**Summary:** A four-step strategy to synthesize well-defined amphiphilic poly(ε-caprolactone-b-[R,S] β-malic acid-b-ε-caprolactone) triblock copolymers [P(CL-b-MLA-b-CL)], which combines the anionic polymerization of [R,S] benzyl β-malolactonate (MLABz), and the coordination-insertion ring-opening polymerization (ROP) of ε-caprolactone (CL), followed by the selective removal of benzyloxy protective groups of the central poly(malolactonate) block is described. The first step involves MLABz initiated 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 reduction of the carboxylic acid end-group of the resulting α-hydroxy, ω-carboxylic poly-([R,S] benzyl β-malolactonate) leading to an α,ω-dihydroxy PMLABz, the polymerization of CL was initiated by each hydroxyl end-groups previously activated by AlEt$_3$. Finally, after catalytic hydrogenation of the benzyl ester functions, the P(CL-b-MLA-b-CL) triblock copolymer was recovered

and the amphiphilic character evidenced by UV spectroscopy. As demonstrated, the CMC of these new P(CL-b-MLA-b-CL) triblock copolymer is higher by one order of magnitude than that of a P(MLA-b-CL) diblock copolymer of similar composition.
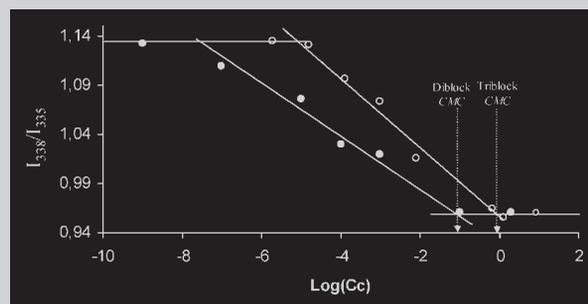
Concentration dependence of pyrene I_{338}/I_{335} intensitiy ratio for P(MLA-b-CL) diblock and P(CL-b-MLA-b-CL) triblock copolymers in water.

Synthesis and Micellization Properties of Novel Symmetrical Poly(ε-caprolactone-b-[R,S] β-malic acid-b-ε-caprolactone) Triblock Copolymers

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Introduction

Amphiphilic block copolymers have drawn special attention in both fundamental and applied research because of their unique chain architecture and physical properties.[1,2] For example, they have been extensively studied as building blocks in supramolecular chemistry for highly ordered self-assembled structures.[1–5] With interesting association and phase behavior in aqueous environment, they also have attracted great interest in biomaterials applications. From micelle formation to thermally induced gelation, these amphiphilic block copolymers find interesting applications in drug delivery and tissue engineering.[6,7] Molecular self-assembly is a powerful approach for fabricating novel

supramolecular architectures.[8,9] Usually, self-organization results from weak, non-covalent interactions (hydrogen bonds, Van der Waals interactions) that guide the three-dimensional organization of molecules. In case of amphiphilic block copolymers, ordered structures are driven mainly by hydrophobic interactions.[8] As a result, when in contact with a solvent, which is selective for only one of the blocks, the material surface becomes richer in the solvent-compatible block and segregation from the non-soluble block occurs. The resulting ordered structure can be dynamic (micelles) or static [(micro)gel]. Many examples have been reported on amphiphilic block copolymers that give organized structures in water. These are being used as matrices for drug and gene delivery applications and as

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self-organizing surfaces for tissue engineering as well as carriers for various contrasting agents in diagnostic imaging techniques.[10,11] When biodegradability is needed, the hydrophobic block is generally the degradable one, and it is usually an aliphatic polyester, such as poly(lactide), poly(lactide-co-glycolide), and poly(ε-caprolactone) (PCL).[12–16] In particular, biodegradable di-, tri-, and multi-arm block copolymers containing poly(ethylene oxide) and PCL segments have been developed.[15–20]

In response to the demand for new biocompatible and biodegradable materials based on synthetic (co)polymers, poly(β-malic acid) (PMLA) appears to be an attractive water-soluble aliphatic polyester with carboxylic acid pendant groups that has proven to be biocompatible and degradable in vivo into malic acid, a non-toxic molecule.[21] As previously reported, amphiphilic block copolymers based on PMLA and PCL have also been reported to self-assemble in water.[22,23]

This work aims at studying the preparation and characterization of biocompatible hydrophilic polymers

to be used in drug release and tissue engineering as micelles or (micro)gels and reports on the controlled synthesis of well-defined biodegradable and biocompatible poly(ε-caprolactone-b–[R,S] β-malic acid-b-ε-caprolactone) triblock copolymers [P(CL-b-MLA-b-CL)] according to an original four-step strategy (Scheme 1). The first step relies up on the polymerization of [R,S] benzyl β-malolactonate (MLABz) using an asymmetric difunctional initiator, i.e., potassium 11-hydroxydodecanoate complexed with 18-crown-6 ether (HDD). This first ring-opening polymerization (ROP) needs to be carried out at low temperature and at low starting concentration of MLABz. These conditions significantly reduce both transfer and termination reactions (by proton abstraction) so that the synthesis of α-hydroxy, ω-carboxylic acid poly(benzyl β-malolactonate) (α-OH, ω-COOH PMLABz) remains controlled.[22] After selective reduction of the carboxylic acid end-group, the controlled polymerization of ε-caprolactone (CL) is then initiated by the α- and ω-hydroxyl extremities of the so-recovered poly(β-malolactonate) chain, previously activated by AlEt₃. The fourth and last step is nothing but the selective
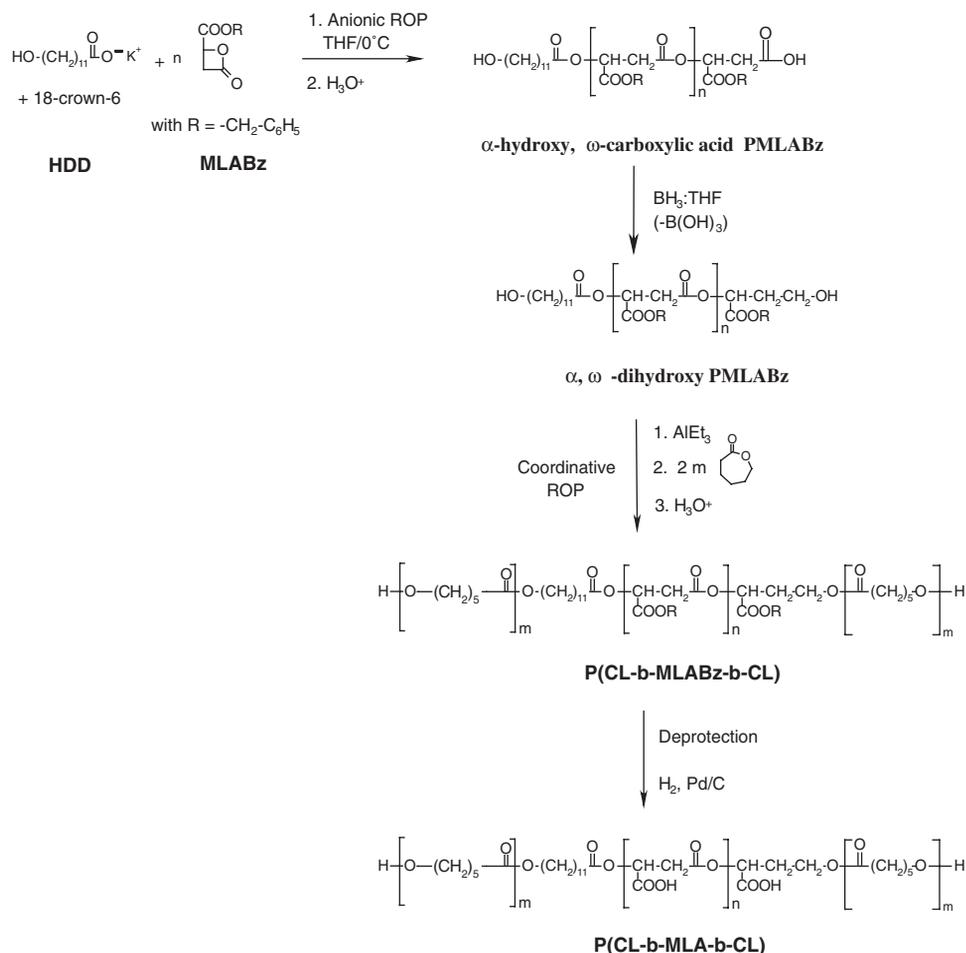
Scheme 1. Four-step synthesis of P(CL-b-MLA-b-CL) triblock copolymer: tandem anionic and coordination polymerization approach.

deprotection of the benzyl ester protecting groups by catalytic hydrogenation reaction. The synthesis of the α,ω-dihydroxy telechelic poly(malolactonate) intermediate represents the key step to reach the target triblock copolyester and needed to find out adequate experimental conditions for the polymerization and reduction reactions preventing any side transfer (transesterification) and/or hydrolytic degradation of the polyester chains.

Experimental Part

Materials

[R,S] Benzyl β-malolactonate was synthesized and purified starting from aspartic acid as published elsewhere.[24] It was stored at $-18\,°C$, distilled under reduced pressure, and dried by three successive azeotropic distillations of toluene just before use. CL (Acros, 99%) was dried over calcium hydride at r.t. 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), tetramethyl ammonium hydroxide (25 wt.-% solution in methanol from Acros), and hydrogen (Air Liquide, N50) were used without further purification. Toluene (Labscan, 99%) was dried by refluxing over CaH_2 and distilled under nitrogen atmosphere. Tetrahydrofuran (Labscan, 99%) was first dried on 4 Å molecular sieves at r.t. for 72 h and then added to low-molecular weight ω-lithium styryl poly(styrene) and distilled under reduced pressure just before use.

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-colored solution of potassium naphthalene radical anion was obtained (conc. $0.2\ mol \cdot L^{-1}$). 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 a stoichiometric amount of the solution of potassium naphthalene radical anion was added (10.0 mL, 1.97 mmol, [HDD] = 0.1 $mol \cdot L^{-1}$). The polymerization of 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 (2.8 mL, 2.8×10^{-4} mol) in THF (43.7 mL) at $0\,°C$. After 120 min, the polymerization was stopped by adding a few drops of aqueous HCl ($0.1\ mol \cdot L^{-1}$). 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 precipitated 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) = 0.8–1.8 (m, 18H), 2.25 (t, 2H), 2.8 (m, 2H), 3.7 (t, 2H), 4.9–5.1 (s, 2H), 5.45 (m, H), and 7.3 (s, 5H).

$\bar{M}_n$NMR = 8 200 $g \cdot mol^{-1}$.

$\bar{M}_w/\bar{M}_n$ = 1.3.

Reduction of α-Hydroxy, ω-Carboxylic Acid Poly(benzyl-β-malolactonate) in α,ω-Dihydroxy Poly(benzyl β-malolactonate)

To a previously flamed and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 0.43 g of α-OH, ω-COOH PMLABz (5.3×10^{-5} mol, $\bar{M}_n$ = 8 200, and $\bar{M}_w/\bar{M}_n$ = 1.3) were dried by three successive azeotropic distillations of toluene (3×10 mL). Then, the dried polymer was dissolved in 5 mL of anhydrous THF and kept at $0\,°C$ for 30 min. Three and half molar equivalents of BH$_3$:THF complex (1.86×10^{-4} mol, 0.2 mL) with regard to the content in carboxylic acid functions were then added while the as-formed hydrogen gas evolved through a connected oil valve. After 5 h at $0\,°C$, the reaction was stopped by the addition of a few drops of water (0.2 mL) and the solvents were removed under reduced pressure. The polymer previously dissolved in CHCl$_3$ (10 mL) and filtered to remove B(OH)$_3$ was recovered by precipitation into 10 volumes of cold heptane (100 mL), filtration and drying under reduced pressure at $40\,°C$ until constant weight, i.e., 0.4 g. Yield = 92%.

^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm, see Figure 1 for attributions) = 0.8–1.8 (m, 18H$_b$), 2.30 (t, 2H$_c$), 2.8 (m, 2H$_e$), 3.7 (t, 4H$_{a+h}$), 4.9–5.1 (s, 2H$_f$), 5.45 (m, H$_d$), and 7.3 (s, 5H$_g$).

$\bar{M}_n$NMR = 7 900 $g \cdot mol^{-1}$.

$\bar{M}_w/\bar{M}_n$ = 1.5.

^{1}H NMR spectroscopy attests to the completion of the reduction reaction to form α,ω-dihydroxy poly(benzyl β-malolactonate) (α,ω-OH PMLABz), with the intensity ratio between α,ω-hydroxy methylene protons (H$_a$ + H$_h$) at 3.7 ppm and α-carbonyloxymethylene ones (H$_c$) at 2.3 ppm being equal to the expected 2:1 ratio.

Block Copolymerization of ϵ-Caprolactone

In a previously flamed and nitrogen-purged round-bottom flask equipped with a three-way stopcock and a septum, 0.4 g of α,ω-OH PMLABz (5.06×10^{-5} mol, $\bar{M}_n$ = 7 900, and $\bar{M}_w/\bar{M}_n$ =1.5) were dried by three successive azeotropic distillations of toluene (3×10 mL). Then, the dried polymer was reacted with 1.05 equivalent of triethylaluminum with regard to the content of hydroxyl functions (1.06×10^{-4} mol, 2 mL) in toluene at $50\,°C$ for 2 h. Ethane evolved through a connected oil valve. After cooling to r.t., CL (8.8 mmol, 1.0 mL) was added and polymerized for 64 h. After addition of a few drops of an HCl aqueous solution ($0.1\ mol \cdot L^{-1}$), the polymer solution was washed three times with an aqueous
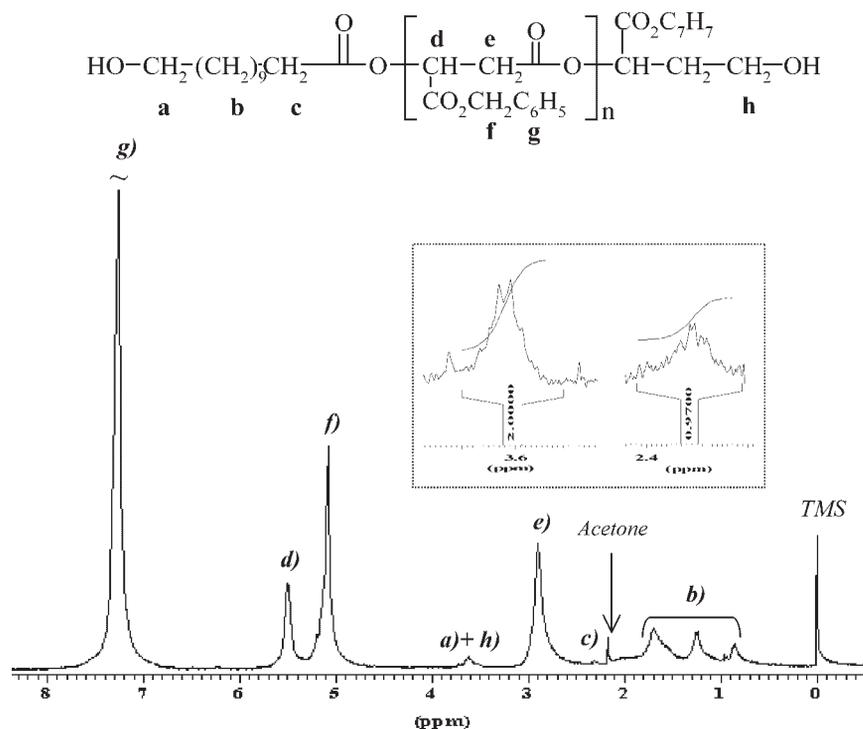
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HO−CH₂−(CH₂)₉CH₂−C(=O)−O−[CH−CH₂−C(=O)−O]ₙ−CH−CH₂−CH₂−OH

(structure labels: a, b, c; d, e; CO₂CH₂C₆H₅ = f, g; CO₂C₇H₇; h)

Figure 1. ^{1}H NMR spectrum of α,ω-OH PMLABz as obtained after reduction of α-OH, ω-COOH PMLABz (solvent: CDCl₃).

solution of ethylenediaminetetraacetic acid (EDTA) buffered 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 (0.8 g). Yield = 41%.

^{1}H NMR (300 MHz, CDCl₃): δ (ppm, see Figure 3 for attributions) = 0.8–1.6 (m, 18H$_b$), 1.4–1.5 (t, 2H$_{o+k}$), 1.55–1.75 (t, 4H$_{j+1}$), 2.25 (t, 2H$_{i+c}$), 2.9–3.0 (m, 2H$_e$), 3.6 (t, 2H$_n$), 4.0–4.15 (t, 2H$_{a+m}$), 4.8 (t, 2H$_p$), 5.1 (s, 2H$_f$), 5.45 (m, H$_d$), and 7.2 (s, 5H$_g$).

$\bar{M}_n$P(MLABz-b-CL) = 15 400.
$\bar{M}_w/\bar{M}_n$ = 1.5.

Removal of Benzyl Ester Protective Groups

In a round-bottom flask, 0.8 g of the copolymer (5.2 × 10^{-5} mol, $\bar{M}_n$ = 15 400) was dissolved into 200 mL of acetone at r.t. 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 (0.64 g). Yield = 99%.

^{1}H NMR (300 MHz, CD₃COCD₃): δ (ppm) = 0.8–1.6 (m, 18H$_b$), 1.4–1.5 (t, 2H$_{o+k}$), 1.55–1.75 (t, 4H$_{j+1}$), 2.25 (t, 2H$_{i+c}$), 2.9–3.0 (m, 2H$_e$), 3.6 (t, 2H$_n$), 4.0–4.15 (t, 2H$_{a+m}$), 4.8 (t, 2H$_p$), 5.1 (s, 2H$_f$), and 5.45 (m, H$_d$).

$\bar{M}_n$P(MLA-b-CL) = 12 500.
$\bar{M}_w/\bar{M}_n$ = 1.3.

Characterization

^{1}H NMR spectra were recorded using a Bruker AMX-300 apparatus at r.t. 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 = 1mL · min^{-1}), a Rheodin manual injection (loop volume = 200 µL, solution conc. = 2 mg · mL^{-1}), a PL-DRI refractive index detector, and four columns: a PL gel 10 µm guard column and three PL gel mixed-B 10 µm columns (linear columns for separation of MW$_{PS}$ ranging from 500 to 10^6 Da). Molar masses and their distribution were calculated with reference to polystyrene standards. UV-Visible absorption spectra were taken onto a Cary-WinUV50 spectrophotometer from 500 to 300 nm. Non-aqueous potentiometric titrations were realized at room temperature using a combined electrode pH-meter (PHM 210).

Preparation of Micellar Solutions Used for UV-Vis Spectroscopy

A Millipore Milli-Ro® 4 water purification system with a specific resistance around 18 MΩ · cm was used to purify water necessary to the preparation of the amphiphilic copolymer solutions. To previous aqueous copolymer solutions of defined concentrations, a given quantity of a pyrene solution in acetone (4.95 × 10^{-4} M) has been added. After 12 h of smooth acetone evaporation, different copolymer solutions have been recovered. The copolymer concentrations varied from 1.98 × 10^{-6} to 1.3 g · L^{-1}, while the pyrene concentration was 4.95 × 10^{-5} M.

Results and Discussion

Synthesis of Poly(ε-caprolactone-b-β-malic acid-b-ε-caprolactone) Triblock Copolymer

According to the previously established experimental conditions that significantly limit the occurrence of undesirable transfer and termination reactions by proton abstraction, well-defined α-OH, ω-COOH PMLABz can be readily prepared by initiating the ROP of MLABz by potassium 11-hydroxydodecanoate added with an equimolar amount of 18-crown-6 ether (HDD) (Scheme 1).[22] Practically, α-OH, ω-COOH PMLABz has been obtained by ROP of MLABz initiated by HDD in THF at 0 °C for a $[MLABz]_0$ of 0.2 mol · L^{-1} and $[MLABz]_0/[HDD]_0$ of 40. After a 3-h polymerization time, the crude reaction product has been recovered by selective precipitation from cold heptane (conv. = 98%) (Table 1, entry 1). Assuming that each chain is end-capped by an hydroxyl group at one end and a carboxylic acid function at the other end, an experimental molar mass of 8 200 g · mol^{-1} can be calculated by ^{1}H NMR spectroscopy from the relative intensity of the methylene protons of the main chain at 2.9 ppm (–CH–(COOR)–CH_2–COO–) and the α-hydroxy methylene protons at 3.6 ppm (HO–CH_2–(CH$_2$)$_{10}$–COO–) $[\bar{M}_n$NMR = $((I_{2.9} \times Mw_{MLABz})/(I_{3.6}) + Mw_{HDD})$ where Mw_{MLABz} and Mw_{HDD} are the molecular weights of MLABz and HDD, respectively]. Within the experimental errors, $\bar{M}_n$NMR is in acceptable agreement with the theoretical number-average molar mass ($\bar{M}_n$theor.) assuming a living polymerization mechanism ($\bar{M}_n$theor. = $([MLABz]_0/[HDD]_0 \times$ conv. $\times Mw_{MLABz}) + Mw_{HDD} = 8 300$ g · mol^{-1}). As evidenced by SEC, the molar mass distribution is monomodal and narrow ($\bar{M}_w/\bar{M}_n = 1.3$).

The reduction of carboxylic acid end-groups into hydroxy ones has been performed with an excess of borane-tetrahydrofuran complex (BH$_3$:THF) (3.5 equivalents) for 5 h at 0 °C in anhydrous THF. After the addition of a few drops of water, the polyester chains have been selectively recovered by precipitation from cold heptane.

^{1}H NMR spectroscopy attests to the completion of the reduction reaction to form α,ω-OH PMLABz, with the intensity ratio between α,ω-hydroxy methylene protons (H$_a$ + H$_h$) at 3.7 ppm and α-carbonyloxymethylene ones (H$_c$) at 2.3 ppm being equal to the expected 2/1 ratio (Figure 1). Assuming the selective formation of α,ω-OH PMLABz, ^{1}H NMR spectroscopy allows calculating an experimental molar mass of 7 900 from the relative intensity of methylene protons of MLABz repeating units at 2.9 ppm and α-hydroxy methylene protons of the end-groups at 3.6 ppm $[\bar{M}_n$NMR = $((I_{2.9} \times Mw_{MLABz})/(I_{3.6}/2) + Mw_{HDD})$ (Table 1, entry 2)]. It is worth noting that reduction of carboxylic acid end-groups does not significantly modify the PMLABz molecular parameters.

In order to get direct evidences of the completion of the carboxylic acid end-groups reduction, non-aqueous potentiometric titrations of PMLABz chains before and after reduction have been carried out using tetramethyl ammonium hydroxide in a toluene/methanol (8:2/v:v) solution. However, due to the high sensitivity of PMLABz towards hydrolysis under such experimental conditions, the absence of residual carboxylic acid functions after reduction cannot be ensured. Figure 2 shows the plots of potential versus volume of added base for both α-OH,ω-COOH PMLABz and α,ω-OH PMLABz chains. Even if a clear-cut difference exists between the two curves, it is hazardous to conclude on the total absence of carboxylic acid after the reduction reaction. Moreover, the number-average molar mass of α-OH,ω-COOH PMLABz as determined from the inflection point reaches 6 000 g · mol^{-1} [curve (1), Figure 2] which does not perfectly match $\bar{M}_n$NMR (entry 1, Table 1) and may reflect the inevitable occurrence of some hydrolytic cleavage. However, additional evidence for the presence of OH groups at both extremities of the polyester chains will be found out in the next section dealing with the synthesis of symmetric triblock copolymers with lateral PCL chains.

In the next step, the polymerization of CL has been initiated by α,ω-OH PMLABz after previous activation of the hydroxy end-groups with a slight excess of triethyl-

Table 1. Molecular characteristics of α-OH,ω-COOH PMLABz, α,ω-OH PMLABz, P(CL-b-MLABz-b-CL), and P(CL-b-MLA-b-CL).

Entry	Sample	DP$_{PMLABz}$[a]	DP$_{PMLA}$[b]	DP$_{PCL}$[c]	$\bar{M}_n$theor.[d] g · mol^{-1}	$\bar{M}_n$NMR[e] g · mol^{-1}	$\bar{M}_n$SEC[f] g · mol^{-1}	$\bar{M}_w/\bar{M}_n$[6]
1	α-OH,ω-COOH PMLABz	39	–	–	8 300	8 100	2 000	1.3
2	α,ω-OH PMLABz	37	–	–	7 800	7 900	2 000	1.5
3	P(CL-b-MLABz-b-CL)	30	–	79	15 400	15 300	4 000	1.5
4	P(CL-b-MLA-b-CL)	–	26	82	12 600	12 400	4 700	1.3

[a] As determined by ^{1}H NMR spectroscopy: $I_{2.9}/I_{3.6}$.
[b] As determined by ^{1}H NMR spectroscopy: $2 \times I_{2.9}/I_{3.6}$.
[c] As determined by ^{1}H NMR spectroscopy: $2 \times I_{4.1}/I_{3.6}$.
[d] Theoretical molecular weight: See text.
[e] As determined by ^{1}H NMR spectroscopy: $\bar{M}_n$NMR = $206 \times$ DP$_{PMABz} + 114 \times$ DP$_{PCL} + 200$ or $116 \times$ DP$_{PMLA} + 114 \times$ DP$_{PCL} + 200$.
[f] Apparent molecular weight ($\bar{M}_n$SEC) and polydispersity index ($\bar{M}_w/\bar{M}_n$) as determined in THF at 35 °C by SEC using PS standards.

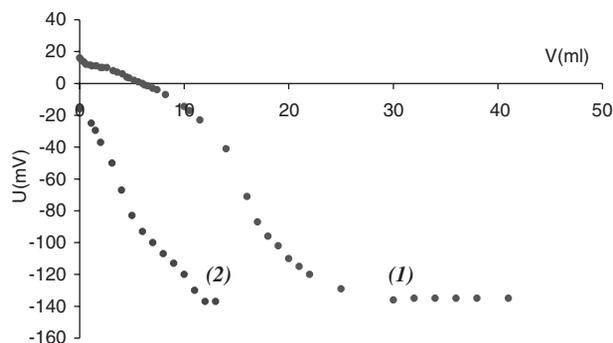Synthesis and Micellization Properties of Novel Symmetrical Poly(ε-caprolactone-*b*-[*R,S*] β-malic . . .

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Figure 2. Non-aqueous potentiometric titration of the carboxylic acid functions before (1) and after (2) reduction of α-OH, ω-COOH PMLABz.

aluminum ($[AlEt_3]_0/[OH]_0 = 1.05$). The ROP has been carried out in toluene at r.t. for an initial CL concentration of $1 \ mol \cdot L^{-1}$ and an initial $[CL]_0/[PMLABz]_0$ molar ratio of 175. After 64 h reaction time, a few drops of an HCl aqueous solution ($0.1 \ mol \cdot L^{-1}$) have been added and the expected poly(ε-caprolactone-*b*-benzyl β-malolactonate-*b*-ε-caprolactone) triblock copolymer [P(CL-*b*-MLABz-*b*-CL)] has been recovered by precipitation from a large excess of heptane (conv. = 41%). Figure 3 shows the ^{1}H NMR spectrum of the P(CL-*b*-MLABz-*b*-CL) triblock copolymer. Number-average molar mass of PCL blocks has been determined from the relative intensity of methylene oxy-

carbonyl protons of CL repeating units at 4.1 ppm (–CH_2–O–C(O)–) and α-hydroxymethylene protons of the end-groups at 3.6 ppm (–CH_2–OH) (total $\bar{M}_n$PCL NMR $= 2 \times (I_{4.1}/I_{3.6}) \times Mw_{CL} = 9\,000 \ g \cdot mol^{-1}$). Taking into account the experimental molar mass of PMLABz central sequence ($\bar{M}_n$NMR $= 6\,200$), a weight fraction in PCL of 53% can be calculated. As evidenced by SEC (Figure 4), the P(CL-*b*-MLABz-*b*-CL) triblock copolymer is characterized by a monomodal molar mass distribution ($\bar{M}_w/\bar{M}_n = 1.5$) shifted to lower retention volume compared to the α,ω-OH PMLABz macroinitiator.

The last step in the synthesis of amphiphilic P(CL-*b*-MLA-*b*-CL) consists of the catalytic hydrogenation of the benzyl ester functions anchored all along the central PMLABz segment. ^{1}H NMR spectroscopy (Figure 3, inset) shows the complete disappearance of the benzylic protons attesting for a quantitative deprotection by catalytic hydrogenation. As already mentioned for the diblock copolymers based on PMLA,[22] any typical resonance signal of carboxylic acid pendant groups could not be detected at low field at ca. 10 ppm. Last but not least, catalytic hydrogenation seems to preserve the copolyester chain integrity since the number-average polymerization degrees (DP) of both PCL and PMLA(Bz) segments are very similar before and after deprotection (Table 1). Indeed, DP$_{PMLABz}$ and DP$_{PMLA}$ reach ca. 30 while DP$_{PCL}$ remains close to 80 as determined by ^{1}H NMR spectroscopy. Figure 4 shows the molar mass distribution of the P(CL-*b*-MLA-*b*-CL) triblock
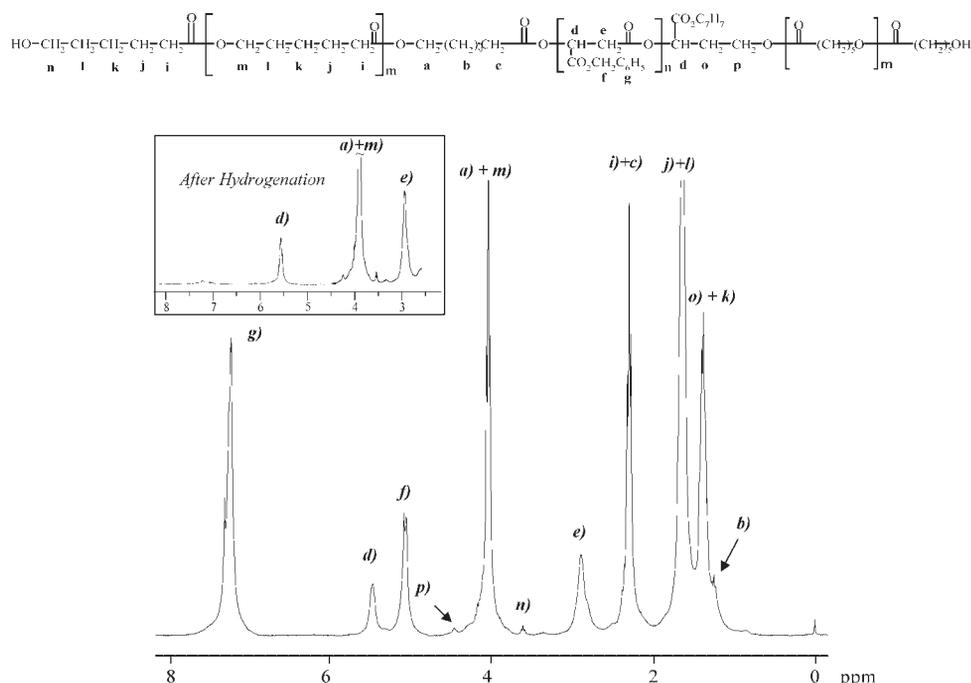

Figure 3. ^{1}H NMR spectrum of P(CL-*b*-MLABz-*b*-CL) (solvent: CDCl$_3$). Inset: ^{1}H NMR spectrum (2−8 ppm zoom) of the P(CL-*b*-MLA-*b*-CL) attesting for deprotection reaction (solvent: CD$_3$COCD$_3$).
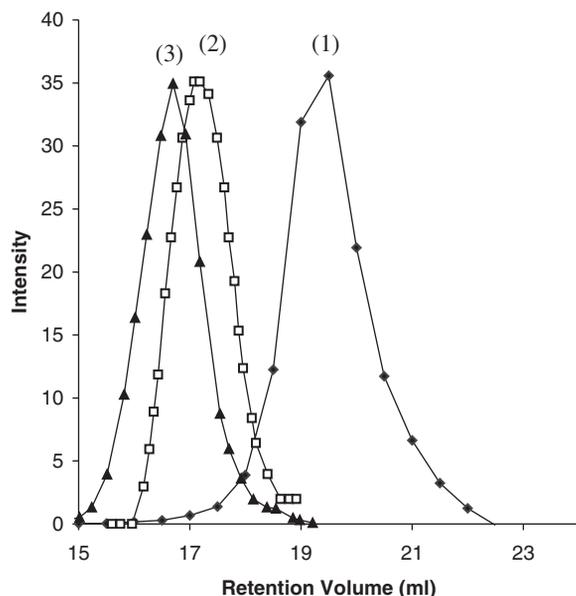
Figure 4. SEC traces of α,ω-OH PMLABz (1), P(CL-*b*-MLABz-*b*-CL) (2), and P(CL-*b*-MLA-*b*-CL) triblock copolymers (3).

copolymer compared to its P(CL-*b*-MLABz-*b*-CL) and α,ω-OH PMLABz precursors. It is worth noting that the modification of the hydrodynamic volume of the amphiphilic triblock copolymer compared to the benzylated triblock is likely due to some hydrogen bonding issued from the pendant carboxylic acid functions.[25]

In order to shed some light on the molar mass distribution of PCL lateral blocks in P(CL-*b*-MLA-*b*-CL) amphiphilic triblock copolymer, it has been taken advantage of the higher sensitivity towards hydrolysis of PMLA segment compared to PCL.[23] In practice, the triblock copolymer has been vigorously stirred in water at r.t. until the ¹H NMR spectrum of the recovered solid product does not show any more protons corresponding to MLA repeating units. SEC of residual PCL as recovered after a one-week treatment shows, in addition to a limited amount of PMLA oligomers at higher retention volume, a single monomodal molar mass distribution ($\bar{M}_n = 4\,400$ and $\bar{M}_w/\bar{M}_n = 1.4$) which is consistent with the formation of lateral PCL blocks of equal molar mass (Figure 5). Moreover, a $\bar{M}_n$ of 4 400 is in perfect agreement with the previously determined PCL block molecular weight average of P(CL-*b*-MLA-*b*-CL) assuming a totally controlled ROP of CL from α,ω-OH PMLABz difunctional macroinitiator.

Preliminary Tensioactive Properties and Micellar Aggregation of P(CL-b-MLA-b-CL) Triblock Copolymer

As already reported for diblock copolymers, the critical micelle concentration (CMC) can be easily determined by surface tension measurements but other methods such as
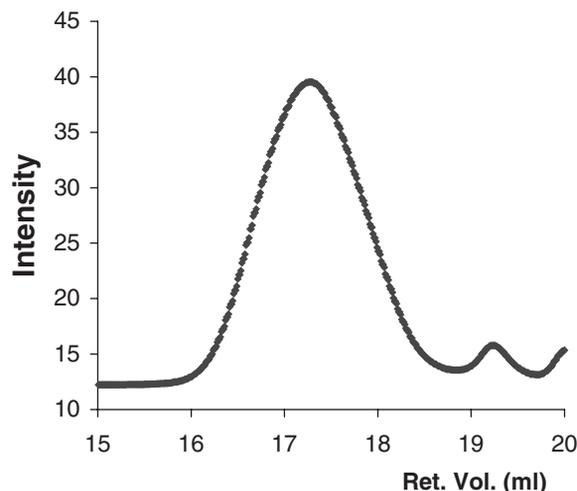

Figure 5. SEC of the PCL hydrophobic lateral segments as-obtained by selective hydrolysis of the P(CL-*b*-MLA-*b*-CL) amphiphilic triblock copolymer.

UV-Visible spectroscopy analysis using pyrene probe has also demonstrated its efficiency.[23] Pyrene is hydrophobic and exhibits low solubility in water (6×10^{-7} mol · L^{-1}) so that changing its environment from polar to non-polar alters its absorption, emission, and excitation spectra. For instance, the absorption peak at 338 nm in water shifts to 335 nm when pyrene is trapped in the hydrophobic core of micelles.[26,27] Theoretically, the intensity ratio I_{338}/I_{335} may change from 1.8 in water to 0.9 in the presence of anionic surfactant micelles and is useful in monitoring micelle formation.[28] Figure 6 shows the UV spectra of pyrene aqueous solutions added with either 6.5×10^{-2} or 1.27×10^{-4} g · L^{-1} of P(CL-*b*-MLA-*b*-CL) triblock copolymer. Interestingly, the evolution of the I_{338}/I_{335} ratio for the P(CL-*b*-MLA-*b*-CL) triblock copolymer ($\bar{M}_n = 4\,500$–$3\,000$–$4\,500$; fw$_{PCL} = 76\%$) has been compared to the one associated to a P(MLA-*b*-CL) diblock copolymer of same
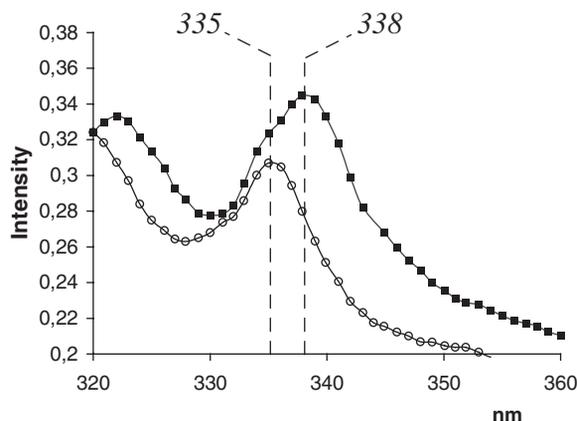

Figure 6. UV spectra of pyrene aqueous solutions containing P(CL-*b*-MLA-*b*-CL) triblock copolymers at concentration equal to 1.27×10^{-4} (■) and 6.5×10^{-2} g · L^{-1} (○).

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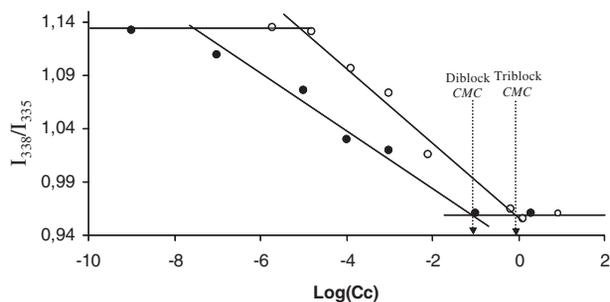
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Figure 7. Concentration dependence of pyrene I_{338}/I_{335} intensitiy ratio for P(MLA-b-CL) diblock (●) and P(CL-b-MLA-b-CL) triblock copolymers (○) in water at r.t. ($\bar{M}_n$diblock = 3 000–11 500; $\bar{M}_n$triblock = 4 500–3 000–4 500; and [pyrene]$_0$ = 4.95×10^{-5} M).

composition ($\bar{M}_n = 3\,800–11\,500$; fw$_{PCL} = 0.79$) obtained as previously detailed in ref.[21] (Figure 7). The CMCs of the diblock and the triblock copolymers in aqueous solutions reached 8.7×10^{-2} and 8.1×10^{-1} g · L^{-1}, respectively. The CMC of the P(CL-b-MLA-b-CL) amphiphilic triblock copolymer is higher than that for the P(MLA-b-CL) diblock copolymer as might be expected from the entropic penalty for bending the PMLA backbone of the triblock copolymer to produce flower micelles. It is also worth pointing out that the CMC of the diblock copolymer has been compared to the one obtained by surface tension measurements, i.e., CMC = 1.26 10^{-2} g · L^{-1} as reported in ref.[22] The difference in the CMCs determined by these two techniques might be related to the detection principles. Usually, a factor of 10 is observed between these two methods,[29] which gives credit to our data.

In conclusion, an original pathway has been studied for the synthesis of well-defined triblock amphiphilic copolymers with a central hydrophilic PMLA sequence and lateral hydrophobic PCL blocks. This totally controlled synthetic route involves the anionic polymerization of MLABz initiated by potassium 11-hydroxydodecanoate added with an equimolar amount of 18-crown-6 ether (HDD), followed by the reduction of α-hydroxy, ω-carboxylic poly([R,S] benzyl β-malolactone) into α,ω-dihydroxy PMLABz able to initiate the ROP of CL, after previous activation by reaction with triethylaluminum (AlEt$_3$). The as-obtained P(CL-b-MLABz-b-CL) triblock copolymer is finally reduced by catalytic hydrogenation of the pendant benzylic ester functions of the central block leading to original amphiphilic and biodegradable P(CL-b-MLA-b-CL) triblock copolymer. As demonstrated by UV spectroscopy such amphiphilic triblock copolymer form flower micelles in pure water. However, due to the entropic penalty for bending the PMLA central block to produce such micelles, the CMC of these new P(CL-b-MLA-b-CL) triblock copolymer is higher by one order of magnitude than that of a P(MLA-b-CL) diblock copolymer of similar composition.

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