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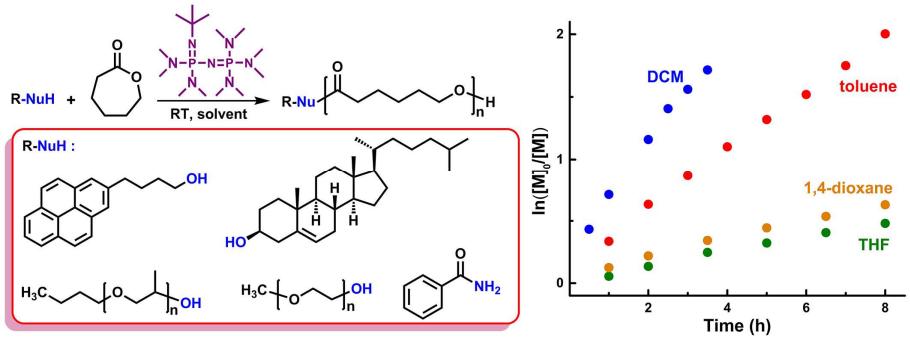
Phosphazene-Catalyzed Ring-Opening Polymerization of ε-Caprolactone: Influence of Solvent and Initiator

Haleema Alamri, Junpeng Zhao, David Pahovnik and Nikos Hadjichristidis*



Metal-free ring-opening polymerization of ε-caprolactone was conducted using a relatively mild phosphazene base catalyst. The influence of solvent and protic initiators on the polymerization rate and control were demonstrated.

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Phosphazene-Catalyzed Ring-Opening Polymerization of ε-Caprolactone: Influence of Solvent and Initiator

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Phosphazene base (*t*-BuP_2) catalysed metal-free ring-opening polymerization of ε-caprolactone (εCL) at room temperature with various protic initiators in different solvents was investigated. The polymerization proceeded, in most cases, in a controlled manner to afford poly(ε-caprolactone) with low dispersities and expected molecular weights. Kinetic studies showed that, when a primary alcohol was used as initiator the polymerization rate in different solvents followed the order of dichloromethane >> toluene > 1,4-dioxane ≈ tetrahydrofuran. Extremely fast polymerization of L-lactide (LLA), which was added as a second monomer, was observed in different solvents giving rise to poly(ε-caprolactone)-*b*-poly(L-lactide) diblock copolymers with neat PLLA blocks despite incomplete conversion of εCL. The dependence of polymerization rate on the concentrations of εCL and *t*-BuP_2 was also revealed. In addition to primary alcohol, the feasibility of using other protic initiators, such as secondary alcohol (either on a small molecule or a polymer chain-end), (aliphatic/aromatic) amide, carboxylic acid, phenol and thiophenol, was also investigated. These studies provided important information for designing metal-free route towards polyester-based (bio)materials.

Introduction

Aliphatic polyesters such as poly(ε-caprolactone) (PCL) and poly(L-lactide) (PLLA) are considered a class of interesting synthetic polymers due to their crystalline, biodegradable and biocompatible nature, which makes them good candidates for many biomedical, pharmaceutical, and packing applications.[1-7] Conventionally, polyesters have been prepared by ring-opening polymerization (ROP) of the corresponding cyclic esters, e.g. ε-caprolactone (εCL) for PCL, using metallic catalysts.[8-13] For most of the advanced applications, the metal residues must be removed from the polymer, which is usually a time-consuming and expensive process. Due to such a fact, a lot of efforts have been devoted into the development of metal-free (organocatalytic) synthetic pathways toward polyester-based materials in the last decade, and now a wide range of organic molecules are in polymer chemists' toolbox to choose an appropriate catalyst for each specific synthetic task.[14-16]

Generally, three mechanistic strategies have been employed for organocatalytic polymerizations, namely, activation of monomer,[17-27] activation of initiator/chain-end,[28-32] and dual activation of both.[33-37] Among all the organic catalysts, phosphazene bases have been reported to have successfully catalysed/promoted the ROP of a wide variety of heterocycles including epoxides, cyclosiloxanes, lactams, cyclopropane derivatives, cyclic esters and cyclic carbonate through the activation of the initiating/propagating species which is usually hydroxyl or alkoxide.[38, 39] In order to achieve fast polymerization and meanwhile avoid extensive occurrence of side reactions, phosphazene catalyst needs to be appropriately chosen for each specific type of monomer in terms of basicity. For instance, *t*-BuP_4, one of the strongest phosphazene bases, is well suited to the polymerization of epoxides,[40-44] but brings about intra- and intermolecular transesterification scrambling reactions in the case of cyclic esters and siloxanes.[45, 46] On the other hand, the relatively mild ones, e.g. *t*-BuP_2 and *t*-BuP_1, can afford much better control in the case of latter monomers.[47-49]

In this work, we aim at expanding the scope of the use of phosphazene bases as organic catalyst through the investigation on different experimental conditions for the ROP of εCL. Firstly, an alcoholic initiator has been used to examine the influence of solvent, i.e. toluene, dichloromethane (DCM), tetrahydrofuran (THF) and 1,4-dioxane, aiming at optimised conditions (e.g. monomer concentration, catalyst/initiator ratio) to achieve the best compromise between polymerization rate and control in each solvent. Then the effectiveness of different protic compounds, i.e. primary/secondary alcohol (small molecules or macromolecules), aromatic/aliphatic amide, carboxylic acid, phenol and thiophenol as initiator has been investigated in toluene in light of the fact that the corresponding functional groups can be used to directly grow polymers from different types of (in)organic substrates (e.g. biomolecules, functional surfaces, nanoparticles).[50-54]

Experimental Section

Chemicals

All the solvents were purchased from Fischer Scientific. Toluene, DCM, and 1,4-dioxane were dried over calcium hydride (CaH_2) and distilled before use. THF was dried successively by Na and *n*-BuLi. εCL (Alfa Aesar; 99%) was stirred with CaH_2 overnight and distilled under reduced pressure. All the other chemicals were purchased from Sigma-Aldrich. Phosphazene base (*t*-BuP_2; 2 M solution in THF), acetic acid (99.7%), 1-pyrenebutanol (PyOH; 99%), thiophenol (99%), cholesterol (94%) and 1-pyrenebutyric acid (PyCOOH; 97%) were used as received. Benzamide (BAM; 99%) and propionamide (PAM; 99%) were recrystallized from acetone/hexane (2/1, v/v) and butylated hydroxytoluene (BHT; 99%) was recrystallized from *n*-hexane. Poly(propylene glycol) monobutyl ether (BPPG) with number-average molecular weight (M_n) of 1 kg mol^{-1} and poly(ethylene glycol) monomethyl ether (MPEG) with a M_n of 2 kg mol^{-1} were purified twice by dissolving in THF and cryo-evaporating THF, followed by drying on the vacuum line overnight. L-Lactide (LLA; 99%) was also purified twice by dissolving in THF and cryo-evaporating THF, and finally dissolved in pure THF into a 0.17 g mL^{-1} solution.

Instrumentation

Size exclusion chromatography (SEC) with RI and UV detection was carried out in THF at 35 °C at a flow rate of 1 mL min^{-1} using two 7.8 mm × 300 mm (5 μm) Styragel columns (Styragel HR 2 and Styragel HR 4). Calibration was done using a series of poly(1,4-butadiene) (PBd) standards to give the apparent number-average molecular weight ($M_{n,SEC}$) and dispersity (M_w/M_n). The use of PBd standards was expected to make $M_{n,SEC}$ of PCL close to the real value (compared to normally used polystyrene standards) due to the structural similarity. Nuclear magnetic resonance (NMR) measurements were performed at room temperature using a Bruker AVANCEDIII 400 spectrometer operating at 400 MHz with $CDCl_3$ (Aldrich) as the solvent. ^{1}H NMR spectroscopy was used to monitor the conversion of cyclic esters during the polymerization by comparing the signal integrals from the methylene (methine) next to the ester groups from both the monomer and the polymer. Molecular weight ($M_{n,NMR}$) of the final products were also calculated from the ^{1}H NMR spectra based on the signal integrals from the end groups and the main bodies of the polyesters. Vapor-pressure osmometry (VPO) measurements were performed in chloroform at 35 °C using a Gonotec Osmomat 070 VPO instrument to determine the absolute number-average molecular weight ($M_{n,VPO}$) of some of the products. Polymer concentrations for VPO analysis ranged between 10 to 60 g kg^{-1}. Instrumental calibration was performed using benzil (Acros) as a standard compound. Matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) measurements were performed on a Bruker Ultraflex III MALDI-TOF mass spectrometer (Bruker Daltonik, Bremen, Germany). Samples were dissolved in THF (10 mg mL^{-1}) and mixed with a solution of sodium trifluoroacetate in THF (10 mg mL^{-1}) in a volume ratio of 5:1. This solution was then mixed with a solution of matrix, 2,5-dihdroxybenzoic acid (DHB) in THF (20 mg mL^{-1}), in a volume ratio of 1:20. Then, 0.4 μL of the final solution was spotted on the target plate (dried-droplet method). The linear positive ion mode was used to acquire the mass spectra of the samples. The calibration was done externally with the poly(methyl methacrylate) standards using the nearest neighbor positions.

Homopolymerization of εCL with *t*-BuP_2 as a catalyst

Polymerization was conducted on a Schlenk-line using a 100 mL glass reactor with a stopcock. Typical procedure (Entry 10, Table 1) is as follows. 0.10 g of cholesterol (0.27 mmol) was dissolved in 3 mL of distilled THF, and added to the flame-dried reactor via a syringe followed by evaporation of THF. Then 0.13 ml of *t*-BuP_2 solution (0.26 mmol of *t*-BuP_2) was added and THF was also evaporated (for experiment carried out in THF or toluene/THF mixture, this portion of THF was not removed). 6.0 mL of distilled toluene was then added in an argon flow and the system was stirred until both the initiator and the catalyst were completely dissolved. After that, 3.0 mL of εCL (27 mmol) was added to start the polymerization. Aliquots were withdrawn (0.1 mL each) in an argon flow in different time intervals. Each aliquot was injected to a mixture of 1 mL of $CDCl_3$ and two drops of acetic acid. This solution was used for ^{1}H NMR measurement to determine the monomer conversion. 0.1 mL of such $CDCl_3$ solution was diluted with 1 mL of THF for SEC analysis. The reaction was finally quenched after 8 h by addition of acetic acid, and the solution was poured into cold methanol to precipitate the polymer. The white powder was then collected, dried in vacuum and used for SEC, ^{1}H NMR, VPO and MALDI-TOF MS analysis. Conv.(εCL) = 78%; theoretical number-average molecular weight ($M_{n,theor}$ in Table 1, calculated from feed ratio of monomer to initiator and monomer conversion) = 8.9 kg mol^{-1}. $M_{n,SEC}$ = 8.8 kg mol^{-1}, M_w/M_n = 1.10. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 5.38-5.35 (double bond protons on cholesteryl end group), 4.64-4.57 (cholesteryl(C*H*O)–CO–PCL), 4.20-3.91 (–OCOCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$–), 3.67-3.61 (–OCOCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 2.43-2.16 (–OCOC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$–), 1.68-1.60 (–OCOCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$–), 1.43-1.33 (–OCOCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$–); $M_{n,NMR}$ = 8.3 kg mol^{-1}. $M_{n,VPO}$ = 8.6 kg mol^{-1}.

Sequential polymerization of εCL and LLA

Typical procedure for Entry 1 in Table 1 (PCL) and entry 1 in Table 2 (PCL-*b*-PLLA) is as follows. εCL was polymerized in a similar manner as described above using 0.074 g of PyOH (0.27 mmol), 0.13 mL of *t*-BuP_2 solution (0.26 mmol of *t*-BuP_2), 6.0 mL of toluene as solvent and 3.0 mL of εCL (27 mmol). εCL conversion reached 86% in 8 h, upon which 12 mL of THF solution of LLA (containing 2.0 g and 14 mmol LLA) was added quickly in an argon flow. Aliquots were withdrawn at 10, 20 and 30 min for ^{1}H NMR and SEC analysis. The

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Table 1. Molecular characteristics of PCL prepared by *t*-BuP_2-catalyzed ROP of εCL.[a]

entry	initiator	time (h)	solvent	conversion[b] (%)	$M_{n,theor}$[c] (kg mol^{-1})	$M_{n,NMR}$[d] (kg mol^{-1})	$M_{n,SEC}$[e] (kg mol^{-1})	M_w/M_n[e]
1	PyOH	8	toluene	86	9.8	10.2	10.8	1.11
2	PyOH	8	toluene/THF (46/1, v/v)	82	9.3	10.3	10.3	1.12
3	PyOH	8	THF	39	4.4	4.4	4.3	1.07
4	PyOH[f]	8	THF	75	8.5	10.0	9.2	1.10
5	PyOH	24	THF	73	8.3	8.5	9.2	1.12
6	PyOH	1	DCM	98	11.1	15.4	17.0	1.42
7	PyOH[g]	3.5	DCM	82	9.3	10.5	9.9	1.23
8	PyOH	8	1,4-dioxane	47	5.3	5.2	5.3	1.08
9	PyOH	24	1,4-dioxane	75	8.6	8.2	8.4	1.15
10	cholesterol	8	toluene	78	8.9	8.3	8.8	1.10
11	BPPG	8	toluene	56	6.3	6.7	7.8	1.13
12	MPEG	8	toluene	56	6.3	6.3	7.5	1.08
13	BAM	8	toluene	53	6.0	19.3	14.5	1.25
14	PAM	8	toluene	0	-	-	-	-
15	PyCOOH	8	toluene	0	-	-	-	-
16	BHT	8	toluene	0	-	-	-	-
17	thiophenol	8	toluene	0	-	-	-	-

[a]The ROP was conducted at RT; $[\varepsilon CL]_0 = 3$ M; $[\varepsilon CL]_0/[t\text{-}BuP_2]_0/[\text{initiator}]_0 = 100/1/1$. [b]Conversion of εCL calculated from ^{1}H NMR spectra of the last kinetic point. [c]Theoretical number-average molecular weight of PCL calculated based on feed ratio of monomer to initiator and conversion. [d]Number-average molecular weight of PCL obtained from ^{1}H NMR and VPO measurements. [e]Apparent number-average molecular weight and dispersity of PCL (or diblock copolymers for entries 11 and 12) determined by SEC in THF at 35 °C calibrated by poly(1,4-butadiene) standards. [f]$[t\text{-}BuP_2]_0/[\text{PyOH}]_0 = 5$. [g]$[\varepsilon CL]_0 = 1$ M.

reaction was finally quenched after 30 min by addition of acetic acid, and the solution was poured into cold methanol to precipitate the polymer. The white powder was then collected, dried in vacuum and used for SEC and ^{1}H NMR analysis. Conv.(εCL) = 86%, conv.(LLA) > 99 %; $M_{n,theor}$(PCL) = 9.8 kg mol^{-1}, $M_{n,theor}$(PLLA) = 7.4 kg mol^{-1}, $M_{n,theor}$(PCL-*b*-PLLA) = 17.2 kg mol^{-1}. $M_{n,SEC}$(PCL) = 10.8 kg mol^{-1}, M_w/M_n(PCL) = 1.11; $M_{n,SEC}$(PCL-*b*-PLLA) = 14.9 kg mol^{-1}, M_w/M_n(PCL-*b*-PLLA) = 1.15. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 8.28-7.85 (aromatic protons on the pyrenyl end group), 5.30-5.09 (–OCOC*H*(CH_3)–), 4.40-4.33 (–OCOC*H*(CH_3)OH), 4.19-3.91 (pyrenyl$CH_2CH_2CH_2CH_2$–PCL–) and (–OCO$CH_2CH_2CH_2CH_2CH_2$–), 3.42-3.36 (pyrenyl$CH_2CH_2CH_2$ CH_2–PCL–), 2.43-2.17 (–OCO$CH_2CH_2CH_2CH_2CH_2$–), 1.97-1.90 (pyrenyl$CH_2CH_2CH_2$ CH_2–PCL–), 1.85-1.78 (pyrenyl$CH_2CH_2CH_2CH_2$–PCL–), 1.77-1.61 (–OCO$CH_2CH_2CH_2CH_2CH_2$–), 1.61-1.44 (–OCOCH(CH_3)–), 1.42-1.33 (–OCO$CH_2CH_2CH_2CH_2CH_2$–); $M_{n,NMR}$(PCL) = 10.2 kg mol^{-1}, $M_{n,NMR}$(PLLA) = 7.1 kg mol^{-1}, $M_{n,NMR}$(PCL-*b*-PLLA) = 17.3 kg mol^{-1}.

Results and discussion

Influence of solvent on the *t*-BuP_2-catalyzed ROP of εCL

Table 1 lists the experimental conditions of the *t*-BuP_2-catalyzed ROP of εCL as well as the molecular characteristics of the corresponding PCL products. Figure 1 shows the kinetic plots obtained in different solvents using a primary alcohol initiator (PyOH) and 1 equiv. of *t*-BuP_2, which indicates the order of DCM >> toluene > 1,4-dioxane ≈ tetrahydrofuran for the polymerization rate. In DCM at the same monomer

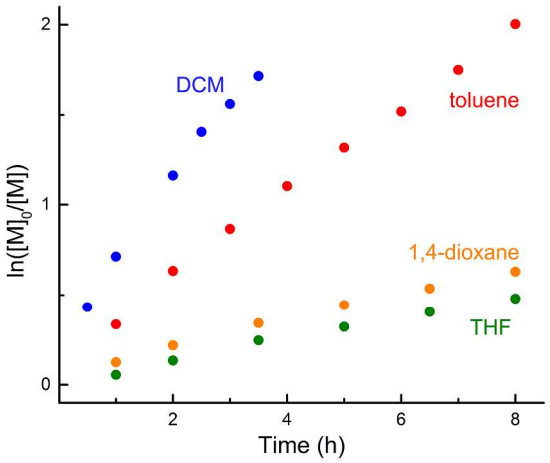


Figure 1. Kinetic plots for *t*-BuP_2-catalyzed ROP of εCL in different solvents using PyOH as initiator ($[\varepsilon CL]_0/[t\text{-}BuP_2]_0/[\text{PyOH}]_0 = 100/1/1$; $[\varepsilon CL]_0 = 3$ M in toluene, THF and 1,4-dioxane, and 1 M in DCM).

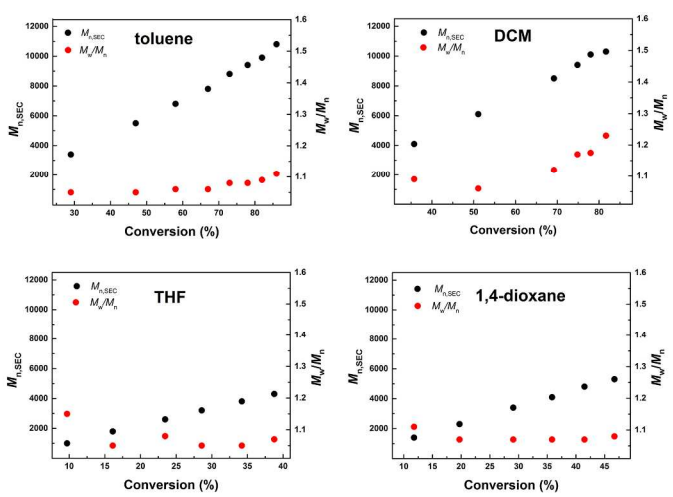
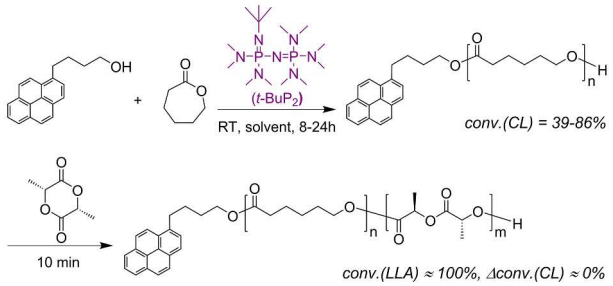


Figure 2. Dependence of apparent molecular weight and dispersity of PCL on monomer conversion during the *t*-BuP$_2$-catalysed ROP of εCL in different solvents ([εCL]$_0$/[*t*-BuP$_2$]$_0$/[PyOH]$_0$ = 100/1/1; [εCL]$_0$ = 3 M in toluene, THF and 1,4-dioxane, and 1 M in DCM).

concentration ([εCL]$_0$ = 3 M, entry 6 in Table 1), the polymerization rate is significantly faster than all the other cases with nearly complete εCL conversion reached in ≤ 1 h. However, the product has a high dispersity most probably due to the extensive occurrence of chain transfer reaction at high conversion. With a lower monomer concentration ([εCL]$_0$ = 1 M, entry 7 in Table 1), the polymerization is still faster than it is in all the other solvents (Figure 1), and a relatively higher dispersity (M_w/M_n > 1.2) is still obtained. The higher polarity of DCM may be the reason, which obviously makes both the ring-opening of εCL monomer and transesterification reaction on PCLs chain much more readily to occur than in the other solvents. A linear dependence of apparent PCL molecular weight ($M_{n,SEC}$) on monomer conversion is obtained from all the solvents (Figure 2). An elevated dispersity with increased conversion is observed in all cases.

In THF and 1,4-dioxane (entry 3 and 8 in Table 1) relatively lower dispersities were obtained compared with the case in toluene (entry 1 in Table 1) when the polymerizations were stopped after the same reaction time (8 h). Extending the reaction time in THF and 1,4-dioxane (entry 5 and 9 in Table 1) to 24 h led to higher εCL conversions as well as slightly elevated dispersities, which indicates that the occurrence of transesterification reaction on PCL chains becomes more extensive with higher monomer conversion regardless of solvents used.

Slower polymerization rates in THF and 1,4-dioxane are surprising at the first glance as their polarities are higher or similar to that of toluene. A possible explanation is their slightly basic nature, which causes the competition between *t*-BuP$_2$ and the cyclic ethers in the coordination with the hydroxyl initiator/chain end. Due to the dominant number of the cyclic ethers (e.g. [THF]/[*t*-BuP$_2$] ≈ 250 for entry 3 in Table 1), and the fact that their coordination with hydroxyl groups is unable to promote the ring-opening of εCL, the ROP is slowed down. Such an assumption is supported by an experiment conducted in THF with an increased amount of *t*-BuP$_2$ (entry 4 in Table 1 where [THF]/[*t*-BuP$_2$] ≈ 50), where faster polymerization is observed (Figure S1) with higher εCL conversion and PCL molecular weight achieved after the same reaction time. Another experiment was conducted in toluene without removing the THF from the original *t*-BuP$_2$ solution ([THF]/[*t*-BuP$_2$] ≈ 6, entry 2 in Table 1) and led to no significant change in the polymerization rate (Figure S1) compared to the results obtained in pure toluene, which further confirms the above-made assumption. The fact that a higher [*t*-BuP$_2$]/[hydroxyl] ratio leads to higher polymerization rate (comparison between entries 3 and 4 in Table 1) demonstrates the previously proposed mechanism for *t*-BuP$_2$-catalyzed ROP of cyclic ester (activation of initiator/chain-end through hydrogen bond between *t*-BuP$_2$ and hydroxyl group).[47]



Scheme 1. Schematic illustration of *t*-BuP$_2$-catalysed ROP of εCL and the sequential polymerization of LLA.

Table 2. Molecular characteristics of PCL-*b*-PLLAs and the corresponding PCLs prepared by *t*-BuP$_2$-catalyzed sequential ROP of εCL and LLA.

entry[a]	solvent	conv.(εCL)[b] (%)		$M_{n,theor}$[c] (kg mol^{-1})		$M_{n,NMR}$[d] (kg mol^{-1})		$M_{n,SEC}$[e] (kg mol^{-1})		M_w/M_n[e]	
		before	after	PCL	PCL-*b*-PLLA	PCL	PCL-*b*-PLLA	PCL	PCL-*b*-PLLA	PCL	PCL-*b*-PLLA
1	toluene	85.8	86.7	9.8	17.2	10.2	17.3	10.8	14.9	1.11	1.15
2	toluene/THF (46/1, v/v)	81.7	82.8	9.3	16.7	10.3	17.3	10.3	14.5	1.12	1.15
3	THF	39.0	39.1	4.4	11.8	4.4	9.7	4.3	8.0	1.07	1.09

[a]Corresponding to the entry number of PCL precursor in Table 1. [b]Conversion of εCL before and after the polymerization of LLA (reaction time of 30 min). [c]Theoretical number-average molecular weight of PCL-*b*-PLLA calculated based on feed ratio of monomer to initiator and conversion. [d]Number-average molecular weight of PCL-*b*-PLLA (isolated product) obtained from ^{1}H NMR measurement. [e]Apparent number-average molecular weight and dispersity of PCL-*b*-PLLA (isolated product) determined by SEC in THF at 35 °C calibrated by poly(1,4-butadiene) standards.

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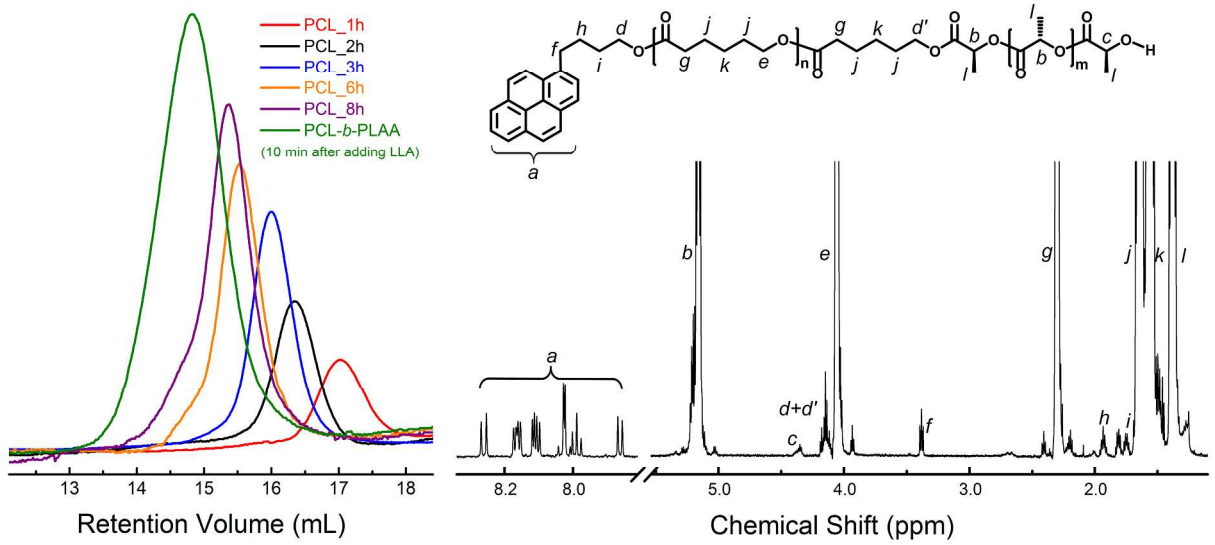

Figure 3. Left: SEC traces obtained from the aliquots withdrawn during the *t*-BuP_2-catalyzed ROP of εCL and the sequential block copolymerization of LLA (entry 1 in Table 1 and 2). Right: ^{1}H NMR spectrum of the corresponding PCL-*b*-PLLA block copolymer isolated.

For entries 1, 2, 3 in Table 1, where the PCLs have low dispersities, sequential polymerization of LLA was conducted by adding a THF solution of LLA to the solution containing PCL, *t*-BuP_2 and residual εCL monomer (Scheme 1). The withdrawn aliquots showed that the polymerization of LLA was completed in ≤ 10 min in all the solvents, and that the conversion of εCL didn't change during the polymerization of LLA or even after the reaction time was extended to 30 min (Table 2).[55] The reason why εCL wasn't further polymerized is not clear yet. An assumption can be made that it is related either to the poorer nucleophilicity which makes it extremely difficult for the secondary alcohol (PLLA chain ends) to coordinate with *t*-BuP_2 and at the same time react with the much less active εCL monomer, or to the possible occurrence of association of the poorly soluble PLLA chains. The addition of LLA as a THF solution may also be a possible reason, due to dilution of the system and the deceleration effect of THF on the polymerization of εCL as discussed above. Anyway, it is considered a great advantage of this polymerization system, as it allows for the achievement of pure PCL-*b*-PLLA diblock copolymer in the presence of residual εCL monomer.

Figure 3 shows the SEC traces obtained from the aliquots withdrawn during the sequential block copolymerization of εCL and LLA (entry 1 in Table 1 and 2, also see Figure S2 for UV signals). A relatively low dispersity was preserved in spite of the extremely fast polymerization of the second monomer (LLA). ^{1}H NMR spectra of the isolated PCL-*b*-PLLA diblock copolymers shows the characteristic signals and fitting integrals from the main bodies of the two blocks, from the end groups and from the monomeric units linking the two blocks (see Figure 3 for a representative spectrum). The rapidness of LLA polymerization doesn't seem to be influenced by the solvent used (Table 2), however, it is not conclusive yet that the polymerization rate of LLA doesn't depend on the solvent at all as the kinetic study is difficult to perform in such a short time scale.

Influence of initiator on the *t*-BuP_2-catalyzed ROP of εCL

$M_{n,NMR}$ (and $M_{n,VPO}$ for some samples) values of PCL obtained are in good agreement with those calculated based on the initial ratios of $[\varepsilon CL]_0/[PyOH]_0$ and the monomer conversion (entries 1−9 in Table 1), indicating that the initiation efficiency of a primary alcohol is practically 100%. Some other protic compounds were also used to investigate the influence of initiating species on the *t*-BuP_2-catalyzed ROP of εCL. Cholesterol was used as a representative small-molecule secondary alcohol (entry 10 in Table 1), and a slightly slower polymerization kinetics was shown (Figure 4) compared with the case of PyOH under the same conditions (entry 1 in Table 1). A slight tailing in the SEC peaks (Figure 5, 1−3 h) together with slightly higher dispersities (Figure S3) are obtained from the aliquots withdrawn at the early stage of the polymerization, which doesn't seem to be the case with PyOH (Figure 2 and 3). Such results indicate a lower initiation efficiency of a secondary alcohol, which, however, doesn't affect the achievement of a well-defined cholesteryl-PCL product with

controlled molecular weight in this case as demonstrated by SEC, ^{1}H NMR (Figure 5 and Table 1) as well as MALDI-TOF analysis (Figure 6).

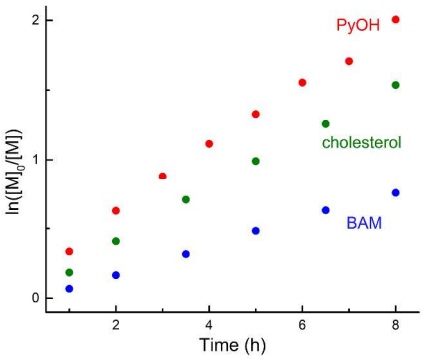

Figure 4. Kinetic plots of *t*-BuP$_2$-catalyzed ROP of εCL using a primary alcohol (PyOH), a secondary alcohol (cholesterol) and an aromatic amide (BAM) as initiators (entries 1, 10 and 13 in Table 1).

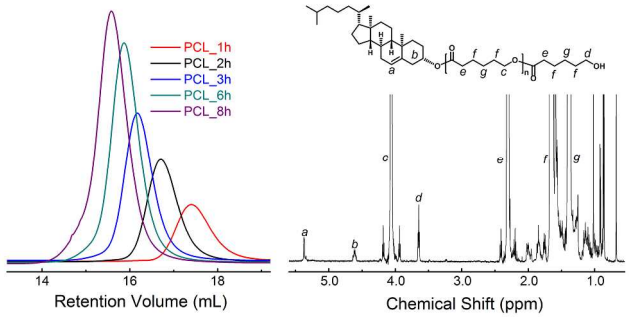

Figure 5. Left: SEC traces obtained from the aliquots withdrawn during the *t*-BuP$_2$-catalyzed ROP of εCL using cholesterol as initiator (entry 10 in Table 1). Right: ^{1}H NMR spectrum of the isolated cholesteryl-PCL.

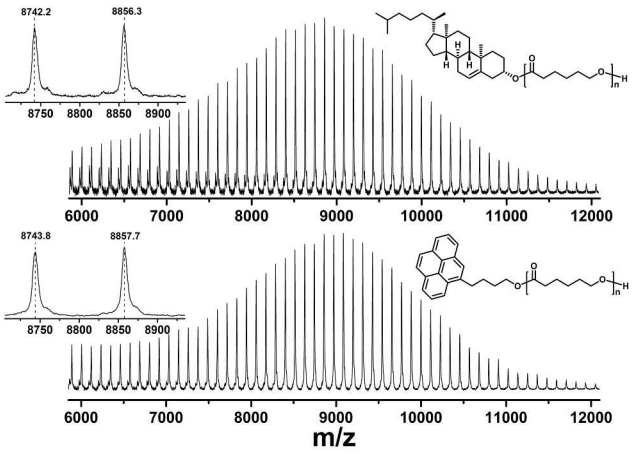

Figure 6. MALDI-TOF spectra of PCL prepared by *t*-BuP$_2$-catalyzed ROP of εCL with cholesterol (upper figure) and 1-pyrenebutanol (lower figure) as initiator (also see Table 1 for entries 10 and 5, respectively). NaTFA was used as cationizer. Calculated molecular weight for [cholesterol-P(CL)$_{73}$H+Na]$^+$ is 8742.1 Da and for [1-pyrenebutanol-P(CL)$_{74}$H+Na]$^+$ is 8743.9 Da, which are in good agreement with the measured values presented in the insets (left signals).

The effectiveness of alcoholic macro-initiators were investigated using a poly(ethylene glycol) monomethyl ether (MPEG) and a poly(propylene glycol) monobutyl ether (BPPG), respectively, as representative macro-primary and secondary alcohols. Figure 7 shows the SEC traces obtained

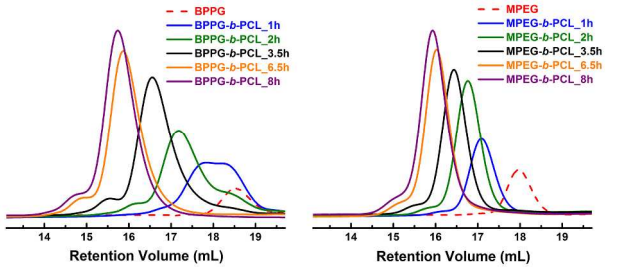

Figure 7. SEC traces obtained from the aliquots withdrawn during the *t*-BuP$_2$-catalyzed ROP of εCL from BPPG (left) and MPEG (right) macro-initiators (entries 11 and 12 in Table 1).

from the aliquots withdrawn at different time during the *t*-BuP$_2$-catalyzed ROP of εCL from MPEG and BPPG. For MPEG-*b*-PCL, the entire SEC peak shifts to the high molecular weight side from the beginning and throughout the polymerization. Whereas for BPPG-*b*-PCL a bimodal distribution is shown at the early stage of the polymerization (1−3.5 h), with a decreasing amount of the BPPG precursor and an increasing amount of the diblock copolymer, which indicates that the secondary alcohol end group of BPPG is a slow initiator for εCL. This assumption is further confirmed by the nonlinear kinetic plot obtained (Figure S4), in the beginning of which an accelerating εCL consumption rate appears indicating that the primary alcohol chain ends are being generated. Although the final BPPG-*b*-PCL obtained in this experiment (entry 11 in Table 1) still possesses a seemingly controlled molecular weight and a low dispersity due to the high block ratio (PCL/BPPG ≈ 7/1, w/w), the fact that the secondary alcohol polyether chain end is a slow initiator for cyclic ester would cause difficulty to precisely control the molecular weight of the polyether-polyester block copolymer when a low (polyester/polyether) block ratio is targeted at. Therefore, chemical modification, e.g. growth of a short PEO block or end-capping, turning the secondary alcohol chain end into a primary alcohol is probably essential for the synthesis of well-defined polyether-polyester block copolymers by this method. It needs to be noted that both MPEG-*b*-PCL and BPPG-*b*-PCL show a protrusion on the high molecular weight side, which is most probably due to the existence of some dihydroxyl PEG (PPG) in the commercial product. The diblock copolymer structures of MPEG-*b*-PCL and BPPG-*b*-PCL are also verified by the ^{1}H NMR spectra of the isolated products (Figure S5).

Other than hydroxyl groups, phosphazene(*t*-BuP$_4$)-promoted ROP of epoxides, especially ethylene oxide, have been proven to be feasible from a few other protic compounds including phenol,[29, 50, 51] amide,[52, 53] and carboxylic acid.[54] Such studies have provided useful information for macromolecular engineering, namely, polyether chains can be grown directly from the (in)organic substrates (e.g. biomolecules, functional surfaces, nanoparticles) containing the corresponding functional

(protic) groups. Therefore, we were inspired to investigate the possibility of using such unusual initiators for the ROP of εCL catalysed by the relatively mild phosphazene base (*t*-BuP_2) used in the present study. As listed in Table 1 (entries 13−17), aromatic amide (BAM), aliphatic amide (PAM), carboxylic acid (PyCOOH), phenol (BHT) and thiophenol were employed as initiators. However, the ROP of εCL only occurred from BAM. Kinetic study shows that the polymerization proceeds slower compared with cases of alcoholic initiators under the same conditions (Figure 4) with a lower conversion reached after the same reaction time (entry 13 in Table 1). However, a much higher molecular weight was obtained as indicated by $M_{n,NMR}$ and $M_{n,SEC}$, which are also much higher than the corresponding $M_{n,theor}$. Tailings are observed in the SEC peaks of the obtained product (both RI and UV signals; Figure 8) with

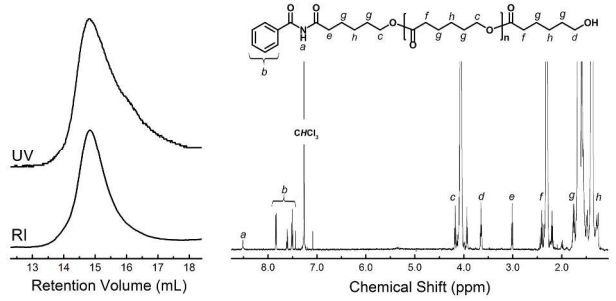

Figure 8. SEC traces (left) and ^{1}H NMR spectrum (right) of the isolated PCL product obtained from the *t*-BuP_2-catalyzed ROP of εCL using benzamide (BAM) as initiator (entry 13 in Table 1).

a correspondingly higher dispersity (M_w/M_n = 1.25). The ^{1}H NMR spectrum confirms the expected structure of the PCL with an imide end group (Figure 8). Such results indicate that BAM indeed initiates the ROP of εCL, however, the BAM−*t*-BuP_2 system works as a slow initiator probably due to the weak nucleophilicity similarly to the case of secondary alcohols discussed above. And clearly, the nucleophilicity of the other protic compounds (in the presence of *t*-BuP_2) is insufficient to react with εCL and start the polymerization. It has to be noted that the relatively low activity of εCL monomer should also be considered as part of the reason, as some of the protic compounds are able to initiate the ROP of much more active lactide monomers with a base catalyst.[56] The fact that the aromatic amide (BAM) initiates the polymerization while the aliphatic amide (PAM) cannot is somewhat surprising, since the former amide has a lower *p*Ka. Maybe this behavior is related to the effectiveness of hydrogen bond formation between the amide proton and *t*-BuP_2.

Conclusions

In summary, *t*-BuP_2-catalyzed ROP of εCL was investigated with emphasis on the influence of solvent and initiator. Higher polymerization rate was obtained in more polar solvent (comparison between DCM and toluene), however, slower polymerizations were observed in cyclic ether solvents (comparison between THF/1,4-dixoane and toluene) probably due to their slight basicity. Dispersity of PCL increased with εCL conversion due to the transesterification reaction occurring on the polyester chains, which appeared to be the fact in all the solvent used. Rapid sequential block copolymerization of LLA (as the second monomer) was observed in all the solvents, leading to well-defined PCL-*b*-PLLA diblock copolymers without the incorporation of residual εCL monomers in the LLA blocks. In addition to primary alcohol, secondary alcohol (both small molecule and macromolecule) and aliphatic amide (BAM) can also be used as initiator, which, however, showed the features of slow initiation. Other protic compounds (PAM, PyCOOH, BHT and thiophenol) were not able to initiate the ROP of εCL with the presently used *t*-BuP_2 catalyst, the search for more adequate organic catalyst to undertake such tasks is essential for the development of polyester-based metal-free macromolecular engineering.

Notes and references

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† Electronic Supplementary Information (ESI) available: [additional SEC traces, ^{1}H NMR spectra and kinetic plots]. See DOI: 10.1039/b000000x/.

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