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Synthesis of biocompatible tadpole-shaped copolymer with one poly(ethylene oxide) (PEO) ring and two poly(ε-caprolactone) (PCL) tails by combination of glaser coupling with ring-opening polymerization

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ABSTRACT

The biocompatible tadpole-shaped copolymers [cyclic-poly(ethylene oxide) (PEO)]-*b*-[linear poly(ε-caprolactone) (PCL)]$_2$ [(***c*-PEO)-*b*-PCL$_2$**] with one PEO ring and two PCL tails were synthesized by combination of glaser coupling with ring-opening polymerization (ROP). First, a linear PEO precursor with two alkyne groups at the chain terminal and two hydroxyl groups at the chain middle was prepared by ROP of EO monomer and the following transformation of functional groups. Then, cyclic PEO with two hydroxyl groups at the same site was obtained by the "Glaser" cyclization. Finally, the hydroxyl groups on cyclic PEO directly initiated the ROP of ε-CL monomer to produce the target copolymers (***c*-PEO)-*b*-PCL$_2$**. The target copolymers and intermediates were all well characterized by GPC, MALDI-TOF MS, ^{1}H NMR and FT-IR.

1. Introduction

Since the properties of polymers are inherently dependent on their architectures, tailored control of polymer architectures has always attracted attention from polymer chemists [1]. Up to now, polymers with various kinds of architectures have been synthesized, including linear [2,3], star-shaped [4–7], grafted [8–14], hyperbranched [15–18], dendrimer [19–22] and cyclic polymers [23–39]. These increasing diversity in polymer architectures has offered opportunities in understanding the relationship of architectures with properties, and developing novel polymer materials with unprecedented properties and functions. Compared with other copolymers, cyclic polymers have been less studied due to the limited accessibility of model compounds. Therefore, the synthesis of cyclic polymers is still an interesting subject for polymer chemists.

The tadpole-shape is a kind of appealing topology, in which one macrocycle is connected with one or more tails. It was discovered that a certain bacterial peptide possessing the tadpole-shape topology adopts a unique folded structure by threading the tail chain into the loop segment [40–42]. At the time being, a few examples of tadpole-shaped polymers with different compositions and architectures have been reported [23–31]. For example, Li et al. reported the synthesis of amphiphilic tadpole-shaped polymers (cyclic polystyrene)-*b*-poly(ethylene oxide) [(*c*-PS)-*b*-PEO] via the "click" cyclization of the linear copolymer PS-*b*-PEO, which contains a alkyne group at the junction point and an azide group at the PS chain end [29]. Recently, Liu et al reported the synthesis of amphiphilic tadpole-shaped copolymer [cyclic-poly(N-isopropylacrylamide)]-*b*-poly(ε-caprolactone) [(*c*-PNIPAM)-*b*-PCL] and investigated the application of micellar assemblies as controlled release drug nanocarriers [25]. Tezuka et al reported the synthesis of unusual topological two-tail tadpole-shaped poly(tetrahydrofuran)s [poly(THF)s] by an electrostatic self-assembly and covalent fixation process [28]. Although much effort has been made, reports of tadpole-shaped polymers, especially biocompatible those, are still rare.

Biocompatible copolymers have been a subject of special attention due to their potential applications in drug delivery, tissue engineering and diagnostic biosensors [43–46]. Among them, the copolymers containing hydrophilic PEO and hydrophobic PCL segments have been extensively studied due to the biocompatibility, hydrophilicity and low protein absorption of PEO, and the biocompatibility and biodegradability of PCL. Up to now, the PEO and PCL copolymers with various of architectures have been synthesized, such as block, star-like, and graft copolymers [47–49]. However, scarce examples of the cyclic polymers containing PEO and PCL segments have been reported due to the synthetic difficulties. Herein, a biocompatible tadpole-shaped copolymer with one PEO ring and two PCL tails was obtained by the combination of

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"Glaser" coupling [50–54] with ring-opening polymerization (ROP) (Scheme 1).

2. Experimental Section

2.1. Materials

Ethylene oxdie (EO) (98%, Sinopharm Chemical Reagent Co., Ltd (SCR)) was dried by calcium hydride (CaH_2) for 48 h and then distilled under N_2 before use. Pentaerythritol (Aldrich, 98%) was dried at 50 °C under vacuum. Copper(I) bromide (Cu(I)Br) (95%, SCR) was stirred overnight in acetic acid, filtered, washed with ethanol and diethyl ether successively, and dried in vacuum. Sodium hydride (NaH) (60% dispersion in mineral oil, Aldrich) and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) (99%, Aldrich) were used as received. Propargyl bromide (>99%) and ε-caprolactone (99%, Aldrich) were purified by distillation from CaH_2 under reduced pressure. Tetrahydrofuran (THF) (99%, SCR) was refluxed and distilled from potassium naphthalenide solution. Tin (II) bis(2-ethylhexanoate) ($Sn(Oct)_2$) (95%, Sigma) was dissolved in dry toluene (10 mg/mL). Diphenylmethyl potassium (DPMK) solution with concentration of 0.64 mol/L was prepared according to the literature [55]. 2-phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane was synthesized according to the literature [56]. All other regents and solvents were purchased from Sinopharm Chemical Reagent Co., Ltd. (SCR) and used as received except for declaration.

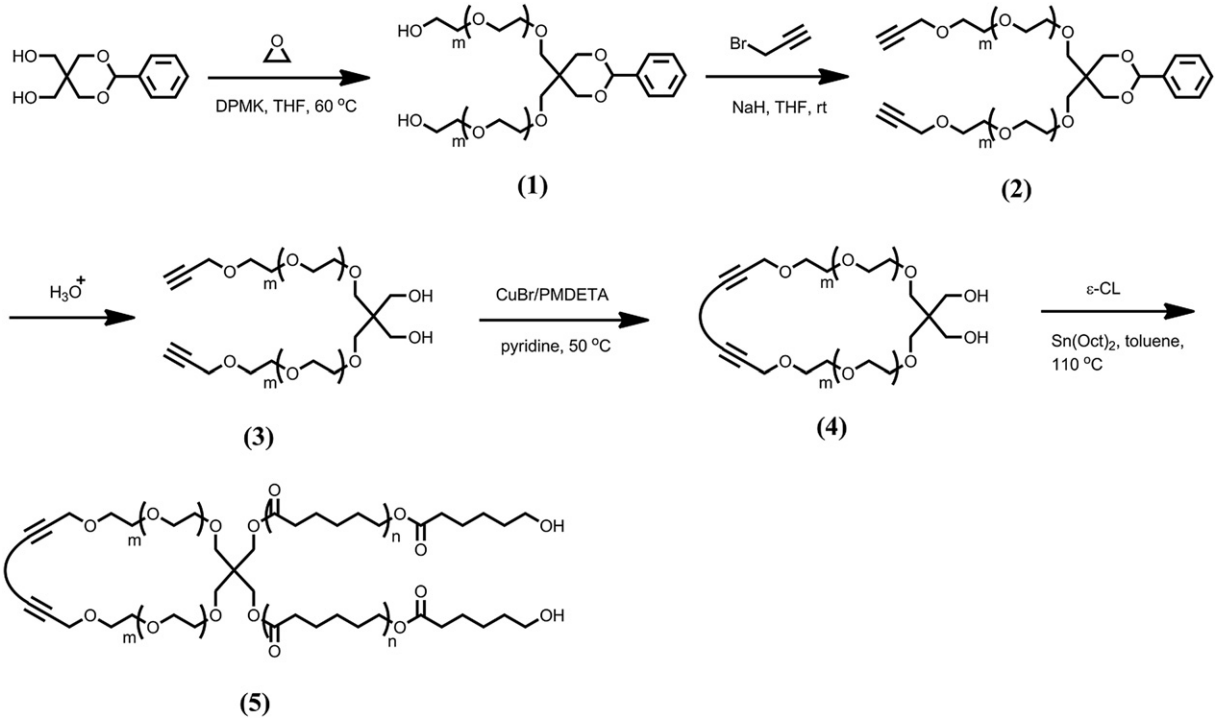
2.2. Characterizaiton

Gel permeation chromatographic (GPC) analysis of PEO homopolymers was performed in 0.1 M $NaNO_3$ aqueous solution at 40 °C with an elution rate of 0.5 mL/min on an Agilent 1100 equipped with a G1310A pump, a G1362A refractive index detector, and a G1315A diode-array detector. Three TSK-gel PW columns in series (bead size: 6, 13, and 13 μm; pore size: 200, >1000, and <100-1000 Å; molecular range: 0-5 × 10^4, 5 × 10^4-8 × 10^6, and (5–8) × 10^6 g/mol, respectively) were calibrated with PEO standard samples. GPC analysis of the copolymers containing PEO and PCL segments was performed in THF at 35 °C with an elution rate of 1.0 mL/min on an Agilent 1100 equipped with a G1310A pump, a G1362A refractive index detector, and a G1314A variable wavelength detector. One 5 LP gel column (500 Å, molecular range 500-2 × 10^4 g/mol) and two 5 μm LP gel mixed bed column (molecular range 200-3 × 10^6 g/mol) were calibrated by PS standard samples. ^{1}H NMR spectra were recorded on a Bruker (500 MHz) spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal reference for chemical shifts. The matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurement was performed using a Perspective Biosystem Voyager DE-STR MALDI-TOF MS (PE Applied Biosystems, Framingham, MA). Matrix solution of dithranol (20 mg/mL), polymer (10 mg/mL), and cationizing salt of sodium trifluoroacetate (10 mg/mL) in THF was mixed in the ratio of 10:4:2. Fourier Tansform infrared (FT-IR) spectra were recorded on a NEXUS 470 FT-IR instrument and the polymer solution was cast on a NaCl disk to form the film.

2.3. Synthesis

2.3.1. Synthesis and characterization of 2-phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane

Typically, a mixture of pentaerythritol (24.0 g, 0.15 mol) and N′,N-Dimethylformamide (DMF, 150 mL) was heated and stirred until the solid was completely dissolved. Benzaldehyde (15.3 mL, 0.15 mol) and p-toluenesulfonic acid monohydrate (1.42 g, 7.5 mmol) were added. The solution was heated at 90 °C for 19 h, and ethyl acetate was added to dissolve the residue after DMF was evaporated under reduced pressure. The organic solution was washed successively with aqueous sodium chloride and water, and then dried over anhydrous $MgSO_4$ overnight. After filtration, the solvent was evaporated. The resultant solid was recrystallized from



Scheme 1. Synthetic route to the tadpole-shaped copolymers (***c*-PEO)-*b*-PCL_2**.

toluene for two times to white solid. ^{1}H NMR (DMSO-d_6,δ): 3.31 ppm (s, 2H, C***H***$_2$OH), 3.65 ppm (s, 2H, C***H***$_2$OH), 3.76 ppm (d, J = 10.8, H$_z$, 2H, H$_a$), 3.88 ppm (d, J = 10.8, H$_z$, 2H, H$_e$), 5.38 ppm (s, 1H, C$_6$H$_5$C***H***), 7.32–7.38 ppm (m, 5H, C$_6$***H***$_5$).

*2.3.2. Synthesis of α,ω-dihydroxy-Poly(ethylene oxide) with two protected hydroxyl groups at the chain middle [**PEO(1)**] (Scheme 1)*

PEO(1) was synthesized by ROP of EO monomers in THF using 2-phenyl-5,5- bis(hydroxymethyl)-1,3-dioxane (which contained two protected hydroxyl groups and two active hydroxyl groups) and DPMK as co-initiator. The initiator of 2-phenyl-5,5-bis(hydro xymethyl)-1,3-dioxane (1.31 g, 5.85 mmol) dried by azeotropic distillation with toluene was dissolved in 140 mL dried THF, then the solution was introduced into a 250 mL ampoule. The solution of DPMK in THF (7.70 mL, 5.85 mmol) was slowly added and the solution took turbid as the alkoxides were formed. The monomers of EO (30.0 mL, 0.589 mol) were then injected into the ampoule under nitrogen and the reaction was carried out at 55 °C for 48 h. After 2.0 mL methanol was added to terminate the polymerization, the solution was concentrated and precipitated into an excess of diethyl ether two times for **PEO(1)**. ^{1}H NMR (CCl_3D, δ): 3.43–3.62 ppm (m,-(C***H***$_2$C***H***$_2$O)$_n$-), 5.40 ppm (s, C$_6$H$_5$C***H***), 7.34–7.46 ppm (m, 5H, C$_6$***H***$_5$). **PEO(1a):** $M_{n,NMR}$ = 3,900 g/mol; $M_{n,GPC}$ = 3,100 g/mol, PDI = 1.09.

*2.3.3. Synthesis of α,ω-dialkyne-Poly(ethylene oxide) with two protected hydroxyl groups at the chain middle [**PEO(2)**] (Scheme 1)*

PEO(2) was synthesized by modification of hydroxyl groups into alkyne groups at the chain terminal of **PEO(1)**. **PEO(1)** (3.51 g, 1.14 mmol) dried by azeotropic distillation with toluene was dissolved in 100 mL dried THF, and NaH (1.88 g, 22.8 mmol) was added into the solution. After the mixture was stirred for 2.0 h, propargyl bromide (4.2 mL, 22.8 mmol) was added and the mixture was stirred at room temperature overnight. The residual NaH was neutralized by adding a few drops of deionized water under rapidly stirring. After filtration of the formed salts, the solution was concentrated and precipitated into an excess of diethyl ether two times for **PEO(2)**. ^{1}H NMR (CCl_3D, δ): 2.44 ppm (s, **H**C≡CCH$_2$-), 3.43–3.62 ppm (m,-(C**H**$_2$C**H**$_2$O)$_n$-), 4.20 ppm (s, HC≡CC***H***$_2$-), 5.40 ppm (s, C$_6$H$_5$C**H**), 7.34–7.46 ppm (m, 5H, C$_6$**H**$_5$).

*2.3.4. Synthesis of α,ω-dialkyne-Poly(ethylene oxide) with two hydroxyl groups at the chain middle [**PEO(3)**] (Scheme 1)*

PEO(3) was obtained by recovery of the protected hydroxyl group at the chain middle of **PEO(2)**. The **PEO(2)** was dissolved in THF and adjusted to be acidic by adding the HCl solution and stirred for 2.0 h at the room temperature. The solvent was evaporated under reduced pressure, then the residual was dissolved in water and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residual was precipitated into an excess of diethyl ether three times for **PEO(3)**. ^{1}H NMR (CCl_3D, δ): 2.44 ppm (s, ***H***C≡CCH$_2$-), 3.43–3.62 ppm (m,-(C***H***$_2$C***H***$_2$O)$_n$-), 4.20 ppm (s, HC≡CC***H***$_2$-). $M_{n,GPC}$ = 3,800 g/mol, PDI = 1.06.

*2.3.5. Synthesis of cyclic Poly(ethylene oxide) with two hydroxyl groups via "Glaser" coupling [(**PEO (4)**) (Scheme 1)*

PEO(4) was obtained by **"**Glaser" cyclization between alkyne groups at the terminal of **PEO(3).** Into a 1 L round-bottomed flask, pyridine (700 mL), PMDETA(2.02 ml, 9.71 mmol), Cu(I)Br (1.39 g, 9.71 mmol) were added. In a separate 150 mL flask, linear **PEO(3)** (0.410 g, 1.05 × 10^{-5} mol) was dissolved in 100 mL pyridine. Under vigorously stirring, the solution of linear **PEO(3)** was slowly added into the 1 L flask (heated to 50 °C) via a peristaltic pump at a rate of 1.4 mL/h. After the addition of the linear **PEO(3)** solution was completed, the final concentration reached to 0.5860 g/L. The reaction mixture was allowed to stir for additional 6.0 h, and the solvent was evaporated under reduced pressure. The residual was dissolved in water and extracted with CH_2Cl_2 (2 × 200 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. After the residual was precipitated into an excess of diethyl ether two times, the product of cyclic **PEO(4)** was vacuum dried at 40 °C to a constant weight (yield: 75%). ^{1}H NMR (CCl_3D, δ): 3.43–3.62 ppm (m,-(C***H***$_2$C***H***$_2$O)$_n$-), 4.62 ppm (s, -C***H***$_2$C≡CC***H***$_2$-). $M_{n,GPC}$ = 3,100 g/mol, PDI = 1.07.

*2.3.6. Synthesis of tadpole-shaped amphiphilic copolymer with one **PEO** ring and two **PCL** tails [(**c-PEO)-b-PCL$_2$**] (Scheme 1)*

The copolymers **(*c*-PEO)-*b*-PCL$_2$** were obtained by ROP of ε-CL monomers using **PEO(4)** as macro-initiator. The dried cyclic **PEO(4a)** (0.300 g, 7.69 × 10^{-5} mol), freshly distilled ε-CL (0.340 g, 2.98 mmol) and the Sn(Oct)$_2$ solution in toluene (2.5 mL, 6.25 × 10^{-5} mol) were added into a 100 ml ampoule. After the polymerization was performed at 110 °C for 12.0 h, the mixture was precipitated into petroleum ether and dried under vaccum for **(*c*-PEO)-*b*-PCL$_2$**. ^{1}H NMR (CCl_3D, δ): 3.43–3.62 ppm (m,-(C***H***$_2$C***H***$_2$O)$_n$-), 4.62 ppm (s, -C***H***$_2$C≡CC***H***$_2$-). 1.38 ppm (m, -(COCH$_2$CH$_2$C***H***$_2$CH$_2$-CH$_2$O)$_n$-), 1.64 ppm (m, -(COCH$_2$C***H***$_2$CH$_2$C***H***$_2$CH$_2$O)$_n$-), 2.31 ppm (m, -(COC***H***$_2$CH$_2$CH$_2$CH$_2$CH$_2$O)$_n$-), 4.06 ppm (m, -(COCH$_2$CH$_2$CH$_2$CH$_2$-C***H***$_2$O)$_n$-); $M_{n,NMR}$ = 9,500 g/mol; $M_{n,GPC}$ = 12,700 g/mol, PDI = 1.32.

3. Results and discussion

The biocompatible tadpole-shaped copolymer **(*c*-PEO)-*b*-PCL$_2$** was synthesized according to the steps shown in Scheme 1. The α,ω-dialkyne-poly(ethylene oxide) with two hydroxyl groups at the chain middle (**PEO(3)**) was prepared by ROP of EO monomers using 2-phenyl-5,5- bis(hydroxymethyl)-1,3-dioxane as initiator, followed by transformation of functional groups. Cyclization of linear **PEO(3)** by "Glaser" coupling offered the cyclic **PEO(4)** with two hydroxyl groups at the same site. The target amphiphilic copolymer **(*c*-PEO)-*b*-PCL$_2$** was obtained by ROP of ε-CL monomers from the hydroxyl groups on cyclic **PEO(4)**.

3.1. Synthesis and characterization of α,ω-dialkyne-poly(ethylene oxide) with two hydroxyl groups at the chain middle

First, the well-defined α,ω-dihydroxy-poly(ethylene oxide) with two protected hydroxyl groups at the chain middle (**PEO(1)**) was synthesized by ROP of EO monomers using 2-phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane as initiator and DPMK as co-initiator. By changing the molar ratio of EO monomers to initiator, two series of **PEO(1)** with different molecular weight were obtained (**PEO(1a):** $M_{n,GPC}$ = 3,100 g/mol, PDI = 1.09. **PEO(1b):** $M_{n,GPC}$ = 6,400 g/mol, PDI = 1.08). Fig. 1A showed the GPC trace of **PEO(1a)**, which showed a unimodal peak with narrow molecular weight distribution. In a typical ^{1}H NMR spectrum of **PEO(1a)** (Fig. 2A), the signals (a) at 7.34 and 7.49 ppm were assigned to the phenyl-ring protons (C$_6$***H***$_5$CH(OCH$_2$-)$_2$) and (b) at 5.40 ppm was assigned to methine proton (C$_6$H$_5$C***H***(OCH$_2$-)$_2$) of the protective group, and the signals (c) 3.43–3.64 ppm were assigned to the methylene protons (-C***H***$_2$C***H***$_2$O-) of EO units. The molecular weights of **PEO(1)** ($M_{n,NMR,\ PEO(1)}$) were derived by ^{1}H NMR spectra according to Formula 1:

$$M_{n,NMR,\ PEO(1)} = \frac{A_c/4}{A_b} \times 44 + 222 \quad (1)$$

Where A$_c$ and A$_b$ were the integral areas of the signals at 5.40 ppm and that at 3.43–3.64 ppm, respectively. The values of 44 and 222

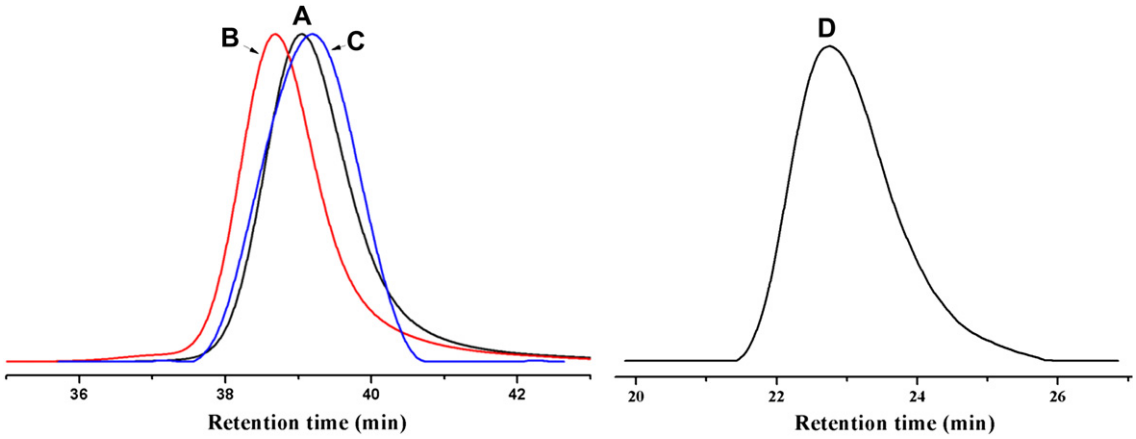


Fig. 1. GPC traces of **PEO(1a)** (M_n = 3,100 g/mol, PDI =1.09) (A), linear **PEO(3a)** (M_n = 3,800 g/mol, PDI =1.06) (B) , cyclic **PEO(4a)** (M_n = 3,100 g/mol, PDI =1.07) (C) and (***c*-PEO)-*b*-PCl$_2$ (5a)** (D) (A, B, C using 0.1 M $NaNO_3$ aqueous solution as eluent; D using THF as eluent).

were the molecular weight of EO monomer unit and the residual of initiator ($C(OCH_2\text{-})_2((OCH_2\text{-})_2CH\ C_6H_5)$), respectively.

The α,ω-dialkyne-poly(ethylene oxide) with two protected hydroxyl groups at the chain middle (**PEO(2)**) were obtained by reaction between hydroxyl groups at the end of **PEO(1)** and propargyl bromide in the presence of NaH. Compared the ^{1}H NMR spectrum of **PEO(2a)** with that of **PEO(1a)** (Fig. 2), the new signals (f) at 2.44 ppm and (g) at 4.20 ppm can be assigned to the alkynyl protons ($\text{-}CH_2C{\equiv}C\boldsymbol{H}$) and methylene protons($\text{-}C\boldsymbol{H}_2C{\equiv}CH$) of the propargyl groups. The relative integration ratio of the signals (f) and (b) was about 2:1, indicating that the propargylation efficiency was almost 100%. The propargylation procedure was also verified by MALDI-TOF mass spectrum. From Fig. 3, we could observe an increase of 2 × 38.9 Da from peak (224.3 ($C_{12}H_{16}O_4$) +44.0 (EO) × n + 23.0 (Na^+) = 4122.5 Da) of **PEO(1a)** to peak (224.3 ($C_{12}H_{16}O_4$) +44.0 (EO) × n +39.1 (C_3H_3) × 2 + 23.0 (Na^+) = 4200.3 Da) of **PEO(2a)**, which corresponded to the molecular weight of two propargyl groups. Moreover, the trace of **PEO(1a)** was not detected in that of **PEO(2a)**, indicating the propargylation was performed completely. The propargylation was further verified by FT-IR analysis, the characteristic signal of the alkyne groups at 3325 cm^{-1} in the spectrum of PEO (2) appeared clearly (Fig. 4).

Under acidic conditions, the recovery of hydroxyl groups on **PEO(2)** gave the α,ω- dialkyne-poly(ethylene oxide) with two hydroxyl groups (**PEO(3)**). In the ^{1}H NMR spectrum of **PEO(3a)** (Fig. 2C), the signals (a) at 7.34 and 7.49 ppm of the phenyl-ring protons ($C_6\boldsymbol{H}_5CH(OCH_2\text{-})_2$) and (b) at 5.40 ppm of methine proton ($C_6H_5C\boldsymbol{H}(OCH_2\text{-})_2$) of the protective group disappeared thoroughly, confirming that the hydrolysis was complete. Compared with the MALDI-TOF mass spectrum of **PEO(2a)**, that of **PEO(3a)** decreased 88.1 Da, nearly the molecular weight of a protective group (Fig. 3). The trace of **PEO(2a)** was not detected in MALDI-TOF mass spectrum of **PEO(3a)**, further confirming the hydrolysis was complete. Thus, the precursor of **PEO(3a)** with two alkyne groups at the chain terminal and two active hydroxyl groups at the chain middle was successfully synthesized.

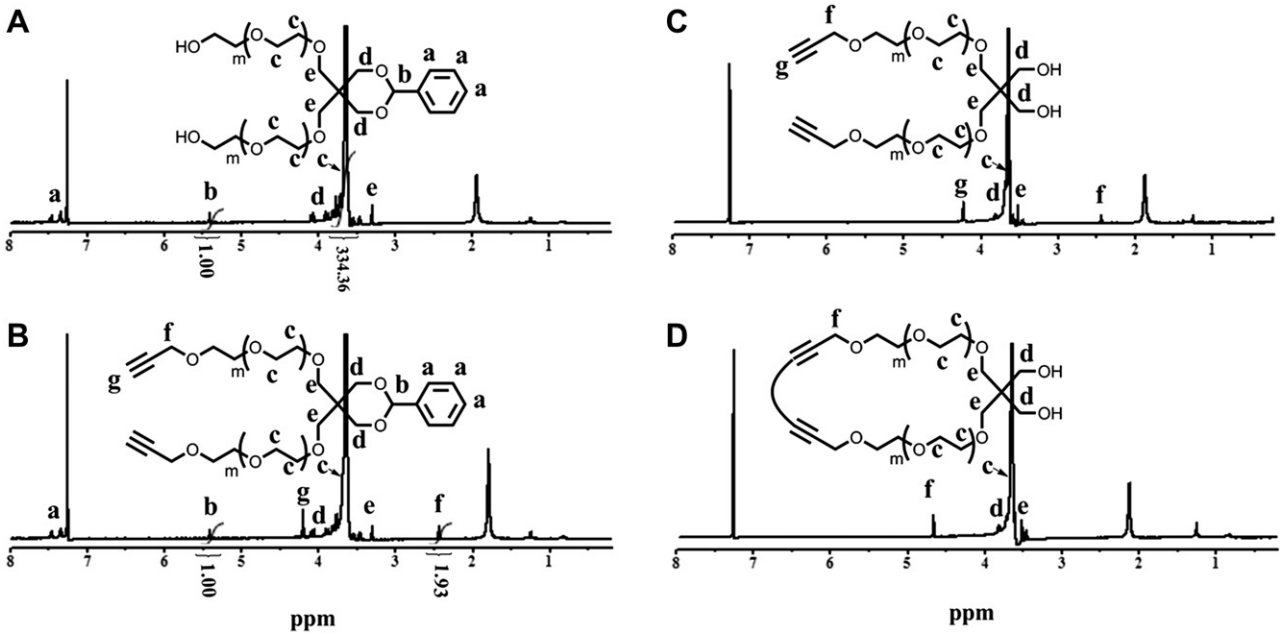


Fig. 2. ^{1}H NMR spectra of **PEO(1a)** (A), **PEO (2a)** (B), linear **PEO(3a)** (C) and cyclic **PEO(4a)** (D) in $CDCl_3$.

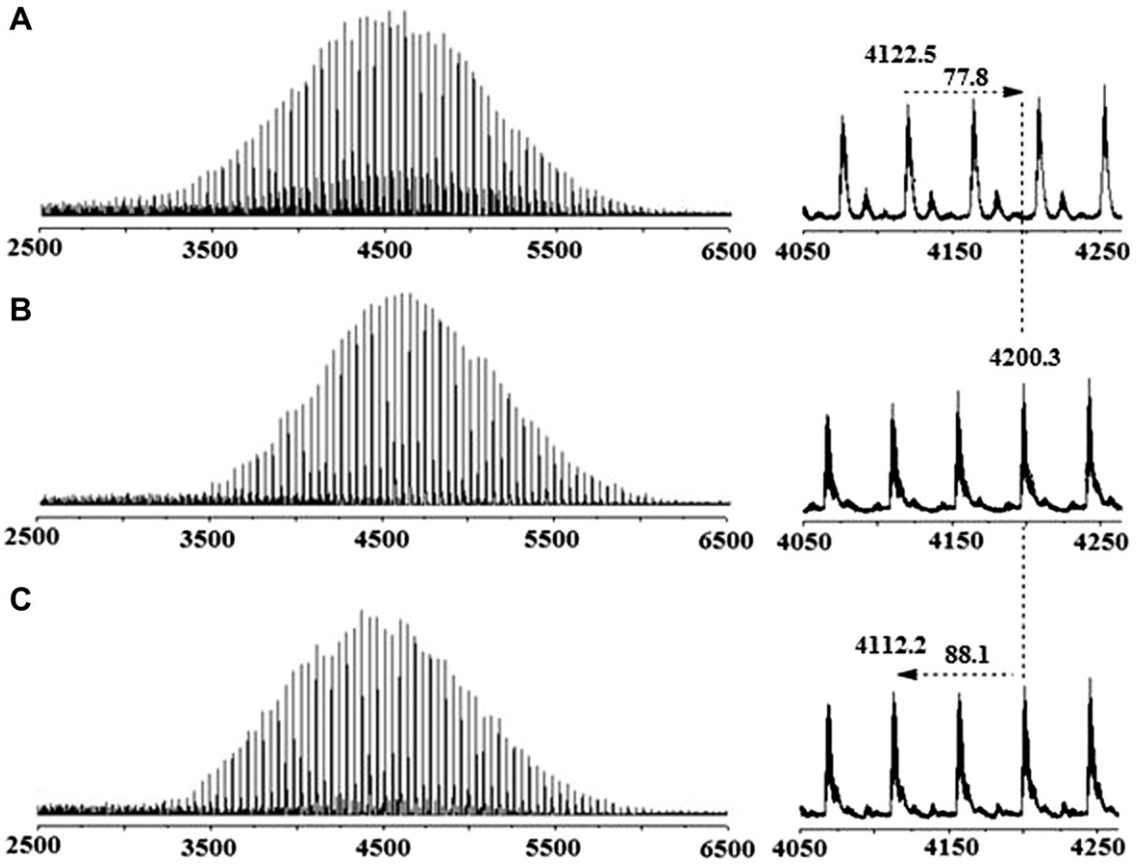


Fig. 3. MALDI-TOF mass spectra of **PEO(1a)** (A), **PEO(2a)** (B), and **PEO(3a)** (C) with dithranol as matrix and sodium trifluoroacetate as cationizing salt.

3.2. Synthesis and Characterization of cyclic Poly(ethylene oxide) with two hydroxyl groups at the same site

The intramolecular cyclization by "Glaser" coupling between alkyne groups on linear **PEO(3)** offered the cyclic **PEO(4)** containing two active hydroxyl groups at the same site. It was well known that the hydrodynamic volume of cyclic polymers is smaller than their linear precursors because of the more compact conformation by cyclization. Compared the GPC trace of cyclic **PEO(4a)** with that of linear **PEO(3a)** (Fig. 1), it can be seen that the former clearly shifted to the lower molecular weight area. The $< G >$ value, the ratio of the apparent peak molar mass of cyclic **PEO(4)** to that of linear **PEO(3)**, were 0.81 and 0.92 (Table 1), which were coincident with the reported data in literatures [23–37]. On the other hand, the

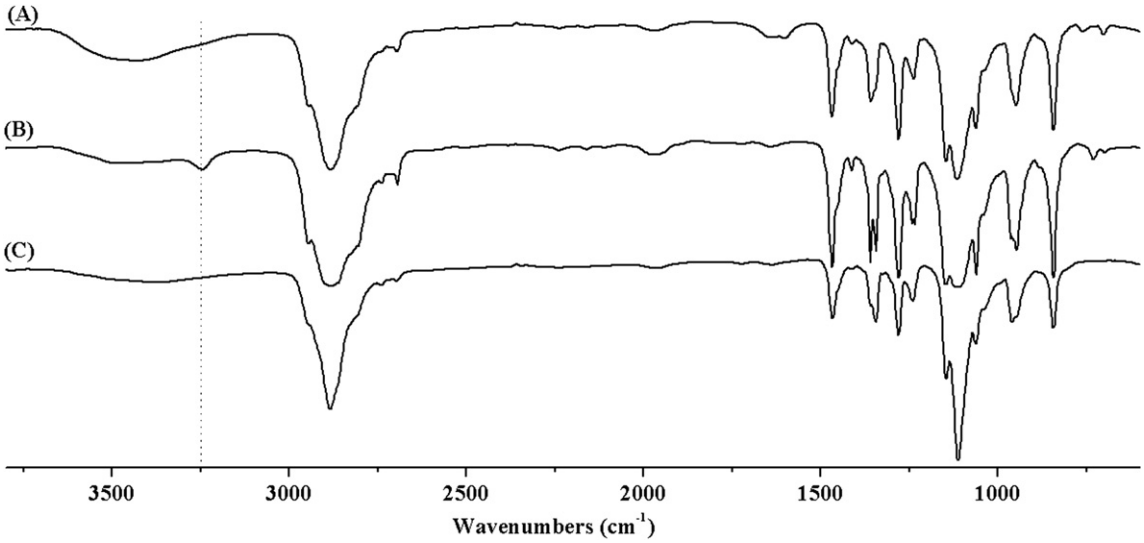


Fig. 4. FT-IR spectra **PEO(1a)** (A), linear **PEO(3a)** (B) and cyclic **PEO(4a)** (C).

Table 1
The data of the tadpole-shaped copolymers (***c*-PEO)-*b*-PCl$_2$**.

Entry	**PEO(3)**			**PEO(4)**			<G>[b]	(***c*-PEO)-*b*-PCl$_2$ (5)**		
	$M_{n,GPC}$[a] [g/mol]	PDI[a]	M_p[a] [g/mol]	$M_{n,GPC}$[a] [g/mol]	PDI[a]	M_p[a] [g/mol]		$M_{n,NMR}$[c] [g/mol]	$M_{n,GPC}$[d] [g/mol]	PDI[d]
a	3,800	1.06	4,100	3,100	1.07	3,300	0.81	9,500	12,700	1.32
b	7,100	1.12	8,500	6,500	1.15	7,800	0.92	16,800	20,900	1.22

[a] Determined by GPC using PEO as standard and 0.1 M aqueous $NaNO_3$ as eluent.
[b] The ratio of the apparent peak molar masses (M_p) were derived from the GPC of cyclic PEO to their linear precursors.
[c] Determined by ^{1}H NMR using Formula 3.
[d] Determined by GPC using THF as eluent.

unimodal peak of GPC trace for cyclic **PEO(4a)** meant that no intermolecular byproduct was produced during the cyclization process. From the ^{1}H NMR spectrum in Fig. 2D, it can be seen that the signal for the methine proton (-CH_2C≡C***H***) of alkynyl group at 2.44 ppm disappeared completely after cyclization. And the molecular weights of **PEO(4)** ($M_{n,\ NMR,\ PEO(4)}$) were derived by ^{1}H NMR spectra according to Formula 2:

$$M_{n,NMR,\ PEO(4)} = M_{n,NMR,\ PEO(1)} - 90 + 38 \times 2 \quad (2)$$

Where the values of 90 and 38 were the mass of the removed acetal groups (C_6H_5CH-) and propargyl groups (-CH_2C≡C-), respectively.

As shown in the MALDI-TOF mass spectra (Fig. 5), the molecular weight of cyclic **PEO(4a)** almost differred 2.0 Da with its precursor of linear **PEO(3a)**, which also confirmed the successful cyclization. After "Glaser" cyclization, the characteristic signal of the alkyne groups at 3325 cm^{-1} in the spectrum of **PEO(2)** also disappeared clearly (Fig. 4). Based on these results above, we can conclude that the cyclization was successful, and the cyclic

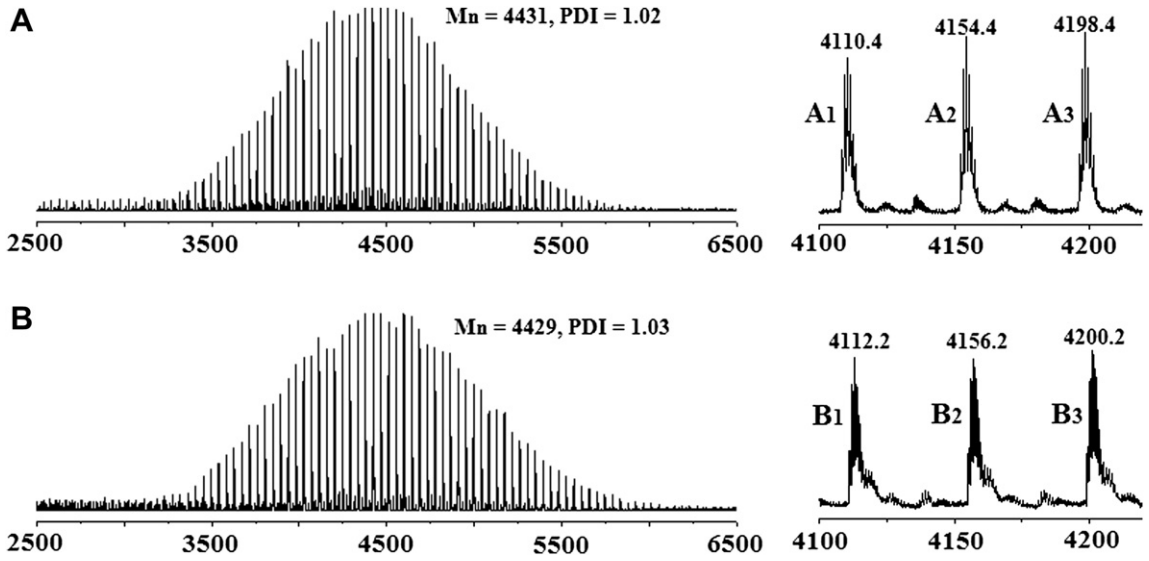


Fig. 5. MALDI-TOF mass spectra of cyclic **PEO(4a)** (A) and linear **PEO(3a)** (B) with dithranol as matrix and sodium trifluoroacetate as cationizing salt.

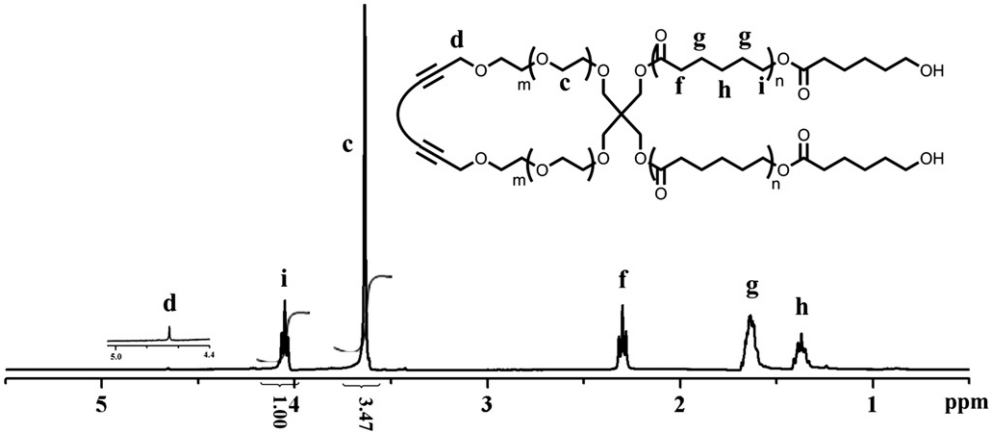


Fig. 6. ^{1}H NMR spectrum of (***c*-PEO)-*b*-PCl$_2$ (5a)** in $CDCl_3$.

PEO(4a) with two active hydroxyl groups at the same site was actually obtained.

3.3. Synthesis and Characterization of biocompatible tadpole-shaped copolymer with one PEO ring and two PCL tails [(*c*-PEO)-*b*-PCL_2]

The target copolymers (***c*-PEO)-*b*-PCL_2** with one PEO ring and two PCL tails were obtained by the ROP of ε-CL monomer using cyclic **PEO(4)** as macro-initiator. In Fig. 1D, the GPC trace of **(*c*-PEO)-*b*-PCL_2 (5a)** was a unimodal peak, which indicated that the polymerization proceeded smoothly. In a typical ^{1}H NMR spectrum of **(*c*-PEO)-*b*-PCL_2 (5a)** (Fig. 6), the signals (h) at 2.31 ppm, (i) at 1.64 ppm, (j) at 1.38 ppm and (k) at 4.06 ppm can be attributed to the characteristic signals of the ε-CL units. The molecular weight of PCL tails can be calculated by the relative integration of signals (c) and (i) (Table 1), and the molecular weights of **(*c*-PEO)-*b*-PCL_2 (5)** ($M_{n,\ NMR,\ (c\text{-}PEO)\text{-}b\text{-}PCL2}$) were derived by ^{1}H NMR spectra according to Formula 3:

$$M_{n,\ NMR,\ (c-PEO)-b-PCL2} = \frac{A_k/2}{A_c/\left(\frac{M_{n,\ NMR,PEO(4)}}{44}\right)\times 4} \times 114 + M_{n,\ NMR,PEO(4)} \quad (3)$$

Where A_k was the integral area of the signals at 4.06 ppm, the value of 114 was the molecular weight of ε-CL monomer unit. The others were the same as defined before and the data were shown in Table 1. These results above showed that the biocompatible copolymer **(*c*-PEO)-*b*-PCL_2 (5)** were successfully synthesized.

4. Conclusion

In summary, a novel biocompatible tadpole-shaped copolymers consisting one PEO ring and two PCL tails were successfully synthesized by the combination of "Glaser" coupling with ROP mechanism. Both of the PEO and PCL segments are the known to be biocompatible, and it is expected that the copolymer **(*c*-PEO)-*b*-PCL_2** may exhibit some unique properties due to the unusual architecture and might be found some biomedical applications. This work also presented a novel method to copolymers with defined architecture and compositions.

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