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Synthesis of Well-Defined Thermoresponsive Polyphosphoester Macroinitiators Using Organocatalysts

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Polyphosphoesters have a high impact in bio-related fields because of their biocompatibility and structural similarities to naturally occurring nucleic acids.[1−3] The phosphoester backbone is degradable through spontaneous hydrolysis; the degradation is accelerated with enzymatic treatment.[4] A variety of synthetic routes for polyphosphoesters have been proposed, including ring-opening polymerization (ROP),[5−7] polycondensation,[8] transesterification,[9,10] and enzymatic polymerization.[11] Although there have been a few reports of synthesizing high molecular weight polyphosphoesters,[12,13] there have been limitations on obtaining high molecular weight with narrow distribution. For reliable properties and advanced applications of polymers, the exploration of novel synthetic processes is needed.

The ROP of cyclic phosphoesters is the most common process used to obtain polyphosphoesters. This is because a variety of polyphosphoesters can be designed in comparison with conventional biodegradable polymers because cyclic phosphoesters are obtained as monomers from the condensation of alcohol and 2-chloro-2-oxo-1,3,2-dioxaphospholane.[14] Using some alcohol compounds, biodegradable macro-cross-linkers[4] and macroinitiators for atom transfer radical polymerization (ATRP)[15] have already been prepared. These polyphosphoesters are building blocks for constructing novel polymer materials.

For the ROP of cyclic phosphoesters, metallic compounds are commonly used as initiators or polymerization catalysts.[5−7,16] Although the polymerization processes are very successful in producing polyphosphoesters, the metal compounds are environmentally sensitive, and a lack of residual metal contaminants is required in biomedical applications. Recently, organocatalysts have been the focus of the modern synthetic processes of polyesters, polycarbonates, and silicones.[17] One of the most successful procedures for making biodegradable polymers is polymerization using guanidine and amidine bases both in bulk and in solution. Nederberg and Hedrick prepared poly(trimethylene carbonate (TMC)) (PTMC) with the base catalysts in the presence of benzyl alcohol.[18] Excellent controlled polymerization conditions were performed with several catalysts, and PTMCs with relatively high molecular weight, narrow distribution, and high yield were obtained. Although organocatalysts have high potency for ROP, they have not been used for the polymerization of cyclic phosphoesters. We report here the first ROP of cyclic phosphoesters using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as an organocatalyst. Compared with polymerization using metallic catalysts, control of the polymerization of cyclic phosphoesters was much less difficult.

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The synthetic routes of poly(2-isopropoxy-2-oxo-1,3,2-dioxaphospholane) (PIPP) and its block copolymer are shown in Scheme 1. According to the new synthetic process, we have succeeded in synthesizing well-defined polyphosphoesters with both a narrow molecular weight distribution and a high molecular weight. Furthermore, block copolymers with 2-methacryloyloxyethylphosphorylcholine (MPC) were synthesized by using PIPP as a macroinitiator. Such well-defined polymer synthesis may be important for obtaining biomimetic and reliable functions because a biopolymer always has an exact molecular weight without any distribution.

IPP and HEBB were synthesized by the previously described method.[15] PIPP was synthesized by ROP using an organocatalyst as an initiator in the presence of HEBB (Scheme 1). In the case of DBU, polymerization was homogeneously performed in a solvent-free condition. In contrast, a small amount of toluene was used for dissolving TBD to make a homogeneous solution. The results of PIPP synthesis are summarized in Table 1. 20 mmol of IPP was first introduced into a polymerization tube under an argon gas atmosphere at 0 °C, and then a given amount of HEBB was added to the tube. Finally, a given amount of organocatalyst was introduced. Polymerization was carried out at 0 °C. The range of molecular weights was approximately $2.0 \times 10^3 - 3.0 \times 10^4$ g/mol by a JASCO gel-permeation chromatography (GPC) system using a calibration curve based on linear polystyrene standards with chloroform as the mobile phase. In every case, the molecular weight distribution was lower than 1.10. Under each condition, the molecular weights of the synthetic polymers agreed with the theoretical values.

Figure 1 shows the M_n versus monomer conversion for the polymerization of IPP by using DBU as a catalyst. The plot of the number-averaged molecular weight (M_n) vs conversion was linear up to 60% conversion. The linearity of the plot suggested that the number of macromolecules in the reaction system was constant during polymerization. The molecular weight distribution of PIPP was narrow and stable during polymerization. The mechanism of ROP with organocatalysts was characterized using ^{1}H NMR by Hedrick and co-workers.[18,19] They indicated that DBU and TBD form hydrogen bonds to the alcohol of an initiator. ROP of IPP with DBU then occurred through a quasi-anionic polymerization mechanism by activation of the alcohol of the initiator. In contrast, the increase in the monomer conversion for the polymerization of IPP between DBU and TBD was significantly different. When TBD was used as a catalyst, the conversion of PIPP reached a level of more than 75% within 20 min. The heightened activity of TBD for the polymerization of lactone and TMC was also observed.[18] TBD has two activation sites in the molecule and is capable of an acyl transfer reaction. From a ^{1}H NMR study, a remarkable shift of the alcohol proton of HEBB at 3.86 ppm was observed in a toluene-d_8 solution containing HEBB and TBD (1:1, 0.05 M); that is, TBD has a hydrogen bond acceptor for the hydroxylic proton of HEBB (see Supporting Information Figure S1). Because the N−H site of the TBD might activate IPP, a ^{1}H NMR analysis of the mixture of TBD and IPP (1:5, 0.05 M) was carried out. The spectra are summarized in Figure 2.

The dashed symbols in Figure 2 represent the shifted signals of the protons of IPP. Although the signal of the original cyclic IPP remained in the solution, ring-opening IPP was also observed. According to previous literature describing ROP of TMC or L-lactide with TBD,[18,19] we assumed that TBD served as a dual activation catalyst for the cyclic phosphoester and initiator. The

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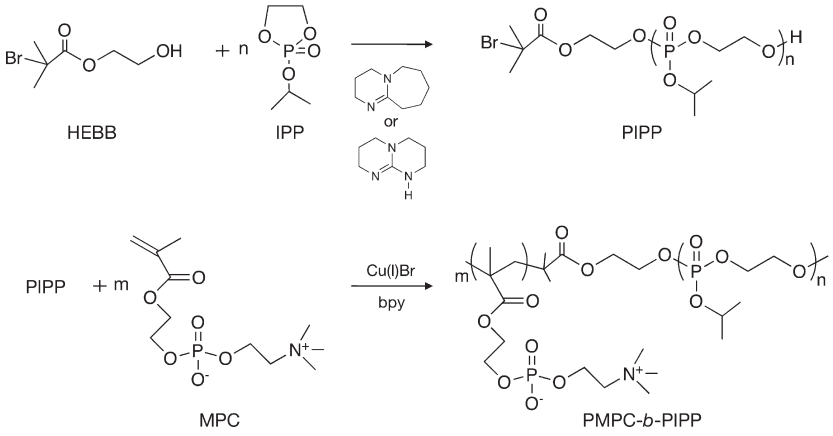
Table 1. Synthetic Results of PIPP

code	catalyst	$[M]_0/[I]$	HEBB (mmol)	catalyst (mmol)	time (min)	conversion (%)	$M_n \times 10^{-3}$	M_w/M_n	$M_{n(Theo)} \times 10^{-3}$
$PIPP_{13}$	DBU	25	0.80	1.20	60	52.8	2.4	1.03	2.2
$PIPP_{32}$	DBU	50	0.40	0.60	90	52.7	4.7	1.07	4.4
$PIPP_{50}$	DBU	100	0.20	0.30	300	50.8	7.7	1.09	8.4
$PIPP_{48}$	TBD	50	0.40	0.20	20	81.2	8.2	1.06	6.7
$PIPP_{77}$	TBD	100	0.20	0.20	20	80.7	13.0	1.09	13.4
$PIPP_{117}$	TBD	150	0.13	0.20	20	75.5	16.9	1.07	18.8
$PIPP_{174}$	TBD	200	0.10	0.20	20	90.3	28.9	1.05	30.0

Scheme 1. Synthetic Routes of Poly(2-isopropoxy-2-oxo-1,3,2-dioxaphospholane) (PIPP) and Poly(2-methacryloyloxyethylphosphorylcholine-*b*-PIPP)



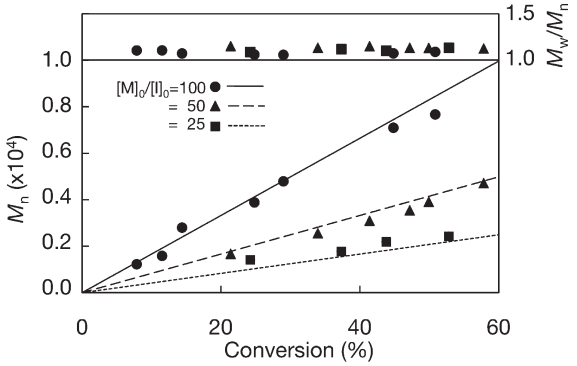


Figure 1. Plot of M_w/M_n and M_n versus monomer conversion for the polymerization of 2-isopropoxy-2-oxo-1,3,2-dioxaphospholane by using 1,8-diazabicyclo[5.4.0]undec-7-ene as a catalyst. Broken lines suggest the theoretical amount of each polymerization condition.

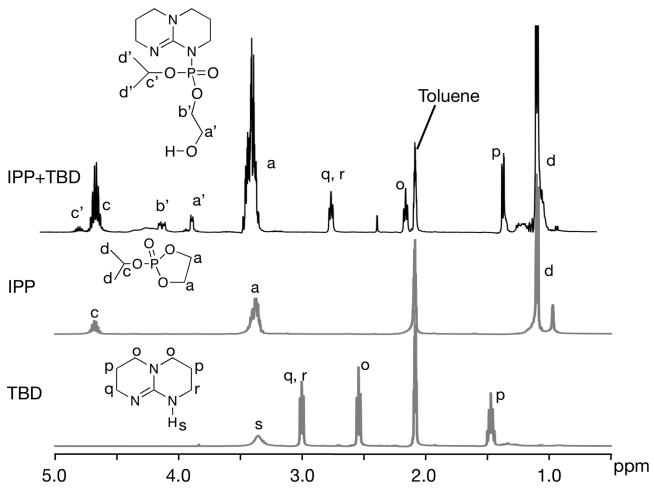


Figure 2. ^{1}H NMR spectra of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 2-isopropoxy-2-oxo-1,3,2-dioxaphospholane (IPP), and their mixture in toluene-d_8. Dashed symbols represent the intermolecular interaction of TBD and IPP in the solution.

N−H site of TBD served as a hydrogen bond donor and might interact with the oxygen of the five-membered ring of IPP. A nucleophilic attack of the imine nitrogen on the phosphorus would then generate TBD aminophosphonate, as shown in Figure 2, following hydrogen-bond activation of the HEBB alcohol, which should facilitate the formation of phosphoester and regeneration of TBD. As expected, every ^{1}H NMR signal was caused by each molecule in the mixture of DBU and IPP (1:1, 0.05 M), and no signals were caused by intermolecular interactions (see Supporting Information Figure S2). DBU only activated HEBB.

The glass transition temperature (T_g) of $PIPP_{77}$, which was determined by differential scanning calorimetry, was −52.7 °C, and that of the highly viscous polymers, summarized in Table 1, was room temperature.

We have recently discovered that aqueous solutions containing polyphosphoesters bearing simple alkyl chains showed LCST-type phase separation behavior.[20,21] The phase separation temperature of polyphosphoesters is influenced by the chemical structure of the side chain and able to control its polarity. Very recently, we synthesized polyphosphoesters bearing enzymatic cleavable chains.[21] The phase separation temperature increased with an increase in the incubation time of the enzyme. Wang and co-workers also observed the thermoresponsivity of polyphosphoesters. They have synthesized well-defined block copolymers of poly(ethylene glycol) and polyphosphoester.[22] The block copolymers can form core−shell type polymeric micelles in an aqueous medium with the effect of temperature caused by self-association of the polyphosphoester block. Although it is clear that polyphosphoester is the new candidate thermoresponsive polymer, its properties have only been partially evaluated. The effect of molecular weight on the cloud point of PIPP has not been discussed. Figure 3 shows the molecular weight dependence of the phase separation temperature of PIPP in phosphate buffered saline (PBS).

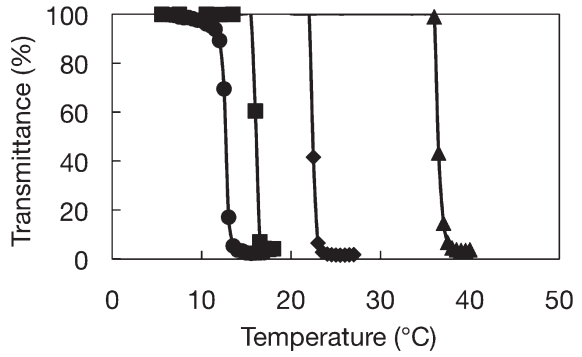


Figure 3. Effect of molecular weight on cloud point of poly(2-isopropoxy-2-oxo-1,3,2-dioxaphospholane) (PIPP) (1 wt %) in PBS: (●) $PIPP_{50(DBU)}$, (■) $PIPP_{48(TBD)}$, (◆) $PIPP_{32(DBU)}$, (▲) $PIPP_{13(DBU)}$.

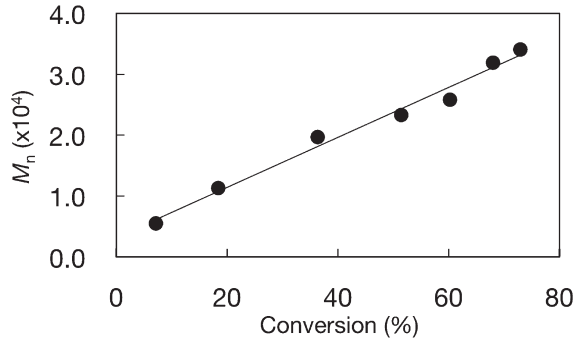


Figure 4. Plot of M_n versus monomer conversion for polymerization of 2-methacryloyloxyethylphosphorylcholine by using a macroinitiator ($PIPP_{77}$).

The cloud point of the polymer solution linearly decreases with an increase in the molecular weight of PIPP. This result indicates that the type of organocatalyst does not influence the phase separation temperature. The phase separation temperature of polyphosphoesters is influenced by the chemical structure of the side chains, the concentration, and the ion strength of the aqueous media.[21] In our previous report, PIPP that was synthesized using triisobutylaluminum as an initiator was not soluble in water even when the molecular weight was less than 1.0×10^4.[15] An uncontrolled reaction might occur when a metallic catalyst was used. Wang reported that long-term polymerization of cyclic phosphoesters with $Sn(Oct)_2$ makes some branch structures with high conversion.[16] In addition, some side reactions might occur in ring-opening polymerization of five-membered cyclic phosphoesters at high temperature.[23] Furthermore, the molecular weight distribution of polyphosphoesters synthesized with an organocatalyst was significantly narrow compared with polymers that used metallic catalysts. The advantages of using organocatalysts can be observed on the synthesis of well-defined polymers with high conversion.

Using $PIPP_{77}$ as a macroinitiator, we synthesized well-defined, biocompatible block copolymers with 2-methacryloyloxyethylphosphorylcholine (MPC)[24] in the presence of copper(I) bromide and 2,2′-bipyridine (bpy), as shown in Scheme 1. M_n and molecular weight distribution of $PIPP_{77}$-*b*-PMPC were measured with a JASCO GPC system with a refractive index detector and size-exclusion columns, using poly(ethylene glycol) (PEG) standard in distilled water containing 10 mM LiBr. The concentration of polymer solution for this measurement was adjusted to below 0.01 wt % to reduce polymer association. Figure 4 shows the dependence, M_n, on conversion for ATRP of MPC from the end of PIPP. The plot of M_n versus monomer concentration was linear up to 80% conversion. The linearity of the plot suggests that the number of polymer molecules remained constant and that polymerization could be controlled on a polymerization time scale. The molecular weight distribution (M_w/M_n) was below 1.5. Although the intermolecular interaction of the block copolymer was too weak to obtain stable polymer associates at this point, it was demonstrated that well-defined block copolymers with narrow molecular weight distributions could be obtained. Recently, it has been also reported that zwitterionic phosphorylcholine showed better stabilization than did PEG.[25] By controlling the structure of the side chains of PIPP to enhance molecular interaction, novel biocompatible nanomaterials might be obtained.

In summary, this study explored a modern synthetic route of polyphosphoesters with the use of organocatalysts. For this synthetic process, various types of alcohols can be used as initiators; that is, the end functionalities of the block copolymers can be controlled.

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Supporting Information Available: Experimental method and ^{1}H NMR spectra representing interactions between organocatalysts and initiators or monomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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