Synthesis and Characterization of Block Copolymer of Polyphosphoester and Poly(ϵ-caprolactone)

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Biodegradable polymers have many advantages for development of appropriate therapies in biological systems. Polyphosphoester (PPE) represents a class of biodegradable polymers with repeated phosphoester linkage in the backbone, which degrades under the physiological conditions via hydrolysis or enzymatic cleavage of the phosphoester bonds.[1,2] The biological potential of PPE has been investigated by Penczek and his colleagues since the early 1980s, typically as analogues of nucleic and teichoic acids.[3,4] More recently, PPE has received considerable attention in biomedical applications due to its biodegradability, good biocompatibility, and functional ability of side chain.[5−8] The degradation rates are controllable by the chemical structure in the backbone and side chain. By choosing biocompatible building blocks of the polymer, degradation products of PPE can have minimal toxic effects and good biocompatibility.[9] Moreover, the pentavalent nature of the phosphorus allows introductions of bioactive molecules and extensive modification of the physical and chemical properties of the polymers. For example, advantages of PPE have been taken for development of tissue engineering scaffolds for bone and nerve regeneration[10−12] as well as drug delivery systems for therapeutical agents including bioactive proteins and anticancer molecules.[13,14] In other examples, amino groups have been introduced into side chains for condensation and sustained release of plasmid DNA in gene delivery.[15,16]

In addition to development of biomaterials based on polyphosphoester homopolymer, recent efforts have been particularly emphasized on random copolymers with polylactide or poly(ϵ-caprolactone).[17−20] The degradation rates of such copolymers can be adjusted with the percentage of incorporated phosphate content. However, no copolymer with PPE block has been reported according to our knowledge. It has been proven that block polymers exhibit local segregation of the different polymer blocks and yield molecular-scale aggregates of nanometer size,[21] showing many advantages in biomedical applications in surface modification, drug targeting, nano- and microparticles, hydrogels, micelles formation, etc.[22,23] In this Communication, it is the first time to report the synthesis and characterization of block copolymer of PPE and poly(ϵ-caprolactone).

Block copolymer of ϵ-caprolactone (CL) and 2-isopropoxy-2-oxo-1,3,2-dioxaphospholane (R = ^{i}Pr) or 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (R = Et) has been selectively synthesized by first initiating CL polymerization with trimer of Al(O^iPr)$_3$ (A_3)[24] in toluene, followed by adding phosphoester monomer to the living PCL macroinitiator solution, as shown in Scheme 1.

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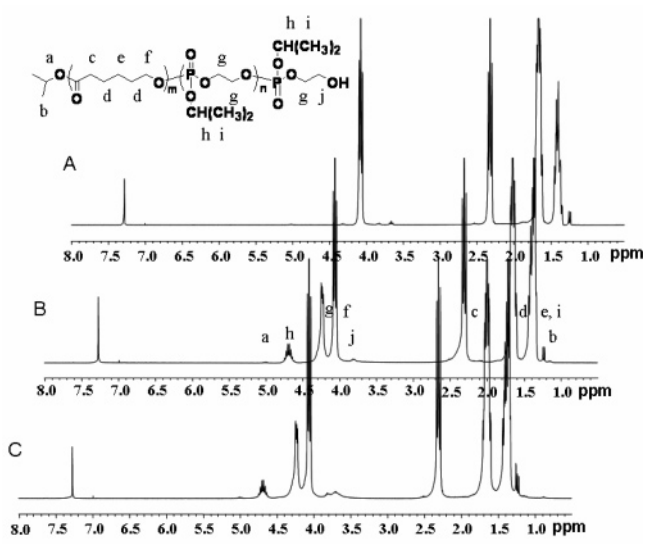

Figure 1. ^{1}H NMR spectra of PCL (A), block copolymer polymerized for 4 days at 70 °C (B), and copolymer polymerized for 12 days at 70 °C (C). The polymerization was stopped by acidification.

The typical ^{1}H NMR spectrum of block copolymer of ϵ-caprolactone (CL) and 2-isopropoxy-2-oxo-1,3,2-dioxaphospholane (R = ^{i}Pr) is shown in Figure 1B. The polymer was obtained after 4 days reaction at 70 °C since adding phosphoester monomer to the living ω-Al alkoxide PCL blocks, which was polymerized at 25 °C for 2 h using A_3 as an initiator. Among those newly appearing signals compared with ^{1}H NMR spectrum of poly(ϵ-caprolactone) (Figure 1A), the resonance at 3.81 ppm was easily observed in Figure 1B in addition to peaks assigned to protons of phosphoester units (−P(O)−O−C***H***−$(CH_3)_2$), 4.70 ppm; −P(O)−O−C***H***$_2$−C***H***$_2$−O−, 4.23 ppm; and (P(O)−CH−$(C\boldsymbol{H}_3)_2$, 1.38 ppm), which should be assigned to the methylene protons conjoint to the end hydroxyl group of phosphoester unit of block copolymer. In contrast, the resonance at 3.65 ppm assigned to the methylene protons conjoint to the hydroxyl end group of PCL was no longer present, demonstrating the complete conversion of PCL macroinitiator to block polymer. Meanwhile, the ^{13}C NMR spectrum of the copolymer attested the block structure of the copolymer and the absence of transfer reactions as illustrated in the Supporting Information (Figure S1A). Indeed, focusing into the carbonyl region, only one well-resolved signal at 173.4 ppm attributed to PCL sequences was observed; however, multisignals were observed in the ^{13}C NMR spectrum of random copolymer of PCL and polyphosphoester (Supporting Information, Figure S1B), which has also been observed by other group in the ^{13}C NMR spectrum of random copolymer poly(DL-lactide-*co*-ethylene methyl phosphate).[25]

The ^{31}P NMR spectrum of block polymer (Supporting Information, Figure S2A) gave a strong resonance at 0.73 ppm, assigned to the phosphorus atoms in polyphosphoester block except the two at the ends that likely generated two separated and very weak signals at 0.03 and −1.37 ppm.

As analysis by gel permeation chromatography shown in Figure 2, the molecular weight distribution for the first block (PCL) is narrow (M_w/M_n = 1.04), and polydispersity changes to 1.20 upon polyphosphate block formation, whereas no homopolymer formation can be detected. As expected, the molecular weight of block polymer is shifted toward higher value, in agreement with the theoretical values. When phos-

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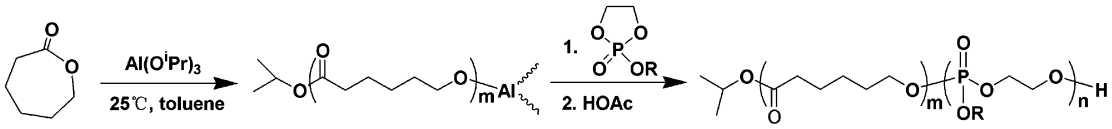
Scheme 1. Synthesis Route of Block Copolymer of Polyphosphoester and Poly(ϵ-caprolactone)



phoester polymerization is initiated by living PCL chains, the phosphoester monomer conversion at 70 °C was 31.2% after 4 days. The increase of M_n of 3030 Da is in well agreement with that of 3110, calculated from the ^{1}H NMR spectrum. The shoulder at the high molar mass may indicate light chain transfer to the side groups of phosphoester block, leading to branched polymer, which has been observed before during syntheses of poly(alkylene phosphates) prepared by ROP, and the mechanism has been proposed by Penczek et al. in the literature.[3]

Distinct transesterification was observed with increase of reaction time. As shown in Figure 1C, the product obtained after 12 days reaction gave two protons resonances at 3.6−3.7 ppm in its ^{1}H NMR spectrum, which indicates formation of hydroxyl end group conjoint with PCL segment at the end of polymer chain and is a reflection of transesterification. Accordingly, the ^{13}C NMR spectrum (Supporting Information, Figure S1 C) of this polymer also showed an evidence of transesterification that four resonances were observed for the carbon of the carbonyl in PCL. They are clearly distinguished and assigned to the central carbon of carbonyl of following sequences: 175.9 ppm, P−C−P; 175.6 ppm, P−C−C; 173.7 ppm, C−C−P; 173.4 ppm, C−C−C, where P and C represent phosphoester unit and CL unit, respectively. This was further reflected in ^{31}P NMR of copolymer with transesterification (Supporting Information, Figure S2B), in which additional weak signals from 0.03 to 2.0 ppm were observed, likely contributions of phosphorus atoms after transesterification.

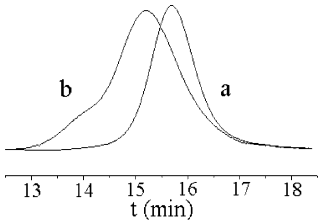


Figure 2. GPC analysis of homopolymer of ϵ-caprolactone (M_w = 20 020) (a) and block copolymer of phosphoester (R = $^iC_3H_7$) with ϵ-caprolactone (M_w = 23 660) (b). Block copolymer was obtained at 4 days after adding phosphoester monomer using A_3 of Al(^{i}OPr)$_3$ as initiator ([CL]:3[A_3] = 200:1).

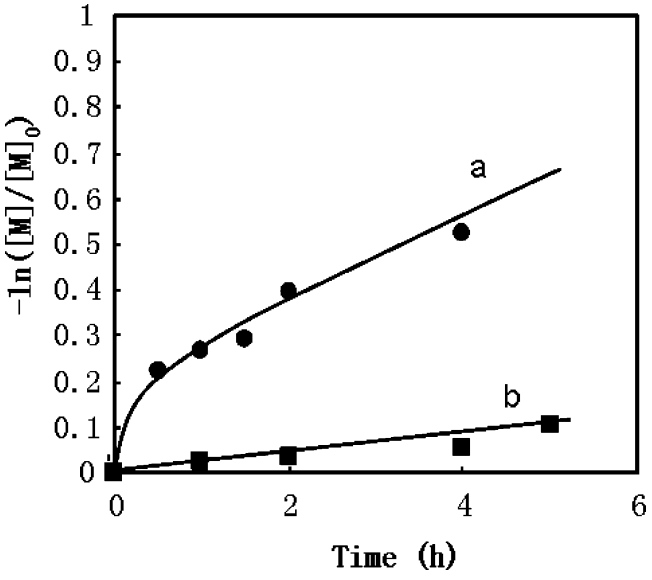


Figure 3. Dependence of the second monomer consumption on the polymerization time. $[M]_0$ = initial monomer concentration and [M] = monomer concentration at selected time. (a) Ethyl side group; (b) isopropyl side group.

We assumed that the rate of propagation of phosphoester block is affected by the structure of pendant group connected to phosphorus. To study this effect, we compared the rate constants of propagation using 2-isopropoxy-2-oxo-1,3,2-dioxaphospholane (with isopropoxy side group) and 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (with ethoxy side group) as the second monomer. As shown in Figure 3, the rate constant was 4.3×10^{-2} L mol^{-1} min^{-1} at 90 °C in toluene when the side group is isopropoxy group, while it increased to 1.6×10^{-1} L mol^{-1} min^{-1} at 50 °C in the same solvent when the side group was replaced with ethoxy group. It is worth pointing out that the ring-opening polymerization of lactones initiated by A_3 has been suggested to proceed through a "coordination−insertion" mechanism.[26] In our experiments, phosphoester monomers might also be polymerized in a similar mechanism due to the structural similarity with lactones. Therefore, the spatial hindrance should be one of the determinants to the polymer chain propagation; then ethoxy group made the coordination easy between aluminum and P═O in comparison with isopropoxy group.

In conclusion, block copolymers of PCL and polyphosphoesters have successfully been synthesized in toluene with trimer of aluminum isopropoxide as an initiator. ^{1}H NMR, ^{13}C NMR, and GPC analysis have confirmed the actual formation of the expected block copolymers. It was also observed that the rate of propagation of phosphate block was affected by the structure of pendant group connected with phosphorus. Since it is possible to replace the pendent groups of polyphosphoester block with other functional groups such as protected amino and carboxyl groups through syntheses of functional phosphoester monomers, these kinds of copolymers are potential for biomedical applications and will be studied and reported in forthcoming papers.

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Supporting Information Available: Synthesis procedure and ^{13}C NMR and ^{31}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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