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Degradation Behavior of Poly(lactide-*co*-carbonate)s Controlled by Chain Sequences

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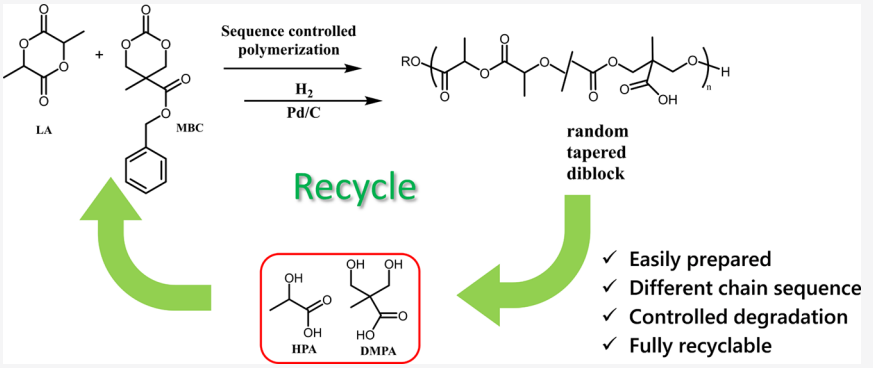

ABSTRACT: Immortal copolymerization of lactide (LA) and 2-methyl-2-benzyloxycarbonyl-1,3-trimethylene carbonate (MBC) affords random, tapered, and diblock microstructured poly(lactide-*co*-carbonate)s. Subsequent debenzylation of these poly(LA-*co*-MBC)s by Pd/C catalytic hydrogenation gives poly(LA-*co*-MCC)s containing carboxylic acid, which show controlled degradation performance during in vitro hydrolytic degradation experiments. The degradation rates of poly(LA-*co*-MCC)s are proved for the first time to be affected significantly by lactide−carbonate linkages in the main chains, following the trend of lactide−carbonate unit (L−C/C−L)>carbonate−carbonate unit (C−C)>lactide−lactide unit (L−L). The resultant hydrolysis products are the precursors for synthesizing the corresponding monomers. Therefore, the degradable and recyclable materials are accomplished.

INTRODUCTION

Producing sustainable and biocompatible polymers based on renewable resources has been the subject of numerous research programs worldwide.[1−3] Over the past few decades, polylactide (PLA), as a representative alternative of nondegradable petroleum-based materials, has been widely used in packaging, agriculture, textile, and biomedical fields.[4−7] A great progress has been made in preparation of stereoregular PLA through ring-opening polymerization (ROP) of *racemic*-lactide (*rac*-LA) by using stereoselective catalysts.[8−14] The resultant stereoblock isotactic PLA can form a stereocomplex with a higher melting point than that of homopolymers poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA).[15−20] On the other hand, when PLA is used as a drug delivery material and other medicine, the slow degradation rate (usually a couple of months or years) limits its application; therefore, how to make the degradation controllable to satisfy various demands has been a research target.[21−23] In 2010, Mayer and co-workers prepared a family of poly(lactic-*co*-glycolic acid)s, (PLGA)s, bearing isotactic, syndiotactic, and atactic sequences through complicated assembly of different segmer units.[24−26] They found that the degradation rate of PLGA is ruled by the content of the LG connecting points of the two monomer units [lactic acid (L); glycolic acid(G)], which relates closely to the sequence distributions. The alternating PLGA composed of LG connections exhibits a more gradual and constant degradation rate than its random analog with the same overall composition. Hence, introducing suitable segments into the PLA main chain to adjust its degradation performance is highly desired; however to date, the research related to the sequence of a PLA-based copolymer matrix versus its degradation property is rather scarce.[27]

Aliphatic polycarbonates (APCs), which represent another important class of biodegradable polymers, have broad biomedical applications in surgical suture, bone fixation, and drug release materials owing to their good biocompatible and elasticity.[28−30] Compared to polyesters like PLA, APCs are easily attacked by nucleophilic reagents on the carbonate groups to give carbon dioxide (CO_2) and corresponding alcohols through hydrolytic degradation;[31] furthermore, it can

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Scheme 1. Diagram of Syntheses of Sequenced Poly(lactide-*co*-carbonate)s and their Recycle Pathway

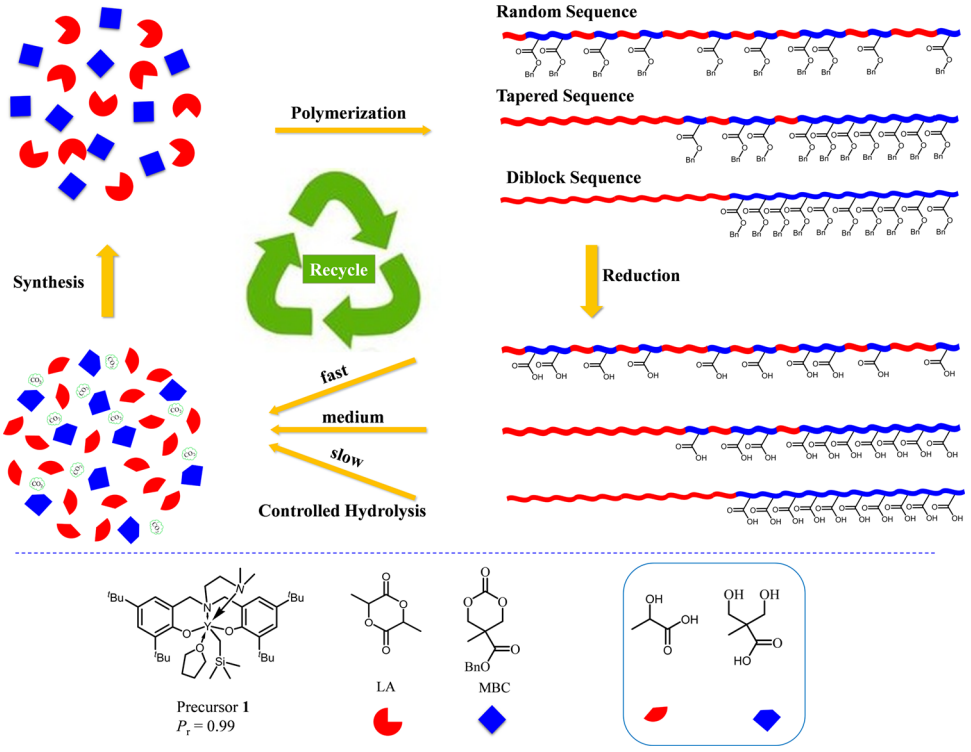

Table 1. Homo- and Copolymerization of LA with MBC Using Precursor 1/Ph_2CHOH

entry[a]	LA	$[Cat.]_0$:$[Ph_2CHOH]_0$:$[LA]_0$:$[MBC]_0$	MBC[b] (mol %)	$M_{n,calcd}$ (kg/mol)	$M_{n,SEC}$[c] (kg/mol)	PDI[c]	T_g/T_m[d] (°C)
1		1:20:0:1000	100	12.2	16.7	1.81	18.0/–
2[f]	L-LA	1:20:1000:0	0	7.38	7.12	1.12	52.5/162.0
3	*rac*-LA	1:20:1000:0	0	7.38	7.54	1.16	44.4/–
4	L-LA	1:20:500:500	49.6	10.0	10.8	1.11	33.1/–
5	*rac*-LA	1:20:500:500	49.4	10.0	12.4	1.41	33.5/–
6[f]	L-LA	1:20:500:500[e]	51.9	9.58	10.2	1.44	32.9/147.1

[a]Polymerization conditions: $[Cat.]_0$ (10 μmol), THF (5 mL), time (5 h), 25 °C, conv.>99%. [b]MBC content in polymers was measured using ^1H NMR spectra. [c]Number–average molecular weights and their distributions were determined by SEC. [d]The glass transition and melt points (T_g and T_m) of copolymers were determined by DSC. [e]Diblock copolymer was synthesized by a sequential monomer addition method. [f]Mg^nBn_2 as the catalyst.

be easily modified by functional substituents like hydroxyl or carboxyl groups.[32−34] For example, Grinstaff et.al., reported that poly(glyceric acid carbonate) shows a remarkable degradation rate with $t_{1/2}$ of ∼2 weeks in deionized water and several hours in buffer solution.[32] It was also reported by his group that poly(1,2-glycerol carbonate) containing primary hydroxyl groups has $t_{1/2}$ of 2−3 days in DMF, significantly faster than poly(1,3-glycerol carbonate) having secondary hydroxyl groups.[33]

The copolymerization of LA with functional cyclic carbonates is one of the most straightforward approaches to improve degradation performance of PLA-based materials.[35,36] Herein, we report syntheses of random, tapered, and diblock poly(LA-*co*-MBC)s (LA = L-LA or *rac*-LA, MBC = 2-methyl-2-benzyloxycarbonyl-1,3-trimethylene carbonate) by using an immortal polymerization strategy (Scheme 1).[37,38] Debenzylation of the resultant poly(LA-*co*-MBC)s by Pd/C catalytic hydrogenation is performed to obtain the corresponding carboxylic acid-containing poly(LA-*co*-MCC)s. Their degradation performances are extensively investigated in basic buffer aqueous solution (pH = 9.97), and the degradation rates of these copolymers are significantly controlled by their own sequence distributions. The hydrolysis products of lactic acid, CO_2, and dialcohol are precursors for fabricating monomers, indicating a green life-circle for these polymer materials, much suitable for being used as medical devices, drug–device combinations, and tissue-engineering scaffolds.

RESULTS AND DISCUSSION

Synthesis and Characterization of Sequenced Poly(Lactide-*co*-Carbonate)s. Following the literature procedure, homopolymers of PMBC, isotactic PLLA, and heterotactic P(*rac*-LA) were prepared using the catalytic system composed of precursor **1** or Mg^nBu_2 and an excess amount of Ph_2CHOH as a chain transfer reagent (entries 1−3, Table 1).[39−42] The random poly(L-LA-*ran*-MBC) was obtained from the copolymerization of MBC with L-LA, and the tapered poly(*rac*-LA-*tap*-MBC) was isolated from the copolymerization of MBC with *rac* -LA (entries 4,5, Table 1), due to the high heteroselectivity of complex **1**.[37] Sequential polymerization of L-LA and MBC afforded the diblock copolymer PLLA-*b*-PMBC using the Mg^nBu_2/Ph_2CHOH system (entry 6, Table

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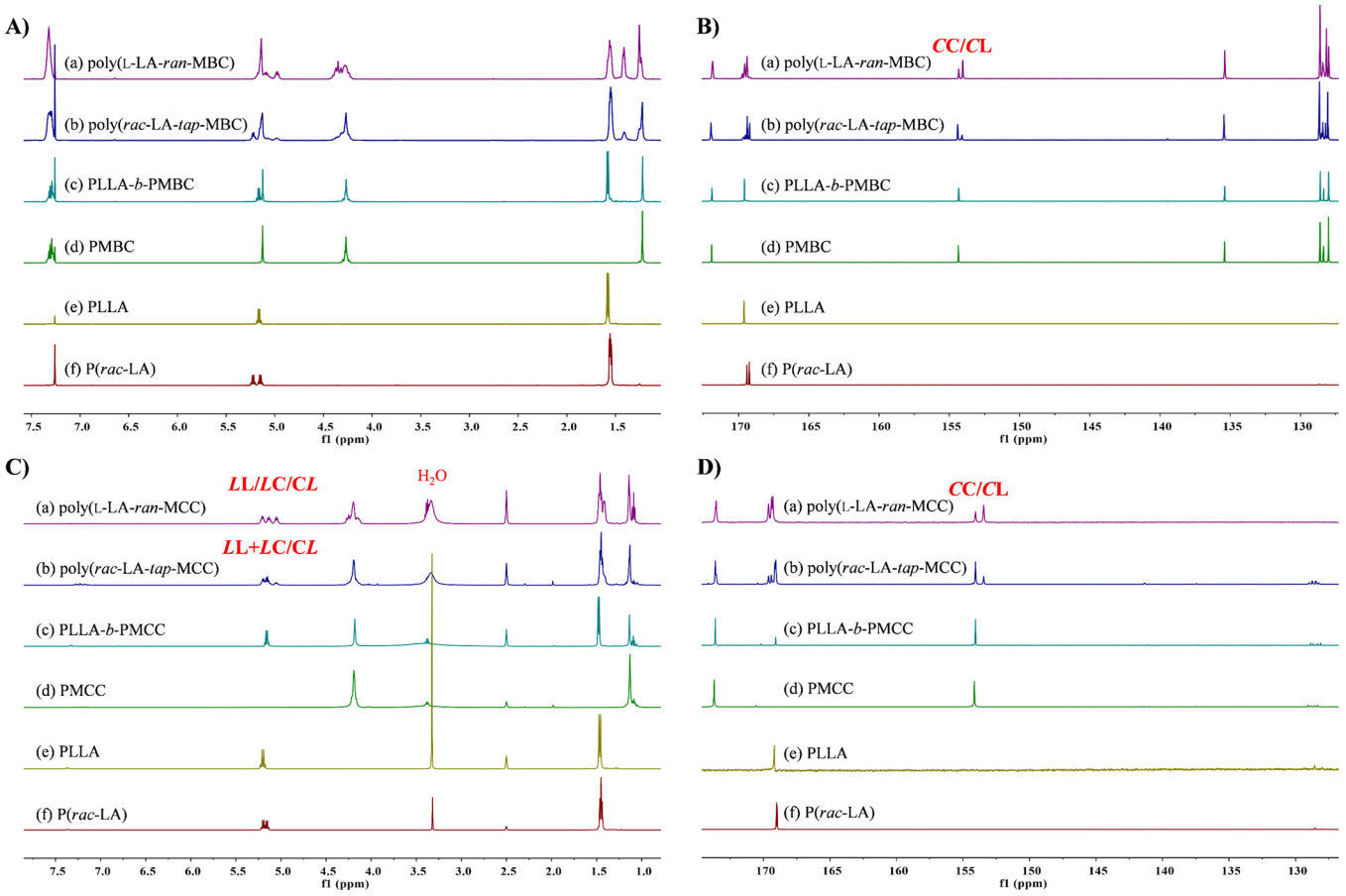

Figure 1. (A) ^{1}H NMR (25 °C, $CDCl_3$, 500 MHz) and (B) ^{13}C NMR (25 °C, $CDCl_3$, 125 MHz) spectra of copolymers (Table 1). (a) Poly(L-LA-*ran*-MBC) and (b) poly(*rac*-LA-*tap*-MBC); (c) PLLA-*b*-PMBC; (d) PMBC; (e) PLLA; (f) P(*rac*-LA). (C) ^{1}H NMR (25 °C, DMSO-d_6, 500 MHz) and (D) ^{13}C NMR (25 °C, DMSO-d_6, 125 MHz) spectra of the corresponding debenzylated (co)polymers: (a) poly(L-LA-*ran*-MCC); (b) poly(*rac*-LA-*tap*-MCC); (c) PLLA-*b*-PMCC; (d) PMCC; (e) PLLA; (f) P(*rac*-LA).

1). A series of statistical copolymers of poly(L-LA$_x$-*stat*-MBC$_{1-x}$) (x = 0.1−0.9) were further prepared through changing the L-LA/MBC feed ratio (Table S1). These statistical copolymers would provide more auxiliary information when analyzing the chain sequence of copolymers and the relationship of the chain sequence with their hydrolysis performance. The benzyl groups in all poly(LA-*co*-MBC)s were easily removed by Pd/C catalytic hydrogenation to give carboxylic acid-containing poly(LA-*co*-MCC)s, as the corresponding peaks in the aromatic region in both ^{1}H NMR and ^{13}C NMR spectra disappeared completely (Figure 1C,D). These polymers mostly show unimodal distributions (Figures S4−S9).

The ^{1}H NMR spectra of random poly(L-LA-*ran*-MBC), tapered poly(*rac*-LA-*tap*-MBC), diblock PLLA-*b*-PMBC, and the corresponding homopolymers are shown in Figure 1A. The resonance signals at 5.00−5.25 ppm arise from the methine proton in LA units and the pendant methylene protons in MBC units. The *LL*, *CL*, and *LC* diads (L represents the lactyl unit, and C represents the carbonate unit) in copolymers poly(L-LA-*ran*-MBC) and poly(*rac*-LA-*tap*-MBC) are overlapped (Figure 1A(a),(b)). Fortunately, three discrete quartet peaks at 5.05, 5.13, and 5.21 ppm are shown clearly in the ^{1}H NMR spectra of debenzylated poly(L-LA-*ran*-MCC), which are assigned to *CL*, *LC*, and *LL* diads, respectively, assisted by the ^{1}H NMR spectra of poly(L-LA$_x$-*stat*-MCC$_{1-x}$)s and PLLA (Figure 1C(c); Figures S11 and S12). The average sequence lengths of lactide (L_L) in poly (LA-*co*-MCC)s were calculated by equation $L_L = 1 + I_{5.25\ ppm}/(I_{5.05\ ppm} + I_{5.13\ ppm})$. The resulting L_L of 1.57 in poly(L-LA-*ran*-MCC) is consistent with its random sequence, while L_L of 3.09 for poly(*rac*-LA-*tap*-MCC) corresponds to the tapered sequence.[37] The unambiguous diads of *CC* and *CL* at δ 154.3 and 154.0 ppm in ^{13}C NMR are easily assigned (Figure 1B,D and Figure S14), and the average sequence lengths of carbonate (L_C) in the copolymers were calculated by the equation $L_C = 1 + I_{154.3\ ppm}/I_{154.0\ ppm}$. The L_C values of 1.55 for poly(L-LA-*ran*-MBC) and 3.55 for poly(*rac*-LA-*tap*-MBC) are in line with their chain sequences, respectively.[37] The values of L_L and L_C of statistical poly(L-LA$_x$-*stat*-MCC$_{1-x}$)s are shown graphically in Figure S15.

These polymers with diverse sequence distributions show different thermal properties, as examined by differential scanning calorimetry (DSC) analyses. For example, except for one glass transition temperature (T_g) for poly(LA-*co*-MBC)s, diblock PLLA-*b*-PMBC shows a melting point (T_m) at 147.1 °C, which is slightly lower than the pure PLLA of 162.0 °C (Figure S16). As for the statistical poly(L-LA$_x$-*stat*-MBC$_{1-x}$)s, T_g decreases constantly with the increase of the MBC content in the copolymers (Figure S17). On the other hand, the T_g values of debenzylated polymers are higher than those of their precursors, probably owing to hydrogen bonds among carboxylic groups and carbonyl groups (Figures S18−S20), of which tapered and block copolymers have a smaller

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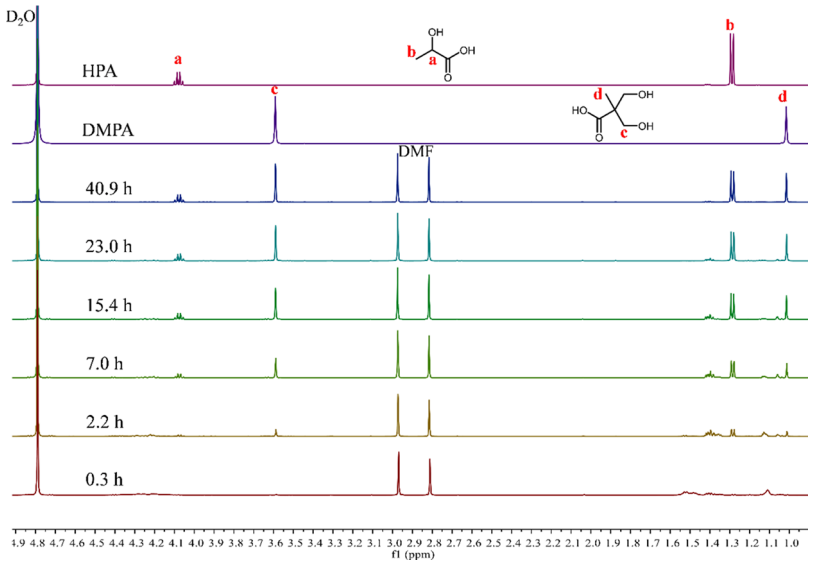

Figure 2. In situ ^{1}H NMR (500 MHz) spectra of random sequenced poly(L-LA-*ran*-MCC) (10.4 mg) with 4 μL of DMF and referenced spectra of pure 2-hydroxypropanoic acid (HPA) and pure 2,2-bis(hydroxymethyl) propionic acid (DMPA) in buffer solution (pH = 9.97) at 25 °C.

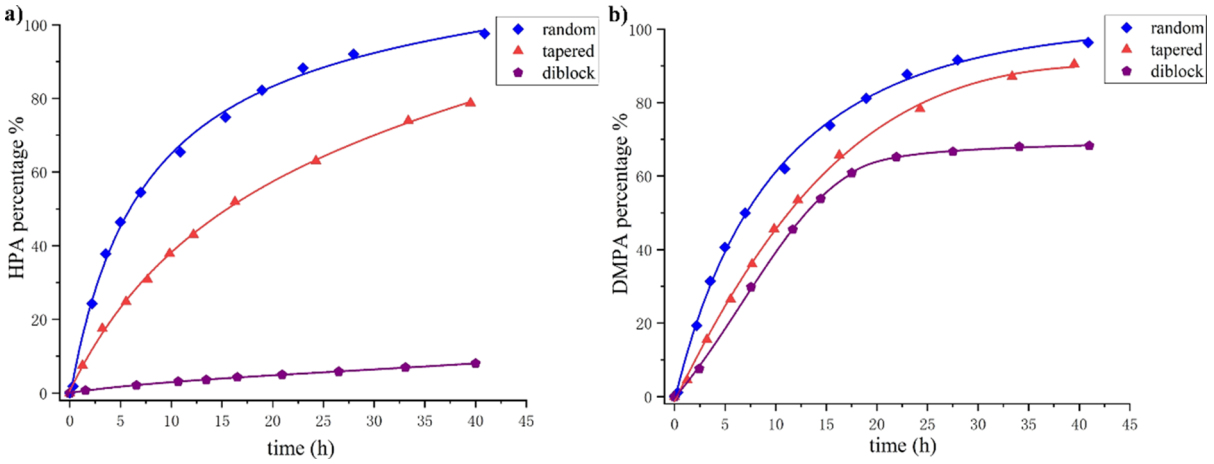

Figure 3. Plots of the percentage of degradation products (a) HPA and (b) DMPA versus degradation time for random poly(L-LA-*ran*-MCC), tapered poly(*rac*-LA-*tap*-MCC), and diblock PLLA-*b*-PMCC.

ΔT_g (T_g difference between debenzylated polymers and their precursors) than that of a random structure arisen by its uneven distributed hydrogen bonds. The water contact angle (WCA), which can indicate the hydrophilicity of related materials, has been measured before degradation experiments. As a result, the trend of PLA (79.3°)[43]≈poly(LA-*co*-MBC) >poly(LA-*co*-MCC)>PMCC (Figure S22) implies unequal degradation performances of copolymers bearing different MCC distributions on the PLA matrix (vide infra).

Hydrolytic Degradation Study. Basic buffer aqueous solution (Na_2CO_3-$NaHCO_3$, pH = 9.97) was applied for degradation research as there is no degradation observed for poly(L-LA-*ran*-MCC) in deuterated water at 25 °C after a week (Figure S24).[32,34,36,44] In the NMR tube, each polymer sample was added with 0.5 mL of buffer solution and 4 μL of DMF as the internal integration standard. ^{1}H NMR monitoring spectra were detected at specified intervals. As shown in Figure 2, the degradation products of poly(L-LA-*ran*-MCC) give mainly four groups of signals: a quartet at δ 4.08 ppm and a doublet at δ 1.29 ppm are assigned to methine H_a and methyl H_b protons in 2-hydroxypropanoic acid (HPA), while two singlets at δ 3.59 and δ 1.01 ppm arise from methylene H_c and methyl H_d protons in 2,2-bis(hydroxymethyl) propionic acid (DMPA). The intensities of all these signals gradually increase over time, indicating the controllable degradation process of random copolymers. The ESI mass spectrum of the hydrolytic mixture acidified with 5% HCl shows strong molecular ion peaks for HPA and DMPA at 89 and 133, respectively; and minor peaks at 45 for HCOOH and 179 for the DMPA·$HNMe_2$ adduct, which are generated from the interaction of HCl with the internal standard DMF (Figure S26). These HCOOH and DMPA·$HNMe_2$ peaks disappear when performing the same experiment without DMF (Figure S27). Note that under the same conditions, no degradation was observed for its precursor poly(L-LA-*ran*-MBC) within a week (Figure S28).

As the carboxylic acid groups in poly(LA-*co*-MCC)s play a crucial role in the degradation reaction, the effects of their distributions on the copolymer's degradation have been further investigated. For the random polymer poly(L-LA-*ran*-MCC), the percentages of HPA and DMPA as degradation products (the amounts of HPA or DMPA produced by full degradation

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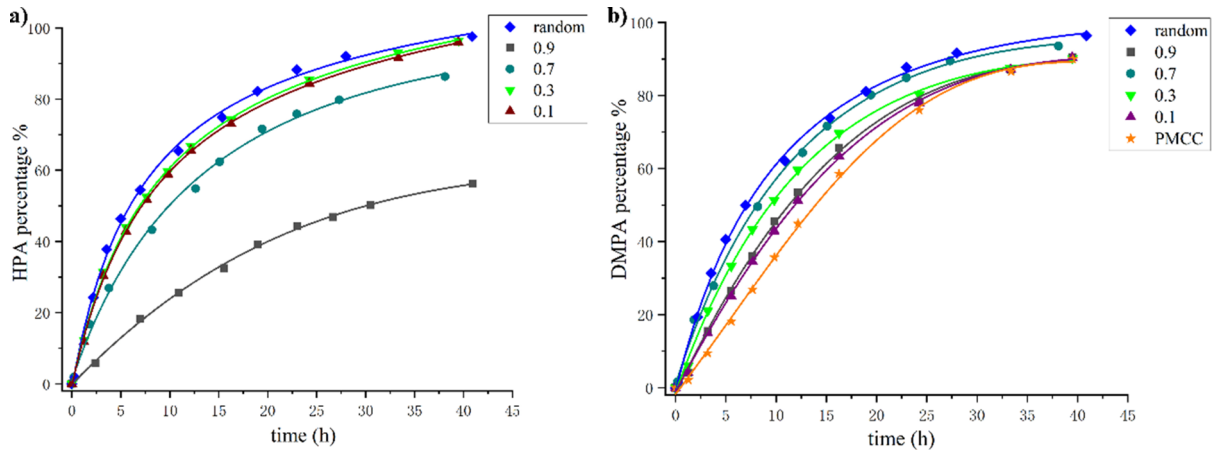

Figure 4. Plots of the percentage of degradation products (a) HPA and (b) DMPA versus degradation time for the statistical poly(L-LA$_x$-*stat*-MCC$_{1-x}$) (x = 0.1, 0.3, 0.7, 0.9), poly(L-LA-*ran*-MCC), and PMCC.

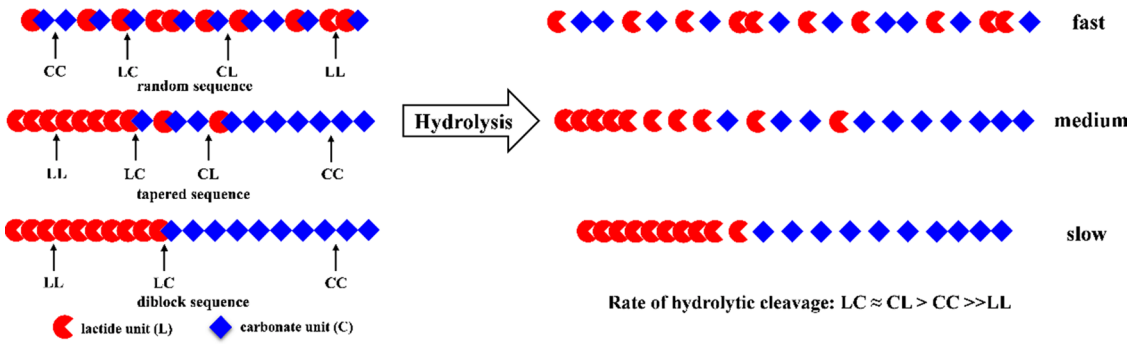

Figure 5. Diagram of the hydrolysis pattern for various sequenced poly(LA-*co*-MCC)s.

of poly(L-LA-*ran*-MCC) are defined as 100%) increase simultaneously over time, as shown in Figure 3a,b (blue line) and Figure S29a. As for the diblock polymer PLLA-*b*-PMCC, DMPA is generated much faster than HPA, indicating that the hydrophilic PMCC chain segment is more easily degraded than the hydrophobic PLLA segment (Figure 3, purple line). However, an obvious inflection point in Figure 3b appeared at 16.5 h reaction, which may be caused because the long PLLA chains wrapped the rest of the PMCC segments. The degradation trace of the tapered poly(*rac*-LA-*tap*-MCC) lies between those of random and blocky ones, and no full percentages of DMPA and HPA are reached over 40 h.

To explain the different degradation performances above, the investigation on degradation of statistical poly(L-LA$_x$-*stat*-MCC$_{1-x}$)s with various MCC contents (x = 0.1, 0.3, 0.7, 0.9) was further applied. As shown in Figure 4a, the rate of producing HPA increases as the MCC content raises up to 50% (random copolymer), which then inversely decreases when the MCC content continues to mount up. A similar tendency is observed from the traces for DMPA % vs time (Figure 4b). Note that the random poly(L-LA-*ran*-MCC) shows the fastest degradation rate (blue line), and the rates of producing DMPA in statistical copolymers are all faster than those in the PMCC homopolymer (Figure 4b, orange line). These results solidly prove that the L−C/C−L links in copolymers are more easily cleaved; thus, the bond fracture follows the trend of L−C≈C−L>C−C>L−L (Figure 5). In other words, the degradation rates of poly(lactide-*co*-carbonate)s are controlled by the numbers of L−C and C−L links in polymer main chains.

CONCLUSIONS

In summary, poly(LA-*co*-MBC)s with random, tapered, and diblock sequences have been synthesized and characterized, which are facilely transformed into the corresponding poly(LA-*co*-MCC)s bearing carboxyl acid (MCC) segments via debenzylation of postpolymerization modification. The degradation rates are significantly affected by the sequence distribution of poly(LA-*co*-MCC)s, following the trend of poly(L-LA-*ran*-MCC)>poly(*rac*-LA-*tap*-MCC)>PLLA-*b*-PMCC. Further investigation shows that the degradation rates of the statistical copolymer poly(L-LA$_x$-*stat*-MCC$_{1-x}$)s are strongly dependent on the contents of L−C/C−L diads rather than C−C units, indicating that the most fragile positions to be broken are L−C/C−L links in the macromolecular main chains, for the first time. The degradation products are HPA and DMPA derived from LA and MCC units, respectively, which are precursors of synthesizing LA and MCC; thus, a complete recycle from renewable monomers to degradable polymers is achieved. The relationship between the monomer sequence and degradation behavior of biocompatible poly(lactide-co-carbonate)s is established, which guides the design of copolymers having controllable degradation rates.

EXPERIMENTAL SECTION

General Procedures. All moisture- or air-sensitive reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques or in a nitrogen gas-filled MBraun glovebox. Solvents, such as toluene and *n*-hexane, were dried over 4 Å molecular sieves for a week and purified using an MBraun solvent purification system. Tetrahydrofuran (THF) was dried by distillation over sodium with

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benzophenone as the indicator under a nitrogen atmosphere and then stored in a glovebox. LA was purchased from Sigma-Aldrich and recrystallized from dry toluene 3 times. Benzhydrol (Ph_2CHOH) was obtained from commercial sources and dried with $MgSO_4$ in THF solution prior to use. Deuterated NMR solvents were purchased from Cambridge Isotopes and dried over sodium (for C_6D_6) or a molecular sieve (for $CDCl_3$ and DMSO-d_6). Mg^nBu_2 (1.0 M in heptane) was purchased from Sigma-Aldrich. Complex **1** was prepared according to the established method.[45] Pd/C (5%) (wetted with ca. 66.7% water) was used as received. Glassware and flasks using in the polymerization were dried in an oven at 120 °C and exposed to a vacuum-nitrogen cycle 3 times. All other reagents and solvents are commercially available and used without further purification.

Instruments and Measurements. NMR spectra were recorded in deuterated solvents at 298 K on a Bruker AV 500 MHz (for ^1H NMR) spectrometer. The number−molecular weight (M_n) and weight distributions (M_w/M_n) of related polymers were characterized by size exclusion chromatography (SEC) on a TOSOH HLC-8220 SEC instrument (Column: Super HZM-Hx3) at 40 °C using THF as an eluent (the flow rate was 0.35 mL min^{-1}) against polystyrene standards. Glass transition temperatures (T_g) and melting points (T_m) of related polymers were measured by differential scanning calorimetry (DSC) using a METTLER TOPEM DSC instrument under a nitrogen flow. Any thermal history difference in the polymers was eliminated by first heating the specimen to 200 °C and then recording the second DSC scan from −10 to 200 °C at 10 °C min^{-1} for 5−10 mg of samples.

Synthesis of 2-Methyl-2-Benzyloxycarbonyl-1,3-Trimethylene Carbonate (MBC). The MBC monomer was synthesized in two steps according to modified procedures.[46] 20 g (149.1 mmol) of 2,2-bis(hydroxymethyl) propionic acid and 9.2 g (164.0 mmol) of KOH were dissolved in 80 mL of DMF in a 250 mL flask equipped with a condenser. The potassium salt was allowed to form at 100 °C for 1 h, and then 18.0 mL (156.4 mmol) of benzyl chloride was added slowly. The reaction kept stirring at 100 °C for 12 h. After removal of DMF under vacuum, the residue was dissolved in a mixture of ethyl acetate (80 mL) with hexane (80 mL) and water (80 mL). After extraction, the water layer was washed with 100 mL of ethyl acetate, and then, the combined organic phase was dried with $MgSO_4$. After the solvent evaporated, the crude product was recrystallized from toluene to produce pure benzyl 2,2-bis(hydroxylmethyl) propionate (24.8 g, 74.2%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.40 (m, 5H), 5.21 (s, 2H), 3.93 (d, J = 11.2, 2H), 3.73 (d, J = 11.2, 2H), 2.92 (br, 2H), 1.08 (s, 3H).

Carbonate was subsequently synthesized. To a solution of 15 g (66.9 mmol) of synthesized benzyl 2,2-bis(hydroxymethyl) propanoate in 400 mL of THF, 19.1 mL (200.7 mmol) of ethyl chloroformate was added, and the mixture was stirred in an ice bath for 30 min. Triethylamine (TEA, 27.9 mL, 200.7 mmol) diluted in 50 mL of THF was added dropwise over a period of 60 min. The reaction mixture was stirred at 0 °C for another 2 h and then stirred at room temperature overnight. The formed TEA-HCl salt was filtered off, and the filtrate was concentrated in a vacuum to obtain a white solid (13.0 g, 77.7%). The crude product was purified by recrystallization 3 times from THF/diethyl ether (1:5, v/v) to give MBC as acicular crystals, then dried, and reserved in a glovebox. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.40 (m, 5H), 5.22 (s, 2H), 4.70 (d, J = 10.7, 2H), 4.20 (d, J = 10.8, 2H), 1.33 (s, 3H).

A Typical Procedure of Copolymerization of LA and MBC. A typical copolymerization of LA and MBC (Table 1, entry 1) was carried out in a 25 mL flask under a nitrogen atmosphere. A THF solution (1 mL) of complex **1** (7.7 mg, 10 μmol) and Ph_2CHOH (9.2 mg, 50 μmol) was added into a stirred solution (4 mL of THF) of LLA (0.720 g, 5 mmol) and MBC (1.25 g, 5 mmol) at room temperature. For the diblock PLLA-*b*-PMBC, 5.0 mmol L-LA in 5 mL of THF was polymerized for 2 h till completely converted (catalyst, the amount used). Then, MBC (5.0 mmol) was added for another 3 h. The polymerization was terminated using several drops of acidified ethanol (1.0 M HCl solution in EtOH), and the viscous solution was poured into abundant ethanol to give a white polymer. After being dried under vacuum at 40 °C to a constant weight, a certain amount of polymer was dissolved in $CDCl_3$ to acquire the NMR spectral data.

The Procedure of Pd/C Catalytic Hydrogenation. In a 50 mL high pressure autoclave, the polymer poly(LA-*co*-MBC) was dissolved in a 4:1 (v/v) mixed solvent of ethyl acetate/methanol (~40 mg/mL), and the Pd/C catalyst in the amount of 5 mol % of the benzyl groups was then added to the solution. The autoclave was charged with hydrogen gas (H_2) to 3.0 MPa. After 10 h at room temperature with stirring, the Pd/C solid was filtered and then washed with the ethyl acetate/methanol mixture. The combined filtrate was evaporated to ca. 1 mL, and then, a large amount of diethyl ether was added to obtain solid poly(LA-*co*-MCC). These carboxyl-containing copolymers were dried at 40 °C for 24 h in vacuo till constant weight, and their NMR spectra were measured in DMSO-d_6.

The Procedure of Hydrolysis Kinetic Study. The hydrolysis experiments of (co)polymers were carried out in Na_2CO_3 (0.53 M) and $NaHCO_3$ (0.25 M) deuterium aqueous buffer solution (pH = 9.97). A certain amount of poly(LA-*co*-MCC) in 0.5 mL of buffer solution was put in a NMR tube, and then, accurate 4 μL of *N,N*-dimethyformamide (DMF) was added as the inert internal standard. ^1H NMR spectroscopy at certain intervals of time was performed to monitor the hydrolytic process. According to the peak integrals of degradation products and the internal standard (DMF), the conversions of the corresponding products were calculated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.0c00938.

Polymerization data of supplement experiments, NMR, ESI-MS characterization data, and SEC, DSC, WCA, and DLS characterization (PDF)

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Notes

The authors declare no competing financial interest.

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