Synthesis of Amphiphilic ABC 3-Miktoarm Star Terpolymer by Combination of Ring-Opening Polymerization and "Click" Chemistry

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ABSTRACT: Novel biodegradable amphiphilic ABC 3-miktoarm star terpolymers composed of poly(ε-caprolactone) (PCL), monomethoxy poly(ethylene glycol) (MPEG), and polyphosphoester (PPE) were synthesized by a combination of ring-opening polymerization and "click" chemistry. MPEG was first end-capped by epoxide ring, which was opened by sodium azide in the presence of ammonium chloride to give modified MPEG bearing reactive azide and hydroxyl groups (MPEG($-$OH,$-N_3$)). "Click" chemistry was then applied to conjugate α-propargyl-ω-acetyl-poly(ε-caprolactone) and MPEG($-$OH,$-N_3$), resulting in a diblock copolymer of MPEG and PCL with reactive hydroxyl groups at the junction point (MPEG($-$OH)-*b*-PCL), which further initiated ring-opening polymerization of 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP) under the catalytic action of stannous octoate to obtain the desired well-defined (MPEG)(PCL)(PEEP) 3-miktoarm star terpolymers. Such terpolymers and their intermediates were characterized by ^{1}H NMR, FT-IR, and gel permeation chromatography. These polymers are expected to be promising vehicles for drug delivery applications.

Introduction

ABC 3-miktoarm star terpolymers are star-shaped copolymers composed of three chemically and molecularly different polymer chains emanating from a central junction point.[1,2] Previous research showed that ABC 3-miktoarm star terpolymers exhibit quite different microdomain morphology in bulk[3] and self-assembly behavior in solution[4,5] as compared to linear ABC triblock copolymers. Interestingly, they could form multicompartmental micelles as reported by Lodge and co-workers.[6,7] This kind of micelle forms segregated microdomains with different chemical environments that may be used to store various drug molecules in desired ratio.[7] This kind of miktoarm star polymers may have potential application in drug delivery.[8]

A preferred polymeric drug delivery system should be biocompatible, biodegradable, and functionable for introducing chemical reactive groups or biologically relevant and compatible molecules.[9] Poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL) are biocompatible materials that have been widely investigated in biomedical applications. PEG can prevent recognition by the reticuloendothelial system, and thus prevents premature elimination of the micelles from the bloodstream and yields a prolonged systemic circulation.[10] PCL is of great interest in biomedical research because of its low cost, slow degradation, high permeability to many drugs, and nontoxicity.[11] Recently, polyphosphoesters (PPE) have received considerable attention in biomedical applications due to their biodegradability, biocompatibility, and pendant functional ability in addition to a variable backbone structure, thereby allowing introduction of bioactive molecules and modification of its chemical and physical properties.[12,13] For example, amino groups have been introduced into the side chains for condensation of plasmid DNA in gene delivery.[14,15] Other functional groups such as hydroxyl,[16] methacrylate,[17] and bromoisobutylate[18] have also been introduced as pendent groups of polyphosphoesters. In addition, Iwasaki et al. have demonstrated that poly(ethyl ethylene phosphate) and its copolymer with poly(isopropyl ethylene phosphate) can be thermo responsive.[19] We hypothesize that incorporation of biocompatible PEG, PCL, and PEEP segments into a 3-miktoarm star terpolymer would render this polymeric structure attractive for building a versatile drug delivery system.

Miktoarm star polymers have been synthesized since the 1990s.[20] Because of the synthesis and purification difficulties, preparation of ABC 3-miktoarm star terpolymers is still challenging. Until recently, limited strategies have been applied to synthesize miktoarm star terpolymers.[1,2] Three synthetic methods have been mainly used to synthesize ABC 3-miktoarm star terpolymers. The first method uses multifunctional chlorosilane to react subsequently with active chain ends of different living linear polymers.[21,22] The second method utilizes linear polymer with an end group of 1,1-diphenylethylene (DPE) or 1,4-bis(1-phenylethenyl)benzene (DDPE) to react with another living macroanion polymer chain, which generates an anionic species at the junction point of the diblock copolymer. Another monomer is then polymerized from this junction point to obtain the desired miktoarm star terpolymers.[23−25] The third method is using a polymer chain capped at one end by two functional groups that are able to initiate independently the polymerization of two different kinds of monomers.[26,27] In addition, trifunctional initiator has also been utilized for miktoarm synthesis.[28] Yet the first two methods are restricted to a few monomers and contain stringent polymerization conditions. Regarding the third method, it is difficult to design and synthesize a capping molecule or an initiator with multifunctional groups for the different polymerization methods, because different polymerization methods generally require different polymerization conditions. Recently, "click" chemistry has been used extensively in polymer and material sciences to construct polymer architecture because of its high selectivity, near-perfect reliability, and high yield. Most importantly, it is exceptionally tolerant toward a wide range of functional groups and reaction conditions.[29,30] Such advantages have been applied for the synthesis of miktoarm polymers. For example, Monteiro et al. used "click" chemistry and the ATRP technique to synthesize 3-miktoarm star terpolymers.[31,32] In the present work, by a combination of ring-opening polymerization and "click" chemistry, we report

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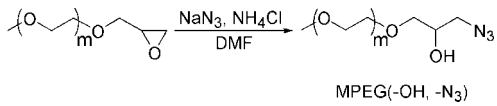
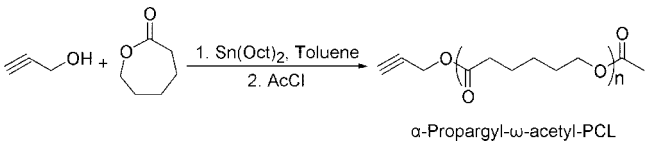
Scheme 1. Synthesis Route of MPEG(−OH,−N_3)



Scheme 2. Synthesis Route of α-Propargyl-ω-acetyl-PCL



a facile and useful method to synthesize ABC 3-miktoarm star terpolymers of MPEG, PCL, and PPE with well-defined structures.

Experimental Section

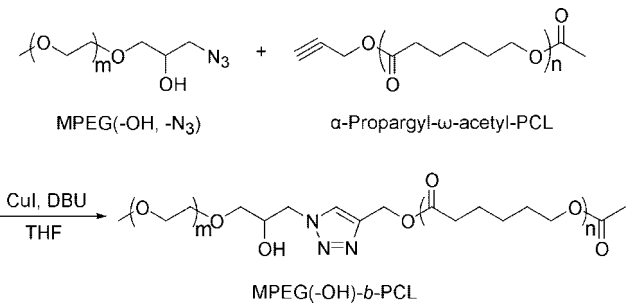
Materials. 2-Ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP) was synthesized by a method described previously[33] and distilled under reduced pressure just before use. Monomethoxy poly(ethylene glycol)s (MPEG, M_n = 750, 2000, 5000 g/mol, Acros Organics, Belgium) were dried by azeotropically distillation from anhydrous toluene. Epichlorohydrin (ECH) and ε-caprolactone (ε-CL) (Acros Organics, 99%) were dried over calcium hydride for 48 h at room temperature, followed by distillation under reduced pressure just before use. Stannous octoate ($Sn(Oct)_2$) (Sinopharm Chemical Reagent Co., Ltd., China) was purified according to a method described in the literature.[34] Acetyl chloride (AcCl) was distilled just before use. Triethylamine (TEA) was refluxed with phthalic anhydride, potassium hydroxide, and calcium hydride in turn and distilled just before use. Tetrahydrofuran (THF) and toluene were refluxed over potassium−sodium alloy under N_2 atmosphere and distilled just before use. Other reagents were used as received.

Synthesis of MPEG(−OH,−N_3) (Scheme 1). First, three α-methoxy-ω-epoxypoly(ethylene glycol)s with different molecular weights were synthesized according to the literature.[35] MPEG(−OH,−N_3) was synthesized by reaction of α-methoxy-ω-epoxypoly(ethylene glycol) with sodium azide in the presence of ammonium chloride as shown in Scheme 1. Typically, α-methoxy-ω-epoxypoly(ethylene glycol) (1.33 mmol) was dissolved in DMF (5 mL), and then sodium azide (3.99 mmol) and ammonium chloride (3.99 mmol) were added to the mixture and stirred at 50 °C for 36 h. After removal of DMF under reduced pressure, the residue was dissolved in dichloromethane and filtered to remove insoluble impurities, followed by precipitation in cold diethyl ether. The product denoted as $MPEG_{750}$(−OH,−N_3) (subscript represents the number average molecular weight of the raw MPEG) was collected and dried under vacuum overnight with a yield of ca. 85%. Other MPEG-(−OH,−N_3)s were prepared with a similar method.

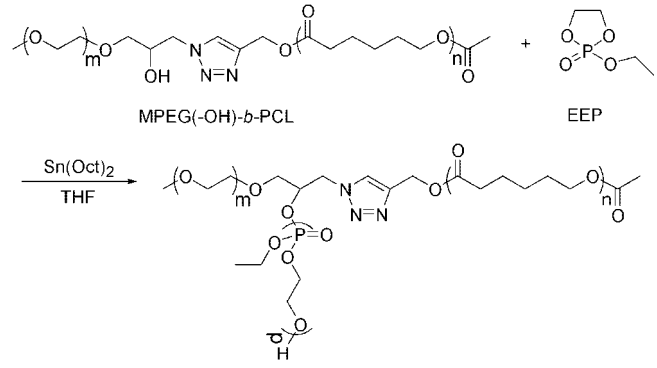
Synthesis of α-Propargyl-ω-acetyl-poly(ε-caprolactone) (Scheme 2). α-Propargyl-ω-acetyl-PCL was synthesized in two steps. First, propargyl-terminated PCL was obtained by ring-opening polymerization of ε-CL under the co-initiation of propargyl alcohol and $Sn(Oct)_2$. The polymerization was performed in a glovebox with a water content of less than 0.1 ppm. In a typical procedure, propargyl alcohol (0.070 g, 1.25 mmol) and ε-CL (10 g, 87.6 mmol) were added to freshly dried toluene (50 mL) in a flask, and then $Sn(Oct)_2$ (0.254 g, 0.63 mmol) was added and the solution was stirred at 80 °C for 4 h. The mixture was concentrated under reduced pressure. After precipitation in cold diethyl ether, the polymer was obtained and dried under vacuum overnight with a yield of ca. 67%. Other propargyl-terminated PCLs were prepared with a similar method.

The hydroxyl end group of the propargyl-terminated PCL was then blocked by acetyl chloride. In a typical example, propargyl-terminated PCL2 (1.0 g, 0.18 mmol) was azeotropically distilled from 50 mL of toluene (removing about 30 mL of toluene), followed by introduction of triethylamine (TEA) (0.036 g, 0.36 mmol) via a syringe. Acetyl chloride (AcCl) (0.028 g, 0.36 mmol) in 5 mL of toluene was added dropwise to the above solution at 0 °C, and the mixture was further stirred overnight. Thereafter, insoluble salt was filtered off, and the solution was concentrated under reduced pressure. The polymer was collected by precipitation in cold diethyl ether, filtration, and dried under vacuum overnight with a yield of ca. 81.5%. Other propargyl-terminated PCLs were end-capped with a similar method.

Scheme 3. Synthesis Route of MPEG(−OH)-*b*-PCL



Scheme 4. Synthesis Route of (MPEG)(PCL)(PEEP) Miktoarm Terpolymers



Synthesis of MPEG(−OH)-*b*-PCL by "Click" Chemistry (Scheme 3). In a typical procedure, α-propargyl-ω-acetyl-PCL2 (0.50 g, 8.80 × 10^{-5} mol) and $MPEG_{750}$(−OH,−N_3) (M_n = 850, 0.15 g, 2 equiv) were dissolved in 5 mL of anhydrous tetrahydrofuran, the mixture was degassed by five freeze−pump−thaw cycles, and then CuI (0.005 g, 0.3 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.270 g, 20 equiv) were added in a glovebox. The solution was stirred at 35 °C for 24 h. After the reaction, the solution was passed through a neutral alumina column to remove copper catalyst. The solution was concentrated and poured into excess water (20 mL) and was dialyzed extensively using Spectra/Por dialysis tubing (MWCO = 15 000). The purified diblock copolymer was obtained by lyophilization.

Synthesis of ABC 3-Miktoarm Star Terpolymers (MPEG)(PCL)(PEEP) (Scheme 4). Typically, $MPEG_{750}$(−OH)-*b*-PCL2 (0.10 g, 0.015 mmol) was azeotropically distilled from toluene (20 mL) and dried under vacuum overnight. EEP (0.233 g, 1.53 mmol) and $Sn(Oct)_2$ (0.003 g, 0.008 mmol) were then added, and the polymerization was carried out at 35 °C in THF (2 mL) for 3 h in a glovebox. The solution was concentrated, and the residue was precipitated into cold diethyl ether containing 10% methanol (v/v). After filtration, miktoarm star terpolymer was obtained by vaccuum-drying overnight.

Characterization Methods. ^{1}H NMR spectra were recorded on a Bruker AV300 NMR spectrometer (300 MHz) at room temperature with $CDCl_3$ as solvent. FT-IR spectra were measured on a Bruker Vector 22 Fourier transform infrared spectrometer at wavenumbers 500−4000 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/

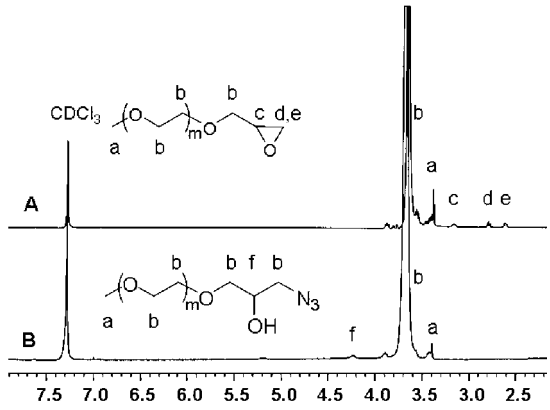


Figure 1. ^{1}H NMR spectra of $MPEG_{2000}$-epoxide (A) and $MPEG_{2000}(-OH,-N_3)$ (B) (in $CDCl_3$, ppm).

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 Waters Styragel High Resolution columns (HR4, HR2, HR1, effective molecular weight range 5000−500 000, 500−20 000, and 100−5000, respectively). 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 at 40 °C. Monodispersed polystyrene standards with a molecular weight range 1310−(5.51×10^4) were used to generate the calibration curve.

Results and Discussion

Synthesis of MPEG(−OH,−N_3) (Scheme 1). MPEG with number average molecule weight (M_n) of 750, 2000, and 5000 ($MPEG_{750}$, $MPEG_{2000}$, $MPEG_{5000}$) were used in this work. The hydroxyl end group of MPEG was first converted to epoxide group according to the literature.[35] Figure 1A shows the representative ^{1}H NMR spectrum of α-methoxy-ω-epoxypoly(ethylene glycol)$_{2000}$ ($MPEG_{2000}$-epoxide, subscript represents the number average molecular weight of the raw MPEG). The signals at 2.62, 2.79, 3.15 ppm are assigned to the protons of the epoxide ring as labeled in Figure 1A, indicating that the reactive epoxide group has been introduced to the $MPEG_{2000}$. By comparing the integral of proton signal of the epoxide ring at 2.79 ppm (d) to that of the methylene protons of $MPEG_{2000}$ at 3.62 ppm (b), the end-capping efficiency was estimated to be about 90.9%. End-capping efficiencies of $MPEG_{750}$ and $MPEG_{5000}$ were 90.3% and 95.0%, respectively.

Subsequently, the epoxide ring was opened by sodium azide in the presence of ammonium chloride to generate $MPEG(-OH,-N_3)$ with both azide and hydroxyl groups. This approach has recently been employed by Matyjaszewski et al. to produce azide-functionalized poly(glycidyl methacrylate-*co*-methyl methacrylate) polymers.[36] Figure 1B shows the typical ^{1}H NMR spectrum of $MPEG_{2000}(-OH,-N_3)$ in $CDCl_3$. It is noteworthy that the signals of the epoxide ring in Figure 1A (c, d, e) have disappeared completely, indicating that the epoxide ring has been opened by sodium azide. The peak at 4.25 ppm (f) should be attributed to the proton of methine proton of $-C\underline{H}OH$, and the signal of methylene protons of $-C\underline{H}_2N_3$ is overlapped with that of methylene protons of MPEG backbone according to the literature.[35,37]

FT-IR measurements were performed to further confirm the formation of $MPEG_{2000}(-OH,-N_3)$. As shown in Figure 2, the appearance of an absorption peak at 2099 cm^{-1} is clearly observed, which corresponds to the vibration frequency of the azide group.[36]

Synthesis of α-Propargyl-ω-acetyl-PCL (Scheme 2). The propargyl-terminated PCL was first synthesized in solution using propargyl alcohol as the initiator and $Sn(Oct)_2$ as the catalyst. The reaction was performed in toluene at 80 °C according to the literature.[38] Three different monomer/initiator ratios were utilized to obtain propargyl-terminated PCL and achieve different molecular weights. Detailed information is listed in Table 1.

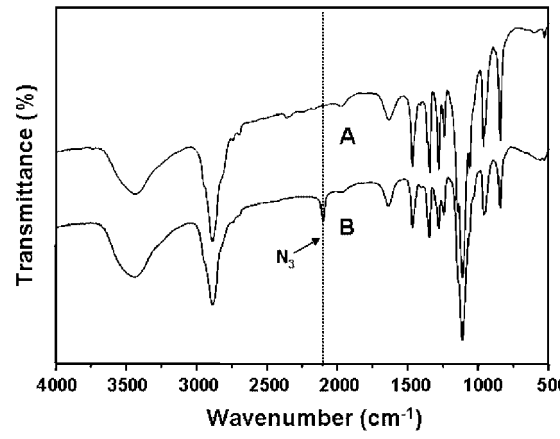


Figure 2. FT-IR spectra of $MPEG_{2000}$-epoxide (A) and $MPEG_{2000}(-OH,-N_3)$ (B).

Table 1. Characteristics of α-Propargyl-ω-acetyl-poly(ε-caprolactone)

code	$[M]_0/[I]_0$[a]	M_w/M_n[b]	DP[c]	M_n[c]
PCL1	30	1.08	15	1710
PCL2	70	1.10	49	5590
PCL3	125	1.08	104	11 860

[a] $[M]_0$ and $[I]_0$ are the initial concentrations of ε-CL and propargyl alcohol, respectively. [b] Determined by GPC. [c] Calculated on the basis of ^{1}H NMR results.

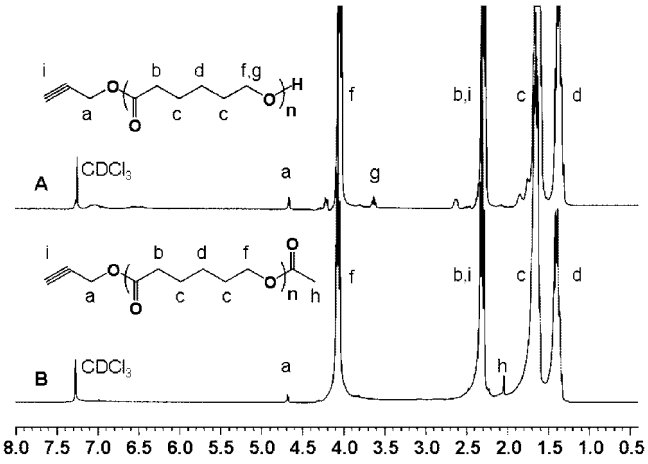


Figure 3. ^{1}H NMR spectra of propargyl-terminated poly(ε-caprolactone) (A) and α-propargyl-ω-acetyl-poly(ε-caprolactone) (B) (in $CDCl_3$, ppm).

The existence of propargyl group is verified by a typical ^{1}H NMR spectrum of the PCL2 as shown in Figure 3A. Resonance at 4.68 ppm (a) is the characteristic signal of the methylene protons of propargyl group ($HC{\equiv}CC\underline{H}_2-$), while resonance of the alkynyl proton (i) is overlapped with that of methylene protons of PCL at 2.35 ppm (b). The triplet at 3.65 ppm (g) is assigned to the PCL methylene protons conjoint with the hydroxyl end group. The degree of polymerization (DP) of PCL can be calculated by the integration ratio of signals at 4.07 ppm (f) of the PCL repeat units and that of signal at 3.65 ppm (g). The DP of PCL1, PCL2, and PCL3 are 15, 49, and 104, respectively, as summarized in Table 1. It should be noted that all of the propargyl-terminated PCL polymers possess a low

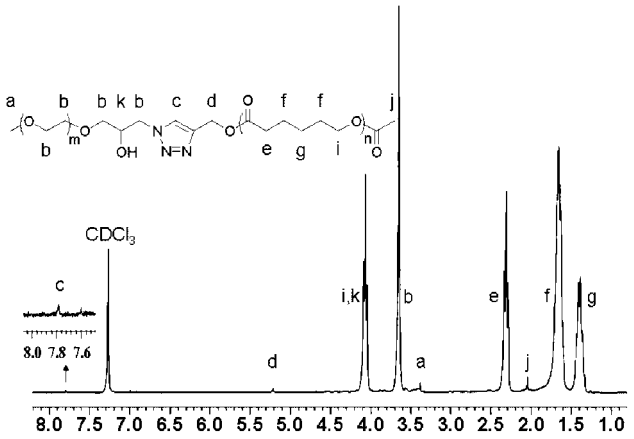


Figure 4. ^{1}H NMR spectrum of $MPEG_{2000}$(−OH)-*b*-PCL2 (in $CDCl_3$, ppm).

polydispersity index (PDI = 1.08−1.10) as determined by GPC analysis.

Because propargyl-terminated PCL contains a reactive hydroxyl end group that can also initiate ring-opening polymerization of EEP,[39] it will interfere with the final procedure of miktoarm terpolymer synthesis. We blocked the hydroxyl end group using acetyl chloride according to a modified procedure as reported previously.[40] From the ^{1}H NMR spectrum shown in Figure 3B, it is clear that the resonance at 3.65 ppm (g) in Figure 3A assigned to methylene protons of PCL conjoint with hydroxyl end groups disappeared completely after end-capping, while a new resonance at 2.03 ppm (h) assigned to methyl protons of acetyl group appeared. Furthermore, the integral of h is in well agreement with the theoretical result, indicating the successful and efficient end-capping of the hydroxyl group of propargyl-terminated PCL.

Synthesis of MPEG(−OH)-*b*-PCL by Click Reaction (Scheme 3). Herein, "click" chemistry was utilized to couple α-propargyl-ω-acetyl-PCL with MPEG(−OH,−N_3) to generate MPEG(−OH)-*b*-PCL block copolymer bearing a reactive hydroxyl group at the junction point for further ring-opening polymerization of EEP. A mild condition with CuI as the catalyst, DBU as the ligand, and THF as the solvent was used according to the literature.[41] Considering that not all of the MPEG molecules were modified with azide group, excess MPEG(−OH,−N_3) was used to react with α-propargyl-ω-acetyl-PCL. Unreacted MPEG(−OH,−N_3) and unmodified MPEG were then removed by subjecting the product to dialysis. In the ^{1}H NMR spectrum shown in Figure 4, all of the protons of MPEG and PCL segments can be assigned. More importantly, resonances at 7.80 ppm (c) and 5.20 ppm (d) are obvious, which should be assigned to the protons of the 1,2,3-trizole ring and the methylene protons of PCL conjoint to the 1,2,3-trizole ring, and this demonstrated the successful performance of the click reaction. From the GPC profiles in Figure 5, we clearly observed that GPC chromatography of $MPEG_{750}$(−OH)-*b*-PCL2 shifts toward high molecular weight direction as compared to that of PCL2 homopolymer and $MPEG_{750}$(−OH,−N_3), while neither PCL2 nor $MPEG_{750}$(−OH,−N_3) traces were found. In addition, by comparing the integral of signals b and i in the ^{1}H NMR spectrum shown in Figure 4, the ratio of protons is in agreement with the theoretical value, verifying the unique existence of $MPEG_{750}$(−OH)-*b*-PCL diblock copolymer. It should be noted that MPEG may contain a small portion of impurities with higher molecular weights or with double hydroxyl end groups, which may contribute to the small shoulder in the GPC spectrum of $MPEG_{750}$(−OH)-*b*-PCL2 block copolymer. The PDI of these diblock copolymers are narrow, and detailed information of the

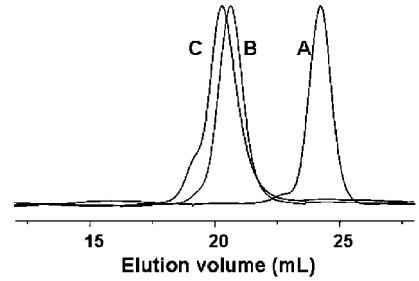


Figure 5. GPC curves of $MPEG_{750}$ (A), PCL2 (B), and $MPEG_{750}$(−OH)-*b*-PCL2 (C).

Table 2. Characteristics of MPEG(−OH)-*b*-PCL Diblock Copolymers

code	M_w/M_n[a]	M_n[b]	yield (%)
$MPEG_{750}$(−OH)-*b*-PCL2	1.13	6360	58.6
$MPEG_{750}$(−OH)-*b*-PCL3	1.15	12 610	58.7
$MPEG_{2000}$(−OH)-*b*-PCL2	1.13	7390	66.7
$MPEG_{2000}$(−OH)-*b*-PCL3	1.16	13 670	62.7
$MPEG_{5000}$(−OH)-*b*-PCL1	1.08	6450	19.1
$MPEG_{5000}$(−OH)-*b*-PCL2	1.15	10 320	63.4

[a] Determined by GPC. [b] Calculated on the basis of ^{1}H NMR results.

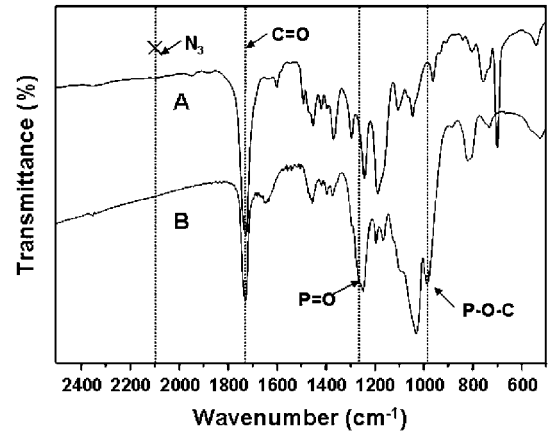


Figure 6. FT-IR spectra of $MPEG_{2000}$(−OH)-*b*-PCL2 (A) and ($MPEG_{2000}$)(PCL2)(PEEP) (B).

obtained polymers has been summarized in Table 2. These results demonstrate the efficient coupling efficiency of "click" chemistry. The molecular weights of MPEG(−OH)-*b*-PCL were calculated from the ^{1}H NMR spectra by the equation: $M_{n,NMR}$(MPEG-*b*-PCL) = $I_b/2I_g \times DP_{NMR}(PCL) \times 44M_{n,NMR}(PCL)$, where I_b and I_g are the integral values of the resonances at 3.62 and 1.35 ppm, respectively, 44 is the molecule weight of the repeating unit of MPEG, and DP_{NMR} (PCL) is the degree of polymerization of PCL calculated by ^{1}H NMR.

FT-IR measurement was also used to characterize the resultant MPEG(−OH)-*b*-PCL diblock copolymer, and the result is shown in Figure 6A. As compared to the FT-IR spectrum of MPEG(−OH,−N_3) in Figure 2B, it is clearly observed that the absorption peak at 2099 cm^{-1} corresponding to the vibration frequency of the azide group disappeared completely after the click reaction. Meanwhile, a strong absorption at 1726 cm^{-1} contributing to the C═O stretching of PCL block is observed. Combined with the proofs of GPC and ^{1}H NMR, it can be concluded that the formation of MPEG(−OH)-*b*-PCL copolymer by "click" chemistry is successful.

Synthesis of Miktoarm Star Terpolymers of (MPEG)(PCL)(PEEP) (Scheme 4). Linear PCL and PPE block copolymers have been synthesized in our laboratory previously.[39] The polymerization was carried out by using an alcohol/$Sn(Oct)_2$

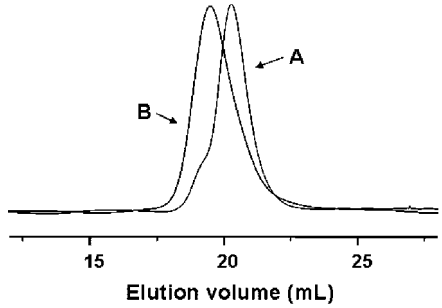


Figure 7. GPC curves of precursor diblock copolymer $MPEG_{750}$(−OH)-*b*-PCL2 (A) and miktoarm star terpolymer ($MPEG_{750}$)(PCL2)(PEEP) (B).

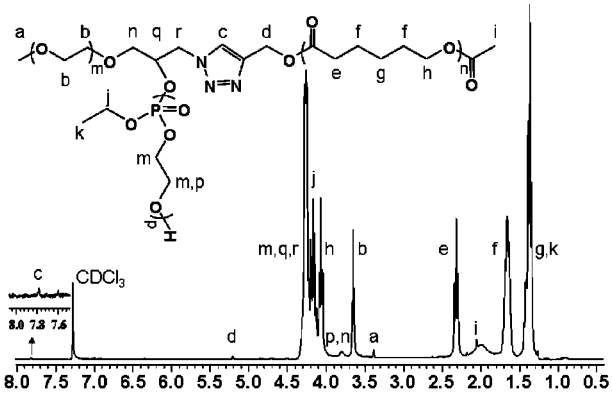


Figure 8. ^{1}H NMR spectrum of miktoarm star terpolymer ($MPEG_{750}$)(PCL2)(PEEP) (in $CDCl_3$, ppm).

co-initiation system. In this work, we used secondary alcohol as initiator for the ring-opening polymerization of EEP using $Sn(Oct)_2$ as catalyst. No miktoarm star polymers containing polyphosphoester (PPE) have been reported previously. The hydroxyl group at the junction point of MPEG(−OH)-*b*-PCL block copolymer was utilized to initiate the polymerization of EEP under the catalysis of $Sn(Oct)_2$ to obtain (MPEG)(PCL)(PEEP) miktoarm star terpolymers. We observed a tailing at high elution volumes in its GPC curve when we precipitated the polymer just in diethyl ether, likely due to the presence of homo PEEP polymer, which was completely removed by precipitation in diethyl ether containing 10% methanol (v/v). A typical GPC curve of ($MPEG_{750}$)(PCL2)(PEEP) was compared to its diblock copolymer precursor in Figure 7. The GPC curve of ($MPEG_{750}$)(PCL2)(PEEP) shifts to the higher molecular weights direction as compared to that of the $MPEG_{750}$(−OH)-*b*-PCL2 precursor, although the PDI increased slightly.

Successful formation of the terpolymers was further evidenced by ^{1}H NMR analysis as shown in Figure 8. Besides the resonances assigned to the protons of the diblock copolymer precursor, characteristic signals of PEEP segments were observed at 1.37 (k), 4.18 (j), and 4.26 ppm (m), which should be assigned to the pendent methyl ($-CH_2C\underline{H}_3$), methylene ($-OC\underline{H}_2CH_3$) protons, and methylene protons ($-POC\underline{H}_2-C\underline{H}_2O-$) of PEEP backbone, respectively. The peak at 3.8 ppm should be assigned to the methylene protons conjoint to hydroxyl end groups of PEEP block (p). The resonance of methylene protons next to the junction point (n) shifts to higher ppm, and it might overlap with that of protons p. The broad peak at around 2.0 ppm is likely due to contaminated water. The average DP of PEEP segments were calculated according to the DP of PCL segments by the following equation: $DP_{NMR}(PEEP) = (2(I_{gk} - I_e)/(3I_e)) \times DP_{NMR}(PCL)$, in which I_{gk} and I_e are the integrals of resonances at 1.37 and 2.30 ppm, respectively, while $DP_{NMR}(PCL)$ is the degree of polymerization of PCL. The information of miktoarm star terpolymers (MPEG)-(PCL)(PEEP) is summarized in Table 3. Furthermore, the FT-IR spectrum shown in Figure 6B confirmed the formation of (MPEG)(PCL)(PEEP) miktoarm star terpolymer as well. As compared to the FT-IR spectrum of the diblock copolymer precursor, the absorbances at 1248 and 986 cm^{-1} are the characteristic contribution of *P*═O and P−O−C stretching due to the presence of PEEP segment.

Table 3. Characteristics of the ABC Miktoarm Star Terpolymers

code	$[M]_0/[I]_0$[a]	M_n[b]	M_w/M_n[b]	DP[c]
($MPEG_{750}$)(PCL2)(PEEP)	100	19 540	1.28	53
($MPEG_{750}$)(PCL3)(PEEP)	25	19 740	1.23	16
($MPEG_{2000}$)(PCL2)(PEEP)	75	15 820	1.22	31
($MPEG_{2000}$)(PCL3)(PEEP)	25	20 290	1.45	17
($MPEG_{5000}$)(PCL1)(PEEP)	100	16 510	1.25	48
($MPEG_{5000}$)(PCL2)(PEEP)	100	26 760	1.42	45

[a] $[M]_0$ and $[I]_0$ are the initial concentrations of EEP and MPEG(−OH)-*b*-PCL, respectively. [b] Determined by GPC. [c] DP is the degree of polymerization of PEEP segments calculated on the basis of ^{1}H NMR spectra.

Conclusion

Amphiphilic ABC 3-miktoarm star terpolymers composed of MPEG, PCL, and PPE were synthesized by combination of ROP and "click" chemistry. GPC, NMR, and FT-IR analyses demonstrated the proper structure and indicated that all of the reactions were controllable, leading to 3-miktoarm star polymers with controlled molecular structure and relative low polydispersity. Therefore, the length of each arm of the ABC 3-miktoarm star terpolymers can be easily tuned. These biocompatible, biodegradable ABC 3-miktoarm star terpolymers with MPEG, PPE, and PCL segments would be attractive for building a versatile drug delivery system.

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