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Synthesis and Characterization of Poly(glyceric Acid Carbonate): A Degradable Analogue of Poly(acrylic Acid)

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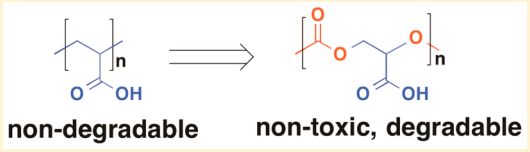
Supporting Information

ABSTRACT: The synthesis and characterization of a degradable version of poly(acrylic acid), poly(glyceric acid carbonate), are reported. Specifically, atactic and isotactic poly(benzyl glycidate carbonate)s are obtained via the ring-opening copolymerization of *rac*-/(*R*)-benzyl glycidate with CO_2 using a bifunctional *rac*-/(*S*,*S*)-cobalt salen catalyst in high carbonate linkage selectivity (>99%) and polymer/cyclic carbonate selectivity (~90%). Atactic poly(benzyl glycidate carbonate) is an amorphous material with a T_g (glass transition temperature) of 44 °C, while its isotactic counterpart synthesized from enantiopure epoxide and catalyst is semicrystalline with a T_m (melting temperature) = 87 °C. Hydrogenolysis of the resultant polymers affords the poly(glyceric acid carbonate). Poly(glyceric acid carbonate) exhibits an improved cell cytotoxicity profile compared to poly(acrylic acid). Poly(glyceric acid carbonate)s also degrade remarkably fast ($t_{1/2}$ ≈ 2 weeks) compared to poly(acrylic acid). Cross-linked hydrogels prepared from poly(glyceric acid carbonate) and poly(ethylene glycol) diaziridine show significant degradation in pH 8.4 aqueous buffer solution compared to similarly prepared hydrogels from poly(acrylic acid) and poly(ethylene glycol) diaziridine.



INTRODUCTION

Poly(acrylic acid) (PAA) and its copolymer with other hydrophilic monomers are produced on the multimillion ton scale per year. These polymers are extensively used in applications such as water/sewage treatment, cleaning detergents, adhesives, cosmetics, as well as drug delivery and serve as workhorse polymers of the chemical industry.[1] Despite its widespread use for both practical applications and fundamental studies, PAA suffers from poor degradability because of its all-carbon backbone (Figure 1). It is well established that only oligomers of PAA with molecular weights (MWs) <600 g/mol (degree of polymerization <8) are biodegradable,[2−6] and yet, the molecular weights of most industrially relevant PAAs are well above this value. For example, low molecular weight PAAs used for detergent applications have an average MW of 4000−5000 g/mol.[2] Furthermore, unlike structural materials (e.g., plastics) that can be easily collected and assorted for recycling or waste treatment such as land filling, composting, and incineration and water-soluble polymers, e.g., PAAs, are difficult to recover. Thus, there is significant interest in degradable PAA analogs. Within the pharmaceutical and biomedical sectors, there is a demand for such polymers that exhibit both biodegradability and biocompatibility for application ranging from drug delivery to tissue engineering.[7−9]

Figure 1. Chemical structures of linear PAA (left) and PGAC (right).

To solve these challenges, a number of approaches have been explored such as oligomer chain extension, vinyl polymerization, etc.[2,10,11] However, these approaches are still acrylate-based with the idea of introducing fragile points such as hydrolyzable or oxidizable sites into the all-carbon polymer backbone. Despite these efforts, limited commercial success has been achieved, and PAA still remains the polymer of choice for industry. Our strategy departs from these previous approaches in that a degradable carbonate linkage is introduced in the polymer backbone giving a structural mimic of PAA, namely, poly(glyceric acid carbonate) (PGAC). This strategy is atom efficient, provides a site for degradation at every repeating unit, and affords safe, nontoxic, and renewable degradation products, CO_2 and glyceric acid.

However, the synthesis of this structural class of poly(1,2-carbonate) is challenging. Traditional polycarbonates are prepared either by ring-opening polymerization of cyclic carbonates or polycondensation of diols with phosgene. Both routes are not favored for poly(1,2-carbonate). Five-membered cyclic carbonate is remarkably thermodynamically stable, and ring-opening polymerization does not occur under mild conditions or proceeds with extensive decarboxylation under vigorous condition (with the exception of trans-fused bicyclic ring structures), unlike poly(1,3-carbonate)s which are polymerized from six-membered cyclic carbonates.[12−14] And, attempts to polycondense 1,2-diols mainly produce five-

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membered cyclic carbonates instead of 1,2-linked polycarbonates.[15]

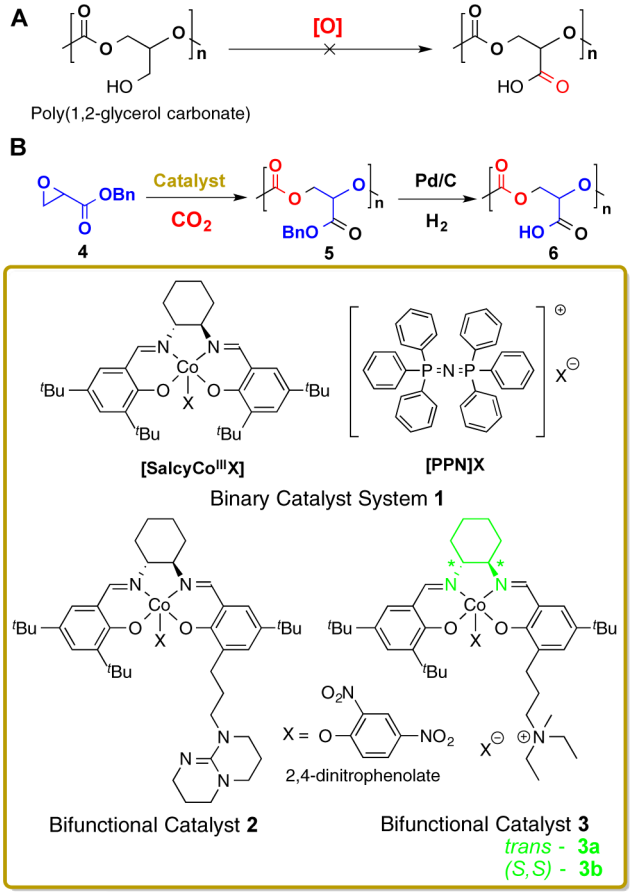
Given the design criterion of a carbonate linkage in the main chain of the polymer, we considered the synthetic strategy of catalytic copolymerization of epoxide/CO_2. This polymerization method is one of several exciting advances in polymer chemistry[16−19] and is receiving increasingly more attention for both environmental and economical reasons. Moreover, the catalytic epoxide/CO_2 copolymerization provides a platform for synthesizing poly(1,2-glycerol carbonate)s that is otherwise not accessible by traditional methods, such as by ring-opening polymerization of the corresponding cyclic carbonate or polycondensation of 1,2-diols.[15,20,21] In addition, glycerol- and glycerol derivative-based polymers are of widespread interest, and various polymers with different compositions and architectures have been synthesized[22−32] and evaluated for a range of biomedical applications.[33−37] Herein, we reported the first synthesis of PGAC. Specifically, atactic and isotactic poly(benzyl glycidate carbonate)s (PBGC's) are synthesized via the ring-opening copolymerization of *rac*-/(*R*)-benzyl glycidate with CO_2 using a bifunctional *rac*-/(*S*,*S*)-cobalt salen catalyst, the deprotection of benzyl protected polymer to give PGACs, the degradation of the polymer in aqueous conditions, and its cytotoxicity profile. Finally, we describe a cross-linked hydrogel prepared from PGAC and characterize the degradation rate compared to a similarly prepared PAA hydrogel.

RESULTS AND DISCUSSION

At the outset of the project, we anticipated that postpolymerization oxidation of poly(1,2-glycerol carbonate)[38] may offer a facile method to access PGAC (Scheme 1A). However, under a range of well-known mild and selective oxidation conditions such as Heyns oxidation,[39] $RuCl_3$-catalyzed oxidation,[40] and TEMPO-mediated oxidation,[41] we were unable to obtain the desired product either due to backbone scission or difficulty of isolation (see SI)

Monomer Design/Synthesis and Polymerization Chemistry. As PGAC was not readily prepared from poly(1,2-glycerol carbonate), we investigated a direct approach and prepared monomer **4**, which bears a benzyl protected carboxylic acid, and three Co Salen catalysts (binary catalyst system **1** and bifunctional catalysts **2** and **3**)[42−44] for the polymerization reaction (Scheme 1). Given the literature precedent on the use of the 2,4-dinitrophenolate (DNP) axial ligand and the resulting high selectivity for polymer over the cyclic carbonate, it was used as both the axial ligand and the counteranion for all of the catalysts.[17,19] Benzyl glycidate (BG) **4** was synthesized via an efficient two-step esterification−oxidation route in high overall yield (~80%).[45] The copolymerization of **4** and CO_2 was investigated using both the binary and bifunctional [SalcyCo^{III}X] complexes, **1**−**3**, as shown in Scheme 1B. Under the screening condition (neat epoxide, 500:1 catalyst loading, 25 °C and 220 psi CO_2 pressure), the binary catalyst system **1** and the bifunctional catalyst **2** were inactive for polymerization. Only the cyclic carbonate product was formed. The lack of activity of catalyst 2 toward BG was surprising given the fact that this catalyst is highly active toward a range of epoxide substrates including ones possessing an electron-withdrawing group, such as styrene oxide and epichlorohydrin.[46,47] Importantly, bifunctional catalyst **3**, bearing a quaternary ammonium salt on the ligand framework, catalyzed the copolymerization.

Scheme 1. (A) Attempts To Synthesize Poly(glyceric Acid Carbonate) By Oxidation of Poly(1,2-glycerol Carbonate) and (B) Copolymerization of Benzyl Glycidate with CO_2 Using Binary and Bifunctional [SalcyCo^{III}X] Catalysts



As shown in Table 1, **3** effectively catalyzed the copolymerization of BG with CO_2 to afford PBGC with excellent carbonate linkage selectivity (>99%) and high polymer/cyclic carbonate selectivity (>90%) to give high molecular weight polymers with narrow molecular weight distribution. The polymers are of high regioregularity and showed a head-to-tail connectivity of 92% (Figure S5). The catalyst activity, however, was significantly lower than that reported for the polymerization of benzyl glycidyl ether (~15 vs ~150 h^{-1}, respectively).[38] This is likely a result of the electron-withdrawing effect of the carbonyl group. Decreasing the catalyst loading from 500:1 to 1000:1 resulted in a slight decrease in activity and polymer selectivity, and a significant increase in molecular weight (MW) while increasing the temperature to 40 °C afforded a significant decrease in polymer selectivity (Table 1, entry 5). Performing the reaction in toluene gave >90% monomer conversion with compromised activity (8 h^{-1}) and polymer selectivity (80%) while the MW remained similar, presumably due to both decreased polymer selectivity and trace amount of water introduced by toluene.

Polymer Microstructure. All the resultant polymers are highly region-regular with a head-to-tail selectivity of 92% by ^{13}C NMR. The carbonyl region of the ^{13}C NMR spectrum also showed the atactic nature of the polymer obtained from racemic BG and racemic catalyst (Figure S5). Size exclusion chromatography (SEC) analysis revealed molecular weights significantly lower than theoretical values and monomodal

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Table 1. Synthesis of Poly(benzyl Glycidate Carbonate) Using [SalcyCo^{III}X] Complexes 1−3[a]

no.	catalyst	temp. (°C)	catalyst loading	conversion (%)	turnover freq (h^{-1})	selectivity (% polymer)	M_n (kg/mol)	PDI
1[b]	**1**	25	500:1	65	–	–	–	–
2[b]	**2**	25	500:1	67	–	–	–	–
3	**3a**	25	500:1	62	12	90	14.2	1.18
4	**3a**	25	1000:1	70	11	89	21.4	1.19
5	**3a**	40	1000:1	58	18	55	18.1	1.21
6[c]	**3a**	25	1000:1	59	8	85	27.2	1.22
7[d]	**3a**	25	1000:1	67	13	92	24.2	1.19
8	**3b**	25	1000:1	69	16	93	30.5	1.14
9	**3a**	25	2000:1	66	10	90	32.2	1.23

[a]The reactions were performed in neat *rac*-BG (1.42 mL, 10 mmol) in an 8 mL autoclave under 220 psi CO_2 pressure unless otherwise noted. All resultant poly(benzyl glycidate carbonate)s (PBGC's) contain >99% carbonate linkage, as determined by ^{1}H NMR spectroscopy. [b]The only product formed was the cyclic carbonate. The binary system **1** was used for entry 1 and the [SalcyCo^{III}X]:[PPN]DNP ratio was 1:1. [c]The reaction was performed in 0.4 mL toluene. [d]The reaction was performed under 440 psi CO_2 pressure.

distribution with narrow molecular weight distribution (PDI < 1.20) (Figure S17). This result is in contrast to most of the previously reported systems where bimodal distributions were observed likely due to trace amounts of water acting as a chain transfer agent, leading to two populations of polymers with different molecular weights.[19,38,48] However, a MALDI-TOF study revealed that the polymer consists of a major and a minor population with overlapping molecular weight distribution and the signals match [1.0 (H) + 178.1 (BG) + 222.1 × *n* (CO_2-*alt*-BG) + 1.0 (H) + 23.0 (Na^+)] and [183.3 (2,4-dinitrophenolate) + 178.1 (BG) + 222.1 × *n* (CO_2-*alt*-BG) + 178.1 (BG) + 1.0 (H) + 23.0 (Na^+)], respectively (Figure 2). Structurally,

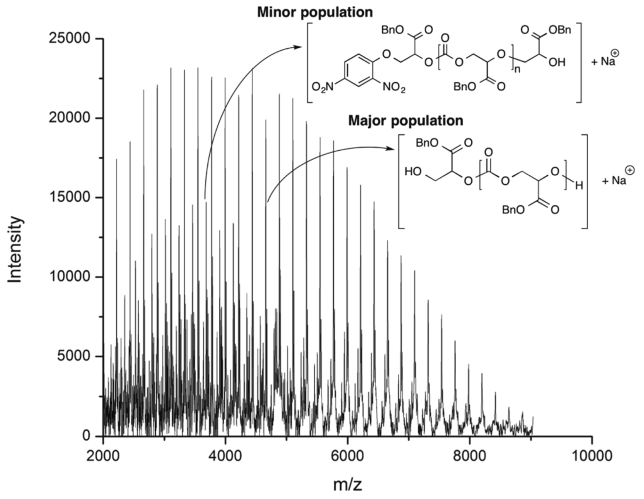

Figure 2. A MALDI-TOF spectrum of PBGC with molecular weight ~5000 g/mol. Note: The structures assigned to major and minor populations above are one representative of the regioisomeric structures. Regioisomeric structures (in-chain and chain end) give the same mass.

these two sets of signals correspond to populations with distinct end groups, e.g., a major population bearing hydroxyl groups on the chain ends and a minor population bearing a 2,4-dinitrophenoxy and a hydroxyl group on each end (Figure 2). This result is consistent with the fact that trace amounts of water serve as a chain transfer agent, leading to a population of telechelic species with two hydroxyl chain end besides the population of polymer chains that are initiated by DNP.

Hydrolytic Kinetic Resolution of Benzyl Glycidate and Synthesis of an Isotactic Version of the Poly(benzyl Glycidate Carbonate). Given the encouraging results above, we synthesized an isotactic version of PBGC. The hydrolytic kinetic resolution (HKR) of BG had not been previously reported. The HKR of racemic BG using (*R*,*R*)-SalcyCo^{III}OTs provided (*R*)-BG in >90% yield with >98% enantiomeric excess (Figure S15).[49,50] Copolymerization of (*R*)-BG with CO_2 using the enantiopure *S*-catalyst **3b**[19,51] afforded a polymer with an isotactic backbone and >95% head-to-tail selectivity (Figure 3A). Degradation of isotactic PBGAC to cyclic carbonate while

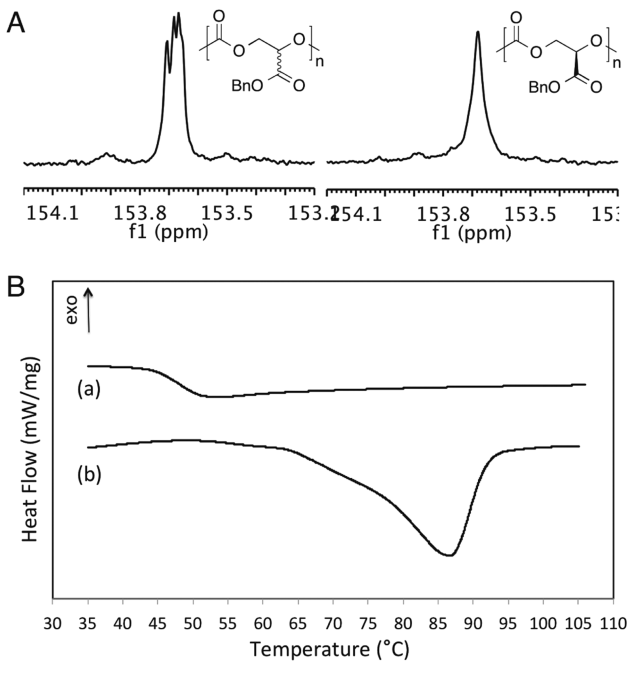

Figure 3. (A) ^{13}C carbonyl region of atactic (left) and isotactic (right) PBGC. (B) DSC trace of (a) atactic (b) isotactic PBGC.

conserving all stereogenic centers[52] yielded (R)-cyclic carbonate and (S)-cyclic carbonate with a ratio of 94:6 (88% e.e.), indicating that 5% of all the stereogenic centers in the starting epoxide were inverted during the polymerization.

Isotactic PBGC is a semicrystalline polymer with a melting temperature (T_m) = 87 °C by differential scanning calorimetry (DSC) (Figure 3B). In contrast, atactic poly(1,2-benzyl glycidate carbonate) is an amorphous material (glass transition temperature (T_g) = 44 °C). Interestingly, poly(benzyl 1,2-glycerol carbonate)s were found to be amorphous materials

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with a T_g of 8 °C regardless of tacticity.[53] While compared to isotactic poly(benzyl 1,2-glycerol carbonate), the only structural difference is that isotactic PBGC has a carbonyl instead of a methylene, which contributes to the rigidity of the backbone. Therefore, we tentatively attribute the observed increased crystallinity to the effect of the side-chain carbonyl group, which imparts backbone rigidity and facilitates interchain packing to form greater crystalline region. A similar effect was also observed for the isotactic version of poly(phenyl 1,2-glycerol carbonate) reported by Lu et al., which was shown to be a semicrystalline polymer with a T_m = 75 °C.[54]

Deprotection of PBGAC and Characterization of PGAC. The benzyl protecting group was removed by hydrogenolysis to give PGAC. Specifically, atactic PBGAC (MW = 25.4 kg/mol, PDI 1.19, Table 1, entry 4) was dissolved in ethyl acetate:methanol = 3:1 with Pd/C (20 wt % loading) and pressurized to 400 psi of H_2 at room temperature for 8 h.[38,55] After isolation of the polymer, ^{1}H NMR analysis revealed the aromatic peaks located at 7.1−7.2 ppm were no longer present, confirming the loss of the benzyl group (Figure 4).

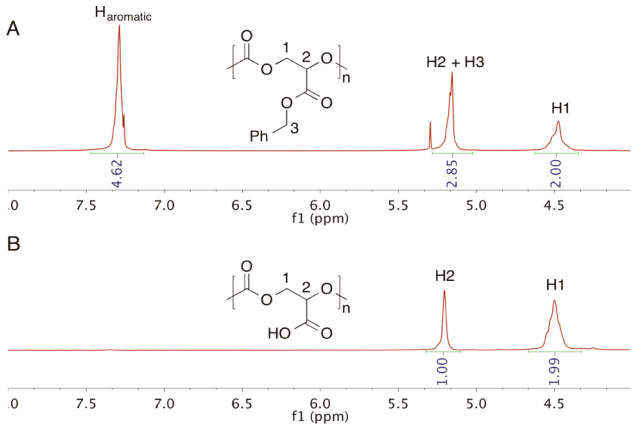

Figure 4. (A) ^{1}H NMR of PBGAC in $CDCl_3$. (B) ^{1}H NMR of atactic PGAC in DMSO-d_6 after hydrogenolysis.

Isotactic PGAC was synthesized using the same reaction condition. The result from SEC in water was significantly higher than expected (~23 kg/mol) likely due to hydrophobic aggregation in aqueous phase. When dimethylforamide (DMF) was used as the GPC eluent, the MW was measured to be ~15 kg/mol, which was in agreement with the theoretical value. PGAC was isolated as a white polymer. It is soluble in polar aprotic or protic solvent such as DMF, dimethyl sulfoxide (DMSO), water, and methanol, while not soluble in relatively nonpolar solvent such as tetrahydrofuran and dichloromethane.

Degradation Study and Cytotoxicity of Poly(glyceric Acid Carbonate). The rate of PGAC degradation in deionized water was monitored by SEC and compared to that of a PAA with a similar molecular weight. In DI water, PGAC showed significant degradation ($t_{1/2}$ ~ 12 days) over a 26 day period, while, as expected, no degradation occurred for PAA (Figure 5). In our recent paper, we reported the synthesis of poly(1,2-glycerol carbonate) which exhibited remarkably accelerated degradation rate compared to poly(1,3-glycerol carbonate), and it was proposed that for poly(1,2-glycerol carbonate)s, the accelerated degradation is a consequence of an intramolecular attack of the primary hydroxyl group onto the carbonate backbone, leading to the formation of the thermally stable five-membered cyclic carbonate. For PGAC, when the degradation

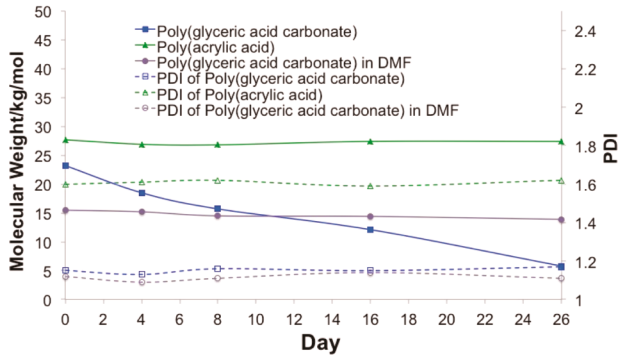

Figure 5. Degradation behavior of PGAC and PAA in water and DMF.

was performed in anhydrous DMF, which eliminated the hydrolysis mechanism, PGAC exhibited negligible degradation over a 26 day period, indicating that intramolecular cyclization of the carboxylic group onto the carbonate backbone to form *O*-carboxyanhydride did not occur. This is likely a consequence of the combined lowered nucleophilicity, relatively higher rigidity of the carboxylic acid group in PGAC compared to the primary hydroxyl group in poly(1,2-glycerol carbonate), and the higher energy of the resultant five-membered cyclic *O*-carboxyanhydride structure compared to the five-membered cyclic carbonate. In contrast, when PGAC is dissolved in pH buffer 8.4 it rapidly degrades within 8 h with formation of the *O*-carboxyanhydride structure, as determined by NMR (Figure S22). This result can be explain by the more nucleophilic nature of the sodium carboxylate formed on treatment of the pH 8.4 buffer solution. We propose that the degradation occurs randomly along the carbonate backbone. In the dry state PGAC remained stable over a few months, while poly(1,2-glycerol carbonate) degraded as monitored by IR (infrared spectroscopy).[27]

The cytotoxicity of PGAC was evaluated at various concentrations against NIH fibroblast 3T3 cells for 24 h and compared to PAA. As shown in Figure 6, PGAC showed no

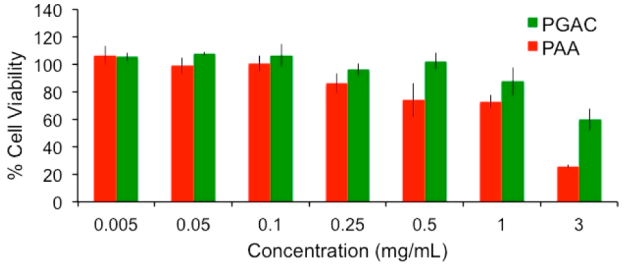

Figure 6. Cytotoxicity study for PGAC against NIH Fibroblast 3T3 cells at different concentrations.

observable cytotoxicity at low concentrations and started to show toxicity at 1 mg/mL. This value is close to some of the previously reported anionic polymers.[56,57] PAA showed a similar cytotoxicity profile with a slightly lower cell viability at 1 mg/mL and a sharp decrease in cell viability when the concentration was increased from 1 mg/mL to 3 mg/mL.

Hydrogel Preparation and Study. PAA and its copolymer with other hydrophilic polymers have been used extensively in preparing hydrogels for various applications.[58−60] Thus, the degradability of a PGAC-based hydrogel was evaluated by preparing a hydrogel using efficient aziridine

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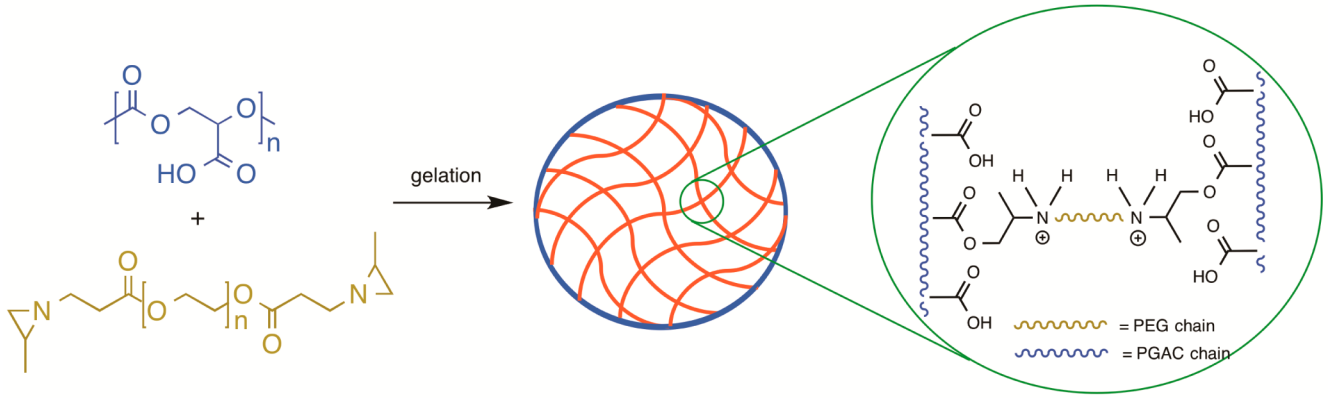

Figure 7. Cross-linking chemistry used to prepare the PGAC–PEG diaziridine-based hydrogels.

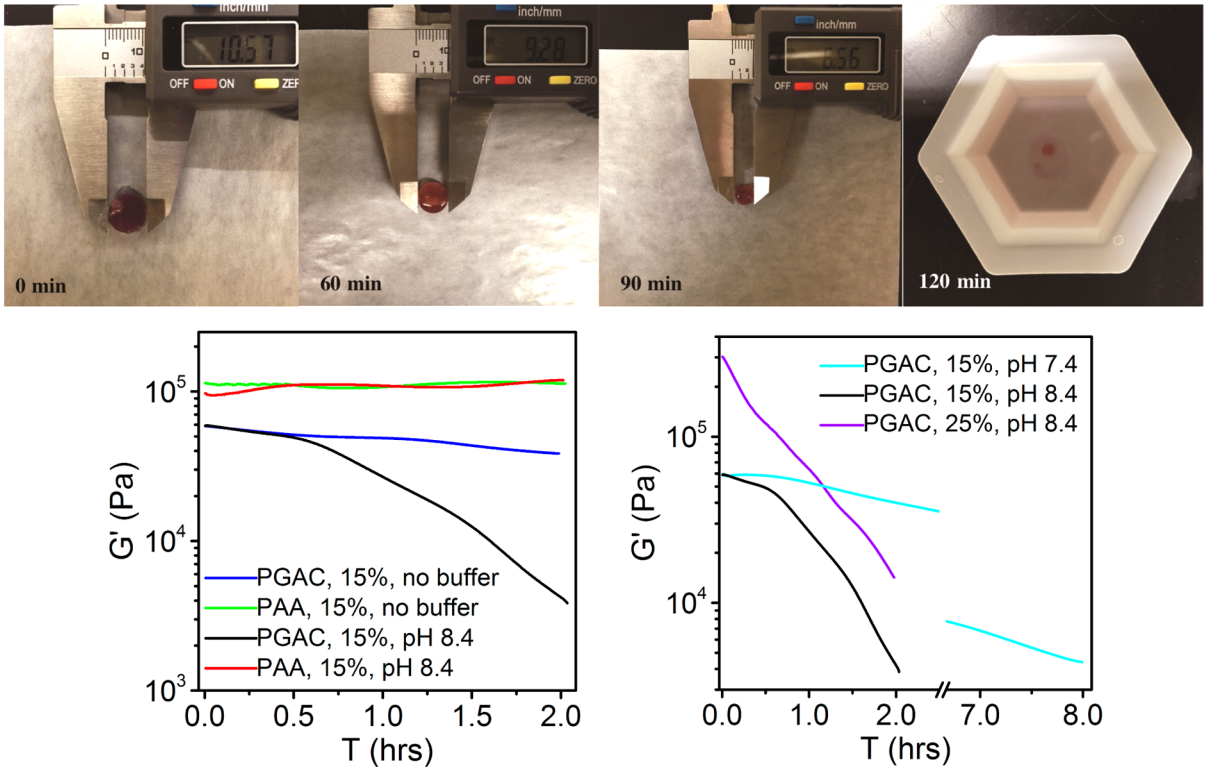

Figure 8. (Upper panel) Degradation study of hydrogels prepared from PGAC with PEG diaziridine (with nile red dye) with 15% degree of cross-linking in pH 8.4 $NaHCO_3$ solution. (Lower panel) Rheological study of PGAC and PAA gels under different conditions.

cross-linking chemistry[61,62] and compared to that of a hydrogel prepared wtith PAA. Specifically, PEG diaziridine was synthesized by Michael addition of methyl aziridine with PEG diacrylate (MW = 3700 g/mol) in one step to afford pure PEG diaziridine product without the need for further purification. PEG diaziridine was then mixed with PGAC in DMF for gelation, followed by dialysis to remove DMF (Figure 7).

As shown in Figure 8, the PGAC hydrogel with a cross-linking degree (mole of aziridine/mol of acid unit) of 15% was stable in deionized (DI) water, but it underwent rapid degradation in a pH 8.4 $NaHCO_3$ solution over a 2 h period as monitored by a significant change in G' from 5.8×10^4 to 3.8×10^3 Pa. Importantly, the corresponding PAA hydrogel with the same degree of cross-linking showed no observable degradation in DI water and in a pH 8.4 $NaHCO_3$ solution over a 2 h period. Increasing the degree of cross-linking to 25% has negligible effect on degradation kinetics, which is consistent with the fact that the degradation mainly occurs via the backbone of PGAC. Interestingly, in a 7.4 PBS buffer, the PGAC hydrogel, although slower, still underwent significant degradation as monitored by the decrease in the G' from 5.8×10^4 to 4×10^4 Pa in 2 h and finally to about 4×10^3 Pa after 8 h. While the polycarbonate backbone and the cross-linking sites within the hydrogel are stable under pH 7.4, we attributed the degradation to the neutralization of the remaining carboxylic acid side chain to form sodium carboxylate on treatment of pH 7.4 PBS buffer and subsequent attack of the carboxylate anion on the carbonate backbone. This is also supported by the degradation study of PGAC in pH 7.4 buffer prepared in D_2O solvent (Figure S22). This result is in sharp contrast to most degradable hydrogels reported which possess degradation half times of several days or weeks.

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CONCLUSION

In summary, a facile route to a degradable version of PAA, PGAC, is described via the copolymerization of benzyl glycidate and CO_2 using the bifunctional [SalcyCo^{III}X] catalyst followed by hydrogenolysis. The polymerizaiton reaction occurs with high carbonate linkage selectivity (>99%) and polymer/cyclic carbonate selectivity (~90%). Deprotection of the resultant polymer gives PGAC which degrades in aqueous solution. With a degradable site introduced into every repeating unit, the hydrogel prepared from PGAC readily degrades, while the one prepared from PAA does not. The current pool of acidic polymers is limited in both size and diversity and includes only a handful of well-defined structures such as poly(malic acid)s,[63] poly(aspartic acid)s, poly(glutamic acid)s, and poly(glyoxylic acid).[64] PGAC expands the repertoire of and serves as an important complement. Along with its degradability and biocompatibility, we envision that PGAC will be of utility for chemists and material scientist working on a wide range of challenges in the chemical, biomedical, and pharmaceutical areas.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07911.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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