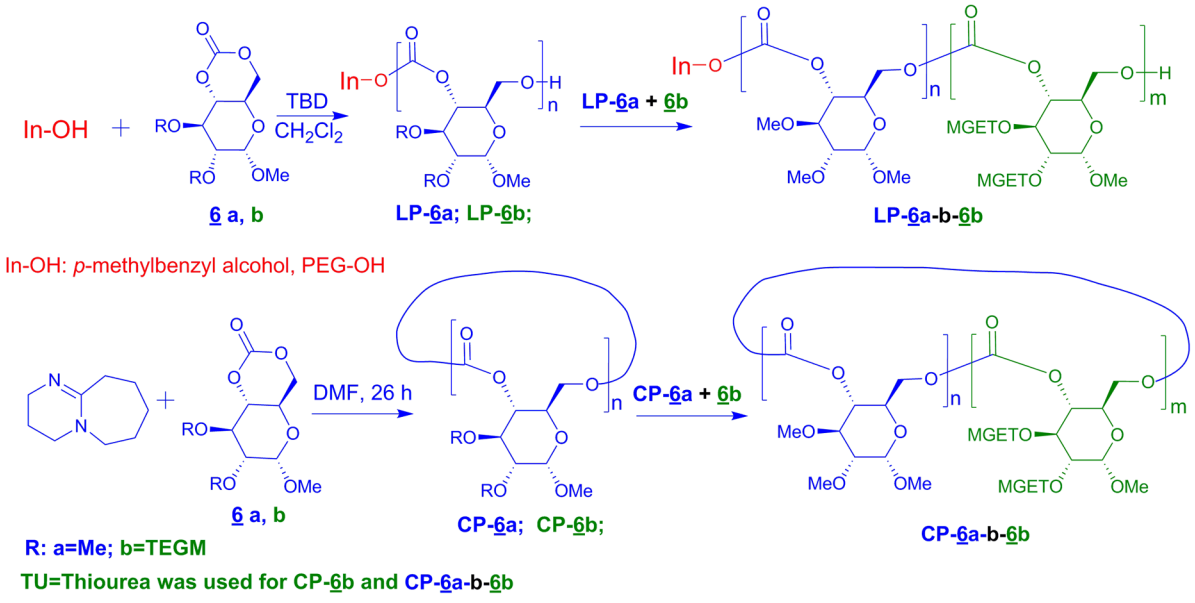
Scheme 2. Organocatalytic Anionic Ring-Opening Polymerization (AROP) of Cyclic Glycocarbonates (6) for the Synthesis of Linear and Macrocyclic Polyglycocarbonates and Block Copolymers



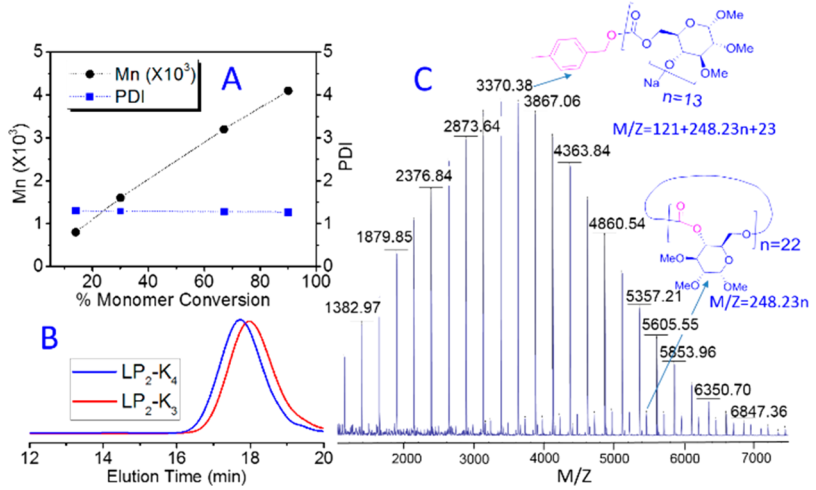


Figure 1. (A) Plot of monomer conversion (%) (^{1}H NMR analysis) vs M_n and PDI values (GPC traces), (B) GPC profiles of the reaction aliquots over time, and (C) MALDI-tof of **LP_2-6a**.

glucopyranoside (**3a**) and of α-methyl-2,3-di-*O*-TEGM-4,6-*O*-benzylidene-D-glucopyranoside (**3b**), respectively, using NBS/CCl_4 in the presence of $CaCO_3$. The benzyl ester deprotection of **4a** and **4b** (Figures S27−S29) was carried out next (step 4) in 2% sodium hydroxide methanol solution at room temperature; these reactions yielded α-methyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-D-glucopyranoside (**5a**) (Figures S12−S17) and α-methyl-6-bromo-6-deoxy-2,3-di-*O*-TEGM-D-glucopyranoside (**5b**) (Figures S30−S32), respectively. In the final step 5, **6a** and **6b** were obtained by carbonylation and cyclization of **5a** and **5b**, respectively, under a 10 bar CO_2 pressure at room temperature in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The yields for the two monomers **6a** and **6b** were equal to 40%, a value comparable to that reported by Wooley and co-workers, who resorted to the use of bis(pentafluorophenyl)carbonate as carbonylation reagent.[27] All NMR (Figures S18−S23 for **6a** and Figures S33−S38 for **6b**) and HRMS (Figures S5 and S7) characterizations confirmed the purity and the structure of monomers **6a** and **6b** synthesized and also those of the intermediate compounds.

Hydrophobic Linear Polyglycocarbonates. The polymerization of **6a** was subsequently carried out in the presence of *p*-methylbenzyl alcohol as initiator and TBD as catalyst in anhydrous dichloromethane and at room temperature: the polymerization occurred in a "living" fashion.[27] The obtained polymer (**LP_1-6a**) was thoroughly characterized by NMR, GPC, and MALDI-tof (Figure 4A and Figures S3, S39, and S40): the data collected confirmed the expected structure of the formed polymer (Table 1 and Scheme 2).

In contrast to the previous case which witnessed a rather fast propagation, with a weak base such as DBU, the polymerization rate was much slower (**LP_2-6a**): the monomer conversion was indeed only 14% after 1 h, then 67% after 21 h, and it took 45 h of reaction to reach 90% of conversion (Figure 1 and Figure S41). As can be seen from Figure 1, the molar mass of the samples isolated over time increased linearly with the monomer

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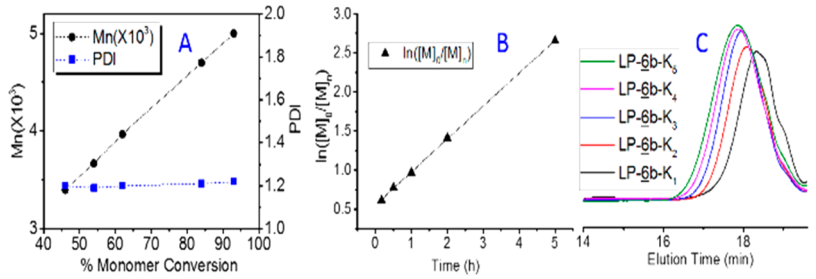

Figure 2. (A) Plot of monomer conversion (%) (^{1}H NMR analysis) vs PDIs and M_n (GPC analysis) of reaction aliquots over time, (B) reaction kinetics plot: $\ln([M]_0/[M]_n)$ vs time, and (C) GPC profiles of reaction aliquots over same time for **LP-6b**.

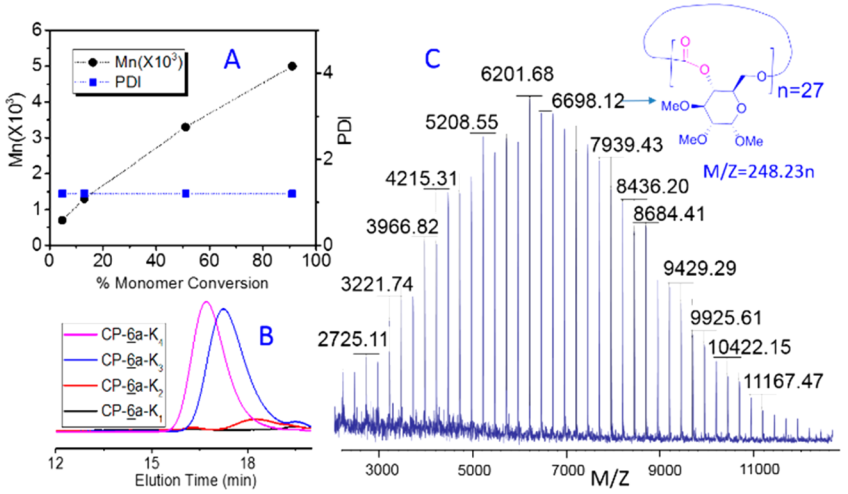

Figure 3. (A) Plots of monomer conversion (%) (^{1}H NMR analysis) vs M_n and PDI (GPC analysis) of the reaction aliquots over time, (B) GPC profiles of the reaction mixture in same time, and (C) MALDI-tof of **CP-6a**.

conversion. Besides its characterization by NMR and GPC the final sample quenched with benzoic acid was also subjected to MALDI-tof analysis. As shown in Figure 1, MALDI-tof characterization confirms the incorporation of the initiator, *p*-methylbenzyl alcohol, at the chain end: the main population exactly matches the expected structure with a peak-to-peak mass difference corresponding to the molar mass of **6a** (248.23 g/mol). Another small population without any terminal group and thus corresponding to macrocyclic polycarbonates can also be seen; the latter are chains that underwent a ring closure reaction. In one of the next sections, we will discuss in detail how to obtain exclusively macrocyclic polyglycocarbonates from either **6a** or **6b**.

Hydrophilic and Amphiphilic Linear Polyglycocarbonates. After **6a** the water-soluble monomer **6b** was also subjected to polymerization using TBD as organic catalyst and *p*-methylbenzyl alcohol as initiator. The progress of the reaction was monitored by GPC, and aliquots of the reaction medium withdrawn over time were characterized by NMR. The monomer conversion was 54% after 30 min of reaction and 94% after 5 h of the reaction (Figure 2). In comparison to **6a**, the polymerization of **6b** was slower due to the hindering presence of the two bulky TEGM moieties. The isolated samples were lyophilized prior to their characterization by GPC, ^{1}H NMR, and ^{13}C NMR spectroscopy (Figures S1A, S45, and S46). The GPC traces showed single monodisperse profiles with no monomeric residues. From the signal due to the methyl group (at 2.4 ppm) in the ^{1}H NMR spectra to that of the initiator taken as reference $M_{n(NMR)}$ values could be easily deduced: as seen from the Table 1, they were in good agreement with the expected values.

One of our other endeavors was to synthesize an amphiphilic diblock copolymer containing both hydrophobic and hydrophilic polyglycocarbonate blocks. We first targeted the synthesis of a diblock copolymer with a composition prone to afford regular micelles in water. We thus used a hydrophilic poly(ethylene oxide) precursor (PEG-OH) as macroinitiator (M_n = 5.0 × 10^3 g/mol) and grew a hydrophobic polyglycocarbonate block of same weight fraction from it by polymerization of **6a**. The reaction was carried out in anhydrous dichloromethane at room temperature, and the catalyst used was TBD; the diblock copolymer synthesized was characterized by GPC and NMR (entry 06, Figures S1B and S42−S44) which confirmed the incorporation of PEG and the formation of the expected amphiphilic diblock copolymer.

We then tried to synthesize amphiphilic copolymers totally made of polyglycocarbonate blocks. Starting from the hydrophobic and hydrophilic monomers **6a** and **6b**, such amphiphilic copolymer could be generated by sequential polymerization of **6a** and **6b** in one pot as shown in Scheme 2. The first polymerization of **6a** was monitored by GPC and NMR. Then the second monomer **6b** was added after consumption of 90% of the first monomer **6a**. After 10 h of reaction, the polymerization of **6b** reached 92% conversion and that of **6a** was complete. The diblock copolyglycocarbonates obtained were purified by dialysis against Milli-Q water. Their GPC traces all exhibited a single monomodal peak clearly shifting to the high molar mass region with monomer conversion (Figure 4B and Figure S1C). The characteristic peaks due to the two

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monomers **6a** and **6b** *O*-methyl and *O*-TEG (3.6−3.3 ppm) could be well detected by ^{1}H NMR spectroscopy (Figure S47), the composition of the copolymer formed corresponding almost perfectly to the feeding ratio of monomers **6a** and **6b**.

Macrocyclic Polyglycocarbonates. As seen in Figure 1 in the presence of DBU used as catalyst initiation occurs by both *p*-methylbenzyl alcohol and DBU; the latter grows chains by a zwitterionic mechanism where both end-to-end ring closure reactions and propagation concomitantly occur (entry 02).[26] We thus used DBU alone as initiator to trigger the polymerization of **6a** in anhydrous dimethylformamide (Scheme 2). The reaction proceeded very slowly, the monomer conversion calculated from NMR reaching only 5% after the first hour reaction and 13%, 51%, and 91% after 6, 21, and 45 h of reaction, respectively (Figure 3). As can be seen from Figures 3A and 3B the molar mass of the growing polymer (**CP-6a**) increased linearly with the increasing monomer conversion and PDIs values revolved around 1.2. The molar mass obtained from GPC was relatively low with respect to the value calculated from monomer conversion (^{1}H NMR analysis) and obtained from MALDI-tof (Figure 3C) likely due to the smaller hydrodynamic volume of the cyclic polymer formed (Figure 4A). The MALDI-tof spectrum of the sample isolated after 91% conversion contained indeed only one series of peaks corresponding exclusively to macrocyclic polycarbonates without end groups with a peak-to-peak mass difference corresponding perfectly to the monomer molar mass (248.5 g/mol). In addition, the average molar mass drawn from MALDI-tof (6700 g/mol) was in excellent agreement with the expected values. Further, the absence of DBU moieties or hydroxyl groups from NMR data also supports the formation of macrocyclic polycarbonates (Figure S49). Next, the polymerization behavior of water-soluble hydrophilic monomer **6b** was also investigated. Because of the hindrance of TEGM groups in **6b**, it took 5 days to reach 70% of monomer conversion with the same DBU organocatalyst. Upon adding in 1:1 molar ratio to DBU 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl-thiourea (TU), which is well-known for its ability to activate carbonyl groups in cyclic monomers (entry 05),[34−38] the conversion of **6b** reached 90% within 60 h without undesired back-biting side reactions. The obtained water-soluble macrocyclic polyglycocarbonate **CP-6b** was then subjected for detailed characterizations by NMR, GPC, and MALDI-tof. The MALDI-tof spectrum (Figure S4) of the polymer **CP-6b** exhibits peaks corresponding exclusively to macrocyclic polycarbonates without end groups and with a peak-to-peak mass difference corresponding perfectly to the monomer molar mass (512.5 g/mol). Further, the absence of DBU moieties or hydroxyl groups from NMR data also supports the formation of macrocyclic polycarbonates (Figures S50 and S51). PDI values obtained from GPC revolved around 1.2. The molar mass obtained from GPC was relatively low with respect to that given by MALDI-tof likely due to the smaller hydrodynamic volume of the cyclic polymer formed (Figure S1A).

Similarly, macrocyclic amphiphilic diblock polyglycocarbonates (**CP-6a-*b*-6b**) could also be prepared in a same manner as in the above case by subjecting sequentially **6a** and **6b** to ROP using DBU as initiator and TU as monomer activator. After consumption of 90% of the first monomer **6a** the second hydrophilic monomer **6b** was added to the reaction mixture. The polymerization was continued for another 3 days until reaching 90% conversion of **6b**. The GPC profile of this sample showed a monomodal signal, the value corresponding to 2/3 of the expected molar mass due to the lower apparent molar masses of macrocyclic structures (Figure 4B and Figure S1D). The ^{1}H NMR characterization confirmed the absence of any end group and the cyclic structure of the copolymer formed (Figures S52 and S53).

The mechanism (Scheme 3) involves first the ring-opening of the carbonate bond of monomer **6a** or **6b** by DBU, followed by repeated monomer addition by the zwitterionic species thus formed (zwitterionic intermediate). End-to-end ring closure reactions also occur but obviously at a much slower rate than propagation. The growing chains can thus undergo at any time a ring closure reaction and generate a macrocyclic poly-

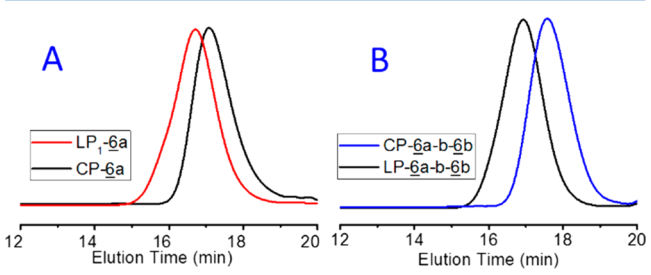
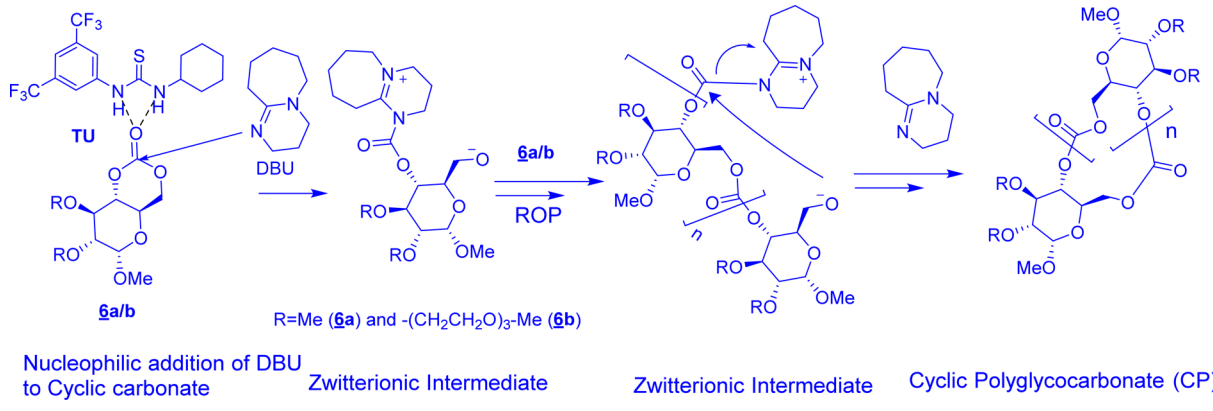


Figure 4. GPC profiles of (A) **LP$_1$-6a** (linear) and **CP-6a** (macrocyclic) as well as (B) **LP-6a-*b*-6b** (linear) and **CP-6a-*b*-6b** (macrocyclic).

Scheme 3. Proposed Zwitterionic Mechanism Occurring with DBU as Catalyst in the Synthesis of Macrocyclic Polycarbonates CP-6a/b



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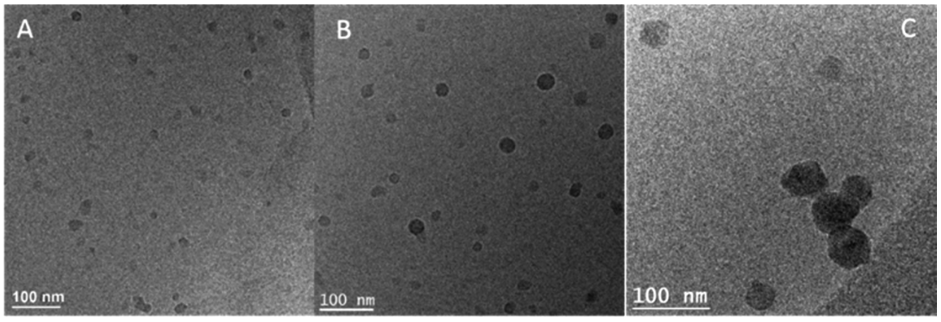

Figure 5. Cryo-TEM images of the nanostructures of the self-assemblies obtained from the amphiphilic polycarbonates (A) **LP$_3$-6a**, (B) **LP-6a-*b*-6b**, and (C) **CP-6a-*b*-6b** in water.

glycocarbonate, allowing the freed DBU to ring-open further monomers. Scheme 3 also features monomer activation by TU. A similar mechanism was proposed by Endo and co-workers in their work on the ROP of five-membered cyclic carbonates, but in their study they observed a mixture of macrocyclic species and linear chains.[26]

Both linear and macrocyclic amphiphilic diblock copolymers were then subjected to self-assembling in water. The aggregates formed were then deposited on a carbon-coated copper-grid and analyzed by cryo-TEM.

All the amphiphilic samples exhibit micellar aggregation with an overall size varying from 20 to 40 nm depending upon the hydrophobic/hydrophilic balance and the overall macrostructure of the initial copolymers (Figure 5). Those with a macrocyclic architecture tended to self-assemble into micelles of bigger size due to entropic constrains. A paper focusing on the manipulation of the morphology of these self-assemblies as a function of the content in **6a** and **6b** and of the overall architecture is in preparation.

CONCLUSION

For the first time different types of bicyclic glycocarbonates both hydrophobic and hydrophilic could be prepared from synthetically modified glucose and CO_2. Phosgene or its derivatives were purposely avoided in the chemistry described in this investigation which opens up the possibility to derive many more synthetically modified natural glycans. We also demonstrated the synthesis of both hydrophobic and hydrophilic linear polyglycocarbonates whose molar mass could be precisely controlled by using an organocatalyst combined with an initiator that mediated the ring-opening polymerization of the above-mentioned bicyclic glycocarbonates under "living" conditions. The chemistry described in this investigation was also versatile enough to allow the direct synthesis of macrocyclic polyglycocarbonates. Both linear and macrocyclic polyglycocarbonates were thoroughly characterized, and their structures were confirmed by GPC, MALDI-tof, ^{1}H NMR, and ^{13}C NMR experiments. We also synthesized an amphiphilic diblock copolymer by using hydrophilic poly(ethylene glycol) (PEG-OH) as macroinitiator and amphiphilic diblock polyglycocarbonates by polymerizing first the hydrophobic monomer **6a** followed by the hydrophilic monomer **6b** in a very controlled manner. Both linear and macrocyclic amphiphilic structures could be obtained. In some instances TU was used to activate the cyclic glycocarbonate monomers and thus accelerate their ROP without provoking side reactions. Further, the self-assembling of the synthesized amphiphilic polycarbonates were characterized by cryo-TEM which all showed micellar aggregation.

EXPERIMENTAL SECTION

Materials and Method. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and *p*-methylbenzyl alcohol (PMBA) were purchased from Sigma-Aldrich. DBU was dried with CaH_2 and stored in a glovebox after distillation. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (TU) was prepared following previously reported literature.[39] TBD was stirred in tetrahydrofuran with calcium hydride and filtered, and solvent was removed under vacuum and kept in a glovebox. Dichloromethane and dimethylformamide were dried with CaH_2 and stored on activated molecular sieves (4 Å) after distillation. CO_2 (99.995%) cylinder purchased from Abdullah Hashim Industrial & Gas Co. was further purified by flowing through the purifier of the VICI Co., USA. The synthesis and characterization of **5a** and **5b** are detailed in the Supporting Information.

FT-IR spectra were recorded on PerkinElmer FT-IR spectrum GX instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometers (400, 500, 600, and 950 MHz). Gel permeation chromatography (GPC) was performed on a VISKOTEK TDA 305-040 triple detector equipped with two columns (T6000M, GENERAL MIXED ORG 300X7.8 MM) using THF (1 mL/mL) as the eluent at 35 °C. MALDI-tof MS experiments were carried out by using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as the matrix in THF at a loading of 1:5 with Na-TFA as ionizing agent. The self-assembled morphology of amphiphilic polycarbonates in water was characterized by the transmission electron microscopy (cryo-TEM model Titan 80-300 Krios from FEI Company (Hillsboro, OR)) by operating it at the accelerating voltage of 300 keV. The specimens for cryo-TEM were prepared by using an automatic plunge-freezing system of model VitrobotTM from FEI Company (Hillsboro, OR). A small amount of sample (4 μL) was placed on a holey-carbon coated hydrophilic copper grid and followed by blotting of the solution, and its plunge freezing into liquid ethane cryogen was done. Then, grids were loaded into the VitrobotTM. In this way, several specimens were prepared for each sample in order to realize a high quality data sets from superior specimens. Further, this microscope was equipped with the low-dose option to keep the sample free of electron beam damage and a charge coupled devices (CCD) of model US4000 from Gatan, Inc. to record the images in digital format. The polymer solution was prepared as following: The synthesized amphiphilic polyglycocarbonate was first dissolved in dimethyl sulfoxide, to which water was slowly added to get the final sample concentration of 1 mg/mL. Then the organic solvent was removed by continuous dialysis with Milli-Q water for 2 days.

Synthesis of α-Methyl-2,3-di-*O*-methyl-D-glucoside 4−6 Cyclic Carbonate (6a). α-Methyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-D-glucopyranoside (**5a**, 0.5 g, 1.75 mmol), DBU (267 mg, 1.75 mmol), and 3 mL of anhydrous DMF were added into a 50 mL of dried autoclave with magnetic stirring bar inside a glovebox. Then the sealed autoclave was taken out and charged with CO_2 to a pressure of

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10 bar. The reactor was kept stirring at room temperature for 5 h. Then, CO_2 was released; the reaction mixture was poured into HCl solution (1.0 M) and extracted by dichloromethane. The crude product was purified by silica gel flash chromatography eluted with a mixture of hexane/ethyl acetate (1:1−1:2) to give **6a** as a white solid (0.2 g 40% yield). FT-IR (dichloromethane) 1755 cm^{-1} for six-membered cyclic carbonate (ν_{co}). ^1H NMR (600 MHz, CD_2Cl_2): δ 4.93 (d, J = 3.6 Hz, 1H), 4.52 (dd, J = 9.8, 5.8 Hz, 1H), 4.28−4.22 (m, 1H), 4.13−4.02 (m, 2H), 3.66 (m, 4H), 3.54 (s, 3H), 3.49 (s, 3H), 3.31 (dd, J = 9.3, 3.6 Hz, 1H). ^{13}C NMR (151 MHz, CD_2Cl_2): δ 147.27, 98.72, 81.06, 79.48, 79.13, 69.81, 60.92, 59.53, 59.05, 55.81. HRMS (M + H^+) (ESI^+) calcd for $C_{10}H_{16}O_7H^+$ 249.09 g/mol; found 249.08 g/mol.

Synthesis of α-Methyl-2,3-di-O-TEGM-D-glucoside 4−6 Cyclic Carbonate (6b). α-Methyl-6-bromo-6-deoxy-2,3-di-*O*-TEGM-D-glucopyranoside (**5b**, 0.3 g, 546 μmol), DBU (91.44 mg, 600 mmol), and 4 mL of anhydrous DMF were added into a 50 mL of dried autoclave with magnetic stirring bar inside a glovebox. Then the sealed autoclave was taken out and charged with CO_2 to a pressure of 10 bar. The reactor was kept stirring at room temperature for 22 h. Then, CO_2 was released, and the reaction mixture was poured into HCl solution (1.0 M) and extracted by dichloromethane. The crude product was purified by silica gel flash chromatography eluted with a mixture of hexane/acetone (1:0.2−1:1) to give **6b** as a colorless liquid (0.1 g, 40% yield). ^1H NMR (950 MHz, $CDCl_3$): δ 4.90 (d, J = 3.7 Hz, 1H), 4.46−4.44 m, 1H), 4.20−4.18 (m, 1H), 4.05−4.01 (m, 2H), 3.95−3.88 (m, 3H), 3.80 (ddd, J = 11.5, 7.6, 3.3 Hz, 1H), 3.75 (t, J = 9.0 Hz, 1H), 3.65−3.63 (m, 3H), 3.63−3.60 (m, 12 H), 3.59 (ddd, J = 10.9, 4.6, 3.4 Hz, 1H), 3.54−3.52 (m, 4H), 3.48 (dd, J = 9.4, 3.7 Hz, 1H), 3.45 (s, 3H), 3.37−3.34 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.36, 99.33, 79.97, 79.26, 78.21, 72.39, 71.85, 71.83, 71.73, 71.008, 70.54, 70.53, 70.48, 70.47, 70.45, 70.42, 70.33, 69.55, 59.42, 59.0, 58.98, 55.94 ppm. HRMS (M + H^+) (ESI^+) calcd for $C_{22}H_{40}O_{13}H^+$ 513.25 g/mol; found 513.25 g/mol.

Synthesis of Linear Polyglycocarbonates. Polymerization of 6 Using TBD and *p*-Methylbenzyl Alcohol. LP-6b is given as an example. Inside a glovebox, a solution of monomer **6b** (71.32 mg, 139.15 μmol) in 300 μL of anhydrous dichloromethane was prepared in a Schlenk tube;a mixture of *p*-methyl benzyl alcohol (1 mg, 8.19 μmol) and TBD (0.6 mg, 4.31 μmol) in 100 μL of anhydrous dichloromethane was then added to the monomer solution. After kept stirring inside the glovebox for 5 h, the polymerization was quenched with benzoic acid. The resulting suspension was dialyzed thoroughly against deionized water using 1 kDa cutoff cellulose membrane for 2 days to remove remaining monomers. The dialyzed solution was lyophilized, and 50 mg of **LP-6b** was obtained (yield 83%). FT-IR (dichloromethane) 1750 cm^{-1} for carbonate (linear ν_{co}). ^1H NMR (400 MHz, $CDCl_3$): δ 4.90−4.81 (m, 1H), 4.79−4.52 (m, 1H), 4.50−4.02 (m, 2H), 3.99−3.73 (m, 6H), 3.72−3.52 (m, 20H), 3.51−3.33 (m, 10H). Initiator incorporation was confirmed by the presence of 7.32−7.27 (m, 2H), 7.23−7.17 (m, 2H), 5.22−5.10 (m, 2H), 2.38 (s, 3H) ppm, $M_{n(NMR)}$ = 8300. ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.02, 154.20, 154.72, 97.98, 97.85, 79.97, 79.26, 78.21, 72.39, 71.85, 71.83, 71.73, 71.008, 70.54, 70.53, 70.48, 70.47, 70.45, 70.42, 70.33, 69.55, 59.42, 59.0, 58.98, 55.94 ppm. The incorporation of the initiator on the chain end was confirmed by the presence of the corresponding peaks; 128.50 (benzyl), 72.5 ($\underline{CH_2}$-benzyl) and 20.29 ($\underline{Me}$-benzyl) ppm.

Synthesis of Linear Amphiphilic Block Polyglycocarbonate LP-6a-*b*-6b. Inside a glovebox, a solution of monomer **6a** (36.57 mg, 147.34 μmol) in 300 μL of anhydrous dichloromethane was prepared in a Schlenk tube; a mixture of *p*-methylbenzyl alcohol (1 mg, 8.19 μmol) and TBD (1.14 mg, 8.19 μmol) in 100 μL of anhydrous dichloromethane was then added to the monomer solution. The reaction was kept stirring inside the glovebox for 10 min; 90% of the monomer was consumed at this time. The second monomer, **6b** (37.76 mg, 73.67 μmol), was added to the reaction mixture. The polymerization continued for another 11 h and quenched by the addition of benzoic acid. The resulting suspension was dialyzed thoroughly against deionized water using 1 kDa cutoff cellulose membrane for 2 days. Then the dialyzed solution was lyophilized to afford the amphiphilic block copolymer, **LP-6a-*b*-6b** as colorless liquid. (60 mg, yield 75%). FT-IR (dichloromethane) 1750 cm^{-1} for carbonate (linear ν_{co}). ^1H NMR (400 MHz, $CDCl_3$): δ 4.88−4.76 (m, 1H), 4.75−4.49 (m, 1H), 4.46−3.98 (m, 2H), 3.96−3.67 (m, 3H), 3.66−3.45 (m, 10H), 3.45−3.30 (m, 5H), 3.30−3.16 (m, 1H). The initiator incorporation at the chain end was confirmed (*p*-methylbenzyl alcohol) by the presence of 7.28−7.22 (m, 2H), 7.15−7.12 (m, 2H), 5.17−5.05 (m, 2H), 2.32 (s, 3H) ppm and $M_{n(NMR)}$ = 8600. ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.02, 154.20, 154.72, 97.98, 97.85, 79.97, 79.26, 78.21, 72.39, 71.85, 71.83, 71.73, 71.008, 70.54, 70.53, 70.48, 70.47, 70.45, 70.42, 70.33, 69.55, 59.42, 59.0, 58.98, 55.94 ppm. Initiator incorporation was confirmed by the presence of the corresponding peaks (*p*-methylbenzyl alcohol); 129.19, 128.50 (benzyl), 72.5 ($\underline{CH_2}$-benzyl) and 20.29 ($\underline{Me}$-benzyl) ppm.

Synthesis of Macrocyclic Polyglycocarbonate (CP-6a) by the Polymerization of 6a. Inside a glovebox, a solution of monomer **6a** (195.06 mg, 786 μmol) in 800 μL of anhydrous DMF was prepared in a Schlenk tube; DBU (3.98 mg, 26.20 μmol) was dissolved in 100 μL of deuterated DMF and added to the monomer solution. The polymerization was kept stirring inside the glovebox for 48 h and then quenched with benzoic acid. Finally, the reaction mixture was precipitated in water; the collected crude product was dissolved in CH_2Cl_2 and precipitated again in diethyl ether to afford the macrocyclic polymer **CP-6a** (126 mg, yield 65%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.73−4.61 (m, 1H), 4.61−4.27 (m, 1H), 4.17−3.93 (m, 2H), 3.80−3.62 (m, 1H), 3.50−3.40 (m, 1H), 3.39−3.28 (m, 6H), 3.27−3.18 (m, 3H), 3.16−3.05 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.1, 154.8, 154.46, 97.92, 81.7, 80.8, 78.1, 75.1, 67.8, 66.6, 61.33, 61.1, 59.1, 55.8 ppm. FT-IR (dichloromethane) 1750 cm^{-1} for carbonate (linear ν_{CO}).

Synthesis of Macrocyclic Polyglycocarbonate (CP-6b) by the Polymerization of 6b. Inside a glovebox, a solution of monomer **6b** (87 mg, 169.74 μmol) in 400 μL of anhydrous DMF was prepared in a Schlenk tube; DBU (2.15 mg, 14.14 μmol) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (TU; 5.24 mg, 14.14 μmol) were dissolved in 100 μL of deuterated DMF and added to the monomer solution. The polymerization was kept stirring inside the glovebox for 60 h and then quenched with benzoic acid. The obtained polymerization mixture was diluted with deionized water and dialyzed against water using 1 kDa cutoff cellulose membrane for 2 days. The dialyzed solution was lyophilized to give the cyclic polyglycocarbonate, **CP-6b** as colorless liquid (52 mg, yield 60%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.90−4.781 (m, 1H), 4.79−4.50 (m, 1H), 4.50−4.0 (m, 2H), 3.99−3.70 (m, 6H), 3.72−3.50 (m, 20H), 3.51−3.30 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.02, 154.20, 154.72, 97.98, 97.85, 80.42, 79.44, 74.87, 72.39, 71.85, 71.83, 71.73, 71.008, 70.54, 70.53, 70.48, 70.47, 70.45, 70.42, 70.33, 69.55, 59.42, 59.0, 58.98, 55.94 ppm. FT-IR (dichloromethane) 1750 cm^{-1} for carbonate (linear ν_{CO}).

Synthesis of Macrocyclic Amphiphilic Polyglycocarbonate (CP-6a-*b*-6b). Inside a glovebox, a solution of monomer **6a** (42.80 mg, 172.80 μmol) in 300 μL of anhydrous DMF was prepared in a Schlenk tube; DBU (1.75 mg, 11.49 μmol) dissolved in 100 μL of deuterated dimethylformamide (DMF) was added to the monomer solution. The reaction was kept stirring inside the glovebox for 28 h; 90% of the monomer was consumed at this time. Then the second monomer, **6b** (41.24 mg, 80.46 μmol), and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (TU; 4.26 mg, 11.49 μmol) were added to the reaction mixture. The polymerization continued for another 3 days before being quenched by a few drops of HCl (1 N). The obtained polymerization mixture was diluted with deionized water and dialyzed against water using 1 kDa cutoff cellulose membrane for 2 days. The dialyzed solution was lyophilized to give the amphiphilic cyclic block copolymer **CP-6a-*b*-6b** as colorless liquid (60 mg, yield 75%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.90−4.78 (m, 1H), 4.77−4.51 (m, 1H), 4.50−4.09 (m, 2H), 4.01−3.67 (m, 2.18 H), 3.66−3.47 (m, 10H), 3.46−3.32 (m, 5H), 3.32−3.15 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.02, 154.20, 154.72, 97.98, 97.85, 79.97, 79.26, 78.21, 72.39, 71.85, 71.83, 71.73, 71.008, 70.54, 70.53, 70.48, 70.47,

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70.45, 70.42, 70.33, 69.55, 59.42, 59.0, 58.98, 55.94 ppm. FT-IR (dichloromethane) 1750 cm^{-1} for carbonate (linear ν_{CO}).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.6b02527.

Synthesis details of the precursors **5a** and **5b** for bicyclic monomers **6**, the characterizations of **2**−**5**, linear and cyclic polyglycocarbonates, Figures S1−S53 (PDF)

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Notes

The authors declare no competing financial interest.

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