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# Synthesis of amphiphilic macrocyclic graft copolymer consisting of a poly(ethylene oxide) ring and multi-poly(ε-caprolactone) lateral chains

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**Abstract**

A series of amphiphilic macrocyclic graft copolymers composed of a hydrophilic poly(ethylene oxide) as ring and hydrophobic poly(ε-caprolactone) as lateral chains with different grafting lengths and densities of side chains were prepared by a combination of anionic ring-opening polymerization and coordination–insertion ring-opening polymerization. The anionic ring-opening copolymerization of ethylene oxide (EO) and ethoxyethyl glycidyl ether (EEGE) was carried out first using triethylene glycol and diphenylmethyl potassium (DPMK) as co-initiators, and a linear α,ω-dihydroxyl poly(ethylene oxide) with pendant protected hydroxymethyls (*l*-poly(EO-*co*-EEGE)) was obtained. The monomer reactivity ratios of these compounds are $r_{1(EO)} = 1.20 \pm 0.01$ and $r_{2(EEGE)} = 0.76 \pm 0.02$, respectively. Then the ring closure of *l*-poly(EO-*co*-EEGE) was achieved via an ether linkage by reaction with tosyl chloride (TsCl) in the presence of solid KOH. The crude cyclized product containing the linear chain-extended polymer was hydrolyzed in acidic conditions first and then purified by treating with α-CD. The pure cyclic copolymer of EO and glycidol (Gly) with multipendant hydroxymethyls [*c*-poly(EO-*co*-Gly)] as the macroinitiator was used further to initiate the ring-opening polymerization of ε-caprolactone (CL), and a series of amphiphilic macrocyclic graft copolymers *c*-PEO-*g*-PCL were obtained. The final products and intermediates were characterized by GPC, NMR and MALDI-TOF in detail.


*Keywords:* Macrocyclic graft copolymer; Anionic ring-opening polymerization; Coordination–insertion ring-opening polymerization

## 1. Introduction

Since the pioneering work done by Pedersen revealed the complexing potential of the crown ethers [1], cyclic molecules with complicated structure derived from the crown ethers were synthesized and the properties are investigated. The fascinating properties and applications of the cyclic molecules include the formation of organic nanotubes, ion complex and ion transport across membranes and so on [2]. For example, cyclic polyamines bearing long paraffin chains displayed a liquid crystal phase in which the macrocyclic units are stacked to form a tubular mesophase [3]. A dibenzo-18-crown-6 with two poly(styrene) chains could be used to fabricate Ag nanoparticles without using any templates [4].

Previous studies about cyclic polymers are only focused on the preparation of single polymer ring including some hydrophobic homo- and copolymers such as cyclic PS, PE, PS-*b*-PI and PS-*b*-PI-*b*-PMMA [5], and the hydrophilic macrocyclic poly(ethylene oxide) [6]. Investigation of the solution and crystallization properties of these macrocyclic polymers was also reported [7].

However, in the family of these macrocycles, limited reports are published on the preparation of amphiphilic macrocyclic graft copolymers. We have described the synthesis of a macrocyclic graft copolymer of poly(ethylene oxide) (PEO) as ring and polystyrene as side chains by anionic

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copolymerization of ethylene oxide (EO) and 4-glycidyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl [8] (G-TEMPO), but this method has two shortcomings: (1) the monomers suited for TEMPO polymerization are limited, so the method is not universal; (2) the separation and purification of the macrocyclic product are complicate and time-consuming.

Graft copolymerization via functional groups of an existing polymer main chain offers an easy and effective approach to incorporate the new properties into the original polymers [9]. Poly(ε-caprolactone) (PCL) has been extensively used as important biomaterial for a wide variety of drug delivery carriers and biomedical devices due to its biodegradability, versatile mechanical properties and proven biocompatibility [10]. On the other hand, PEO presents some unique and outstanding properties, e.g. hydrophilicity, nontoxicity and solubility in water and organic solvents [11]. In order to meet the increasing demands for better performances and satisfy the requirements of some specific applications, the biodegradable polymers, PCL modified by PEO, have attracted much attention. PEO/PCL diblock, triblock, and star-shaped block copolymers have been prepared, and the thermal properties and morphology of the copolymers are affected significantly by the chain length of the PCL and PEG and by the type of copolymers [12–14]. These copolymers can be employed in biomedical and pharmacological fields as synthetic biomaterials, injectable materials, and drug carriers in a controlled delivery system [15–17]. However, amphiphilic macrocyclic graft copolymer consisting of a poly(ethylene oxide) ring and multi-poly(ε-caprolactone) lateral chains is not known up to now due to the difficulty of synthesis.

In the present work, we report the synthesis of amphiphilic macrocyclic graft copolymers consisting of a hydrophilic PEO as ring and hydrophobic multi-PCL as lateral chains by a combination of anionic ring-opening polymerization and coordination–insertion ring-opening polymerization.

## 2. Experimental

### 2.1. Materials

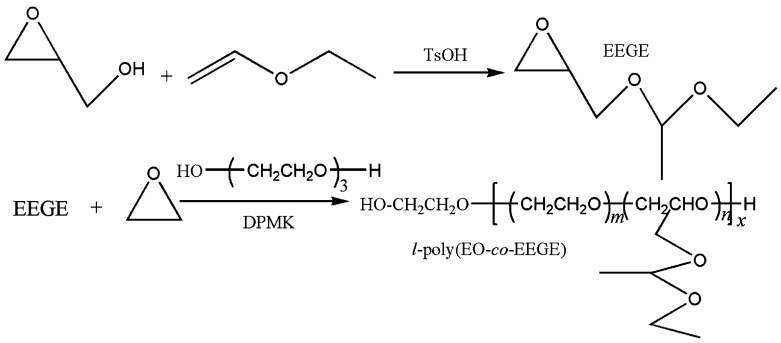
Glycidol (Gly) (tech.) was purchased from Acros and dried over calcium hydride for 48 h and then distilled under reduced pressure just before use. *p*-Toluene sulphonic acid (TsOH, >98%) and ethyl vinyl ether (98%) were purchased from Aldrich and Sinopharm Chemical Reagent Co., Ltd. (SCR), respectively, and used as-received. α-Cyclodextrin (α-CD, Aldrich) was used as-received. *p*-Toluenesulfonyl chloride (TsCl, 98%, Aldrich) and potassium hydroxide (KOH, 96%, Aldrich) were dried under vacuum prior to use. ε-Caprolactone (ε-CL, Acros organics) was dried over calcium hydride for 48 h and distilled under reduced pressure just before use. DMSO (SCR, 98%) was distilled over calcium hydride under reduced pressure just before use. Triethylene glycol was distilled from $CaH_2$ under reduced pressure and the fraction at 134 °C/90 Pa was collected. 1,1-Diphenylethylene (99%) was also distilled from $CaH_2$ under reduced pressure and the fraction at 105 °C/80 Pa was collected. THF (99%) was refluxed over potassium wire and distilled from potassium naphthalenide solution. EO (SCR, 98%) was dried over calcium hydride for 48 h and then distilled under $N_2$ before use. All other reagents were purified by common purification procedures.

### 2.2. Measurements

GC/MS (gas chromatographic–mass spectrometric) analysis was carried for EEGE using a Finnigan Voyager system with mass selective detection operating in electronic ionization (EI). The GC/MS parameters were as follows: ion source temperature was 200 °C, carrier gas helium, column flow 1 mL/min; temperature program, from 100 to 200 °C at 15 °C/min, splitless injection at 250 °C; ionization was achieved at 70 eV. GPC was performed on an Agilent 1100 with a G1310A pump, a G1362A refractive detector, and a G1314A variable wavelength detector. THF was used as eluent at 35 °C at 1.0 mL/min. One 5 μm LP gel column (500 Å, molecular range 500–$2 \times 10^4$ g/mol) and two 5 μm LP gel mixed bed columns (molecular range 200–$3 \times 10^6$ g/mol) were calibrated with polystyrene standard samples. For *l*-poly($EO_{43.5}$-*co*-EEGE) and *c*-poly($EO_{10.6}$-*co*-Gly), GPC analyses were performed in 0.1 M aqueous $NaNO_3$ at 40 °C with an elution rate of 0.5 mL/min on the same instrument except a G1315A diode-array detector was used to substitute the G1314A variable wavelength detector. Three TSK-gel PW columns in series (bead size: 6, 13, 13 μm; pore size: 200 Å, greater than 1000 Å, less than 100–1000 Å; molecular range: 0–$5 \times 10^4$, $5 \times 10^4$–$8 \times 10^6$, 5–$8 \times 10^6$ g/mol, respectively) were calibrated with PEO standard samples. The injection volume was 20 μL and the concentration was 5 mg/mL. MALDI-TOF-MS analysis was carried out on a Voyager DE-STR from Applied Biosystems. The matrix α-cyano-4-hydroxycinnamic acid was dissolved in THF at a concentration of 40 mg/mL. Potassium trifluoroacetate was used as cationization agent at typical concentrations of 5 mg/mL. The sample was dissolved in THF at approximately 1 mg/mL. At last, matrix, salt, and polymer solution were premixed in a molar ratio of 5:1:5. The premixed solutions were hand-spotted on the target well and left to dry. All mass spectra were recorded in the reflector mode and about 1000 laser shots were collected per spectrum. $^1$H NMR spectra were obtained at a DMX 500 MHz spectrometer. All the samples were dissolved in $CDCl_3$. IR spectra were obtained on a Magna 550 Fourier transform infrared (FTIR) spectrometer. The ultrafiltration separator was purchased from the Shanghai Institute of Nuclear Research, Chinese Academy of Science, and the cutoff molecular weight of the poly(ether sulfone) membrane was 20,000 g/mol (calibrated by globular protein).

### 2.3. Synthesis of 2,3-epoxypropyl-1-ethoxyethyl ether (EEGE)

The hydroxyl group of glycidol was protected with ethyl vinyl ether according to a previously described procedure [18] as shown in Scheme 1. Typically, the operation was




Scheme 1. Anionic copolymerization of EEGE with EO.

carried out in a 250 mL three-neck flask with a magnetic stirrer; 1.25 g of TsOH was added in batch to 50 g (0.675 mol) of glycidol in 200 mL of ethyl vinyl ether solution, the temperature was kept below 40 °C, and 100 mL of saturated $NaHCO_3$ aqueous solution was added after the mixture was stirred for 3 h. The organic layer was separated and dried with $MgSO_4$. After filtration, the ethyl vinyl ether was evaporated, the remainder was distilled under reduced pressure, and the fraction at 51 °C/80 Pa was collected. The product EEGE (b.p. 152–154 °C) was a colorless liquid and weighted 80.3 g (84%). Elem. Anal. Calcd. for $C_7H_{14}O_3$: C, 57.58%; H, 9.66%. Found: C, 57.77%; H, 9.55%. GC (99.6%)/MS (70 eV) *m/z* (%): 131 (33) $[M-CH_3]^+$, 101 (27) $[M-C_2H_5O]^+$, 73 (88) $[M-C_4H_9O]^+$. $^1H$ NMR ($CDCl_3$, $\delta$, ppm): 4.76 [m, $-O-CH(CH_3)-O-$], 3.35–3.90 (m, $-O-CH_2CH_3$ and $-O-CH_2-C_2H_4O$), 3.15 (m, methine *CH* of the epoxy ring), 2.61–2.91 (m, methylene $CH_2$ of the epoxy ring), 1.33 [d, $-OCH(CH_3)-O-$], 1.19 (t, $-O-CH_2-CH_3$). FTIR (film, $\nu$): 1350, 1254 $cm^{-1}$.

### 2.4. Anionic copolymerization of EEGE with EO

Diphenylmethyl potassium (DPMK) was prepared according to the literature [19]: to a 150 mL three-neck flask, 100 mL of dry THF and 7.7 mL (0.06 mol) of naphthalene were added. Then 2.34 g (0.06 mol) of potassium with fresh surface was added in nitrogen atmosphere, after stirring for 4 h, 11.1 g (0.066 mol) of diphenylmethane was introduced by a syringe and the system was refluxed at 80 °C for 24 h and titrated with 0.1 M HCl after filtration, the concentration of DPMK was 0.57 M.

The typical procedure was shown as follows: a 150 mL kettle was vacuumed at 80 °C for 2 h and cooled to room temperature and then to 0 °C. Given volumes of initiator solution [triethylene glycol (0.29 mL, 2.19 mmol) with DPMK (2.0 mL, 1.14 mmol) in a mixture of THF and DMSO (10/40 v/v, 50 mL)], EEGE (11.1 g, 75.8 mmol) and EO (30.0 g, 681.8 mmol) were introduced successively into the kettle under magnetic stirring. Subsequently, it was heated to 60 °C under stirring for 48 h. The reaction was terminated by the addition of a few drops of acidified methanol. After all the solvents were removed by reduced distillation, the crude product was dissolved in $CH_2Cl_2$, dried over anhydrous $MgSO_4$ and filtered. The yellowy viscous wax-like product, a linear α,ω-dihydroxyl poly(ethylene oxide) with pendant protected hydroxymethyls [*l*-poly($EO_{10.6}$-*co*-EEGE)] was obtained in a yield of 94% after $CH_2Cl_2$ was removed. The model copolymer *l*-poly($EO_{43.5}$-*co*-EEGE) was synthesized by the same method.

### 2.5. Determination of reactivity ratio of EO and EEGE

The copolymerization of EO and EEGE with different feed ratios was carried out under the same conditions mentioned above. The copolymerization experiments were terminated at less than 10% conversion. After a definite reaction time (2 h), all the solvents and residual monomers were removed by reduced distillation, the products were dried, weighed, and then characterized by $^1H$ NMR. The reactivity ratios were calculated by YBR [20] method by Eq. (1):

$$\left(x/\sqrt{y}\right)r_1 - \left(\sqrt{y}/x\right)r_2 + \left(1/\sqrt{y} - \sqrt{y}\right) = 0 \quad (1)$$

where $x$ is the feed ratio of EO to EEGE, $y$ is the molar ratio of EO to EEGE in the copolymer. $r_1$ and $r_2$ are reactivity ratios of EO and EEGE, respectively.

### 2.6. Cyclization of l-poly(EO-co-EEGE) and purification

In a flask, finely ground KOH (1.0 g) was dispersed in a mixture of THF and heptane (70/30 v/v, 100 mL) and stirred under nitrogen at 40 °C. The purpose of the poor solvent, heptane, was to improve ring closure by reducing the end-to-end distance [21,22]. *l*-Poly($EO_{10.6}$-*co*-EEGE) (7.0 g) and TsCl (161 mg) were dissolved in 100 mL of THF in a separate flask. This solution was then added dropwise to the KOH dispersion via a syringe pump over 48 h. After a further 72 h under reflux (40 °C) the mixture was filtered and the filtrate was evaporated under reduced pressure. The crude cyclized product was obtained.

### 2.7. Purification of crude cyclized product

The typical purification procedure was shown as follows: the crude cyclized product with high contents of EEGE (*l*-poly($EO_{10.6}$-*co*-EEGE) as precursor) was insoluble in water, so it should be hydrolyzed in acidic conditions, then the hydroxyl groups were recovered by breaking of acetal linkage of EEGE units of copolymer chains. The hydrolysis of EEGE segments of copolymer [23] required two steps: (a) the crude cyclized product (6.0 g) was mixed with 80 mL of formic acid, and the solution was stirred at 20 °C for 30 min and then poured into

methanol. The precipitate was separated and dried in vacuo at 50 °C; (b) the dried product dissolved in a mixture of dioxane (50 mL), methanol (30 mL) and KOH methanol solution (1 N, 20 mL) was refluxed for 24 h and then neutralized with 5% HCl. After removal of solvents under reduced pressure, the polymer was dissolved in water and purified by ultrafiltration membrane. The typical procedure was shown as follows: an aqueous solution of the polymer was added to the ultrafiltration separator with the poly(ether sulfone) membrane under magnetic stirring, then the formed salts were separated under nitrogen pressure. The filtrated aqueous solution was concentrated to dryness, dissolved in $CH_2Cl_2$, dried over anhydrous $MgSO_4$ and filtered. The filtrate was distilled in vacuum to remove $CH_2Cl_2$ and dried in vacuo at 50 °C. The hydrolyzed product with pale yellow color was obtained with a yield of 93%.

The crude hydrolyzed product (4.0 g) was then dissolved in 40 mL of distilled water (100 g/L), to which an aqueous solution of α-CD (100 mL, 100 g/L) was added at room temperature; the ratio of α-CD to linear byproducts (about 25%) which was estimated from the GPC was 10/1 (w/w) [24]. The resulting clear solution was ultrasonically stirred for 30 min and then turbid solution appeared. It was allowed to stand overnight at room temperature and a white precipitate formed. The mixture was centrifuged and filtered to obtain a clear aqueous solution. The solvent was distilled and a solid mixture of the cyclic product, unthreaded α-CD or a small quantity of linear byproducts remained. This solid mixture was dissolved in dichloromethane and filtered to remove the unthreaded α-CD. The filtrate was distilled by rotating evaporation to obtain the product. The procedure was repeated twice to obtain the pure cyclized product [*c*-poly($EO_{10.6}$-*co*-Gly)]. It was a white waxy solid.

### 2.8. Synthesis of graft copolymers c-PEO-g-PCL

In a typical process, a dried ampoule containing ε-caprolactone (1.4 mL, 13.1 mmol), and *c*-poly($EO_{10.6}$-*co*-Gly) ($M_n = 6800$, 0.14 g, 0.02 mmol) was bubbled with nitrogen for 1 h at room temperature and then a given amount of catalyst ([Sn($Oct_2$)]/[OH] = 0.5) was injected under nitrogen by a syringe. The reaction was allowed to proceed for 24 h at 100 °C. After cooling to room temperature, the products were dissolved in THF and precipitated in cold diethyl ether. The copolymers were purified twice by dissolution/precipitation with THF/ether.

## 3. Results and discussion

### 3.1. Characterization of parent copolymers l-poly(EO-co-EEGE)

In Scheme 1, the procedure for the synthesis of *l*-poly(EO-*co*-EEGE) was described. In the anionic copolymerization of EO and glycidol, glycidol should be protected because the exchanging reaction between hydroxyl of glycidol and DMPK will occur, so the side reaction would be unavoidable. Glycidol (Gly) was protected with ethyl vinyl ether first and then was copolymerized with EO using the mixture solution of triethylene glycol and DPMK as initiator. A linear α-methyl-ω-hydroxyl poly(EO-*co*-EEGE) was formed. In order to control the polymerization reasonably, it was important that only 20–40% of the hydroxyl groups of the triethylene glycol were activated, otherwise alkoxides would be precipitated [25]. A mixture of DMSO and THF (4/1 v/v) was used as solvent for polymerization instead of THF because propagating alkoxides would be aggregated in pure THF [26]. Under such conditions, all of the hydroxyl groups of triethylene glycol could efficiently initiate the copolymerization of EO and EEGE because of the rapid exchange of protons between dormant hydroxyls and propagating alkoxides, and all the chains grew at the same rate [26]. Two kinds of parent copolymers with different contents of EEGE and different molecular weights could be prepared by varying the monomer feed ratio and initiator volume (Table 1).

According to the theory of copolymerization, the copolymer composition and its distribution are dependent on the monomer reactivity ratios. So, it is necessary to determine the monomer reactivity ratios. The monomer reactivity ratios of EO and EEGE could be derived by YBR [20] method based on the results given in Table 2; the values are $r_{1(EO)} = 1.20 \pm 0.01$, $r_{2(EEGE)} = 0.76 \pm 0.02$, and $r_1 \times r_2 \approx 1$. Because of $r_{1(EO)} > 1$, $r_{2(EEGE)} < 1$, and $r_1 \times r_2 \approx 1$, the theory of copolymerization leads to the conclusion that the anionic copolymerization of EO and EEGE is apt to the ideal nonazeotropic copolymerization and the incorporation of the comonomer is random.

Fig. 1 plot (I) is a typical $^1$H NMR spectrum of the copolymer *l*-poly(EO-*co*-EEGE), the quadruplets at $\delta = 4.70$–$4.73$ are assigned to the methine protons ($H_f$) of EEGE moiety, the doublets at $\delta = 1.30$, 1.29 and the triplet at $\delta = 1.21$, 1.19, 1.18 are assigned to methyl protons of EEGE moiety ($H_g$, $H_i$), the chemical shift at $\delta = 3.53$–$3.80$ are assigned to protons of main chain ($H_a$, $H_b$, $H_c$, $H_d$) and protons of lateral chains ($H_h$, $H_e$). The copolymer composition can be readily obtained by using the following formula based on the $^1$H NMR spectrum:

$$R_T = \frac{4A_f}{A_{sum} - 7A_f} \tag{2}$$

where $R_T$ is the molar ratio of EEGE to EO in the copolymer; $A_{sum}$ and $A_f$ represent the peak area sum of the protons a–e and h and the peak areas of the methine protons of the EEGE moiety, respectively. The $R_T$ values of copolymers A and B are 1/10.6 and 1/43.5, respectively, which are nearly

Table 1
The data for parent copolymers *l*-poly(EO-*co*-EEGE)

| Sample | $R_f$[a] | $R_T$[b] | $M_n$[c] | $M_w/M_n$[d] | $N_{EEGE}$[e] |
|---|---|---|---|---|---|
| A | 1/9 | 1/10.6 | 12,500 | 1.06 | 20 |
| B | 1/39 | 1/43.5 | 6400 | 1.16 | 3 |

[a] The feed ratio of EEGE to EO.
[b] The molar ratio of EEGE to EO in copolymer poly(EO-*co*-EEGE) measured by $^1$H NMR.
[c] Number-average molecular weight determined by GPC, calibrated against PS standard.
[d] The polydispersity determined by GPC.
[e] The number of EEGE units in poly(EO-*co*-EEGE) calculated by the integration of protons from $^1$H NMR.

Table 2
Determined and analyzed results of EO and EEGE copolymerization

| Sample | $R_f$[a] | $R_T$[b] | Conversion[c] (%) |
|---|---|---|---|
| 1 | 1/18 | 1/21.7 | 7.2 |
| 2 | 1/14 | 1/16.8 | 6.3 |
| 3 | 1/9 | 1/10.8 | 5.1 |
| 4 | 3/7 | 1/2.9 | 4.9 |
| 5 | 1/1 | 1/1.2 | 4.2 |
| 6 | 7/3 | 1/0.6 | 3.8 |

[a] The feed ratio of EEGE to EO.
[b] The molar ratio of EEGE to EO in copolymer poly(EO-*co*-EEGE) measured by $^1$H NMR.
[c] Determined by gravimetric method.

equivalent to the monomer feed ratio of EEGE to EO (1/9 and 1/39). So, the linear α,ω-dihydroxyl poly(ethylene oxide)s with pendant protected hydroxymethyls (*l*-poly(EO-*co*-EEGE)) can be described as *l*-poly($EO_{10.6}$-*co*-EEGE) (A) and *l*-poly($EO_{43.5}$-*co*-EEGE) (B). The number of the protected hydroxyls on the PEO chain could be evaluated by the combination of the molecular weight determined by GPC and $^1$H NMR data using Eq. (3):

$$N_{EEGE} = \frac{M_n}{(146 + 44/R_T)} \quad (3)$$

in which $M_n$ is the molecular weight of *l*-poly(EO-*co*-EEGE), 146 and 44 are the molar masses of EEGE and EO, and $R_T$ is the molar ratio of EEGE units to EO units in *l*-poly(EO-*co*-EEGE); the calculated $N_{EEGE}$ values are about 20 and 3, respectively.

### 3.2. Cyclization of l-poly(EO-co-EEGE) and purification

The ring closure of *l*-poly(EO-*co*-EEGE) was achieved via ether linkage by reaction with tosyl chloride (TsCl) in the presence of solid KOH. End-to-end intramolecular coupling was promoted over intermolecular chain extension by conducting the reaction at high dilution [$C^* < 10^{-5}$ mol/L]. This synthesis was based on a method reported by Booth et al. for preparation of cyclic poly(ethylene oxide) [21,22]. They also reported a second method for ring closure via an acetal linkage (reaction of α,ω-dialkoxide with $CH_2Cl_2$) [27]. We have followed the first method because of the relative chemical stability of the ether linkage compared to the acetal linkage, which is subjected to scission under acidic conditions.

The crude product obtained from the above reaction was a mixture of linear precursor, chain-extended polymer, and cyclic polymer as depicted by the GPC chromatogram [Fig. 2 curve (b)]. The GPC chromatogram of the starting material [Fig. 2 curve (a)] contained a single narrow peak. After cyclization, the major elution peak was shifted to the larger volume and the peak molecular weight of $M_{pl} = 15{,}000$ for *l*-poly($EO_{10.6}$-*co*-EEGE) was changed to $M_{pc} = 11{,}800$ for *c*-poly($EO_{10.6}$-*co*-EEGE) owing to the smaller hydrodynamic volume of the latter ($M_{pc}/M_{pl} = 0.79$), indicating the formation of the cyclic polymer [28], and a broad shoulder assigned to chain-extended polymer

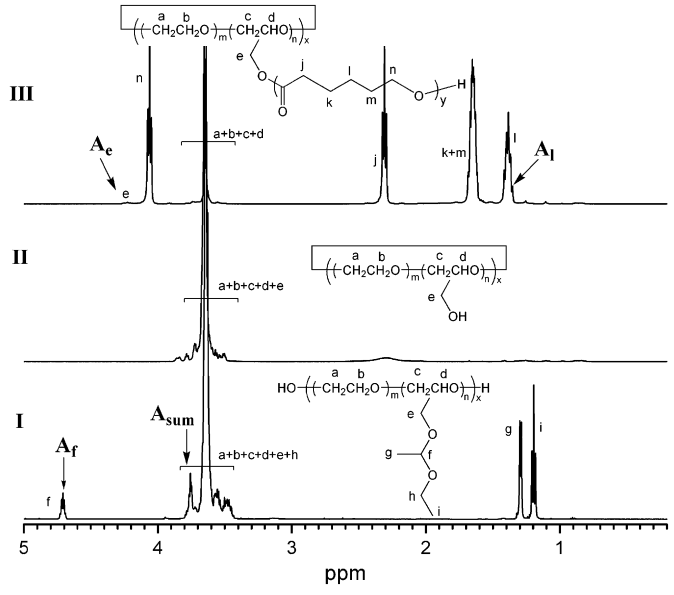



Fig. 1. $^1$H NMR spectrum of the amphiphilic macrocyclic graft copolymers *c*-PEO-*g*-PCL and its precursor in $CDCl_3$: (I) *l*-poly($EO_{10.6}$-*co*-EEGE; entry A in Table 1), (II) *c*-poly($EO_{10.6}$-*co*-Gly) ($M_n = 6.8 \times 10^3$), (III) *c*-PEO-*g*-PCL (entry $A_2$ in Table 3).

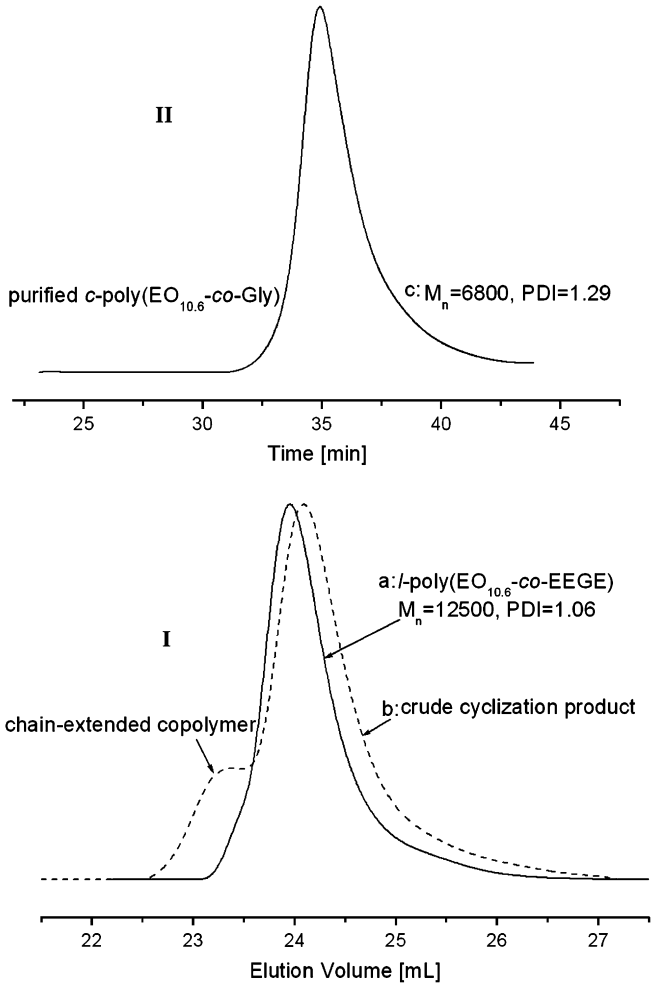



Fig. 2. Typical GPC traces: (curve a) linear copolymer *l*-poly($EO_{10.6}$-*co*-EEGE) (sample A in Table 1), (curve b) crude cyclized product of *l*-poly($EO_{10.6}$-*co*-EEGE), (curve c) purified cyclized product. (I): THF as eluent; (II) 0.1 M aqueous $NaNO_3$ as eluent.

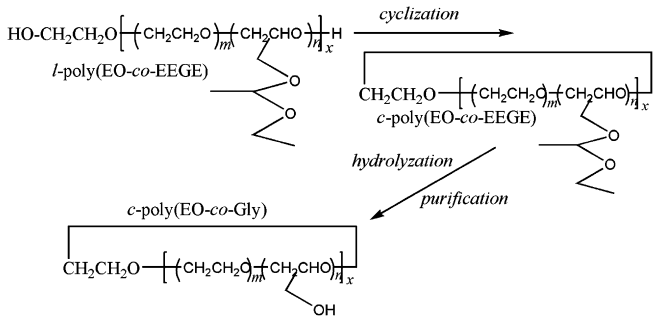
was found at lower elution time. For *l*-poly($EO_{43.5}$-*co*-EEGE), the peak molecular weight of $M_{pl} = 8000$ was changed to $M_{pc} = 6500$ ($M_{pc}/M_{pl} = 0.81$), the ratio ($M_{pc}/M_{pl}$) decreases with increasing the molecular weight of linear precursors.

### 3.3. Preparation of the pure cyclized product as macroinitiator

The separation and purification of cyclized product are very important step for next syntheses of macrocyclic graft copolymers. It was reported that the cyclodextrins (α, β, and γ) can form inclusion complexes with a wide variety of low molecular weight compounds as well as linear polymers, both organic and inorganic [29–31].

Because the crude product of cyclization (*l*-poly($EO_{10.6}$-*co*-EEGE) as precursor) was insoluble in water, the crude cyclized product containing the linear chain-extended polymer was hydrolyzed first and then treated with α-CD. After that, the pure cyclic copolymer of EO and glycidol (Gly) with multipendant hydroxymethyls [*c*-poly($EO_{10.6}$-*co*-Gly)] was obtained. As Fig. 2 plot (c) shows, the peak of linear chain-extended polymer at lower elution time disappeared after the interaction of crude cyclized product with α-CD, and the purification of the cyclized product of *c*-poly($EO_{10.6}$-*co*-Gly) was quite successful. The whole process is outlined in Scheme 2.

In order to obtain direct evidence for the formation of macro-ring, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) was used. However, this technique was difficult to be used to characterize the copolymers directly [32], so the model linear copolymer *l*-poly($EO_{43.5}$-*co*-EEGE) with high EO content which was soluble in water was synthesized and cyclized first, and then purified directly by α-CD for the determination of MALDI-TOF. Fig. 3 shows the MALDI-TOF spectra of linear precursor *l*-poly($EO_{43.5}$-*co*-EEGE) (I) and cyclized product *c*-poly($EO_{43.5}$-*co*-EEGE) (II), the spacings 44.3 and 43.8 amu between the peaks are ascribed to the molar mass of the EO unit and the spacings 146.1 and 146.2 amu for the molar mass of EEGE unit. The spacings 14.7, 29.6, 15.2 and 29.9 amu between the peaks are ascribed to the difference of the molar mass of different combinations of EEGE and EO units, and the molecular-weight decrease of 18 amu after cyclization reaction supports the formation of the ether linkage, consistent with loss of a water molecule upon ring closure.




Scheme 2. Synthesis of cyclic poly(EO-*co*-Gly).

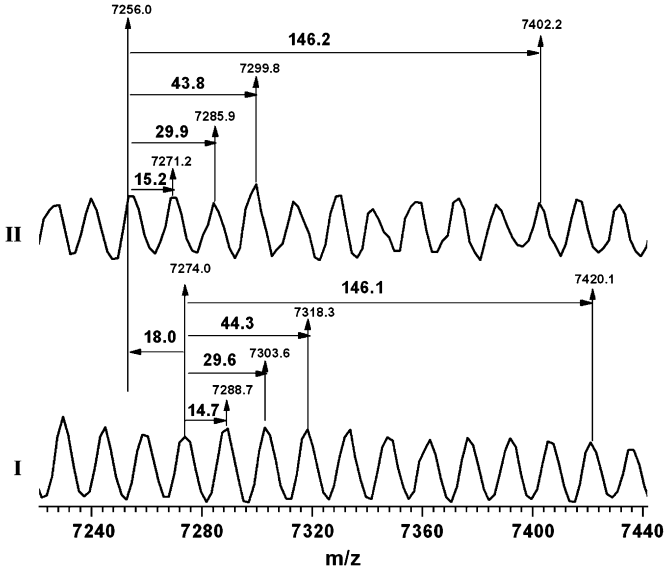



Fig. 3. MALDI-TOF mass spectra of model copolymer for (I) linear precursor *l*-poly($EO_{43.5}$-*co*-EEGE) (sample B in Table 1) and (II) cyclization product *c*-poly($EO_{43.5}$-*co*-EEGE).

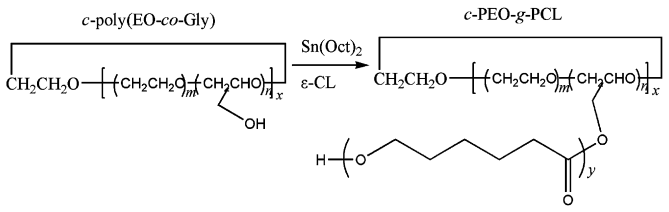
### 3.4. Synthesis of amphiphilic graft copolymers c-PEO-g-PCL

In Scheme 3, the procedure for the synthesis of amphiphilic graft copolymers *c*-PEO-*g*-PCL was described. *c*-Poly(EO-*co*-Gly) with hydroxyl groups could be used as the macroinitiator in the presence of $Sn(Oct)_2$ to initiate the polymerization of CL. The final products were characterized by GPC as shown in Fig. 4. The single peak in all GPC traces confirmed there were no any macroinitiators *c*-poly(EO-*co*-Gly) remained.

Fig. 1 plot (III) shows the $^1H$ NMR spectrum of the *c*-PEO-*g*-PCL. The chemical shift of protons of the methylene (e) of glycidol in *c*-poly(EO-*co*-Gly) at 3.88 ppm was moved to 4.23 ppm after polymerization of CL and the peaks at 1.41, 1.68, 2.36 and 4.06 ppm were attributed to the protons of PCL. The initiating efficiency of *c*-poly(EO-*co*-Gly) with multi-hydroxyl groups for CL polymerization can be calculated by the following formula:

$$E = \frac{A_e/2}{(A_{sum})/(3 + (4/R_T))} \times 100\% \quad (4)$$

where $E$ is the initiating efficiency of hydroxyl groups of *c*-poly(EO-*co*-Gly), $A_{sum}$ and $A_e$ represent the integral area of the protons of the PEO main chain (the peaks at $\delta = 3.35$–$3.90$) and the integral area of the methylene protons (e) linked to ester (the peaks at $\delta = 4.23$), respectively, $R_T$ is




Scheme 3. Synthesis of *c*-PEO-*g*-PCL.

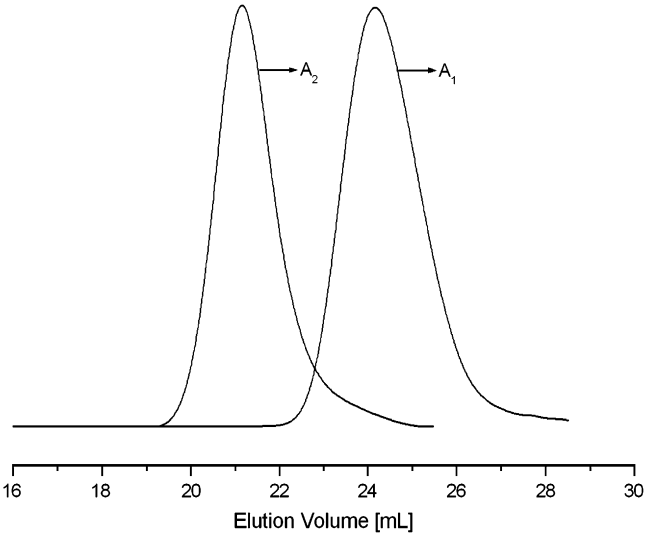



Fig. 4. GPC traces of the graft copolymer: *c*-PEO-*g*-PCL ($A_1$, $A_2$ were prepared as shown in Table 3).

the molar ratio of EEGE to EO in the original copolymer *l*-poly(EO-*co*-EEGE), and it is equivalent to the composition of Gly/EO in copolymer *c*-poly(EO-*co*-Gly). The calculated *E* value is 98.7%. It suggests that nearly all the hydroxyl groups take part in the initiation.

As shown in Table 3, all the conversions of ε-CL are nearly 100%. So the chain length of PCL can be controlled by varying the molar ratio of CL monomer to *c*-poly(EO-*co*-Gly), and the molecular weight of grafted PCL and following the graft copolymer *c*-PEO-*g*-PCL can also be obtained by $^1$H NMR spectrum as shown in the following formula:

$$M_{n,g} = \frac{A_l}{A_e} \times 114 \quad (5)$$

where $M_{n,g}$ is the number-average molecular weight of grafted PCL side chain. $A_e$ and $A_l$ are the integrals of methylene of glycidol segments of *c*-poly(EO-*co*-Gly) and that of methylene in the repeating unit of PCL, respectively. Table 3 summarizes the data for graft copolymerization of CL. As Table 3 shows the molecular weight of grafted PCL derived from $^1$H NMR was near to the theoretical values, but was different from the value from GPC due to the different hydrodynamic volumes of amphiphilic macrocyclic graft copolymer from the linear polystyrene standard.

Table 3
The data for the amphiphilic macrocyclic graft copolymers *c*-PEO-*g*-PCL

| Initiator[a] | Entry | Time (h) | Conversion[b] (%) | $M_n$[c] | $M_w/M_n$[d] | $M_{n\ NMR}$[e] | $M_{n,g}$[f] | $M_{n,t}$[g] |
|---|---|---|---|---|---|---|---|---|
| 1 | $A_1$ | 24 | 98 | 10,200 | 1.22 | 16,900 | 513 | 500 |
| | $A_2$ | 24 | 99 | 63,400 | 1.20 | 84,000 | 3865 | 3760 |
| 2 | $B_1$ | 24 | 98 | 10,200 | 1.22 | 12,700 | 2098 | 2100 |
| | $B_2$ | 24 | 96 | 12,700 | 1.23 | 15,300 | 2975 | 2865 |

[a] For initiators 1 and 2, *c*-poly($EO_{10.6}$-*co*-Gly) ($M_n = 6800$, $M_w/M_n = 1.29$) and *c*-poly($EO_{43.5}$-*co*-Gly) ($M_n = 5200$, $M_w/M_n = 1.23$) were used.
[b] Monomer conversion is determined by gravimetry.
[c] Number-average molecular weight determined by GPC, calibrated against PS standard.
[d] The polydispersity determined by GPC.
[e] $M_{n\ NMR}$ is calculated by the formula: $M_{n\ NMR} = M_{n\ c\text{-poly(EO-}co\text{-Gly)}} + N_{OH} \times M_{n,g}$, $M_{n\ c\text{-poly(EO-}co\text{-Gly)}}$ is the molecular weight of *c*-poly(EO-*co*-Gly) derived by GPC, $N_{OH}$ is the hydroxyl number on *c*-poly(EO-*co*-Gly).
[f] $M_n$ of grafted PCL obtained by $^1$H NMR.
[g] $M_n$ of grafted PCL obtained in theory.

The density of lateral hydroxyl unit on *l*-poly(EO-*co*-EEGE) and *c*-poly(EO-*co*-Gly) could be controlled by varying the monomer feed ratio of EO and EEGE in the anionic copolymerization, so the density of side chain PCL is also controlled.

## 4. Conclusions

A series of amphiphilic macrocyclic graft copolymers composed of a hydrophilic PEO as ring and hydrophobic PCL as lateral chains were prepared by a combination of anionic ring-opening polymerization and coordination–insertion ring-opening polymerization. The synthesized macrocyclic graft copolymers had narrow molecular-weight distributions, and the grafting length and density of side chains were well controlled.

## References

[1] (a) Pedersen CJ. J Am Chem Soc 1967;89:2495;
(b) Pedersen CJ. J Am Chem Soc 1967;89:7017.
[2] (a) Gokel GW, Leevy WM, Weber ME. Chem Rev 2004;104:2723;
(b) Gibson SE, Lecci C. Angew Chem Int Ed 2006;45:1364.
[3] Lehn JM, Malthete J, Levelut AM. Chem Commun 1985:1794.
[4] Gao JP, Fu J, Lin CK, Lin J, Han YC, Yu X, et al. Langmuir 2004;20:9775.
[5] (a) Oike H, Hamada M, Eguchi S, Danda Y, Tezuka Y. Macromolecules 2001;34:2776;
(b) Bielawski CW, Benitez D, Grubbs RH. Science 2002;297:2041;
(c) Pantazis D, Schulz DN, Hadjichristidis N. J Polym Sci Part A Polym Chem 2002;40:1476;
(d) Takano A, Kadoi O, Hirahara K, Kawahara S, Isono Y, Suzuki J, et al. Macromolecules 2003;36:3045.
[6] (a) Sun T, Yu GE, Price C, Booth C. Polym Commun 1995;36:3775;
(b) Sinnathamby P, Yu GE, Price C, Booth C. Chem Commun 1996:31;
(c) Yang Z, Yu GE, Attwood D, Price C, Booth C. Macromolecules 1996;29:8479;
(d) Tezuka Y, Mori K, Oike H. Macromolecules 2002;35:5707;
(e) Singla S, Zhao T, Beckham HW. Macromolecules 2003;36:6945.
[7] (a) Yang Z, Cooke J, Viras K, Gorry PK, Ryan AJ, Booth C. J Chem Soc Faraday Trans 1997;93:4033;
(b) Cooke J, Viras K, Sun T, Yu GE, Yonemitsu T, Ryan AJ, et al. Macromolecules 1998;31:3030.
[8] Jia ZF, Fu Q, Huang JL. Macromolecules 2006;39:5190.
[9] Xu XW, Huang JL. J Polym Sci Part A Polym Chem 2004;42:5523.
[10] Vert M, Li S, Splenehauer G, Guerin P. J Mater Sci Mater Med 1992;3:432.
[11] Herold CB, Keil K, Bruns DE. Biochem Pharmacol 1989;38:73.
[12] Li S, Garreau H, Pauvert B, Mcgrath J, Toniolo A, Vert M. Biomacromolecules 2002;3:525.
[13] Wang SG, Qiu B. Polym Adv Technol 1993;4:363.
[14] Bogdanov B, Vidts A, Van Den Bulcke A, Verbeeck R, Schachet E. Polymer 1998;39:1631.
[15] Jeong B, Choi YK, Bae YH, Zentner G, Kim SM. J Controlled Release 1999;62:109.
[16] Zhou SB, Deng XM, Yang H. Biomaterials 2003;24:3563.
[17] Sosnik A, Cohn D. Polymer 2003;44:7033.
[18] Fitton A, Hill J, Jane D, Miller R. Synthesis 1987:1140.
[19] Normant H, Angelo B. Bull Soc Chim Fr 1960:354.

[20] Yezuielev AI, Brohkina EL, Roskin YS. Vysokomol Soedin Ser 1969;A11:1670.
[21] Yan ZG, Yang Z, Price C, Booth C. Makromol Chem Rapid Commun 1993;14:725.
[22] Yu GE, Sinnathamby P, Price C, Booth C. Chem Commun 1996;1:31.
[23] Taton D, Borgne A, Sepulchre M, Soassky N. Macromol Chem Phys 1994;195:139.
[24] Harada A, Li J, Kamachi M. Macromolecules 1993;26:5693.
[25] Angot B, Taton D, Gnanou Y. Macromolecules 2000;33:5418.
[26] Feng XS, Taton D, Chaikof EL, Gnanou Y. J Am Chem Soc 2005;127:10956.
[27] Sun T, Yu GE, Price C, Booth C, Cooke J, Ryan AJ. Polymer 1995;36:3775.
[28] Semlyen JA. Cyclic polymers. New York: Elsevier; 1986.
[29] Harada A. Coord Chem Rev 1996;148:115.
[30] Harada A, Nishiyama T, Kawaguchi Y, Okada M, Kamachi M. Macromolecules 1997;30:7115.
[31] Harada A, Nishiyama T, Kawaguchi Y, Okada M, Kamachi M. Macromolecules 2000;33:4472.
[32] Willemse RXE, Staal BBP, Donkers EHD, van Herk AM. Macromolecules 2004;37:5717.