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Controlled/living ring-opening polymerization of ε-caprolactone catalyzed by phosphoric acid

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The bulk ring-opening polymerization (ROP) of ε-caprolactone (ε-CL) by various phosphoric acids using phenylmethanol as the initiator was conducted. 1,1'-bi-2-Naphthol (BINOL)-based phosphoric acid was found to be an effective organocatalyst for ROP leading to polyesters at 90°C. The overall conversion to poly(ε-caprolactone) was more than 96% and poly(ε-caprolactone) with M_w of 8400 and polydispersity index of 1.13 was obtained. ^{1}H NMR spectra of oligomers demonstrated the quantitative incorporation of the protic initiator in the polymer chains and showed that transesterification reactions did not occur to a significant extent. The controlled polymerization was indicated by the linear relationships between the number-average molar mass and monomer conversion or monomer-to-initiator ratio. In addition, the present protocol provided an easy-to-handle, inexpensive and environmentally benign entry for the synthesis of biodegradable materials as well as polyesters for biomedical applications.

polyester, organocatalysis, phosphoric acid, controlled/living ring-opening polymerization, ε-caprolactone

1 Introduction

Polyesters such as poly(ε-caprolactone) (PCL) and their copolymers are an important class of biocompatible materials, which makes them interesting materials for a range of biomedical and commodity applications, including controlled drug release, tissue engineering, medical implants or environmentally friendly packaging materials [1–5]. The ring-opening polymerization (ROP) of ε-caprolactone (ε-CL) and other cyclic esters provides an efficient and convenient route to the direct synthesis of these macromolecules [6–10]. The ROP process can be performed with a wide range of catalysts such as metal-based complexes [6, 8], enzymes [10] and organic molecules [7]. Although spectacular progress has been made in metal-catalyzed ROPs, the catalytic metal contaminant of the polymer products must be removed prior to application as biomedical and pharmaceutical materials. This limitation triggered many current research efforts in enzymatic and organocatalytic methodologies. Lipase-catalyzed ROPs are highly efficient for less strained cyclic esters, but show relatively low catalytic activities for substrates such as lactide [8, 9, 11].

In this context, organocatalysis represents a highly attractive and elegant alternative to organometallic and enzymatic processes. Pioneered in 2001 by Hedrick and Waymouth using 4-dimethylaminopyridine (DMAP) as the organocatalyst for the ROP of lactide [12], the past decade has witnessed extraordinary advances in organo-catalyzed ROPs. Various structurally diverse organocatalysts for ROPs of cyclic esters and carbonates have been developed according to different means of the activation of the reagents: (i) nucleophilic or electrophilic activation of the monomer with DMAP derivatives [12], *N*-heterocyclic carbenes (NHCs) [13–16], phosphines [17], fluorinated alcohols [18], Brønsted acids [19–27] and hydrogen-bonding

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organocatalysts [28]; (ii) basic activation of the initiator/growing polymer chain ends by phosphazenes [29, 30], DBU and MTBD [31–33]; (iii) the dual activation of both the monomer and initiating/propagating alcohol using bifunctional organocatalysts such as thiourea/amines [34, 35], TBD [36] and amino-thiazolines [37].

Among the organocatalysts, Brønsted acids represent a very effective class of catalysts for polymerization due to a number of intrinsic advantages: controlled molar masses, narrow distribution combined with a broader range of potential reaction conditions. Although the acid-catalyzed ROP has been reported, in which trifluoromethanesulfonic acid (TfOH), methanesulfonic acid, $HNTf_2$, and $HCl\text{-}Et_2O$ complex were utilized as effective acid catalysts for the ROP of cyclic esters, it is important to elucidate the scope and limit of applicable acid catalysts in connection with suitable cyclic monomers for the ROP. Of great interest is studying the catalytic activity of weak acids for the ROP of cyclic monomers compared to those using strong Brønsted acids, such as TfOH and $HNTf_2$. In this context, we herein report that phosphoric acids as weak acid can be used as organocatalysts for ROP of ε-CL with controlled molar masses and narrow dispersities using phenylmethanol as the initiator, as shown in Scheme 1 [24].

2 Experimental

2.1 Materials

BINOL, catechol, *cis*-2-butene-1,4-diol and *trans*-1,2-cyclohexanediol were purchased from Acros Organics and used as received. Phosphorus oxychloride, ethylene glycol, 1,3-propanediol, 1,4-butanediol, phenylmethanol, pyridine and solvents were purified by standard techniques prior to use. ε-Caprolactone was distilled over CaH_2 under reduced pressure. All reactions were carried out in oven-dried glassware.

2.2 Characterizations

^{1}H NMR measurements were used to determine the number-average molecular weight (M_n) of the polymers and the chain end groups. ^{1}H NMR spectra were recorded on a Bruker-400 MHz spectrometer. Chemical shifts (δ) are given in parts per million (ppm) downfield relative to $CDCl_3$. Coupling constants are given in hertz (Hz). Unless otherwise stated, deuterochloroform ($CDCl_3$) was used as the solvent. The weight-average molecular weight (M_w) and polydispersity (M_w/M_n) of the polymers were determined by gel-permeation chromatography (GPC). Weighed samples (5–10 mg) were diluted in tetrahydrofuran to a concentration of 10 mg/mL and filtered through a 0.45 μm PTFE membrane prior to injection into the GPC system (Rheodyne 7125 injector, 20 μL sample loop, a Waters HPLC pump 510, and a Waters 410 differential refractometer). The separation was accomplished at 25 °C in three columns connected in series (50, 100, and 500 Å, bead size 5μm, Ultrastyragel, Waters). Tetrahydrofuran was used as the eluent at a flow rate of 1 mL/min. The GPC system was calibrated using polystyrene standards, 266-34500 Da (Machery Nagel).

2.3 General procedure for the synthesis of phosphoric acid 1

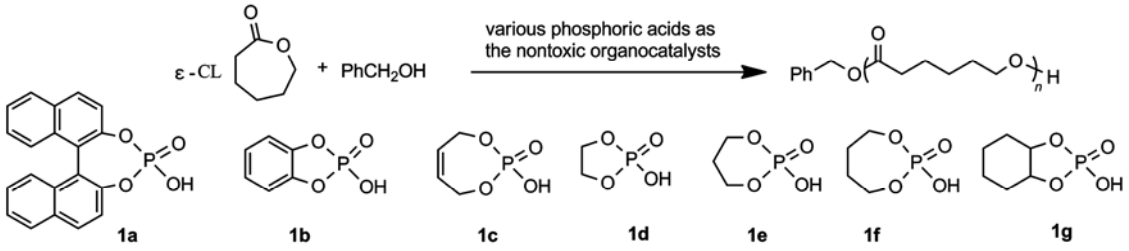
A diol (1.75 mmol) was dissolved into 5 mL of pyridine. To the resulting solution was added phosphorus oxychloride (0.326 mL) at room temperature and the reaction mixture was stirred for three hours. Water (5 mL) was then added and the resulting suspension was stirred for over 30 min. Dichloromethane was added and pyridine was removed by extraction with 1 N HCl. Organic phase was dried over Na_2SO_4 and purified by column chromatography (ethyl acetate : methanol : dichloromethane = 10:1:1). The title compound was isolated as white solid.

1a was prepared in 95 % yield [38]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07–8.02 (m, 4H), 7.47–7.43 (m, 4H), 7.31 (t, J = 8.0 Hz, 2H), 7.24–7.22 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.2, 131.9, 130.3, 129.7, 128.3, 126.0, 125.9, 124.4, 122.6, 121.6.

1b was prepared in 55 % yield [39]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88–6.86 (m, 2H), 6.74–6.72 (m, 2H), 2.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 122.9, 118.6.

1c was prepared in 62 % yield [40]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br, 1H), 5.82–5.78 (m, 2H), 4.71–4.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6, 75.4.

1d was prepared in 52 % yield [41]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (br, 1H), 4.12 (s, 4H),. ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.4.



Scheme 1 Ring-opening polymerization of ε-caprolactone (ε-CL) organocatalyzed by different organic phosphoric acids.

1e was prepared in 57 % yield [41]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (br, 1H), 4.12 (s, 4H),. ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.7, 27.1.

1f was prepared in 63 % yield [41]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (br, 1H), 4.17 (t, J = 8.0 Hz, 4H), 1.91 (t, J = 8.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.1, 29.8.

1g was prepared in 68 % yield [42]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (br, 1H), 3.56–3.50 (m, 2H), 2.34–2.30 (m, 2H), 1.93–1.86 (m, 2H), 1.58-1.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.2, 27.6, 21.8.

2.4 General procedure for the organic phosphoric acid-catalyzed polymerization

ε-Caprolactone (CL) (422 mg, 3.7 mmol) was mixed with benzyl alcohol (5.8 uL, 0.055 mmol) as the initiator and phosphoric acid **1** (0.185 mmol) as the catalyst. The mixture was then stirred for 7–12 h at 90 °C. The ROP was quenched by decreasing the temperature to room temperature and the polymer was purified by dilution with THF followed by precipitation in cold methanol to give a white powder and dried in vacuum at 30 °C for 24 h. Yield, 80%–94%. PCL: ^{1}H NMR ($CDCl_3$): δ 1.34–1.42 (m, CH_2, PCL-chain), 1.61–1.69 (m, CH_2, PCL-chain), 2.28–2.32 (t, J = 6.0 Hz, CH_2CO, PCL-chain), 3.64 (t, J = 5.0 Hz, 2H, CH_2OH, PCL-end group), 4.04–4.07 (t, J = 5.2 Hz, CH_2OR), 5.11 (bs, 2H, $ArCH_2OR$), 7.33 (m, 5H, ArH).

3 Results and discussion

To determine the feasibility of the ring-opening polymerization process using phosphoric acid as the organocatalyst, BINOL-based phosphoric acid **1a** was chosen to examine the polymerization of ε-caprolactone (ε-CL) with benzyl alcohol as the initiator at $[\varepsilon\text{-CL}]_0/[\text{BnOH}]_0/[\mathbf{1a}]$ ratio of 200/3/10, and the relative conversions were determined by ^{1}H NMR spectra (Table 1). No polymerization was observed at 30 °C for 48 h, however, the conversion of ε-CL increased to 35% at 50 °C for 12 h (Table 1, entries 1 and 2). Then a set of experiments were carried out to reveal the crucial role of the reaction temperature. Table 1 illustrates that the conversion increased with increasing reaction temperature. Polymers with narrow polydispersities (1.08–1.20) can be obtained below 100 °C. When polymerization was performed at 100–120 °C, the polydispersity index of the resulting poly(ε-caprolactone) increased to 1.58 (Table 1, entries 7–9). At higher temperature, phosphoric acid perhaps behaved as the cationic polymerization catalyst instead of a bifunctional catalyst via its acidic hydrogen atom and basic oxygen atoms. To obtain poly(ε-caprolactone) with high molecular weight and narrow molecular weight distribution, all the following polymerization experiments were further conducted at 90 °C.

Table 1 The bulk ROP of ε-caprolactone (ε-CL) catalyzed by **1a** at different temperature [a]

Entry	Temperature (°C)	t (h)	Conv. (%) [b]	M_n [b]	PDI [c]
1	30	48	–	–	–
2	50	12	35	3246	1.19
3	60	12	40	3878	1.17
4	70	12	61	5286	1.20
5	80	12	95	7672	1.08
6	90	12	99	8369	1.13
7	100	12	99	9979	1.58
8	110	12	99	9893	1.58
9	120	7	99	8881	1.53

a) Reaction was performed with 1.5 mol% phenylmethanol as an initiator and 5 mol% **1a** as the catalyst. b) Determined by ^{1}H NMR spectroscopy. c) Determined by gel-permeation chromatography using polystyrene standards.

^{1}H NMR analyses revealed the incorporation of the initiator in PCL prepared with the **1a**/BnOH combination. Figure 1 shows ^{1}H NMR spectrum of the resulting PCL obtained at $[\varepsilon\text{-CL}]_0/[\text{BnOH}]_0$ ratio of 200/3 at 120 °C. Three signals were observed for the chain ends. The multiplet at 7.33 ppm is typically associated with the aromatic protons of the benzyl units. The methylene protons (a) adjacent to the phenyl ring and the ester linkage appear at 5.11 ppm. The multiplet at 3.65 ppm is attributed to the methylene protons (g) adjacent to the chain end of the hydroxyl group. These results showed that polymerizations were initiated from benzyl alcohol. In addition, the number-average molecular weight of the polymer determined by ^{1}H NMR spectra agrees with $M_{n,theo}$ calculated from the molar mass of ε-CL (114 g/mol) × $[\varepsilon\text{-CL}]_0/[\text{BnOH}]_0$ plus the molar mass of the initiator (BnOH).

The organic phosphoric acid compounds **1a**–**1g** were then evaluated as organocatalysts for ROP of ε-caprolactone (Scheme 1). With 5 mol% of **1** as the catalyst at 90℃, the bulk ROP of ε-CL initiated from phenylmethanol (target degree of polymerization, DP = 67) was investigated. Some results from that study are summarized in Table 2. Catechol-based phosphoric acid **1b** showed inferior activity towards polymerization than other catalysts (Table 2, entry 2). The polymerization catalyzed by phosphoric acid **1a**–**1f** exhibited narrow distribution (M_w/M_n = 1.09–1.14), and **1g** gave the higher PDI value (1.31). This initial screening of the catalyst revealed that diol-based phosphoric acids with high steric hindrance resulted in broader molecular weight distribution.

Therefore, further investigations focused on elucidating the behavior of the catalyst in the ROP of ε-caprolactone.

The molecular weight (M_n) values obtained with catalyst **1a** (determined by ^{1}H NMR spectra) varied linearly with the conversion, with low polydispersity values being maintained throughout the polymerization process (Figure 2). The linear dependence of M_n on monomer conversion demonstrated the controlled characteristic of the polymeri-

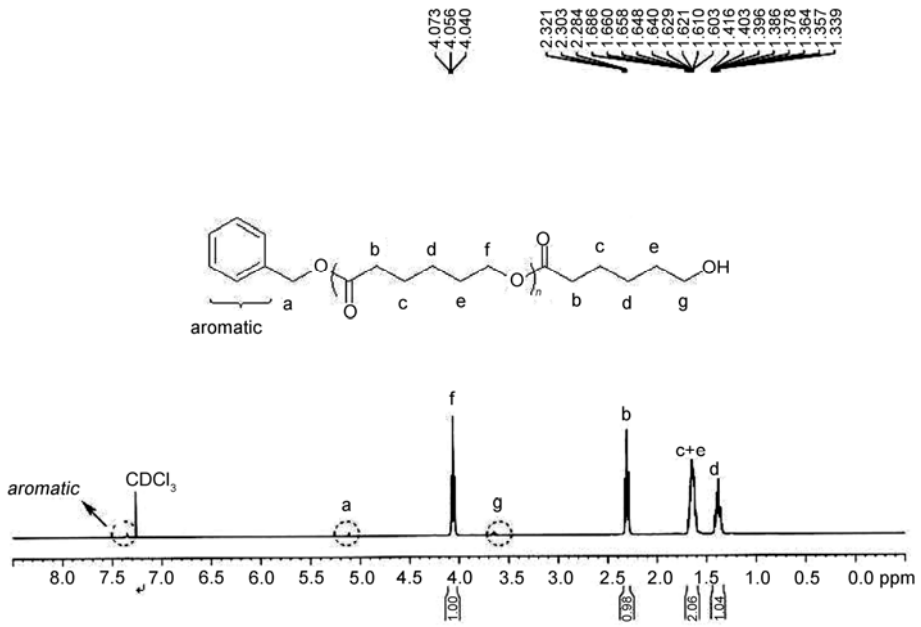


Figure 1 ^{1}H NMR spectrum of the PCL (Table 1, entry 9).

Table 2 Data for the polymerization of ε-CL catalyzed by phosphoric acids [a]

Entry	Catalyst	Conv. (%) [b]	M_n (g/mol) [b]	*PDI* [c]
1	**1a**	99	8369	1.13
2	**1b**	85	7448	1.09
3	**1c**	98	7524	1.11
4	**1d**	90	7606	1.11
5	**1e**	98	7841	1.12
6	**1f**	97	8202	1.14
7	**1g**	99	9982	1.31

a) Reaction was performed at 90 °C for 12 h with 1.5 mol% phenylmethanol as an initiator and 5 mol% **1** as the catalyst. b) Determined by ^{1}H NMR spectroscopy. c) Determined by gel-permeation chromatography using polystyrene standards.

zation and indicated that little chain transfer occurred [43]. The living nature of organic phosphoric acid-catalyzed ROP of ε-CL was obtained by demonstration of a linear dependence of M_n on $[\varepsilon\text{-CL}]_0/[\text{BnOH}]_0$ ratio varying from 10 to 100 (in all cases, the monomer was completely consumed) and the polydispersities remained low. (Figure 3). The number-average molecular weight of the polymer agrees with $M_{n,theo}$ calculated from the initial ratios of $[\varepsilon\text{-CL}]_0/[\text{BnOH}]_0$ and the monomer conversions. To provide further support for the controlled/living nature of this polymerization, two chain extension experiments were also performed from an initial polymerization using ε-CL ($[\varepsilon\text{-CL}]_0/[\text{BnOH}]/[\mathbf{1a}]$ = 200:3:10) carried out at 90 °C for 12 h to give a poly(ε-caprolactone) with M_n = 8674 g/mol (*PDI* = 1.13), as determined by ^{1}H NMR spectroscopy. Additional ε-CL (1.85 mmol, 0.5 equivalents) was added and the mixture was allowed to react for an additional 14 h at

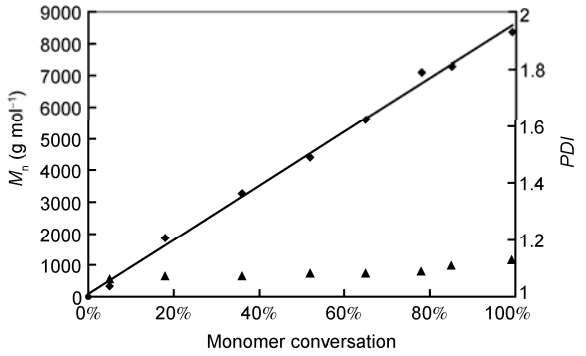


Figure 2 Relationship between M_n or *PDI* of PCL and monomer conversion for the polymerization of ε-caprolactone catalyzed by **1a** (DP 67).

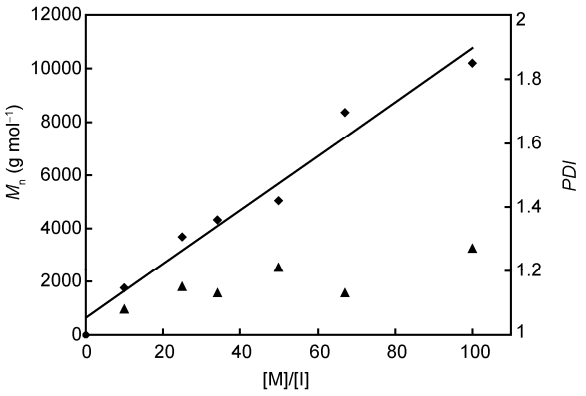
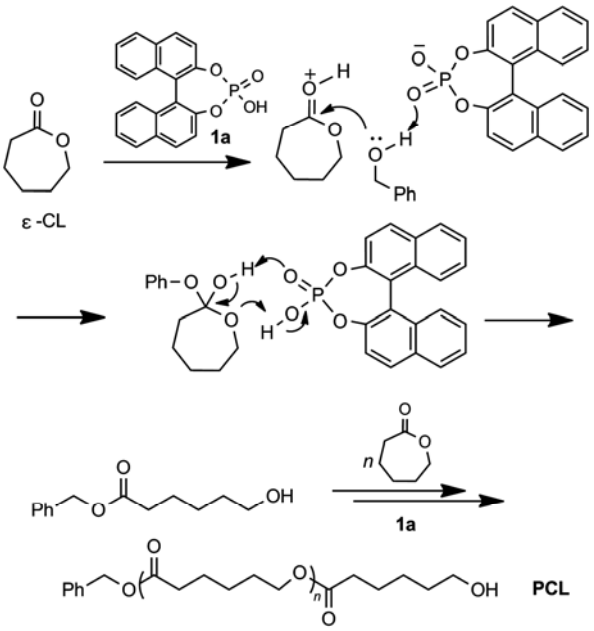


Figure 3 The average number molecular weights (M_n) and *PDI* of polymers obtained at different [M]/[I] ratios for polymerizations of ε-caprolactone catalyzed by **1a**.

90 °C. The M_n of the sample increased to 10766 g/mol (*PDI*

= 1.14). The reaction mixture was charged again with 1.85 mmol (0.5 equiv) of ε-CL, and the final molecular weight of the polymer increased to 14808 g/mol with 1.12 in the polydispersity after 16 h. These characteristics are typical of a living system.

A proposed mechanism of ring-opening polymerization of ε-CL catalyzed by phosphoric acid is shown in Scheme 2. The initial nucleophilic addition proceeded via activation of both the monomer and the alcohol to give tetrahedral intermediate, and the C–O bond in the intermediate was further cleaved in the ring-opening step via concomitant proton transfer. In these two elementary steps, phosphoric acid acted as a bifunctional catalyst via its acidic hydrogen atom and basic oxygen atoms [44–46].



Scheme 2 A proposed bifunctional activation mechanism for ROP of ε-CL catalyzed by phosphoric acids.

4 Conclusion

The bulk ring-opening polymerization of ε-caprolactone (ε-CL) using various phosphoric acids as weak acid organocatalysts and phenylmethanol as the initiator was carried out at 90 °C. The living polymerization of ε-caprolactone has been achieved, and polyesters with desired number-average molecular weights and narrow molecular weight distributions could be synthesized. This readily accessible and easily removed acid catalyst afforded an alternative metal-free entry to PCLs of tailored properties as biomaterials as well as microelectronics. The mechanism of the phosphoric acid-catalyzed ROP and the extension of this catalytic system to other cyclic monomers for the synthesis of polyesters including block copolymers are currently under investigation.

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