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Synthesis and Characterization of Poly(glyceric acid carbonate): A Degradable Analogue of Poly(acrylic acid)

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KEYWORDS: poly(acrylic acid), polycarbonate, glyceric acid, glycerol, biocompatible, degradable, hydrogel, isotactic.

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 CO₂ 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 materials 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)s. 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) and its copolymer with other hydrophilic monomers are produced on the multi-million 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, poly(acrylic acid) suffers from poor degradability because of its all-carbon backbone (Figure 1). It is well established that only oligomers of poly(acrylic acid) with molecular weights (MWs) less than 600 g/mol (degree of polymerization < 8) are biodegradable²⁻⁶ and yet, the molecular weights of most industrially relevant poly(acrylic acid)s are well above this value. For example, low molecular weight poly(acrylic acid)s 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, water soluble polymers, e.g., poly(acrylic acid)s, 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

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 poly(acrylic acid) still remains the pol-



Poly(acrylic acid)

Degradable Poly(acrylic acid) Mimic - poly(glyceric acid carbonate)

Figure 1. Chemical structures of linear poly(acrylic acid) (left) and poly(glyceric acid carbonate) (right).

ymers 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 poly(acrylic acid) – namely, poly(glyceric acid carbonate). This strategy is atom efficient, provides a site for degradation at every repeating unit, and affords safe, nontoxic, and renewable degradation products – CO₂ 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 are 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 5-membered cyclic carbonates instead of 1,2-linked polycarbonates.¹⁵

Table 1. Synthesis of Poly(benzyl glycidate carbonate) Using [SalcyCo^{III}X] Complexes 1-3

#	Catalyst	Temp.	Catalyst loading	Conversion (%)	Turnover Freq. (h ⁻¹)	Selectivity (% polymer)	M _n (kg/mol)	PDI
1 ¹	1	25 °C	500:1	65	-	-	-	-
2 ¹	2	25 °C	500:1	67	-	-	-	-
3	3a	25 °C	500:1	62	12	90	14.2	1.18
4	3a	25 °C	1000:1	70	11	89	21.4	1.19
5	3a	40 °C	1000:1	58	18	55	18.1	1.21
6 ²	3a	25 °C	1000:1	59	8	85	27.2	1.22
7 ³	3a	25 °C	1000:1	67	13	92	24.2	1.19
8	3b	25 °C	1000:1	69	16	93	30.5	1.14
9	3a	25 °C	2000:1	66	10	90	32.2	1.23

The reactions were performed in neat *rac*-BG (1.42 mL, 10 mmol) in an 8 mL autoclave under 220 psi CO₂ pressure unless otherwise noted. All resultant poly(benzyl glycidate carbonate)s (PBGC's) contain >99% carbonate linkage, as determined by ¹H NMR spectroscopy. ¹The 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. ²The reaction was performed in 0.4 mL toluene. ³The reaction was performed under 440 psi CO₂ pressure.

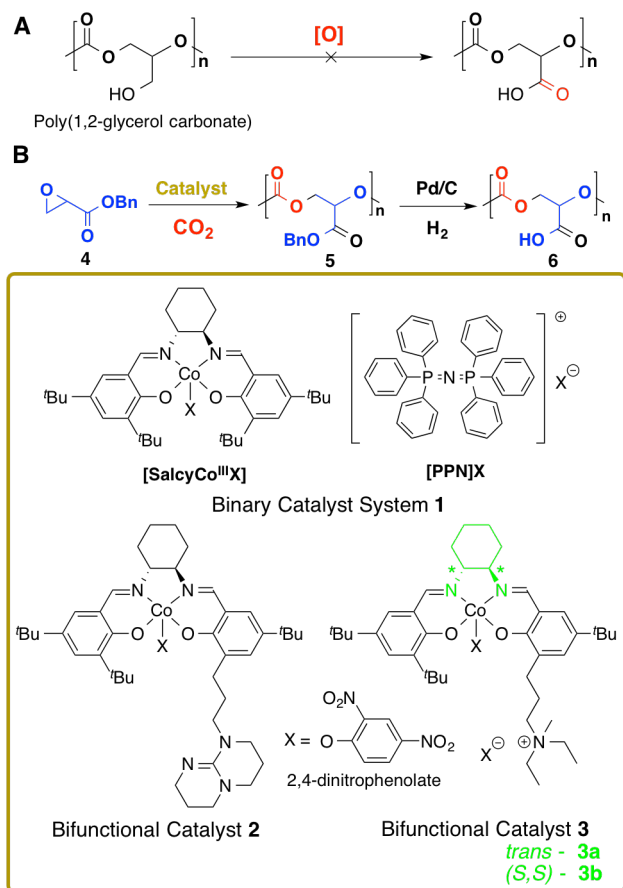
Given the design criterion of a carbonate linkage in the main chain of the polymer, we considered the synthetic strategy of catalytic copolymerization of epoxide/CO₂. This polymerization method is one of several exciting advances in polymer chemistry,¹⁶⁻¹⁹ and is receiving increasingly more attention for both environmental and economical reasons. Moreover, the

catalytic epoxide/CO₂ copolymerization provides a platform for synthesizing poly(1,2-glycerol carbonate)s that are 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 synthesized²²⁻³² and evaluated for a range of biomedical applications.³³⁻³⁷ Herein, we reported the first synthesis of poly(glyceric acid carbonate). Specifically, atactic and isotactic poly(benzyl glycidate carbonate)s are synthesized via the ring-opening copolymerization of *rac*-(*R*)-benzyl glycidate with CO₂ using a bifunctional *rac*-(*S,S*)-cobalt salen catalyst, the deprotection of benzyl protected polymer to give poly(glyceric acid carbonate)s, the degradation of the polymer in aqueous conditions, and its cytotoxicity profile. Finally, we describe a cross-linked hydrogel prepared from poly(glyceric acid carbonate) and characterize the degradation rate compared to a similarly prepared poly(acrylic acid) hydrogel.

RESULTS AND DISCUSSION

At the outset of the project, we anticipated that post-polymerization oxidation of poly(1,2-glycerol carbonate)³⁸ may offer a facile method to access poly(glyceric acid carbonate) (Scheme 1A). However, under a range of well-known mild and selective oxidation conditions such as Heyns oxidation,³⁹ RuCl₃-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 poly(glyceric acid carbonate) 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 counter anion for all of the catalysts.^{17,19} Benzyl glycidate



Scheme 1. (A) Attempts to synthesize poly(glyceric acid carbonate) by oxidation of poly(1,2-glycerol carbonate). (B) Copolymerization of benzyl glycidate with CO₂ using binary and bifunctional [SalcyCo^{III}X] catalysts.

(BG) **4** was synthesized via an efficient two-step esterification-oxidation route in high overall yield (~80%).⁴⁵ The copolymerization of **4** and CO₂ 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 CO₂ 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** towards BG was surprising given the fact that this catalyst is highly active towards 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.

As shown in Table 1, **3** effectively catalyzed the copolymerization of BG with CO₂ to afford poly(benzyl glycidate carbonate) 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% (Fig. S5). The catalyst activity, however, was significantly lower than that reported for the polymerization of benzyl glycidyl ether (~15 h⁻¹ 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.

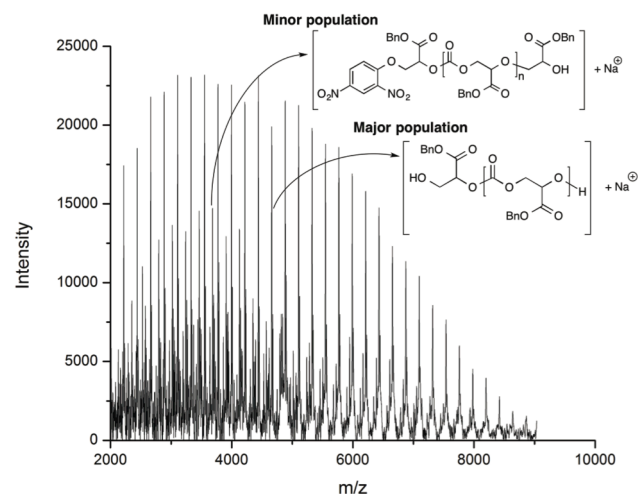


Figure 2. A MALDI-TOF spectrum of poly(benzyl glycidate carbonate) with molecular weight ~ 5000 g/mol. NOTE: The structures assigned to major and minor populations above are one representative of the regioisomeric structures. Regioisomeric structures (in-chain and chain end) give the same mass.

Polymer Microstructure. All the resultant polymers are highly region-regular with a head-to-tail selectivity of 92% by ¹³C NMR. The carbonyl region of the ¹³C 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 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 amount of water acting as 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 (CO₂-alt-BG) + 1.0 (H) + 23.0 (Na⁺)] and [183.3 (2,4-dinitrophenolate) + 178.1 (BG) + 222.1 × n (CO₂-alt-BG) + 178.1 (BG) + 1.0 (H) + 23.0 (Na⁺)], respectively (Figure 2). Structurally, 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

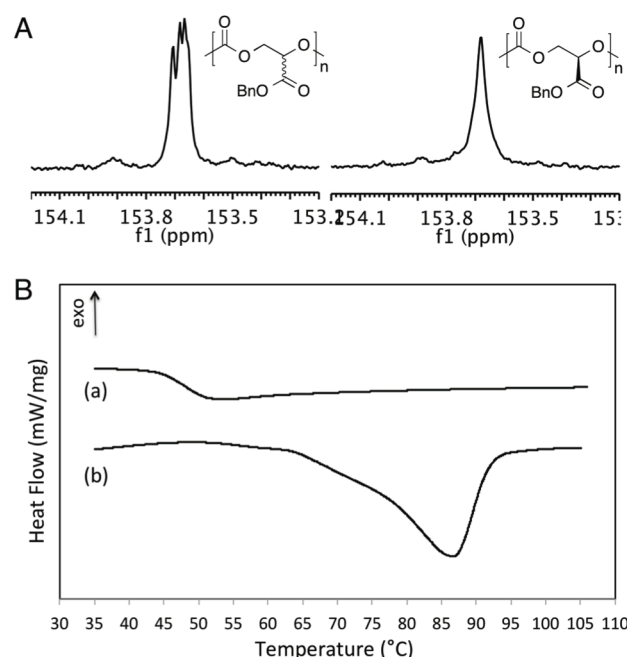


Figure 3. (A) ¹³C carbonyl region of atactic (left) and isotactic (right) poly(benzyl glycidate carbonate). (B) Differential scanning calorimetry (DSC) trace of (a) atactic (b) isotactic poly(benzyl glycidate carbonate).

amount of water serves as 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 (HKR) 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 poly(benzyl glycidate carbonate). 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 CO₂ using the enantiopure *S*-catalyst **3b**^{19,51} afforded a polymer with an iso-

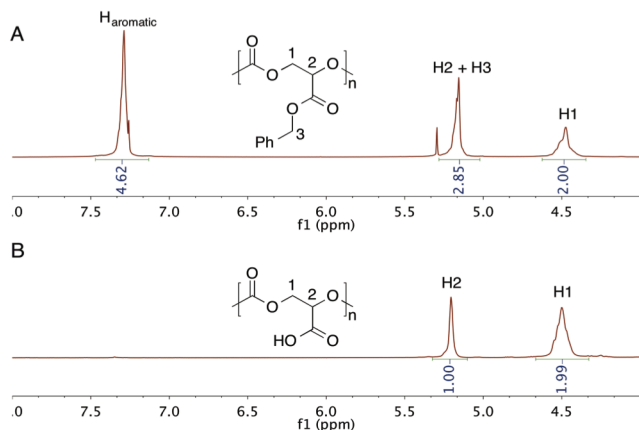


Figure 4. (A) ¹H NMR of PBGAC in CDCl₃. (B) ¹H NMR of atactic PGAC in DMSO-*d*₆ after hydrogenolysis.

tactic backbone and >95% head-to-tail selectivity (Figure 3A). Degradation of isotactic PBGAC to cyclic carbonate while conserving all stereogenic centers⁵² 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 poly(benzyl glycidate carbonate) is a semicrystalline polymer with a *T_m* (melting temperature) = 87 °C by DSC (differential scanning calorimetry) (Figure 3B). In contrast, atactic poly(1,2-benzyl glycidate carbonate), is an amorphous material (*T_g* (glass transition temperature) = 44 °C). Interestingly, poly(benzyl 1,2-glycerol carbonate)s were found to be amorphous materials 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 poly(benzyl glycidate carbonate) 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 inter-chain 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 poly(glyceric acid carbonate) (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 H₂ at room temperature for 8 h.^{38,55} After isolation of the polymer, ¹H 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). 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 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 dimethylformide, dimethylsulfoxide, water, and methanol, while not soluble in relatively non-polar solvent such as tetrahydrofuran and dichloromethane.

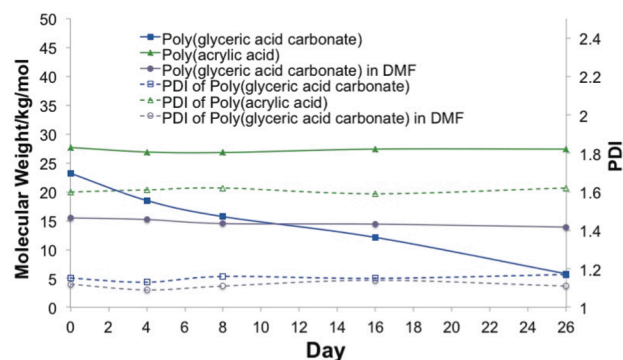


Figure 5. Degradation behavior of PGAC and PAA in water and DMF.

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 poly(acrylic acid) 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 poly(acrylic acid) (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 was performed in anhydrous DMF, which eliminated the hydrolysis mechanism, PGAC exhibited negligible degradation over a 26-day period, indicating that intramolecular cyclization of 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 hours with formation of the O-carboxyanhydride structure, as determined by NMR (Figure S22). This result can be explained 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-

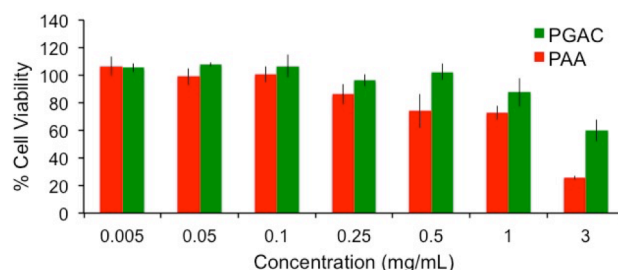


Figure 6. Cytotoxicity study for PGAC against NIH Fibroblast 3T3 cells at different concentrations.

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 hours and compared to PAA. As shown in Figure 6, PGAC showed no 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} Poly(acrylic acid) 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. Poly(acrylic acid) 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 cross-linking chemistry^{61,62} and compared to that of a hydrogel prepared with poly(acrylic acid). Specifically, PEG diaziridine were 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/mole of acid unit) of 15%

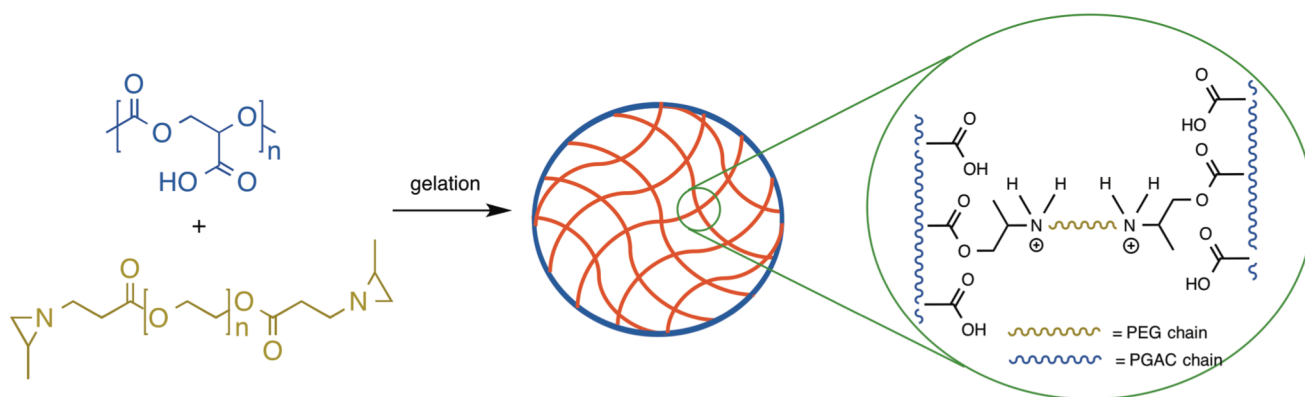


Figure 7. Cross-linking chemistry used to prepare the PGAC-PEG diaziridine based hydrogels.

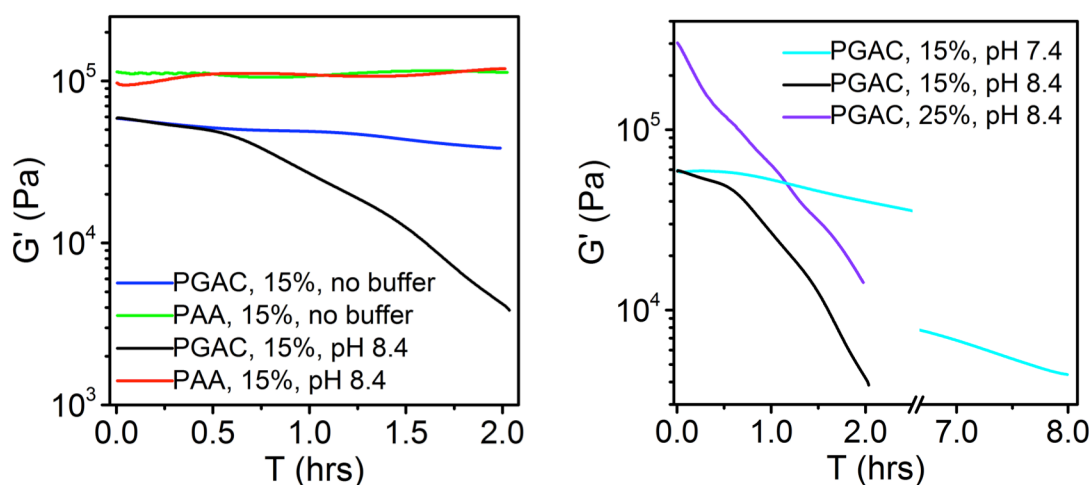
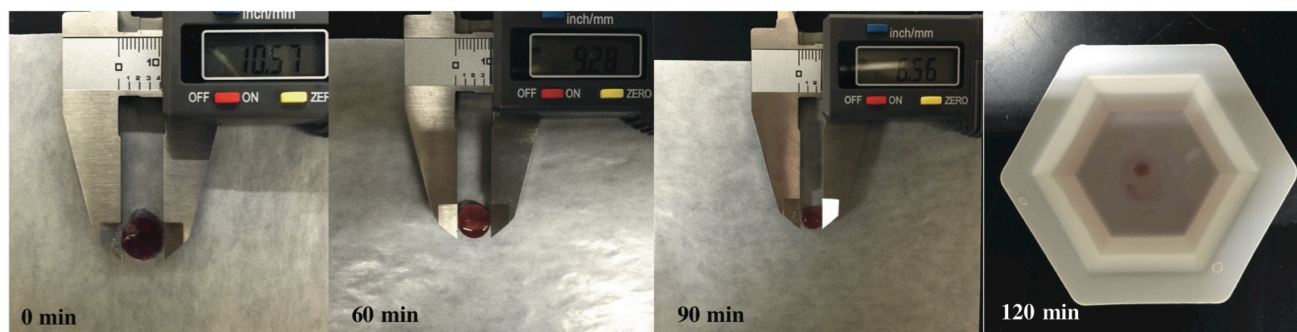


Figure 8. (Upper Panel) Degradation study of hydrogels prepared from PGAC with PEG diaziridine (with Nile red dye) with 15% degree of cross-linking in pH 8.4 NaHCO₃ solution; (Lower Panel) Rheological study of PGAC and PAA gels under different conditions.

was stable in deionized (DI) water but it underwent rapid degradation in a pH 8.4 NaHCO₃ solution over a two-hour period as monitored by a significant change in G' from 5.8 × 10⁴ to 3.8 × 10³ 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 NaHCO₃ solution over a two-hour 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 × 10⁴ to 4 × 10⁴ Pa in 2 hours and finally to about 4 × 10³ Pa after 8 hours. 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 D₂O solvent (Figure S22). This result is in sharp contrast to most degradable hydrogels reported which possess degradation half times of several days or weeks.

CONCLUSION

In summary, a facile route to a degradable version of poly(acrylic acid) – poly(glyceric acid carbonate) –, is described via the copolymerization of benzyl glycidate and CO₂ using the bifunctional [SalcyCo^{III}X] catalyst followed by hydrogenolysis. The polymerization reaction occurs with high carbonate linkage selectivity (>99%) and polymer/cyclic carbonate selectivity (~90%). Deprotection of the resultant polymer gives poly(glyceric acid carbonate) 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 poly(acrylic acid) 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 Poly(glyceric acid carbonate) expands the repertoire of and serves as an important complement. Along with its degradability and biocompatibility, we envision that poly(glyceric acid carbonate) 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

Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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