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Controlled Synthesis of an ABC Miktoarm Star-Shaped Copolymer by Sequential Ring-Opening Polymerization of Ethylene Oxide, Benzyl β-Malolactonate, and ϵ-Caprolactone

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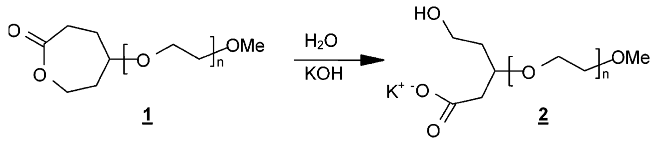
ABSTRACT: This paper reports on the synthesis of an amphiphilic miktoarm ABC star-shaped copolymer, s[(PEO)(PMLABz)(PCL)], consisting of biocompatible/bioresorbable arms. Indeed, PEO is a hydrophilic biocompatible poly(ethylene oxide) arm, PMLABz is a poly(benzyl β-malolactonate) arm precursor of a pH-sensitive bioresorbable poly(β-malic acid) block, and PCL is a hydrophobic bioresorbable poly(ϵ-caprolactone) arm. Each constitutive arm was prepared by ring-opening polymerization. A double-headed PEO macroinitiator [PEO-(OH)-COO$^-$K$^+$] was first prepared by selective hydrolysis of the α-lactone (2-oxepanone) end group of PEO chains end-capped by a ω-methoxy group. The anionic polymerization of benzyl β-malolactonate (MLABz) was selectively initiated by the α-potassium carboxylate end group of PEO in the presence of 18-crown-6 ether. The polymerization of ϵ-caprolactone (ϵ-CL) was initiated by the hydroxyl group left at the junction of the two blocks of the as-prepared PEO-*b*-PMLABz diblock copolymer, in the presence of tin(II) bis(2-ethylhexanoate) (Sn(Oct)$_2$). The macroinitiator, the intermediate diblock, and the final miktoarm star-shaped copolymer were analyzed by ^{1}H NMR spectroscopy and size exclusion chromatography.

Introduction

Increasing attention is paid nowadays to the synthesis and characterization of ABC miktoarm star-shaped copolymers that consist of three different polymer chains emanating from a central junction point.[1−9] Whenever the three arms are sufficiently long and immiscible, a nanophase separation occurs, with formation of long-range nanostructures different from those formed by the linear counterparts of the same composition.[4−6] Adsorption of triarm star-block copolymers of polystyrene, poly(ethylene oxide), and poly(ϵ-caprolactone) at the surface of titanium dioxide particles in toluene is significantly different from that of the parent diblock copolymers.[7] Micellization of this type of ABC copolymers in organic solvents[4,8] and, very recently, in water has also been investigated.[9]

Several methods have been used to synthesize ABC star-shaped terpolymers, including the use of a trifunctional initiator and the sequential polymerization of the parent monomers.[2] An alternative method consists of adding a living polymer A to the reactive end group of a preformed polymer B with formation of an initiator species for the polymerization of the third comonomer C at the junction point of the diblock copolymer.[10] The sequential polymerization of the comonomers A and B can also be initiated by an α,α′-bifunctional macroinitiator C.[11] This strategy has been used in this work to prepare an ABC miktoarm star-shaped terpolymer, in which the three arms are biocompatible/bioresorbable. Indeed, hydrophilic α-hydroxy-α′-carboxylate-ω-methoxypoly(ethylene oxide) [PEO-(OH)-COO$^-$] has been designed as a macroinitiator for the sequential synthesis of two biocompatible/biodegradable polyesters, i.e., poly(benzyl β-malolactonate) (PMLABz) and poly(ϵ-caprolactone) (PCL). Although these two polyesters are hydrophobic, PMLA is easily converted into hydrophilic pH-responsive poly(β-malic acid) (PMLA). Some of us previously reported the anionic polymerization of ethylene oxide initiated by the potassium alkoxide of 1,4-dioxaspiro[4.5]decan-8-ol, followed by the Bayer−Villiger oxidation of the cyclohexanone end group into an ϵ-caprolactone one.[12] The hydrolysis of the lactone end group can release the desired carboxylate and hydroxyl species, as shown in Scheme 1. Polymerization of benzyl β-malolactonate (MLABz) is initiated by potassium carboxylate even in the presence of hydroxyl groups.[13] Moreover, the polymerization of ϵ-caprolactone is commonly initiated by alcohols in the presence of a tin catalysts.[14,15]

Scheme 1. Hydrolysis of γ-Poly(ethylene oxide)(ϵ-caprolactone) [γPEO·CL] to α-Hydroxy-α′-carboxylate Poly(ethylene oxide), [PEO-(OH)-COO$^-$K$^+$]



The composition of the envisioned copolymer makes it unique. It is indeed potentially biocompatible,[14,16] two of the constitutive blocks are biodegradable,[17,18] and the third one (PEO) can be eliminated form the human body if it is of low enough molar mass. Moreover, the amphiphilicity of this copolymer is largely tunable because one block is hydrophilic (PEO), another one is

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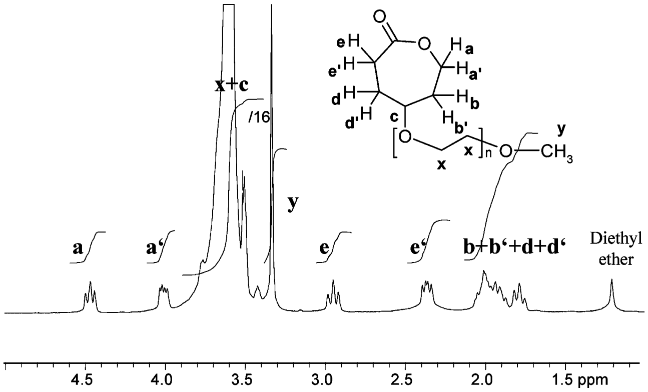


Figure 1. ^{1}H NMR spectrum for the γ-poly(ethylene oxide)-(ϵ-caprolactone) macromonomer [γPEO·CL], **4a** (Table 1) in $CDCl_3$, after precipitation in diethyl ether.

hydrophobic (PCL), and the third one (PMLABz) can be made hydrophilic upon hydrogenation into a pH-responsive block. Because of the unique combination of three different blocks in the star-shaped architecture, the new s[(PEO)(PMLABz)(PCL)] copolymer is expected to have potential in the biomedical field.

Experimental Section

Materials. ϵ-Caprolactone (ϵ-CL) (Aldrich, 99%) was dried over calcium hydride under stirring at room temperature for 48 h and distilled under reduced pressure before use. Methylene chloride (CH_2Cl_2) and pyridine were dried by refluxing over calcium hydride for at least 48 h and distilled prior to use. 1,4-Dioxaspiro[4.5]decan-8-one (Fluka, >97%), lithium aluminum hydride ($LiAlH_4$) (Aldrich, 95%), ethylene oxide (EO) (Messer), potassium hydroxide (KOH) (ChemLab, >85%), methyl iodide (CH_3I) (Aldrich, 99,5%), *m*-chloroperbenzoic acid (*m*-CPBA) (Fluka, 70%), and diethyl ether (Vel) were used as received. (*R,S*)-Benzyl β-malolactonate (MLABz) was synthesized from aspartic acid and purified as reported elsewhere.[19] It was stored at −18 °C, distilled under reduced pressure, and dried by three successive distillations of toluene prior to use. 18-Crown-6 ether (ChemLab, 99%) was dried by three successive azeotropic distillations of toluene. A 0.06 M solution of tin(II) bis(2-ethylhexanoate) ($Sn(Oct)_2$) (ABCR) was prepared in dry toluene. Toluene and tetrahydrofuran (THF) (Labscan, 99%) were dried by refluxing over CaH_2 and Na/benzophenone complex, respectively. THF was further dried over lithium polystyryl oligomers and distilled under reduced pressure, just prior to use.

Synthesis of ϵ-Caprolactone End-Capped PEO (γPEO·CL), 1. The living anionic polymerization of ethylene oxide was initiated by the potassium alkoxide of 1,4-dioxaspiro[4.5]-decan-8-ol, followed by derivatization of the α-acetal end group of PEO into a ketone, followed by the Baeyer−Villiger oxidation of this ketone into a lactone, as detailed elsewhere.[12] The ω-hydroxyl end group was methylated by reaction with 2.5 equiv of CH_3I in toluene at 40 °C for 12 h. The macromonomer (γPEO·CL) was purified by repeated precipitations (four times) in diethyl ether in order to remove impurities (e.g., residual acid after the Baeyer−Villiger reaction). γPEO·CL was dried by three azeotropic distillations of toluene, heated at 45 °C in vacuo overnight, and stored at −20 °C. Purity and end-functionalization were assessed by matrix-assisted laser desorption/ionization time-of-flight (MALDI-Tof) analysis and ^{1}H NMR spectroscopy (Figure 1). MALDI-Tof analysis confirmed the complete methylation of the ω-chain ends.[12]

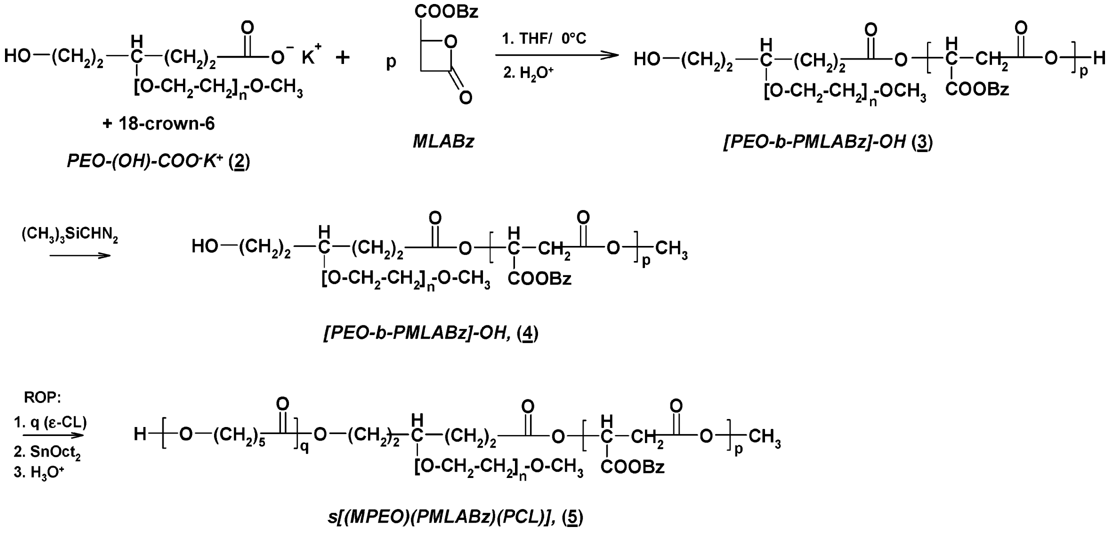
Yield: 31 wt %, $M_{n,NMR} = 600$ g/mol, $M_w/M_n = 1.10$ (where M_n and M_w stand for the number- and weight-average molecular weight, respectively). ^{1}H NMR ($CDCl_3$, δ ppm, Figure 1): 1.8−2.1 (*m*, $4H_{b+b'+d+d'}$), 2.40 (*m*, $1H_{e'}$) 2.98 (*m*, $1H_e$), 3.36 (*s*, $3H_y$), 3.6 (*M*, n × $4H_x$)), 4.05 (*m*, $1H_{a'}$), 4.5 (*t*, $1H_a$).

Synthesis of the α-Hydroxy-α′-carboxylate PEO Macroinitiator [PEO-(OH)-COO^-K^+], 2 (Scheme 1). In a typical experiment, 0.8 mL of a 1 M KOH aqueous solution (0.8 mmol) was added to 0.5 g of γPEO·CL, **1** ($M_n = 600$ g/mol, 0.83 mmol), previously dissolved in 5 mL of double-distilled water. The reaction proceeded under vigorous stirring at room temperature for 2 h. The solution was filtered through a 0.2 μm Millex syringe filter unit, then lyophilized for one night, and dried by repeated azeotropic distillation of toluene. The product (0.4 g) was stored under nitrogen at −20 °C.

Yield: 80 wt %, $M_{n,NMR} = 600$ g/mol, $M_w/M_n = 1.34$. ^{1}H NMR (D_2O + KOH, δ ppm, Figure 4): 1.7−1.85 (*m*, $4H_{b+d}$), 2.25 (*m*, $2H_e$), 3.35 (*s*, $3H_y$), 3.5−3.8 (*m*, $2H_a + 1H_c$ + n × $4H_x$).

Synthesis of the [PEO-*b*-PMLABz]-OH Diblock Copolymer, 3 (Scheme 2). In a previously flame-dried and nitrogen-purged round-bottom flask, 0.12 g of **2** ($M_n = 600$ g/mol, 2.0×10^{-4} mol) was dried by three azeotropic distillations of toluene, then dried at 50 °C in vacuo overnight, and dissolved in 6 mL of dried THF. This solution was added to 0.058 mg of previously dried 18-crown-6 ether (2.2×10^{-4} mol) and thermostated at 0 °C for 20 min. The polymerization of (*R,S*)-benzyl β-malolactonate (0.626 g, 3.0×10^{-3} mol) was typically conducted in a previously flame-dried and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum by initiation with the complex formed between **2** and the 18-crown-6 ether in 14 mL of THF at 0 °C. The monomer conversion was monitored by IR spectroscopy until completeness (170 min) (disappearance of the carbonyl absorption at 1846 cm^{-1}($\nu_{C=O}$)).[13] After addition of a few drops of

Scheme 2. Synthesis of the Star-Shaped s[(PEO)(PMLABz)(PCL)] Copolymer



aqueous HCl (0.1 M), the solvent was evaporated, the solid residue was dissolved in chloroform (10 mL), and the solution was extracted three times with a saturated aqueous solution of KCl (3 × 10 mL) and with deionized water (2 × 10 mL). Finally, the organic phase was poured into 8 volumes of cold heptane (100 mL); the polymer was recovered by filtration and dried under reduced pressure at 35 °C until constant weight, i.e., 0.625 g.

Yield: 89 wt %, $M_{n,NMR}$ = 3700 g/mol, M_w/M_n = 1.32. ^{1}H NMR ($CDCl_3$, δ ppm, Figure 9): 1.6−1.9 (*m*, $4H_{b+d}$), 2.9 (*m*, p × $2H_h$), 3.35 (*s*, $3H_y$), 3.6 (*M*, n × $4H_x$), 5.15 (*m*, p × $2H_i$), 5.51 (*m*, p × $1H_g$), 7.30 (*m*, p × $5H_j$).

The carboxylic acid end group of the diblock copolymer **3** was esterified to **4**, as follows. In a previously flame-dried and nitrogen-purged round-bottom flask, 0.30 g of **3** (8.11 × 10^{-5} mol, M_n = 3700 g/mol) was dried by three azeotropic distillations of toluene (3 × 5 mL) and then dissolved in a mixture of 20 mL of toluene and 2 mL of anhydrous methanol. 9 equiv of trimethylsilyldiazomethane (0.50 mL, 9.84 × 10^{-4} mol) was added, and the reaction was carried out under nitrogen at room temperature.[20] Nitrogen was evolved through an oil valve. After 3 h, the reaction was stopped by addition of a few drops of 0.1 M aqueous acetic acid, and the volatile compounds were removed under reduced pressure. The copolymer was recovered by precipitation in cold heptane, filtered, and dried under reduced pressure at 35 °C until constant weight (0.26 g).

Yield: 85 wt %. ^{1}H NMR ($CDCl_3$, δ ppm): 1.6−1.9 (*m*, $4H_{b+d}$), 2.9 (*m*, p × $2H_h$), 3.35 (*s*, $3H_y$), 3.6 (*M*, n × $4H_x$), 3.7 (*s*, $3H_z$), 5.15 (*m*, p × $2H_i$), 5.51 (*m*, p × $1H_g$), 7.30 (*m*, p × $5H_j$).

Synthesis of the s[(PEO)(PMLABz)(PCL)] Star-Shaped Copolymer, 5 (Scheme 2). In a previously flame-dried and nitrogen-purged round-bottom flask, 0.16 g of **4** (0.043 mmol, M_n = 3700 g/mol, M_w/M_n = 1.32) was dried by three azeotropic distillations of toluene (3 × 10 mL), kept in vacuo at 45 °C overnight, dissolved in 10 mL of dry toluene, and finally added with 0.11 mL of freshly distilled ϵ-caprolactone (1 mmol). After heating under stirring at 80 °C, 0.36 mL of 0.06 M $Sn(Oct)_2$ (0.5 equiv with respect to the hydroxyl groups) was rapidly injected through a septum, and the polymerization occurred for 24 h. After addition of a few drops of 0.1 M aqueous HCl solution, the polymer solution was filtered and poured into 10 volumes of cold heptane (100 mL). After one night at −20 °C, the polymer was recovered by filtration and dried in vacuo until constant weight (0.18 g).

Yield: 66%, $M_{n,NMR}$ = 6200 g/mol, M_w/M_n = 1.50. ^{1}H NMR ($CDCl_3$, δ ppm, Figure 11): 1.38 (*m*, q × $2H_m$); 1.64 (*m*, q × $4H_{n,l}$); 1.6−1.9 (*m*, $4H_{b+d}$); 2.30 (*t*, q × $2H_o$); 2.9 (*m*, p × $2H_h$); 3.35 (*s*, $3H_y$); 3.64 (*M*, n × $4H_x$); 4.05 (*t*, q × $2H_k$); 5.15 (*m*, p × $2H_i$); 5.51 (*m*, p × $1H_g$); 7.30 (*m*, p × $5H_j$).

Characterization. ^{1}H NMR (400 MHz) spectra were recorded in $CDCl_3$ at 25 °C with a Bruker AM 400 apparatus. The molecular weight of the PEO chains was calculated from the relative intensity of the protons of the methoxy end group ($I_{3.35\ ppm}$: 3) and the methylene protons ($-CH_2-CH_2-O$) ($I_{3.6\ ppm}$: 4) of the monomer unit. The completeness of the conversion of the PEO hydroxyl end group into a methoxy one as assessed by the relative intensity of the protons characteristic of both the α ($I_{4.5\ ppm}$) and the ω ($I_{3.35\ ppm}$: 3) end groups and confirmed by matrix-assisted laser desorption/ionization time-of-flight (MALDI-Tof) analysis. MALDI-Tof spectra were recorded with a PerSeptive Biosystem Voyager-DE STR MALDI-Tof spectrometer equipped with 2 m linear and 3 m reflector flight tubes and a 337 nm nitrogen laser (3 ns pulse). Mass spectra were recorded at an accelerating potential of 20 kV in positive ion linear or reflectron mode. The data ($M_{n,MALDI}$ values in Table 1) were processed with the Polymerix software, and the isotope calculator tool of Data Explorer (software supplied by Applied Biosystems) was used for making the isotopic distributions available. A PEO standard with a molecular weight of 1900 (1 mg/mL THF) was used for calibration. Polymer samples were dissolved in THF (1 mg/mL THF). Dithranol (20 mg/mL THF) was used as a matrix, and no cationating agent was added. Size-exclusion chromatography (SEC) was carried out in THF at a flow rate of 1 mL/min at 45 °C using a SFD S5200 autosampler liquid chromatograph equipped with a SFD refractometer index detector 2000 and columns PL gel 5 μm (columns porosity: 10^2, 10^3, 10^4, 10^5 Å). Polystyrene (PS) and PEO standards were used for calibration. FTIR analysis was carried out with a Bio-Rad Excalibur FTIR spectrometer (resolution: 0.2 cm^{-1}). Spectra were recorded (from 4000 to 700 cm^{-1}) with a single reflection crystal system (Split PEA from Harrick) and a DTGS detector. Films of PEO and derivatives were solvent-cast on NaCl and analyzed with a Perkin-Elmer FTIR 1720X spectrometer.

Table 1. Macromolecular Characteristics of Poly(ethylene oxide) (PEO) Derivatives: γ-Poly(ethylene oxide)(ϵ-Caprolactone) [γPEO·CL] (1) and (2) γPEO·CL after Hydrolysis with KOH

	PEO derivative	$M_{n,NMR}$[a]	$M_{n,MALDI}$[b]
1	γPEO·CL	780	750
2a	PEO-(OH)-COOH	800	760 1400[c] 2200[d]
2b	PEO-(OH)-COOH	800	760

[a] M_n calculated by ^{1}H NMR. [b] Determined by MALDI-Tof, linear mode. [c] Second population observed by MALDI-Tof, linear mode. [d] Third population observed by MALDI-Tof, linear mode. M_n stands for number-average molecular weight and MALDI-Tof for matrix-assisted laser desorption/ionization time-of-flight.

Results and Discussion

Synthesis of the α-Hydroxy-α′-carboxylate Poly(ethylene oxide) (PEO) Macroinitiator [PEO-(OH)-COO^-K^+], 1 and 2 (Scheme 1). An α,α′-heterobifunctional PEO macroinitiator was designed for the synthesis of a s[(PEO)(PMLABz)(PCL)] miktoarm star-shaped copolymer, in which PEO stands for poly(ethylene oxide), PMLABz stands for poly(benzyl β-malolactonate), and PCL stands for poly(ϵ-caprolactone). This macroinitiator is actually a PEO chain with two functional α end groups: (i) a potassium carboxylate function, which selectively initiates the ring-opening polymerization (ROP) of benzyl β-malolactonate, and (ii) a hydroxyl group, which is commonly used for the controlled polymerization of ϵ-caprolactone (ϵ-CL) in the presence of a tin octoate catalyst ($Sn(Oct)_2$). Some of us reported elsewhere the α-end-capping of ω-methoxy-PEO by an ϵ-caprolactone unit (**1**), or conversely the substitution of ϵ-caprolactone in the γ-position by a PEO chain (γPEO·CL), so leading to a PEO macromonomer.[12]

A typical ^{1}H NMR spectrum of γPEO·CL is shown in Figure 1 with peak assignment. The broad signal at 3.6 ppm is characteristic of the methylene protons (H_x) of the PEO chain. Because of substitution by the PEO segment, the quick interconversion of the axial and equatorial protons (H_a and $H_{a'}$ or H_e and $H_{e'}$) of the CL ring is limited. Therefore, these four protons (a and a′ and e and e′) next to the ester group are not magnetically equivalent, which is quite consistent with the structure expected for the macromonomer and are evidence for the polymerizable lactone head. Figure 1 also shows two multiplets for protons b, b′ and d, d′. The first multiplet at 1.7 ppm (triplet) is for one proton and the second one at about 2.0 ppm is for three protons, as result of inequivalent chemical shift for protons in the α-position of an asymmetric carbon that cannot be exchanged by rotation. Upon hydrolysis of the lactone ring by KOH, the γPEO·CL macromonomer has been converted into the desired dual macroinitiator (**2**, Scheme 1). An excess of KOH (2.5 equiv) (with respect to the lactone end-group) was used in the first experiments, and this excess was neutralized by HCl after hydrolysis, followed by dialysis against distilled water (desalting).

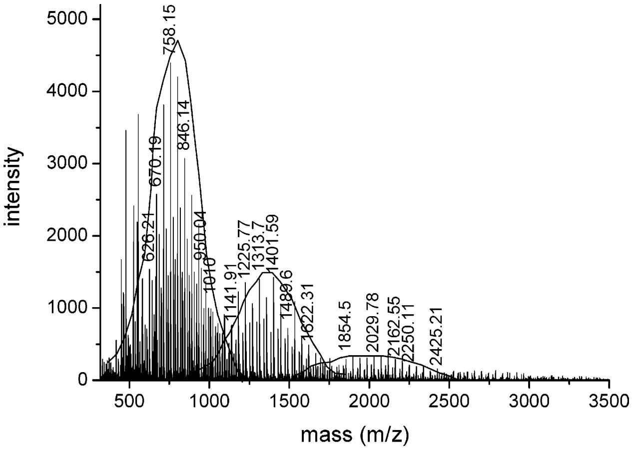


Figure 2. MALDI-Tof spectrum (linear mode) of γ-poly(ethylene oxide)(ϵ-caprolactone) [γPEO•CL] treated by KOH according to nonoptimized conditions (product **2a**, Table 1).

The polymer was recovered by lyophilization, dried by azeotropic distillations of toluene, heated at 40 °C for one night in vacuo, and finally analyzed by SEC, MALDI-Tof, and ^{1}H NMR spectroscopy. The SEC chromatogram is bimodal with a shoulder on the high molecular weight side and a main peak at the same elution volume as the initial γPEO•CL (chromatogram not shown).

Consistently, higher molecular weight species have been observed by MALDI-Tof. Figure 2 shows the MALDI-Tof spectrum in the 319−3000 *m/z* mass range, which emphasizes that three mass populations coexist. The first one has the expected molecular weight ($M_{\mathrm{n,NMR}} = 800$ g/mol, $M_{\mathrm{n,MALDI}} = 760$ g/mol; Table 1, entry 2a, and Figure 2), the second population appears at the double molecular weight ($M_{\mathrm{n,MALDI}} = 1400$ g/mol; Table 1, entry 2a) and the molar mass of the third population is 3 times the molar mass of the first distribution ($M_{\mathrm{n,MALDI}} = 2200$ g/mol). The molecular weight and shape for the main series of the first population fit the $\mathrm{Na^+}$ and $\mathrm{K^+}$ adducts of the α-hydroxy-α′-carboxylate-ω-methoxy-PEO [PEO-(OH)-$\mathrm{COO^-}$] (detailed spectrum not shown). The main series of the higher molecular weight compounds shown in Figure 3 (detailed experimental isotope distribution of the second (Figure 3a) and third (Figure 3b) mass population) can be accounted for by the dimerization and trimerization of the γPEO•CL macromonomer (assignment in Table 2).

To prevent this undesired condensation reaction from occurring, the experimental conditions were modified. KOH (1 equiv) was used instead of an excess previously used. Just after hydrolysis, the polymer was recovered, dried (cf. supra), and directly used to initiate the polymerization of benzyl β-malolactonate (MLABz) in the presence of 18-crown-6 ether.

The ^{1}H NMR spectrum of the lactone end-capped PEO after treatment with ca. 1 equiv of KOH (Figure 4) is significantly different from the initial ^{1}H NMR spectrum (Figure 1).

Fewer peaks are observed because of more rotation freedom for the alkyl chains as result of the ring-opening. Therefore, only one signal is observed for protons "a" and "e" instead of the original splitting. These peaks are observed at lower chemical shifts, peak "a" being hidden by the broad peak of PEO. ^{1}H NMR spectroscopy confirms the completeness of the ring-opening of the lactone by the complete disappearance of the initial signals for protons "e" and "a". Similarly, protons "b" and "b′" and "d" and "d′" (Figure 1) are now chemically equivalent and observed as a broad peak at 1.7 ppm. However, whenever an excess of KOH is used, the hydrolysis product is contaminated by condensation products; an additional peak is observed at 4.15 ppm, as previously observed for copolymers of the γPEO•CL macromonomer with ϵ-caprolactone.[12]

SEC analysis of γPEO•CL before and after alkaline hydrolysis with 1 equiv of KOH shows that M_n remains seemingly unchanged with a slight shift toward smaller M_n and a slight increase in M_w/M_n (Table 4, chromatograms not shown). Moreover, MALDI-Tof analysis of the as-prepared PEO macroinitiator (not shown in Figure

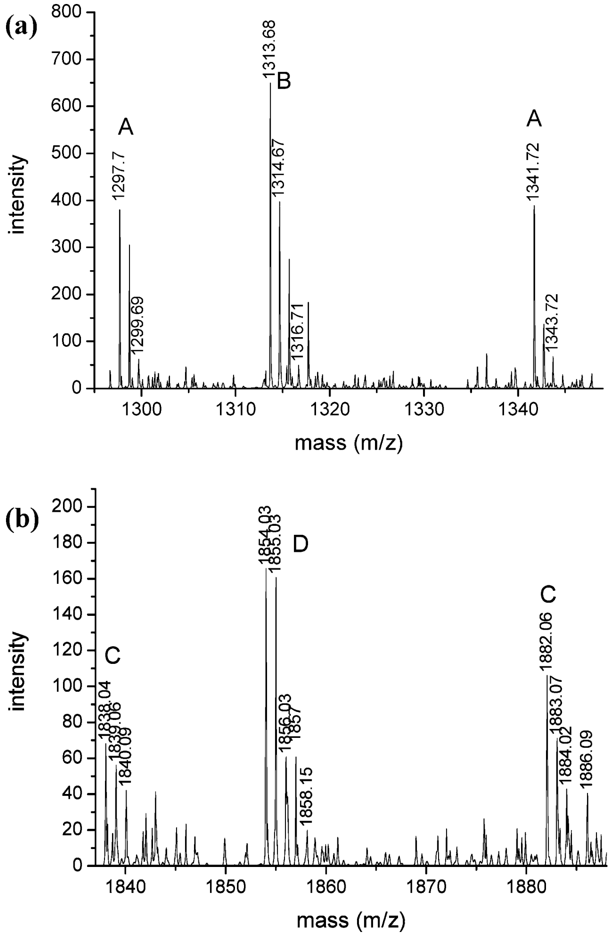


Figure 3. Details of the experimental isotope distribution MALDI-Tof spectrum for sample **2a** (Table 1) (reflectron mode): (a) second molecular weight population (dimerization), (b) third molecular weight population (trimerization). MALDI-Tof stands for matrix-assisted laser desorption/ionization time-of-flight.

Table 2. Peak Assignments for the Second and Third Molecular Weight Population of Sample 2a (Table 1) in Figure 3a,b

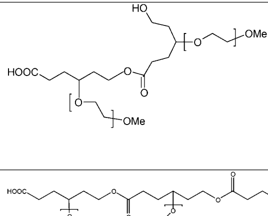
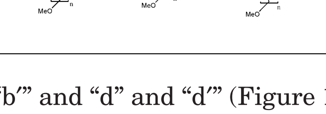
code	description	cation	structure	bruto formula
A	dimer	Na		$(C_2H_4O)_{22}C_{14}H_{26}O_7Na$
B	dimer	K		$(C_2H_4O)_{22}C_{14}H_{26}O_7K$
C	trimer	Na		$(C_2H_4O)_{31}C_{21}H_{38}O_{10}Na$
D	trimer	K		$(C_2H_4O)_{31}C_{21}H_{38}O_{10}K$

Table 3. Peak Assignments for the Matrix-Assisted Laser Desorption/Ionization (MALDI) Spectrum of Figure 6 (Sample 2b)

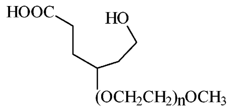
code	description	cation	structure	bruto formula
A	desired	Na		$(C_2H_4O)_{14}C_7H_{14}O_4Na$
B	desired	K		$(C_2H_4O)_{14}C_7H_{14}O_4K$
C	desired	H		$(C_2H_4O)_{15}C_7H_{14}O_4H$
D	unmodified PEG	Na	$CH_3OCH_2CH_2(OCH_2CH_2)nOCH_3$	$(C_2H_4O)_{16}C_4H_{10}O_2Na$
E	unmodified PEG	K	$CH_3OCH_2CH_2(OCH_2CH_2)nOCH_3$	$(C_2H_4O)_{16}C_4H_{10}O_2K$

Table 4. Macromolecular Characteristics of the (Co)polymer Formed at Each Synthesis Step

	description	$M_{n,\mathrm{theor}}$	$M_{n,\mathrm{NMR}}{}^{b}$	$M_w/M_n{}^{e}$
1	γPEO·CL		600	1.10
2	PEO-(OH)-COO$^-$K$^+$		600	1.34
3a	[PEO-*b*-PMLABz]-OH	3700^a	3750^c	1.32
3b	[PEO-*b*-PMLABz]-OH	3150^a	2800^c	1.28
5	s[(MPEO)(PMLABz)(PCL)]	6350^b	6200^d	1.50

[a] $M_{n,\mathrm{theor}} = M_n(\mathrm{PEO}) + [\mathrm{MLABz}]_0/[\mathrm{PEO}] \times \mathrm{MW}_{\mathrm{MLABz}}$. [b] $M_{n,\mathrm{theor}} = M_n(\mathrm{PEO}) + M_n(\mathrm{PMLABz}) + [\epsilon\text{-CL}]_0/[[\mathrm{PEO}\text{-}b\text{-PMLABz}]\text{-OH}] \times \mathrm{MW}_{\epsilon-\mathrm{CL}}$, at 100% of conversion. [c] Calculated by ^{1}H NMR according to eq 1. [d] Calculated by ^{1}H NMR according to eq 2. [e] As determined by SEC calibrated by PS standards.

5) shows only one population at $M_{n,\mathrm{MALDI}} = 760$ g/mol (Table 1, entry 2b) and no chains of higher molecular weight (Figure 5).

Figure 6 shows details of the experimental isotope distribution of the MALDI-Tof spectrum, and the peak assignment is reported in Table 3. The main series have the shape and isotope distribution expected for the desired product, which confirms the success of the lactone hydrolysis.

Finally, the IR spectrum of the γPEO·CL (Figure 7, trace A) shows a strong absorption at 1740 cm^{-1}, characteristic of the C$-$O stretching to the lactone group. Upon hydrolysis by KOH, this absorption disappears in favor of a peak at 1576 cm^{-1}, assigned to the C$-$O stretching of the carboxylate group (Figure 7, trace B). Furthermore, the broad absorption from 2700 to 3500 cm^{-1} in spectrum B confirms the formation of hydroxyl groups.

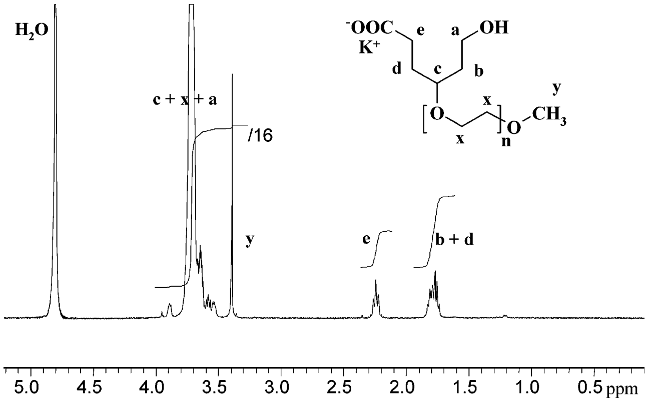


Figure 4. ^{1}H NMR spectrum for α-hydroxy-α′-carboxylate poly(ethylene oxide) [PEO-(OH)-COO$^-$K$^+$] recorded in D_2O after hydrolysis with KOH (the integral c + x + a has been reduced by 16 for being observed completely).

Therefore, an equimolar amount of KOH (~1 equiv) with respect to the PEO end group has been systematically used in this work, and the hydrolysis products have been characterized by SEC, ^{1}H NMR, and MALDI-Tof in order to confirm systematically the structure of the dual macroinitiator.

Synthesis of the [PEO-*b*-PMLABz]-OH Copolymer (3) and Selective Esterification of the Carboxylic Acid End Group (4). Poly(benzyl β-malolactonate), i.e., an aliphatic polyester with pendant protected carboxylic acid groups, can be prepared by an anionic

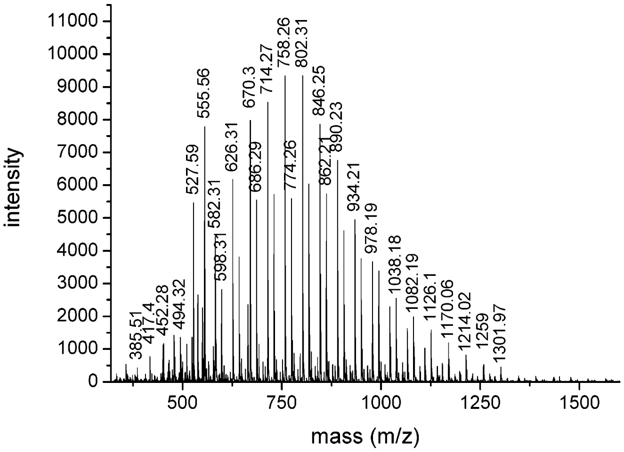


Figure 5. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-Tof) spectrum (linear mode) for γ-poly(ethylene oxide)(ϵ-caprolactone) [γPEO·CL] treated by KOH according to optimized conditions (Table 1, product **2b**).

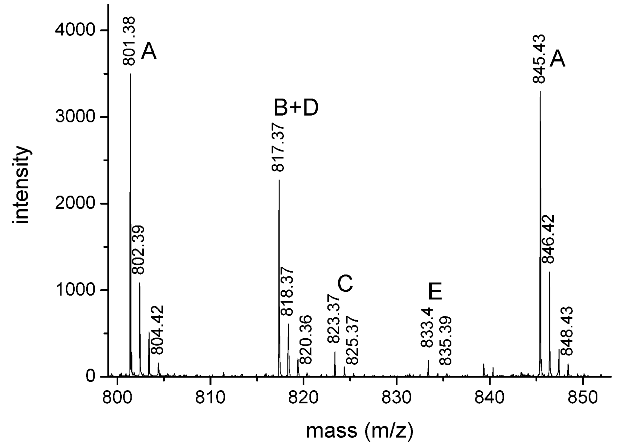


Figure 6. Details of the experimental isotope distribution MALDI-Tof spectrum for sample **2b** (Table 1) (reflectron mode).

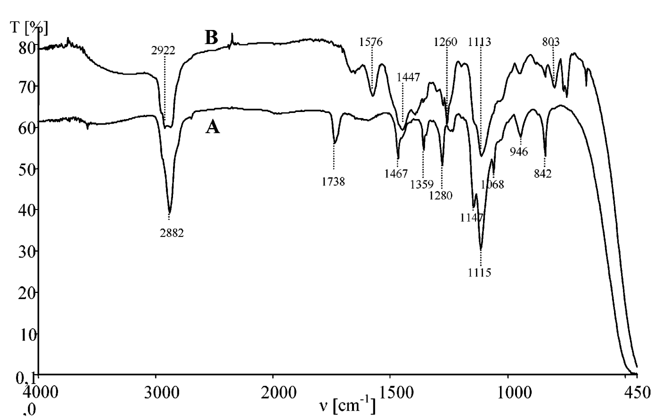


Figure 7. IR spectrum of (A) γPEO·CL and (B) γPEO·CL after treatment with KOH.

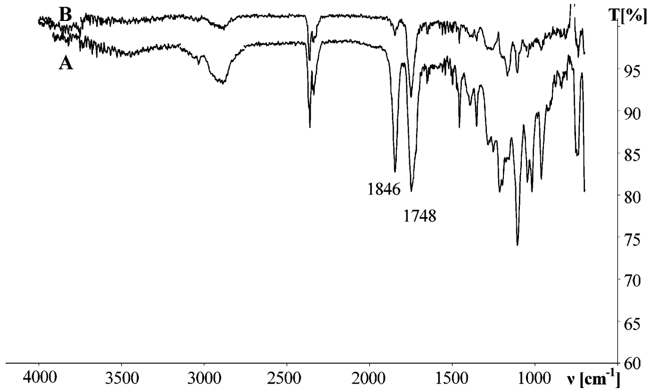


Figure 8. IR spectrum for the benzyl β-malolactonate [MLABz] polymerization initiated by α-hydroxy-α′-carboxylate poly(ethylene oxide) [PEO-(OH)-COO$^-$K$^+$]/18-crown-6 ether in THF at 0 °C under nitrogen: (A) after 80 min of polymerization and (B) after 160 min.

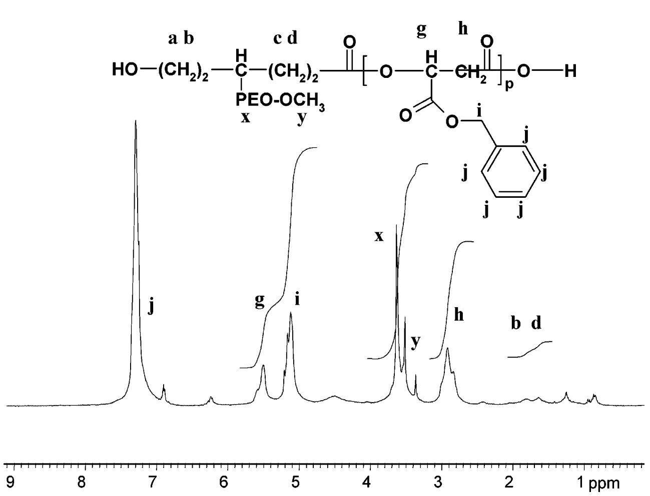


Figure 9. ^{1}H NMR spectrum for the [PEO-*b*-PMLABz]-OH copolymer in CDCl$_3$.

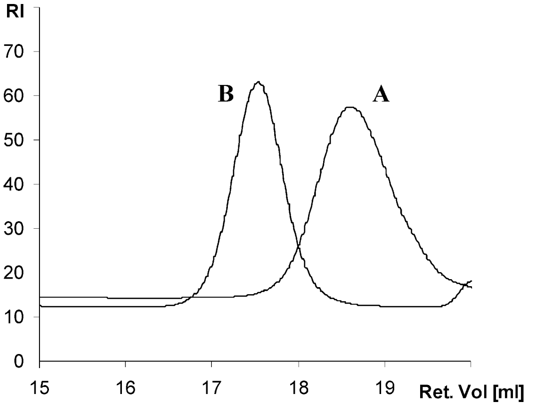


Figure 10. SEC traces for PEO-(OH)-COO$^-$K$^+$ (A) and [PEO-*b*-PMLABz]-OH (B).

ring-opening polymerization of benzyl β-malolactonate, initiated by either tetraalkylammonium benzoate[21] or potassium alkanoate added with a ligand, such as 18-crown-6 ether.[22] In this work, polymerization of carefully purified MLABz was initiated by PEO-(OH)-COO$^-$K$^+$ ligated by 18-crown-6 ether in THF.[13] Indeed, the potassium carboxylate species are unable to initiate the polymerization of ϵ-CL.[23] A 0.2 mol/L MLABz solution was polymerized in THF at 0 °C, with a $[M]_0/[I]_0$ ratio of 15. The progress of polymerization was monitored by FTIR, based on the carbonyl absorption at 1846 cm^{-1} for the monomer and at 1748 cm^{-1} for the polymer. Figure 8 shows the FTIR spectra for samples withdrawn from the reaction medium after 80 min (Figure 8, trace A) and 160 min (Figure 8, trace B), without any purification). Because the absorption by the lactone at 1846 cm^{-1} was weak after 160 min, the polymerization was stopped 10 min later.

Figure 9 shows the ^{1}H NMR spectrum of the [PEO-*b*-PMLABz]-OH copolymer after purification by precipitation in heptane. Peaks “g” and “h” present at 5.5 and 2.9 ppm, respectively, can be assigned to the methine and methylene protons of the PMLABz chain. The methylene protons “i” of the protecting benzyl group are observed at 5.1 ppm. The aromatic protons overlap the CHCl$_3$ protons at 7.3 ppm. The intensity of the methylene protons “i” is 2 times higher than that one of proton “g”, which indicates that the protecting group is preserved during polymerization. The number-average molecular weight ($M_{n,NMR}$) of the diblock copolymer has been calculated by eq 1, and the result is listed in Table 4.

$$M_{n,NMR}([\text{PEO-}b\text{-PMLABz}]\text{-OH}) = I_{5.5}/(I_{3.6}/4) \times \text{DP}(\text{PEO}) \times 206 + M_{n,NMR}(\text{PEO}) \quad (1)$$

$I_{5.5}$ and $I_{3.6}$ are the intensities of the peaks for the protons “g” of PMLABz at 5.5 ppm (see Figure 9) and at 3.6 ppm for the methylene protons of PEO. The molecular weight of the MLABz monomer is 206; DP(PEO) and $M_{n,NMR}$ (PEO) are the degree of polymerization and molecular weight of the PEO block, respectively. The experimental M_n agrees well with the theoretical value at 100% conversion (Table 4, samples **3a** and **3b**). As previously reported, polymerization of MLABz is sensitive to temperature and monomer concentration.[13] Therefore, polymerization has been carried out at 0 °C with an initial MLABz concentration of 0.2 mol/L to restrict undesirable transfer and termination reactions.[13] Nevertheless, small quantities of fumarate derivatives, i.e., transfer reaction products, are formed as observed by ^{1}H NMR spectroscopy (vinyl protons of fumaric esters: ROOC−CH=CH−COO$^-$) at 6.8 ppm. High conversion (higher than 90%) and long polymerization time might be an explanation. The success of copolymerization has been assessed by SEC.

Figure 10 compares the SEC traces for the PEO macroinitiator (trace A) and the [PEO-*b*-PMLABz]-OH diblock (trace B). The final chromatogram (trace B) is monomodal, symmetric, and completely shifted to smaller elution volumes compared to the initial trace A, consistent with apparently complete initiation by the macroinitiator. It must be noted that the unreacted lactone end-capped PEO (γPEO•CL) was completely eliminated by precipitation and washing with water. The polydispersity index (Table 4) is seemingly the same before (1.34) and after (1.32) polymerization of MLABz.

Prior to synthesis of the third block, the carboxylic acid end group has been esterified in order to avoid any interference with the subsequent ϵ-caprolactone (ϵ-CL) polymerization. For being selective in the presence of a hydroxyl group at the junction point of the diblock, esterification has been carried out with 9 equiv of trimethylsilyldiazomethane[20] (with respect to the carboxylic group). Resonance of the ω-methoxycarbonyl end group has been observed by ^{1}H NMR at 3.7 ppm.

Synthesis of the s[(PEO)(PMLABz)(PCL)] Miktoarm Star-Shaped Copolymer by Ring-Opening Polymerization of ϵ-CL, 5 (Scheme 2). Ring-opening polymerization of ϵ-caprolactone (ϵ-CL) has been initiated by the pendant hydroxyl group at the junction of the PEO and PMLABz blocks using tin(II) bis(ethyl hexanoate) ($Sn(Oct)_2$) as a catalyst. $Sn(Oct)_2$ has been reported to react with hydroxyl groups with the fast and reversible formation of tin(II) alkoxide initiating species.[14,15] So, for a [ROH]/[$Sn(Oct)_2$] ratio higher than 2, ROH is not only an initiator but also a chain transfer agent.[14]

The ϵ-CL polymerization has been initiated in toluene at 80 °C, with an initial monomer to hydroxyl molar ratio of 23 and with 0.5 equiv of $Sn(Oct)_2$ with respect to the hydroxyl groups. After 5 h, the ϵ-CL conversion is only 10% as estimated by ^{1}H NMR, which points out a much slower polymerization compared to the ϵ-CL homopolymerization initiated by α-hydroxymonomethoxy-PEO. After 24 h, the polymer has been collected by precipitation in heptane. A typical ^{1}H NMR spectrum for the star-shaped copolymer recorded in $CDCl_3$ is shown in Figure 11.

The characteristic methylene protons of PCL appear at 4.05 (k), 2.3 (o), 1.7 (l, n), and 1.4 ppm (m). On the basis of the molecular weight of the initiating diblock copolymer, the number-average molecular weight of the terpolymer has been calculated by eq 2

$$M_{\mathrm{n,NMR}}(\mathrm{s[(PEO)(PMLABz)(PCL)]}) = [(I_{4.05}/2)/(I_{3.6}/4)] \times \mathrm{DP(PEO)} \times 114 + M_{\mathrm{n,NMR}}([\mathrm{PEO\text{-}}b\mathrm{\text{-}PMLABz}]\text{-OH}) \quad (2)$$

where $I_{4.05}$ and $I_{3.6}$ are the intensities for the protons "k" of PCL values of the peaks at 4.05 ppm (see Figure 11) and for the methylene protons of PEO at 3.6 ppm. 114 is the molecular weight of ϵ-CL, DP(PEO) is the degree of polymerization of the PEO block, and $M_{\mathrm{n,NMR}}$([PEO-*b*-PMLABz]-OH) is the molecular weight of the diblock copolymer. The experimental degree of ϵ-CL polymerization agrees well with the theoretical value (Table 4, sample 5).

Figure 12 shows the traces for the [PEO-*b*-PMLABz]-OH diblock copolymer (trace A) and the s[(PEO)-(PMLABz)(PCL)] star-shaped copolymer (trace B). The chromatogram B is monomodal with a maximum of the peak shifted toward smaller elution volumes and a substantially increased polydispersity, more likely in relation to a slow initiation. The slow polymerization of the second and the third block might result from interactions of the propagating species with the first PEO block, which needs however further investigation.

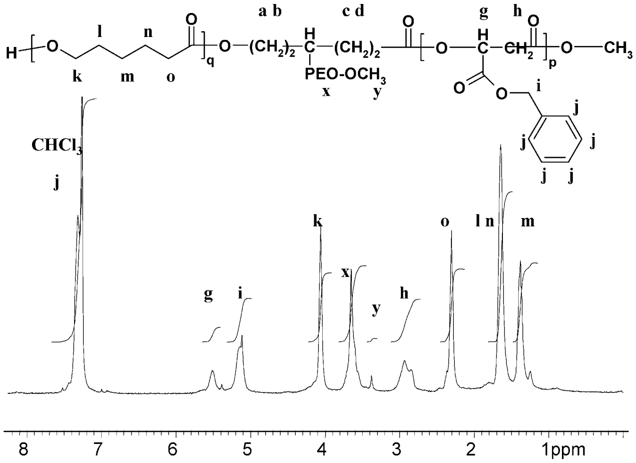


Figure 11. ^{1}H NMR spectrum for the ABC s[(PEO)(PMLABz)(PCL)] star-shaped copolymer in $CDCl_3$.

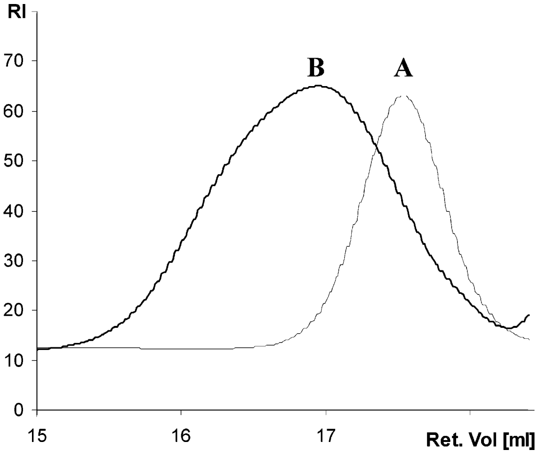


Figure 12. SEC traces for (A) the [PEO-*b*-PMLABz]-OH and (B) the star-shaped s[(PEO)(PMLABz)(PCL)].

Conclusions

The envisioned ABC miktoarm star-shaped copolymer consisting of PEO, PMLABz, and PCL was successfully synthesized, by using a dual PEO macroinitiator. Although the anionic polymerization of the first two segments (PEO and PMLABz) is well controlled and leads to blocks with low polydispersity, the synthesis of the third arm, PCL, is more touchy. This polymerization failed in the presence of $AlEt_3$ (not discussed herewith). Although it occurred with $Sn(Oct)_2$, it is slow and the molecular weight distribution is broad. This step needs optimization before considering the catalytic hydrogenolysis of the benzyl ester functions of the PMLABz block. Then, a pH-sensitive ABC star-shaped copolymer will be formed, with a polyacid block soluble at high pH and able to trigger micellization at low pH as result of insolubility.

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