Articles

Ring-Opening Polymerization of γ-Bromo-ϵ-caprolactone: A Novel Route to Functionalized Aliphatic Polyesters

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ABSTRACT: The synthesis, characterization, and polymerization of a new cyclic ester, γ-bromo-ϵ-caprolactone (γBrCL), are reported. The ring-opening polymerization (ROP) of this new monomer initiated from $Al(O^iPr)_3$ as initiator in toluene at 0 °C was found to be living and proceeds by a coordination−insertion mechanism. Random and block copolymerizations of this γBrCL with ϵ-caprolactone (ϵCL) were also found to be living as evidenced by the experimental molecular weight which is consistent with that expected from the monomer to initiator molar ratio, the narrow polydispersity, and the good agreement between the comonomers molar fraction in the comonomer feed and the copolymer. The thermal transitions (T_g and T_m) in the ϵCL/γBrCL random copolymers depend strongly on the γBrCL content. Increasing the γBrCL content in the copolymer (F_{BrCL}) increased the T_g of the copolymer from −61 °C for poly(ϵ-caprolactone) to −16.5 °C for the PγBrCL homopolymer but decreased the T_m of the PCL to contents of ∼ 30 mol % of γBrCL ($F_{BrCL} = 0.3$). Beyond this value, the copolymers were found to be amorphous and exist as viscous liquids.

Introduction

Aliphatic polyesters, such as polylactones, polylactides, and polyglycolide, have received increased attention for applications in medicine and surgery over the past 20 years. Aliphatic polyesters are well-known for "in vitro" and "in vivo" hydrolytic degradation with release of nontoxic byproducts. They are thus biodegradable, biocompatible, and permeable to many drugs which makes them excellent candidates as components in drug delivery systems, biodegradable sutures, resorbable protheses, chemotherapy, and galenic formulations.[1] However, it is quite a problem to chemically attach active molecules (drug, recognition agent, adhesion promoter, probe) onto these polyesters, which is a severe limitation for a series of applications. The purpose of this paper is to alleviate this problem by reporting on the functionalization of poly(ϵ-caprolactone).

Aliphatic polyesters are currently prepared by the ring-opening polymerization (ROP) of cyclic ester monomers. Furthermore, conditions for living polymerizations can be met with specific initiators. For example, aluminum alkoxides are effective initiators for the preparation of polyesters with well-defined molecular weight, narrow polydispersity, and functionalized end groups as well as of random, block, and graft copolymers.[2] The synthesis of functionalized cyclic ester monomers is certainly the most straightforward way to functional polyesters. Only a few examples of them have been reported in the scientific literature,[3] although they are essential to upgrade the potential of these materials in biomedical applications.

The synthesis of aliphatic polyesters with alkyl bromide substituents is of particular interest due to the numerous subsequent transformations possible. In this article, we report on the synthesis of γ-bromo-ϵ-caprolactone (γBrCL), the polymerization of this new functional ϵ-caprolactone, the random and block copolymerization of this monomer with ϵ-caprolactone, and the influence of the molar fraction of the γBrCL in the random copolymers on the thermal transitions of these copolyesters.

Experimental Section

Materials. 7-Oxabicyclo[2.2.1]heptane (Aldrich), 48% (aqueous) HBr (Fluka), pyridinium chlorochromate (Janssen Chimica), 75% *m*-chloroperoxybenzoic acid (ACROS), CH_2Cl_2 (ACROS), diethyl ether (ACROS), and hexane (ACROS) were used as received. γ-Bromo-ϵ-caprolactone (γBrCL) was dried by repeated (three times) azeotropic distillation of toluene just before polymerization. ϵ-Caprolactone (ϵCL) (Janssen Chimica) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. Toluene and THF (ACROS) were dried by refluxing over calcium hydride and a benzophenone−Na mixture, respectively, and distilled under nitrogen atmosphere. Aluminum isopropoxide [$Al(O^iPr)_3$] (Aldrich) was twice sublimated and then dissolved in toluene under nitrogen.

Synthesis of 4-Bromocyclohexanone. Synthesis of *trans*-4-bromocyclohexanol starting from 7-oxabicyclo[2.2.1]heptane was described elsewhere.[4] Recrystallized *trans*-4-bromocyclo-

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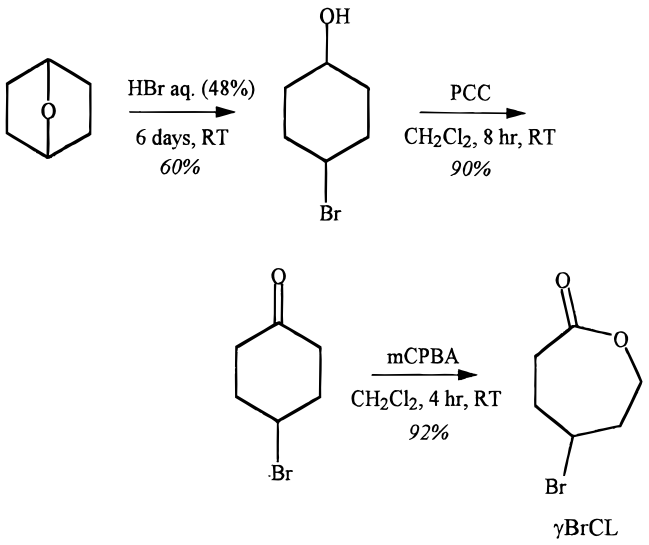
Scheme 1



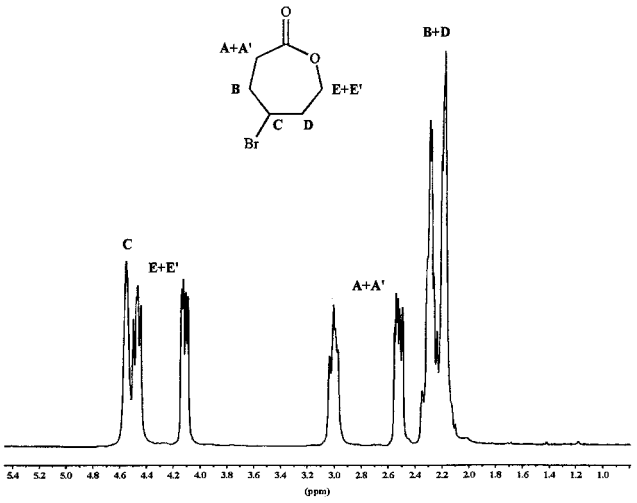


Figure 1. ^{1}H NMR spectrum of γ-bromo-ϵ-caprolactone in $CDCl_3$.

hexanol (20 g, 0.112 mol) was then solubilized in 200 mL of CH_2Cl_2, and 37 g (0.171 mol) of pyridinium chlorochromate (PCC) was added to the flask. After 8 h at room temperature, the precipitate was filtered and washed with 50 mL of dichloromethane. The solvent was then eliminated under reduced pressure, and 200 mL of ether was added to the residue. The precipitate was filtered and rinsed twice with 50 mL of ether. The organic phase was washed three times with water, dried under $MgSO_4$, and filtered, and ether was removed under vacuum to obtain a light yellow oil of pure 4-bromocyclohexanone (90% yield). ^{1}H NMR ($CDCl_3$): $\delta = 4.56$ (m, 1H, CHBr), 2.64 (m, 2H, CH_2CO), 2.4−2.1 (m, 6H, CH_2-$CO + CH_2$) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 207.8$ (C═O), 49.1 (CHBr), 38.1 (CH_2), 35.2 (CH_2).

Synthesis of γ-Bromo-ϵ-caprolactone. A 30 g (0.13 mol) sample of mCPBA was added to a solution of 15 g (0.085 mol) of 4-bromocyclohexanone in 150 mL of dichloromethane at room temperature. After 4 h of reaction, the reaction flask was placed in the refrigerator in order to precipitate mCBA. The solution was then filtered and washed with a saturated solution of $Na_2S_2O_3$ (three times), with a solution of $NaHCO_3$ (three times), and finally with water. After drying over $MgSO_4$, the organic phase was filtered, and the solvent was removed under reduced pressure. The residue was distilled under reduced pressure (10^{-2} mmHg), and the collected liquid crystallized (white crystals) upon standing at room temperature (92%). ^{1}H NMR ($CDCl_3$): $\delta = 4.57$ (m, 1H, CHBr), 4.49 (m, 1H, CH_2O), 4.14 (m, 1H, CH_2O), 3.03 (m, 1H, CH_2CO), 2.55 (m, 1H, CH_2CO), 2.4−2.05 (m, 4H, CH_2) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 174.3$ (C═O), 64.4 (CH_2O), 51.4 (CHBr), 38.2 (CH_2CO), 31.8 (CH_2), 30.2 (CH_2) ppm. Elemental analysis calculated for $C_6H_9O_2Br$: C, 37.4; H, 4.6; O, 16.6; Br, 41.4. Found: C, 37.47; H, 4.82; O + Br, 58. The purity analyzed by GC was better than 99.5%.

Polymerization Technique. Homopolymerization and random copolymerization were carried out at 0 °C in toluene. γ-Bromo-ϵ-caprolactone was dried by repeated (three times) azeotropic distillation of toluene just before polymerization. Then solvent, ϵ-caprolactone (for random copolymerization only) and initiator [$Al(O^iPr)_3$ in toluene] were successively added through a rubber septum with a syringe or a stainless steel capillary. After polymerization (2.5 h), an excess of 1 N HCl was added, and the polymer was recovered by precipitation in cold methanol.

Block copolymerization was carried out as follows. The ϵ-caprolactone polymerization was initiated by $Al(O^iPr)_3$ in toluene at 0 °C. After 45 min, an aliquot of the "living" poly(ϵ-caprolactone) (PCL) solution was deactivated and precipitated into cold methanol for analysis by size exclusion chromatography (SEC) and ^{1}H NMR. A known amount of the solution of γ-bromo-ϵ-caprolactone in toluene was transferred to the "living" PCL solution. After the complete conversion of γBrCL (2.5 h), an excess of 1 N HCl was added, and the copolymer was precipitated in cold methanol.

Characterization. Size exclusion chromatography (SEC) was performed in THF at 40 °C using a Hewlett-Packard 1090 liquid chromatograph equipped with a Hewlett-Packard 1037A refractive index detector. Columns HP PL gel 5μ (10^5 Å, 10^4 Å, 10^3 Å, 100 Å) were calibrated with polystyrene standards. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz in the FT mode with a Brucker AN 400 apparatus at 25 °C. Molecular weights were calculated by ^{1}H NMR from the relative intensity of the signals of the isopropyl ester end group ($\delta = 5$ ppm) and the methylene CH_2CO group ($\delta = 2.45-2.7$ ppm) for the P(γBrCL) homopolymer and the methylene CH_2O group ($\delta = 4.03$ ppm) for the P(ϵCL) homopolymer. ϵCL/γBrCL block copolymers were characterized by SEC, and their composition was determined by ^{1}H NMR from the signal intensities of the poly(ϵ-caprolactone) methylene protons (CH_2O, $\delta = 4.03$) and the poly(γ-bromo-ϵ-caprolactone) methylene protons (CH_2CO, $\delta = 2.45-2.7$ ppm), respectively. From the overall composition and M_n of the first block (SEC and/or ^{1}H NMR), the molecular weight of the second block was calculated. Differential scanning calorimetry (DSC) was carried out with a Dupont 910 DSC thermal analyzer calibrated with indium. The glass transition temperature and the melting temperature were measured after cooling the sample down to −120 °C and heating it up to 100 °C (at a 10 °C/min rate).

Results and Discussion

The reaction pathway for the synthesis of γ-bromo-ϵ-caprolactone (γBrCL) is shown in Scheme 1. The bicyclic cyclohexane-1,4-oxide (*cis*-1,4-epoxycyclohexane) is converted into the *trans*-4-bromocyclohexanol using a 48% aqueous hydrobromic acid solution with 60% yield.[4] The quantitative oxidation of *trans*-4-bromocyclohexanol into 4-bromocyclohexanone is carried out using pyridinium chlorochromate (PCC) as oxidative reagent. The 4-bromocyclohexanone is subsequently oxidized to γ-bromo-ϵ-caprolactone by the Baeyer−Villiger reaction using 3-chloroperoxybenzoic acid (mCPBA). The ^{1}H NMR spectrum of γBrCL is shown in Figure 1, and the spectrum is consistent with the assigned structure.

The molecular characteristics of poly(γ-bromo-ϵ-caprolactone) samples, initiated by aluminum isopropoxide [$Al(O^iPr)_3$] in toluene at 0 °C, from different monomer to $Al(O^iPr)_3$ molar ratios are shown in Table 1. Polymerizations are quantitative within less than 1.5 h. A close agreement between the theoretical molecular

Table 1. Molecular Characteristics of Poly(γBrCL) Initiated by Al(O^{i}Pr)$_3$ in Toluene at 0 °C

entry	conversion (%)	[M]/[I]	$M_{n,th}$[a]	$M_{n,exp}$ NMR	M_n SEC[b]	M_w/M_n
1	>99	10.3	2000	2000	2100	1.35
2	>99	26	5000	4600	4600	1.30
3	>99	52	10000	9900	11600	1.30
4	>99	104	20000	23000	15600	1.15

[a] Theoretical molecular weight for a living polymerization. [b] $M_{n,SEC}$ based on the universal calibration valid to PSty.

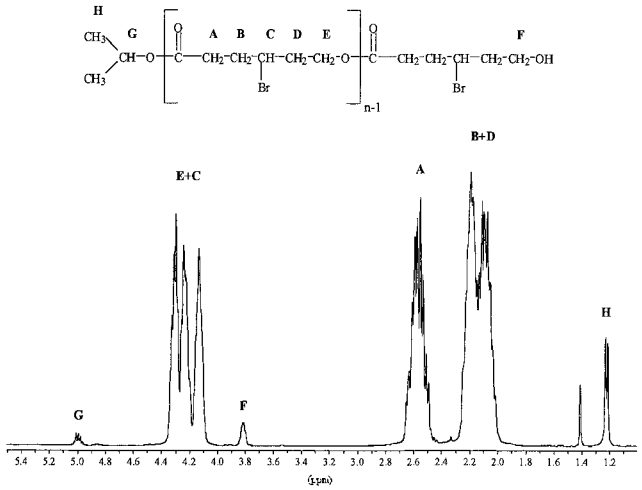


Figure 2. ^{1}H NMR spectrum of poly(γ-bromo-ϵ-caprolactone) in $CDCl_3$.

Table 2. Molecular Characteristics of Random Copolymers of ϵCL and γBrCL Initiated by Al(O^{i}Pr)$_3$ in Toluene at 0 °C

entry	$f_{\gamma BrCL}$[a]	conv (%)	$F_{\gamma BrCL}$[b]	$M_{n,th}$	$M_{n,exp}$ NMR	M_n SEC	M_w/M_n
1	0.1	>99	0.092	17 000	16 800	25 500	1.15
2	0.3	>99	0.28	17 000	16 500	23 600	1.15
3	0.5	>99	0.49	17 000	16 000	20 700	1.15

[a] Molar fraction of γBrCL in the comonomer feed. [b] Molar fraction of γBrCL in the random copolymer (determined by ^{1}H NMR analysis).

weight, based on the monomer-to-initiator molar ratio and the monomer conversion, and the experimental one (^{1}H NMR analysis) is observed, consistent with a well-controlled polymerization process. Furthermore, the molecular weight distribution of poly(γBrCL) homopolymer is narrow, indicating fast initiation with respect to propagation and fast propagation compared to chain transfer or other adverse termination reactions, if any. Figure 2 shows the ^{1}H NMR spectrum for a typical poly(γBrCL) homopolymer (M_n(NMR) = 4600, M_w/M_n = 1.28). This spectrum confirms the major peaks associated with the polyester backbone, the presence of the isopropyl ester (δ = 5 ppm), and the hydroxyl functional (δ = 3.8 ppm) end groups. These data are consistent with a coordination−insertion polymerization mechanism which implies the selective cleavage of the acyl−oxygen bond of the cyclic monomer. Furthermore, no evidence for transesterification side reactions is observed.

The molecular characteristics of random copolymers of γ-bromo-ϵ-caprolactone with ϵCL initiated by aluminum isopropoxide [Al(O^{i}Pr)$_3$] in toluene at 0 °C are shown in Table 2. The experimental molecular weight agrees with the value calculated from the monomer-to-initiator molar ratio, and the molecular weight distribution remains narrow. Furthermore, the molar fraction of the comonomers in the copolymer has been measured by ^{1}H NMR and fits comonomer feed, consistent with the quantitative conversion. These combined data suggest very well-controlled copolymerization of mixtures of ϵCL and γBrCL. Figure 3 shows a comparison of the carbonyl region of the ^{13}C NMR spectra for both the homopolymers and the copolymer 3 (Table 2). The peaks a and b (Figure 3c) are associated with the homodiads of PCL and PγBrCL, respectively. The two additional a′ and b′ peaks observed in the carbonyl region for the copolyester are thus characteristic of the ϵCL/γBrCL heterodiads and confirm the randomness of the structure. The thermal transitions in the ϵCL/γBrCL copolymers have been analyzed by differential scanning calorimetry (DSC). Copolymerization of ϵCL with increasing amounts of γBrCL has a strong effect on both the glass transition temperature (T_g) and the melting temperature (T_m) (Figure 4). PCL shows a T_g at −61 °C and a T_m at 57 °C, whereas the brominated polyester (poly(γBrCL)) is amorphous with a T_g at −16.5 °C. Increasing γBrCL content results in decrease of T_m of PCL until F_{BrCL} = 0.3. Beyond this γBrCL content, copolymers are amorphous. Finally, T_g increases with F_{BrCL} in the copolymer, in agreement with the Fox−Flory relationship, which confirms indirectly the randomness of the copolymers (Figure 5).

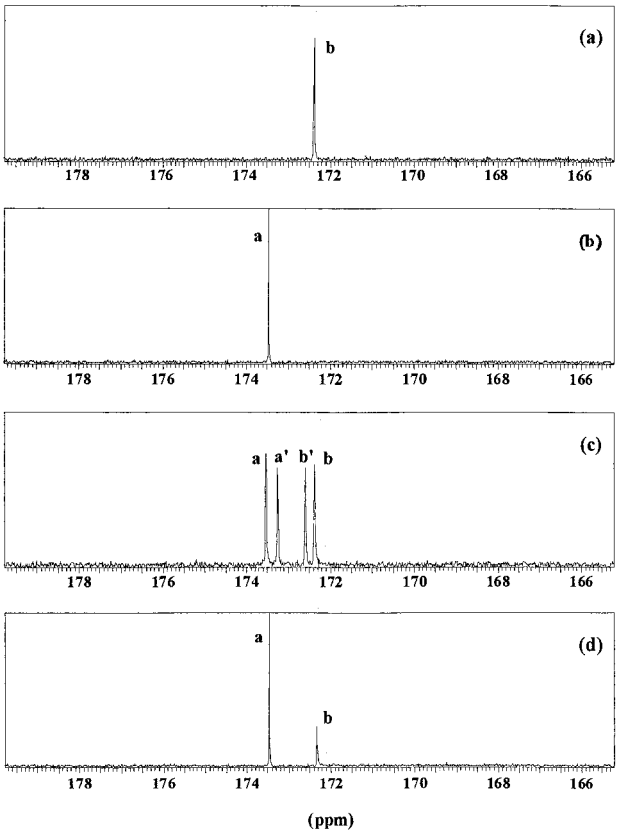


Figure 3. Expanded ^{13}C NMR spectra (carbonyl region) for (a) PγBrCL, (b) PCL, (c) poly(CL-*co*-γBrCL) (copolymer 3, Table 2), and (d) poly(CL-*b*-γBrCL) (copolymer 2, Table 3).

In a last demonstration of the versatility of the new monomer, block copolymers of ϵCL and γBrCL have been prepared by the sequential polymerization of the comonomers. First, polymerization of ϵCL was initiated by Al(O^{i}Pr)$_3$, followed by the addition of γBrCL, where the living chain end of PCL initiated the polymerization of γBrCL. The experimental molecular weight of each

Table 3. Sequential Polymerization of ϵCL and γBrCL Initiated by Al(O^{i}Pr)$_3$ in Toluene at 0 °C

	first block: PCL			second block: P(γBrCL)			
entry	$M_{n,th} \times 10^{-3}$	$M_{n,exp}$ (SEC) $\times 10^{-3}$	M_w/M_n	$M_{n,th} \times 10^{-3}$	$M_{n,exp}$(NMR) $\times 10^{-3}$	M_w/M_n	conversion, %
1	10	10.3	1.15	3	3.1	1.15	>99
2	10	10.2	1.15	5	5.2	1.20	>99
3	10	10.6	1.15	10	8.8	1.20	>99

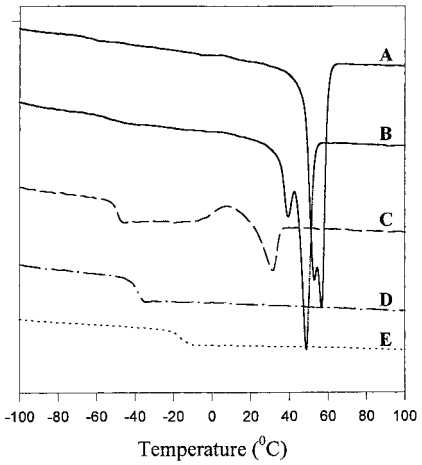


Figure 4. DSC traces for poly(CL-*co*-γBrCL) copolyesters of various molar compositions: (A) $F_{BrCL} = 0$; (B) $F_{BrCL} = 0.1$; (C) $F_{BrCL} = 0.3$; (D) $F_{BrCL} = 0.5$; (E) $F_{BrCL} = 1$.

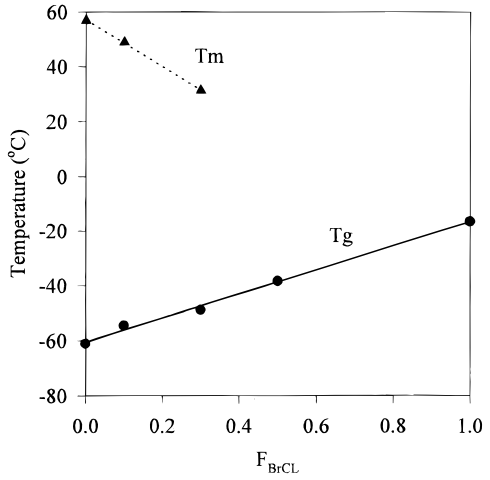


Figure 5. Phase diagram for poly(CL-*co*-γBrCL) copolymers.

block is consistent with the value expected for living polymerization at complete monomer conversion (Table 3). Furthermore, the molecular weight distribution of the copolymer remains narrow compared to the PCL first block ($M_w/M_n \leq 1.2$). Figure 6 compares the SEC chromatograms for the PCL first block and poly(CL-*b*-γBrCL) diblock copolymers. As expected, the molecular weight of the macroinitiator is systematically shifted toward higher values, and no trace of homopolymer can be detected. To assess that the copolymerization product is a pure diblock, i.e., that no transesterification has occurred between the PCL and the PγBrCL blocks, the ^{13}C NMR spectrum has been recorded. This transesterification reaction must result in mixed sequences easily detected by the additional resonances a′ and b′ observed in the carbonyl region for the random copolymer (Figure 3c). Figure 3d only shows the two homodiad peaks characteristic of each homopolymer and no trace of heterodiad peaks, consistent with the expected diblock structure. Furthermore, the relative intensity of the homodiad peaks confirms the percentage of each monomer in the copolymer, in agreement with the ^{1}H NMR analysis.

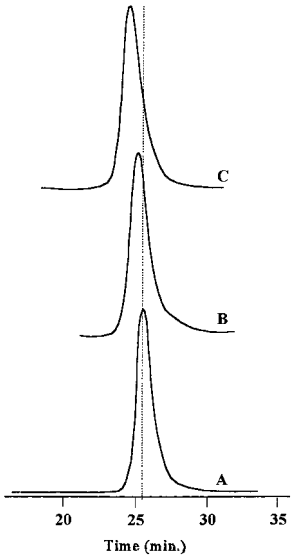


Figure 6. SEC chromatograms for diblock copolymers and the PCL precursor: (A) first PCL block, $M_n = 10\,000$; (B) poly(CL-*b*-γBrCL), $M_n = 10\,000/5200$; (B) poly(CL-*b*-γBrCL), $M_n = 10\,000/8800$.

Conclusions

The strategy for the easy synthesis of a new lactone monomer suitable to ROP, γ-bromo-ϵ-caprolactone, is reported. Homopolymerization of γ-bromo-ϵ-caprolactone initiated by Al(O^{i}Pr)$_3$ in toluene at 0 °C leads to polyesters of predictable molecular weight and narrow molecular weight distribution. The observation of the isopropyl α-end group and the hydroxy ω-end group is consistent with a coordination−insertion mechanism. The poly(γBrCL) homopolymer is amorphous with a glass transition temperature at −16.5 °C. Living random and block copolymerizations of ϵCL and γBrCL are successful in toluene at 0 °C. Similarly, block copolymers are easily prepared in a controlled way, by polymerizing ϵCL first in toluene at 0 °C. Increasing the γBrCL content of the random copolymers is responsible for decreased T_m and increased T_g compared to PCL. For γBrCL contents higher than 30 mol %, the random copolymers are amorphous.

This brominated polyester opens the way to new functional polyesters by straightforward transformation of the alkyl bromide. For instance, the bromide can be converted into ammonium salt or unsaturated group by reaction of the polymer with tertiary amine or a dehydrohalogenating reagent, respectively. So, quaternization of polyϵCL-*b*-polyγBrCL is a direct way to produce (at least partially) degradable surfactants or starting materials for the gene therapy. The formation of unsaturated groups along the polyester backbone by dehydrohalogenation can make the polyester prone to cross-linking which is useful for the synthesis of biodegradable (hydro)gels. The experimental conditions have

to be optimized in order to avoid the degradation of the polyester, as will be reported in a forthcoming paper.

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Supporting Information Available: Figure showing the ^{1}H NMR spectrum of poly(CL-*co*-γBrCL) (30% γBrCL in the copolymer, $M_{n,exp}$(NMR) = 16 500, M_w/M_n = 1.15) in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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