New Amphiphilic Poly[(*R*,*S*)-β-malic acid-*b*-ϵ-caprolactone] Diblock Copolymers by Combining Anionic and Coordination−Insertion Ring-Opening Polymerization

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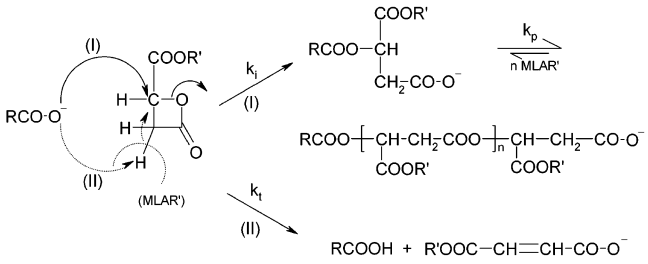
ABSTRACT: A three-step strategy to synthesize well-defined amphiphilic poly[(*R*,*S*)-β-malic acid-*b*-ϵ-caprolactone] diblock copolymers (P(MLA-*b*-CL)), which combines the anionic polymerization of benzyl β-malolactonate (MLABz) with the coordination−insertion ring-opening polymerization (ROP) of ϵ-caprolactone (CL), followed by the selective removal of benzyloxy protective groups is described. The first step involves initiation of the anionic polymerization of MLABz by potassium 11-hydroxydodecanoate in the presence of 18-crown-6 ether. This step was carried out at 0 °C with an initial monomer concentration of 0.2 mol L^{-1} in order to limit the occurrence of undesirable transfer and termination reactions by proton abstraction. After selective methylation of the carboxylic acid end group of the resulting α-hydroxy, ω-carboxylic acid poly(β-malolactonate), the polymerization of CL was initiated by the hydroxyl end group previously activated by $AlEt_3$. Finally, after catalytic hydrogenation of the benzyl ester functions, the P(MLA-*b*-CL) diblock copolymer was recovered and the amphiphilic character evidenced by proton NMR spectroscopy with varying the solvent polarity.

Introduction

The controlled synthesis and thorough characterization of macromolecules with a well-defined molecular architecture is a prerequisite to new polymeric materials. This requires understanding the relationship between molecular parameters and properties for a given application. For instance, drug delivery systems made from biodegradable, biocompatible, and amphiphilic diblock copolymers must meet specific material properties that can only be accomplished by totally controlled polymerization mechanisms. The synthesis of such diblock copolymers can be achieved by sequential addition of hydrophobic and hydrophilic monomers starting from an asymmetric difunctional initiator. Because of the versatile functionalities available, the polymerization of β-malolactonic acid esters has been chosen as a precursor for the hydrophilic block.[1] High molecular weight polymers are usually prepared by anionic ring-opening polymerizations (ROP) of substituted β-malolactonates using either tetraalkylammonium benzoate[2] or potassium alkanoate (added with 18-crown-6 ether) as initiator.[3] The anionic ROP proceeds by nucleophilic attack of the carboxylate anion on the carbon β to the carbonyl group of the cyclic ester, with inversion of configuration but without any racemization.[4,5] However, it has also been reported that proton abstraction reactions between the initiator and the monomer occur during the polymerization, thus reducing the effective initiator concentration and limiting the control over both the polyester molecular weight and chain end groups[2] (Scheme 1).

Scheme 1. Initiation/Propagation Steps (I) and Termination Step by Proton Abstraction (II) in the Anionic Polymerization of MLAR′ Initiated by Carboxylate Anions



This paper reports on the controlled synthesis of well-defined biodegradable and biocompatible poly(β-malic acid-*b*-ϵ-caprolactone) diblock copolymers (P(MLA-*b*-CL)) according to a three-step strategy (Scheme 2). The first step polymerizes benzyl β-malolactonate (MLABz) using an asymmetric difunctional initiator, i.e., potassium 11-hydroxydodecanoate (HDD) added with 18-crown-6 ether, at low temperature. These conditions significantly reduce both transfer and termination reactions by proton abstraction so that the α-hydoxyl, ω-carboxylic acid poly(β-malolactonate) synthesis is totally controlled. After selective protection of the carboxylic acid end group, the controlled polymerization of ϵ-caprolactone (CL) is then initiated by the α-hydroxyl extremity of the poly(β-malolactonate) chain, previously activated by $AlEt_3$. The third and final step is selective deprotection of the benzyl ester groups by catalytic hydrogenation reaction. Clearly, a large range of new biodegradable (functionalized) diblock copolyesters should

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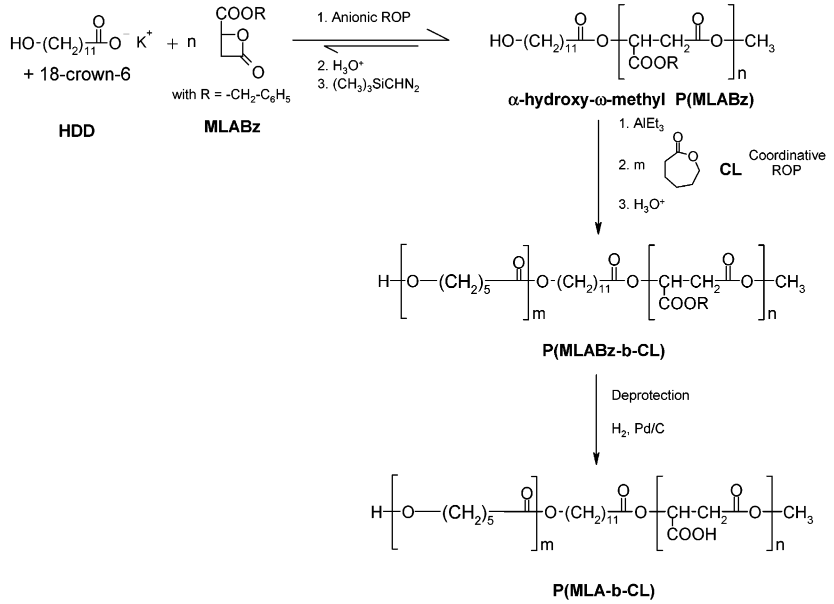
Scheme 2. Three-Step Synthesis of Poly(β-malic acid-*b*-ϵ-caprolactone) (P(MLA-*b*-CL)) Diblock Copolymers



be accessible using this synthetic strategy and known (functionalized) alkyl β-malolactonate[6] with other (di)-lactones[7] polymerizable by "coordination−insertion" ROP initiated with Al alkoxides.

Experimental Section

Materials. (*R,S*)-Benzyl β-malolactonate (MLABz) was synthesized and purified starting from aspartic acid as published elsewhere.[8] It was stored at −18 °C, distilled under reduced pressure, and dried by three successive azeotropic distillations of toluene just before use. ϵ-Caprolactone (Acros, 99%) was dried over calcium hydride at room temperature for 48 h and then distilled under reduced pressure. 11-Hydroxydodecanoic acid (Aldrich, 97%) and 18-crown-6 (Acros, 99%) were dried by three successive azeotropic distillations of toluene. Potassium (Acros, 98%), naphthalene (Acros, 99%), trimethylsilyldiazomethane (2 N in hexane from Aldrich), triethylaluminum (1.8 M in toluene from Fluka), Pd/C (10 wt % from Aldrich), and hydrogen (Air Liquide, N50) were used without further purification. Toluene (Labscan, 99%) and tetrahydrofuran (Labscan, 99%) were dried by refluxing over CaH_2 and Na/benzophenone complex, respectively. Just before use, THF was further dried over low molecular weight ω-lithium styryl poly(styrene) and then distilled under reduced pressure.

Anionic Ring-Opening Polymerization of Benzyl β-Malolactonate. In a previously flamed and nitrogen-purged round-bottom flask, 1.0 g (7.8 mmol) of naphthalene was added with 0.37 g (9.5 mmol) of potassium and 39 mL of THF. After an overnight reaction, a deep green solution of potassium naphthalene radical anion was obtained (concentration 0.2 mol L^{-1}). In another previously flamed and nitrogen-purged round-bottom flask, 0.52 g (1.97 mmol) of 18-crown-6 ether and 0.43 g (1.97 mmol) of 11-hydroxydodecanoic acid were dissolved in 10 mL of THF and then added with a stoichiometric amount of the solution of potassium naphthalene radical anion (10.0 mL, 1.97 mmol, [HDD] = 0.1 mol L^{-1}). The polymerization of (*R,S*)-benzyl β-malolactonate (MLABz) (2.0 g, 9.7 mmol) was typically conducted in a previously flamed and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum by initiation with the complex formed between potassium 11-hydroxydodecanoate and 18-crown-6 ether (2.0 mL, 2.0×10^{-4} mol) in THF (44.5 mL) at 0 °C. After 120 min, the polymerization was stopped by adding a few drops of aqueous HCl (0.1 mol L^{-1}). After evaporation of the solvent, the product was dissolved in dichloromethane (20 mL) and extracted three times each with a saturated aqueous KCl solution (3 × 20 mL) and with deionized water (3 × 20 mL). Finally, the organic layer was poured into 8 volumes of cold heptane (160 mL). The polymer was recovered by filtration and dried under reduced pressure at 40 °C until constant weight, i.e., 1.6 g. Yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, see Figure A for attribution): 1.0−1.8 (m, 18H_b), 2.25 (t, 2H_c), 2.8 (m, 2H_e), 3.7 (t, 2H_a), 4.9−5.1 (s, 2H_f), 5.45 (m, H_d), and 7.3 (s, 5H_g). $M_n = 7900$. $M_w/M_n = 1.2$.

Methylation of α-Hydroxy, ω-Carboxylic Acid Poly(benzyl-β-malolactonate). In a previously flamed and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 1.3 g of α-hydroxy, ω-carboxylic acid poly(benzyl-β-malolactonate) (1.64×10^{-4} mol, $M_n = 7900$, $M_w/M_n = 1.2$) was dried by three successive azeotropic distillations of toluene (3 × 10 mL). Then, the dried polymer was dissolved in a mixture of 20 mL of toluene and 2 mL of anhydrous methanol. Three equivalents of trimethylsilyldiazomethane (4.94×10^{-4} mol, 0.25 mL) compared to the content of carboxylic acid functions was then added. Nitrogen gas evolved through a connected oil valve. After 1 h, the reaction was stopped by the addition of a few drops of acetic acid (0.1 mol L^{-1}), and the volatiles were removed under reduced pressure. The polymer was recovered by precipitation into 8 volumes of cold heptane (160 mL), filtration, and drying under reduced pressure at 40 °C until constant weight, i.e., 1.3 g. Yield >99%. ^{1}H NMR (300 MHz,, $CDCl_3$, δ ppm): 1.0−1.8 (m, 18H), 2.25 (t, 2H), 2.8 (m, 2H), 3.7 (t, 2H), 3.8 (s, 3H from −C(O)OMe), 4.9−5.1 (s, 2H), 5.45 (m, H) and 7.3 (s, 5H). $M_n = 7900$. $M_w/M_n = 1.2$. ^{1}H NMR spectroscopy attests to the completion of the methylation reaction to form α-hydroxy, ω-methyloxycarbonyl poly(benzyl β-malolactonate), with the intensity ratio between ω-methyloxycarbonyl protons at 3.8 ppm and α-hydroxymethylene ones at 3.7 ppm being equal to the expected 3/2 ratio.

Block Copolymerization. In a previously flamed and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 1.3 g of α-hydroxy, ω-methyloxycarbonyl poly(benzyl-β-malolactonate) (1.64×10^{-4} mol, $M_n = 7900$, $M_w/M_n = 1.2$) was dried by three successive azeotropic distillations of toluene (3 × 10 mL). Then, the dried polymer was reacted with 1.2 equiv of triethylaluminum compared to the content of hydroxyl functions (1.97×10^{-4} mol, 2 mL) in toluene at 50 °C for 2 h. Ethane evolved through a connected oil valve. After cooling to room temperature, ϵ-caprolactone (7.2 mmol, 0.80 mL) was added and polymerized for 48 h. After addition of a few drops of a HCl aqueous solution (0.1 mol L^{-1}), the polymer solution was washed three times with an aqueous solution of ethylenediaminetetraacetic acid (EDTA) buffered

Table 1. Molecular Characteristics of PMLABz Synthesized by Ring-Opening Polymerization of MLABz As Initiated by Potassium 11-Hydroxydodecanoate Added with 18-Crown-6 Ether (HDD) in THF at 25 °C for $[\mathrm{MLABz}]_0 = 1.1$ mol L^{-1} and $[\mathrm{MLABz}]_0/[\mathrm{HDD}] = 50$

entry	polym time (min)	conv (%)	$M_{\mathrm{n,theor}}$[a]	$M_{\mathrm{n,NMR}}$[b]	$M_{\mathrm{n,SEC}}$	M_w/M_n	R[c]
1	10	100	11 300	9300	6000	1.53	ND[d]
2	20	100	11 300	8500	5200	1.50	35
3	30	100	11 300	8300	5200	1.43	40

[a] $M_{\mathrm{n,theor}} = ([\mathrm{MLABz}]_0/[\mathrm{HDD}] \times \mathrm{conv} \times \mathrm{MW}_{\mathrm{MLABz}}) + \mathrm{MW}_{\mathrm{HDD}}$. [b] $M_{\mathrm{n,NMR}} = ((I_{5.5} \times \mathrm{MW}_{\mathrm{MLABz}})/(I_{3.6}/2)) + \mathrm{MW}_{\mathrm{HDD}}$. [c] $R = 2(I_{5.5}/I_{6.8})$ (from ^{1}H NMR, see text). [d] ND = not determined.

at pH 4.8 (0.1 mol L^{-1}) (3 × 20 mL) and with deionized water (3 × 20 mL). The organic layer was poured into 8 volumes of heptane (160 mL). The copolymer was recovered by filtration and dried under reduced pressure at 40 °C until constant weight (2.1 g). Yield > 99%. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$, δ ppm, see Figure 3): 1.6 (m, 18$\mathrm{H_b}$), 1.65−1.8 (t, 2$\mathrm{H_k}$), 1.8−2.2 (t, 4$\mathrm{H_{j+l}}$), 2.55 (t, 2$\mathrm{H_{i+c}}$), 3.1 (m, 2$\mathrm{H_e}$), 3.7 (t, 2$\mathrm{H_n}$), 3.8 (s, 3$\mathrm{H_h}$), 4.15 (t, 2$\mathrm{H_{a+m}}$), 5.1 (s, 2$\mathrm{H_f}$), 5.45 (m, $\mathrm{H_d}$) and 7.2 (s, 5$\mathrm{H_g}$). M_n block$k_{\mathrm{PMLABz}} = 7900$; M_n blockPCL = 11 500 and $M_{\mathrm{n(PMLABz-b-CL)}} = 19\,400$. $M_w/M_n = 1.5$.

Removal of Benzyl Ester Protective Groups. In a round-bottom flask, 1.0 g of the copolymer (5.2 × 10^{-5} mol, $M_n = 19\,400$) was dissolved into 200 mL of acetone at room temperature and then added with 0.2 g of Pd/C (10 wt %). A continuous flow of hydrogen was bubbled into the solution for 7 h. After filtration through Celite, a clear copolymer solution was obtained. The solvent was evaporated under reduced pressure (10 mmHg) before recovering the polymer by extensive drying at 40 °C under reduced pressure (0.8 g). Yield > 99%. ^{1}H NMR (300 MHz, $\mathrm{CD_3COCD_3}$ added with few drops of $\mathrm{D_2O}$, δ ppm, see Figure 6): 1.4 (m, 18$\mathrm{H_b}$ and 2$\mathrm{H_k}$), 1.6−1.8 (t, 2$\mathrm{H_{j+l}}$), 2.55 (t, 2$\mathrm{H_{i+c}}$), 3.1 (m, 2$\mathrm{H_e}$), 3.7 (t, 2$\mathrm{H_n}$), 3.8 (s, 3$\mathrm{H_h}$), 4.15 (t, 2$\mathrm{H_{a+m}}$), 5.45 (m, $\mathrm{H_d}$). M_n block$_{\mathrm{PCL}} = 11\,300$; M_n block$_{\mathrm{PMLA}} = 3300$ and $M_{\mathrm{n(PMLA-b-PCL)}} = 14\,600$.

Characterization. ^{1}H NMR spectra were recorded using a Bruker AMX-300 apparatus at room temperature in various deuterated solvents (30 mg/0.6 mL). Size exclusion chromatography (SEC) was performed in THF at 35 °C using a Polymer Laboratories liquid chromatograph equipped with a PL-DG802 degasser, an isocratic HPLC pump LC 1120 (flow rate = 1 mL/min), a Marathon autosampler (loop volume = 200 μL, solution concentration = 1 mg/mL), a PL-DRI refractive index detector, a LC1200 UV detector, and three columns: a PL gel 10 μm guard column and two PL gel Mixed-B 10 μm columns (linear columns for separation of $\mathrm{MW_{PS}}$ ranging from 500 to 10^6 Da). Polystyrene standards were used for calibration. FTIR analysis was carried out with a Bio-Rad Excalibur FTIR spectrometer with a 0.2 $\mathrm{cm^{-1}}$ resolution. Spectra were recorded (from 4000 to 700 $\mathrm{cm^{-1}}$) owing to a single reflection crystal system (Split Pea from Harrick) and a DTGS detector. DSC measurements were carried out with a 2920 CE DSC from TA instruments (heating rate 10 °C/min) under nitrogen.

Results and Discussion

The polymerization of 4-benzyloxycarbonyl-2-oxetanone, also called benzyl β-malolactonate (MLABz), requires first its synthesis and careful purification. Since several very synthetic routes have already been reported,[9−12] the “aspartic route”[4] was used in this study.

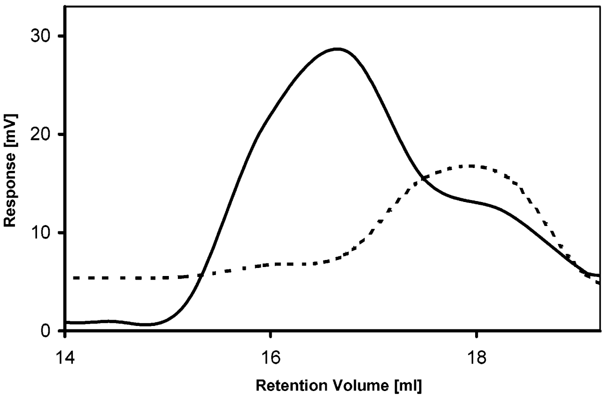


Figure 1. SEC of PMLABz using a DRI detector (full line) and UV detector at 300 nm (dashed line) (entry 1 in Table 1).

According to the three-step strategy depicted in Scheme 2, the polymerization of 1.1 mol L^{-1} of MLABz was initiated by potassium 11-hydroxydodecanoate added with 18-crown-6 ether in THF at room temperature and an initial $[\mathrm{M}]_0/[\mathrm{I}]_0 = 50$. Complete monomer conversion was reached within 10 min (Table 1, entry 1). Assuming that each chain is end-capped by a hydroxyl group at one end and a carboxylic acid function at the other chain end, the experimental molar mass can be calculated by ^{1}H NMR spectroscopy ($M_{\mathrm{n,NMR}}$) from the relative intensity of the methine protons of the main chain at 5.5 ppm ($-\mathrm{C}H(\mathrm{COOR})-\mathrm{CH_2}-\mathrm{COO}-$) and α-hydroxyl methylene protons at 3.7 ppm ($\mathrm{HO}-\mathrm{C}H_2-(\mathrm{CH_2})_{10}-\mathrm{COO}-$). After a polymerization time of 10 min, the calculated $M_{\mathrm{n,NMR}}$ value is somewhat slightly lower than the theoretical molar mass, assuming quantitative initiation and a “living” mechanism, i.e., the absence of transfer and irreversible termination reactions. However, SEC shows that the molecular weight distribution is bimodal with a population at very high retention volume ($M_p \sim 900$ with reference to a polystyrene calibration). The discrepancy between experimental ($M_{\mathrm{n,NMR}}$) and theoretical molar mass of poly(benzyl β-malolactonate) (PMLABz) increases with increasing reaction time (entries 2 and 3 in Table 1). Figure 1 demonstrates that there is a 300 nm absorbance distributed all along the chromatogram. An absorption band at 1650 $\mathrm{cm^{-1}}$ ($\upsilon_{\mathrm{C=C}}$) also emerges in the FTIR spectrum of the PMLABz (see Figure A given in the Supporting Information), while ^{1}H NMR spectroscopy exhibits a doublet at 6.8 ppm (see Figure B). This is consistent with the formation of fumarate derivatives ($\mathrm{R'OOC}-CH{=}CH-\mathrm{COO}-$), whose relative content can be calculated from the relative intensity of the methine protons of the repeat units at 5.5 ppm ($-\mathrm{C}H(\mathrm{COOR})-\mathrm{CH_2}-\mathrm{COO}-$) and the vinyl protons of the fumaric acid esters at 6.8 ppm ($\mathrm{R'OOC}-\mathrm{C}H{=}\mathrm{C}H-\mathrm{COO}-$): $R = 2(I_{5.5}/I_{6.8}) \sim 35-40$. Since all of the monomer has been consumed within 10 min, these observations can only be explained by the occurrence of undesirable transfer reactions between active species and growing polymer chains to form α-benzyl fumarate PMLABz chains (Scheme 3). We do not know of any previous reports of inter- or intramolecular proton abstraction reactions in the polymerization of MLABz.

To avoid, or at least to drastically limit, these undesirable transfer and termination reactions, further polymerizations were carried out at lower temperature (0 °C), while maintaining all other experimental conditions (Table 2). Reducing the polymerization temperature reduces the propagation rate but also significantly decreases the kinetics of transfer reactions by proton abstraction between growing species and the polyester chains. Monomer conversion continuously increases with time with no evidence by SEC (with DRI/UV detectors) of α-benzyl fumarate PMLABz within 15 min (90% monomer conversion). The molecular weight distribution remains bimodal, with a population at very

Scheme 3. Proton Abstraction Transfer Reactions between Active Sites and Polymer Chains

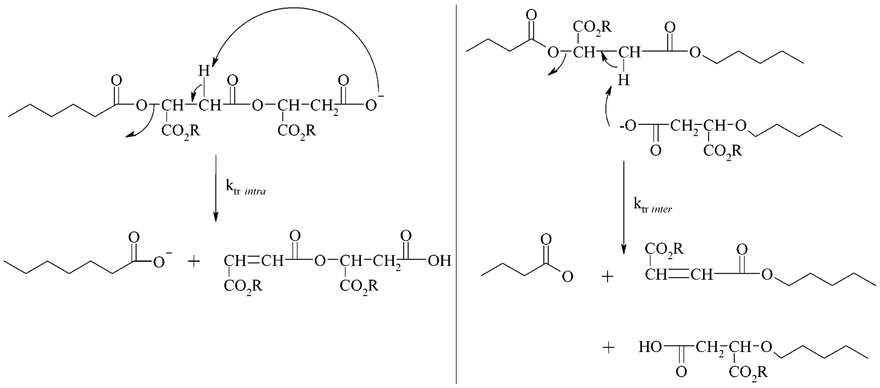


Table 2. Molecular Characteristics of PMLABz Synthesized by Ring-Opening Polymerization of MLABz As Initiated by Potassium 11-Hydroxydodecanoate Added with 18-Crown-6 Ether (HDD) in THF at 0 °C for $[MLABz]_0 = 1.0$ mol L^{-1} and $[MLABz]_0/[HDD] = 50$

entry	polym time (min)	conv (%)	$M_{n,theor}$[a]	$M_{n,NMR}$[b]	$M_{n,SEC}$	M_w/M_n	R[c]
1	5	53	5500	4800	6600	1.01	20
2	10	85	8700	6200	8000	1.05	20
3	15	90	9200	6600	8200	1.06	20
4	20	91	9300	9200	8300	1.15	ND[d]

[a] $M_{n,theor} = ([MLABz]_0/[HDD] \times conv \times MW_{MLABz}) + MW_{HDD}$. [b] $M_{n,NMR} = ((I_{5.5} \times MW_{MLABz})/(I_{3.6}/2)) + MW_{HDD}$. [c] $R = 2(I_{5.5}/I_{6.8})$ (from ^{1}H NMR, see text). [d] ND = not determined.

high retention volume; however, the polydispersity index is remarkably narrow ($M_w/M_n \sim 1.1$) (see Figure C given in the Supporting Information). ^{1}H NMR spectra demonstrate that the relative content of fumarate derivatives is constant up to at least 90% monomer conversion (see Figure D). Therefore, the majority of fumarate derivatives is formed at low temperature at the earliest stage of the polymerization, most likely by proton abstraction between the initiator and the monomer. Because of the attractive mesomeric effect through the conjugated carbon−carbon double bond, the resulting potassium benzylfumarate is not nucleophilic enough to initiate the polymerization of MLABz. The polymerization proceeds thus without transfer reactions involving the propagating active sites (narrow molecular weight distribution). It comes out that carboxylate anions in initiator and in propagating species behave differently toward the proton abstraction onto the monomer. Such a difference in reactivity might find some explanations in the likely higher basicity of the propagating carboxylate anions due to the presence in β-position of a benzyl ester group, i.e., an electron-withdrawing group. This benzyl ester group is able to enhance the proton acidity of the carboxylic acid functions corresponding to the propagating end groups. Furthermore, the selective formation of monobenzyl fumarate derivatives homogeneously mixed within the PMLABz chains might account for the decrease of the glass transition temperature from 30 °C (for PMLABz chains deprived of monobenzyl fumarates, see hereafter) to 8 °C as detected by DSC. Such low molecular weight fumarate derivatives would thus behave as plasticizers of PMLABz.

Table 3. Molecular Characteristics of PMLABz Synthesized by Ring-Opening Polymerization of MLABz As Initiated by Potassium 11-Hydroxydodecanoate Added with 18-Crown-6 Ether (HDD) in THF at 0 °C for $[MLABz]_0 = 0.2$ mol L^{-1} and $[MLABz]_0/[HDD] = 50$

entry	polym time (min)	conv (%)	$M_{n,theor}$[a]	$M_{n,NMR}$[b]	M_w/M_n	R[c]
1	15	73	7700	8400	1.17	400
2	45	75	7900	8600	1.18	400
3	90	83	8800	9000	1.31	ND[d]
4	120	87	9200	9300	1.23	400
5	150	94	10600	10000	1.32	550

[a] $M_{n,theor} = ([MLABz]_0/[HDD] \times conv \times MW_{MLABz}) + MW_{HDD}$. [b] $M_{n,NMR} = ((I_{5.5} \times MW_{MLABz})/(I_{3.6}/2)) + MW_{HDD}$. [c] $R = 2(I_{5.5}/I_{6.8})$ (from ^{1}H NMR, see text). [d] ND = not determined.

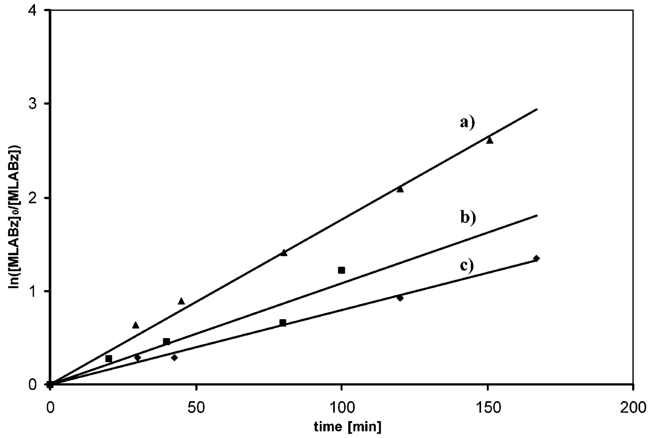


Figure 2. Time dependence of monomer conversion in MLABz polymerization as initiated with potassium 11-hydroxydodecanoate added with 18-crown-6 ether (HDD) in THF at 0 °C for $[MLABz]_0$ of 0.2 mol L^{-1} and various $[MLABz]_0/[HDD]$: (a) 24, (b) 48, and (c) 73.

In the next series of experiments, the initial monomer concentration was also reduced. Thus, MLABz was polymerized at 0 °C using an initial monomer concentration of 0.2 mol L^{-1}; all other experimental conditions were unchanged. The monomer conversion continuously increased with polymerization time to reach 94% after 150 min (Table 3). The experimental molar mass agreed well with the theoretical value at all monomer conversions, assuming a “living” polymerization. As calculated from the relative intensity of the methine protons of the repeat units at 5.5 ppm (−C*H*(COOR)−CH$_2$−COO−) and the vinyl protons of monobenzylfumarate at 6.8 ppm (R′OOC−C*H*═C*H*−COO−), only a very low fraction (below 0.2 wt %) of monobenzylfumarate is formed by proton abstraction reaction, at least up to 94% monomer conversion ($R = 2(I_{5.5}/I_{6.8}) \geq 400$). The polydispersity index of PMLABz remains quite narrow at all monomer conversions. Therefore, reduction of both reaction temperature and monomer concentration significantly decreases the extent of transfer and termination reactions

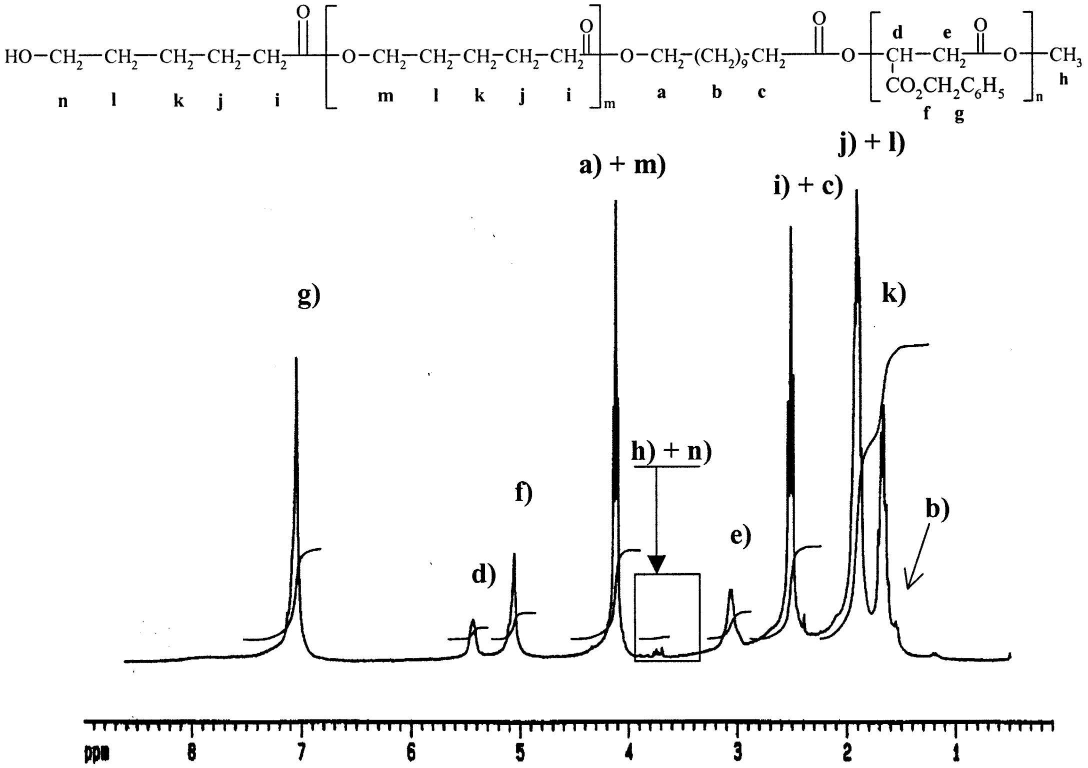


Figure 3. ^{1}H NMR spectrum of P(MLABz-*b*-CL) block copolymer (in CDCl3). $M_{\text{n,block PCL}} = 11\,500$, $M_{\text{n,block PMLABz}} = 7900$, and $M_{\text{n,P(MLABz-b-CL)}} = 19\,400$.

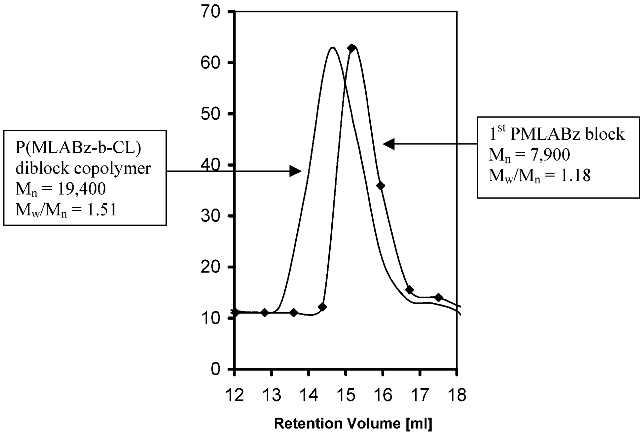


Figure 4. SEC traces of P(MLABz-*b*-CL) block copolymer (full line) ($M_{\text{n,block PCL}} = 11\,500$, $M_{\text{n,block PMLABz}} = 7900$, and $M_{\text{n,P(MLABz-b-CL)}} = 19\,400$) and PMLABz macroinitiator (full line with squares) ($M_n = 7900$).

by proton abstraction (see step II in Scheme 1 and Scheme 3). The lower monobenzylfumarate content in PMLABz is also consistent with its glass transition temperature of 29.6 °C.

A kinetic study of the polymerization of MLABz initiated by HDD was performed at 0 °C using an initial monomer concentration of 0.2 mol L^{-1} while varying the initial monomer-to-initiator molar ratios ($24 \leq [\text{MLABz}]_0/[\text{HDD}] \leq 73$). The linear dependence of ln([MLABz]$_0$/[MLABz]) vs time demonstrates that the polymerization is first order in monomer and that the number of growing species does not change appreciably during polymerization (Figure 2). The slope of the linear relationships corresponds to apparent propagation rate constant (k_{app}) values of 0.8×10^{-2}, 1.08×10^{-2}, and 1.77×10^{-2} min^{-1} for [MLABz]$_0$/[HDD] ratios of 73, 48, and 24, respectively. The order in initiator, *a*, and the absolute rate constant, k_p, have then been tentatively approximated by assuming that $k_{\text{app}} = k_p[\text{HDD}]^a$. A linear regression of ln(k_{app}) vs ln[HDD] using the initial initiator concentrations results in a k_p value of 0.53 L mol^{-1} min^{-1} and a partial order in initiator *a* equal to 0.7. This partial order in initiator may be consistent with termination reactions by proton abstraction between monomer and initiator at the very beginning of the polymerization; i.e., a minimal amount of the initiator is lost to form inactive potassium benzylfumarate monoacid salt.

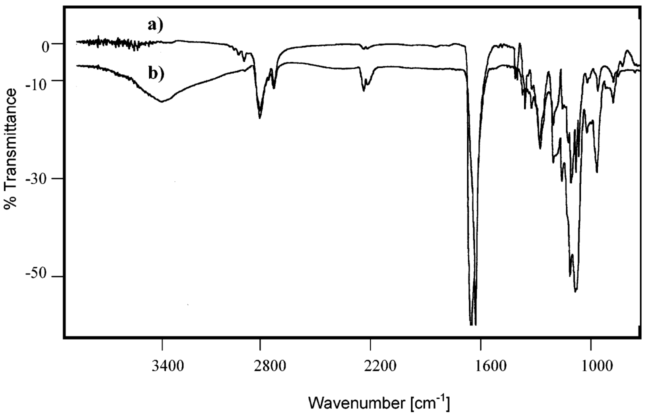


Figure 5. FT-IR spectra of the diblock copolymers P(MLABz-*b*-CL) (a: $M_{\text{n,block PCL}} = 11\,500$, $M_{\text{n,block PMLABz}} = 7900$, and $M_{\text{n,P(MLABz-b-CL)}} = 19\,400$) and P(MLA-*b*-CL) (b: $M_{\text{n,block PCL}} = 11\,500$, $M_{\text{n,block PMLA}} = 3300$, and $M_{\text{n,P(MLA-}b\text{-CL)}} = 14\,600$).

Before sequential polymerization of ϵ-caprolactone (CL), α-hydroxy, ω-carboxylic acid poly(benzyl β-malolactonate) ($M_n = 7900$, see entry 2 in Table 3) was reacted with excess of trimethylsilyldiazomethane for 1 h at room temperature in toluene/methanol (9:1) to selectively protect the carboxylic acid end group (see

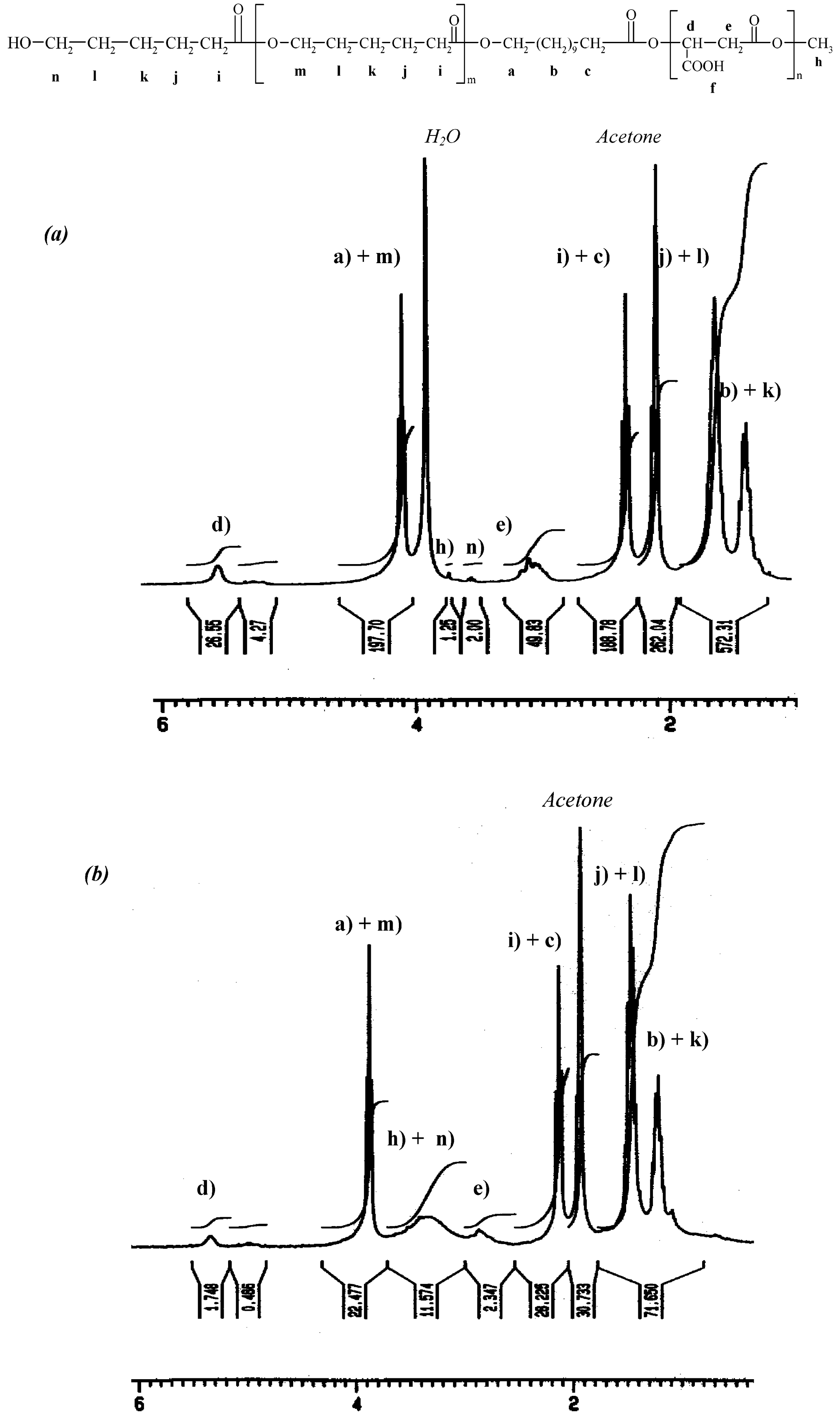


Figure 6. ^{1}H NMR spectra of P(MLA-*b*-CL) diblock copolymer ($M_{n,\text{block PCL}} = 11\,500$, $M_{n,\text{block PMLA}} = 3300$, and $M_{n,\text{P(MLA-b-CL)}} = 14\,600$) in $(CD_3)_2CO$ (added with a few drops of D_2O; see text) (a) and in $(CD_3)_2CO$/ $CDCl_3$ solvent mixture (50:50 in volume) (b).

Scheme 2). ^{1}H NMR spectroscopy attests to the completion of the methylation reaction (see Experimental Section). Both the polydispersity index and molar mass of PMLABz chains remain unchanged and controlled.

In the next step, the polymerization of CL was initiated by the α-hydroxy, ω-methyloxycarbonyl poly(benzyl β-malolactonate) ($M_n = 7900$, $M_w/M_n = 1.18$) after previous activation of the hydroxyl end group by reaction with a slight excess of triethylaluminum (1.2 equiv). The resulting diethylaluminum primary alkoxide functions initiate the polymerization of CL, which was carried out in toluene at room temperature with an initial monomer concentration of 0.46 mol L^{-1} and an initial monomer-to-macroinitiator ratio of 83. After 48 h, the diethylaluminum alkoxide growing species were deactivated by the addition of a few drops of a HCl aqueous solution (0.1 mol L^{-1}), and the copolymer was recovered by precipitation from heptane. Monomer conversion was complete as determined by gravimetry. Figure 3 shows the ^{1}H NMR spectrum of the precipitated poly(benzyl-β-malolactonate-*b*-ϵ-caprolactone) diblock copolymer (P(MLABz-*b*-CL)). In addition to the signals assigned to PMLABz and PCL blocks, two minor resonances at 3.7 and 3.8 ppm, respectively attributed to α-hydroxymethylene and ω-methyloxycarbonyl protons end groups, allowed for calculating the number-average molecular weight of each block [$M_{n,PCL} = (I_{4.2}/2)/(I_{3.7-3.8}/5)MW_{CL} = 11\,500$; $M_{n,PMLABz} = (I_{5.5}/(I_{3.7-3.8}/5)MW_{MLABz}) + MW_{HDD} = 7000$ and $M_{n,P(MLABz-b-PCL)} = M_{n,PCL} + M_{n,PMLABz} = 18\,500$]. Assuming an inherent experimental error close to 10%, a good agreement thus exists between theoretical and experimental molecular weights. The molecular weight distribution of P(MLABz-*b*-CL) block copolymer is monomodal and shifted to lower retention volume compared to the α-hydroxy PMLABz used as macroinitiator (Figure 4).

The last step in the synthesis of the amphiphilic P(MLA-*b*-CL) diblock copolymer consists of the catalytic hydrogenation of benzyl ester functions anchored all along the PMLABz block.[13] The deprotection of carboxylic acid functions is followed by FTIR spectroscopy, which displays a broad absorption around 3400 cm^{-1} typical of the carboxylic acid groups (Figure 5). ^{1}H NMR spectroscopy shows the complete disappearance of benzylic protons attesting for a quantitative deprotection by the catalytic hydrogenation. The generated carboxylic acid functions form strong hydrogen bonding with the ester carbonyl functions, at least in a solvent such as acetone-d_6 ($(CD_3)_2CO$). Indeed, any resonance signal typical of carboxylic acids could not be detected at low field, i.e., around 10 ppm, while a broad and intense signal centered at 3.4 ppm overlaps the signals corresponding to the copolyester end groups. Addition of a few drops of D_2O directly into the NMR tube allows to refine the peaks structure (Figure 6a) and to determine the molar weight of the poly(β-malic acid-*b*-ϵ-caprolactone) diblock copolymer (P(MLA-*b*-CL)): M_n $\text{block}_{PCL} = (I_{4.2})/(I_{3.6}) \times MW_{CL} = 11\,300$; M_n $\text{block}_{PMLA} = (I_{5.5}/(I_{3.6}/2) \times MW_{MLA}) + MW_{HDD} = 3300$ and $M_{n,P(MLA-b-PCL)} = M_{n,PCL} + M_{n,PMLA} = 14\,600$. Catalytic hydrogenation preserves polyester chain integrity since polymerization degrees (DP) of both PCL and PMLA are very similar before and after deprotection. The calculated DP_{PMLABz} and DP_{PMLA} are 30 ± 10%, while DP_{PCL} remains close to 100 according to ^{1}H NMR spectroscopy.

PMLABz first block, P(MLABz-*b*-CL) diblock copolymer, and finally deprotected P(MLA-*b*-CL) diblock copolymer were analyzed by DSC (Table 4). The glass transition temperature (T_g) and melting temperature (T_m) of a homoPCL (with M_n close to 10 000) are also included in Table 4. As expected,[1] the PMLABz block is totally amorphous with a T_g at 29.6 °C. After copolymerization with CL, the copolymer has a melting endotherm at 53.0 °C due to the melting of crystalline PCL domains. Only one T_g is detected at 12.2 °C, which is between the T_g's of PMLABz and PCL. After deprotection of the carboxylic acid functions along the poly(β-malic acid) sequence, the copolyester remains semicrystalline with a T_g and a T_m at 6.4 and 51 °C, respectively.

Table 4. Thermal Transitions in PMLABz and PCL Homopolyesters and P(MLABz-*b*-CL) and P(MLA-*b*-CL) Diblock Copolyesters As Determined by DSC (Heating Rate: 10 °C/min, Second Scan Recorded, under Nitrogen Flow)

polyester	M_n	T_g (°C)	T_m (°C)
PMLABz	7900	29.6	
PCL	10000	−58.0	57.5
P(MLABz-*b*-CL)	7900-*b*-11500	12.2	53.0
P(MLA-*b*-CL)	3300-*b*-11500	6.4	51.2

The amphiphilic character of the P(MLA-*b*-CL) diblock copolymer was characterized by some preliminary ^{1}H NMR experiments in selected solvents. Large amounts of a selective solvent of each block (D_2O for the hydrophilic PMLA block and $CDCl_3$ for the hydrophobic PCL sequence) were added to a homogeneous copolymer solution in $(CD_3)_2CO$. Figure 6b shows the ^{1}H NMR spectrum of P(MLA-*b*-CL) diblock copolymer in a mixture of $(CD_3)_2CO$/ $CDCl_3$ (50:50 in volume). Signals corresponding to PMLA protons are broadened while the DP_{PCL}/DP_{PMLA} ratio increases from 3.7 to 6.4. The PMLA block protons are hidden due to a restriction of chain mobility and a decrease of relaxation times. As expected, the DP_{PCL}/DP_{PMLA} ratio decreases by adding a large volume of D_2O (not shown here).

In conclusion, we described a versatile route for the controlled synthesis of block copolymers combining anionic and coordination−insertion ROP of lactones. The new biodegradable and amphiphilic P(MLA-*b*-CL) diblock copolymers form micelles. We are currently investigating the tensioactivity of these block copolyesters and their ability to form micelles at varying molecular composition. The result of this study and the polymerization of other functionalized alkyl β-malolactonates will be reported in a forthcoming paper.

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Supporting Information Available: FT-IR spectra of PMLABz synthesized by ring-opening polymerization of MLABz as initiated with potassium 11-hydroxydodecanoate added with 18-crown-6 ether (HDD) in THF at 25 °C (a) for 10 min ($M_n = 9300$) and (b) 30 min ($M_n = 8300$) $[MLABz]_0 = 1.1$ mol L^{-1} and $[MLABz]_0/[HDD] = 50$ (Figure A); ^{1}H NMR spectrum (in $CDCl_3$) of PMLABz ($M_n = 9300$) synthesized by ring-opening polymerization of MLABz as initiated with potassium 11-hydroxydodecanoate added with 18-crown-6 ether (HDD) in THF at 25 °C for 10 min, $[MLABz]_0 = 1.1$ mol L^{-1} and $[MLABz]_0/[HDD] = 50$ (Figure B); SEC trace of PMLABz ($M_n = 6000$, $M_w/M_n = 1.08$) obtained by ring-opening polymerization of MLABz as initiated with potassium 11-hydroxydodecanoate added with 18-crown-6 ether (HDD) in THF at 0 °C for 15 min, $[MLABz]_0 = 1.0$ mol L^{-1} and $[MLABz]_0/[HDD] = 50$ (Figure C); ^1H NMR spectrum (in $CDCl_3$) of PMLABz ($M_n = 6600$) synthesized by ring-opening polymerization of MLABz as initiated with potassium 11-hydroxydodecanoate added with 18-crown-6 ether (HDD) in THF at 0 °C for 15 min, $[MLABz]_0 = 1.0$ mol L^{-1} and $[MLABz]_0/[HDD] = 50$ (Figure D). This material is available free of charge via the Internet at http://pubs.acs.org.

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