PAPER

Check for updates

Copolyesters of ε-caprolactone and L-lactide catalyzed by a tetrabutylammonium phthalimide-*N*-oxyl organocatalyst†

Zhiheng Feng,[a] Li Wu,[a] Huan Dong,[a] Boping Liu[b] and Ruihua Cheng (ID) *[a]

Aliphatic polyesters are biocompatible materials that can be used in biomedical applications. We report here the use of tetrabutylammonium phthalimide-*N*-oxyl catalyst (**TBAPINO**), as a thermally stable organocatalyst for the ring-opening polymerization (ROP) of cyclic esters under mild conditions. In the solution ROP of ε-caprolactone (ε-CL), quantitative conversion and M_n of ~20 000 g mol^{-1} are achieved in a wide temperature range from −15 to 60 °C. Under bulk condition, the conversion of ε-CL reaches over 85% at 120 °C within 2 h. The living ROP character of L-lactide (L-LA) catalyzed over **TBAPINO** is proved by multiple additions of monomer in the bulk polymerization. The catalyst shows comparable selectivity towards the ring-opening polymerization of L-LA and ε-CL. Their copolymerization over **TBAPINO** is carried out in one-pot bulk condition in terms of the reaction time, monomer feed ratio, and sequence of addition. The colorless poly(ε-caprolactone-*co*-lactide) (PCLA) is obtained with considerable conversion of both monomers with the M_n over 22 000 g mol^{-1}.

Introduction

Aliphatic polyesters, such as poly(lactide) (PLA), poly(ε-caprolactone) (PCL), poly(glycolide) (PGA), *etc.* and their copolymers are found to be excellent biodegradable and biocompatible materials, with applications in drug delivery,[1–3] tissue engineering,[4] orthopedic stents[5] and agricultural production.[6] As they are gaining more awareness in daily production and medical fields, higher requirements are put forward for the performance of biodegradability and biocompatibility *etc.* To improve the properties, copolymerization of two or more monomers provides an alternative way to create materials with complementary properties. For example, poly(lactide-*co*-glycolide) (PLGA) is extensively used in biomedical applications for its hydrolysis-mediated degradation.[7] Poly(caprolactone-*co*-lactide) (PCLA) is more permeable and has a tunable degradation and hydrolysis rate.[8,9] Thus, more compatible catalysts to activate diverse monomers are crucial to the copolymerization system.

Up to now, diverse and versatile catalysts were applied in the ring-opening polymerization (ROP) of cycloesters.[10] Stannous octoate is the commercial metal catalysts for the homo- and copolymerization of various cyclic esters.[11] However, the tin

residue should be removed due to its toxicity, especially in biomedical application.[8] Alternatively, Al, Mg, and Zn with various anions have been studied for ROP of polyesters.[12] Aluminum complexes modified by varying the ligand were utilized to produce well-defined polymers with high catalytic efficiency and selectivity to ROP of lactones.[13,14] Zinc alkoxides were friendly substitution of Tin analogue due to their bio-resorbable characteristic[15] and proved to be high effective for ROP of L-LA at room temperature with good control of polymer structure.[16]

In recent years, the application of metal-free strategies to ROP reactions has been developed into an important aspect of the field. These systems offer advantages including the absence of metal contamination, simple synthesis, wide scope of monomers and enhanced stability to trace impurities such as water and oxygen.[17]

Hedrick and coworkers[18] first reported 4-(dimethylamino) pyridine (DMAP) as a simple organocatalyst for the ROP of L-LA in solution at room temperature, while several days were needed to reach considerable conversion of lactones (ε-CL and δ-valerolactone, δ-VL). 1, 5, 7-Triazabicyclo[4.4.0]dec-5-ene (TBD) could present the comparative catalytic efficiency as metal catalysts.[19] Up to now, various types and chemical structures catalysts, including *N*-heterocyles, *N*-heterocyclic carbenes (NHCs), (thio)ureas, acids, phosphazene bases *etc.* have been reported.[20]

Beyond that, the organocatalysts derived from multi-component catalysts, as the combinations of the acidic/basic catalysis modes have been proven useful for the ROP reactions, demonstrating advantages of efficiency, stableness, and

[a]School of Chemical Engineering, East China University of Science and Technology, Meilong Road 130, Shanghai, 200237, China. E-mail: rhcheng@ecust.edu.cn

[b]College of Materials and Energy, South China Agricultural University, Guangzhou, 510642, China

mildness. In addition to the DMAP·HX complex,[21,22] the DBU·BA (benzoic acid) conjugate catalyst could also catalyze the ROP of L-LA, demonstrating a more controlled manner on polymerization.[23] The combination of *N*-methyl-TBD (MTBD) with trifluoro-methanesulfonic acid (TFA) was proved to be efficient for ROP in synthesis of block copolymer poly(trimethylene carbonate)-*b*-poly(L-lactide) (PTMC-*b*-PLA).[24] Some of these organocatalysts demonstrated bifunctional ability, which could activate the monomer and initiator at the same time.[25,26]

Commercially, the copolymer PCLA was prepared by the organometallic promoters at temperatures ranged from 100 to 180 °C. Bulk copolymerization could be carried out with high conversion and without disposing of tons of toxic solvent and trouble of separation. For example, using $Sn(Oct)_2$ catalyst, Kim *et al.* synthesized block PCLA copolymers using the hydroxyl-terminated PCL macroinitiator, which was previously synthesized at 140 °C for 24 h, followed by addition of L-LA at 110 °C for 48 h.[27]

Although some organocatalysts have showed excellent catalytic activity towards certain kinds of cyclic esters, the relative reactivity of different monomers, *e.g.* L-LA and ε-CL, varies greatly on the same catalyst. For the ROP using (thio)urea systems catalyst, thiourea catalysts were more active than their urea analogues in the bulk ROP of L-LA conducted at 100 °C, which was contrary to the case of ROP of ε-CL with better performance by urea catalyst.[28] Using TBD catalyst, the polymerization of ε-CL in benzene-d_6 was less active than that of L-LA in CH_2Cl_2, the reaction time being 5 h *vs.* 15 s.[19] MTBD and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) could catalyze the ROP of L-LA within 1 h, but 120 h was required to obtain PCL with M_n of 8000 g mol^{-1}. DMAP·HCl showed excellent catalytic activity towards L-LA, achieving conversion of 95% within 1.5 h at 140 °C, but failed to activate ε-CL or VL at 90 °C.[21]

The attempt to copolymerize L-LA and ε-CL simultaneously using TBD catalyst achieved limited success, only PLA homopolymer was observed.[19] Alternatively, by the sequential reaction of ε-CL by TBD in toluene for 7 h, and DL-Lactide in CH_2Cl_2 solution for 30 s, the block copolymer PCLA was obtained. Applying a similar methodology, block PCLA copolymers were prepared by sequential reaction by DBU/phenol dual catalytic system in 6 days.[29] Based on the H-bonding activated Brønsted acid, Guo and coworkers[30] reported the block copolymerization of ε-CL and L-LA in CH_2Cl_2 by the combination of thiophosphoric triamide and methanesulfonic acid. The two monomers were sequentially added and stirred for 45 h and 20 h respectively to obtain the block PCLA with 95% conversion. The pentablock terpolymers were synthesized by one-pot sequential polymerization of ethylene oxide (EO), ε-CL, and L-LA by mild phosphazene base (*t*-BuP$_2$).[31]

The bulk ROP of L-LA is still identified as a challenge for organocatalysts,[32] not to mention the copolymerization with other monomers. Due to the selectivity of organocatalysts towards ROP of L-LA and ε-CL, it is difficult to find a compatible organocatalyst to obtain PCLA copolymer in bulk condition. Apart from the selectivity, the elevated reaction temperature can also be problematic. At least 100 °C is required for L-LA to reach its melting point. However, the organocatalysts might
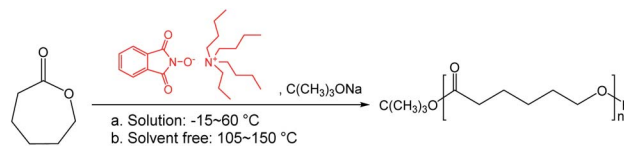

Fig. 1 ROP of ε-CL catalyzed by **TBAPINO**.

decompose,[33] and some binary organocatalysts could be deactivated due to the weakened H-bonding at high temperature.

To date, only few organocatalysts have been reported in the copolymerization in bulk manner. Benzoic acid accompanied with the alcohol initiator was proved to be active for copolymerization of ε-CL and L-LA mixture to obtain the PCLA at 155 °C.[34] More than 24 h was required to reach reasonable conversion, apart from which, another equivalent catalyst was added along with the other monomer to obtain block copolymers. The dibenzoylmethane (DBM) was studied to catalyze the PCLA at 155 °C, M_n of which ranged from 1000 to 4100 g mol^{-1}, while long reaction time over 48 h was also inevitable.[35]

The air/moisture-tolerant tetrabutylammonium phthalimide-*N*-oxyl (**TBAPINO**), synthesized with cheap raw materials, have found applications in cyanosilylation of carbonyl compounds, cyclotrimerization of aryl and alkyl isocyanates, *etc.*[36–38] Our previous work has proved its excellent catalytic efficiency towards ROP of L-LA both in bulk and solution polymerization.[39] Therefore, in present work, we expanded the application of **TBAPINO** and further described the catalytic activity towards ROP of ε-CL (Fig. 1) and L-LA to obtain the optimal condition. Furthermore, their copolymerization in bulk condition was studied in terms of feed ratios and addition sequences, reaction times and the structure of product was characterized by nuclear magnetic resonance (NMR), size exclusion chromatography (SEC) and differential scanning calorimetry (DSC) analysis.

Experimental

Materials and methods

ε-Caprolactone (ε-CL, 99%) was dried over CaH_2 for 48 h prior to distillation under reduced pressure. L-lactide (L-LA, 98%) was dissolved in ethyl acetate, recrystallized after reflux for 4 h, and dried under vacuum for 24 h. Toluene (99.5%, Sinopharm Chemical Reagent Co.) using benzophenone as indicator and nitrogen as protective gas, was purified by refluxing until benzophenone turned dark purple. Sodium *tert*-butoxide (*t*BuONa, 99%), benzoic acid (BA, 99.5%), absolute ethyl alcohol (EtOH, AR), phthalimide (98%), tetrabutylammonium hydroxide (25 wt% in water) were used as received. Compounds were stored in a glove box ($O_2 \leq 1$ ppm, $H_2O \leq 0.1$ ppm). All reagents and chemicals, except for those specified, were purchased from Shanghai Titan Scientific Co.

^{1}H NMR spectra was recorded on a AVANCE 500 spectrometer at 25 °C in $CDCl_3$ to determine the monomer conversion, using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra was recorded on an ASCEND 600 spectrometer with

1024 scans in CDCl$_3$ to investigate the copolymer composition, using tetramethylsilane (TMS) as an internal standard. The molecular weights (M_n) of products were measured using a size exclusion chromatography (SEC) system (Waters-1515 gel permeation chromatograph). The SEC system was calibrated by a series of polystyrene standards with polydispersities of 1.02, and tetrahydrofuran (THF) was used as the mobile phase at an elution rate of 1 mL min^{-1} Differential scanning calorimetry (DSC) measurements were carried out with a TA Q200 DSC apparatus under nitrogen flow. Thermal procedure of polymers is showed as follow. The PCL/PLA/PCLA samples were melted at 100/200/200 °C for 3 min to eliminate the thermal history. Then they were cooled to −80/0/−80 °C at the cooling rate of −10 °C min^{-1}, after which the samples were reheated to 100/200/200 °C at the heating rate of 10 °C min^{-1}, respectively.

Synthesis of TBAPINO

6.8 mmol phthalic diamide and equivalent tetrabutylammonium hydroxide were added to 25 mL flask, and the mixture was stirred for 5 min at room temperature. Then 5 mL deionized water was added to the mixture. The reaction was conducted at 100 °C for 4 h under reflux condition. After the mixture was cooled to room temperature, the solvent was evaporated. The residue was cooled under 0–4 °C for 1 h to afford a white crystal and then dried at vacuum at 60 °C for 12 h.

Homopolymerization

Solution polymerization of ε-caprolactone. All solution polymerization experiments were conducted in a glovebox. Magnetic heating plate was preheated to the desired temperature. 10 mL Schlenk tube was charged with desired amount of catalyst, tBuONa and toluene solvent. After the catalyst was completely dissolved, 300 mg (2.6 mmol) ε-CL were added. After the reaction quenched by isopropyl alcohol, excess ethanol was used to precipitate the polymer. The solid residue was centrifuged and dried at vacuum at 50 °C for 12 h and a white solid PCL was obtained.

Bulk polymerization of ε-caprolactone/ʟ-lactide. All bulk polymerization experiments were conducted in a glovebox. Magnetic heating plate was preheated to the desired temperatures. 10 mL Schlenk tube was charged with 300 mg (2.6 mmol) ε-CL/ʟ-LA and desired amount of catalyst and tBuONa. After reaction, isopropyl alcohol was added as the quenching agent, and the dichloromethane was used to dissolve the crude product. The polymer was precipitated by dropping into excess fast-stirring ethanol. The following processing of product mixture was identical with solution polymerization.

Living polymerization of ʟ-lactide. Living polymerization experiments were conducted in a glovebox. Magnetic heating plate was preheated to the desired temperatures. 10 mL Schlenk tube was charged with 300 mg (2.6 mmol) ʟ-LA and desired amount of catalyst and tBuONa. After 30 min, a drop of reaction mixture was removed from the tube, and meanwhile another equivalent of ʟ-LA was added to the tube. This procedure was repeated for several times. The samples were dissolved in

dichloromethane, and excess ethanol was used to precipitate the polymer.

Block copolymerization of ʟ-lactide and ε-caprolactone. All block copolymerization was conducted in a glovebox. Magnetic heating plate was preheated to the desired temperature. Desired amount of ʟ-LA or ε-CL, catalyst and tBuONa were added to 10 mL Schlenk tube. After a certain reaction time, the other monomer was added. The benzoic acid was added to quench the reaction. Then the dichloromethane was used to dissolve the crude product, and the copolymer was precipitated by dropping into excess fast-stirring ethanol. The solid residue was centrifuged and dried at vacuum at 50 °C for 12 h and a white solid copolymer was obtained. Addition sequence of monomers and reaction time were adjusted according to experiment condition.

Results and discussion

Solution polymerization of ε-caprolactone

First, the ROP of ε-CL were presented in solution in terms of the feed ratio of catalyst to initiator. In Table 1, when the [ε-CL] : [**TBAPINO**] = 200 : 2, the conversion was 78% in 5 h, while the similar conversion could be obtained in 4 h at 200 : 5. And 88.5% conversion was achieved within 2 h when the [ε-CL] : [**TBAPINO**] ratio increased to 200 : 10. With the increasing conversion, the molecular weight of PCL changed slightly, but

Table 1 Solution polymerization of ε-CL^a

Entry	ε-CL/**TBAPINO**/^{t}BuONa	t (h)	Conv.^{b} (%)	M_n^c (g mol^{-1})	$Đ^c$
1	200 : 2 : 4	5.0	78.0	26 770	1.49
2	200 : 5 : 4	4.0	80.4	25 640	1.73
3	200 : 10 : 4	2.0	88.5	26 030	2.78

^{a} Polymerization condition: toluene = 5 mL, ε-CL: 300 mg (2.6 mmol) and desired amount of **TBAPINO** and ^{t}BuONa, pressure: 0.1 MPa, 25 °C, inert atmosphere. ^{b} Measured by ^{1}H NMR. ^{c} Measured by SEC.

Table 2 Influence of ε-CL concentration and reaction time on solution polymerization of ε-CL^a

Entry	ε-CL (mol L^{-1})	t (h)	Conv.^{b} (%)	M_n^c (g mol^{-1})	$Đ^c$
1	0.52	2.0	78.0	26 770	1.49
2	0.65	2.0	85.3	35 250	2.55
3	0.87	2.0	96.9	37 490	2.75
4	1.30	2.0	87.7	36 900	2.78
5	0.52	1.0	84.9	29 110	1.57
6	0.52	2.0	86.8	30 230	1.70
7	0.52	3.0	92.1	30 930	1.71
8	0.52	4.0	86.5	28 540	1.67
9	0.52	5.0	78.0	26 770	1.49

^{a} Polymerization condition: toluene = 2/3/4/5 mL, [ε-CL] : [**TBAPINO**] : [^{t}BuONa] = 200 : 2 : 4, ε-CL: 300 mg (2.6 mmol), pressure: 0.1 MPa, 25 °C, inert atmosphere. ^{b} Measured by ^{1}H NMR. ^{c} Measured by SEC.
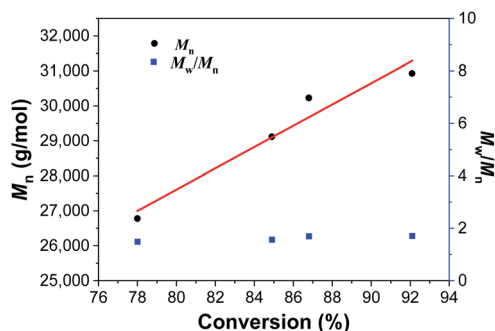
Fig. 2 Relationship curve of monomer conversion with molecular weight and M_w/M_n of ε-CL polymerization.

Fig. 3 SEC curve of PCL (entry 5, Table 2).

polydispersity increased from 1.49 to 2.78, which was likely due to the intensive transesterification reaction.

The effect of monomer concentration on polymerization (entry 1–4, Table 2) was studied by varying the volume of toluene. The monomer concentration varied from 0.5 to 0.87 mol L^{-1} led to an elevated conversion and M_n and broader polydispersity. The highest conversion and M_n were 98.0% and 37 490 g mol^{-1} at 0.87 mol L^{-1}. When the monomer concentration was over 0.87 mol L^{-1}, both the conversion and M_n dropped with the increasing concentration, which might be owing to faster reaction rate of ROP causing partial blockage of catalyst active center and limited contact of ε-CL monomer with catalyst. On the other hand, the increased viscosity of generated PCL during the polymerization process resulted in slower movement of ε-CL monomer and eventually led to the decreased conversion.

In Table 2, the conversion and M_n (entry 5–9) both increased with prolonged reaction time. The highest conversion and M_n of 92.1% and 30 930 g mol^{-1} were obtained when the reaction time reached 3 h, and then decreased dramatically with longer reaction time. The polydispersity remained stable with prolonged time. The correlation between M_n and conversion is plotted in Fig. 2, the M_n increased with conversion with linearly dependence coefficient of $R_2 \geq 0.93$, suggesting the living polymerization character of ε-CL solution polymerization over **TBAPINO**.

In Table 3, the catalyst showed good activity in a wide temperature range, proved by conversion over 85% from −15 °C to 60 °C and M_n of PCL reaching 10 430 g mol^{-1} at −15 °C and 15 170 g mol^{-1} at 60 °C within 1 h. Higher M_n over 20 000 g mol^{-1} were obtained from 0 °C to 40 °C. When temperature was below 25 °C, the conversion and M_n increased with higher temperature, and M_n reached the highest 33 920 g mol^{-1} at 25 °C, but then, M_n decreased. Higher temperature led to faster reaction rate and consumption of monomer, but when polymerization further proceeded, more intensive transesterification reaction caused broader polydispersity.

Fig. 3 shows the monomodal SEC curve of PCL (entry 5, Table 2). The asymmetrical profile with a slight tailing indicated side reactions occurred during the polymerization procedure, resulting in a broader molecular weight distribution. In Fig. 4, a typical melting and crystallization point of PCL sample are at 56.4 and 31.2 °C, respectively.[40,41]

Bulk polymerization of ε-caprolactone

At the same time, the ROP of ε-CL was conducted in bulk condition. The onset decomposition temperature of **TBAPINO** was nearly 180 °C (ESI, Fig. S1†), suggesting its stableness at the reaction temperature from 100 to 150 °C. In Table 4, 56.1% conversion of ε-CL was observed in 1 h at 120 °C (entry 1), while for the case of DMAP and ionic acid catalyst system, 15 h was required to reach 10% conversion.[13]

According to Table 4, the catalyst loading was the most important to obtain high conversion in the bulk ROP of ε-CL, followed by reaction time and temperature. Within the range of 120 to 150 °C, a decreasing conversion was observed. Another

Table 3 Effect of temperature on ε-CL solution ROP[a]

Entry	T (°C)	Conv.[b] (%)	M_n[c] (g mol^{-1})	$Đ$[c]
1	−15	84.8	10 430	1.51
2	0	86.5	22 160	1.50
3	5	87.0	26 770	1.53
4	10	87.7	27 340	1.49
5	25	88.1	33 920	1.57
6	40	94.4	24 260	3.05
7	60	84.9	15 170	3.36

[a] Polymerization condition: solvent: toluene = 3 mL; [ε-CL] : [**TBAPINO**] : [^{t}BuONa] = 200 : 2 : 4; ε-CL: 300 mg (2.6 mmol), t = 1.0 h, pressure: 0.1 MPa, inert atmosphere. [b] Measured by ^{1}H NMR. [c] Measured by SEC.
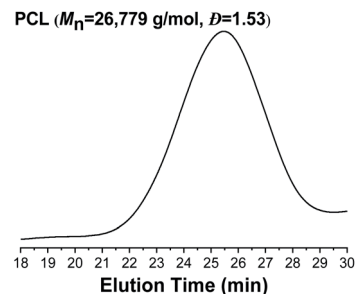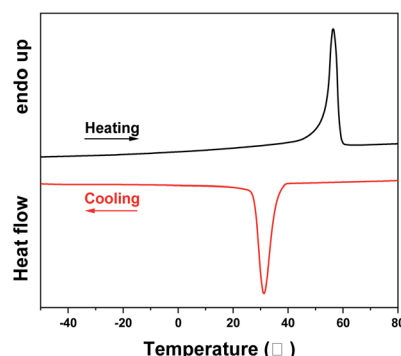

Fig. 4 DSC curve of PCL (entry 5, Table 2).

Table 4 Bulk polymerization of ε-CL[a]

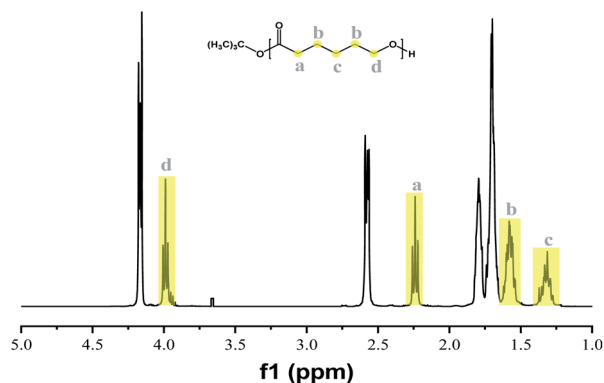| Entry	T (°C)	t (h)	ε-CL/**TBAPINO**/^{t}BuONa	Conv.[b] (%)
1	120	1.0	200/2/1	56.1
2	120	2.0	200/5/1	86.8
3	120	4.0	200/10/1	87.1
4	135	1.0	200/5/1	68.9
5	135	2.0	200/10/1	86.5
6	135	4.0	200/2/1	68.4
7	150	1.0	200/10/1	85.7
8	150	2.0	200/2/1	46.4
9	150	4.0	200/5/1	57.7
10	120	2.0	200/10/1	88.3
11	105	4.0	200/10/1	85.4
12	120	2.0	200/10/4	72.3
13	120	2.0	200/10/2	83.5
14	120	2.0	200/10/0.4	89.5

[a] Polymerization condition: solvent free, ε-CL: 300 mg (2.6 mmol), pressure: 0.1 MPa, inert atmosphere. [b] Measured by ^{1}H NMR.

Table 5 Effect of reaction time and temperature on bulk polymerization of L-LA[a]

Entry	T (°C)	t (h)	Conv.[b] (%)	M_n[c] (g mol^{-1})	$Ð$[c]
1	120	0.5	85.7	2630	1.27
2	120	1.0	95.5	2930	1.23
3	120	2.0	95.7	3220	1.19
4	120	4.0	97.2	1880	1.28
5	95	4.0	81.8	2330	1.20
6	105	4.0	89.1	2350	1.32
7	135	4.0	90.0	1570	1.68
8	150	4.0	88.0	1430	1.72

[a] Polymerization condition: solvent free, [L-LA] : [**TBAPINO**] : [^{t}BuONa] = 200 : 10 : 1, pressure: 0.1 MPa, inert atmosphere. [b] Measured by ^{1}H NMR. [c] Measured by SEC.

controlled experiment at 105 °C (entry 11, Table 4) suggested the conversion with a tendency of first increasing and then decreasing. And 2 h was selected as the optimal reaction time.

To further investigate the influence of initiator concentration, the initiator feeds of [ε-CL] : [^{t}BuONa] were changed from 50 to 500 (entry 10, 12–14, Table 4). The monomer conversion was as high as 89.5%, then slowed down. The lower initiator concentration meant less activated polymer chains, and therefore more monomers were gathered on each chain. No obvious change in $Ð$ was found with various initiator concentration. The synthesized PCL was confirmed by ^{1}H NMR (Fig. 5) and IR spectrum (ESI Fig. S2†), respectively. The integral value ratio of representative methylene protons (a, b, c and d, Fig. 5) of PCL was approximately the theory value of 1 : 2 : 1 : 1.[41] In Fig. S2,† the absorption peak at 1727 cm^{-1} attributed to the C=O stretching, and the 1260–1140 cm^{-1} for the C–O stretching and the 1421–1367 cm^{-1} and 2948–2864 cm^{-1} for the C–H bending and stretching respectively.[42]

Bulk polymerization of L-lactide

In our previous work, the catalyst showed strong air/moisture tolerance and thermal stableness. The polymerization of L-LA

could be carried out in 120 °C with high conversion in inert atmosphere or even in open air.

In Table 5, the influence of reaction time and temperature on bulk polymerization at inert atmosphere was investigated. At 120 °C, the conversion reached 85.7% in 0.5 h and the M_n was 2630 g mol^{-1}, then increased to 3220 g mol^{-1} with the reaction time prolonged to 2 h. When reaction was conducted for 4 h, the conversion reached 97.2%, but the M_n decreased to 1880 g mol^{-1} suggested the occurrence of transesterification.

When 4 h for reaction was fixed, the conversion of the monomer increased from 81.8% at 95 °C to 97.2% at 120 °C (entry 5–8, Table 5), and a slight drop of conversion to 88% was observed at 150 °C. With the increased temperature, the M_n of the polymers decreased from 2350 to 1570 g mol^{-1} (entry 6&7, Table 5), and the polydispersity increased to 1.72. At the higher temperature, the chain initiation and extension were accelerated, shortage of monomer for chain extension led to the slowed down chain growth. Due to the influence of severe transesterification reaction, the reaction suffered from reduced conversion and M_n and broader polydispersity.

The living polymerization experiments were also conducted (Table 6). The concentration of active groups was of vital importance to the living polymerization reaction, and therefore 0.5 h was selected as the interval of monomer feed. Utilizing **TBAPINO**, the M_n increased from 2310 to 5420 g mol^{-1} after the addition of L-LA for three times, confirming efficient re-initiation from the PLA chain. Then the M_n decreased to 2330 and 1980 g mol^{-1} after the following additions. This might be

Fig. 5 ^{1}H NMR spectrum of PCL (entry 10, Table 4).

Table 6 Living polymerization of L-LA over **TBAPINO**[a]

Entry	No. of L-LA addition	M_n[b] (g mol^{-1})	$Ð$[b]
1	1	2310	2.79
2	2	4350	2.04
3	3	5420	1.74
4	4	2330	1.46
5	5	1980	1.66

[a] Polymerization condition: solvent free, [L-LA] : [**TBAPINO**] : [^{t}BuONa] = 200 : 10 : 1, pressure: 0.1 MPa, inert atmosphere. [b] Measured by SEC.

due to the degradation and transesterification during long reaction. It is worth noting that the polydispersity generally decreased upon chain extension with L-LA showing that the ROP was well controlled. At the same time, the living polymerization performed according to the same mechanism suggested the active chain end group could activate monomers when the chain continued to grow, leading to the potential of experiments conducted by sequential polymerization with addition various monomers using a single organocatalyst. And therefore, we explored the copolymerization of L-LA and ε-CL by **TBAPINO** in bulk condition.

Copolymerization of ε-caprolactone and L-lactide

Based on the above homopolymerization work, the optimized condition of both L-LA and ε-CL was 120 °C. Therefore, the similar reaction conditions were applied in the copolymerization of ε-CL and L-LA.

As shown in Table 7, the living character of ROP over **TBAPINO** was further supported by a second-feed experiment in terms of the feed ratios and reaction times. The ε-CL was first activated and the polymerization was then restarted by subsequent addition of L-LA. The individual reaction of each monomer was carried out for 1 or 2 h, respectively. As the feed ratios of ε-CL to L-LA increased from 1 : 3 to 3 : 1, the conversion of ε-CL in 1 h was decreased from 88.1% to 75.6%, while that of L-LA increased from 39.4% to 48.7%. Reasonable conversion and dispersity could be obtained with the equivalent ratio of ε-CL and L-LA. When the individual reaction time was prolonged to 2 h, the conversions of ε-CL and L-LA were greatly improved to 96.5% and 75.2% respectively, and the M_n of the copolymer reached 22 100 g mol^{-1} (entry 4, Table 7). Either increasing the initiator concentration or lower catalyst loading (entry 5&6, Table 7) was not beneficial to copolymerization, leading to reduced M_n and conversion. It is worth noting that the addition sequence of monomers also had influence on the copolymerization (entry 7, Table 7). The reversed addition led to the ε-CL conversion leaped from 96.5% (entry 4, Table 7) to 32.5%, while the L-LA conversion changed slightly. For the sequential polymerization of monolactones, e.g. ε-CL, with L-LA, the latter was usually added as the second monomer.[20] Despite faster polymerization rate of ε-CL than that of L-LA, L-LA was usually
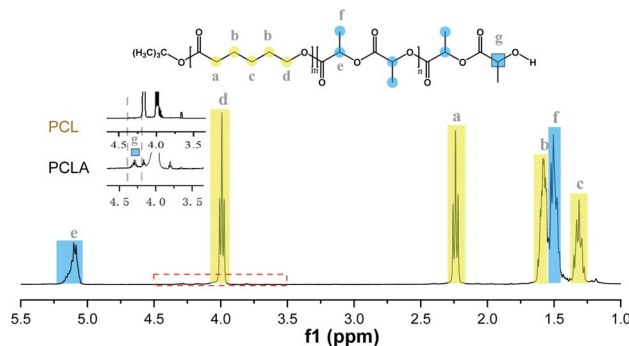

Fig. 6 ^{1}H NMR spectrum of PCLA (entry 4, Table 7).

incorporated first.[19,28,35,43] Furthermore, we also synthesized the PCLA by the reaction of equivalent molar feed of ε-CL and L-LA at 120 °C for 2 min. The ^{1}H NMR spectrum in ESI Fig. S3† indicated that both monomers were inserted into the polymer chains and the CL : LA ratio of product was around 1 : 4 according to the integral value, which was consistent with the preferential insertion of L-LA in the polymer chains.[34,43] The strong evidence showed the comparable selectivity towards the two monomers over **TBAPINO** at high temperature. The copolymerization of L-LA with ε-CL using TBD as the catalyst only resulted in homopolymerization of L-LA and transesterification reaction on PLA. It might be due to the lower reactivity of ε-CL and cannot be initiated by the end group of PLA chain. For the case of PLA-b-PCL-b-PLA triblock copolymer synthesized by sequential addition of ε-CL and L-LA with benzoic acid as catalyst, 75% conversion of ε-CL and M_n of 7730 g mol^{-1} were achieved after 26 h, while the reverse order resulted in only 27% conversion.[41]

The synthesized copolymers were characterized by ^{1}H NMR, ^{13}C NMR, SEC and DSC analysis. In the ^{1}H NMR spectrum (Fig. 6), the formation of block PCLA was confirmed by representative protons of both blocks, 1.58 and 5.17 ppm for the methyl and methine protons of PLA, and 1.30, 1.66, 2.24 and 3.97 ppm for the methylene protons of PCL, which was supported by the hydroxyl-methine PLA end groups at 4.32 ppm.[41] Furthermore, analysis by ^{13}C NMR spectroscopy analysis (Fig. 7) also proved the microstructure of the copolymer.[34,44]

Table 7 Copolymerization of L-LA and ε-CL over **TBAPINO**^{a}

Entry	CL/LA	t_{CL} (h)	t_{LA} (h)	Conv. of CL^b (%)	Conv. of LA^b (%)	M_n^c (g mol^{-1})	$Đ^c$
1	1 : 3	1	1	88.1	39.4	12 340	1.52
2	1 : 1	1	1	85.6	45.4	10 500	1.26
3	3 : 1	1	1	75.6	48.7	10 930	1.46
4	1 : 1	2	2	96.5	75.2	22 100	1.85
5^d	1 : 1	2	2	92.1	71.5	17 330	2.21
6^e	1 : 1	1	1	71.2	41.3	8700	1.27
7^f	1 : 1	2	2	32.5	74.4	10 500	1.87

^{a} Polymerization condition: solvent free, [Monomer] : [**TBAPINO**] : [^{t}BuONa] = 200 : 10 : 1, 120 °C, pressure: 0.1 MPa, inert atmosphere. ^{b} Measured by ^{1}H NMR. ^{c} Measured by SEC. ^{d} [Monomer] : [**TBAPINO**] : [^{t}BuONa] = 200 : 10 : 4. ^{e} [Monomer] : [**TBAPINO**] : [^{t}BuONa] = 200 : 2 : 1. ^{f} L-LA was first added.
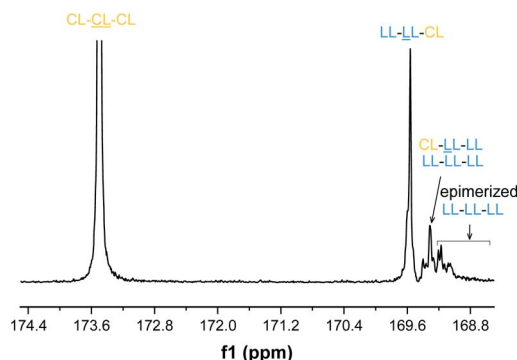
Fig. 7 ^{13}C NMR spectrum of PCLA (entry 4, Table 7); LL and CL refer to the lactidyl and caproyl units respectively.
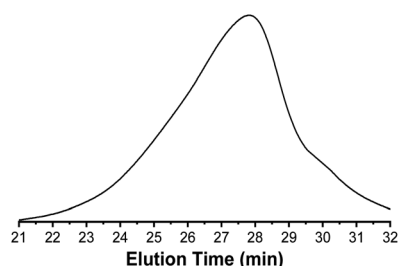

Fig. 8 SEC curve of PCLA (entry 4, Table 7).

Representative peaks at 173.5 ppm attributed to the CL–CL–CL triads, and those at 169.6 ppm for the LL units sandwiched by LL and CL. Peaks between 169.2 and 169.6 ppm belonged to the LL–LL–LL and CL–LL–LL triads, and the broad ones from 168.8 to 169.2 ppm were the LL–LL–LL in epimerized sequences. The transesterification reactions might be rather negligible due to the absence of various heterotraids.[34,45]

In Fig. 8, a monomodal SEC curve of PCLA suggested the synthesis of block PCLA. The slight tailing of SEC curve indicated the occurrence of transesterification reaction. As shown in Fig. 9, a typical glass transition temperature (T_g) of PLA and
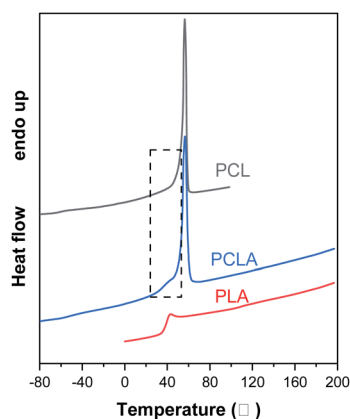

Fig. 9 DSC curves of PLA (entry 3, Table 5), PCL (entry 10, Table 4) and PCLA (entry 4, Table 7).

a melting peak of PCL are at 39.9 °C and 56.4 °C, respectively. The PCLA copolymer showed a combined characteristic of the two homopolymers.

Conclusion

In summary, this thermally stable catalyst (**TBAPINO**) could activate the metal-free and bulk ROP of ε-CL and L-LA, and substantial conversion of both monomers was observed within 4 h at 120 °C. The solution ROP of ε-CL could be conducted in a wide temperature range from −15 to 60 °C with conversion over 80%.

The catalyst demonstrated stableness at high temperature and similar selectivity towards ε-CL and L-LA in bulk condition, and PCLA copolymer of 22 100 g mol^{-1} was obtained with sequential addition of ε-CL and L-LA. The living character was further proved.

Author contributions

Conceived and designed experiments: R. Cheng, B. Liu. Performed experiments: Z. Feng, L. Wu, H. Dong. Analyzed data: Z. Feng, R. Cheng, B. Liu. Contributed materials/analysis tools: R. Cheng, B. Liu. Wrote the paper: all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

References

1 M. Qiao, D. Chen, T. Hao, X. Zhao, H. Hu and X. Ma, *Int. J. Pharm.*, 2007, **345**, 116–124.

2 M. Qiao, D. Chen, X. Ma and Y. Liu, *Int. J. Pharm.*, 2005, **294**, 103–112.

3 H. Chen, F. Jia, C. Zhu, J. Xu, X. Hua, Z. Xi, L. Shen, S. Zhao and L. Cen, *Chem. Eng. J.*, 2018, **339**, 346–358.

4 H. K. Kim, W. S. Shim, S. E. Kim, K. H. Lee, E. Kang, J. H. Kim, K. Kim, I. C. Kwon and D. S. Lee, *Tissue Eng., Part A*, 2009, **15**, 923–933.

5 M. J. Sandker, A. Petit, E. M. Redout, M. Siebelt, B. Müller, P. Bruin, R. Meyboom, T. Vermonden, W. E. Hennink and H. Weinans, *Biomaterials*, 2013, **34**, 8002–8011.

6 M. Tosin, F. Degli-Innocenti and C. Bastioli, *J. Environ. Polym. Degrad.*, 1998, **6**, 79–90.

7 D. Pappalardo, T. Mathisen and A. Finne-Wistrand, *Biomacromolecules*, 2019, **20**, 1465–1477.

8 A. Petit, M. Sandker, B. Müller, R. Meyboom, P. Van Midwoud, P. Bruin, E. M. Redout, M. Versluijs-Helder, C. H. A. Van Der Lest, S. J. Buwalda, L. G. J. De Leede, T. Vermonden, R. J. Kok, H. Weinans and W. E. Hennink, *Biomaterials*, 2014, **35**, 7919–7928.

9 X. Leng, Y. Ren, Z. Wei, Y. Bian and Y. Li, *Macromol. Chem. Phys.*, 2017, **218**, 1700178.

10 C. Jérôme and P. Lecomte, *Adv. Drug Delivery Rev.*, 2008, **60**, 1056–1076.

11 M. D. Deokar, S. B. Idage, B. B. Idage and S. Sivaram, *J. Appl. Polym. Sci.*, 2016, **133**, 43267.

12 E. Stirling, Y. Champouret and M. Visseaux, *Polym. Chem.*, 2018, **9**, 2517–2531.

13 H. Du, X. Pang, H. Yu, X. Zhuang, X. Chen, D. Cui, X. Wang and X. Jing, *Macromolecules*, 2007, **40**, 1904–1913.

14 Y. A. Piskun, I. V. Vasilenko, K. V. Zaitsev, Y. F. Oprunenko and S. V. Kostjuk, *Macromol. Chem. Phys.*, 2017, **218**, 1600580.

15 D. M. Gonzalez, N. B. Cruz, L. A. Hernandez, J. Oyarce, R. Benavente and C. Manzur, *J. Polym. Sci.*, 2020, **58**, 557–567.

16 B. Gao, R. Duan, X. Pang, X. Li, Z. Qu, H. Shao, X. Wang and X. Chen, *Dalton Trans.*, 2013, **42**, 16334–16342.

17 N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. Lohmeijer and J. L. Hedrick, *Chem. Rev.*, 2007, **107**, 5813–5840.

18 F. Nederberg, E. F. Connor, M. Möller, T. Glauser and J. L. Hedrick, *Angew. Chem., Int. Ed.*, 2001, **40**, 2712–2715.

19 B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2006, **39**, 8574–8583.

20 S. Hu, J. Zhao, G. Zhang and H. Schlaad, *Prog. Polym. Sci.*, 2017, **74**, 34–77.

21 H. Wang, Z. Yao, Z. Li, Y. Zhu, C. Zhang, Z. Luo, T. Guo, Y. Gao, L. Zhang and K. Guo, *Eur. Polym. J.*, 2020, **127**, 109570.

22 J. Kadota, D. Pavlovic, H. Hirano, A. Okada, Y. Agari, B. Bibal, A. Deffieux and F. Peruch, *RSC Adv.*, 2014, **4**, 14725–14732.

23 D. J. Coady, K. Fukushima, H. W. Horn, J. E. Rice and J. L. Hedrick, *Chem. Commun.*, 2011, **47**, 3105–3107.

24 X. Wang, S. Cui, Z. Li, S. Kan, Q. Zhang, C. Zhao, H. Wu, J. Liu, W. Wu and K. Guo, *Polym. Chem.*, 2014, **5**, 6051–6059.

25 M. K. Kiesewetter, E. J. Shin, J. L. Hedrick and R. M. Waymouth, *Macromolecules*, 2010, **43**, 2093–2107.

26 A. P. Dove, *ACS Macro Lett.*, 2012, **1**, 1409–1412.

27 J. K. Kim, D. J. Park, M. S. Lee and K. J. Ihn, *Polymer*, 2001, **42**, 7429–7441.

28 J. U. Pothupitiya, N. U. Dharmaratne, T. M. M. Jouaneh, K. V. Fastnacht, D. N. Coderre and M. K. Kiesewetter, *Macromolecules*, 2017, **50**, 8948–8954.

29 C. Thomas, F. Peruch and B. Bibal, *RSC Adv.*, 2012, **2**, 12851–12856.

30 X. Li, Q. Zhang, Z. Li, S. Xu, C. Zhao, C. Chen, X. Zhi, H. Wang, N. Zhu and K. Guo, *Polym. Chem.*, 2016, **7**, 1368–1374.

31 J. Zhao, D. Pahovnik, Y. Gnanou and N. Hadjichristidis, *Polym. Chem.*, 2014, **5**, 3750–3753.

32 L. Mezzasalma, A. P. Dove and O. Coulembier, *Eur. Polym. J.*, 2017, **95**, 628–634.

33 D. N. Coderre, K. V. Fastnacht, T. J. Wright, N. U. Dharmaratne and M. K. Kiesewetter, *Macromolecules*, 2018, **51**, 10121–10126.

34 L. Mezzasalma, S. Harrisson, S. Saba, P. Loyer, O. Coulembier and D. Taton, *Biomacromolecules*, 2019, **20**, 1965–1974.

35 L. Mezzasalma, J. De Winter, D. Taton and O. Coulembier, *J. Polym. Sci., Part A: Polym. Chem.*, 2018, **56**, 475–479.

36 M. G. Dekamin, S. Sagheb-Asl and M. Reza Naimi-Jamal, *Tetrahedron Lett.*, 2009, **50**, 4063–4066.

37 M. G. Dekamin, M. Ghanbari, M. R. Moghbeli, M. Barikani and S. Javanshir, *Polym.-Plast. Technol. Eng.*, 2013, **52**, 1127–1132.

38 M. G. Dekamin, M. Alikhani and S. Javanshir, *Green Chem. Lett. Rev.*, 2016, **9**, 96–105.

39 H. Li, J. Wang, L. Wu, W. Liu, R. Cheng and B. Liu, *Acta Polym. Sin.*, 2019, **50**, 1290–1297.

40 K. Van de Velde and P. Kiekens, *Polym. Test.*, 2002, **21**, 433–442.

41 L. Mezzasalma, J. De Winter, D. Taton and O. Coulembier, *Green Chem.*, 2018, **20**, 5385–5396.

42 N. Bölgen, Y. Z. Menceloğlu, K. Acatay, İ. Vargel and E. Pişkin, *J. Biomater. Sci. Polym. Ed.*, 2005, **16**, 1537–1555.

43 M. Baśko and P. Kubisa, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 7071–7081.

44 J. Kasperczyk and M. Bero, *Makromol. Chem.*, 1991, **192**, 1777–1787.

45 J. Kasperczyk and M. Bero, *Makromol. Chem.*, 1993, **194**, 913–925.