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Synthesis of Atactic and Isotactic Poly(1,2-glycerol carbonate)s: Degradable Polymers for Biomedical and Pharmaceutical Applications

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Supporting Information

ABSTRACT: The synthesis and characterization of atactic and isotactic linear poly(benzyl 1,2-glycerol carbonate)s are reported. The poly(benzyl 1,2-glycerol carbonate)s were obtained via the ring-opening copolymerization of *rac*-/(*R*)-benzyl glycidyl ether with CO_2 using [SalcyCo^{III}X] complexes with high carbonate linkage selectivity and polymer/cyclic carbonate selectivity (>99%). Deprotection of the resultant polymers afforded poly(1,2-glycerol carbonate)s with a functionalizable pendant primary hydroxyl group. Poly(1,2-glycerol carbonate) showed a remarkable increase in degradation rate compared to poly(1,3-glycerol carbonate) with a $t_{1/2} \approx 2-3$ days. These polymers fulfill an unmet need for a readily degradable biocompatible polycarbonate.

Glycerol based polymers are of widespread interest for industrial, cosmetic, and pharmaceutical applications. Various polymer architectures from linear to dendritic are reported for pure polyglycerol ethers and carbonates as well as copolymers with hydroxyacids, for example, to give polyether esters or polycarbonate esters.[1] Within the biomedical arena, these polymers possess the following advantages: (1) a free hydroxyl for functionalization with chemotherapeutic agents, antibacterial compounds, anti-inflammatory agents,[2] fluorescent tags,[3] or material property modifiers;[4] (2) a defined biodegradation route to afford nontoxic and nonacidic byproducts, e.g., glycerol and carbon dioxide; (3) physical properties ranging from semicrystalline or amorphous materials based on the polymer or copolymer composition; and (4) amenability to manufacturing methods such as electrospinning.[5] In many ways, these polymers provide users the capabilities of well-known polymers like PLA (polylactic acid) or PLGA (poly(lactic-*co*-glycolic acid)) with the additional benefits of an easily modifiable structure and nonacidic products upon biodegradation. These advantages have been put to use, and poly(1,3-glycerol carbonate)[2b,6] based biomaterials are being investigated as drug-loaded buttressing films for the prevention of tumor recurrence after surgical resection,[7] particles for drug delivery,[3,6a,8] and coatings for the prevention of seroma.[9] Surprisingly, linear poly(1,2-glycerol carbonate)s are far less explored (Figure 1), and yet, one would hypothesize that these materials would degrade more readily than the 1,3-glycerol analogs fulfilling an unmet need for readily degradable biocompatible polycarbonates. Herein, we report a facile and efficient method to synthesize linear atactic poly(1,2-glycerol carbonate)s using readily available starting material benzyl glycidyl ether (**1**), the hydrolytic kinetic resolution of **1** using Jacobsen's catalyst and subsequent polymerization to afford the chiral isotactic polymer, the deprotection of the benzyl to afford the polymer with a primary hydroxyl group, and the degradation rate of the polymer.

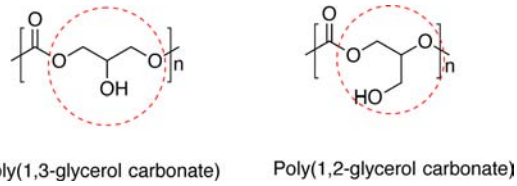

Figure 1. Chemical structures of a linear poly(1,3-glycerol carbonate) and poly(1,2-glycerol carbonate).

Linear poly(1,3-glycerol carbonate)s are synthesized via ring-opening polymerization of the six-membered cyclic 3-benzyloxytrimethylene carbonate[2b,10] or dimethylacetal dihydroxyacetone carbonate[6b,11] monomers. Postpolymerization, the benzyl group is hydrogenated or the ketone is reduced to afford a hydroxyl group, respectively. Although these routes provide ample materials, the monomers require 2−3 steps for preparation and the resulting polymers possess a secondary, less reactive hydroxyl for subsequent use and are usually of broad molecular distribution. Poly(1,2-glycerol carbonate)s would likely be challenging to synthesize via the ring opening of the corresponding five-membered cyclic glycerol carbonate monomer, as five-membered cyclic carbonate monomers are thermodynamically stable and, generally, unreactive toward ring-opening polymerization.[12] However these polymers may be accessed via the ring-opening copolymerization of the corresponding glycidyl ether with CO_2. Given the elegant work of Coates,[13] Darensbourg,[14] Lu,[15] and Nozaki[16] on expoxide ring-opening copolymerization with carbon dioxide using metal salen catalysts, we explored this approach to prepare linear poly(1, 2-glycerol carbonate)s.

The benzyl protected poly(1,2-glycerol carbonate) was synthesized via ring-opening copolymerization of benzyl glycidyl ether (BGE), **1**, with CO_2 (220 psi) using the [SalcyCo^{III}X] complexes, **2a**−**2e**, shown in Figure 2. We first examined a series of catalysts with different axial ligands including nitrate, chloride, bromide, trichloroacetate, and 2,4-dinitrophenoxy (DNP) (Table 1). All of the resultant polymers

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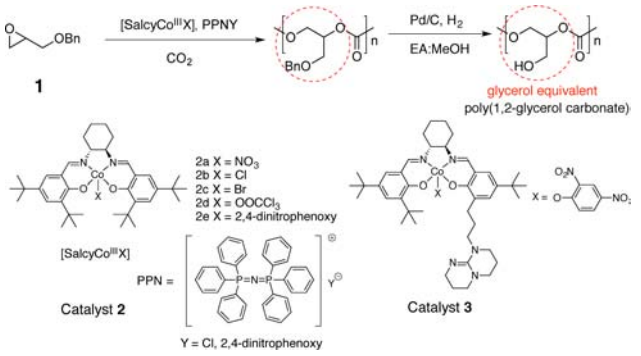


Figure 2. Synthesis of poly(benzyl 1,2-glycerol carbonate)s (PBGCs) using [SalcyCo^{III}X]/PPNY.

Table 1. Axial Ligand Effect on the Polymerization of *rac*-BGE with Carbon Dioxide Using [(*S,S*)-SalcyCoIIIX]/[PPN]Y[a]

no.	catalyst	turnover freq. (h^{-1})	selectivity (% PBGC)	M_n (kg/mol)[b]	PDI
1	**2a**	123	96	32.3	1.13
2	**2b**	142	94	34.4	1.12
3	**2c**	146	73	19.7	1.15
4	**2d**	160	96	25.5	1.09
5	**2e**	140	98	41.3	1.10
6[c]	**2e**	150	>99	33.6	1.13
7[c,d]	**2e**	200	87	27.3	1.12

[a]The reactions were performed in neat *rac*-BGE (3.81 mL, 25 mmol) in a 45 mL autoclave under 220 psi of CO_2 pressure with 1000:1:1 *rac*-BGE/[(*S,S*)-SalcyCo^{III}X]/[PPN]Cl loading at 22 °C for 4 h. All resultant poly(benzyl 1,2-glycerol carbonate)s (PBGCs) contain >99% carbonate linkage, determined by ^{1}H spectroscopy. [b]All resultant polymers exhibit a bimodal distribution; the values are averaged over two peaks. [c]The reaction was performed with cocatalyst [PPN]DNP. [d]The reaction was performed at 50 °C.

contained >99% carbonate linkage, as determined by ^{1}H NMR, and the selectivity for polycarbonate over cyclic carbonate ranged from 73% to 98% depending on the axial ligand. The selectivity was highest for DNP and lowest for bromide. When DNP serves as both an axial ligand and a cocatalyst anion, the highest selectivity was achieved. All resultant polymers showed a head-to-tail selectivity of 92%. The catalyst activity, however, was significantly lower than that reported for the polymerization of propylene oxide (~150 h^{-1} vs ~500 h^{-1},[13a,17] respectively). This may be a result of the more sterically hindered side chain or trace water coordinating to the Co reducing catalytic activity.[18] Increasing the temperature to 50 °C led to moderately increased activity, but the selectivity was still compromised. SEC analysis revealed molecular weights significantly lower than theoretical values and bimodal but narrow PDIs (<1.07 for each and <1.15 combined). A plot of molecular weight versus conversion (see Supporting Information (SI)) showed a linear increase of M_n with conversion. These results are consistent with an immortal polymerization mechanism involving fast and reversible chain transfer, as has been reported for the polymerization of propylene oxide.[13a,19]

As observed in the copolymerization of propylene oxide with CO_2, we also noticed that the cyclic carbonate product was being produced when the conversion reached ~70%. Based on the work by Lu who reported that a tethered 1,5,7-triabicyclo[4,4,0]-dec-5-ene coordinating [SalcyCo^{III}X] complex was a more thermally stable and robust catalyst (even under diluted solutions) for CO_2/epoxide polymerizations,[20] we investigated this catalyst, **3**, for the polymerization of monomer **1** (Figure 2). Catalyst **3** was synthesized following a slightly modified literature procedure (see SI for details).[20] The polymers ranged in M_n from 30 to 50 kg/mol, contained >99% carbonate linkage with >97% polycarbonate selectivity, and possessed narrow PDIs (Table 2). Increasing the temperature

Table 2. Copolymerization of *rac*-BGE with CO_2 Using Catalyst 3[a]

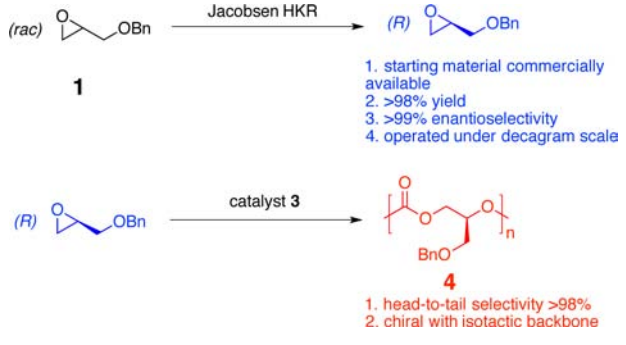
no.	catalyst loading	temp (°C)	turnover freq. (h^{-1})	selectivity (% PPC)	M_n (kg/mol)/ PDI[b]
1	2000:1	20	148	>99	34.9/1.10
2	2000:1	40	362	>99	33.6/1.11
3	4000:1	40	328	>99	48.1/1.13
4	10000:1	40	288	>99	38.1/1.09
5	10000:1	60	620	97	32.2/1.14
6[c]	4000:1	40	235	>99	37.3/1.15

[a]The reactions were performed in neat *rac*-BGE (3.81 mL, 25 mmol) in a 45 mL autoclave under 220 psi of CO_2 pressure to 50%–60% conversion using catalyst **3**. All resultant poly(benzyl 1,2-glycerol carbonate)s (PBGCs) contain >99% carbonate linkage, determined by ^{1}H spectroscopy. [b]All resultant polymers exhibit a bimodal distribution; the values are averaged over two peaks. [c]The reaction was performed in 1 mL of toluene.

or decreasing the catalyst loading afforded an increase in the catalyst turnover number with the greatest value, 620 h^{-1}, achieved at a temperature of 60 °C and a 10000:1 monomer-to-catalyst ratio, with slightly compromised polymer selectivity (97%). Running the reaction in 1 mL of toluene at a 4000:1 catalyst loading (entry 6, Table 2) resulted in nearly complete conversion (>97%) of the monomer. The poly(benzyl 1,2-glycerol carbonate) polymers were soluble in DCM, THF, and toluene, but not in alcohols or water.

Given the encouraging results above, we next synthesized a chiral, isotactic version of the polymer and compared it to an atactic version of the polymer. A hydrolytic kinetic resolution of monomer **1** was performed with Jacobson's catalyst in greater than 98% yield to afford the *R*-enantiomer, following a published procedure.[21] Subsequent polymerization of the *R*-enantiomer with CO_2 using catalyst **3** afforded an isotactic polymer **4** of 20.3 kg/mol with a PDI of 1.11 (Scheme 1). The atactic polymer was prepared by copolymerization of *rac*-BGE with CO_2 using [*rac*-SalcyCo^{III}DNP].[22] The isotactic nature of

Scheme 1. Synthesis of Isotactic Poly(benzyl 1,2-glycerol carbonate)



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the polymer is evident from the ^{13}C NMR spectrum as shown in Figure 3. The atactic polymer is characterized by the

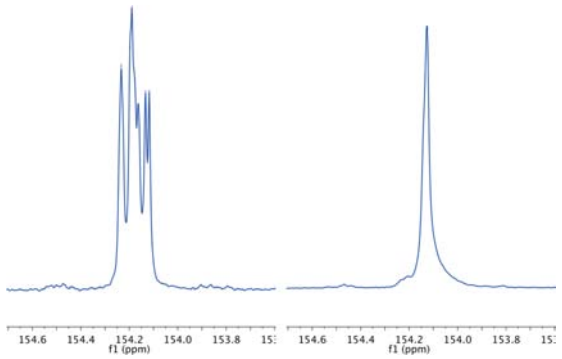

Figure 3. ^{13}C carbonyl region of atactic (left) and isotactic (right) polymer (125 MHz, $CDCl_3$).

overlapping carbonyl peaks that are similar in intensity, while the isotactic polymer exhibits one single sharp peak at 154.1 ppm. The ^{13}C spectrum also shows a head-to-tail selectivity of 98%. When the polymer is dissolved in THF, it possesses a specific rotation of −15.2° at 27 °C.

Next, the benzyl-protecting group of the primary hydroxyl of the polymer was removed using hydrogenation. Specifically, the atactic (M_n = 25.5 kg/mol; PDI 1.09; entry 4, Table 1) or isotactic (20.3 kg/mol; PDI 1.11; **4**) polymer was dissolved in 7:3 ethyl acetate/methanol with Pd/C (20% catalyst loading based on Pd) and pressurized to 600 psi of H_2 for 24 h. After isolation of the polymer, NMR analysis revealed that the aromatic peaks located at 7.1−7.2 ppm were no longer present, confirming the loss of the benzyl group from the polymer. The result from SEC analysis was consistent with the proposed structure (M_n = 13.7 kg/mol; PDI 1.11 and 9.8 kg/mol; PDI 1.16, respectively). Hydrogenation reactions performed in THF and DCM and at low H_2 pressure did not give the deprotected polymer. The poly(1,2-glycerol carbonate) is not soluble in common organic solvent (DCM), but is soluble in DMF and DMSO.

Finally, the rate of poly(1,2-glycerol carbonate) degradation in DMF at 37 °C was monitored by SEC and compared to that of a poly(1,3-glycerol carbonate). As shown in Figure 4, atactic and isotactic poly(1,2-glycerol carbonate)s degrade significantly faster than poly(1,3-glycerol carbonate) with a $t_{1/2}$ of ∼2−3

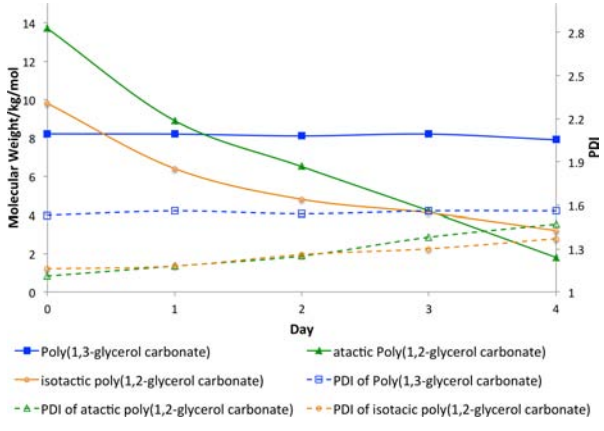

Figure 4. Degradation of poly(1,2-glycerol carbonate) compared to poly(1, 3-glycerol carbonate) in DMF at 37 °C.

days. No degradation occurred over the 4 day period with poly(1,3-glycerol carbonate). The increase in degradation is attributed to the lower activation energy required for intramolecular attack of the pendant 1° OH, compared to the 2° OH group in poly(1,3-glycerol carbonate), to the carbonate linkage, as the 2° OH group requires greater movement of the polymer backbone chain with formation of the thermodynamically stable five-membered cyclic glycerol carbonate.

In summary a facile route to atactic and isotactic poly(1,2-glycerol carbonate)s is reported via copolymerization of benzyl glycidyl ether with CO_2 using Co-salen complexes. These polycarbonates, from simple and abundant starting materials, expand the repertoire of readily degradable polymers available for biomedical applications, including one that is chiral. Currently used polymers are generally limited in composition and functionalizability being based on pure polyhydroxyacids, although a few significant exceptions exist including polyphosphoesters, copolymers of lactic acid with lysine or xylofuranose, and hydroxyl/carboxyl-functionalized polycaprolactones.[23] Continued investigation into new polymer compositions, methods of polymerization, and catalysts is critical to meet the changing and varied demands of polymer properties for medical devices, drug-device combinations, and tissue-engineered scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMRs, and SEC traces. 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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