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Well-controlled synthesis of biodegradable polyesters using edible catalysts

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Biodegradable polyesters, represented by polylactic acid and poly(ε-caprolactone), are regarded as not only environmentally friendly alternatives to current nondegradable polyolefins but also important polymer materials for biomedical applications. The ring-opening polymerization (ROP) of the corresponding cyclic esters is a typical approach for synthesizing these polyesters in a well-controlled and efficient manner. A wide variety of organometallics and organocatalysts have been developed for this polymerization process. Organocatalysts are considered safer than organometallic catalysts because they do not release toxic metal residues, but not all of them are necessarily harmless to humans or the environment. Some truly safe and edible catalysts, including sodium acetate and vitamin C, have been reported to catalyze the ROP of lactide or ε-caprolactone. In this study, we explore the concept of "edible catalysts" by screening the structures of various organic acids and their sodium or potassium salts as catalysts for the ROP of cyclic esters. We demonstrate the suitability of various edible compounds for different cyclic ester monomers. The synthesized polyesters had a relatively narrow dispersity ($Đ$ = 1.1–1.3) with a well-controlled polymer chain-end structure, identical to those obtained using conventional catalysts. Moreover, by mixing different edible catalysts, random and block copolymers can be synthesized in a well-controlled manner. These findings demonstrate that unassuming edible compounds in our daily lives possess significant potential as safe and effective catalysts for the synthesis of biodegradable polymer materials.

Green foundation

1. In this work, we established a well-controlled ROP of cyclic esters to synthesize biodegradable polyesters, such as polylactic acid (PLA) and poly(ε-caprolactone) (PCL), by screening edible compounds comprised of organic acids and their alkali metal salts.

2. Homopolymers and copolymers, including random-like copolymer PLA-*stat*-PCL and block copolymer PLA-*b*-PCL, were successfully synthesized by mixing different types of edible catalysts.

3. The use of truly safe and edible catalysts can eliminate the costly process of residual catalyst removal, thereby benefiting polymer production, particularly for biomedical applications.

1. Introduction

With the increasing concern about environmental issues caused by nondegradable polymer materials, the development of (bio) degradable polymers is becoming urgent. Aliphatic polyesters

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(APEs) have emerged as prominent candidates owing to their widely tunable material properties and (bio)degradability.[1–3] Polycondensation is a widely applied method for synthesizing these types of polymers; however, precisely controlling their molecular weights and dispersities is difficult. Ring-opening polymerization (ROP) of cyclic esters or cyclic carbonate monomers is another well-known approach for synthesizing APEs and aliphatic polycarbonates in a well-controlled manner, including controlling the molecular weight, distribution, chain-end functionality, and synthesis of block copolymers. Polylactic acid (PLA), poly(ε-caprolactone) (PCL), and poly(trimethylene carbonate) (PTMC) are among the most important and widely used biodegradable, biocompatible, and bioresorbable polymers, usually synthesized *via* ROP of their corresponding cyclic monomers:

lactide (LA), ε-caprolactone (ε-CL), and trimethylene carbonate (TMC), respectively. To date, numerous catalysts, including organometallic, enzymatic, and organocatalysts, have been developed for ROP processes.[4–7]

Since the landmark study by Hedrick *et al.*, who accomplished the ROP of LA catalyzed by 4-dimethylaminopyridine (DMAP) in 2001,[8] numerous reports on organocatalyzed polymerizations, particularly the ROP of the above-mentioned cyclic esters, have been published.[9–13] Organocatalysts are generally recognized as more environmentally friendly and safer than organometallic catalysts because they are free of toxic metal residues. However, this claim is not necessarily valid. For example, DMAP is categorized as "Dangerous" in the materials safety data sheet, and it is toxic when placed in contact with skin or swallowed. Recent studies have demonstrated that phosphazene bases are cytotoxic.[14] By contrast, Sn(Oct)$_2$, a widely used organometallic catalyst for the ROP of cyclic esters,[15] has been approved by the United States Food and Drug Administration, with an upper limit of 1 wt% tin in products that do not directly contact food. However, for biomedical applications such as bioresorbable sutures, implants, and drug delivery carriers, higher standards need to be met. For example, Evonik Industries AG launched RESORMER ZERO® products by cleanly removing the tin catalyst residues (<1 ppm) after polymerization. Therefore, truly safe polymer synthesis catalysts that do not require costly catalyst removal processes are needed.

Some truly safe and edible acid compounds (*e.g.*, amino acids, citric acid (CA), tartaric acid) have been examined in the ROP of ε-CL.[16] Our group has reported that alkali metal carboxylates (AMCs), some of which are safe as food additives, and a safe natural compound, trimethyl glycine, can catalyze the ROP of L-LA and TMC in a well-controlled manner.[17–19] Other safe catalysts, including sodium or potassium carbonates, ascorbic acid (vitamin C), and its sodium salt, have also been reported to catalyze the abovementioned ROPs.[20,21] Not only homopolymerization, but also random copolymerization of L-LA and ε-CL—a challenging yet useful task for the synthesis of biodegradable polymers with desired mechanical properties—have also been realized by benzoic acid, a commonly used preservative.[22,23]

These scattered successes inspired us to further investigate the potential of truly safe and edible catalysts for the abovementioned ROPs. Here, we report our evaluation of safe catalysts selected from the food additive list or those rich in edible natural products, such as fruits, for the synthesis of biodegradable, biocompatible, and bioresorbable polymers *via* ROPs, with the goals of efficient catalytic performance, better controllability, and the synthesis of copolymers with various monomer sequences (Fig. 1).

2. Experimental

2.1. Chemicals

L-Lactide (L-LA; >98.0%, Tokyo Kasei Kogyo (TCI)) was purified twice *via* recrystallization from dry toluene. Trimethylene carbonate (TMC, >98.0%, TCI) was purified by recrystallization from dry tetrahydrofuran and diethyl ether. ε-Caprolactone (ε-
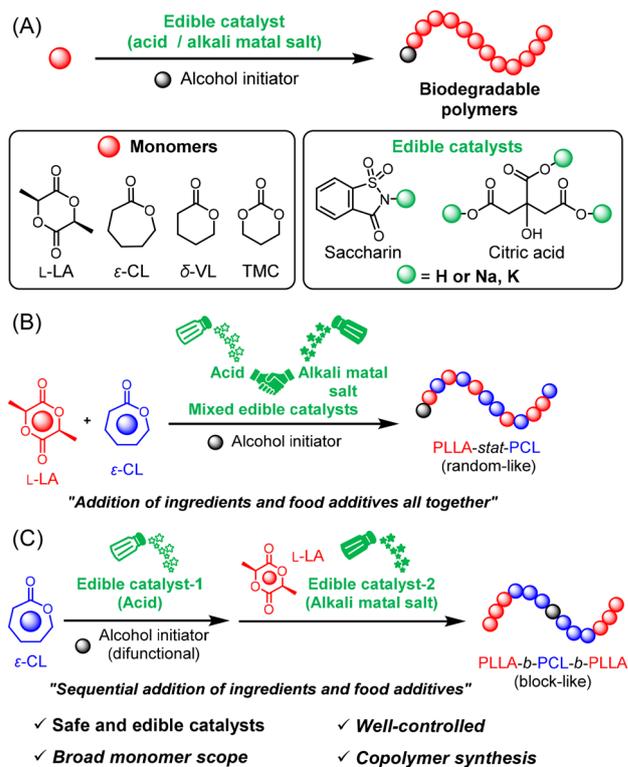

Fig. 1 (A) Edible catalyst for the ROP of various cyclic esters; synthesis of copolymers of PLLA and PCL using mixed edible catalysts (B) or sequential addition of edible catalysts and monomers (C).

CL; >99.0%, TCI), δ-valerolactone (δ-VL; >99%, Sigma-Aldrich), and 3-phenyl-1-propanol (PPA; >98.0%, TCI) were distilled over CaH$_2$ under reduced pressure. 1,4-Benzenedimethanol (BDM; >99.0%, TCI) was dried under high vacuum prior to use. CA (>98.0%, TCI), sodium dihydrogen citrate anhydrous equivalent (CNa$_1$; ≥97.0%, Nacalai Tesque), disodium dihydrogen citrate 1.5 hydrate (CNa$_2$; ≥98.0%, TCI) trisodium citrate (CNa$_3$; ≥98.0%, Sigma-Aldrich), potassium dihydrogen citrate (CK$_1$; 95%, Fujifilm Wako Pure Chemicals), tripotassium citrate monohydrate (CK$_3$; ≥99.0%, Kanto Chemical), saccharin (SA; >99.0%, TCI), saccharin sodium salt dihydrate (SNa; >98.0%, TCI), and tetrasodium ethylenediaminetetraacetate tetrahydrate (EDTANa$_4$; >98.0%, TCI) were dried by heating at 100 °C under high vacuum for at least 72 h prior to use. Malonic acid (MA; >99.0%, TCI), disodium malonate (MNa$_2$; >99.0%, TCI), and ethylenediaminetetraacetic acid (EDTA; >98.0%, Kanto Chemical) were used as received.

Chloroform-*d* (CDCl$_3$; >99.8%), methanol (>99.8%, Sigma-Aldrich), dichloromethane (CH$_2$Cl$_2$; >98.0%, JUNSEI CHEMICAL), tetrahydrofuran (THF; >99.0%, JUNSEI CHEMICAL), and dry toluene (>99.5%, water content <0.001%, KANTO CHEMICAL) were used as received.

2.2. Instruments

Polymerization was set up in a MBRAUN stainless steel glovebox equipped with a gas purification system (molecular sieves

and copper catalyst) in a dry argon atmosphere (H_2O, O_2 < 0.1 ppm). MB-MO-SE 1 and MB-OX-SE 1 were used to monitor the moisture and oxygen contents in the glovebox, respectively.

^1H and ^{13}C NMR spectra were recorded at 25 °C on JEOL JNM-ECS 400, JEOL JNMECX 400 (400 MHz), and JNM-ECZ600R (600 MHz) instruments using chloroform-*d* as the solvent, and chemical shifts were referenced to an internal standard.

The Fourier transform infrared spectroscopy (FT-IR) spectra were obtained using a PerkinElmer Frontier MIR spectrometer equipped with a single reflection diamond universal attenuated total reflection (ATR) accessory.

Size exclusion chromatography (SEC) was conducted at 40 °C in THF (flow rate, 1.0 mL min^{-1}) using a Jusco high-performance liquid chromatography system (PU-4180 HPLC pump, AS-4550 auto sampler and CO-4060 column oven) equipped with a Shodex K-800D guard column (8.0 mm × 100 mm; particle size, 10 μm) and two Shodex columns (K-806L and K-804L; linear, 8.0 mm × 100 mm; particle size, 10 μm). A polystyrene standard curve ranging from 2170 to 1 320 000 was used for calibration to determine the molecular weights ($M_{n, SEC}$) and polydispersity indices ($Đ$) of the polymers.

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was performed using a Bruker Daltonics (Germany) Ultraflex MALDI TOF/TOF system equipped with a 355 nm Nd:YAG laser. Five hundred shots were accumulated for the spectra, and the acceleration voltage was adjusted between 10 and 30 kV, depending on the molecular weight and nature of each analyzed compound in reflector mode. The poly(L-lactide) (PLLA) and PTMC samples for MALDI-TOF MS were prepared by depositing a mixture of the polymer (4.0 mg mL^{-1}, 0.5 μL) and a matrix (2,5-dihydroxybenzoic acid, 60 mg mL^{-1}, 0.5 μL) in THF on a sample plate, which was coated by an acetone solution (1.0 mmol L^{-1}, 1.0 μL) of NaI as the cationic agent. For poly(ε-caprolactone) (PCL) and poly(δ-valerolactone) (PVL) samples, only the polymer (1.0 mg mL^{-1}) and matrix (15 mg mL^{-1}) in THF were changed.

2.3. Polymerization

2.3.1. ROP of L-LA and ε-CL using food additives as a catalyst. A typical procedure for the ROP of ε-CL is as follows. In an argon-filled glovebox, ε-CL (457 mg, 4.00 mmol, 100 eq.), SA (36.6 mg, 200 μmol, 5.00 eq.), and BDM (5.5 mg, 40 μmol, 1.00 eq.) were placed in the reaction vessel. The reaction mixture was stirred at 100 °C in an oil bath. After 24 h, polymerization was terminated by cooling to room temperature and diluting the reaction mixture with CH_2Cl_2. The reaction mixture was purified by reprecipitation from CH_2Cl_2 solution into cold methanol to obtain PCL (352 mg, yield: 76.2%) as a white powder.

$M_{n, NMR}$ = 8930; $M_{n, SEC}$ = 15 200; $Đ$ = 1.13.

2.3.2. ROP of cyclic monomers using CA or CNa$_3$ as a catalyst. A typical procedure of the ROP of δ-VL is as follows: in an argon-filled glovebox, δ-VL (250 mg, 2.50 mmol, 50.0 eq.), CA (48.0 mg, 250 μmol, 5.00 eq.), and PPA (6.8 μL, 50 μmol, 1.00 eq.) were placed in the reaction vessel. The reaction mixture

was stirred at 100 °C under an argon atmosphere in an oil bath. After 2.0 h, polymerization was terminated by cooling to room temperature and diluting the reaction mixture with CH_2Cl_2. The reaction mixture was purified by reprecipitation from CH_2Cl_2 solution into cold methanol to produce PVL (177 mg, yield: 68.8%) as a white powder.

$M_{n, NMR}$ = 4340; $M_{n, SEC}$ = 4500; $Đ$ = 1.24.

2.3.3. Ring-opening copolymerization (ROcP) of L-LA and ε-CL. A typical procedure for the ROcP of L-LA and ε-CL is as follows. In an argon-filled glovebox, L-LA (721 mg, 5.00 mmol, 50.0 eq.), ε-CL (571 mg, 5.00 mmol, 50.0 eq.), SA (55.0 mg, 300 μmol, 3.00 eq.), SNa (41.0 mg, 200 μmol, 2.00 eq.), and PPA (13.6 μL, 100 μmol, 1.00 eq.) were placed in a reaction vessel. The reaction mixture was stirred at 130 °C in an oil bath. After 305 h, polymerization was terminated by cooling to room temperature and diluting the reaction mixture with CH_2Cl_2. The reaction mixture was purified by reprecipitation from a CH_2Cl_2 solution into cold methanol to give PLLA-*stat*-PCL (743 mg, 56.9% yield) as a viscous solid.

$M_{n, NMR}$ = 9400; $M_{n, SEC}$ = 9800; $Đ$ = 1.46.

2.3.4. One-pot synthesis of PLLA-*b*-PCL-*b*-PLLA. In an argon-filled glovebox, ε-CL (285 mg, 2.5 mmol, 50.0 eq.), CA (9.6 mg, 50 μmol 1.00 eq.), BDM (6.9 mg, 50 μmol 1.00 eq.), and dry-toluene (100 μL) were added to a the reaction vessel. The reaction mixture was stirred and heated at 100 °C in an oil bath. After 8.0 h, heating was stopped, and in the glovebox, L-LA (360 mg, 2.5 mmol, 50.0 eq.), CNa$_3$ (64.5 mg, 250 μmol, 5.00 eq.), and dry toluene (100 μL) were added. Polymerization was then carried out in an oil bath at 100 °C. After stirring at 100 °C for 47 h with no observable reaction progress, the temperature was raised to 130 °C. After 21 h at elevated temperature, the polymerization was terminated by cooling to room temperature and diluting the reaction mixture with CH_2Cl_2. The reaction mixture was purified by reprecipitation from CH_2Cl_2 solution into cold methanol to yield PLLA-*b*-PCL-*b*-PLLA (239 mg, yield: 37.0%) as a pale yellow solid.

$M_{n, NMR}$ = 7800; $M_{n, SEC}$ = 14 000; $Đ$ = 1.18.

3. Results and discussion

3.1. Catalyst Screening

Carboxylic acids and their corresponding alkali metal salts have been demonstrated to be active catalysts for the ROP of cyclic esters, according to our previous research and other researchers. We examined a list of food additives and natural products to select safe catalysts.

Saccharin is a non-nutritive artificial sweetener with a moderately strong acidity similar to that of diphenyl phosphate (DPP), a well-known organocatalyst for the ROP of ε-caprolactone (ε-CL); the pK_a values of saccharin and DPP are 4.0 and 3.88 in DMSO, respectively.[24–26] Saccharins and their derivatives have been used as catalysts in various organic reactions.[27] Notably, the DMAP–saccharin (1 : 1) salt has been reported to catalyze the ROP of L-LA.[28] Therefore, we anticipated that sac-

charin and its sodium or potassium salts could be safe catalysts for ROP of cyclic esters, such as L-LA and ε-CL.

From the viewpoint of chemical structure, saccharin is a monofunctional Brønsted acid. The integration of two or more identical functional groups into one molecule, producing bifunctional or multifunctional catalysts, is a common strategy to improve catalytic performance, which is attributed to their synergistic effect.[29] Therefore, we investigated safe di-, tri-, and tetracarboxylic acids and their corresponding alkali metal salts.[30] With this consideration in mind, malonic acid (MA), citric acid (CA), ethylenediaminetetraacetic acid (EDTA), and their sodium salts were selected as safe catalysts in the ROP of L-LA and ε-CL (Fig. 2 and Table S1). The initial screening for ROP was conducted using BDM as an initiator at a [monomer]$_0$/[BDM]$_0$/[catalyst] ratio of 100/1/5 for 24 h at 100 °C in bulk.

In the ROP of L-LA using acid catalysts, the monomer conversion was less than 10%, and the formation of PLLA was not confirmed (runs 1–4 in Table S1). By contrast, employing sodium salts as catalysts led to significantly improved monomer conversion, and white powdered solid PLLA was obtained as the product for all catalysts (runs 5–8 in Table S1). When ε-CL was employed as the monomer, significant polymerization progress was observed only for saccharin and CA (runs 9–12 in Table S1). By contrast, their sodium salts showed considerably low catalytic activities in the ROP of ε-CL (runs 13–16 in Table S1). These results indicate that sodium salts are effective catalysts for the ROP of L-LA, while organic acid catalysts are effective for the ROP of ε-CL. This trend aligns with previous reports indicating that base catalysts are more active for L-LA and acid catalysts for the ROP of ε-CL.[17,30,31]

Based on a rough catalyst screening that considered performance in the acid-catalyzed ROP of ε-CL and the corresponding sodium salt-catalyzed ROP of L-LA, CA and citrate

were selected as optimal catalysts. Therefore, we applied them in a more detailed investigation of the polymerization conditions, including the catalyst loading, monomer-to-initiator ratio, alkali metal species, and polymerization in the presence or absence of solvent. The investigation commenced with the bulk polymerization of L-LA at 100 °C. 3-Phenyl-1-propanol (PPA) was used as the initiator, and polymerization was conducted at a [L-LA]$_0$/[PPA]$_0$/[CNa$_3$] = 50/1/1 (run 1 in Table 1). After 66.5 h of polymerization initiation, the monomer conversion reached 76.9%. The viscosity of the reaction mixture increased progressively during the reaction, indicating PLLA formation. The number-average molecular weight ($M_{n, NMR}$) determined from ^{1}H NMR measurements was 6050, which was in reasonable agreement with the theoretical value ($M_{n, th.}$ = 5680), calculated based on the initial monomer-to-initiator ratio and monomer conversion. The dispersity of the obtained PLLA was as narrow as 1.13. By increasing the catalyst loading to [L-LA]$_0$/[PPA]$_0$/[CNa$_3$] = 50/1/5, the polymerization rate increased, with a result similar to that obtained for PLLA (run 2 in Table 1 and Fig. 3a). When the targeted degree of polymerization (DP) was increased to 150, viz. [L-LA]$_0$/[PPA]$_0$/[CNa$_3$] = 150/1/5, the molecular weight of the obtained PLLA increased accordingly, without sacrificing controllability (run 3 in Table 1 and Fig. 3b). When tripotassium citrate (CK$_3$) was employed as a catalyst, 91.1% of the monomer was converted 18.5 h after the onset of polymerization, indicating a faster progression of polymerization compared with that using sodium citrate (run 1 vs. 4 in Table 1). This trend is the same as that observed in our previous study on the counter-cation effect of AMCs in the ROP of L-LA.[17,19] Given that CK$_3$ exhibited higher reactivity than CNa$_3$, the targeted DP was increased to 150, and the polymerization as scaled up to 5 g to evaluate its scalability (run 5 in Table 1 and Fig. S1a). The polymerization proceeded at a reasonably fast rate while maintaining good control over the polymerization, indicating the promising potential of this system for scale-up. The ^{1}H NMR spectrum of the obtained PLLA showed signals from both the PLLA main chain and 3-phenyl-1-propoxy group (Fig. 3a). In the MALDI-TOF mass spectrum of PLLA, two series of peaks were apparent, corresponding to PPA as the major peak and water at the initiating end as the minor peak (Fig. 4).

A detailed investigation of the ROP of ε-CL using CA as the catalyst was initially conducted in a [ε-CL]$_0$/[PPA]$_0$/[CNa$_3$] ratio of 50/1/1 (run 6 in Table 1). The monomer conversion was 72.9% after 12.5 h. The obtained PCL showed a narrow dispersity, Đ = 1.11, and $M_{n, NMR}$ = 4360 is nearly the same as $M_{n, th.}$ = 4300 (Fig. 5a). When the target DP was increased to 150, the polymerization proceeded well, with a slightly broader molecular weight distribution (run 7 in Table 1 and Fig. 5b). A similar result was obtained when the polymerization was scaled up 5 g (run 8 in Table 1 and Fig. S1a). Regarding the role of CA in the polymerization of ε-CL, CA has been used either as a catalyst or initiator.[16,32] Therefore, we aimed to clarify the role of CA in our study. The ^{1}H-NMR spectrum and MALDI-TOF mass spectra of the synthesized PCL were obtained (Fig. 5a and 6). Signals corresponding to PPA were
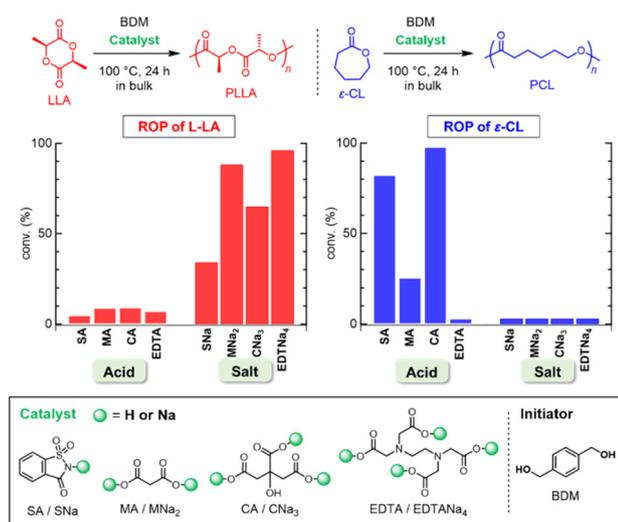

Fig. 2 Bar graph illustrating monomer conversion (conv.) in the ROP of L-LA (left) and ε-CL (right) using various catalysts.

Table 1 Investigation of polymerization conditions in ROP of L-LA and ε-CL[a]

Run	Monomer	Catalyst	[Monomer]$_0$/[PPA]$_0$/[catalyst]	Time (h)	Conv.[b] (%)	$M_{n, th.}$[c] (g mol^{-1})	$M_{n, NMR}$[b] (g mol^{-1})	$M_{n, SEC}$[d] (g mol^{-1})	Đ[d]
1	L-LA	CNa$_3$	50/1/1	66.5	76.9	5680	6050	8000	1.13
2	L-LA	CNa$_3$	50/1/5	39.0	80.8	5960	6050	7700	1.12
3	L-LA	CNa$_3$	150/1/5	134.0	75.3	16 400	16 700	16 000	1.19
4	L-LA	CK$_3$	50/1/1	18.5	91.1	6700	6620	7200	1.13
5[e]	L-LA	CK$_3$	150/1/1	48.0	78.8	17 200	11 800	12 700	1.15
6	ε-CL	CA	50/1/1	12.5	72.9	4300	4360	7600	1.11
7[f]	ε-CL	CA	150/1/1	103.0	79.0	13 800	14 400	19 400	1.29
8[e,f]	ε-CL	CA	150/1/1	120.0	76.8	13 300	14 700	17 300	1.27

[a] Polymerization conditions: atmosphere, Ar; initiator, PPA; temperature, 100 °C. [b] Determined using ^{1}H NMR spectroscopy. [c] Calculated from [monomer]$_0$/[PPA]$_0$ × conv. × (M.W. of the monomer) + (M.W. of PPA). [d] Determined using SEC in THF with a polystyrene standard. [e] 5 g scale polymerization. [f] Polymerization was conducted in the presence of toluene (ε-CL/toluene = 25 mmol/1 mL).
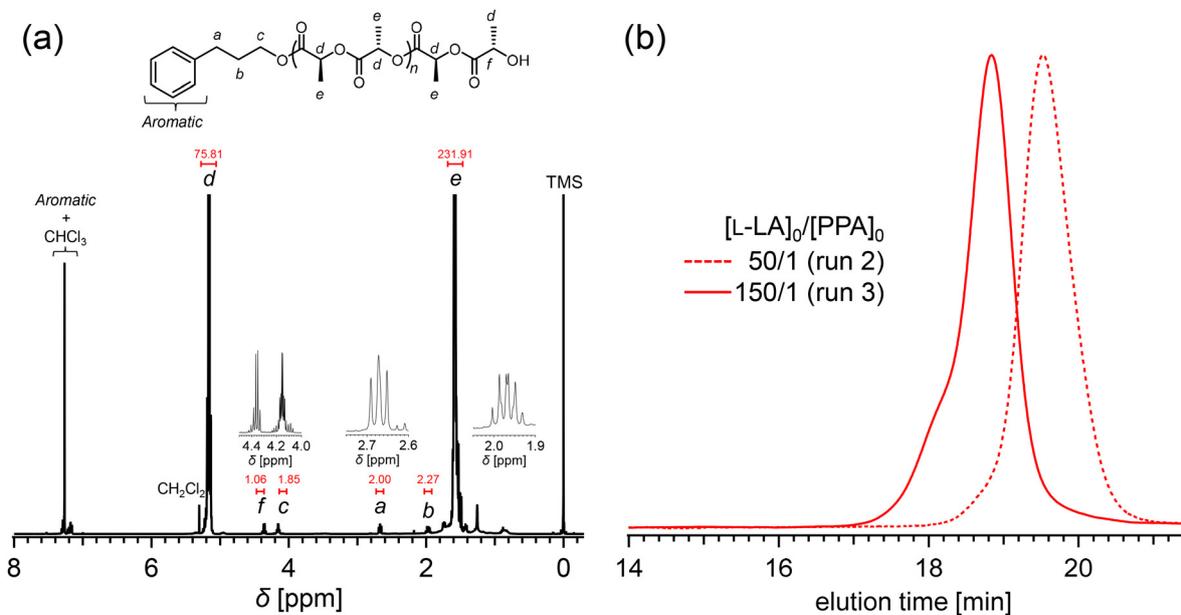

Fig. 3 (a) ^{1}H NMR spectrum of the PLLA obtained from run 2 in Table 1 (solvent, CDCl$_3$; 400 MHz), and (b) SEC traces of the PLLAs obtained from runs 2 and 3 in Table 1 (eluent, THF; flow rate, 1.0 mL min^{-1}).
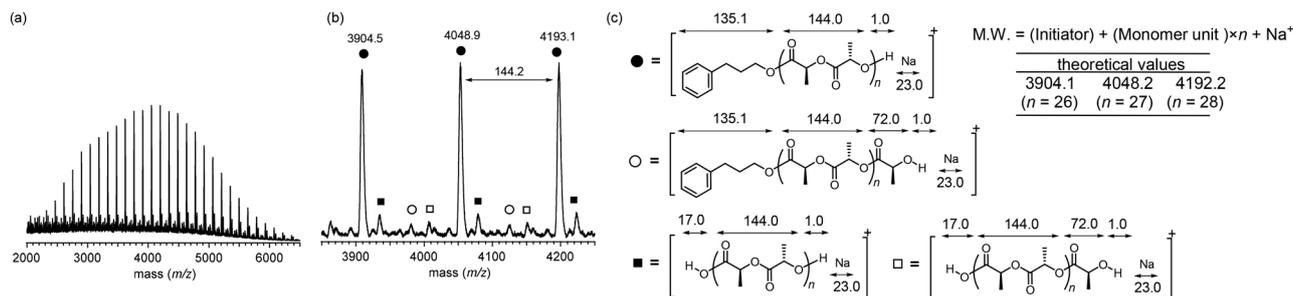

Fig. 4 (a) MALDI-TOF mass spectrum of PLLA (run 2 in Table 1), (b) expanded spectrum (ranging from 2000 to 6500), and (c) theoretical values.

observed in the ^{1}H-NMR spectrum. Moreover, the MALDI spectrum showed only one series of peaks, which were assumed to correspond to the ones with PPA structure. Therefore, in this polymerization system, CA functions only as a catalyst, whereas PPA acts as an initiator. Notably, the level of dispersity control achieved in this study is comparable to, or even superior to, that reported in representative works employing benzoic acid, vitamin C, or its sodium salt, while simul-
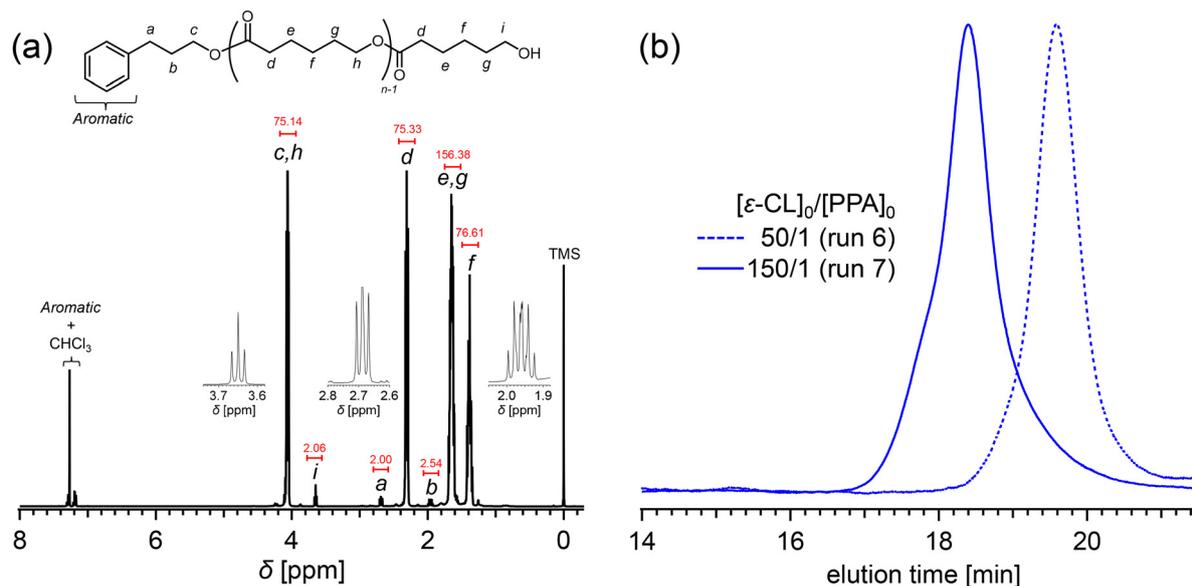
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Fig. 5 (a) ^{1}H NMR spectrum of the PCL obtained from run 6 in Table 1 (solvent, CDCl$_3$; 400 MHz), and (b) SEC traces of the PCLs obtained from runs 6 and 7 in Table 1 (eluent, THF; flow rate, 1.0 mL min^{-1}).
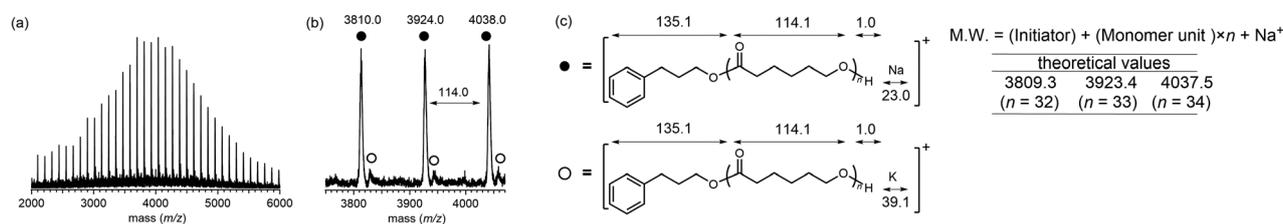

Fig. 6 (a) MALDI-TOF mass spectrum of PCL (run 6 in Table 1), and (b) expanded spectrum (ranging from 4750 to 4070), and (c) theoretical values.

taneously exhibiting significantly higher catalytic activity. In contrast, those studies typically require substantially higher reaction temperatures (155–170 °C).[20,22]

3.2. Monomer scope

To further investigate the catalytic activity in the ROP of other cyclic monomers, TMC and δ-VL were polymerized (Scheme 1). Each ROP was performed in bulk at 100 °C with a [monomer]$_0$/[PPA]$_0$/[catalyst] ratio of 50/1/5 (Table 2). For the ROP of TMC using CA as a catalyst, the monomer conversion reached 56.9% 9.5 h after polymerization initiation, confirming polymer formation (run 1 in Table 2). By contrast, when CNa$_3$ was used as a catalyst, the conversion reached 86.0% after only 1.5 h, demonstrating a much higher catalytic activity than that of run 1, involving an acidic catalyst (run 2 in Table 2). However, the molecular weight distribution was slightly broad ($Đ = 1.30$) (Fig. S2a). The ^{1}H NMR spectrum of the obtained PTMC showed signals attributed to both the PTMC main-chain and PPA residues (Fig. S2b). In the MALDI-TOF mass spectrum, small subpeaks corresponding to transesterification and 1,3-propanediol initiation were observed (Fig. S3). This may explain the slightly broader dispersion observed. When the tar-
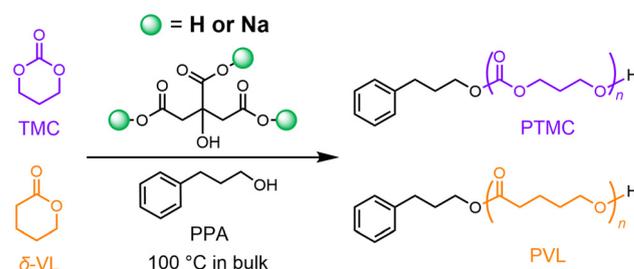
Scheme 1 ROP of other cyclic monomers.

geted DP was increased to 150 with a decreased CNa$_3$ catalyst loading, *viz.* [TMC]$_0$/[PPA]$_0$/[CNa$_3$] = 150/1/1, the molecular weight of the resulting PTMC increased accordingly, accompanied by a slightly higher dispersity (run 3 in Table 1 and Fig. S2c). These results demonstrated that CNa$_3$ could function as a catalyst for the controlled synthesis of PTMC, although, upon comparison with our previous finding, it did not outperform sodium acetate.[33]

The ROP of δ-VL yielded similar results to the ROP of ε-CL. When CA was used as the catalyst, 88.5% of the monomer was

Table 2 Monomer scope[a]

Run	Monomer	Catalyst	[Monomer]$_0$/[PPA]$_0$/[catalyst]	Time (h)	Conv.[b] (%)	$M_{n, th.}$[c] (g mol^{-1})	$M_{n, NMR}$[b] (g mol^{-1})	$M_{n, SEC}$[d] (g mol^{-1})	$Đ$[d]
1	TMC	CA	50/1/5	9.5	56.9	3040	4320	3800	1.20
2	TMC	CNa$_3$	50/1/5	1.5	86.0	4530	4830	6400	1.30
3[e]	TMC	CNa$_3$	150/1/1	15.0	74.2	11 500	11 900	15 500	1.38
4	δ-VL	CA	50/1/5	2.0	88.5	4570	4340	4500	1.24
5	δ-VL	CNa$_3$	50/1/5	24.0	11.0	n.d.	n.d.	n.d.	n.d.
6[f]	δ-VL	CA	150/1/1	30.0	82.3	12 500	12 500	17 100	1.13

[a] Polymerization conditions: atmosphere, Ar; initiator, PPA; temperature, 100 °C. [b] Determined from ^{1}H NMR spectrum of the obtained polymer in CDCl$_3$. [c] Calculated from [monomer]$_0$/[PPA]$_0$ × conv. × (M.W. of the monomer) + (M.W. of PPA). [d] Determined using SEC in THF with a polystyrene standard. [e] Temperature, 70 °C. [f] Polymerization was conducted in the presence of toluene (δ-VL/toluene = 25 mmol/1 mL). (n.d = not determined).

converted within 2 h and produced PVL with fairly good control of the molecular weight dispersity (run 4 in Table 2 and Fig. S4a). Good polymerization control also reflects the good agreement between $M_{n, NMR}$ and $M_{n, th.}$, together with the ^{1}H NMR and MALDI-TOF mass spectra (Fig. S4b and S5). By contrast, the ROP of δ-VL was sluggish when using CNa$_3$ as the catalyst: only 11% of the monomer was consumed after 24 h (run 5 in Table 2). This result is consistent with our previous study on AMC-catalyzed ROP of δ-VL, in which a low polymerization rate was observed.[17] Given that CA exhibited higher catalytic activity in the ROP of δ-VL, polymerization targeting a DP of 150 using CA catalyst was conducted. As a result, PVL with narrow dispersity ($Đ$ = 1.13) and correspondingly higher molecular weight was obtained (run 6 in Table 2 and Fig. S4c). These investigations demonstrate that the ROP of cyclic esters and carbonate monomers with drastically different reactivities can be accomplished by screening the edible catalysts, particularly acids with sufficient acidity and their corresponding alkali metal salts.
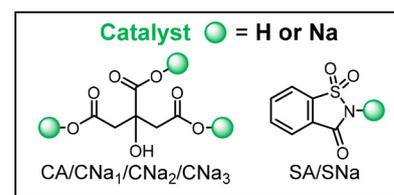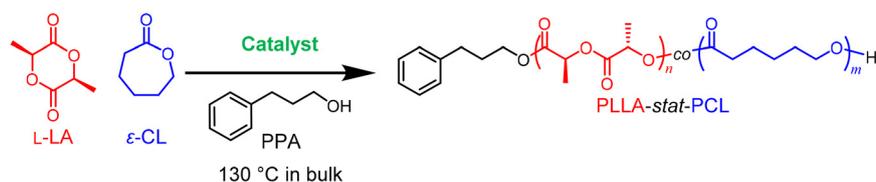
3.3. Copolymerization of L-LA and ε-CL

Except for the polyester and polycarbonate homopolymers mentioned above, copolymers including statistical and block copolymers could further tune the material properties to meet broader application demands. In particular, the copolymers of LA and ε-CL are the most widely applied.

The statistic copolymers of LA and ε-CL are mostly synthesized via copolymerization of LA and ε-CL using organometallic catalysts such as Sn(Oct)$_2$ and alumina-based catalysts. In most cases, LA is consumed faster than ε-CL, thus resulting in a monomer sequence gradient.[34–38] By carefully

tuning the structure of ligands in the Salen complex of aluminum, Nomura et al. realized a nearly perfect random copolymerization of L-LA and ε-CL.[39] More recently, Taton et al. used simple and safe benzoic acid as a catalyst for the random copolymerization of L-LA and ε-CL, although a reaction temperature of as high as 155 °C was required.[22,23] Pang et al. used sodium ascorbate to catalyze the copolymerization of L-LA and ε-CL under 170 °C, claiming to obtain the random copolymer based on an analysis of the copolymer; however, they did not analyze the polymerization kinetics.[20]

In this study, we have already demonstrated that the ROP of ε-CL and L-LA can proceed efficiently and in a well-controlled manner using the edible catalysts CA and CNa$_3$, respectively. Between CA and CNa$_3$, there are medium states, viz. monosodium citrate (CNa$_1$) and disodium citrate (CNa$_2$). These can be regarded as mixtures of CA and CNa$_3$. As a preliminary experiment, the homopolymerizations of L-LA and ε-CL conducted using CNa$_1$, CNa$_2$, CK$_1$, and CK$_3$ as a catalyst (Scheme S1). These results confirmed that CNa$_1$ and CNa$_2$ exhibited catalytic behaviors intermediate to those of CA and CNa$_3$ (Tables S2, S3 and Fig. S6). We wondered if CNa$_1$ and CNa$_2$ could catalyze the copolymerization of ε-CL and L-LA in the fashion between CA and CNa$_3$, thus resulting in the copolymers having near-random monomer sequences. With this idea in mind, the copolymerization of L-LA and ε-CL was conducted using CA, CNa$_1$, CNa$_2$, and CNa$_3$, respectively (Scheme 2 and runs 1–4 in Table 3). The copolymerizations were conducted in the ratio of [L-LA]$_0$/[ε-CL]$_0$/[PPA]$_0$/[catalyst] = 50/50/1/1 under 130 °C in bulk. When CA was utilized, after 80 h, the conversion of L-LA and ε-CL reached 49.1% and 78.0%, respectively (run 1 in Table 3). By contrast, when CNa$_3$ was used as the

Scheme 2 Synthesis of statistical copolymer.

Table 3 Ring-opening copolymerization of L-LA and ε-CL[a]

Run	Catalyst	Time (h)	Conv.$_{L\text{-}LA}$[d] (%)	Conv.$_{\varepsilon\text{-}CL}$[d] (%)	L-LA : ε-CL in copolymer[d]	$M_{n, th.}$[e]	$M_{n, NMR}$[d]	$M_{n, SEC}$[f]	$Đ$[f]
1[b]	CA	80.0	49.1	78.0	n.d.	8130	n.d.	2800[g]	1.40[g]
2[b]	CNa$_3$	25.0	72.5	4.9	n.d.	5640	n.d.	3700[g]	1.55[g]
3[b]	CNa$_1$	22.5	91.6	19.7	n.d.	7860	n.d.	4100[g]	1.62[g]
4[b]	CNa$_2$	22.5	91.3	18.0	n.d.	7740	n.d.	4100[g]	1.61[g]
5[c]	SA	164.0	22.6	78.3	24 : 75	6220	6090	6600	1.39
6[c]	SNa	50.0	85.9	10.1	90 : 10	6900	5200	6800	1.22
7[c]	SA/SNa = (1 : 4)	168.0	83.8	53.4	62 : 38	9220	8900	7900	1.30
8[c]	SA/SNa = (3 : 2)	305.0	73.0	73.8	49 : 51	9610	9400	9800	1.46
9[c,h]	SA/SNa = (3 : 2)	48.0	96.0	83.0	55 : 45	11 800	10 600	6700	1.62

[a] Polymerization conditions: atmosphere, Ar; initiator, PPA; temperature, 130 °C. [b] [L-LA]$_0$/[ε-CL]$_0$/[PPA]$_0$/[catalyst] = 50/50/1/1. [c] [L-LA]$_0$/[ε-CL]$_0$/[PPA]$_0$/[catalyst] = 50/50/1/5. [d] Determined by ^{1}H NMR spectroscopy of the obtained polymer in CDCl$_3$. [e] Calculated from [L-LA]$_0$/[PPA]$_0$ × conv.$_{L\text{-}LA}$ × (M.W. of L-LA) + [ε-CL]$_0$/[PPA]$_0$ × conv.$_{\varepsilon\text{-}CL}$ × (M.W. of ε-CL) + (M.W. of PPA). [f] Determined by SEC in THF using a polystyrene standard. [g] Determined from the crude product. [h] Temperature, 160 °C.

catalyst, the copolymerization demonstrated the opposite polymerization kinetics, with 72.5% and 4.9% consumption of L-LA and ε-CL, respectively, after 25 h (run 2 in Table 3). These results align with our previous results for the homopolymerization of L-LA and ε-CL using these two catalysts, respectively, although the difference in their reactivity in the copolymerization is not as obvious as that in their homopolymerization, when CA is used at the catalyst (Fig. 2). When CNa$_1$ and CNa$_2$ were applied as catalysts under the same polymerization condition, to our surprise, they exhibited similar reactivities, with 91%–92% and 18%–20% conversion of L-LA and ε-CL, respectively, after 22.5 h (runs 3 and 4 in Table 3). In both cases, L-LA was consumed faster than ε-CL, whose catalytic kinetics were closer to the CNa$_3$-catalyzed polymerization. These results indicate that in the catalytic system using CNa$_1$ and CNa$_2$, the catalyst forms are in equilibrium among the four possible states (CA, CNa$_1$, CNa$_2$, and CNa$_3$), among which CNa$_3$ may have the highest catalytic reactivity (Scheme S2). The obtained copolymers under these four copolymerization conditions have relatively broad molecular weight distributions, $Đ$ = 1.40–1.61 (Fig. S7–S10). The $M_{n, SEC}$ values of the obtained four copolymers are obviously lower than $M_{n, th.}$ compared with the results in homopolymerizations (Table 1). This presumably indicates an undesired initiation from a species other than the PPA initiator.

The possible equilibrium between the four states in the CA and sodium citrate systems was too complicated to analyze. To simplify the system, we focused on a saccharin/saccharin sodium salt (SA/SNa) system, in which the catalysts have only two possible states. When SA was used as the catalyst for copolymerization, 22.6% of L-LA and 78.3% ε-CL were converted, respectively, after 164 h (run 5 in Table 3). By contrast, when using SNa, the consumption of L-LA and ε-CL were 85.9% and 10.1%, respectively, after 50 h (run 6 in Table 3). The selectivity of the two monomers was in good agreement with their homopolymerization results, although decreased reactivity was observed during copolymerization. When SA and SNa were mixed at a molar ratio of 1 : 4, L-LA was still consumed faster than ε-CL (83.8% vs. 53.4% conversion, respectively); however, the difference in consumption rates was smaller than that

observed when using SNa alone as the catalyst (run 7 vs. run 6 in Table 3 and Fig. S11). When mixing SA and SNa in a molar ratio of 3 : 2, L-LA and ε-CL were consumed at almost the same rate, but the reaction time was long (run 8 in Table 3, Fig. 7 and S12). In terms of the copolymers obtained using the SA/SNa catalytic system, although the dispersity index was still slightly broad ($Đ$ = 1.22–1.46), $M_{n, NMR}$ and $M_{n, SEC}$ were in good agreement with $M_{n, th.}$, indicating fairly good polymerization control (runs 5–8 in Table 3 and Fig. S13–S16). Increasing the polymerization temperature to 160 °C indeed shortened the reaction time; however, a broader dispersity ($Đ$ = 1.62) and a lower $M_{n, SEC}$ compared with $M_{n, NMR}$ were observed, indicating a reduced level of polymerization control (run 9 in Table 3, Fig. S17 and S18). The obtained PLLA-stat-PCL copolymer was characterized using ^{1}H-NMR and quantitative ^{13}C-NMR (run 8 in Table 3, Fig. 8 and S19). In particular, the ^{13}C NMR spectrum revealed multiple peaks arising from the complex arrangement of L-LA and ε-CL units, confirming the formation of a statistical copolymer. Notably, the absence of peaks corresponding to the CLC sequence at ~171 ppm (C = ε-CL, L = lactic acid) indicates that transesterification does not occur in this copolymerization.[40] The average sequence lengths of L-LA and ε-CL units in the copolymer were calculated to be $L_{L\text{-}LA}$ = 2.7 and $L_{\varepsilon\text{-}CL}$ = 2.9, respectively (Fig. S20).[41] Although these values are slightly higher than those for an ideal random copolymer ($L_{L\text{-}LA}$ = $L_{\varepsilon\text{-}CL}$ = 2.0), they demonstrate that the obtained copolymer exhibits random-like characteristics.

Block copolymers made from PLA and PCL, including ABA-type triblock and multiblock copolymers, are biodegradable and bioresorbable thermoplastic elastomers used in various biomedical applications. Jikei et al. synthesized multiblock copolymers via self-polycondensation of PLA-b-PCL diblock copolymers and demonstrated their effectiveness as adhesion barrier films in surgeries.[42] Liu et al. reported that star-shaped PCL-b-PLLA block copolymers are promising candidates for cardiovascular tissue engineering and absorbable medical devices.[43] However, in both cases, Sn(Oct)$_2$ was used as the catalyst.

In our previous study on AMCs, we successfully synthesized a PTMC-b-PLLA block copolymer using sodium acetate as a
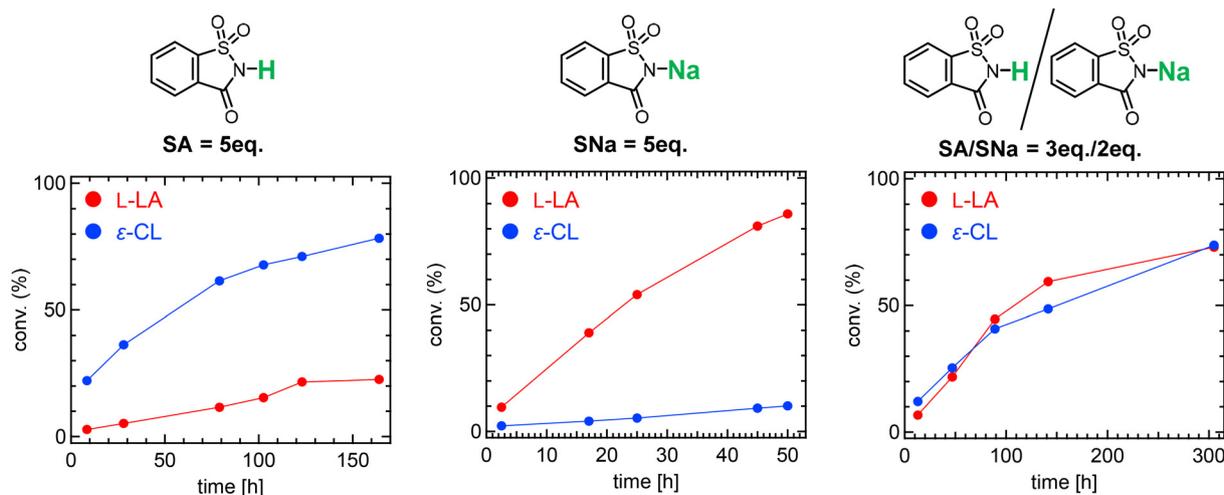
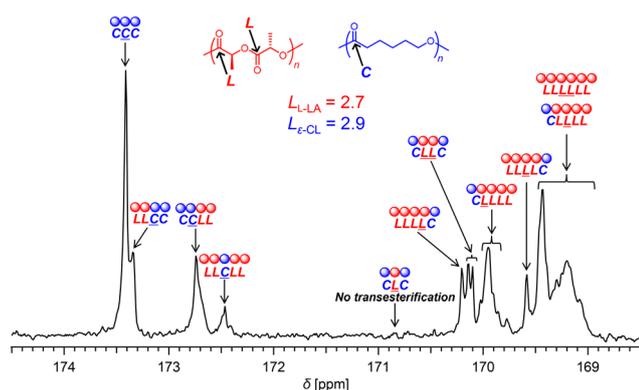**Fig. 7** Plots of monomer conversion *vs.* time (runs 5, 6, and 8 in Table 3).

Fig. 8 ^{13}C NMR spectrum of the PLLA-*stat*-PCL obtained from run 8 in Table 3 (solvent, CDCl$_3$; 100 MHz).

catalyst.[33] However, this remains a challenge for PLA-*b*-PCL block copolymers. Using benzoic acid, Taton *et al.* synthesized a PLLA-*b*-PCL-*b*-PLLA triblock copolymer *via* the sequential addition of monomers in a one-pot/two-step fashion; however, the ROP of L-LA required harsh conditions and a long reaction time.[22]

Owing to the drastically different characteristics of ε-CL and L-LA in terms of their polymerization conditions when using organocatalysts, a two-step synthesis involving a catalyst change is often needed.[44–46] In this study, we have already demonstrated that the ROP of ε-CL and L-LA can proceed efficiently and in a well-controlled manner when catalyzed by edible CA and sodium citrate, respectively. We wondered whether these two catalysts could be used to synthesize PCL-*b*-PLLA block copolymers in a one-pot/two-step fashion. As shown in Scheme 3, from the bifunctional initiator BDM, the ROP of ε-CL was first performed using CA as the catalyst. When ε-CL was almost completely consumed, L-LA together with CNa$_3$ were added to synthesize the subsequent PLLA block. Mixing CA and CNa$_3$ generates a complex equilibrium of four species, including two new species: CNa$_1$ and CNa$_2$. According to the performance of CA, CNa$_1$, CNa$_2$, and CNa$_3$ in
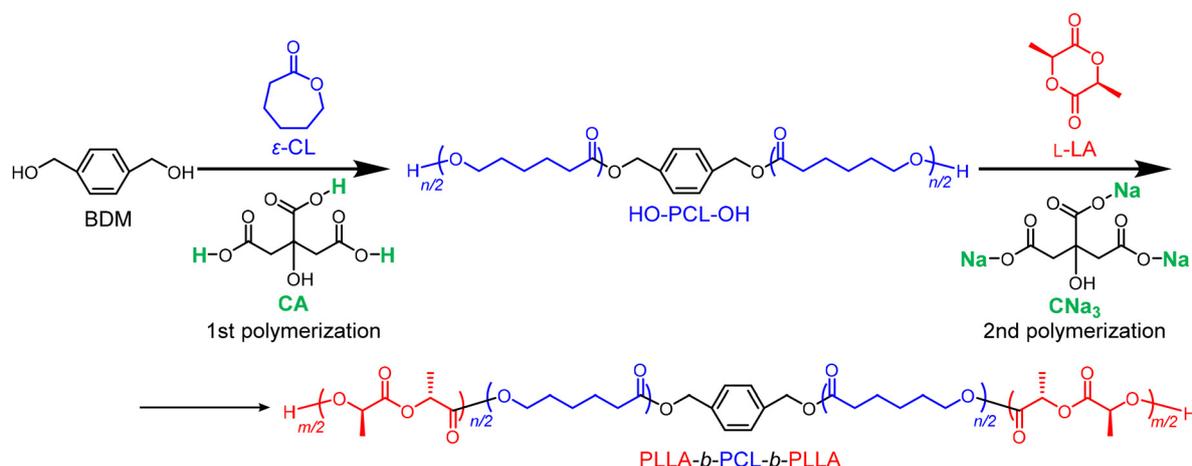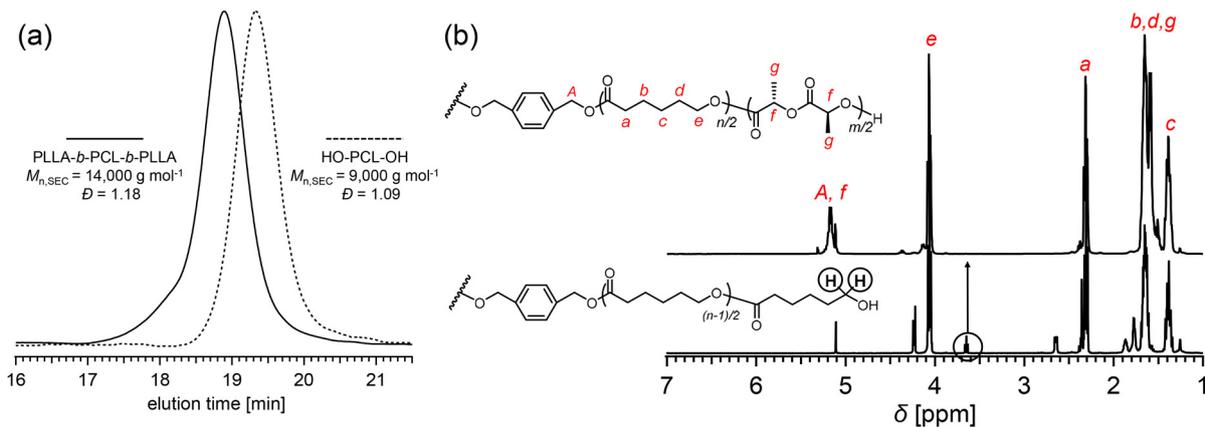

Scheme 3 One-pot synthesis of block copolymer.

Fig. 9 (a) SEC trace of HO-PCL-OH (dotted line) and PLLA-*b*-PCL-*b*-PLLA (solid line) (eluent, THF; flow rate, 1.0 mL min⁻¹); (b) ¹H NMR spectrum of HO-PCL-OH (crude; lower) and PLLA-*b*-PCL-*b*-PLLA (after purification; upper) (solvent, CDCl₃; 400 MHz).

the copolymerization of L-LA and ε-CL (runs 1–4 in Table 3), the catalyst generated by mixing CA and CNa₃ should be able to catalyze L-LA with sufficient reactivity and selectivity. Following this hypothesis, the synthesis of the inner PCL block was first performed in a [ε-CL]₀/[BDM]₀/[CA] ratio of 50/1/1 with a small amount of toluene (ε-CL/toluene = 1 mmol/40 μL) at 100 °C. After reacting for 8 h, the conversion of ε-CL reached 84.5%. At this moment, L-LA, CNa₃, and a small amount of toluene ([L-LA]₀/[BDM]₀/[CNa₃] = 50/1/5, L-LA/toluene = 1 mmol/40 μL) were added without purification. The reaction mixture was heated to 130 °C for 21 h. A 74.3% conversion of L-LA and 89.8% final conversion of ε-CL were obtained. The SEC trace of the obtained copolymers exhibited a good shift to the high-molecular-weight region while maintaining a narrow dispersity, that is, from $M_{n,\,SEC}$ = 9000 g mol⁻¹, $Đ$ = 1.09 (PCL) to $M_{n,\,SEC}$ = 14 000 g mol⁻¹, $Đ$ = 1.18 (PLA-*b*-PCL-*b*-PLA) (Fig. 9a). Comparing the ¹H-NMR spectra before and after the chain extension of PLLA, the peak representing the chain-end hydroxyl groups of PCL disappeared and the peak corresponding to PLLA appeared (Fig. 9b). These experimental results demonstrate that using CA and CNa₃ as catalysts, PLLA-*b*-PCL-*b*-PLLA was successfully synthesized in a one-pot, two-step fashion, albeit with an almost negligible amount of the CL monomer incorporated into the PLLA block (Table S4 and Fig. S21).

4.   Conclusions

In this study, a series of edible compounds, specifically organic acids and their sodium or potassium salts, were systematically examined as safe catalysts for the ROP of cyclic esters and cyclic carbonates. We confirmed that the appropriate selection of organic acids and alkali metal salt catalysts enabled the synthesis of biodegradable, biocompatible, and bioresorbable polyesters (PLLA, PCL, and PVL) and polycarbonates (PTMC). The obtained polymers exhibited narrow distributions ($Đ$ = 1.1–1.3) and well-defined chain-end structures.

Copolymers with different sequence structures can be synthesized using binary catalytic systems comprising a mixture of edible organic acids and sodium salts. Random-like PLLA-*stat*-PCL was synthesized using a saccharin/sodium-saccharin mixed catalyst system. The PLLA-*b*-PCL-*b*-PLLA triblock copolymer was synthesized using a one-pot, two-step method using CA/CNa₃. These examples represent innovative approaches that yield high-value-added biodegradable polymers through the simple technique of mixing two types of edible catalysts. Therefore, unassuming edible compounds in our daily lives have the potential to be safe and effective catalysts that replace conventional metal catalysts and organocatalysts, thereby contributing to the practical application of biodegradable polymer materials.

Author contributions

Toshiki Miwa: writing – original draft, methodology, visualization, and data curation. Ryota Suzuki: conceptualization, methodology, data curation, and funding acquisition. Tianle Gao: supervision, writing – review and editing, and funding acquisition. Takuya Yamamoto: supervision. Feng Li: supervision, conceptualization, methodology, writing – original draft, writing – review and editing, and funding acquisition. Takuya Isono: conceptualization, supervision, and writing – review and editing. Toshifumi Satoh: supervision, conceptualization, writing – review and editing, and funding acquisition.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary infor-

mation is available. See DOI: https://doi.org/10.1039/d5gc05933j.

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