# Kinetics and Mechanism of 2-Ethoxy-2-oxo-1,3,2-dioxaphospholane Polymerization Initiated by Stannous Octoate

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ABSTRACT: The ring-opening polymerization (ROP) of the cyclic phosphoester 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP) in tetrahydrofuran solution with co-initiation of stannous octoate and dodecanol yields poly(ethylene ethlyl phosphate) (PEEP) with defined linear molecular structure. NMR analyses reveal every molecule of dodecanol starts growth of one PEEP chain and each polymer chain bears one hydroxyl end group. Kinetics studies for different co-initiator ratios and temperatures reveal that the ROP is a first-order reaction with respect to EEP monomer and suggest the formation of active center stannous alkoxide and a coordination−insertion polymerization mechanism. Side chain transfer leading to branched polymeric structure was observed particularly when the reaction time was extended after monomer consumption reaching equilibrium due to the pentavalent nature of phosphorus. By controlling the polymerization conditions, such side reaction can be suppressed to synthesize polyphosphoester with confined structure. This polymerization procedure is expected to facilitate the synthesis of polyphosphoesters with defined molecular architectures and properties for further biomedical applications.

## Introduction

There are continuous interests in development of polyphosphoesters (PPE) for biomedical applications due to their good biocompatibility, potential biodegradability, and pendant functional possibility.[1,2] Flexibility in adjusting the structures and consequently the physicochemical properties of polyphosphoesters has led PPE to a wide range of applications from drug and gene delivery to tissue engineering. It has been demonstrated that water-insoluble polyphosphoesters are promising in delivery of chemotherapeutics and other pharmaceutical agents[3−6] as well as in fabrication of tissue engineering scaffold.[7−9] On the other hand, water-soluble polyphosphoesters, particularly the cationic polyphosphoesters, have comprised a new family of nonviral gene carriers.[1,10] Amphiphilic polyphosphoesters have also been synthesized and evaluated recently for drug and gene delivery.[11,12] Furthermore, biocompatible and biodegradable hydrogels based on polyphosphoesters have been synthesized and reported for cell encapsulations.[13−15]

Synthesis of polyphosphoesters was pioneered by Penczek and his colleagues at the end of the 1970s, initially as analogues of nucleic and teichoic acids, latter on as biomembranes toward polymer−inorganic hybrids or mimicking biomineralization.[16] They have studied extensively the synthesis and elucidated many of the mechanisms of different routes, including anionic and cationic ring-opening polymerizations,[17,18] polycondensation,[19,20] and polyaddition.[21] Until now these methods were still the main approaches for synthesizing polyphosphoester biomaterials, though interfacial polymerization[22] and recently reported enzyme catalyzed polymerization[23,24] are possibly alternative methods.

We have reported that cyclic phosphoester can be polymerized with initiation of poly($\epsilon$-caprolactone) macroinitiator obtained by aluminum isopropoxide initiation.[25] Our kinetics studies demonstrated that such polymerization is likely by means of coordination−insertion, similar to polymerization of cyclic esters such as $\epsilon$-caprolactone (CL) and L,L-dilactide (LA). Stannous octoate, as one of the most widely used initiators for cyclic esters polymerization, has been reported recently to induce polymerization of CL, LA, or analogues by formation of stannous alcoholate active centers with ROH or $RNH_2$ as co-initiator;[26,27] however, its use has not yet been reported in cyclic phosphoester monomer polymerization. The polymer chain propagation has been described as simple monomer insertion into the −Sn−OR bond in CL and LA or analogues polymerizations. Such a process has been widely used in syntheses of polyesters with various architectures including block,[28,29] grafted,[30,31] star-shaped,[32,33] and hyperbranched structures.[34,35] We present here the first time that a five-membered cyclic phosphoester ethylene ethyl phosphate, namely, 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP), can be polymerized under co-initiation of $Sn(Oct)_2$ and dodecanol. Kinetics studies suggested that polymerization of this cyclic phosphoester EEP initiated by $Sn(Oct)_2$ with dodecanol is by a similar mechanism following the stannous alkoxide species formation.

## Experimental Section

**Materials.** 2-Ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP) was synthesized as previously described in the literature[6] and purified with two consecutive vacuum distillations. Dodecanol (Sinopharm Chemical Reagent Co., Ltd.) was freshly distilled under reduced pressure prior to use. Stannous octoate ($Sn(Oct)_2$, Sinopharm Chemical Reagent Co., Ltd.) was purified according to a method described in the literature.[36] Tetrahydrofuran (THF, Sinopharm Chemical Reagent Co., Ltd.) was refluxed with calcium hydride and distilled over Na−K alloy prior to use.

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**Polymerization Procedure.** The polymerization was conducted in a 25-mL reaction flask carrying a Teflon stopcock. The flask was treated with trimethylchlorosilane solution in methylene chloride for 12 h, flame dried under vacuum, and purged with nitrogen three times before use. In a typical polymerization, EEP monomer (2.0 g, 13.2 mmol) was introduced into the flask using a syringe, followed by adding 10 mL of THF via a stainless steel capillary under nitrogen atmosphere. The mixture was subsequently stirred in a bath at the designed temperature. To this solution was added dodecanol (0.66 mmol in 1.3 mL of THF) through a syringe, followed rapidly by addition of $Sn(Oct)_2$ (0.33 mmol in 0.66 mL of THF). Samples (50 $\mu$L each) were taken out at various time intervals and quenched immediately into and stored in liquid nitrogen until analyses.

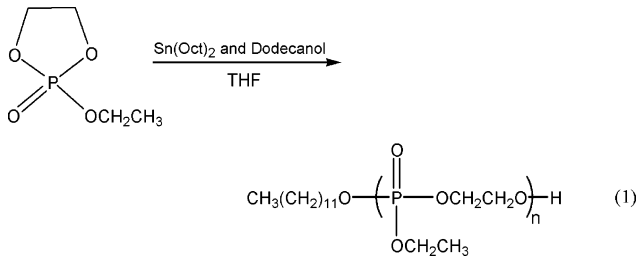
**Characterizations.** Samples were diluted with 1 mL of chloroform and immediately analyzed by gel permeation chromatography. The GPC system is composed of a Waters 1515 pump and a Waters 2414 refractive index detector equipped with Waters Styragel high-resolution columns (1×HR4, 1×HR2, 1×HR1, and 1×HR0.5). Chloroform was used as mobile phase at a flow rate of 1 mL $min^{-1}$ at 40 °C. Molecular weights and molecular weight distributions were analyzed using Waters Breeze software. Monodispersed polystyrene standards were used to generate the calibration curve.

Monomer conversion was determined at the same time by monitoring the disappearance of the peak centered at the elution volume 36.377 mL in the RI detector using Waters Breeze HPLC software. The monomer concentrations at different reaction time were determined by peak height comparison to a standard curve with known EEP concentrations. The equilibrium concentration of monomer was obtained when monomer was no longer consumed with further extension of reaction time.

Samples for NMR analyses were obtained by precipitation of concentrated reaction mixture into toluene/ether (8:1, v/v), which were further dried overnight under vacuum. $^{1}H$, $^{31}P$, and $^{13}C$ NMR spectra were recorded on a Brucker AV300 NMR spectrometer at room temperature with $CDCl_3$ as solvent and TMS as internal reference. Phosphoric acid (85%) was used as external reference for $^{31}P$ NMR analyses.

## Results and Discussion

**Synthesis of PEEP and Characterization.** The synthesis of poly(ethyl ethylene phosphate) (PEEP) through polymerization of EEP monomer initiated by $Sn(Oct)_2$ and dodecanol is shown in eq 1.




(1)

In a typical procedure, EEP was polymerized under $[EEP]_0$:$[Sn(Oct)_2]_0$:$[dodecanol]_0$ = 20:0.5:1 for 1 h in THF at 40 °C. Polymer PEEP was obtained by precipitation in toluene/ether (8:1, v/v) and analyzed by NMR. The data shown in Figure 1 are consistent with PEEP chain microstructure with expectation. As shown in Figure 1A, resonances at 4.28, 4.18, and 1.37 ppm with rough intensities ratio of 4:2:3 can be assigned to the protons f, g, and h (including proton b), respectively. Resonances of protons from initiator dodecanol (a−e) appearing in Figure 1A demonstrated that dodecanol had been involved in the ring-opening polymerization of EEP because dodecanol itself is well-soluble in toluene/ether (8:1, v/v). It should be emphasized that the resonance at 3.79 ppm (i) is the contribution of methylene protons conjoint to the hydroxyl end group of polymer chains and the intensity ratio of i to a is 2:3, indicating that every molecule of dodecanol starts growth of one polyphosphoester chain under the above polymerization conditions; therefore, the molecular weights can be calculated by a comparison between the intensities of the protons a and h + b from the dodecyl tail end group and phosphoester units.

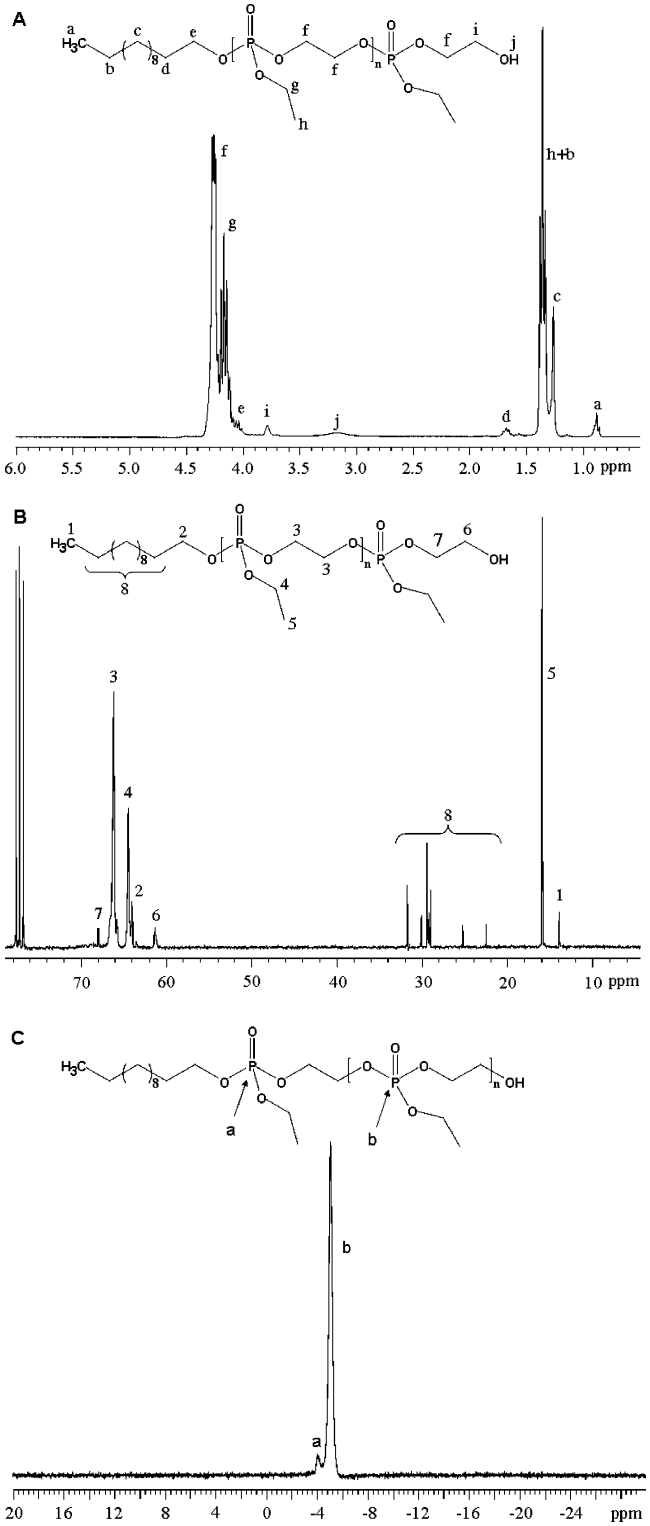



**Figure 1.** NMR spectra of the PEEP in $CDCl_3$: (A) $^{1}H$ NMR, (B) $^{13}C$ NMR, (C) $^{31}P$ NMR. Polymerization was carried out under $[EEP]_0$ = 1.0 mol $L^{-1}$, $[Sn(Oct)_2]_0$ = 0.025 mol $L^{-1}$, and $[dodecanol]_0$ = 0.05 mol $L^{-1}$ in THF at 40 °C.

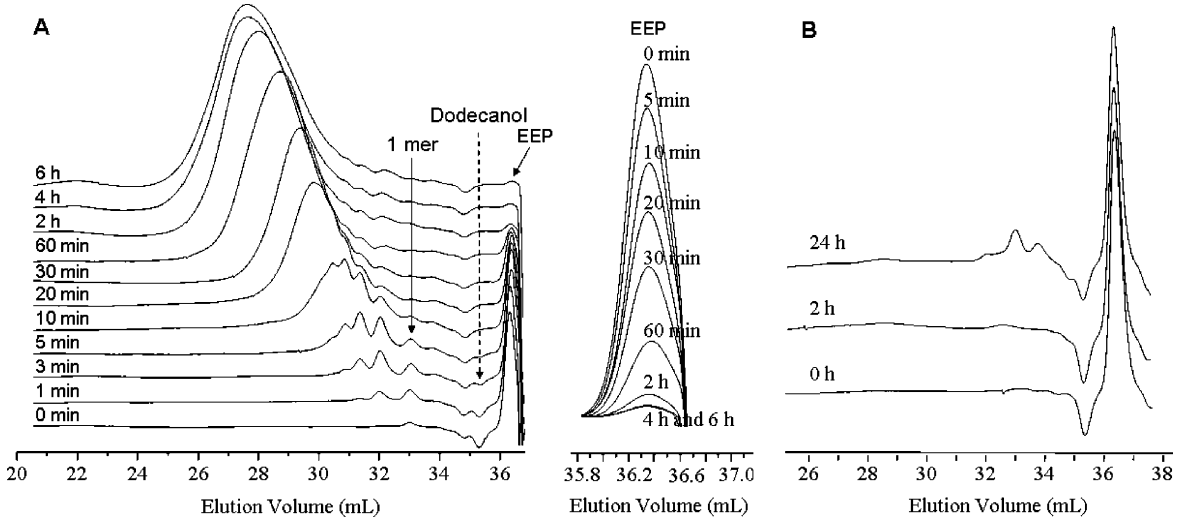
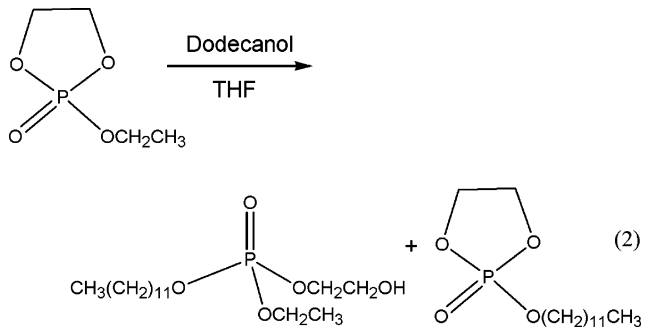



**Figure 2.** GPC chromatograms of aliquots removed from the reaction mixtures: (A) $[EEP]_0 = 1$ mol $L^{-1}$, $[dodecanol]_0 = 0.05$ mol $L^{-1}$, and $[Sn(Oct)_2]_0 = 0.025$ mol $L^{-1}$, 25 °C in THF; (B) $[EEP]_0 = 1$ mol $L^{-1}$, $[dodecanol]_0 = 0.05$ mol $L^{-1}$, and $[Sn(Oct)_2]_0 = 0$ mol $L^{-1}$, 40 °C in THF.

$^{13}C$ NMR also revealed that resonances of carbon atoms from the dodecanol and the repeat phosphoester unit were all presented as assigned in Figure 1B. It should be emphasized that resonances at 61.3 and 67.9 ppm must be from the carbons of methylene conjoint to the hydroxyl end group. The $^{31}P$ NMR spectrum of this polymer shown in Figure 1C gave a strong resonance at −5.10 ppm, assigned to the phosphorus atoms in polyphosphoester except the phosphorus atom connected to the dodecanol, which generated the signal at −4.05 ppm.

**Mechanism and Kinetics of EEP Polymerization.** Cyclic phosphoester monomer, which has been previously polymerized under cationic or anionic polymerization,[17,18] was recently polymerized by aluminum alkoxide intiators.[6,25] Kinetics studies showed polymerization initiated by aluminum alkoxide macrointiators was controllable by means of coordination−insertion (the results will be reported elsewhere) propagation. Polymerization of ϵ-caprolactone or lactide in both bulk and solution with alcohol and $Sn(Oct)_2$ is probably the most often used synthesis method, and several initiation pathways have been proposed.[37] By MALDI-TOF mass spectrometry, Kowalski et al. directly observed the formation of OctSnOR and revealed that the actual initiator is the tin(II) alkoxide.[26,27,38] To investigate the mechanism of EEP polymerization with co-initiation of dodecanol and $Sn(Oct)_2$, we first compared the reactions of EEP initiated with dodecanol at 25 °C either with $Sn(Oct)_2$ or without $Sn(Oct)_2$ in THF. The reactions were followed by GPC analyses of aliquots taken out at various time points. It was observed in Figure 2 that EEP consumption rates were significantly different. In the presence of $Sn(Oct)_2$, 96% of EEP was consumed in 4 h and clear RI signals of polymeric products were observed after a few minutes reaction. In contrast, only around 4% of EEP was consumed after 24 h reaction and no polymeric product could be detected by GPC analysis in the absence of $Sn(Oct)_2$. These results demonstrated that $Sn(Oct)_2$-catalyzed EEP polymerization was possibly by formation of active stannous alkoxide species, which has been reported to further initiate the polymerization in cyclic ester monomers polymerization. Another possibility might lie in the activation of EEP monomer by $Sn(Oct)_2$. When we carefully looked into the GPC chromatograms shown in Figure 2A, we found that the peak of dodecanol at elution volume of 35.318 mL disappeared in 5 min, indicating that dodecanol took part in the reaction in a very short time. However, in the absence of $Sn(Oct)_2$, when polymerization was carried out under the otherwise identical conditions, the depletion of dodecanol was much slower, which was evidenced by GPC analyses shown in Figure 2B. In fact, the overlayed GPC chromatograms in Figure 2A also showed a peak with elution volume of 33.050 mL, most likely being a contribution of the intermediate formed by the reaction between the hydroxyl group from dodecanol and one unit of EEP (1 mer). Although this peak is also present in Figure 2B, it is worth noting that a lower molecular weight compound with retention time at 33.733 min, which is not present in Figure 2A, was detected when the reaction was not catalyzed by $Sn(Oct)_2$. On the basis of this observation, we assume that in the absence of $Sn(Oct)_2$ there may be a reaction between EEP and dodecanol, as shown in eq 2.

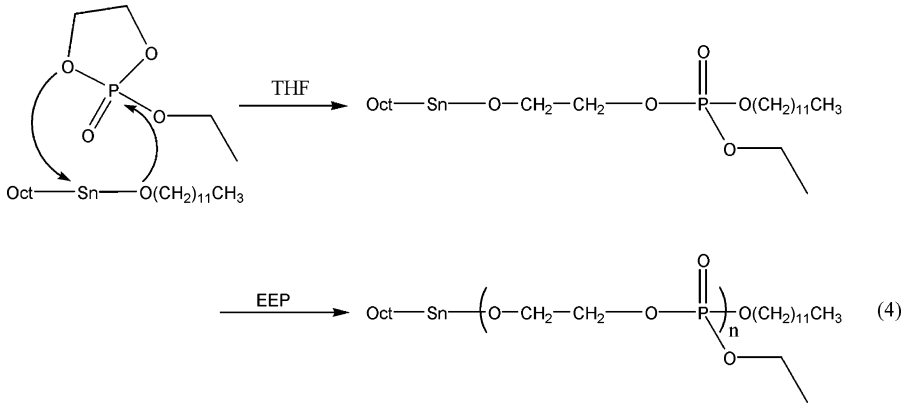



(2)

However, in the presence of $Sn(Oct)_2$, most probably, these results suggested that there might be a much faster or unique interaction between dodecanol and $Sn(Oct)_2$, leading to active stannous alkoxide response for the chain initiation in ϵ-caprolactone or lactide polymerization, as observed by other groups.[36,38,39]

According to the mechanism proposed for ϵ-CL or LA polymerization initiated by $Sn(Oct)_2$ and alcohol either in solution or in bulk,[26,36,39,40] purposely added alcohol first complexes and subsequently reacts with $Sn(Oct)_2$, producing a stannous alkoxide species. Reaction of this stannous alkoxide with monomer by means of coordination−insertion generates the first actively propagating chain end (1 mer*) consisting of both the initiating alcohol fragment and the active propagating center derived from the first monomer unit and stannous alkoxide. Considering the possible active stannous alkoxide formation as analyzed above

**Scheme 1. EEP Polymerization Mechanism: Initiation and Propagation**



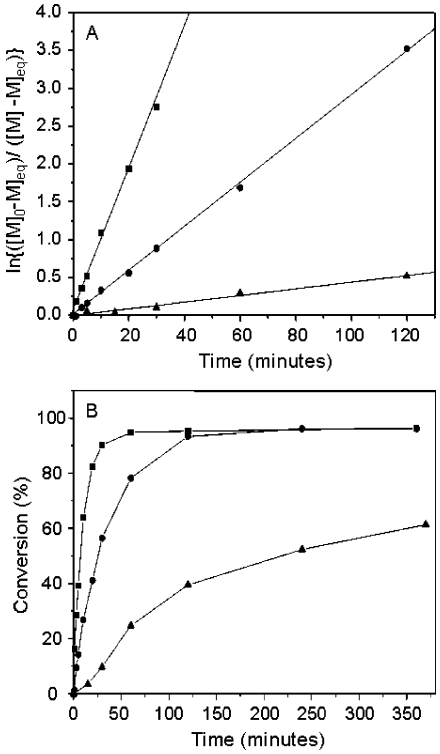




**Figure 3.** Kinetics of EEP ring-opening polymerization initiated with $Sn(Oct)_2$ and dodecanol. Conditions: $[EEP]_0 = 1.0$ mol $L^{-1}$, $[Sn(Oct)_2]_0 = 0.025$ mol $L^{-1}$, $[dodecanol]_0 = 0.05$ mol $L^{-1}$, THF solvent; (A) effect of reaction temperature 40 °C (■), 25 °C (●), 0 °C (▲); (B) EEP conversion at various reaction time, 40 °C (■), 25 °C (●), 0 °C (▲).

as well as the similar cyclic ester structure of EEP monomer, we proposed the mechanism of EEP polymerization including chain initiation and propagation as shown in Scheme 1. Stannous octoate and dodecanol were believed to form a new active center, the stannous alkoxide as shown in eq 3.

$$Sn(Oct)_2 + CH_3(CH_2)_{11}OH \rightleftharpoons CH_3(CH_2)_{11}OSnOct + OctH \quad (3)$$

The 1 mer* species was then formed and the polymer chain was propagated (eq 4).

To further prove our hypothesis, we studied the kinetics of this polymerization. Figure 3A shows the first-order kinetic plots for polymerizations at different temperatures, where $[M]_0$, [M], and $[M]_{eq}$ are concentrations of EEP at time 0, time *t*, and equilibrium. Using the generally accepted kinetic form for the polymerization with $Sn(Oct)_2$ and alcohol, the linearity of these plots is consistent with polymerization process that is first-order in EEP consumption with reaction time and can be described by

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

where $R_p$ is the rate of polymerization and $k_{app}$ is the apparent propagation rate constant. Since the relationships shown in Figure 3A are linear, the slopes of these plots are equal to the $k_{app}$. The $k_{app}$ increases by a factor of 20 upon increasing the polymerization temperature from 0 to 40 °C, and an Arhennius analysis revealed that the relationship between $k_{app}$ and polymerization temperature is consistent with the following equation, where ln $k_{app}$ is linearly dependent on $1/T$.

$$k_{app} = A \exp\left(-\frac{E_a}{RT}\right)$$

Figure 3B shows the conversion dependence of EEP on reaction time. Practically, at 40 °C approximately 90% conversion of EEP can be achieved in 30 min, while only less than 40% conversion of EEP was observed at 0 °C under otherwise identical polymerization conditions.

Figure 4 shows another set of kinetics plots, obtained from polymerization carried out with fixed initial EEP concentration but varied $[Sn(Oct)_2]_0/[dodecanol]_0$ ratios. In one series of experiments the starting concentration of $Sn(Oct)_2$ was kept constant. As shown in Figure 4A, where the concentration of dodecanol was varied from 0.0125 to 0.10 mol $L^{-1}$, results of the kinetic measurements are presented in the form of semilogarithmic coordinates. The data indicate the same first-order kinetics of the polymerization as demonstrated above, showing the same linear dependence of $\ln\{([M]_0 - [M]_{eq})/([M] - [M]_{eq})\}$ on polymerization time.

The $k_{app}$ was plotted against the ratio of $[dodecanol]_0/[Sn(Oct)_2]_0$ and shown in Figure 4B. At lower starting concentrations of $[dodecanol]_0$, the rate increases nearly proportionally to $[dodecanol]_0$. When a certain ratio is reached, the rate becomes independent of $[dodecanol]_0$. This phenomena is similar to that observed in the polymerization of ϵ-CL or LA co-initiated with $Sn(Oct)_2$ and alcohol.[26,27,38]

In another series of polymerization, we kept the initial concentrations of EEP and dodecanol constant but altered the feed ratio of $Sn(Oct)_2$ to dodecanol. As shown in Figure 4C, a similar dependence was observed that the rate increased with increasing $[Sn(Oct)_2]_0$. After a certain $[Sn(Oct)_2]_0/[dodecanol]_0$ was reached, practically no more increase of rate was observed.

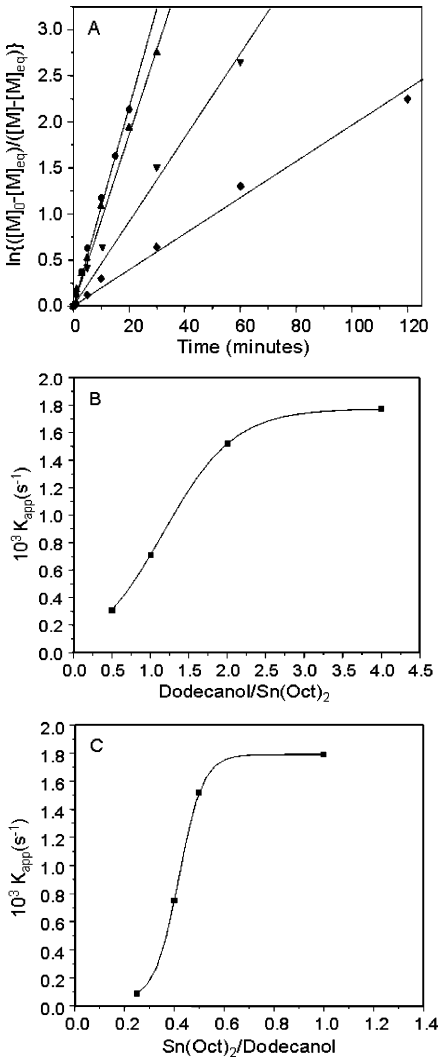



**Figure 4.** (A) First-order kinetics dependences for EEP polymerization initiated with $Sn(Oct)_2$ and dodecanol. Conditions: $[EEP]_0 = 1.0$ mol $L^{-1}$, $[Sn(Oct)_2]_0 = 0.025$ mol $L^{-1}$, and $[dodecanol]_0$ (in mol $L^{-1}$) = 0.10 (●), 0.05 (▲), 0.025 (▼), 0.0125 (◆); tetrahydrofuran (THF) solvent, 40 °C; (B) Dependence of $k_{app}$ on the $[dodecanol]_0/[Sn(Oct)_2]_0$ ratio. Conditions: $[EEP]_0 = 1.0$ mol $L^{-1}$, $[Sn(Oct)_2]_0 = 0.025$ mol $L^{-1}$, THF, 40 °C; (C) Dependence of $k_{app}$ on the $[Sn(Oct)_2]_0/[dodecanol]_0$ ratio. Conditions: $[EEP]_0 = 1.0$ mol $L^{-1}$, $[dodecanol]_0 = 0.05$ mol $L^{-1}$, THF, 40 °C.

As analyzed previously by Penczek et al.[26,27,38] and Storey et al.[39] for the polymerization of CL and LA with co-initiation of $Sn(Oct)_2$ and alcohol, increase of rate results from shifting the equilibrium to formation of active species until almost all of the alcohol is converted in stannous alkoxide. Further increase of $[Sn(Oct)_2]_0$ does not provide any more active species, which is an indication of a coordination−insertion mechanism. In EEP polymerization, the results were consistent with that observed by Penczek et al.[26,27,38] and Storey et al.,[39] which demonstrated the formation of active stannous alkoxide and polymerization of EEP proceeds by means of coordination−insertion mechanism.

**Chain Transfer Side Reactions in EEP Polymerization.** Unlike tetravalent carbon atoms in aliphatic cyclic esters and polyesters, the phosphorus atom in EEP and the linear backbone of polyphosphoester is pentavalent with an additional ethoxyl side chain through the P−O bond. It is not surprising if the side chain transfer reaction occurred during the ring-opening polymerization.

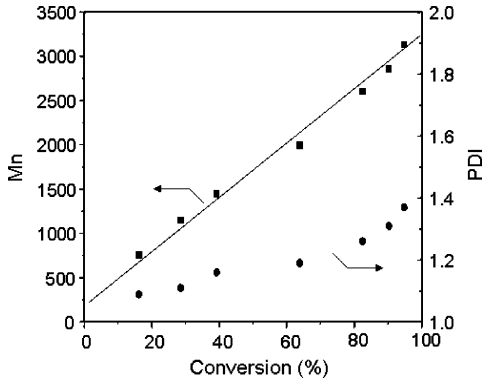
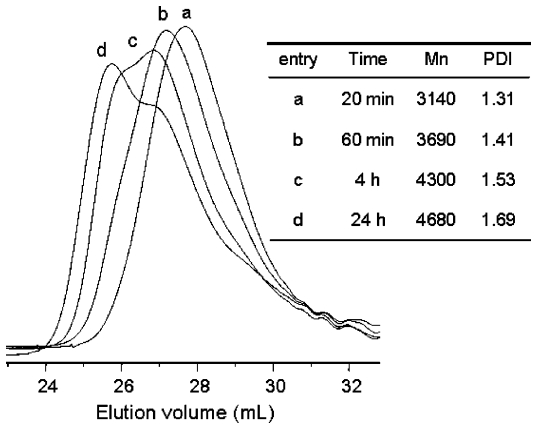


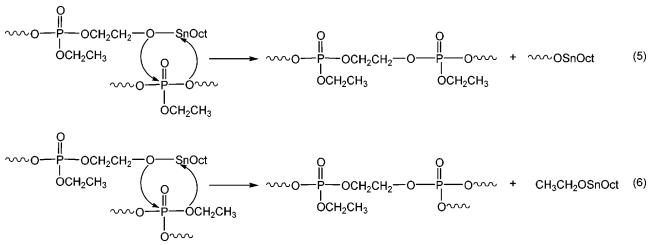

**Figure 5.** Dependence of molecular weights and molecular weight distributions of the polymers on EEP conversion. Conditions: $[EEP]_0 = 1.0$ mol $L^{-1}$, $[Sn(Oct)_2]_0 = 0.025$ mol $L^{-1}$, $[dodecanol]_0 = 0.05$ mol $L^{-1}$, THF solvent, 40 °C.




| entry | Time | Mn | PDI |
|---|---|---|---|
| a | 20 min | 3140 | 1.31 |
| b | 60 min | 3690 | 1.41 |
| c | 4 h | 4300 | 1.53 |
| d | 24 h | 4680 | 1.69 |

**Figure 6.** GPC analyses of EEP polymerization conducted at 40 °C in THF under $[EEP]_0 = 1.0$ mol $L^{-1}$, $[Sn(Oct)_2]_0 = 0.025$ mol $L^{-1}$, $[dodecanol]_0 = 0.05$ mol $L^{-1}$: (a) 20 min, (b) 60 min, (c) 4 h, and (d) 24 h.

Figure 5 shows the dependence of Mn and PDI on monomer conversion. The conversion of monomer reached 95% in 60 min and the molecular weights increased with the increase of monomer conversion. The PDI of the polymer was below 1.2 at EEP conversion less than 70%. Although the molecular weights distribution became broader with prolonged reaction time, for example, the PDI of the polymer increased to 1.41 when conversion of EEP was 95% (1 h reaction in THF), no detectable shoulder was found in the GPC chromatograms. It is believed that deploymerization competes with polymerization at high monomer conversions, which will result in a higher molecular weight distribution for the polymer. In this experiment, when the monomer concentration reached the equilibrium concentration of 0.036 mol $L^{-1}$, corresponding to EEP conversion of 96.4%, the PDI was 1.45, showing a competition of chain propagation and depolymerization. However, with further extension of the reaction time, for example to 4 h, as shown in Figure 6, a clear shoulder at high molar mass was present, and the PDI increased to 1.53, implying that side chain transfer was happening. When the reaction time was further extended to 24 h, such side reaction became more apparent, with the PDI increasing to 1.69. Meanwhile, $M_n$ increased to 4680, which is significantly higher than that of 20 repeated units as designed. Such an increase of $M_n$ and PDI indicates significant side chain transfer besides the chain transfer depicted in eq 5, leading to branched polymeric structure as shown in eq 6.



Similar results have also been observed by Penczek et al. during syntheses of poly(alkylene phosphates) prepared by ROP[41] and us when using aluminum isoproxide macroinitiator.[25]

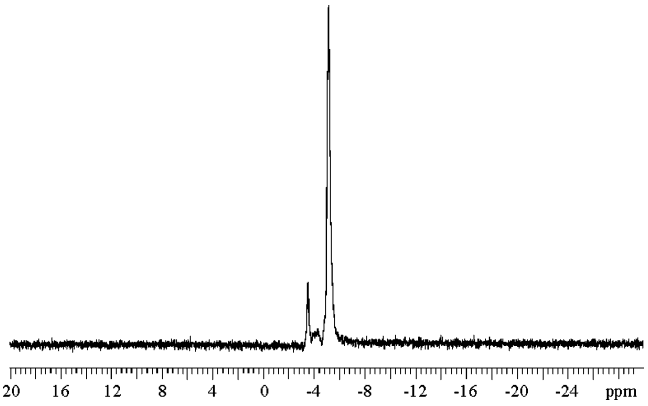



**Figure 7.** $^{31}$P NMR of PEEP polymer obtained after 24 h reaction. Polymerization conditions are given in the caption for Figure 6.

$^{31}$P NMR analysis shown in Figure 7 supported the branched polymeric structure. Besides the resonances at −5.10 and −4.05 ppm, the peak at −3.56 ppm is an indication of the otherwise micro environment of phosphorus atoms, which is the contribution of phosphorus atoms at the branching points.

There have been detailed mechanism studies on cyclic esters polymerization, particularly those of CL and LA induced by $Sn(Oct)_2$ and alcohols. Penczek et al. have observed Sn atoms bonded through alkoxide groups to macromolecules in $Sn(Oct)_2$-induced CL and LA polymerizations using MALDI-TOF mass spectrometry.[26,27,38] They concluded that polymerization of CL or LA was initiated by the product of reaction of an alcohol and $Sn(Oct)_2$, namely, stannous alkoxide, and propagated by simple monomer insertion into the −Sn−OR bond. In our study, polymerization of cyclic phosphoester monomer EEP initiated by $Sn(Oct)_2$ with dodecanol as the co-initiator shows a first-order kinetics. The dependence of the rate of polymerization on either $[Sn(Oct)_2]_0$ or $[dodecanol]_0$ practically levels off at a certain ratio when the initial concentration of the other component is constant. This type of kinetic behavior is consistent with that reported for the cyclic ester/$Sn(Oct)_2$/ROH system, suggesting a similar insertion mechanism on polyphosphoester chain growth following the stannous alkoxide species formation.

On the other hand, according to this mechanism, every molecule of dodecanol starts growth of one polyphosphoester chain in the polymerization, and the monomer conversion can be above 90% under appropriate polymerization conditions; therefore, by adjusting the $[EEP]_0/[dodecanol]_0$ feed ratio, the molecular weights of polymers can be well controlled. By this method, PEEP polymers with molecular weights ($M_n$) from nearly 1000 to $1.5 \times 10^4$ have been synthesized and the molecular weight distributions were narrow with PDI less than 1.5.

Though significant side reaction was observed with prolonged reaction time due to the side chain transfer and branched polymer chain possibly generated owing to the pentavalent nature of phosphorus, polyphosphoester with confined structure will still be able to be synthesized through $Sn(Oct)_2$ and alcohol initiation by ceasing the reaction before high monomer conversion is achieved. This polymerization procedure is expected to facilitate the synthesis of polyphosphoesters with defined molecular architectures and properties for further biomedical applications.

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## References and Notes

(1) Zhao, Z.; Wang, J.; Mao, H. Q.; Leong, K. W. *Adv. Drug Delivery Rev.* **2003**, *55*, 483−499.
(2) Wang, J.; Gao, S. J.; Zhang, P. C.; Wang, S.; Mao, M. Q.; Leong, K. W. *Gene Ther.* **2004**, *11*, 1001−1010.
(3) Li, K. W.; Dang, W. B.; Tyler, B. M.; Troiano, G.; Tihan, T.; Brem, H.; Walter, K. A. *Clin. Cancer Res.* **2003**, *9*, 3441−3447.
(4) Xu, X. Y.; Yu, H.; Gao, S. J.; Mao, H. Q.; Leong, K. W.; Wang, S. *Biomaterials* **2002**, *23*, 3765−3772.
(5) Sen Gupta, A.; Lopina, S. T. *Polymer* **2004**, *45*, 4653−4662.
(6) Wen, J.; Kim, G. J. A.; Leong, K. W. *J. Controlled Release* **2003**, *92*, 39−48.
(7) Renier, M. L.; Kohn, D. H. *J. Biomed. Mater. Res.* **1997**, *34*, 95−104.
(8) Wan, A. C.; Mao, H. Q.; Wang, S.; Phua, S. H.; Lee, G. P.; Pan, J.; Lu, S.; Wang, J.; Leong, K. W. *J. Biomed. Mater. Res. B Appl. Biomater.* **2004**, *70*, 91−102.
(9) Wang, S.; Wan, A. C.; Xu, X.; Gao, S.; Mao, H. Q.; Leong, K. W.; Yu, H. *Biomaterials* **2001**, *22*, 1157−1169.
(10) Mao, H. Q.; Leong, K. W. *Adv. Genet.* **2005**, *53PA*, 275−306.
(11) Iwasaki, Y.; Akiyoshi, K. *Macromolecules* **2004**, *37*, 7637−7642.
(12) Wen, J.; Mao, H. Q.; Li, W. P.; Lin, K. Y.; Leong, K. W. *J. Pharm. Sci.* **2004**, *93*, 2142−2157.
(13) Li, Q.; Wang, J.; Shahani, S.; Sun, D. D. N.; Sharma, B.; Elisseeff, J. H.; Leong, K. W. *Biomaterials* **2006**, *27*, 1027−1034.
(14) Iwasaki, Y.; Komatsu, S.; Narita, T.; Akiyoshi, K.; Ishihara, K. *Macromol. Biosci.* **2003**, *3*, 238−242.
(15) Wang, D. A.; Williams, C. G.; Li, Q. A.; Sharma, B.; Elisseeff, J. H. *Biomaterials* **2003**, *24*, 3969−3980.
(16) Penczek, S.; Pretula, J.; Kaluzynski, K. *Biomacromolecules* **2005**, *6*, 547−551.
(17) Lapienis, G.; Penczek, S. *J. Polym. Sci. A* **1977**, *15*, 371−382.
(18) Lapienis, G.; Penczek, S. *Macromolecules* **1977**, *10*, 1301−1306.
(19) Pretula, J.; Penczek, S. *Makromol. Chem., Macromol. Chem. Phys.* **1990**, *191*, 671−680.
(20) Penczek, S.; Pretula, J.; Kaluzynski, K. *J. Polym. Sci. A* **2005**, *43*, 650−657.
(21) Biela, T.; Kubisa, P.; Penczek, S. *Makromol. Chem., Macromol. Chem. Phys.* **1992**, *193*, 1147−1164.
(22) Richards, M.; Dahiyat, B. I.; Arm, D. M.; Lin, S.; Leong, K. W. *J. Polym. Sci. A* **1991**, *29*, 1157−1165.
(23) Feng, J.; Zhuo, R. X.; He, F. *Sci. China Ser. B−Chem.* **2003**, *46*, 160−167.
(24) Li, F.; Zhuo, R. X. *Chem. J. Chin. Universities Chin.* **2004**, *25*, 1780−1782.
(25) Chen, D. P.; Wang, J. *Macromolecules* **2006**, *39*, 473−475.
(26) Kowalski, A.; Duda, A.; Penczek, S. *Macromolecules* **2000**, *33*, 7359−7370.
(27) Kowalski, A.; Libiszowski, J.; Biela, T.; Cypryk, M.; Duda, A.; Penczek, S. *Macromolecules* **2005**, *38*, 8170−8176.
(28) Du, Y. J.; Lemstra, P. J.; Nijenhuis, A. J.; Vanaert, H. A. M.; Bastiaansen, C. *Macromolecules* **1995**, *28*, 2124−2132.
(29) Mohammadi-Rovshandeh, J.; Farnia, S. M. F.; Sarbolouki, M. N. *J. Appl. Polym. Sci.* **2002**, *83*, 2072−2081.
(30) Breitenbach, A.; Kissel, T. *Polymer* **1998**, *39*, 3261−3271.
(31) Li, Y. X.; Nothnagel, J.; Kissel, T. *Polymer* **1997**, *38*, 6197−6206.
(32) Kricheldorf, H. R.; Ahrensdorf, K.; Rost, S. *Macromol. Chem. Phys.* **2004**, *205*, 1602−1610.
(33) Kim, S. H.; Han, Y. K.; Ahn, K. D.; Kim, Y. H.; Chang, T. *Makromol. Chem., Macromol. Chem. Phys.* **1993**, *194*, 3229−3236.
(34) Yu, X. H.; Feng, J.; Zhuo, R. X. *Macromolecules* **2005**, *38*, 6244−6247.

(35) Gottschalk, C.; Frey, H. *Macromolecules* **2006**, *39*, 1719−1723.
(36) Kricheldorf, H. R.; Kreiser-Saunders, I.; Stricker, A. *Macromolecules* **2000**, *33*, 702−709.
(37) Albertsson, A. C.; Varma, I. K. *Biomacromolecules* **2003**, *4*, 1466−1486.
(38) Kowalski, A.; Duda, A.; Penczek, S. *Macromolecules* **2000**, *33*, 689−695.
(39) Storey, R. F.; Sherman, J. W. *Macromolecules* **2002**, *35*, 1504−1512.
(40) Ryner, M.; Stridsberg, K.; Albertsson, A. C.; von Schenck, H.; Svensson, M. *Macromolecules* **2001**, *34*, 3877−3881.
(41) Penczek, S. In *Models of Biopolymers by Ring-Opening Polymerization;* Penczek, S., Ed.; CRC Press: Boca Raton, FL, 1990; p 291

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