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Facile Synthesis of Clickable, Water-Soluble, and Degradable Polyphosphoesters

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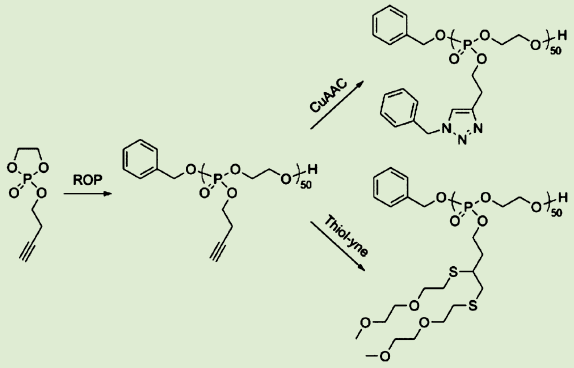
Supporting Information

ABSTRACT: "Click" chemistry is a library of efficient and reliable reactions, which have been used to functionalize various classes of bio- and synthetic macromolecular systems for the incorporation of designed properties and functions. In this report, azide−alkyne Huisgen cycloaddition and thiol-yne reactions, two classical "click" chemistries, were employed to functionalize biodegradable, clickable polyphosphoester homopolymers, and their water-soluble copolymers. A stable alkyne-functionalized phospholane monomer was synthesized, its organocatalyzed polymerization kinetics were evaluated, and the resulting (co)polymers were utilized to develop this facile method that provides the synthesis of clickable, water-soluble, and degradable polyphosphoesters, which can be adapted for various applications.



Biodegradable synthetic polymers have been attracting considerable attention due to their potential for environmental and biological clearance, which allows for many applications, including in medical devices, for instance, in tissue engineering, regenerative medicine, gene therapy, and controlled drug delivery.[1,2] High molecular weight degradable polymers, including polyesters, polycarbonates, and polyphosphoesters, are often prepared by ring-opening polymerization (ROP) of cyclic monomers, which mechanistically offer control over the polymer molecular weights, molecular weight distributions, compositions, and structures. Furthermore, chemical functionalizations of these polymers expands their specific properties to tune their physical, chemical, biological, and mechanical behaviors.[3] Chemical modification of polymers via "click" chemistry has advantages including quantitative conversion, rapid reaction, and high functional group tolerance, with an absence of byproducts and side reactions. A library of chemical reactions has been advanced for the preparation and functionalization of new polymeric materials.[4,5] Recently, several classes of biodegradable polyesters[6−10] and polycarbonates[11−14] bearing "click" functionalities have been synthesized and postfunctionalized. With the increasing breadth of the types of "click" chemistry reactions, several can be identified for combinations with ROP to afford functional degradable polymers, while avoiding incompatibilities with ROP conditions. Although initial systems have involved multistep monomer syntheses, tedious isolations, and limited water solubility,[6−14] a key goal is to increase the efficiency of monomer production and broaden the chemical and physical properties.

Besides polyesters and polycarbonates, polyphosphoesters are attractive for biorelated fields due to their biocompatibility, biodegradability (through hydrolysis that is either spontaneous or catalyzed by certain enzymes), and their structural similarity to nucleic and teichoic acids.[15] The ROP of cyclic phospholane monomers, which are prepared from the condensation of an alcohol and 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP, **1**), is the most common process to obtain well-defined high molecular weight polyphosphoesters. Tailoring of the polyphosphoester structure by manipulation of pendant groups on the pentavalent phosphorus atom enables precise control over the chemical functionalities and topological structures of the polymers.[16] Iwasaki et al. reported the first organocatalyzed ROP of cyclic phospholanes, by using 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), which eliminated the usage of environmentally sensitive metal compounds, to fulfill the requirements of biomedical applications.[17] In this report, we synthesized a new type of reactive polyphosphoester bearing alkynyl groups, **2**, by using organocatalysis for the ROP of an alkynyl-functionalized phospholane monomer, **3**, and investigated the chemical availability of the alkyne groups by employing "click" type azide−alkyne Huisgen cycloaddition[4] and thiol-yne[18,19] reactions, as shown in Scheme 1. In addition, a series of clickable, water-soluble, and degradable polyphosphoester copolymers with tunable solubilities is also reported.

The monomer, butynyl phosphate (BYP, **3**) was synthesized by coupling COP to 3-butyn-1-ol, according to the approach that has been reported for a variety of cyclic phospholane monomers toward the preparation of functional degradable

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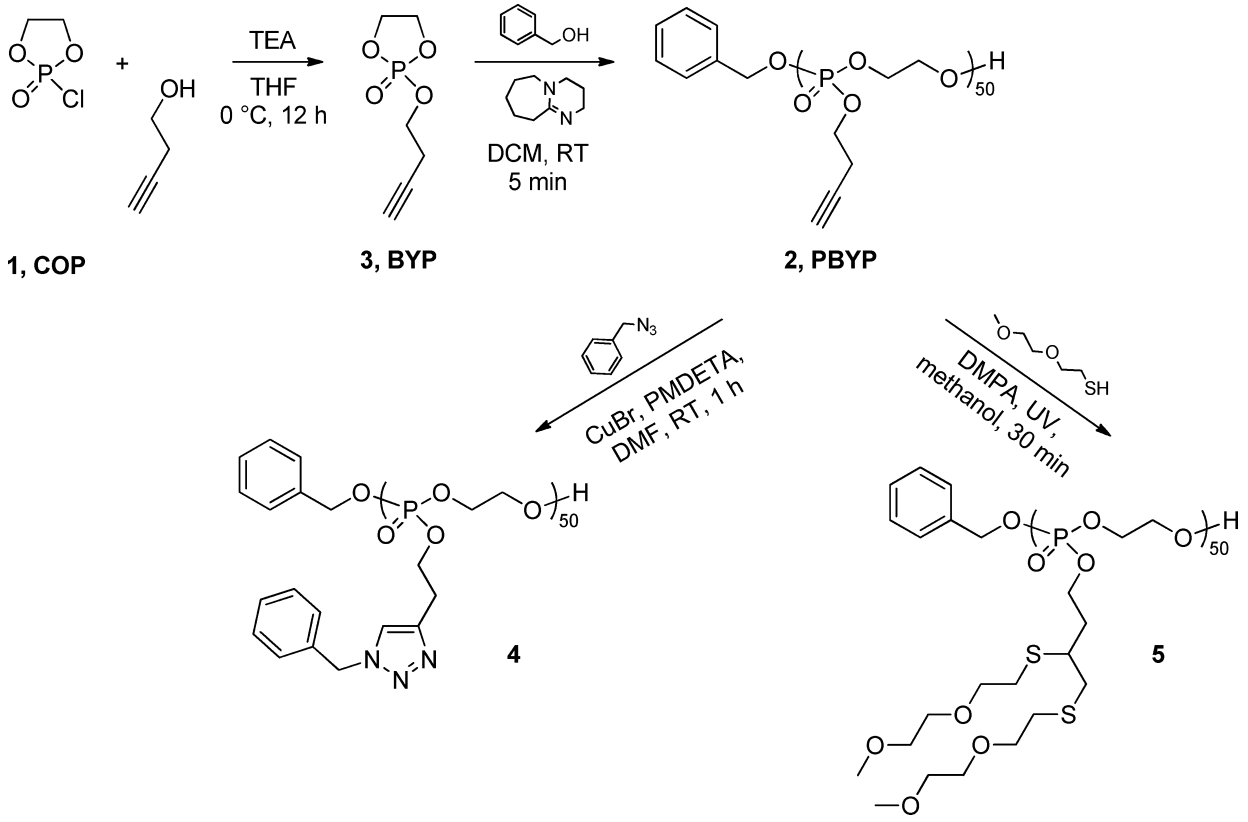
Scheme 1. Synthetic Routes from Monomer, 2-(But-3-yn-1-yloxy)-2-oxo-1,3,2-dioxaphospholane (BYP, 3), Synthesis, to Poly(2-(but-3-yn-1-yloxy)-2-oxo-1,3,2-dioxaphospholane) (PBYP, 2), and Two "Click" Type Reactions



polymers.[20−24] In contrast, initial attempts at the preparation and isolation of the propargyl analog (PAP) was not successful. As monitored by ^{31}P NMR spectroscopy, two major products, among others, were generated during the reaction of propargyl alcohol with COP in the presence of triethylamine (Figure S1). Pure PAP could be obtained by vacuum distillation in only a low yield (<20%). Although the preparation and ROP of PAP, followed by the azide−alkyne Huisgen cycloaddition on the resulting polymers has been reported,[25] in our hands, we suspect that reactions via the S_N2' mechanism might be responsible for the decomposition of the monomer. In fact, in the published work,[25] the expected signal of the terminal acetylene proton is absent or of too low intensity in the ^{1}H NMR spectra provided for PAP-based polyphosphoesters, suggesting loss or partial loss of the alkynyl functionality. For S_N2', unlike ordinary S_N2, the nucleophile attacks indirectly at the electrophilic site but in a conjugate addition over the double or triple bond (as depicted in Scheme S1).[26,27] Because the phosphate group is a good leaving group,[28] it can be expelled even in the absence of a strong nucleophile. To eliminate the potential for S_N2' reaction, a methylene spacer between the phosphate and the propargyl group was incorporated. The resulting product, BYP (**3**), with high yield and purity, as shown in Figure S2, was obtained through a one-step esterification reaction between two commercially available compounds, 3-butyn-1-ol and COP, followed by simple filtration and vacuum distillation. In contrast, most clickable monomers for ROP involve multistep syntheses and tedious isolations.

The ROP of **3** was conducted by using DBU as the catalyst and benzyl alcohol as the initiator. After Iwasaki et al. reported organocatalytic ROP of cyclic phospholane monomer in solvent-free conditions,[17] Yan et al. also reported the ROP from a macroinitiator by using DBU as the catalyst under solvent-free conditions.[29] When employing DBU as the catalyst, the reported monomer conversion reached about 60% after more than 1 h, and the reactions were halted once the magnetic stirrer stopped moving due to high viscosity of the polymerization mixture. To achieve higher monomer conversion, we applied dichloromethane (DCM) as the solvent with a monomer concentration of 1 g/mL. Interestingly, the polymerization under this low viscosity condition proceeded rapidly to high monomer conversion. The conversion of **3** quickly reached over 95% after only 6 min, with good control of the polymerization being retained. The reaction also proceeded faster than reported typically for $Sn(Oct)_2$-catalyzed polymerizations.[15,24,25,30] However, when monomer concentration was lowered to 0.1 g/mL, a high molecular weight polymer was not observed, even after more than 24 h.

We studied the kinetics of this ROP by conducting parallel experiments, which allowed for monitoring of this extremely fast reaction. First, **3** and benzyl alcohol (molar ratio of 100: 1) were premixed in anhydrous DCM and the solution was divided equally into ten portions, to each of which was added solutions of DBU (molar ratio to initiator of 1.5:1) in anhydrous DCM. After being stirred for preset periods of time, the reactions were quenched by addition of acetic acid. The conversion of each individual polymerization was obtained from ^{31}P NMR, while the molecular weight and its distribution were determined by gel permeation chromatography (GPC), calibrated against linear polystyrene standards with DMF as the mobile phase. The linearity of M_n versus monomer conversion

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suggested that the number of macromolecules in the reaction system was constant during polymerization, up to 95% conversion (Figure 1A). The polydispersity indices (PDI)

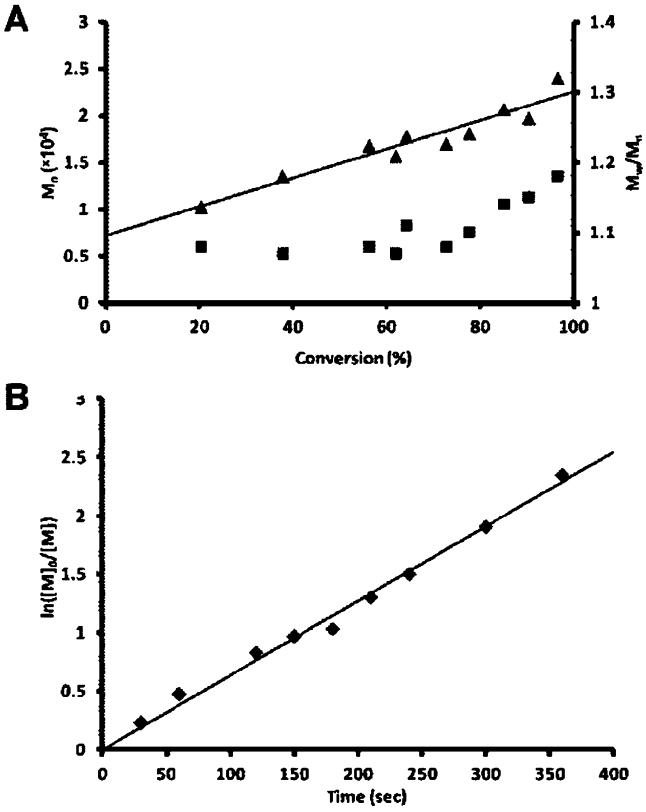

Figure 1. (A) Plot of M_n and M_w/M_n vs monomer conversion for the polymerization of **3** by using DBU as the catalyst and benzyl alcohol as the initiator, obtained from GPC analyses; monomer/initiator/DBU ratio was 100:1:1.5. (B) Kinetic plots of $\ln([M]_0/[M])$ vs time, obtained from ^{31}P NMR spectroscopy data.

were all less than 1.20, and when the conversion was controlled at lower than 80%, even lower PDI values were obtained (<1.10). The increased polydispersity could be attributed to adverse transesterification of the polymer backbone at high monomer conversions.[31] Kinetic plots of $\ln([M]_0/[M])$ versus time showed first order kinetics, characteristic of ring-opening polymerization of **3** (Figure 1B) and suggesting that the rate constant of initiation was more than or equal to the rate constant of propagation.[32]

A series of **2** with different molecular weights was synthesized by controlling monomer to initiator ratios, as summarized in Table S1. The degrees of polymerization calculated from ^{31}P NMR-determined monomer conversion values agreed with those calculated from ^{1}H NMR chain end analyses, based on a comparison of the integration values of the benzyl group chain terminus protons and resonances for protons of the side groups of **2**. In each case, the terminal acetylene proton (2.18−2.04 ppm) was present within each repeat unit, as confirmed by being observed with the correct integration compared to the methylene protons (Figure 2A). The glass transition temperature (T_g) for all samples of **2** was measured to be −35 ± 1 °C, which is attributed to their highly viscous liquid form at room temperature and was independent of chain length over the range of DP_n = 25−100. The high monomer conversion (>98%) and stability of the clickable

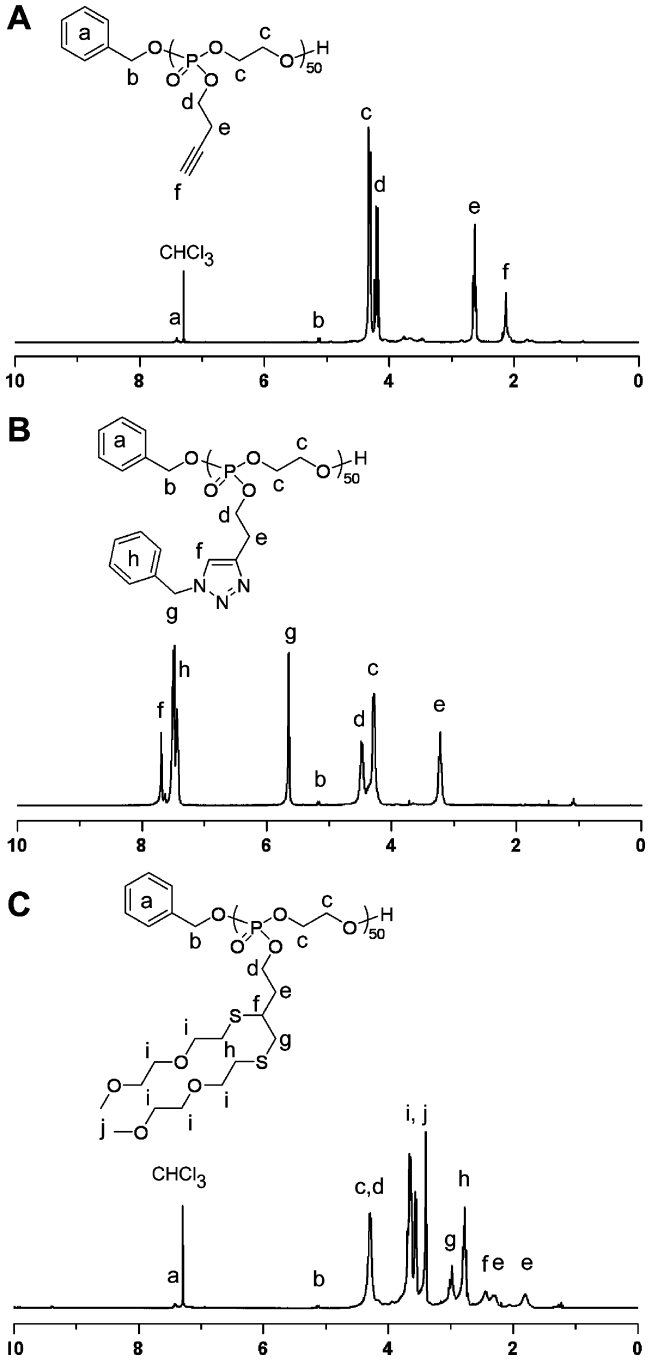

Figure 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$, ppm) of **2** (A) and product polymers after azide−alkyne Huisgen cycloaddition, **4** (B), and thiol-yne reaction, **5** (C).

functionality enabled easy and fast synthesis of **2** with different chain lengths.

To demonstrate the presence and chemical availability of alkyne groups on **2**, we conducted azide−alkyne Huisgen cycloaddition to couple benzyl azide onto this degradable backbone, as shown in Scheme 1. Benzyl azide was chosen because this compound is commercially available, and the resulting polymer was able to be analyzed by GPC and has no proton signals that overlap with resonance frequencies of the reactant polymer. ^{1}H NMR spectroscopy showed 100% conversion from the alkyne group to triazole five-membered rings after a 1 h reaction time, as observed by loss of the

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terminal acetylene proton signal at 2.06 ppm and appearance of the triazole proton resonating at 7.80 ppm. The GPC curve was shifted to higher molecular weight and retained a narrow distribution with a PDI of 1.15 (Figure 3). These results

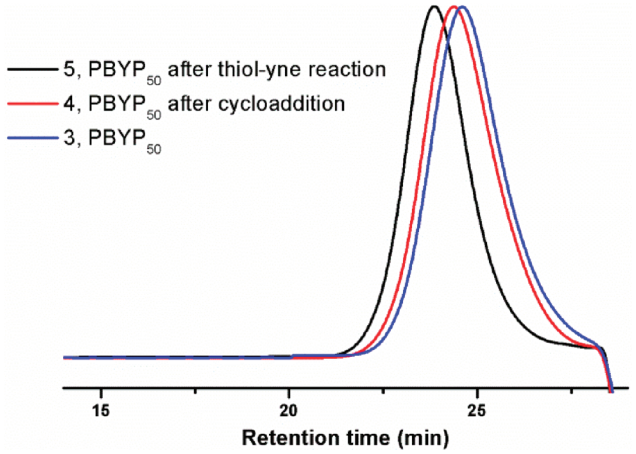


Figure 3. GPC traces of PBYP50 and PBYP50 after two "click" type reaction.

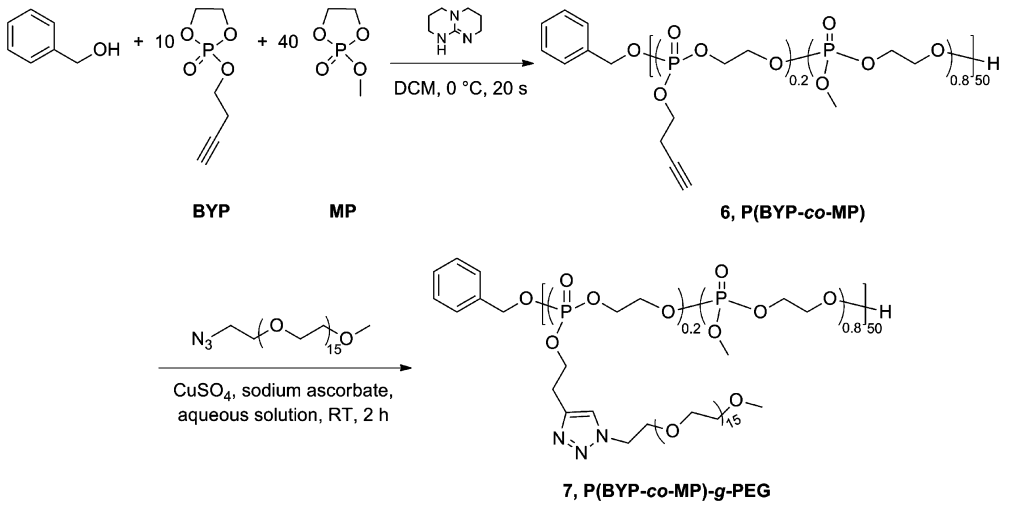
indicated that azide−alkyne Huisgen cycloaddition is compatible with the polyphosphoester backbone. TGA analysis under N_2 atmosphere also showed that benzyl groups and triazoles were attached onto the polymer backbone to make the polymer more thermally stable (Figure S3).

Radical-mediated thiol-yne chemistry, another "click" type reaction, is a robust and versatile method that tolerates a variety of functional groups to achieve high degrees of functionalization on alkyne groups.[33] Here, we utilized this reaction to densely functionalize PBYP, in the manner that two equivalents of thiol are coupled onto one alkyne to form a double addition product with 1,2-regioselectivity by using a chemical radical source. A total of 20 equiv of thiols were used in the radical reaction to avoid chain−chain coupling and ensure high efficiency.[34] A comparison of ^{1}H NMR spectra of PBYP and PBYP after two types of click reactions is shown in Figure 2. The terminal acetylene protons were completely consumed and converted into the corresponding functional groups. The observed diastereotopic splitting of the methylene group agreed with 1,2-regioselectivity of thiol-yne chemistry. The success of the thiol-yne reaction was also demonstrated by GPC analyses (Figure 3), which indicated that radical-mediated thiol-yne did not cause coupling or cross-linking of the backbone.

The polyphosphoester is regarded as a new candidate for thermoresponsive polymer, because its lower critical solution temperature (LCST) can be tuned with changing alkyl side chains of the monomer.[30,35] Incorporation of a hydrophobic monomer, 2-isopropoxy-2-oxo-1,3,2-dioxaphospholane, produced lower LCST, while copolymerization with a more hydrophilic monomer, 2-methyl-2-oxo-1,3,2-dioxaphospholane (MP), resulted in higher LCST. Copolymerizations of BYP with MP at various molar fractions to tune the copolymer water solubilities were performed to overcome the poor water solubility of PBYP, which is barely soluble over the temperature range from 5 to 85 °C. However, DBU was found to be an ineffective catalyst for the copolymerization of BYP and MP. TBD, a stronger base, was, therefore, chosen to catalyze the reaction (Scheme 2). To avoid increasing polydispersity resulting from adverse transesterification (Figure S4 showing GPC traces of reactions quenched after longer copolymerization times), the polymerizations were conducted at 0 °C in DCM at 1 g/mL and quenched by acetic acid solution only 20 s after TBD was added into the monomer and initiator mixture. Even under these conditions, over 98% monomer conversion was achieved.

By employing this ultrafast ROP, a series of copolymers from 10% to 50% BYP incorporation with ten percent increment was synthesized (Table S2). MP and BYP had almost identical conversion in 20 s with TBD as the more active catalyst. We assume, therefore, that all copolymers were statistical copolymers. PBYP10%, PBYP20%, and PBYP30% contained the least amounts of hydrophobic units and were all water-soluble in the temperature range from 5 to 85 °C with no thermoresponsive behaviors observable by UV−vis spectroscopy studies. The copolymers having more than 50% of hydrophobic units were not water-soluble over the same temperature range. Interestingly, PBYP40% exhibited increased solubility with increased temperatures, suggesting an upper

Scheme 2. Schematic Representation of the Copolymerization of BYP and MP and Aqueous Azide−Alkyne Huisgen Cycloaddition



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critical solution temperature (UCST) type phase separation behavior; however, the transition as observed by temperature-ramped UV−vis spectroscopic measurements was quite broad and ill-defined. The aqueous solution-state behavior is unusual in comparison to the reported LCST-type phase behavior of alkyl-functionalized phosphoester copolymers.[30,35]

One of the water-soluble copolymers, incorporated with 20% BYP, was chosen to couple with CH_3O-PEG-azide in aqueous solution by using copper sulfate and sodium ascorbate catalyst system (Scheme 2).[36] GPC traces of the PEGylated copolymer **7** and its precursor **6** (Figure 4) demonstrated that the grafting

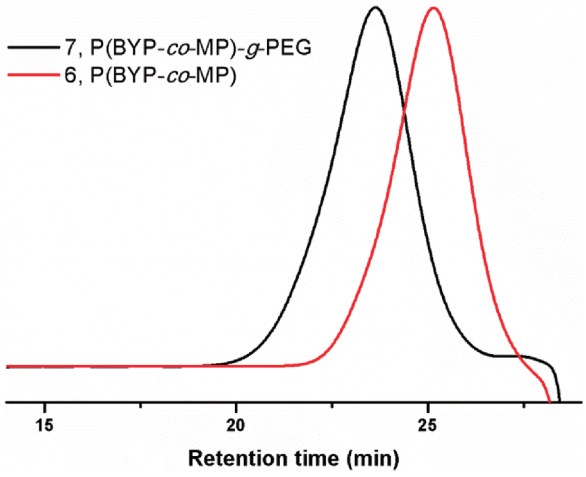

Figure 4. GPC traces of P(BYP-*co*-MP)$_{50}$, **6**, and PEGylated P(BYP-*co*-MP)$_{50}$, **7**, after aqueous azide−alkyne Huisgen cycloaddition.

of PEG in water was successful. In ^{1}H NMR analysis, integration of the proton of the triazole ring (7.69 ppm) to the benzylic protons on the chain end (5.07−5.15 ppm) was 10 to 2, confirming the quantitative conversion from alkyne to triazole groups.

In summary, a stable alkyne-functionalized phospholane monomer was synthesized and its organocatalyzed polymerization kinetics and subsequent azide−alkyne and thiol-yne coupling reactions within the functional polymer materials were explored. By copolymerization of a water-soluble monomer with this monomer, a series of clickable and water-soluble polyphosphoesters was achieved. Although only two types of "click" reactions were demonstrated, others are available to derivatize this alkyne-functionalized polyphosphoester and its water-soluble copolymer with different moieties. Furthermore, with the control offered during the ROP and the ability to conjugate small molecules or polymers onto the backbone, the chemistry developed here has the potential to lead to highly complex and multifunctional polymer structures that can lead then also to complex, functional, and degradable nanostructured materials. Efforts in this direction are being actively pursued.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental section, images, and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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