Lactone End-Capped Poly(ethylene oxide) as a New Building Block for Biomaterials

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ABSTRACT: This paper reports on the synthesis of a novel poly(ethylene oxide) (PEO) macromonomer, which can be copolymerized with ϵ-caprolactone (ϵ-CL) by ring-opening polymerization (ROP). PEO chains end-capped by an ϵ-caprolactone unit (γPEO·CL) have been synthesized by living anionic ring-opening polymerization of ethylene oxide (EO) initiated by the potassium alkoxide of 1,4-dioxaspiro[4.5]decan-8-ol, followed by derivatization of the acetal into a ketone and the Baeyer−Villiger oxidation of the ketone into a lactone. The end-capping of PEO by ϵ-CL was assessed by FTIR, MALDI−TOF, and ^{1}H NMR spectroscopy.This type of macromonomer is a precursor of amphiphilic comblike copolymers consisting of a biodegradable hydrophobic backbone of poly-(ϵ-caprolactone) (PCL) and hydrophilic PEO grafts. Copolymerization of γPEO·CL with ϵ-CL was successfully initiated by aluminum alkoxide.

Introduction

Poly(ethylene oxide) (PEO) is known for solubility in both organic and aqueous media, hydrophilicity and biocompatibility.[1] It has great potential in biomedical applications, being for instance very efficient in preventing protein adsorption at surfaces as illustrated by reduction in cell adhesion in aqueous systems,[2] nonrecognition of surfaces by the mononuclear phagocyte system (MPS),[3] and reduced complement activation in the human body.[4] PEO-containing amphiphilic graft copolymers may therefore be useful to modify biomedical polymer surfaces[5,6] and to design drug-delivery systems.[7−10] Grafting of poly(ethylene oxide) brushes on a solid surface reduces efficiently the nonspecific adsorption of biomolecules and biospecies, such as proteins and platelets.[6,11] Griffith et al. prepared comblike copolymers composed of a poly(methyl methacrylate) backbone and PEO grafts whose chain ends are partially capped by arginin-glycin-asparagin so-called "RGD" tripeptides.[12] Functional surfaces were prepared by spin-coating a solution of these comblike copolymers in a water/ethanol mixture on solid substrates (e.g., glass dishes and tissue culture polystyrene (TCPS)). RGD peptides then form nanoclusters on a protein-resistant (PEO) polymer surface, which allows for controlled cell adhesion.[12,13]

Micelles of amphiphilic PEO graft copolymers have also been used for delivery of genes[14] and sustained drug release.[15] The PEO corona of the micelles inhibits protein adsorption, which prolongs the circulation time of the micelles in the blood (prolonged drug release).[7,16]

Several techniques have been reported for the synthesis of amphiphilic graft copolymers of poly(ethylene oxide). The "grafting onto" method consists of grafting PEO chains onto a reactive backbone by traditional organic reactions. This method has been extensively reported for (meth)acrylic or styrene (co)polymers.[17−19] For example, Wesslen et al. grafted poly(ethylene glycol) monomethyl alkoxides (MPEO−alkoxides) onto copolymers of acrylic and methacrylic ester by transesterification reactions in the melt or in solution.[19] They also reported on the grafting of MPEO−alkoxides onto epoxy groups attached to the main chain. Although the grafting efficiency was higher compared to the transesterification strategy, occurrence of cross-linking was however a problem.[19]

In the so-called "grafting from" method, anions generated along a hydrophobic polymer backbone are used to initiate the anionic polymerization of ethylene oxide (EO). For instance, a polystyrene-*g*-PEO copolymer was prepared from styrene chains containing 5−15% of (meth)acrylamide, whose amide units were metalated and used to initiate the anionic polymerization of ethylene oxide.[20,21] This method is restricted to backbones that are stable toward charged nucleophiles, which thus rules out ester-containing chains such as poly(ϵ-caprolactone) and polylactide.

Because these two grafting techniques are usually time-consuming, attention has been paid to the copolymerization of PEO macromonomers ("grafting through"). Macromonomer copolymerization is a convenient and effective method to access amphiphilic graft copolymers without post-polymerization grafting. Controlled radical copolymerization, e.g., atom transfer radical copolymerization of vinylic monomers with poly(ethylene oxide) end-capped by a (meth)acrylate (PEO·AA or PEO·MA)[22−25] or a *p*-vinylphenylalkyl group, has been reported.[26] Styrene has also been copolymerized with PEO macromonomers of the vinylbenzyl and acrylamide type, with potassium persulfate as an initiator.[27]

Only few papers have been published about the preparation of PEO graft copolymers by ring-opening metathesis polymerization (ROMP). Breitenkamp et al.[28] synthesized novel poly(ethylene oxide) macromonomers with a cyclooctene end group (co)polymerizable by ROMP. Polynorbornene-*graft*-poly(ethylene oxide) copolymers (PNB-*g*-PEO) were accordingly prepared.[29]

All of the aforementioned amphiphilic graft copolymers consist of a non-(bio)degradable hydrophobic backbone. In contrast to diblock copolymers of PEO and

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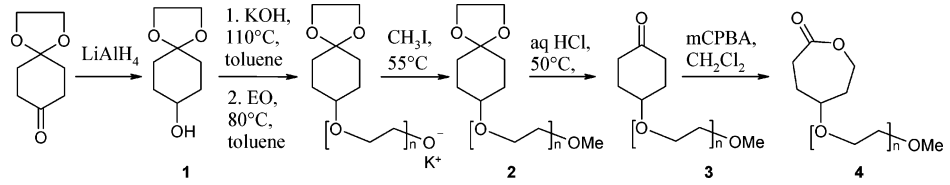
Scheme 1. Synthesis of Macromononer (α-(γ-ϵ-Caprolactone)-ω-methoxy−Poly(ethylene oxide)) (γPEO·CL)[a]



[a] mCPBA = *m*-chloroperbenzoic acid

Table 1. Molecular Characteristics of Various Functional PEOs 2, 3, and 4 from Scheme 1

no.	product	DP_{th}[a]	$M_{n,th}$	$M_{n,NMR}$	$M_{n,MALDI}$[b]	$M_{n,SEC}$[c]	$M_w/M_{n,SEC}$
1	**2a**	10	600	600	n.d.	550	1.15
2	**2b**	21	1100	1200	n.d.	1100	1.11
3	**2c**	47	2200	1900	n.d.	1850	1.12
4	**3a**	10	550	650	750	600	1.18
5	**3b**	21	1050	1300	1150	1100	1.17
6	**3c**	47	2200	2000	1950	1900	1.13
7	**4a**	10	600	1000[d]	850[e]	800[e]	1.09
8	**4b**	21	1100	1300	1350	1250	1.12

[a] Theoretical degree of polymerization = $[M]_0/[I]_0$. [b] MALDI−TOF linear mode. [c] Calibration by poly(ethylene oxide) standards. [d] After purification by three precipitations in diethyl ether. [e] After purification by one precipitation in diethyl ether.

biodegradable aliphatic polyesters, such as poly(ϵ-caprolactone) (PCL) and polylactide (PLA), PCL(PLA)-*g*-PEO copolymers have not been reported yet. Although they do not contain PEO, degradable amphiphilic copolyesters have been prepared by copolymerization of ϵ-CL with ϵ-CL comonomers substituted in the γ-position by a hydrophilic group, both charged or neutral.[30−35]

Because aliphatic polyesters are very sensitive to hydrolysis and transesterification reactions, grafting of PEO via the macromonomer technique is best suited. This paper reports on the synthesis of new PEO macromonomers (Scheme 1, **4**) copolymerizable with ϵ-CL by ring-opening polymerization (ROP) and therefore suitable for the preparation of amphiphilic comblike copolymers with a (bio)degradable hydrophobic backbone.

Experimental Section

Materials. ϵ-CL (Aldrich, 99%) was dried over calcium hydride for 48 h while stirring and distilled under reduced pressure before use. Triethylaluminum ($AlEt_3$) (Fluka, 1.9 M in toluene) was diluted in dry toluene, and the solution concentration was determined by addition of an excess of hydrogen chloride and measurement of the ethane released. Toluene was dried by refluxing it from Na/benzophenone for 48 h and distilled under nitrogen. Methylene chloride (CH_2Cl_2) was dried by refluxing it from calcium hydride for at least 48 h before distillation. 1,4-Dioxaspiro[4.5]decan-8-one (Fluka, >97%), lithium aluminum hydride ($LiAlH_4$) (Aldrich, 95%), ethylene oxide (Messer), potassium hydroxide (KOH) (Acros, > 85%), methyl iodide (CH_3I) (Aldrich, 99,5%), *m*-chloroperbenzoic acid (m-CPBA) (Fluka, 70%), and diethyl ether (Vel) were used as received. *p*-Methoxy benzyl alcohol (Janssen Chimica, 98%) was dried by repeated azeotropic distillation of toluene just before use.

Synthesis of the Macromonomer. Synthesis of 1,4-Dioxaspiro[4.5]decan-8-ol (Scheme 1, 1). 1,4-Dioxaspiro-[4.5]decan-8-ol was synthesized by reduction of 1,4-dioxaspiro-[4.5]decan-8-one (1,4-cyclohexanedione monoethylene ketal) with lithium aluminum hydride in THF as published elsewhere.[36] The product was recovered by distillation in vacuo and characterized by ^{1}H NMR ($CDCl_3$, δ): 1.6 (m, 4H, CH_2−CH(OH)), 1.85 (m, 4H, CH_2−CH_2−CH), 3.77 (m, 1H, CH-CH_2), 3.92 (m, 4H, −O−CH_2−CH_2−O). FTIR: 3400 (OH), 2940 (CH), 1100 (C−O) cm^{-1}.

Synthesis of α-(4-Oxocyclohexy)-ω-methoxy—Poly-(oxy-1,2-ethanediyl) (2). Compound **1** (30 g, 0.19 mol) was reacted with 80 mol % (8.53 g, 0.152 mol) of potassium hydroxide in 300 mL toluene in a "Dean-Stark" apparatus under nitrogen. The crude reaction product was transferred under nitrogen in a Zipperclave (Autoclave 316Ti) reactor together with 300 mL of dried toluene (theoretical concentration of 0.15 mol/L). For the synthesis of PEO **2a** (Table 1, entry 1, $M_{n,th}$ = 600), approximately 80 g (84 g, 1.9 mol) of ethylene oxide (EO) was added and polymerized under vigorous stirring at 80 °C for 5 h. The EO pressure decreased accordingly from 2 to 0.8 bar. The living chains were killed by an excess of methyl iodide (35.5 mL, 0.57 mol) at 55 °C for 20 h. The polymer was recovered by precipitation in heptane and dried in vacuo. Methylation was however partial (∼45% for PEO **2b** (Table 1, entry 2, $M_{n,th}$ = 1100) and **2c** (Table 1, entry 3, $M_{n,th}$ = 2200) and ∼75% for PEO **2a**, Table 1) and repeated as follows: PEO **2a**, **2b** and **2c** (0.19 mol) were reacted with 60 mol % of KOH with respect to PEO, followed by azeotropic distillation of toluene in order to convert the remaining hydroxyl groups into the potassium alkoxides. To the reaction mixture containing compound **2b** or **2c**, 0.7 equiv of CH_3I (0.133 mol) in toluene (0.5 M solution) was added and allowed to react for 2 h at room temperature ("mild" conditions). On the other hand, the sample **2a** (114 g, 0,19 mol) was reacted with 2.5 equiv of methyl iodide (30 mL, 0.475 mol) at 40 °C for 12 h ("stringent" conditions). In the first case, the methylation yield slightly increased (e.g., from 45% to 50%), in contrast to full methylation under the more stringent conditions. The excess of CH_3I was removed by precipitation in heptane, and the polymer dried under reduced pressure. (Conversion: 100%. Yield: 95%.) ^{1}H NMR ($CDCl_3$, δ): 1.4−1.9 (m, 8H, CH−CH_2−CH_2−), 3.36 (s, 3H, OCH_3), 3.6 (M, 4*n*H, −O−[CH_2−CH_2−O]$_n$), 3.9 (s, 4H, −O−CH_2−CH_2−O).

Synthesis of α-(4-Ethylene ketalcyclohexyl)-ω-methoxy—Poly(oxy-1,2-ethanediyl) (α-4-Cyclohexanone-ω-methoxy—Poly(ethylene oxide)) (3). The protecting acetal group of compound **2a** (40 g, 0.067 mol) was hydrolyzed in 300 mL 0.1 M HCl in water at 50 °C for 90 min under nitrogen. $NaHCO_3$ was added until the pH was 7, and **3** was recovered by 3-fold extraction with 250 mL dichloromethane. After removal of CH_2Cl_2, 29 g of compound **3a** were recovered. (Conversion: 100%.) ^{1}H NMR ($CDCl_3$, δ): 1.93 (m, 2H, C(O)-CH_2−CH_2), 2.07 (m, 2H, C(O)CH_2−CH_2), 2.25 (m, 2H, C(O)-CH_2−CH_2), 2.57 (m, 2H, C(O)CH_2−CH_2), 3.36 (s, 3H, OCH_3), 3.6 (M, 4*n*H, −O-[CH_2−CH_2−O]$_n$).

Synthesis of α-(4-Oxo-5-oxepanyl)-ω-methoxy—Poly-(oxy-1,2-ethanediyl),(α-(γ-ϵ-Caprolactone)-ω-methoxy—Poly-(ethylene oxide)), (γPEO·CL) (Scheme 1, 4). A solution of 10 g (0.015 mol) of compound **3a** (10 w/v %) in 50 mL of methylene chloride was reacted with 1.4 equiv of *m*-chloroperbenzoic acid (m-CPBA) (5.3 g, 0.0215 mol) at 25 °C for 72 h. After reaction, approximately half of the solvent was removed;

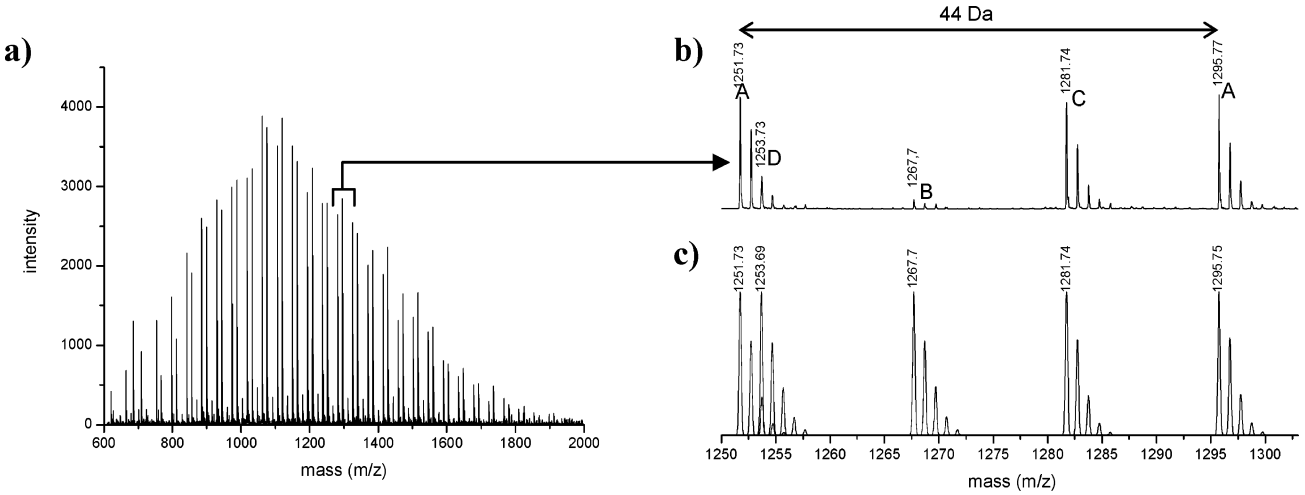


Figure 1. Reflectron mode MALDI−TOF spectrum of PEO 3b (Table 1) ($M_{n,th}$ = 1050), methylated under mild conditions: (a) full spectrum, (b) detail of the experimental isotope distribution, and (c) theoretical isotope distribution.

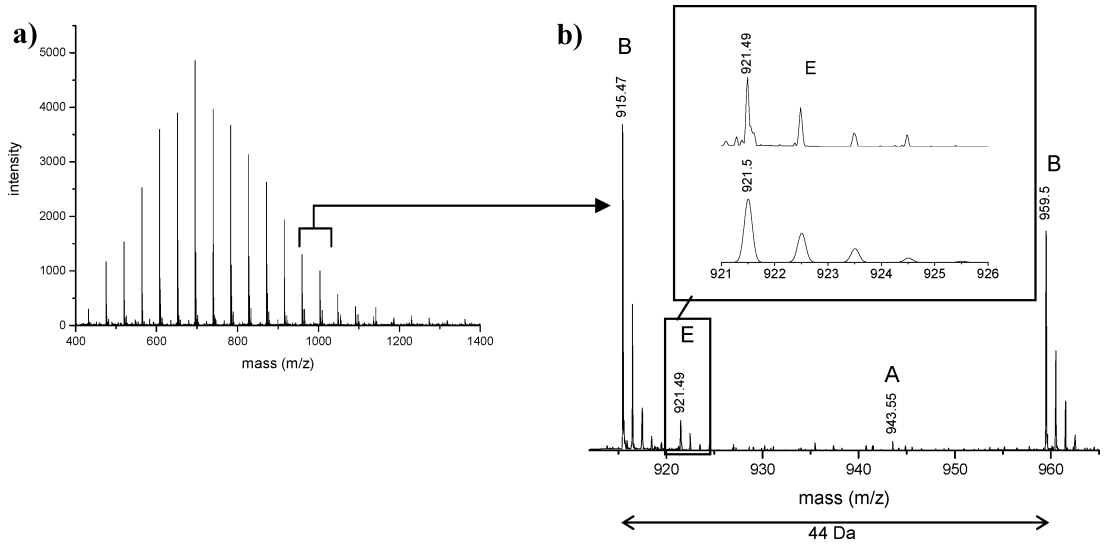


Figure 2. Reflectron mode MALDI−TOF spectrum of PEO 3a (Table 1) ($M_{n,th}$ = 550), methylated under stringent conditions: (a) full spectrum and (b) detail of the experimental isotope distribution with an inset for the comparison of the expermental (top) and the theoretical (bottom) isotope distribution for series E.

the solution was cooled to −20 °C, filtered at −20 °C, and washed with 5 mL of cold CH_2Cl_2. The CH_2Cl_2 solution was recovered. This procedure was repeated three times. The CH_2Cl_2 solution (40 mL) was then washed, first with 10 mL of a saturated aqueous solution of $Na_2S_2O_3$ (the aqueous phase was reextracted with CH_2Cl_2), followed by 10 mL of a saturated solution of $NaHCO_3$ (the aqueous phase was reextracted with CH_2Cl_2), and 5 mL of a saturated solution of NaCl, and finally dried over $MgSO_4$. Compound **4** was precipitated in diethyl ether at 0 °C (three times), and finally dried under reduced pressure at room temperature. It was stored under nitrogen at −20 °C. (Conversion = 100%; yield (**4a**) = 45%.) ^{1}H NMR ($CDCl_3$, δ): 1.8−2.1 (m, 4H, CH−CH_2−CH_2), 2.40 (m, 1H, C(O)−CH_2−), 2.98 (t, 1H, C(O)−CH_2−), 3.36 (s, 3H, OCH_3), 3.6 (M, 4*n*H, −O−[CH_2−CH_2−O]$_n$), 4.05 (m, 1H, C(O)−O−CH_2−), 4.5 (t, 1H, C(O)−O−CH_2−) (see also Figure 4). ^{13}C NMR ($CDCl_3$, δ): 28.3 (CH_2−CH_2COO), 28.7 (CH_2−CH_2−OCO), 34.9 (CH_2COO), 59.9 (OCH_3), 64.3 (CH_2−OCO), 71.7 (O-[CH_2−CH_2−O−]$_n$), 72.8 (CH−CH_2), 178 (COO).

Copolymerization of 4 (γPEO·CL) and ϵ-Caprolactone (Scheme 2). Diethyl aluminum alkoxide was prepared by reacting triethylaluminum ($AlEt_3$) with *p*-methoxybenzyl alcohol. A 0.36 M solution of the previously dried alcohol (13.2 mg, 0.0001 mol) in CH_2Cl_2 was slowly added into a carefully dried Pyrex flask containing 1.1 equiv of a 0.71 M solution of $AlEt_3$ in toluene. The reaction proceeded under nitrogen under vigorous stirring for 2 h at room temperature.

γPEO·CL **4a** (1 g, 0.001 mol, $M_{n,th}$ = 1000) was dried by three azeotropic distillations of toluene and heated at 45 °C under vacuum, overnight. A solution of dried ϵ-CL (0.02 mol, 2.2 mL) and γPEO·CL **4a** (1 g, 0.001 mol) in CH_2Cl_2 (10% w/v) was added to the required amount of diethyl aluminum alkoxide (0.0001 mol). The copolymerization was conducted in 25 mL of CH_2Cl_2 at room temperature and stopped after 20 h by addition of an excess of HCl (0.1 M solution). The copolymer was precipitated in heptane, filtered, and precipitated again in methanol, to remove the nonreacted γPEO·CL. The copolymer was recovered by centrifugation, dried in vacuo, and stored in vacuo at −20 °C. (Yield = 50%.)

Characterization Techniques. 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. To generate the isotopic distributions, the isotope calculator tool of Data Explorer (software supplied by Applied Biosystems) was used. Dithranol (20 mg/mL THF) was used as a matrix and no cationating agent was added. Polymer was dissolved in THF (1 mg/mL THF). A PEG standard with a molecular weight of 1900 (1 mg/mL THF) was used for calibration, with dithranol as matrix (20 mg/mL THF) and without additional cation.

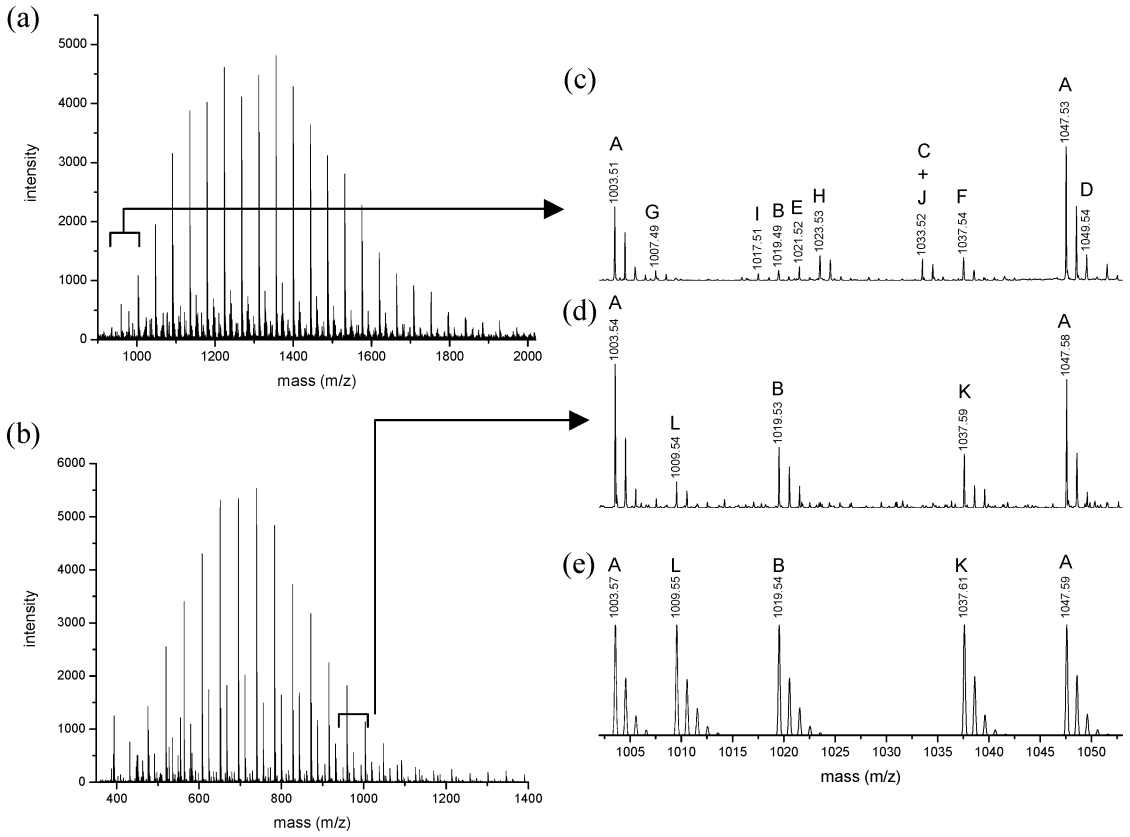


Figure 3. Reflectron mode MALDI−TOF spectra for γPEO·CL: (a) full spectrum for PEO **4b**, (b) full spectrum for PEO **4a**, (c) experimental isotope distribution for sample **4b**, (d) experimental isotope distribution for sample **4a**, and (e) theoretical isotope distribution.

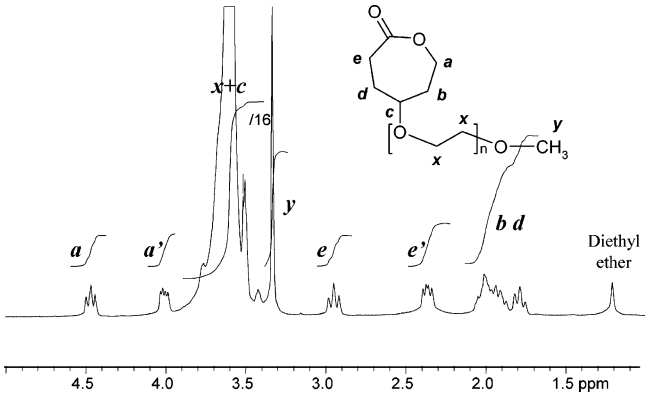
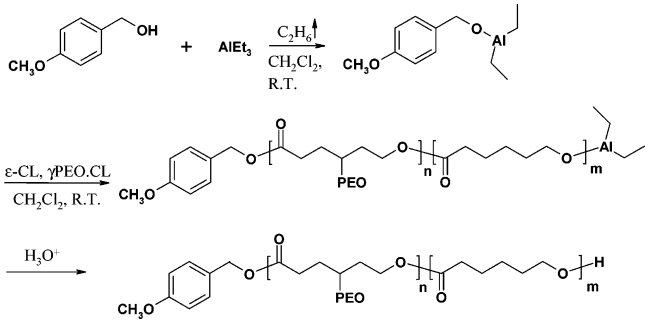


Figure 4. ^{1}H NMR spectrum for the macromonomer γPEO·CL **4a** (Table 1) in $CDCl_3$, after precipitation in diethyl ether

Scheme 2. Copolymerization of ϵ-CL and γPEO·CL (4a) into PCL-*g*-PEO Copolymer



^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded in $CDCl_3$ with a Bruker AM 400 apparatus at 25 °C. The molecular weight of the PEO derivatives was calculated from the relative intensity of the methoxy end group peak and the $-CH_2-CH_2-O$ peak. The completeness of the PEO end group derivatization was estimated from the relative intensity of both the α and the ω end groups.

Size-exclusion chromatography (SEC) was carried out in THF at a flow rate 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 5μm (columns porosity: 10^2, 10^3, 10^4, 10^5 Å). PS and PEO standards were used for calibration.

FTIR spectra of polymer films deposited on NaCl were recorded with a Perkin-Elmer FTIR 1720X spectrometer.

Results and Discussion

Synthesis of the Macromonomer. To prepare comblike copolymers of poly(ϵ-caprolactone) with poly(ethylene oxide) grafts, new macromonomers were synthesized, i.e., PEO chains prepared by living anionic polymerization and end-capped by an ϵ-caprolactone ring at one end (Scheme 1).

Copolymerization of these macromonomers with ϵ-caprolactone by a controlled ring-opening mechanism should be an efficient way to control the length of both the PEO graft and the polyester backbone. This route should be an improved alternative for the grafting of hydroxyl end-capped PEO onto carboxylic acid containing PCL chains. In the latter case, parasitic transesterification reactions would occur and increase the polydispersity of the PCL chains. Similarly, this type of side reaction could perturb the EO polymerization initiated by hydroxyl-containing PCL chains.[30−32]

PEO macromonomers were synthesized by the multistep process shown in Scheme 1. To control both the molecular weight and the end group functionality, EO was polymerized by living anionic ring-opening polymerization initiated by a precursor of the polymerizable

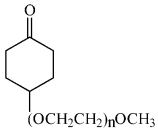
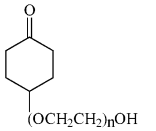
ϵ-CL end group. Potassium alkoxide of 1,4-dioxaspiro-[4.5]decan-8-ol (**1**) was used as the initiator because of its stability under the alkaline conditions of the anionic polymerization of EO. The cyclohexanone ethylene acetal is easily derivatized into lactone (Scheme 1). Compound **1** was prepared from the commercially available 1,4-cyclohexanedione monoethylene ketal as reported elsewhere.[36] By changing the ethylene oxide/alcohol molar ratio, PEO of different M_n were synthesized (series a−c in Table 1; entries 1−3).

The number-average molecular weight of these samples was determined by ^{1}H NMR from the ratio of the integrated signal at 3.6 ppm (CH_2-CH_2-O from PEO) to the one at 3.36 ppm ($O-CH_3$), by SEC with PEO standards and by MALDI−TOF, respectively. These experimental data at total monomer conversion are self-consistent and agree well with theoretical M_n. As reported by Vangeyte et al.,[37] the KOH content has no noticeable influence on the EO polymerization, as a result of a fast alcohol/alkoxide exchange and growth of all the chains at a comparable rate. In this work, 0.8 equiv of KOH (with respect to the alcohol) was used, and the narrow molecular weight distribution (estimated by SEC, Table 1) confirms that the initiation step and the alcohol/ alkoxide exchange are fast compared to propagation. At the end of the polymerization, the living PEO chains were end-capped by a methoxy group, by addition of CH_3I to the medium. Because this reaction is not complete (e.g., yield ∼75% for PEO **2a**; entry 1 in Table 1), it was repeated in order to get rid of the residual hydroxyl end groups that could interfere with subsequent reactions, including copolymerization of the macromonomer with ϵ-caprolactone. Completeness of the end-capping was determined by ^{1}H NMR and by MALDI−TOF for samples **3**, i.e., after deprotection of the acetal by reaction with 0.1 mol HCl for 90 min at 50 °C (see Scheme 1).

As mentioned in the Experimental Section, methylation was carried out under "mild" and "stringent" conditions. Methylation under mild conditions remains incomplete as exemplified by the macromonomer **2b** ($M_{n,th}$∼1100; Table 1), whose methylation yield has increased from 45% to 50% during the second methylation step. In contrast, methylation is complete under the stringent conditions applied to macromonomer **2a** ($M_{n,th}$ ∼ 600; Table 1). Both the partially (**3b**) and the fully (**3a**) methylated PEO−cyclohexanone chains were oxidized (Baeyer−Villiger reaction) and analyzed by MALDI−TOF. For all series of peaks in the MALDI−TOF spectrum, the mass and shape of the experimental isotope distribution fit the theoretical ones.

A typical MALDI−TOF spectrum of the PEO **3b** of 1050 molecular weight (Table 1, entry 5) and methylated under "mild" conditions (see Experimental Section) is shown in Figure 1a. Several series of peaks are observed, and the mass difference between two peaks of the same series is 44 Da (molar mass of EO). Figure 1b also shows a detail of Figure 1a in a mass window of 44 Da (EO monomer unit), which allows assigning the peaks more precisely. The assignment of the different series of peaks is reported in Table 2. Several families of polymers can be discerned in Figure 1b: the main families can be attributed to the expected polymer (A, B), and to ω-hydroxyl-terminated chains (signal C, D). For each family, the most intense peaks correspond to the Na adduct (A and C), whereas peaks with a much lower intensity (B and D) are K adducts because PEO

Table 2. Peak Assignments of the MALDI Spectra of Figure 1b (Sample 3b) and Figure 2b (Sample 3a)

code	description	structure
A	desired + Na	
B	desired + K	
C	ω-hydroxyl terminated chains + Na	
D	ω-hydroxyl terminated chains + K	
E	α,ω-dimethoxy-PEO + K	$CH_3OCH_2CH_2(OCH_2CH_2)_nOCH_3$

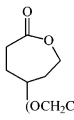
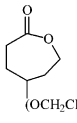
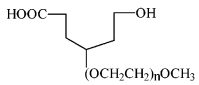
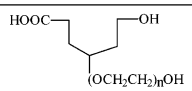
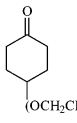
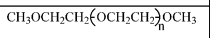
3b was initiated by KOH and treated with $NaHCO_3$ (see Experimental Section). The experimental isotope distribution of each signal (Figure 1b) is in good agreement with the theoretical simulation. (Figure 1c)

Figure 2a shows the MALDI−TOF spectrum of PEO **3a** ($M_{n,th}$ = 550) methylated under "stringent" conditions (see Experimental Section).

M_n of the PEO chains remains unchanged upon methylation as assessed by SEC. Compared to **3b**, **3a** shows a smaller number of peaks, consistent with a higher purity. Figure 2b illustrates the detailed isotope distribution of PEO **3a**, the peak assignment is reported in Table 2. Mainly, the K adduct of the desired ω-methylated PEO **3a** is observed (series B), the presence of the Na adduct is quasi negligible (series A). The reason lies in the polymer posttreatment by $KHCO_3$ (neutralization of the aqueous solution of **3a** after hydrolysis of the acetal by HCl) instead of $NaHCO_3$ in the case of **3b**. Signals for the hydroxyl-terminated chains (C or D) are no longer observed. In addition, there is a new peak, E (K cationated), of lower intensity. The experimental isotope distribution of E agrees well with the theoretical isotope distribution of α,ω-dimethoxy PEO (see inset, Figure 2b). It possibly results from a loss of cyclohexanone end groups during methylation under stringent conditions. These contaminating chains were not removed before polymerization, because of low content and lack of reactivity.

α-ϵCL-ω-methoxy-PEO (**4**) was prepared by the Baeyer−Villiger oxidation of the cyclohexanone by *m*-chloroperbenzoic acid (*m*-CPBA). This reaction was performed on both the partially (PEO **3b**) and the fully methylated PEO-cyclohexanone chains (PEO **3a**). The reaction progress was monitored by ^{1}H NMR and stopped at 100% conversion. The PEO macromonomer was contaminated by excess of peracid (*m*-CPBA) and by *m*-chlorobenzoic acid (*m*-CBA) formed as a byproduct. It was purified before polymerization because traces of acid have a detrimental effect on the control of the ROP process. Therefore, the crude product was carefully purified as reported in the Experimental Section. The major part of *m*-CBA was precipitated at 20 °C. After filtration, residual *m*-CPBA was reduced by $Na_2S_2O_3$ to *m*-CBA, that was transferred to the water phase in the presence of $NaHCO_3$. Purity was checked by ^{1}H NMR, particularly the absence of residual acid. Only 45% of the original PEO **4a** with $M_{n,th}$ = 600 was recovered as γPEO·CL by precipitation in cold diethyl ether[38] and centrifugation (15000 rpm at −5 °C). After purification, the fully methylated (**4a**) and partially methylated (**4b**)

Table 3. Peak Assignments for the MALDI Spectra of Figure 3a (Sample 4b) and Figure 3b (Sample 4a)

code	description	n	structure
A	desired α-lactone-ω-methoxy PEO + Na	19	
B	desired α-lactone-ω-methoxy PEO + K	19	
C	ω-hydroxyl–terminated γPEO.CL + Na	20	
D	ω-hydroxyl–terminated γPEO.CL + K	20	
E	Hydrolyzed α-lactone ω-methoxy PEO + Na	19	
F	Hydrolyzed α-lactone ω-methoxy PEO + K	19	
G	Hydrolyzed α-lactone ω-hydroxyl PEO + Na	19	
H	Hydrolyzed α-lactone ω-hydroxyl PEO + K	19	
I	non-reacted ω-hydroxyl-terminated PEO 3 + Na	20	
J	non-reacted ω-hydroxyl-terminated PEO 3 + K		
K	α,ω-dimethoxy-PEO + Na	21	
L	α,ω-dimethoxy-PEO + K	20	

macromonomers **4** (γPEO·CL) were characterized by FTIR, SEC, ^{1}H NMR, and MALDI−TOF.

Parts a and b of Figure 3 are the MALDI−TOF spectra for PEO **4b** and PEO **4a**, respectively. Parts c and d of Figure 3 emphasize part of the spectra for sake of comparison of the experimental data and the theoretical isotope distribution (Figure 3e).

The experimental isotope distribution for the partially methylated γPEO·CL (**4b**) (Figure 3c) shows the main series A and B, assigned to the sodium and potassium forms of the desired α-lactone-ω-methoxy PEO (Table 3). ω-hydroxyl-terminated γPEO·CL series (C and D) and series of nonreacted ω-hydroxyl-terminated PEO **3b** (I and J) are also observed. Although it is out of the scope of this work, it must be noted that synthesis of ω-hydroxyl-terminated γPEO·CL is straightforward. Polymerization of this macroinimer could be initiated by Al or Sn alkoxide and lead to hyperbranched chains.

Figure 3c also confirms the sensitivity of the lactone end group to hydrolysis. Indeed, signals for the hydrolyzed version of γPEO·CL (**4b**) are observed for both the series of PEO chains, with the ω-methoxy end group (signals E and F) and the ω-hydroxyl end group (signals G and H), respectively. Therefore, the contact time with water during purification of the Baeyer−Villiger oxidation product should be minimized. Furthermore, the final macromonomer should be dried by azeotropic distillation of toluene before storage under nitrogen at −20 °C. Whenever these conditions were applied to the fully methylated γPEO·CL chains, the MALDI−TOF spectrum (Figure 3d) shows the two main series (A and B) assigned to the desired α-lactone-ω-methoxy-terminated γPEO·CL, together with peaks K and L which refer to the sodium and potassium forms of the unmodified α,ω-dimethoxy-PEO observed before the Baeyer−Villiger oxidation (Figure 2b, E). In contrast to macromonomer **4b** analyzed in Figure 3c, no ω-hydroxyl-terminated and no hydrolyzed products contaminate the

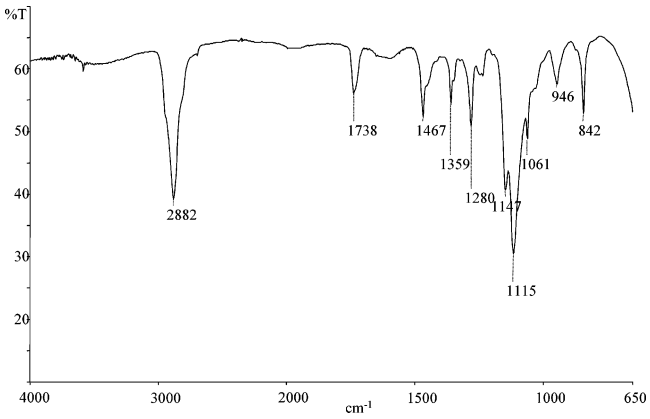


Figure 5. FTIR spectrum for the macromonomer γPEO·CL **4a** (Table 1).

macromonomer **4a** in Figure 3d. The experimental isotope distribution fits the theoretical one (Figure 3e). Moreover, the average molecular weight (M_n) and the molecular weight distribution (M_w/M_n) of the ω-methoxy-terminated γPEO·CL (**4a**) are the same as before the Baeyer−Villiger reaction (**3a**), which confirms the stability of PEO during the functionalization process, in agreement with previous SEC analysis.

The average molecular weight calculated by MALDI−TOF is close to the data determined by SEC with PEO standards (Table 1). As far as sample **4a** is concerned, M_n determined by MALDI is lower compared to NMR data. The explanation is that the sample analyzed by MALDI was purified by only one precipitation in diethyl ether, whereas the sample analyzed by ^{1}H NMR (Figure 4) was precipitated three times, with loss of the lower molecular weight chains.

Figure 4 shows a typical ^{1}H NMR spectrum with peak assignment for the completely methylated macromonomer **4a**, precipitated three times in diethyl ether. The broad signal at 3.6 ppm is characteristic of the methylene protons of the PEO chain. Small peaks in the vicinity of the methylene protons of PEO at 3.45 and 3.8 ppm, are proton−carbon correlation peaks. The ω-methoxy protons are detected at 3.36 ppm (peak y). Six additional peaks are observed at 4.5 and 4.05 ppm (a and a′) and 2.9 and 2.4 ppm (e, e′), each of them corresponding to one proton, and at 2.0 and 1.8 ppm which contribute altogether to four protons (b and d). These chemical shifts are typical of γ-substituted ϵ-caprolactone as was, e.g., previously reported in the case of a protected γ-hydroxyl-ϵ-caprolactone of a similar structure.[39,32] The protons vicinal to the ester group (a and a′; e and e′) are not equivalent because of the asymmetry of the lactone ring after the Baeyer−Villiger reaction. The chemical shifts of a, a′ and e, e′ differ by approximately 0.5 ppm, consistent with lactone-vicinal protons in ϵ-CL derivatives.[39]

From the relative intensity of peak a′ (4.5 ppm, for the vicinal proton of the lactone) and peak y (3.36 ppm, for the methoxy end group), the amount of α,ω-dimethoxy−PEO is estimated at approximately 10%. The number-average molecular weight (M_n) agrees well with the MALDI−TOF results (Table 1).

The FTIR spectrum for the new macromonomer is reported in Figure 5 and shows the expected main absorptions of the lactone ring at 1739 cm^{-1} (C═O stretching) and at 1280 cm^{-1} (C−O stretching). The strong absorption at 1115 cm^{-1} is characteristic of the

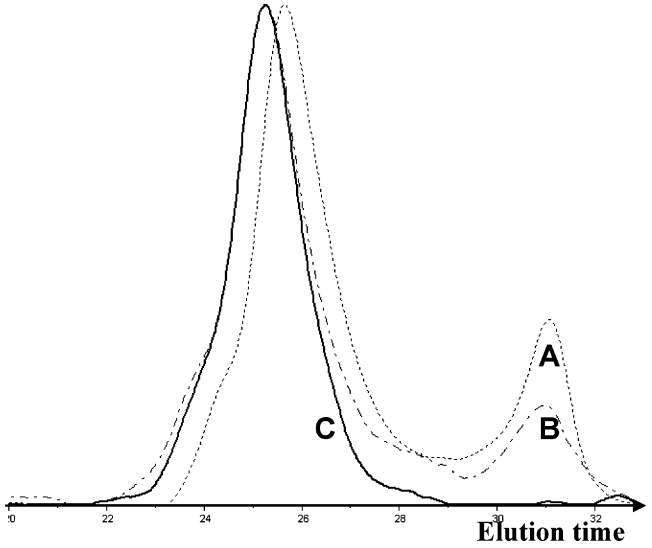


Figure 6. SEC traces of the copolymerization medium: (A) after 4 h (dotted line), (B) after 24 h (dotted broken line), and (C) after 24 h and purification by sequential precipitation in heptane and methanol (thick full line).

ether bonding (C−O−C stretching) in the EO repeating units.

Copolymerization of γPEO·CL and ϵ-Caprolactone. Ring-opening polymerization (ROP) of four-, six-, and seven-membered lactones can be initiated by a variety of protic compounds and metal derivatives. [40] ROP of ϵ-CL was successfully carried out by coordination−insertion polymerization of the anionic type, for instance by aluminum alkoxide[41] and tin octoate.[42] In the case of aluminum alkoxide, molecular weight is controlled not only by the monomer/ initiator molar ratio (and conversion) but also by hydroxyl-containing additives as result of an alkoxide−alcohol exchange.[43] Therefore, it was mandatory to convert the ω-hydroxyl end group of the PEO chains into methyl ether as quantitatively as possible, before copolymerization of the γPEO·CL macromonomer with ϵ-CL. To identify easily the α-end group of this copolymer (by ^{1}H NMR), the aluminum alkoxide of *p*-methoxybenzyl alcohol was used as an initiator in methylene chloride at room temperature (Scheme 2).

As a typical example, the fully ω-methylated γPEO·CL, **4a**, ($M_{n,NMR} \sim 1000$) was copolymerized with ϵ-CL. The theoretical molar fraction of γPEO·CL in the comonomer feed was 5 mol %, and the monomer/initiator ratio was 220. After 3 h, the first sample was picked out and analyzed by ^{1}H NMR and SEC. Copolymerization was stopped after 20 h by addition of 0.1 M HCl. Figure 6 compares the normalized SEC traces for the copolymer precipitated in heptane, a nonsolvent for both the copolymer and the γPEO·CL macromonomer, after 3 h (Figure 6, A) and 20 h (Figure 6, B), respectively.

A bimodal molecular weight distribution is observed, as result of contamination of the copolymer by unreacted macromonomer. Indeed, the area of the higher elution volume peak decreases when the copolymerization time is increased (Figure 6, trace B), whereas the major peak of higher molecular weight is shifted toward lower elution volumes. The PEO chains, which are not incorporated into the copolymer after 20 h, are mixtures of nonreacted macromonomer and nonreactive α,ω-dimethoxy PEO. These PEO chains are easily removed from the copolymer by precipitation in methanol, i.e., a

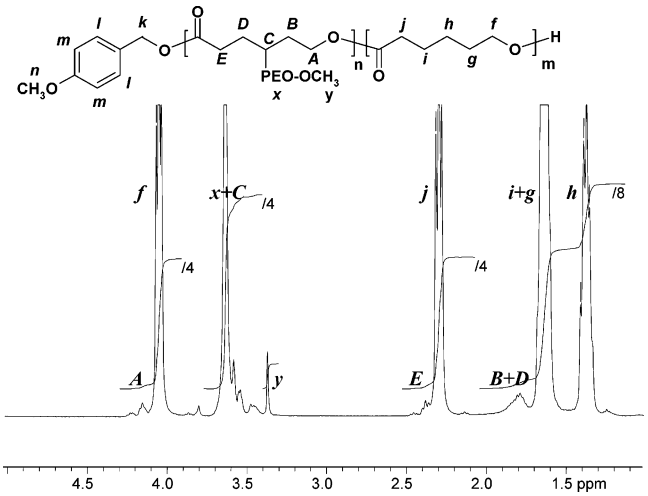


Figure 7. ^{1}H NMR spectrum for the PCL-*g*-PEO copolymer in $CDCl_3$, after precipitation in methanol.

good solvent for PEO and a nonsolvent for PCL and the copolymer, as shown by curve C in Figure 6. The origin of the shoulder on the high molecular weight side of the copolymer peak is not clear yet. The molecular weight of the graft copolymer was estimated at $M_{n,SEC} = 35\,000$ g/mol by SEC with a polystyrene calibration.

The ^{1}H NMR spectrum for the purified copolymer (Figure 7) shows signals typical of PCL and PEO. The methylene protons of PEO are observed at 3.6 ppm, and resonances for the protons of PCL are detected at 4.05 (f) (C(O)OC−CH_2), 2.30 (j) (*C*(*O*)-CH_2), 1.63 (i + g) (*C*(*O*)−CH$_2$−CH_2) and 1.37 ppm (h) (O−CH$_2$−CH_2), respectively. No resonance can be assigned to residual macromonomer. Indeed, the non chemically identical protons—a′ (4.0 ppm) and a (4.5 ppm), e′ (2.4 ppm) and e (2.98 ppm)—of the lactone group completely disappeared, whereas new peaks are observed as result of the lactone opening polymerization. The resonance of proton a′ is shifted from 4.0 to 4.15 ppm (Figure 7, proton A), and that of b is also shifted to a lower chemical shift, from 2.0 ppm (proton b) to 1.8 ppm (proton B).

The number-average molecular weight (M_n) of the polyester backbone was determined by ^{1}H NMR from the relative intensity of the signals at 4.05 ppm for PCL and at 6.9 ppm for the benzyl end group (not shown). M_n of the PCL backbone ($M_{n,NMR} = 30000$) is consistent with the theoretical value ($M_{n,th} = 25000$), and the molecular weight distribution (M_w/M_n) is 1.21.

The experimental composition of the copolymer was calculated from the integration of the ^{1}H NMR peaks at 4.05 ppm for PCL and at 3.65 ppm for PEO. Conversion of ϵ-caprolactone after 20 h is complete, whereas that one of γPEO·CL is approximately 66%. Conversion of γPEO·CL (at 100% ϵ-CL conversion) was calculated by comparison of the PEO/ PCL ratios (calculated by ^{1}H NMR) for the copolymer recovered by precipitation in heptane (removal of ϵ-CL) and in methanol (removal of PEO), respectively. It appears that approximately 34% of the original PEO has not been copolymerized, which means a conversion of approximately 76% taking into account contamination of the macromonomer by approximately 10% dimethoxy-PEO. From the ^{1}H NMR spectrum recorded after precipitation in methanol, composition of the copolymer was estimated at PEO/PCL = 0.75. The molar fraction of γPEO·CL in the copolymer is therefore 3.5 mol % compared

to 5 mol % in the comonomer feed. The total molecular weight of the copolymer can also be estimated from NMR ($M_{n,NMR}$ is about 39000 g/mol). Optimization of the copolymerization conditions, such as polymerization time, addition of pyridine,[32] and comonomer feed composition, is under current investigation.

Conclusions

A well-defined PEO macromonomer (γPEO·CL) was synthesized by polymerization of ethylene oxide (EO) initiated by a potassium alkoxide of 4-monoethylene acetal cyclohexanol with high control of the macromolecular parameters. After deprotection of the ketone and oxidation by the Baeyer−Villiger reaction (100% conversion), ϵ-caprolactone-terminated PEO (γPEO·CL) of controlled molecular weight was produced. This macromonomer was copolymerized with ϵ-CL with formation of amphiphilic graft copolymers. This copolymerization was initiated by Et_2Al alkoxide and found to be controlled. It could be carried out from hydroxylated surfaces of biomaterials in order to make them more hydrophilic and impart to them a stealth behavior. This will be the topic of a forthcoming paper. Another prospect would be the quantitative hydrolysis of the α-end group (ϵ-caprolactone) of γPEO·CL in order to make a pair of hydroxyl and carboxylic acid groups available at one chain-end. Supramolecular assemblies could be built up by chelating ability of the dual end groups. They could also be used to initiate the selective polymerization of two different monomers, with formation of mikto-arm ABC star copolymers. Finally, α-caprolactone, ω-hydroxy−PEO, could also be made available by the synthetic route reported in this work. Polymerization of this inimer could lead to amphiphilic hyperbranched macromolecules.

The ϵ-CL-terminated PEO is thus an original elementary building block for the synthesis of novel amphiphilic biocompatible and biodegradable macromolecular architectures.

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