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Environmentally Benign CO_2-Based Copolymers: Degradable Polycarbonates Derived from Dihydroxybutyric Acid and Their Platinum–Polymer Conjugates

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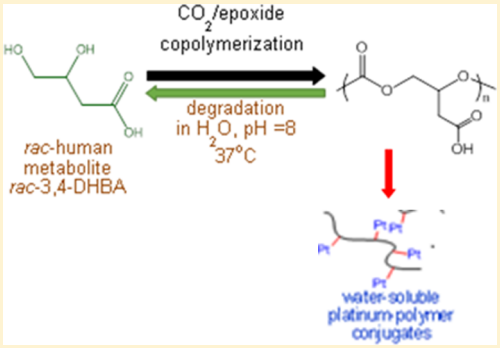
Supporting Information

ABSTRACT: (*S*)-3,4-Dihydroxybutyric acid ((*S*)-3,4-DHBA), an endogenous straight chain fatty acid, is a normal human urinary metabolite and can be obtained as a valuable chiral biomass for synthesizing statin-class drugs. Hence, its epoxide derivatives should serve as promising monomers for producing biocompatible polymers via alternating copolymerization with carbon dioxide. In this report, we demonstrate the production of poly(*tert*-butyl 3,4-dihydroxybutanoate carbonate) from *racemic-tert*-butyl 3,4-epoxybutanoate (*rac*-^{t}Bu 3,4-EB) and CO_2 using bifunctional cobalt(III) salen catalysts. The copolymer exhibited greater than 99% carbonate linkages, 100% head-to-tail regioselectivity, and a glass-transition temperature (T_g) of 37 °C. By way of comparison, the similarly derived polycarbonate from the sterically less congested monomer, methyl 3,4-epoxybutanoate, displayed 91.8% head-to-tail content and a lower T_g of 18 °C. The *tert*-butyl protecting group of the pendant carboxylate group was removed using trifluoroacetic acid to afford poly(3,4-dihydroxybutyric acid carbonate). Depolymerization of poly(*tert*-butyl 3,4-dihydroxybutanoate carbonate) in the presence of strong base results in a stepwise unzipping of the polymer chain to yield the corresponding cyclic carbonate. Furthermore, the full degradation of the acetyl-capped poly(potassium 3,4-dihydroxybutyrate carbonate) resulted in formation of the biomasses, *β*-hydroxy-*γ*-butyrolacetone and 3,4-dihydroxybutyrate, in water (pH = 8) at 37 °C. In addition, water-soluble platinum–polymer conjugates were synthesized with platinum loading of 21.3–29.5%, suggesting poly(3,4-dihydroxybutyric acid carbonate) and related derivatives may serve as platinum drug delivery carriers.



INTRODUCTION

Petroleum derived chemicals currently are by far the most important sources of polymeric materials. Considering their vast utilization as fuels which lead to their rapid depletion, finding alternative carbon sources for producing polymers based on renewable monomers has been the subject of numerous research programs worldwide.[1] A significant contribution to this area is the production of biodegradable polycarbonates via the alternating copolymerization of bioderived epoxides and the renewable C1 feedstock, carbon dioxide.[2] The recent development of single-site metal catalysts with well-defined structures have provided active catalytic systems which operate under mild reaction conditions, and in some instances afford regio-and/or stereoselective copolymers.[3]

Because of their biocompatibility, biodegradability, and approval for use in biomedical devices by the United States Food and Drug Administration (FDA), aliphatic polycarbonates are very important synthetic biomaterials.[4] Since it has been reported that aliphatic polycarbonates undergo hydrolytic degradation to give carbon dioxide and the corresponding alcohol,[5] there has been a significant interest in the preparation of CO_2-based polymers that originate from renewable epoxides that undergo degradation to yield nontoxic metabolites in the human body. For this purpose, (*S*)-*tert*-butyl 3,4-epoxybutanoate ((*S*)-^{t}Bu 3,4-EB) is a promising monomer due to its similarity to (*S*)-3,4-dihydroxybutyric acid ((*S*)-3,4-DHBA). (*S*)-3,4-DHBA, an endogenous straight chain fatty acid, is a normal human urinary metabolite. It originates from the degradation of carbohydrates or from the metabolism of *γ*-hydroxybutyrate, a naturally occurring substance found in the human central nervous system. Normal adults excrete (0.37 ± 0.15) mmol of 3,4-dihydroxybutyrate per 24 h. The compound is also detectable in blood (18.0 (0.0–54.0) mM) and in cerebrospinal fluid (CSF) (15.0 ± 15.0 mM).[6] Moreover, (*S*)-3,4-DHBA is a highly useful chiral intermediate in synthesizing statin-class drugs such as CRESTOR, LIPITOR, and carnitine. In addition, in the microbial (*E. coli*) glucose metabolism process, (*S*)-3,4-DHBA is obtained as a valuable chiral biomass, as recently reported by Dhamankar and Martin et al.[7]

In chemotherapy-based small-molecule platinum-containing drugs, cisplatin, carboplatin, and oxaliplatin have been extensively used in the treatment of solid cancers, such as ovarian, bladder, testicular, and non-small-cell lung cancers. However, clinical use of platinum-containing drugs has been limited due to several major side effects, including nephrotox-

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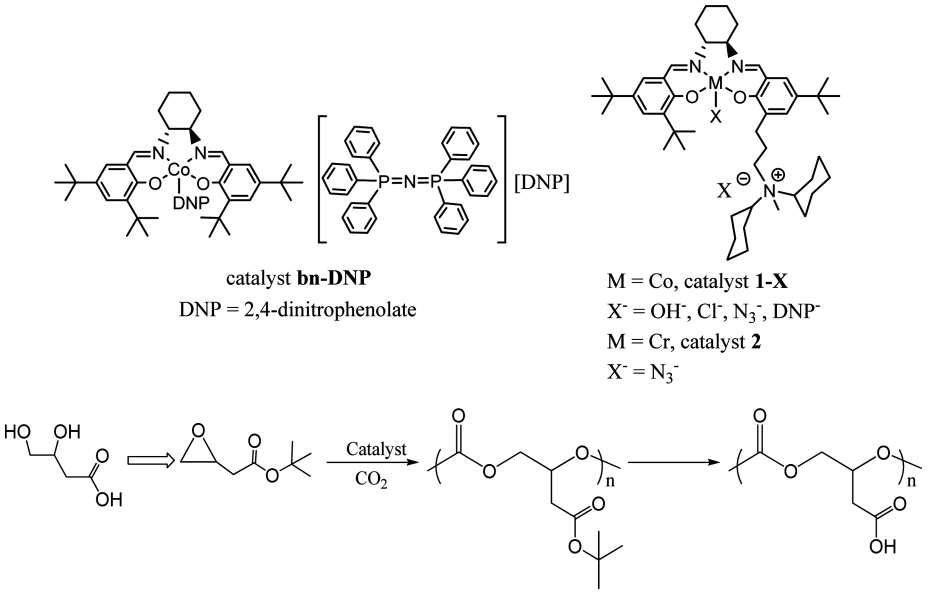
Scheme 1



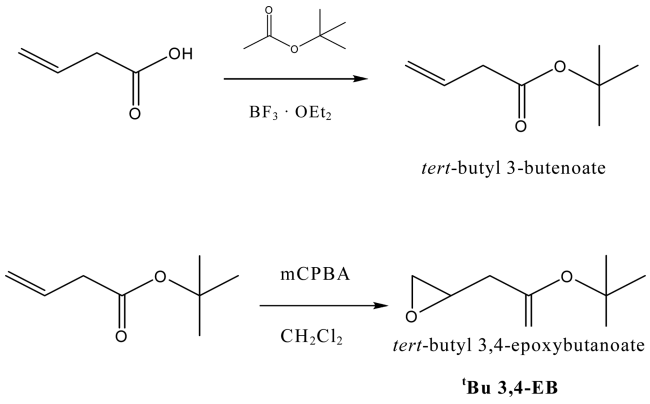
icity and neurotoxicity. Because of the drug's nonselectivity, normal and transformed cells are equally affected. Further, poor water solubility leads to suboptimal distribution in the circulation. The electrophilic nature of platinum in its aquated form, which is partly present when dissolved in the circulation system, results in its high affinity for amino acids. Because of these limitations, research efforts in creating carrier-bound platinum complexes are aimed at the development of platinum−polymer conjugates. Hence, it has been proposed to employ polymers for the delivery of platinum to protect the drugs from nonspecific binding, to increase circulation time, and to use the enhanced permeation and retention effect (EPR) of cancer cells.[8]

In efforts aimed at expanding the availability of biorelated polycarbonates obtained by the alternating copolymerization of CO_2 and renewable epoxides, the *tert*-butyl protected poly(*tert*-butyl 3,4-dihydroxybutanoate carbonate) (P^{t}BuDHBC) was synthesized from *rac*-^{t}Bu 3,4-EB or (*S*)-^{t}Bu 3,4-EB with CO_2 using the binary [(1*R*,2*R*-salen)Co(III) (DNP)]/[PPN][DNP] (bn-DNP) or bifunctional catalysts [(1*R*,2*R*-salen)M(III)$(X)_2$] (catalyst 1-X: M = Co, X = OH^-, Cl^-, N_3^-, DNP^- (2,4-dinitrophenolate); catalyst 2: M = Cr, X = N_3^-), as shown in Scheme 1. Additionally, *rac*-methyl 3,4-epoxybutanoate (*rac*-Me 3,4-EB) was used to explore the steric effect of the epoxide on the copolymerization process. In order to construct platinum−polymer conjugates for potential biomedicinal applications, postpolymerization functionalization was conducted by anchoring aspartate/glycine-aspartate and (DACH)$PtCl_2$ (DACH = (1*R*,2*R*)-diaminocyclohexane) onto the biorelated polycarbonate scaffold.

RESULTS AND DISCUSSION

Epoxide Synthesis. Synthesis of *tert*-butyl 3,4-epoxybutanoate (^{t}Bu 3,4-EB) was achieved by the two-step process depicted in Scheme 2. This pathway is greener than the three-step literature procedure.[9] In the process described here, a catalytic quantity of $BF_3{\cdot}OEt_2$ triggers the coupling reaction of 3-butenoic acid with *tert*-butyl acetate to afford *tert*-butyl 3-butenoate. Epoxidation of *tert*-butyl 3-butenoate was carried out with *m*CPBA (*meta*-chloroperoxybenzoic acid) to provide

Scheme 2



the epoxide in good yield. See the Supporting Information (SI) for the details of the synthetic procedure, as well as ^{1}H NMR spectra (Figures S1 and S2).

Copolymerization Reactions. Initially, the copolymerization reactions of twice-distilled over CaH_2 (~0.043% water content) *rac*-^{t}Bu 3,4-EB with CO_2 were carried out employing bifunctional catalysts 1-X (X = Cl^-, N_3^-, DNP^-). As noted in Table 1, in the absence of *added* water, only catalyst 1-Cl afforded any coupling product which was exclusively the corresponding cyclic carbonate. However, upon adding 10 equiv of water to catalyst 1-DNP, copolymerization of CO_2/*rac*-^{t}Bu 3,4-EB readily occurred at 40 °C. A similar reactivity pattern was observed under identical reaction conditions for the copolymerization process involving the sterically less hindered *rac*-methyl 3,4-epoxybutanoate (*rac*-Me 3,4-EB) monomer and CO_2 (Table 2). These results suggest that small, good nucleophiles with poor leaving group properties, that is, resulting from chain-transfer with water or the diol resulting from epoxide hydrolysis, initiates the alternating copolymerization process.[10]

To further examine this hypothesis, the use of once-dried *rac*-^{t}Bu 3,4-EB monomer which contains traces of adventitious water was subjected to the copolymerization process with CO_2. As shown in Table 3, the catalyst 1-DNP was found to

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Table 1. Coupling Reaction of CO_2 and Twice-Distilled *tert*-Butyl 3,4-Epoxybutanoate (^{t}Bu 3,4-EB)[a]

catalysts	t (h)	T (°C)	conversion (%)[e]	TOF (h^{-1})	selectivity (polymer %)[e]	carbonate linkages (%)[e]	M_n (GPC) (Da/mol)	PDI
1-DNP[b]	18	40	0	0				
1-DNP[c]	18	40	91.3	25.4	98.5	100	5600	1.19
1-DNP[d]	88	40	81.8	9.3	91.8	100	12 565	1.57
1-Cl[b]	18	40	50	13.9	0			
1-N_3[b]	18	40	0	0				
2[b]	18	40	0	0				

[a]The coupling reaction was conducted in neat *rac*-^{t}Bu 3,4-EB in a 25 mL autoclave at 30 bar of CO_2 pressure. [b]Catalyst/*rac*-^{t}Bu 3,4-EB = 1:500. [c]Catalyst/H_2O/*rac*-3,4-E^{t}BuB = 1:10:500. [d]Catalyst/H_2O/*rac*-^{t}Bu 3,4-EB = 1:10:1000. [e]Characterized by ^{1}H NMR spectrum of crude product.

Table 2. Coupling Reaction of CO_2 and Twice-Distilled Methyl 3,4-Epoxybutanoate (Me 3,4-EB)[a]

catalysts	t (h)	T (°C)	conversion (%)[d]	TOF (h^{-1})	selectivity (polymer %)[d]	carbonate linkages (%)[d]	M_n (GPC) (Da/mol)	PDI
1-DNP[b]	18	40	0	0				
1-DNP[c]	18	40	88.7	24.6	97.7	100	5375	1.53
1-Cl[b]	18	40	69.7	19.4	0			
1-N_3[b]	18	40	0	0				
2[b]	18	40	0	0				

[a]The coupling reaction was conducted in neat *rac*-Me 3,4-EB in a 25 mL autoclave at 30 bar of CO_2 pressure. [b]Catalyst/*rac*-Me 3,4-EB = 1:500. [c]Catalyst/H_2O/*rac*-Me 3,4-EB = 1:10:500. [d]Characterized by ^{1}H NMR spectrum of crude product.

Table 3. Coupling Reaction of CO_2 and Once-Distilled (>0.5% Water Content) *tert*-Butyl 3,4-Epoxybutanoate (^{t}Bu 3,4-EB)[a]

catalysts	t (h)	T (°C)	conversion (%)[e]	TOF (h^{-1})	selectivity (polymer %)[e]	carbonate linkages (%)[e]	M_n (GPC) (Da/mol)	PDI
bn-DNP[b]	22	25	72.5	16.5	61.7	100	4936	1.17
1-DNP[b]	22	25	98.5	22.4	100	100	15 847	1.07
1-DNP[c]	22	25	96.1	21.8	100	100	14 692	1.08
1-DNP[b]	8	40	100	62.5	100	100	16 901	1.04
1-DNP[d]	16	40	100	62.5	100	100	20 850	1.08
2[b]	18	40	8.9	2.5	100	100		

[a]The coupling reaction was conducted in neat ^{t}Bu 3,4-EB in a 25 mL autoclave at 30 bar of CO_2 pressure. [b]Catalyst/*rac*-^{t}Bu 3,4-EB = 1:500. [c]Catalyst/(*S*)-^{t}Bu 3,4-EB = 1:500. [d]Catalyst/*rac*-^{t}Bu 3,4-EB = 1:1000. [e]Characterized by ^{1}H NMR spectrum of crude product.

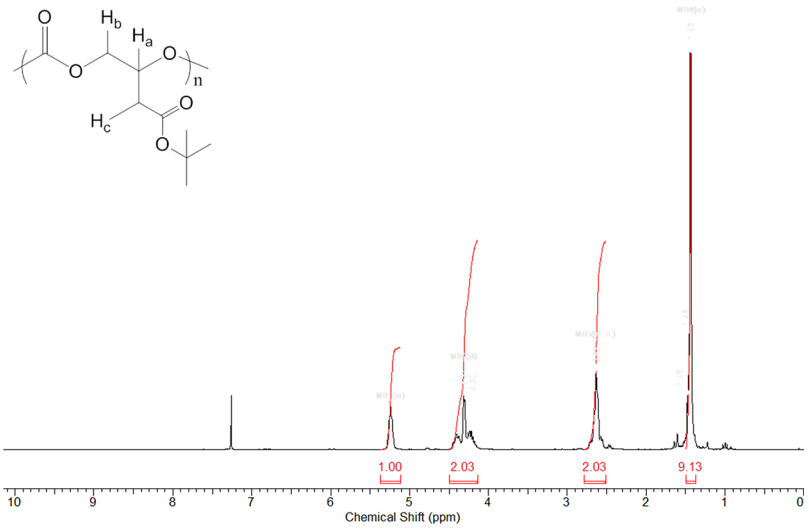

Figure 1. ^{1}H NMR spectra ($CDCl_3$) of copolymer poly(*tert*-butyl 3,4-dihydroxybutanoate carbonate) (P^{t}BuDHBC).

selectively copolymerize CO_2 and *rac*-^{t}Bu 3,4-EB to afford the corresponding polycarbonate with greater than 99% carbonate linkages. This is in contrast to the lower TOF for catalyst 2, and the poor polymer selectivity of the bn-DNP catalyst (61.7% at 25 °C). The isolated copolymers exhibited narrow molecular weight distributions with PDI values less than 1.10 and displayed bimodal distributions. The main-chain sequence of the resulting poly(*tert*-butyl 3,4-dihydroxybutyrate carbonate) (P^{t}BuDHBC) was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum, the resonance of the methine CH was observed at 5.24 ppm, and signals at δ = 3.3–3.6 ppm assignable to ether linkages were not evident (Figure 1). By way of contrast with poly(methyl 3,4-dihydroxybutyrate carbonate) (PMeDHBC) which exhibited 91.8% head-to-tail region-selectivity, the ^{13}C NMR spectrum of the atactic P^{t}BuDHBC copolymer shows it to consist of 100% head-to-

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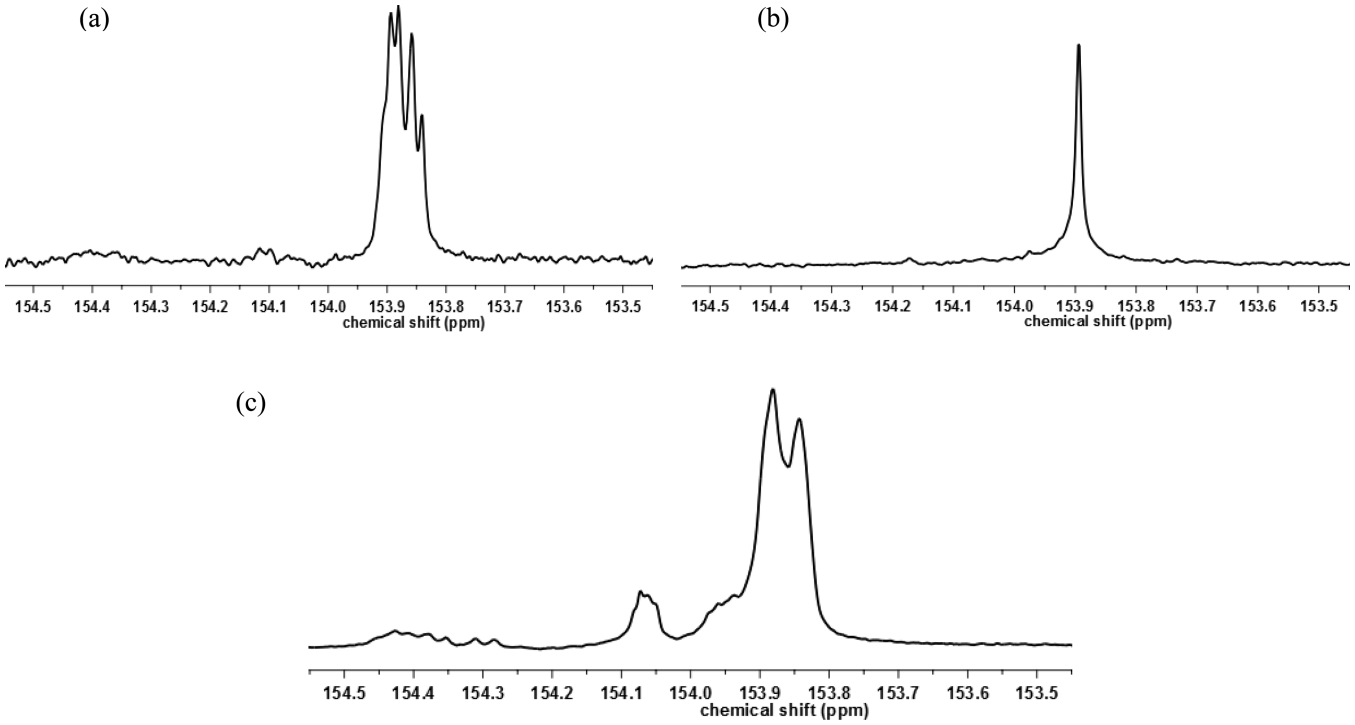

Figure 2. ^{13}C NMR spectra ($CDCl_3$) of carbonate region for copolymers (a) poly(*tert*-butyl 3,4-dihydroxybutanoate carbonate), (b) poly((*S*)-*tert*-butyl 3,4-dihydroxybutanoate carbonate), and (c) poly(methyl 3,4-dihydroxybutanoate carbonate).

tail regio-chemistry (Figure 2). This observation implies that the sterically congested *tert*-butyl group promotes ring-opening of *rac*-^{t}Bu 3,4-EB to occur exclusively at the C_β–O bond during its copolymerization with CO_2.

Provided with this encouraging regioregular result, it was of interest to synthesize a chiral, isotactic version of this copolymer. To this end, a hydrolytic kinetic resolution of *rac*-^{t}Bu 3,4-EB was carried out with Jacobson's catalyst in a 44% yield (based on the racemic epoxide) to afford the S-enantiomer following the published procedure.[9b] Subsequent copolymerization of (*S*)-^{t}Bu 3,4-EB and CO_2 in the presence of catalyst 1-DNP afforded an isotactic poly((*S*)-*tert*-butyl 3,4-dihydroxybutyrate carbonate) (S-P^{t}BuDHBC) with a molecular weight of 14.7 kg and a PDI of 1.08 (entry 3 in Table 3). In the ^{13}C NMR spectrum, the isotactic polymer shows 100% head-to-tail selectivity and exhibits a single sharp signal at 153.9 ppm (Figure 2b).

With the polycarbonates, P^{t}BuDHBC and S-P^{t}BuDHBC, in hand, the *tert*-butyl protecting groups of the pendent carboxylate groups were removed using trifluoroacetic acid (TFA) in dry CH_2Cl_2 at ambient temperature over 12 h. Upon isolation, the resulting copolymer's ^1H NMR spectrum (Figure S3) revealed the absence of the *tert*-butyl resonance at 1.43 ppm, confirming its removal from the polymer. The poly(3,4-dihyroxybutyric acid carbonate) (PDHBAC) is not soluble in water or common organic solvents, but was soluble in methanol and DMSO. However, subsequent deprotonation of PDHBAC by 0.45 equiv of K_2CO_3 in wet MeOH afforded the water-soluble poly(potassium 3,4-dihydroxybutyrate carbonate) (PKDHBC) (see Figure S4 for ^1H NMR spectrum). The thermal properties of the various isolated polycarbonates were examined by conducting DSC analyses. As shown in Table 4, the glass transition temperatures (T_g), which are a function of changes in the polymer properties such as modulus, increase as the flexible methyl group is replaced by the sterically more congested *t*-butyl group. Because of the polar carboxylic acid pendent groups and the intrinsic ionic character of the potassium salts, PDHBAC/S-PDHBAC and PKDHBC, stronger interchain interactions lead to these polycarbonates exhibiting higher T_g values than the others.

Table 4. Glass Transition Temperature (T_g) for Polycarbonate

polycarbonates	M_n (g/mol) (GPC (THF))	T_g (°C) (DSC)
PMeDHBC	5375	18
P^{t}BuDHBC	5600/15847	37
S-P^{t}BuDHBC	14 692	40
PDHBAC		65
S-PDHBAC		74

Depolymerization and Degradation Reactions. It is of interest to investigate depolymerization and degradation reaction pathways of these polycarbonates under anaerobic conditions. In our previous studies, base-initiated depolymerization of polycarbonates derived from CO_2 and epoxides generally occurred via a backbiting process of the deprotonated copolymer chain end, resulting in an unzipping of the polymer chain to provide the corresponding cyclic carbonate.[11] As illustrated in Scheme 3, the depolymerization of poly(*tert*-butyl 3,4-dihydroxybutyrate carbonate) is found to proceed by way of a similar end-scission pathway following deprotonation of the hydroxyl chain end by the strong non-nucleophilic base NaHMDS (sodium bis(trimethylsilyl)amide). Upon addition of base, immediate depolymerization was noted as evidenced by the appearance of ^1H NMR resonances at δ = 3.63 and 3.25 ppm in d_8-toluene. These chemical shifts are assigned to the methylene hydrogens of the generated cyclic carbonate (Figure S5). At 40 °C, P^{t}BuDHBC slowly depolymerized cleanly to its cyclic carbonate counterpart, reaching a molar ratio of cyclic carbonate to copolymer of 1.79 after 12 days (Figure 3).

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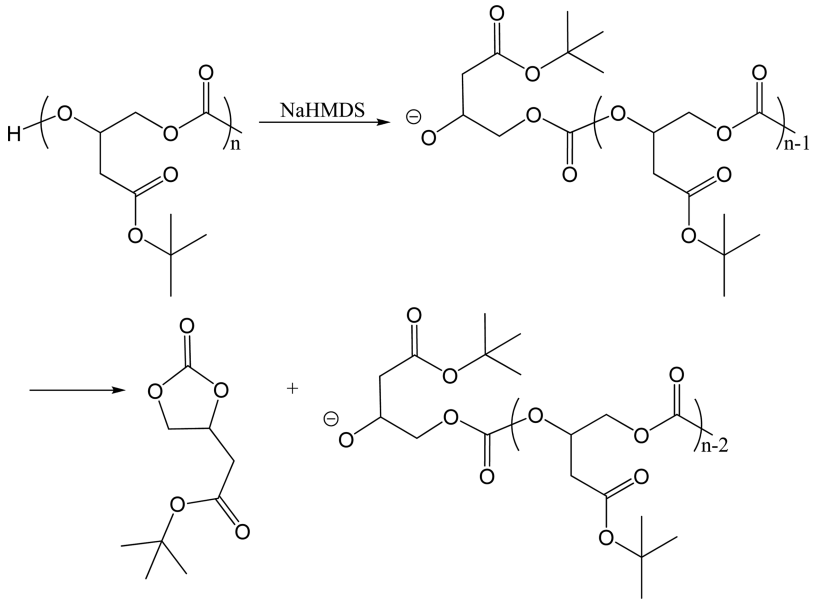
Scheme 3



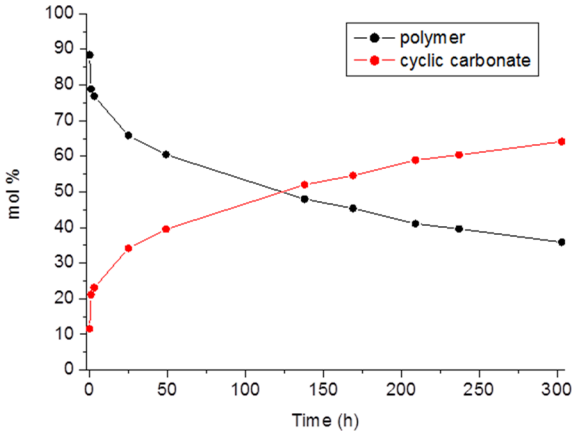


Figure 3. Depolymerization of poly(*tert*-butyl 3,4-dihydroxybutanoate carbonate) in d_8-toluene at 40 °C subsequent to deprotonation with NaHMDS.

On the other hand, for poly(3,4-dihydroxybutyric acid carbonate), neither depolymerization nor degradation was observed by ^{1}H NMR spectroscopy upon heating the d_7-DMF dissolved polymer in the absence of NaHMDS at 37 °C for 12 days. This indicates that intramolecular cyclization of the carboxylic acid group onto the carbonate backbone to afford *O*-carboxyanhydride does not occur. Such an observation is likely a consequence of the lower nucleophilicity of the carboxylic acid group in PDHBAC as compared to the primary hydroxyl group in poly(1,2-glycerol carbonate).[2b] In contrast, when acetyl-capped poly(potassium 3,4-dihydroxybutyrate carbonate) was dissolved in water (D_2O, pH = 8) and heated at 37 °C, degradation occurred with formation of cyclic carbonate, *β*-hydroxy-*γ*-butyrolacetone and 3,4-dihyroxybutyrate as determined by ^{1}H NMR spectroscopy (Figure S6). Over a 3 day period, polycarbonate and cyclic carbonate fully degraded into *β*-hydroxy-*γ*-butyrolacetone and 3,4-dihyroxybutyrate. To further corroborate cyclic carbonate degradation and *β*-hydroxy-*γ*-butyrolacetone hydrolysis, samples composed of cyclic carbonate or *β*-hydroxy-*γ*-butyrolacetone were dissolved in D_2O (pH = 8) and heated at 37 °C while monitoring by ^{1}H NMR spectroscopy. The complete degradation of cyclic carbonate occurred within 3 days with the formation of *β*-hydroxy-*γ*-butyrolacetone and 3,4-dihydroxybutyrate (Figure S7). Similarly, the hydrolysis of *β*-hydroxy-*γ*-butyrolacetone to afford 3,4-dihydroxybutyrate was observed (Figure S8). Based on these results, the degradation of acetyl-capped poly(potassium 3,4-dihyroxybutyrate carbonate) can be attributed to the more nucleophilic nature of the carboxylate in D_2O, and it is proposed that the degradation occurs randomly along the carbonate backbone. As illustrated in Scheme 4, it is presumed that intramolecular cyclization of the carboxylate onto the carbonate backbone forms intermediate A containing an *O*-carboxyanhydride.[2e] Subsequent hydrolysis of *O*-carboxyanhydride furnishes the polycarbonate containing a hydroxyl chain end. Deprotonation of a hydroxyl polymer chain end in weak basic condition triggers end-scission depolymerization, leading to the formation of cyclic carbonate. Presumably, hydrolysis of cyclic carbonate and concomitant nucleophilic attack of the carboxylate at C_α–O bond in intermediate B yields *β*-hydroxy-*γ*-lactone, with hydrolysis generating 3,4-dihydroxybutyrate. The complete degradation of acetyl-capped poly(potassium 3,4-dihydroxybutyrate carbonate) into the biomasses, *β*-hydroxy-*γ*-butyrolacetone and 3,4-dihydroxybutyrate, in water (pH = 8) at 37 °C indicates that this polycarbonate is biodegradable, human-friendly, and environmentally benign.

Synthesis of Platinum–Polymer Conjugates. Efficient delivery of therapeutics into tumor cells to increase the intracellular drug concentration is a major challenge for cancer therapy due to drug resistance and inefficient cellular uptake. The strategy of using delivery vehicles to selectively transport more of anticancer agents to tumors is clinically attractive. This can be achieved by linking a platinum-based drug to a water-soluble, biocompatible, biodegradable polymer in order to exploit the enhanced permeability and retention (EPR) effect of macromolecules in tumors.[8] The aim of the current study is to construct water-soluble polycarbonates which can serve as anticancer drug carriers. In this regard, the coupling reaction of poly(3,4-dihydroxybutyric acid chloride carbonate) (PDHBAC-Cl) and di-*tert*-butyl-L-aspartate or glycine-di-*tert*-butyl-L-aspartate was conducted in dry CH_2Cl_2 under an argon

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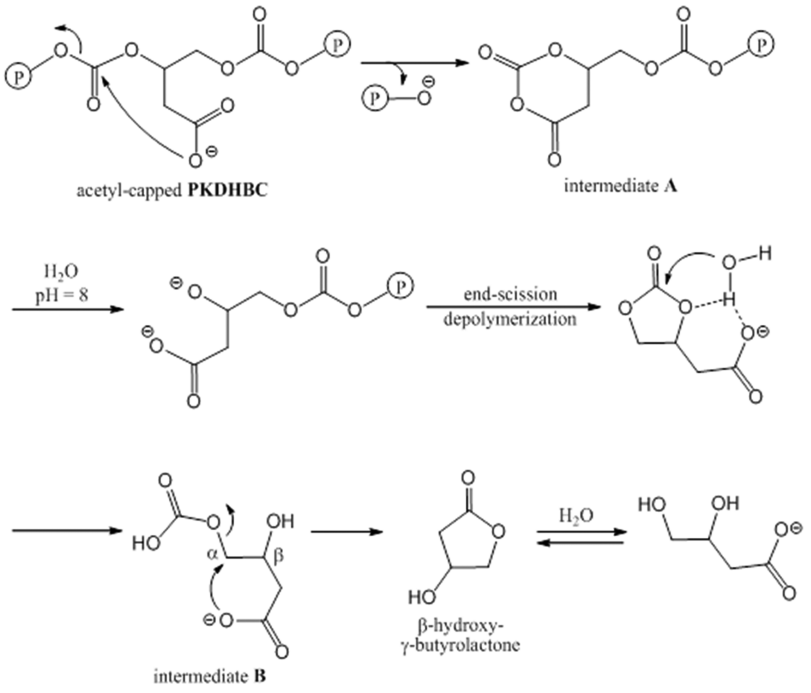
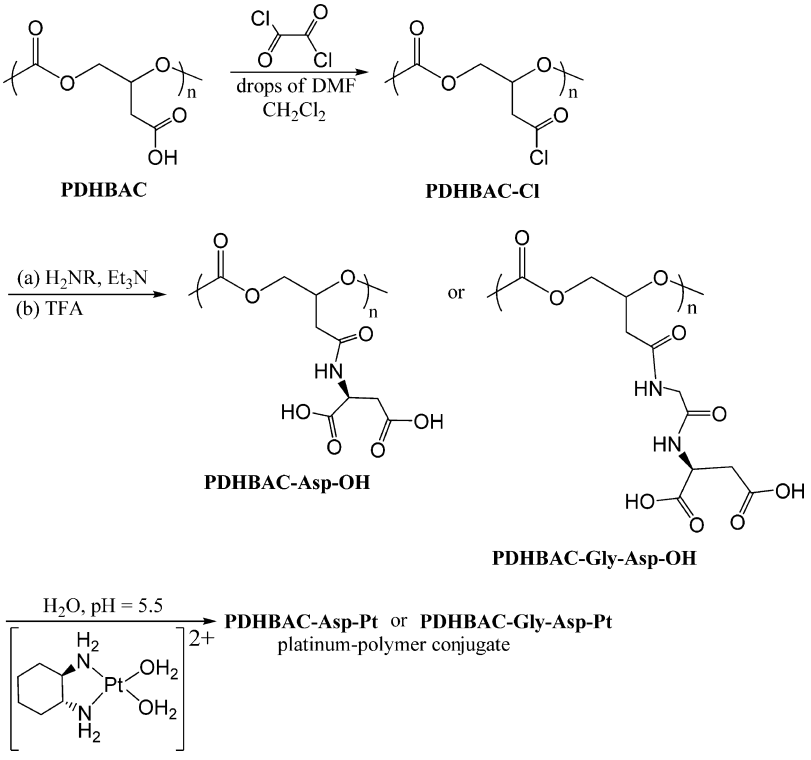
Scheme 4



Scheme 5



atmosphere. The subsequent deprotection by TFA and dialysis against water afforded water-soluble polycarbonates PDHBAC-Asp-OH and PDHBAC-Gly-Asp-OH (Scheme 5). The ^{1}H NMR spectra of the water-soluble polymers containing the pendant carboxylic acid groups is shown in SI Figures S9 and S10, where the chemical shifts at 8.20 and 4.52 ppm (in DMSO) are assigned to the amide proton (−C(O)N*H*CH−) and the methine proton (−C(O)NHC*H*−) of aspartic acid, respectively. For PDHBAC-Gly-Asp-OH, the resonance of methylene protons (−C(O)NHCH_2C(O)−) of glycine was found at 3.74 ppm (in DMSO). Because of the large number of pendant carboxylic acid groups in the resulting polymers, both PDHBAC-Asp-OH and PDHBAC-Gly-Asp-OH are not soluble in CH_2Cl_2, but are completely soluble in water and DMSO.

In an effort to construct platinum−polymer conjugates, PDHBAC-Asp-Pt and PDHBAC-Gly-Asp-Pt, the reaction of

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PDHBAC-Asp-OH or PDHBAC-Gly-Asp-OH with aqueous $[(DACH)Pt(OH_2)_2][NO_3]_2$ (DACH = (1*R*,2*R*)-diaminocyclohexane) was conducted. The carboxylic acid residues from PDHBAC-Asp-OH and PDHBAC-Gly-Asp-OH were deprotonated at pH 10 using K_2CO_3, and subsequently neutralized by cautious addition of aqueous 1 N HNO_3. Since the coordination bonds between water ligands and platinum are usually labile and subject to ligand substitution reactions,[6] it is presumed that carboxylate and amide (−C(O)NH−) groups would coordinate to the Pt center, generating a variety of derivatives in the aqueous environment. After removal of excess $[(DACH)Pt(OH_2)_2][NO_3]_2$ by dialysis, the light yellow solid was characterized by ^{1}H NMR spectra (Figure S11), and the loaded amounts of platinum were determined by neutron activation analysis (NAA) spectrometry (Table 5). In the ^{1}H NMR spectra (D_2O), chemical shifts ranging from 5.00 to 6.00 ppm are assigned to methine C*H* protons in polycarbonate backbone. The broadening of methine resonance is due to the combination of various polymer conformations as Pt is coordinated by carboxylate and amide side chains. Moreover, the resonances of DACH are found within the range of 1.00−2.50 ppm. For PDHBAC-Asp-Pt, the loading was as high as 29.5% (wt/wt, relative to the polymer), while a lower loading (21.3%) was found with PDHBAC-Gly-Asp-Pt. As compared with the theoretical Pt loading (full Pt loading), the loaded percentage of Pt (86.0%) onto PDHBAC-Asp-OH is higher than that (68.3%) onto PDHBAC-Gly-Asp-OH. The water solubilities of PDHBAC-Asp-Pt and PDHBAC-Gly-Asp-Pt were determined to be 11 and 13 mg/mL, respectively. Dynamic light scattering (DLS) analysis shows no hydrodynamic diameter distribution observed in PDHBAC-Asp-Pt and PDHBAC-Gly-Asp-Pt aqueous solutions, demonstrating platinum−polymer conjugates dissolve completely in water. In combination with NAA and DLS data, it is presumed that carboxylate, amide-chelating (*N*,*O*-coordinate mode), and amide, amide-chelating (*N*,*N*-coordinate mode) are dominant in the platinum−polymer conjugates. These results suggest that poly(3,4-dihydroxybutyric acid carbonate) and the related derivatives have the potential to serve as platinum drug delivery carriers for future anticancer pharmaceutical applications.

Table 5. Neutron Activation Analyses for Platinum Determination

platinum−polymer conjugates	Pt (wt %)	Pt (wt %) (full loading)	% of Pt loading
PDHBAC-Asp-Pt	29.5	34.3	86.0
PDHBAC-Gly-Asp-Pt	21.3	31.2	68.3

CONCLUSIONS

Because the endogenous straight chain fatty acid, (*S*)-3,4-dihydroxybutyric acid, is a normal human urinary metabolite and can be obtained as a valuable chiral biomass for the synthesis of statin-class drugs, its epoxide derivative *racemic-tert*-butyl 3,4-epoxybutanoate represents a renewable monomer for copolymerization with CO_2 to afford a biodegradable polycarbonate. In summary, we have synthesized new copolymers from this group of epoxides and carbon dioxide utilizing bifunctional cobalt(III) salen catalysts in the presence of sterically unhindered nucleophiles as initiators. The isolated polycarbonates contained more than 99% carbonate linkages and exhibited narrow molecular weight distributions. Poly(*tert*-butyl 3,4-dihydroxybutyrate carbonate) was shown to possess 100% head-to-tail regioselectivity and a glass transition temperature of 37 °C. A chiral, isotactic poly((*S*)-*tert*-butyl 3,4-dihydroxybutyrate carbonate) was synthesized which displayed a slightly higher T_g of 40 °C, and was characterized by a single ^{13}C NMR resonance in the carbonate region at 153.9 ppm. Depolymerization of poly(*tert*-butyl 3,4-dihydroxybutyrate carbonate) was found to occur via an end-scission pathway following deprotonation of its hydroxyl terminal group by base. Moreover, full degradation of acetyl-capped poly(potassium 3,4-dihydroxybutyrate carbonate) into the biomasses, β-hydroxy-γ-butyrolacetone and 3,4-dihydroxybutyrate, in water (pH = 8) at 37 °C indicates that this polycarbonate is biodegradable, human-friendly, and environmentally benign. Relevant to protecting anticancer drugs from nonspecific binding, increased circulation time, and taking advantage of the enhanced permeation and retention effect (EPR) of macromolecules in cancer cells, platinum−polymer conjugates, PDHBAC-Asp-Pt and PDHBAC-Gly-Asp-Pt, were synthesized with platinum loading of 29.5% and 21.3%, respectively. As a result of their high Pt content (>65%) and the absence of a hydrodynamic diameter distribution being observed in PDHBAC-Asp-Pt and PDHBAC-Gly-Asp-Pt aqueous solutions, it may be concluded that carboxylate, amide-chelating (*N*,*O*-coordinate mode), and amide, amide-chelating (*N*,*N*-coordinate mode) are predominant in the platinum−polymer conjugates. Potentially, these polycarbonates and their platinum−polymer conjugates could expand the repertoire of biocompatible, biodegradable polymers available for future anticancer pharmaceutics.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01327.

Figures, experimental details and characterization data for racemic epoxides, CO_2-based polymers, degradation of cyclic carbonate potassium salt, and β-hydroxy-γ-butylrolacetone hydrolysis (PDF)

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Notes

The authors declare no competing financial interest.

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