Block Copolymerization of ϵ-Caprolactone and 2-Methoxyethyl Ethylene Phosphate Initiated by Aluminum Isopropoxide: Synthesis, Characterization, and Kinetics

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ABSTRACT: Novel biodegradable and biocompatible block copolymers of poly(ϵ-caprolactone) (PCL) and polyphosphoester were prepared in tetrahydrofuran by a two-step sequential ring-opening polymerization of ϵ-caprolactone and 2-methoxyethyl ethylene phosphate (MOEEP) using aluminum isopropoxide as an initiator. Kinetics studies revealed that homopolymerization of MOEEP initiated by aluminum isopropoxide was in the first-order kinetics with living polymerization characteristics. Polymerization of MOEEP with living PCL macroinitiator obtained by aluminum isopropoxide initiation was efficient in forming block copolymer with narrow molecular weight distribution, which was demonstrated by gel permeation chromatography and ^{13}C NMR analyses. The molecular weight and linear molecular architecture of block copolymer can be controlled by adjusting the molar ratios of monomers and the initiator as well as reaction time. Transesterification side reaction from pendent groups of poly(2-methoxyethyl ethylene phosphate) block, leading to branched molecules, was only observed when the reaction was carried out for relatively long time at high MOEEP conversion. These materials have potential for applications in biomaterials surface modification, drug delivery, and tissue engineering.

Introduction

Aliphatic polyesters such as poly(ϵ-caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(hydroxybutyrate) (PHB), and their copolymers are generally considered useful for biomedical applications such as surgical sutures, drug delivery vehicles, and reconstructive materials due to their favorable biocompatibility and biodegradability.[1−5] Their hydrophobicity and slow degradation rate, however, may not be ideal for some applications.[6−8] Moreover, the absence of functionality on the polymer backbone, which could otherwise be used for tailoring physical properties and introducing bioactive moieties, limits their further biomedical applications.[9−13]

Polyphosphoester (PPE) is a class of biodegradable polymers with repeated phosphoester linkage in the backbone, where phosphorus is pentavalent and thereby allows introduction of bioactive molecules and extensive modification of the physical and chemical properties of the polymers. The favorable biocompatibility, biodegradability, and relatively controllable hydrophilicity of PPE through pendent modification have demonstrated its potential in biomedical applications such as in drug, gene delivery, and tissue engineering.[14−19]

One way of combining the advantages of aliphatic polyesters and polyphosphoester is copolymerization, which enables the material's degradation and mechanical characteristics to be adjusted. Synthesis of copolymers with controlled composition as well as precise structure, so as to tailor and tune the properties of the final materials, is indeed the key strategy to accede the specific properties required for application.[20−23] Besides, association of aliphatic polyester to PPE would provide, upon monitoring the composition of the blocks and allowing introduction of functional pendent groups, original amphiphilic materials potentially able to self-organize into versatile nanostructures.[24−27]

Our laboratory previously reported the first synthesis and characterization of block copolymer of PPE and poly(ϵ-caprolactone) in the communication.[28] More recently, we also synthesized the brush−coil block copolymer based on poly(ϵ-caprolactone) and PEGylated polyphosphoester.[29] Our preliminary kinetics study on block copolymerization of cyclic phosphoester monomer initiated with PCL macroinitiator through aluminum isopropoxide initiation revealed living polymerization characteristics,[28] while the mechanism and kinetics of polymerization of such cyclic phosphoester monomers, which are actually important in the design of novel PPE-based block copolymers, are not fully understood. This study emphasizes the kinetics of the block copolymerization of ϵ-caprolactone and a cyclic phosphoester monomer, 2-methoxyethyl ethylene phosphate.

Experimental Section

Reagents. ϵ-Caprolactone (CL) (Acros Organics, 99%) was dried over calcium hydride for 48 h at room temperature, followed by distillation under reduced pressure just before use. Aluminum isopropoxide ($Al(O^iPr)_3$), mainly composed of trimer (A_3), was obtained according to the literature.[30,31] 2-Methoxyethanol was analytical grade and distilled just before use. Triethylamine was refluxed with phthalic anhydride, potassium hydroxide, and calcium hydride in turn and distilled just before use. Tetrahydrofuran (THF) was refluxed over potassium−sodium alloy under N_2 atmosphere and distilled just before use. Other solvents were used as received.

Synthesis of 2-Methoxyethyl Ethylene Phosphate (MOEEP). 2-Methoxyethanol (7.67 g, 100.8 mmol) and a mol equiv of

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triethylamine (10.20 g, 100.8 mmol) were dissolved in 100 mL of THF and cooled to −5 °C. A mixture of 2-chloro-2-oxo-1,3,2-dioxaphospholane (14.36 g, 100.8 mmol) in 100 mL of THF was then added dropwise under magnetic stirring. The mixture was further stirred at −5 °C for 12 h, and the precipitate was filtered off using a Schlenk funnel under N_2. The filtrate was concentrated and distilled twice under vacuum to obtain the product (bp 120 °C, 20 Pa), yield 78%. ^{1}H NMR ($CDCl_3$, ppm): 4.24 (2H, $-OCH_2$-$CH_2OP(O)CH_2CH_2OCH_3$), 4.38 (4H, $-OCH_2CH_2OP(O)CH_2CH_2$-OCH_3), 3.59 (2H, $-OCH_2CH_2OP(O)CH_2CH_2OCH_3$), 3.38 (3H,$-OCH_2CH_2OP(O)CH_2CH_2OCH_3$). ^{13}C NMR ($CDCl_3$, ppm): 58.88 ($-OCH_2CH_2OCH_3$), 66.02 ($P(O)OCH_2CH_2O-$), 67.51 ($P(O)OCH_2$-$CH_2OCH_3$), 71.23 ($-OCH_2CH_2OCH_3$). ^{31}P NMR ($CDCl_3$, ppm): 13.65 (see Supporting Information Figure S1).

Homopolymerization of MOEEP. Homopolymerization of MOEEP with initiation of A_3 was performed in THF at 20 °C in a glove box with water content less than 0.1 ppm. Typically, Al(O^i-Pr)$_3$ (155 μmol in 92 μL of THF) was added to the solution of MOEEP (2.39 g, 13.1 mmol) in THF (22.51 g), and samples were taken out for GPC analyses, as described below. The resultant solution was deactivated with 20-fold acetic acid, concentrated, and precipitated into excess methanol/diethyl ether (1:10, v/v). The precipitate was dried under vacuum to a constant weight at room temperature to obtain the product (yield 90%).

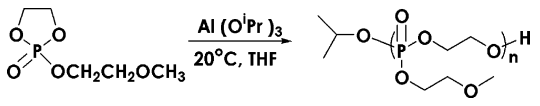
Block Copolymerization of CL and MOEEP. To CL (4.57 g, 40.0 mmol, 1 mol L^{-1} in 35.5 g THF) in a fresh-flamed and nitrogen-purged round-bottom flask was added a designated amount of A_3 of Al(O^iPr)$_3$ (94 μmol in 85 μL of THF) in a glove box (H_2O and O_2 contents <0.1 ppm). The solution was stirred at 25 °C for 1 h. The temperature of this solution was then adjusted to 20 °C, and to this solution was added quantitative MOEEP in THF with equal volume (7.28 g, 40.0 mmol, 1 mol L^{-1} in 35.5 g of THF). Aliquots (40 μL) were taken out using a microsyringe and diluted into 800 μL of $CHCl_3$ for GPC analyses. Solution was also occasionally taken out, deactivated with 20-fold acetic acid, and precipitated into excess methanol/diethyl ether (1:10, v/v). The precipitate was dried under vacuum to a constant weight at room temperature to obtain the product for other analyses (yield 89%).

Random Copolymerization of CL and MOEEP. To the mixture of MOEEP (1.05 g, 5.76 mmol) and CL (3.86 g, 33.8 mmol) in THF (34.6 g) was added Al(O^iPr)$_3$ (397 μmol in 235 μL of THF) in the glove box. The reaction was performed at 20 °C for 1 h, and the resultant solution was deactivated with 20-fold acetic acid, concentrated, and precipitated into excess methanol/diethyl ether (1:10, v/v). The precipitate was dried under vacuum to a constant weight at room temperature to obtain the product (yield 85%).

Characterization. Structural characterization of polymers was performed via ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies, which were recorded on a Bruker AV300 NMR spectrometer (300 MHz) at room temperature with $CDCl_3$ as solvent and TMS as internal reference. Phosphoric acid (85%) was used as an external reference for ^{31}P NMR analyses. FT-IR spectra were measured on a Bruker Vector 22 Fourier transform infrared spectrometer at wavenumbers 400−4000 cm^{-1} with a resolution of 2 cm^{-1} using the KBr disk method. Number- and weight-average molecular weights (M_n and M_w) and molecular weight distributions (polydispersity index, PDI $= M_w/M_n$) were determined by gel permeation chromatography (GPC) measurements on a Waters GPC system, which was equipped with a Waters 1515 HPLC solvent pump, a Waters 2414 refractive index detector, and four Waters Styragel high-resolution columns (HR4, HR2, HR1, HR0.5, effective molecular weight range 5000−500 000, 500−20 000, 100−5000, 0−1000, respectively) at 40 °C. Chloroform (HPLC grade, J. T. Baker, stabilized with 0.75% ethanol) was used as eluent and delivered at a flow rate of 1.0 mL min^{-1}. Monodispersed polystyrene standards with a molecular weight range 1310−5.51 × 10^4 were used to generate the calibration curve.

MOEEP conversion was determined by monitoring the disappearance of the peak centered at elution volume 35.65 mL in the RI detector using Waters Breeze HPLC software. The concentrations at different reaction times were determined by peak height comparison to a standard curve with known MOEEP concentrations as described above. The equilibrium concentration of monomer was obtained when monomer was no longer consumed with further extension of reaction time.

Scheme 1. Synthesis of Poly(2-methoxyethyl ethylene phosphate) Using Aluminum Isopropoxide (Al(O^iPr)$_3$) as Initiator



Results and Discussion

Homopolymerization of MOEEP. A mechanism of living ring-opening polymerization of two cyclic monomers probably is the prerequisite of the synthesis of copolymers through a two-step sequential monomer polymerization.[32] As one of the most widely used initiators in the ring-opening polymerization of ϵ-caprolactone, Al(O^iPr)$_3$ is proven to initiate CL living polymerization through a "coordination−insertion" mechanism. The polymerization process can be readily controlled, and it involves the selective cleavage of the acyl−oxygen bond of the monomer, accordingly making a hydroxyl end group after hydrolysis or acidlysis.[33]

The phosphoester bond $-OP(O)O-$ of the cyclic phosphoester monomers is structurally similar to the lactone. Therefore, we hypothesize that cyclic phosphoester monomer such as MOEEP follow the same "coordination−insertion" mechanism as lactone polymerization initiated with Al(O^iPr)$_3$ and hence could be block copolymerized by simple addition to PCL active chain ends obtained by Al(O^iPr)$_3$ initiation. In fact, Wen and his co-workers demonstrated that random copolymers of poly(ethyl ethylene phosphate) and PLA can be synthesized by ring-opening polymerization using Al(O^iPr)$_3$ as the initiator.[34,35] To prove our hypothesis, we studied the homopolymerization of MOEEP and its kinetics (Scheme 1). MOEEP was selected in this study for several reasons because it can be easily purified by vacuum distillation and the existence of pendent methoxyethoxy group can increase the hydrophilicity of polyphosphoester block. Its proton signal at 3.38 ppm in ^{1}H NMR from $-OCH_3$ in the side group can also be used to determine the average polymerization degree (DP).

The linear dependence of $\ln\{([M]_0 - [M]_{eq})/([M] - [M]_{eq})\}$ to polymerization time shown in Figure 1 is in agreement with the first-order kinetic plots for polymerizations, indicating a living polymerization of MOEEP monomer, where $[M]_0$, [M], and $[M]_{eq}$ are concentrations of MOEEP at time 0, time *t*, and equilibrium.

Figure 2A shows a typical ^{1}H NMR spectrum of homopolymer PMOEEP. Resonances at 4.68 and 1.34 ppm with intensities ratio of 1:6 were assigned to methine and methyl protons, respectively, of the isopropyl end group conjoined to polyphosphoester backbone, which was originated from Al(O^iPr)$_3$, demonstrating the involvement of Al(O^iPr)$_3$ in initiation.

Synthesis and Characterization of Poly(ϵ-caprolactone)-*block*-poly(2-methoxyethyl ethylene phosphate) (PCL-*b*-PMOEEP). The block copolymer was then synthesized according to the procedure shown in Scheme 2 through a two-step sequential monomer addition polymerization. Such block copolymerization was initially done in toluene;[28] however, due to the relatively poor solubility of polyphosphoester block in toluene, we selected THF as the solvent rather than toluene in this study, considering THF is also a good solvent for A_3-initiated CL living polymerization.[30]

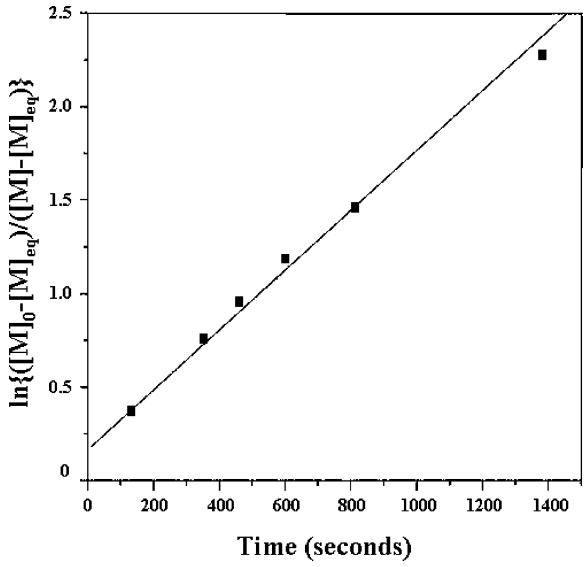


Figure 1. Kinetics of homopolymerization of 2-methoxyethyl ethylene phosphate (MOEEP) initiated with aluminum isopropoxide trimer (A_3). Conditions: 20 °C in THF, $3[A_3] = 5.0 \times 10^{-3}$ mol L^{-1}, initial concentration of MOEEP $[M]_0 = 0.25$ mol L^{-1}. [M] and $[M]_{eq}$ are concentrations of MOEEP at time *t* and equilibrium, respectively.

Figure 2B and C depict the ^{1}H NMR spectrum comparison of PCL and a typical diblock copolymer PCL-*b*-PMOEEP. The newly appeared resonances at 3.38 (j), 3.59 (i), and 4.21 ppm (h) (in Figure 2C, compared with Figure 2B) are assigned to methyl ($-OCH_3$) and methylene ($-OCH_2CH_2OCH_3$) protons from the phosphoester pendent group. In addition, resonance at 4.29 ppm (g, in Figure 2C) is the characteristic signal of methylene protons ($-POCH_2CH_2O-$) from the polyphosphoester backbone. It is particularly worth pointing out that resonances at 1.34 and 4.68 ppm in Figure 2A assigned to methyl $(CH_3)_2CH-$ and methine $(CH_3)_2CH-$ protons, respectively, linked to the polyphosphoester backbone, are distinguished from that at 1.22 and 5.00 ppm, which are contributions of protons of $(CH_3)_2CH-$ linked to the PCL backbone (Figure 2A and C). Instead of a signal at 3.65 ppm in Figure 2B corresponding to protons of PCL methylene conjoint with the hydroxyl end group, resonance at 3.81 ppm appeared in the ^{1}H NMR spectrum of PCL-*b*-PMOEEP, indicating successful copolymerization of the MOEEP block with the initiation of PCL macroinitiator. The presence of the hydroxyl group at the end of the PMOEEP block is expected for further modification and preparation of block copolymers with other molecular architectures for biomedical applications.

FT-IR analyses of PCL and PCL-*b*-PMOEEP block copolymer are shown in Figure 3. Besides the typical stretching frequencies at 1730 cm^{-1} of C═O stretching and C−O stretching at 1045 cm^{-1}, which are contributions of PCL block, absorption (bands) at 1276 and 1130 cm^{-1} marked in Figure 3a are attributed to the asymmetrical and symmetrical P═O stretchings, respectively. The P−O−C stretching was also verified at 980 cm^{-1} in the PCL-*b*-PMOEEP spectrum. Moreover, the broad bands at around 3430 cm^{-1} again confirmed the existence of hydroxyl end groups in both the PCL homopolymer and block copolymer PCL-*b*-PMOEEP.

To further determine the sequence distribution of two components in the copolymer, ^{13}C NMR spectrum of copolymer was measured and shown in Figure 4A. It has been reported previously that the resonances of carbons from carbonyl of CL units are sensitive to the chemical environment, namely the sequence of backbone of copolymer.[35,36] Multiple signals have been normally observed in the carbonyl region (around 173 ppm) in the ^{13}C NMR spectra of PCL random copolymers. In this

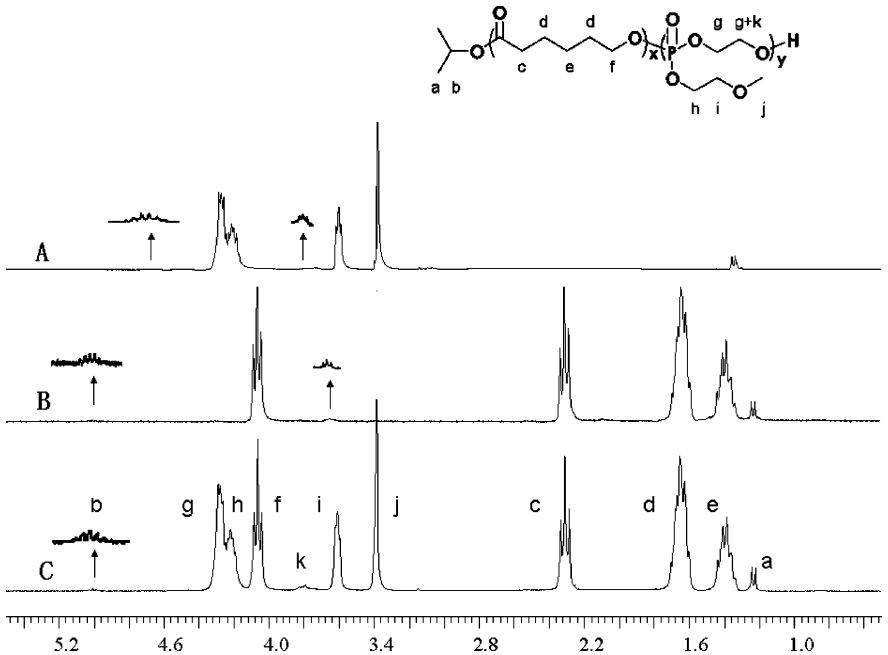
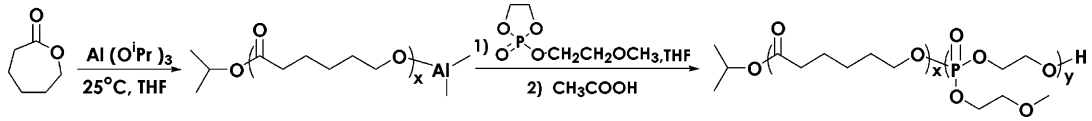


Figure 2. ^{1}H NMR spectra (in $CDCl_3$, ppm) of (A) poly(2-methoxyethyl ethylene phosphate), (B) poly(ϵ-caprolactone), and (C) poly(ϵ-caprolactone)-*block*-poly(2-methoxyethyl ethylene phosphate).

Scheme 2. Synthesis Route of Poly(ϵ-caprolactone)-*block*-poly(2-methoxyethyl ethylene phosphate)



CDV

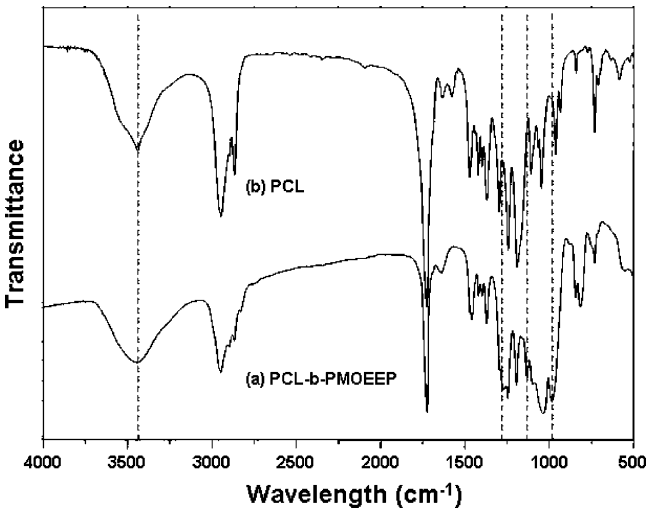


Figure 3. FT-IR spectra of (a) poly(ϵ-caprolactone)-*block*-poly(2-methoxyethyl ethylene phosphate) (PCL-*b*-PMOEEP) and (b) poly(ϵ-caprolactone) (PCL).

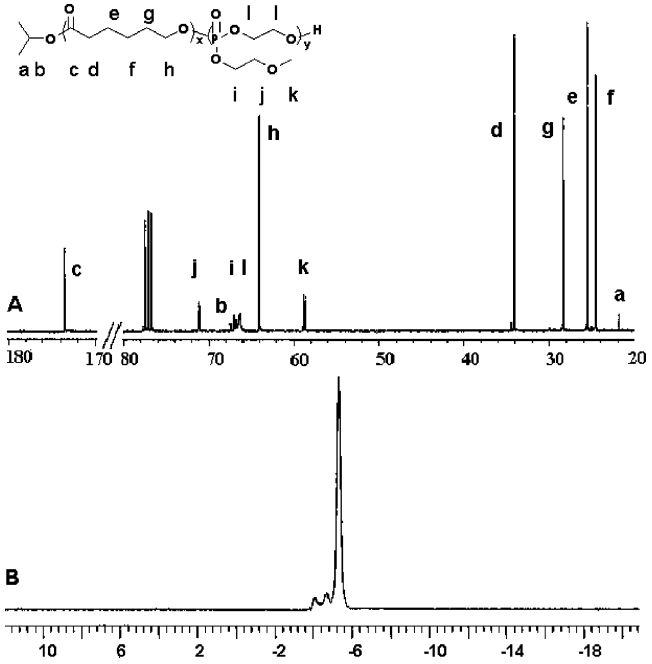


Figure 4. ^{13}C NMR (A) and ^{31}P NMR (B) spectra of poly(ϵ-caprolactone)-*block*-poly(2-methoxyethyl ethylene phosphate) (in $CDCl_3$, ppm).

case, a single peak at 173.6 ppm in the carbonyl region is in agreement with the diblock structure of this copolymer. In contrast, the random copolymer of PCL and PMOEEP exhibited multiple signals around 173 ppm (see Supporting Information Figure S2). The ^{31}P NMR spectrum (Figure 4B) of block copolymer gave a strong resonance at −5.30 ppm, assigned to the phosphorus atoms in polyphosphoester block, except the two at the ends that likely generated two separated and weak signals at −4.05 ppm and −4.72 ppm.

Kinetics of MOEEP Polymerization Initiated with PCL Macroinitiator. Polymerization of MOEEP initiated with PCL macroinitiator was studied for kinetics analysis. The reaction was conducted in THF solvent at various temperatures and initiator concentrations.

Figure 5 shows overlaid GPC chromatograms of a typical reaction, which clearly demonstrated increased molecular weights of PCL-*b*-PMOEEP with MOEEP monomer consumption. The conversion of MOEEP reached 94.3% in 15.0 min, and molecular weight increased to 10520 from 6020, corresponding to that of PCL block. Polydispersities remained narrow in 1 h, which are around 1.2 in this reaction, as summarized in Table 1. Close scrutiny of the GPC chromatograms revealed several small peaks eluted from 31 to 34 mL. A significant low-molecular-weight tail was also observed in a short reaction time (after 2.1 min). The tail and small peaks could come from backbiting cleavage or the transesterification of chains,[37] which would indicate that side reactions are occurring at the short times. Those side products with low molecular weights can be easily removed by precipitation into 10:1 (v/v) cool ethyl ether/methanol. The molecular weights and PDI listed in Table 1 were determined after precipitation.

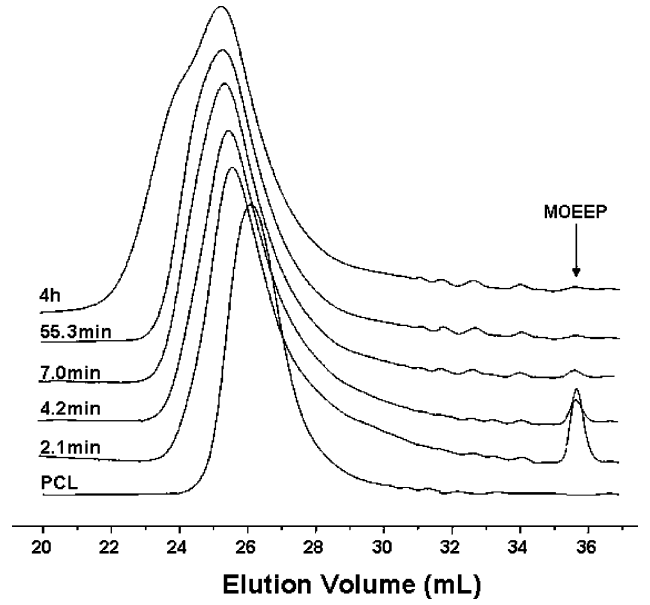


Figure 5. GPC monitoring of 2-methoxyethyl ethylene phosphate (MOEEP) polymerization initiated with poly(ϵ-caprolactone) macroinitiator at 20 °C in tetrahydrofuran. Conditions: poly(ϵ-caprolactone) macroinitiator concentration $[PCL_3\text{-}Al^*] = 10.0 \times 10^{-3}$ mol L^{-1} and initial concentration of MOEEP, $[MOEEP]_0 = 0.50$ mol L^{-1}.

Molecular weights were also calculated from ^1H NMR spectroscopy. M_n for the PCL and PMOEEP blocks were obtained based on the integration ratios of signals at 2.30 ppm ($-C(O)CH_2CH_2-$, 2H) and at 4.29 ppm ($-P(O)OCH_2CH_2OCH_2CH_2OCH_3$, 4H) to the end isopropyl group proton signal at 1.34 ppm ($(CH_3)_2CH-$, 6H), originated from $Al(O^iPr)_3$, respectively. The molecular weights thus obtained were in agreement with the theoretical values, namely $M_{n,PCL} + \lambda[MOEEP]_0/3[PCL_3\text{-}Al^*]$, where λ is the monomer conversion rate and $[PCL_3\text{-}Al^*]$ is the concentration of PCL macroinitiator in MOEEP polymerization, which equals $3[A_3]_0$ timed by the dilution factor. Notably, the molecular weights of block copolymers calculated from ^1H NMR were lower than from GPC, which was referred to by literature due to the structural differences between copolymers and polystyrene standards.[38]

The relationship between monomer conversion and number-average molecular weight (M_n), PDI is depicted in Figure 6. It reveals that M_n follows a linear relationship to monomer conversion, and molecular weight distribution remains narrow with PDI around 1.2. The linear dependence of M_n on monomer conversion indicates that a limited amount of inter- or intramolecular transesterification reactions occurred up to 94.3% monomer conversion, which ensures narrow molecular weight distribution as well as controllable molecular weight and composition.

Table 1. Block Copolymerization of ϵ-Caprolactone (CL) and 2-Methoxyethyl Ethylene Phosphate (MOEEP) Initiated with Aluminum Isopropoxide ($Al(O^iPr)_3$)[a]

no.	feed molar ratio (CL/MOEEP)	$[CL]_0/3[A_3]_0$	$[PCL_3\text{-}Al^*]$[b] (mmol L^{-1})	reaction time[c] (min)	MOEEP conversion[d] (%)	M_n[e] PCL/PMOEEP	M_n[d]	PDI[d]
1	1.0	50	10.0	2.1	50.0	1870/1340	8870	1.18
2	1.0	50	10.0	4.2	70.2	1870/1930	9510	1.19
3	1.0	50	10.0	7.0	81.7	1870/2230	9900	1.20
4	1.0	50	10.0	15.0	94.3	1870/2560	10 520	1.24
5	1.0	50	10.0	55.3	97.2	1870/2500	11 000	1.24
6	1.0	50	10.0	240	97.0	*h*	12 800	1.60
7	2.0	50	10.0	21.9	93.8	1910/1280	9090	1.18
8	2.0	75	6.8	28.5	91.2	2800/1560	12 800	1.16
9	2.0	100	5.0	45.0	88.2	3800/2430	19 600	1.18
10	2.0	143	3.5	60.5	85.3	5440/3430	25 890	1.26
11	2.0	250	2.0	76.1	84.3	9510/5500	38 970	1.26
12[f]	2.0	100	5.0	12.2	90.5	3800/2520	19 550	1.19
13[g]	2.0	100	5.0	9.5	91.2	3800/2580	19 990	1.19

[a] $[CL]_0$ was kept at 1.0 mol L^{-1} in all experiments. MOEEP polymerization was carried out at 20 °C in tetrahydrofuran except otherwise stated. [b] Concentration after MOEEP solution addition. [c] Timed when MOEEP monomer was introduced. [d] Calculated from HPLC. [e] Calculated from ^1H NMR. [f] Reaction carried out at 30 °C. [g] Reaction carried out at 40 °C. [h] Not determined.

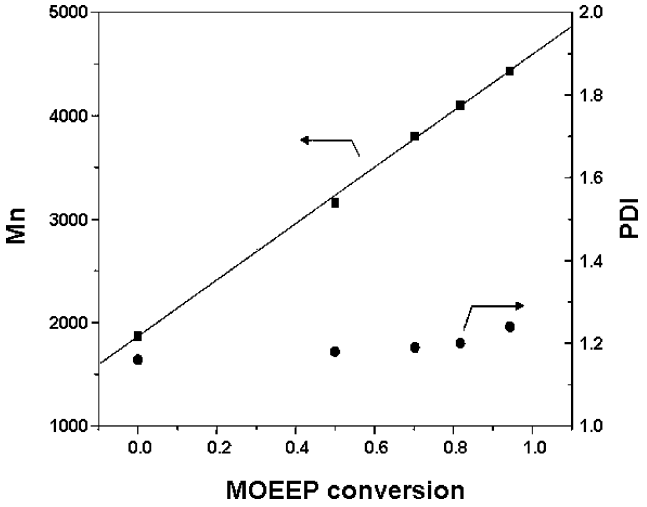


Figure 6. Dependence of molecular weight measured by ^1H NMR and molecular weight distribution (PDI) of block copolymer on 2-methoxyethyl ethylene phosphate (MOEEP) conversion. Conditions: poly(ϵ-caprolactone) macroinitiator concentration $[PCL_3\text{-}Al^*] = 10.0 \times 10^{-3}$ mol L^{-1}; initial concentration of MOEEP $[MOEEP]_0 = 0.5$ mol L^{-1}. Reaction was carried out at 20 °C in tetrahydrofuran.

It must be noted that extending the reaction time will lead to higher molecular weight distribution. As shown in Figure 5, the chromatogram of an aliquot taken out after 4 h reaction exhibited a shoulder and the molecular distribution was broader with increased PDI to 1.60, indicating side chain transfer occurred and led to branched molecules with higher molecular weight. Such a side reaction was also observed in the homopolymerization of MOEEP (see Supporting Information Figure S3) and is likely due to the pentavalent nature of the phosphorus atom, as suggested by Penczek et al. in the literature.[39] Meanwhile, similar results have also been observed in our previous work of ring-opening polymerization of 2-ethoxy-2-oxo-1,3,2-dioxaphospholane initiated by stannous octoate.[40]

^{31}P NMR analysis also revealed additional peaks at −3.67 and −6.00 ppm, likely attributable to phosphorus atoms with otherwise microenvironments at the branching points (see Supporting Information Figure S4).

It is worth noting that the reaction rates in THF are much faster when compared with that in toluene, as reported previously.[28] The difference is most likely due to the relatively poor solubility of the polyphosphoester block in toluene. As a result, the active center at polyphosphoester chain end would be hindered in toluene and this would prevent chain propagation.

Block Copolymerization: Variation of Reaction Temperature. The first-order kinetic plots for polymerizations at different temperatures are shown in Figure 7. Using the kinetic form widely accepted for $Al(O^iPr)_3$-initiated CL polymerization, the linearity of these plots is consistent with the polymerization process that is first order in MOEEP consumption with reaction time and can be described by

$$R_p = -\frac{d[M]}{dt} = k_{app}([M] - [M]_{eq})$$

where R_p is the rate of polymerization, and k_{app} is the apparent propagation rate constant. The slopes of these plots are equal to the apparent rate k_{app}.

The apparent rate constant at 20 °C was 1.20×10^{-3} S^{-1}, slightly smaller than that of MOEEP homopolymerizaton initiated by $Al(O^iPr)_3$ (1.59×10^{-3} S^{-1}) at the same temperature, which may indicate that PCL macroinitiator (PCL_3-Al*) is somewhat less reactive than $Al(O^iPr)_3$ owing to the polymer chain hindrance effect. It is also worth pointing out that no induction period was observed in MOEEP polymerization with PCL macroinitiator, contrary to systems initiated with $Al(O^iPr)_3$ reported in the literature, because no disassociation is necessary for PCL macroinitiator.[41] Higher temperature led to faster monomer consumption, as shown in Table 1 (entries 9, 12, and 13). Approximate 90% MOEEP conversion was achieved in 9.5 min at 40 °C, while 12.2 and 45.0 min were spent at 30 and at 20 °C, respectively, to reach roughly the same conversion in otherwise identical polymerization conditions. Arhennius analysis revealed that the relationship between k_{app} and polymerization temperature is consistent with the equation $k_{app} = A \exp(-E_a/RT)$, where $\ln k_{app}$ is linearly dependent on $1/T$, as shown in Figure 7B.

Block Copolymerization: Variation of PCL Macroinitiator Concentration. It has been proven that the apparent rate constant k_{app} is a function of the initiator concentration in $Al(O^iPr)_3$-initiated lactone ring-opening polymerization.[32] A linear relationship is also observed in our study when k_{app} is plotted against the concentration of PCL macroinitiator (Figure 8). In these experiments, the starting concentration of MOEEP was kept at 0.25 mol L^{-1}, and the reaction temperature was set at 20 °C, but macroinitiator concentration was varied. The linear relationship demonstrated that MOEEP polymerization initiated

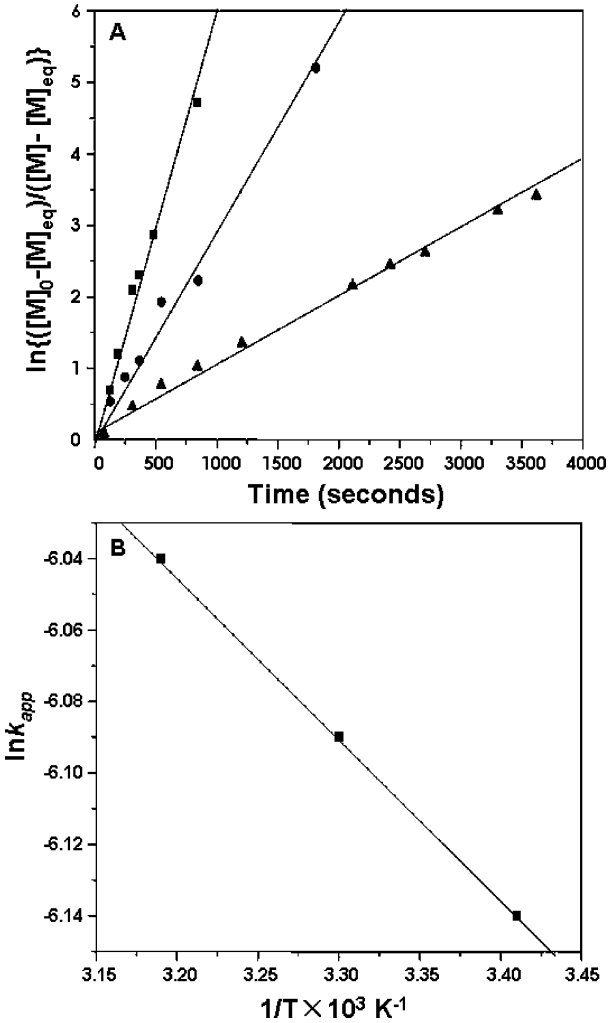


Figure 7. (A) Kinetics of 2-methoxyethyl ethylene phosphate (MOEEP) ring-opening polymerization initiated with poly(ϵ-caprolactone) macroinitiator at 40 °C (■), 30 °C (●), 20 °C (▲) in tetrahydrofuran. (B) Dependence of the apparent propagation rate constant k_{app} on polymerization temperature. Conditions: poly(ϵ-caprolactone) macroinitiator concentration [PCL_3-Al*] = 5.0×10^{-3} mol L^{-1}; initial concentration of MOEEP, $[MOEEP]_0 = 0.25$ mol L^{-1}; [M] and $[M]_{eq}$ are concentrations of MOEEP at time t and equilibrium, respectively.

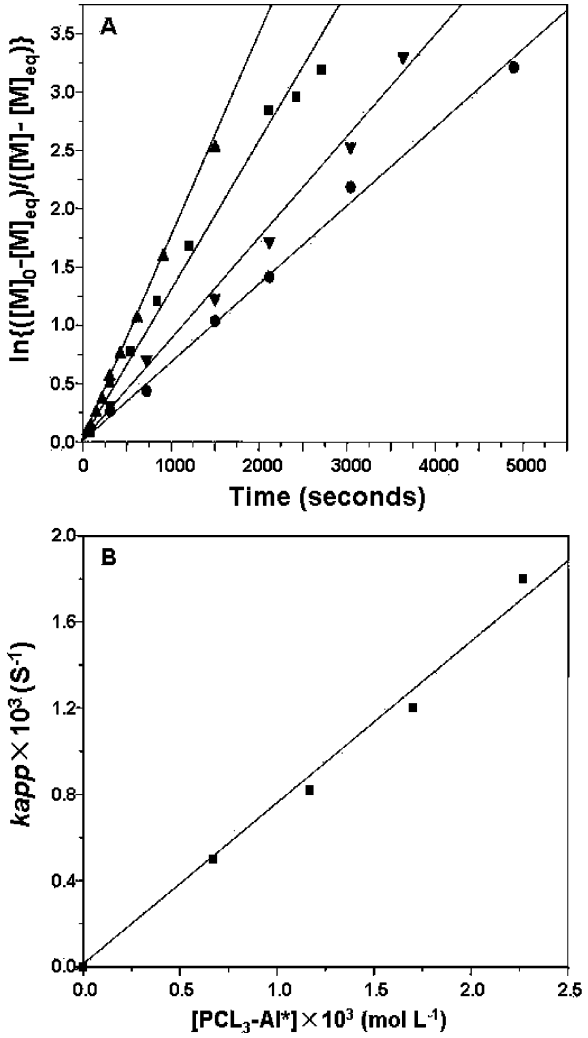


Figure 8. (A) Kinetics of 2-methoxyethyl ethylene phosphate ring-opening polymerization initiated with poly(ϵ-caprolactone) macroinitiator at concentration [PCL_3-Al*] = 6.8×10^{-3} mol L^{-1} (▲), 5.0×10^{-3} mol L^{-1} (■), 3.5×10^{-3} mol L^{-1} (▼), and 2.0×10^{-3} mol L^{-1} (●). (B) Linear dependence of the apparent propagation rate constant k_{app} on macroinitiator concentration. The reactions were carried out at 20 °C in tetrahydrofuran with an initial MOEEP concentration of 0.25 mol L^{-1}. [M] and $[M]_{eq}$ are concentrations of MOEEP at time t and equilibrium, respectively.

with PCL macroinitiator is also first order in initiator. The kinetic constant k obtained from the slope of Figure 8 was 14.4 L mol^{-1} min^{-1} at 20 °C. k values are 36.6 L mol^{-1} min^{-1} for CL at 0 °C and 0.6 L mol^{-1} min^{-1} for LA at 70 °C when initiated with $Al(O^iPr)_3$ in toluene, respectively.[31,36] On the other hand, as a result of changing initiator amounts to MOEEP, block copolymers with different molecular weights were obtained as summarized in Table 1 (entry 8−11).

In conclusion, block copolymers of PCL and polyphosphoesters have successfully been synthesized through a two-step sequential ring-opening polymerization of CL and MOEEP, with trimer of aluminum isopropoxide as an initiator. NMR, FT-IR, and GPC characterizations have confirmed the actual formation of the expected block copolymers. It has also been revealed that the polymerization of MOEEP is in the first-order kinetics, indicating the living polymerization characteristics either by aluminum isopropoxide or PCL macroinitiator in THF. The molecular architecture can be well-controlled through adjusting the feed ratios between monomers and initiator, and side reaction on the other hand can be limited by properly ceasing the reaction. Although the rate of propagation of the phosphate block was affected by the structure of pendent group connected with phosphorus, this polymerization procedure will facilitate the synthesis of the block copolymer of the aliphatic polyester and polyphosphoester to achieve defined molecular architectures and properties for biomedical applications.

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Supporting Information Available: NMR spectra of MOEEP, ^{13}C NMR spectrum of random copolymer of CL, and MOEEP and ^{31}P NMR of block copolymer with transesterification side reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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