Notes

Synthesis of Polyester−Polypeptide Diblock and Triblock Copolymers Using Amino Poly(ϵ-caprolactone) Macroinitiators

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Introduction

Polyesters and especially poly(ϵ-caprolactone) (PCL) are versatile polymers, being both biocompatible and biodegradable.[1−4] Their association to poly(α-amino acid *N*-carboxyanhydrides) (poly(NCAs)) in polyester-*b*-polypeptide copolymers makes them extremely attractive and leading candidates in biomedical and pharmaceutical industries as controlled drug delivery systems, resorbable implant devices, or tissue engineering supports.[1,4,5] Synthesis of copolymers of controlled composition, so as to tailor and tune the properties of the final material as well as to combine the features of both homopolymers, is indeed the actual key strategy to accede the specific properties required for a precise application. While the hydrolytic and enzymatic degradation ability of polyesters induces a new stability to the polyester-*b*-polypeptide copolymers for which enzymatic degradation is often mandatory (since peptide bonds are not hydrolyzed by water only), the facility of the peptide moiety to interact with other peptides or proteins through hydrogen bonds allows stabilization regarding living tissues. Besides, association of polyester to polypeptide would provide, upon monitoring the composition of the blocks, original versatile amphiphilic materials potentially able to self-organize into versatile nanoparticles, vesicles, or macromolecular micelles.[1,4,6]

Aliphatic primary amines are known to initiate the ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydrides to give synthetic poly(NCA).[7,8] This approach has been applied in the few reports which have focused on polyester−polypeptide blocks, namely, poly(ϵ-caprolactone)- or poly(lactide)-*b*-poly(γ-benzyl L-glutamate) structures.[5,6,9−12] Initially, Jérôme prepared ω-NH_2-PCL upon conversion of the Br-PCL (synthesized from aluminum alkoxide initiator) bromo end-group into an azido one subsequently reduced to a primary amine, which then initiated the polymerization of (γ-benzyl L-glutamate *N*-carboxyanhydride) (BLG).[10] Höcker and Mingotaud then prepared poly(lactide)-*b*-PBLG from amino-terminated poly(lactide) (obtained in situ from diethylzinc and *N*-*tert*-butoxycarbonyl-1-amino-3-propanol), followed by deprotection of the amino group.[6,12] The other method developed by Höcker was the end-capping of poly(lactide) with *N*-*tert*-butoxycarbonylphenylalanine prior to the cleavage of the protecting group. The aminopolylactide then allowed the formation of the PBLG block.[12] Later on, Kricheldorf made some triblock copolymers of various peptides, including BLG, prepared from the 4-aminobenzoyl telechelic PCL (obtained from a cyclic tin alkoxide initiator) used as macroinitiators for the NCA polymerization.[9] However, with the BLG monomer, mixtures of diblock and triblock copolymers were recovered, and rather high degrees of polymerization (relative to theoretical values) were obtained, because the 4-aminobenzoyl end-groups had to compete with the more reactive amino groups of the growing PBLG. Finally, Chen polymerized the BLG from ω-aminophenyl-terminated PCL, prepared using an organic aminocalcium initiator as macroinitiator.[11]

Our particular approach in the design of novel polyester−polypeptide-based block copolymers results from our previous investigations on the polymerization of cyclic esters using rare-earth alkoxide and borohydride initiators, which led to the synthesis of hydroxy-terminated poly(ϵ-caprolactone), HO-PCL-OiPr, **1**, and HO-PCL-OH, **1′**, respectively.[13−18] Indeed, one way to expand the applications of these polymers is through chemical modification and especially by end functionalization. Because amino-terminated PCL is a desirable macromolecular initiator for the preparation of block copolymers containing polypeptide segments, we synthesized the amino analogues of **1** and **1′**, namely, H_2N-PCL-OiPr, **3**, and H_2N-PCL-NH_2, **3′**, respectively. These new amino-PCL prepolymers **3** and **3′** were subsequently used as macroinitiators for the polymerization of γ-benzyl L-glutamate *N*-carboxyanhydride to give the poly(ϵ-caprolactone)-*b*-poly(γ-benzyl L-glutamate) (PCL-*b*-PBLG), **4**, and poly(γ-benzyl L-glutamate)-*b*-poly(ϵ-caprolactone)-*b*-poly(γ-benzyl L-glutamate) (PBLG-*b*-PCL-*b*-PBLG), **4′**, copolymers. These seminal results allowing access to valuable polyester−polypeptide macromolecular architectures are presented in this paper.

Experimental Section

Materials. All manipulations were performed under inert atmosphere (argon, <3 ppm of O_2) by using standard Schlenk, vacuum line, and glovebox techniques. Solvents (Aldrich) were thoroughly dried and deoxygenated by standard methods and distilled before use.[19] $CDCl_3$, CF_3COOH-*d* (TFA-*d*) were dried over a mixture of 3Å and 4Å molecular sieves. ϵ-Caprolactone (CL, Lancaster) was successively dried over CaH_2 (at least one week) and 4,4′-methylenebis(phenylisocyanate). $Nd(BH_4)_3(THF)_3$ was synthesized from $NdCl_3$ (Aldrich) following the literature procedure.[20,21] 4-(Dimethylamino)pyridine toluenesulfonate (DPTS) was synthesized according to the literature.[22] $La(OiPr)_3$ (Appolo), γ-benzyl L-glutamate *N*-carboxyanhydride (BLG) (Isochem) and all other reagents (dicyclohexylcarbodiimide (DCC), *N*-(9-fluorenylmethoxycarbonyl)-glycine (*N*-Fmoc-glycine), piperidine, 5-(*tert*-butoxy carbonylamino)valeric acid (*t*-Boc-VA)) were used as received (Aldrich). Both $H\{O(CH_2)_5C(O)\}_nO(CH_2)_5C(O)OiPr$, HO-PCL-OiPr, **1**, and $H\{O(CH_2)_5C(O)\}_nO(CH_2)_6OH$, HO-PCL-OH, **1′**, polymer samples were synthesized following reported polymerization procedures and characterized accordingly.[13,16−18] The theoretical molar mass values of polymers **1** and **1′** were calculated from the initial concentration in rare earth complex on the basis of three active sites per metal available for polymerization with $[OiPr]_0 = 3[La(OiPr)_3]_0$ and $[BH_4]_0 = 3[Nd(BH_4)_3(THF)_3]_0$.[13,16−18]

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Instrumentation and Measurements. ^{1}H (400 or 200 MHz) and ^{13}C (100 or 50 MHz) NMR spectra were recorded in $CDCl_3$ or TFA-*d* on an Avance DPX 400 or AC200 (Bruker) at 21°C. ^{1}H and ^{13}C NMR data of compounds **1**−**3** and **1′**−**3′** are reported in the Supporting Information. Average molar mass ($\bar{M}_n$) and molar mass distribution ($\bar{M}_w/\bar{M}_n$) values for polyesters **1**−**3** and **1′**−**3′** were determined by size exclusion chromatography (SEC) in THF at 20 °C on a Jasco apparatus equipped with a refractive index detector and one Polymer Laboratories Poly Pore column. $\bar{M}_n$ and $\bar{M}_w/\bar{M}_n$ values of polymers **1**−**3** and **1′**−**3′** were calculated from the polystyrene calibration curve using the correction coefficient (0.56) previously established.[13,15] $\bar{M}_n$ and $\bar{M}_w/\bar{M}_n$ values for copolymers **4** and **4′** were determined in DMF with LiBr (1 g·L^{-1}) at 60 °C on a Waters Alliance 2000 apparatus equipped with three HHR (G2000, G3000, G4000) columns and a refractive index detector coupled to a viscosimeter, thus allowing a universal calibration. Accurate molar masses, independent of both the molecular structure and the calibration standards used, are thus obtained. Molar mass values (<10 000) were also calculated from ^{1}H NMR analyses. $\bar{M}_{n,NMR}$ values for the PCL-OH polymers **1** and **1′** resulted from the integration ratio of the main chain signal (OCH_2, (2n + 2)H, $n = \overline{DP}_n$) at δ = 4.15−4.05 ppm relative to the end-group methylene proton signal (CH_2OH, 2 or 4H) at δ = 3.72−3.64 ppm. $\bar{M}_{n,NMR}$ values for the PCL-OiPr type polymers **1**, **2**, and **3** resulted from the integration ratio of the main chain signal (OCH_2, (2n + 2)H, $n = \overline{DP}_n$) at δ = 4.15−4.06 ppm relative to methyl isopropyl protons (CH(CH_3)$_2$, 6H) at δ = 1.31−1.22 ppm signals. $\bar{M}_{n,NMR}$ values for the RNH-PCL-RNH polymers **2′a** and **2′b** resulted from the integration ratio of the main chain signal (OCH_2, (2n + 2)H, $n = \overline{DP}_n$) at δ = 4.04−3.99 ppm relative to the end-group methylene proton (fluorenyl-CH_{F2}OC(O)NH, 4H) at δ = 4.34 ppm for **2′a** or relative to the end-group methylene protons (*t*-Boc-NHCH_2C(O)O) at δ = 3.11 ppm for **2′b** signals. $\bar{M}_{n,NMR}$ values for the H_2N-PCL-NH_2 polymers **3′** (**3′a** and **3′b**) were determined from the terminal methylene proton (H_2NCH_2C(O), 4H) at δ = 3.43 ppm or (H_2NCH_2(CH_2)$_3$C(O), 4H) at δ = 3.30 ppm signal, respectively. $\bar{M}_{n,NMR}$ values for the diblock copolymers **4** were determined from the integration ratio of the methyl isopropyl protons (CH(CH_3)$_2$, 6H) at δ = 1.28 ppm relative to the main polyester chain signal (OCH_2, (2n + 2)H, $n = \overline{DP}_n$) at δ = 4.09 ppm and relative to the CH_2Ph signal (2*m*H) at δ = 5.01 ppm of the polypeptide. $\bar{M}_{n,NMR}$ values for the triblock copolymers **4′** were determined, assuming the polyester $\overline{DP}_n$ is maintained upon synthesizing **4′** from **3′**a, from the integration ratio of the main polyester chain signal (OCH_2, (2n + 2)H, $n = \overline{DP}_n$) at δ = 4.03 ppm and relative to the CH_2Ph signal (4*m*H) at δ = 4.95 ppm of the polypeptide. The monomer conversions were calculated from ^{1}H NMR spectra of the crude polymer samples (**1**−**3**, **1′**−**3′**). Infrared spectra ranging from 600 to 4000 cm^{-1} were recorded as KBr pellets on a Bruker Tensor spectrometer with a 4 cm^{-1} resolution. Differential scanning calorimetry (DSC) analyses were performed on a TA DSC Q100 apparatus at a heating rate of 10 °C·min^{-1} under nitrogen.

Synthesis of RNHCH_2C(O){O(CH_2)$_5$C(O)}$_n$O(CH_2)$_5$C(O)OiPr, R = (fluorenyl)CH_2OC(O) = *N*-Fmoc, RNH-PCL-OiPr, 2. CH_2Cl_2 (50 mL) was added to a mixture of **1** ($\bar{M}_{n,NMR}$= 4600, 598 mg, 0.13 mmol), dicyclohexylcarbodiimide (DCC; 6 equiv, 161 mg, 0.78 mmol), 4-(dimethylamino)pyridine toluenesulfonate (DPTS; 1 equiv, 38 mg, 0.13 mmol), and *N*-(9-fluorenylmethoxycarbonyl)-glycine (*N*-Fmoc-glycine; 3 equiv, 116 mg, 0.39 mmol) previously dissolved in DMF (2.5 mL). After stirring at 21 °C over 48 h, the dicyclohexylurea side product was removed by filtration. The polymer was successively precipitated in methanol (in which DPTS, DCC, and the excess of amino acid are soluble), then in pentane, and finally dried under vacuum to give **2** ($\bar{M}_{n,NMR}$ = 5000, 500 mg, 78.5%).

Synthesis of H_2NCH_2C(O){O(CH_2)$_5$C(O)}$_n$O(CH_2)$_5$C(O)OiPr, H_2N-PCL-OiPr, 3. Piperidine (large excess, 1 mL, 10 mmol) was added to a CH_2Cl_2 solution (10 mL) of **2** ($\bar{M}_{n,NMR}$ = 5000, 500 mg, 0.10 mmol), and the solution was stirred over 24 h at 21 °C. The solution was then washed twice with a saturated NaCl aqueous solution. The organic phase containing the polymer was dried over $MgSO_4$, and the polymer, subsequently recovered by precipitation in methanol, was finally dried under vacuum to afford **3** ($\bar{M}_{n,NMR}$ = 5500, 450 mg, 94%).

Synthesis of H{HNCH[(CH_2)$_2$C(O)OCH_2Ph]C(O)}$_m$NHCH_2C(O)-{O(CH_2)$_5$C(O)}$_n$ O(CH_2)$_5$C(O)OiPr, PBLG-*b*-PCL, 4. A CH_2Cl_2 (2.5 mL) solution of **3** ($\bar{M}_{n,NMR}$ = 5500, 200 mg, 0.04 mmol) was added via cannula to a CH_2Cl_2 (10 mL) solution of γ-benzyl L-glutamate (BLG; 1.0 g, 0.80 mmol). The solution was then stirred over 20 h at 21 °C during which gas (CO_2) evolution and increase in viscosity were observed. After precipitations in diethyl ether and diethyl ether/acetone, quantitative BLG conversion was observed, and copolymer **4** was isolated ($\bar{M}_{n,NMR}$ = 28 900, 1.09 g). ^{1}H NMR of PBLG$_{46}$-*b*-PCL$_{100}$ (400 MHz, $CDCl_3$/TFA; 90:10): δ = 8.35 (br s, *m*H, N*H*CH[CH_2CH_2C(O)OCH_2Ph]); 7.25 (br s, 5*m*H, C(O)OCH_2C$_6H_5$ and $CDCl_3$); 5.01 (br s, 2*m*H, CH_2Ph); 4.38 (quintuplet, 1H, C*H*(CH_3)$_2$); 4.09 (t, (2n + 2)H, C(O)OCH_2); 3.94 (br s, *m*H, NHC*H*[CH_2CH_2C(O)OCH_2Ph]); 2.54, 2.10 (2 br s, (1m + 1m)H, CHCH_2CH_2C(O)OCH_2Ph); 2.42, (t, (2n + 2)H, CH_2C(O)); 2.33 (br s; 2*m*H, CH_2CH_2C(O)OCH_2Ph); 1.64 (quintuplet, (4n + 4)H, CH_2CH_2CH_2); 1.36 (quintuplet, (2n + 2)H, CH_2CH_2CH_2); 1.28 (d, 6H, CH(CH_3)$_2$); (Figure 1). ^{13}C NMR (100 MHz, $CDCl_3$/TFA (90:10)): δ = 175.5, 173.7, 172.1 (NHCHCH_2CH_2*C*(O)OCH_2Ph, NHCH[CH_2CH_2C(O)OCH_2Ph]*C*(O)NH, NHCH_2*C*(O)O, CH_2*C*(O)O, CH_2*C*(O)OiPr); 128.5, 128.1 (NHCHCH_2CH_2C(O)OCH_2C$_6H_5$); 66.2, (NHCHCH_2CH_2C(O)O*C*H$_2$Ph); 64.2 (C(O)O*C*H_2); 52.9 (NH*C*H-[CH_2CH_2C(O)OCH_2Ph]C(O)); 34.1 (*C*H_2C(O)); 30.9 (CHCH_2*C*H_2C(O)-OCH_2Ph); 28.3 (*C*H_2CH_2CH_2); 27.4 (NHCH[*C*H_2CH_2C(O)OCH_2Ph]-C(O)); 25.5 (CH_2*C*H_2CH_2); 24.6 (*C*H_2CH_2*C*H_2); 21.8 (OCH(*C*H_3)$_2$). ^{1}H and ^{13}C NMR chemical shifts appeared to depend on the amount of TFA added.

Synthesis of RHNCH_2C(O){O(CH_2)$_5$C(O)}$_n$O(CH_2)$_6$OC(O)-CH_2NHR, R = (fluorenyl)CH_2OC(O) = *N*-Fmoc, RHN-PCL-NHR, 2′a. CH_2Cl_2 (50 mL) was added to a mixture of **1′** ($\bar{M}_{n,NMR}$ = 1400, 1.0 g, 0.71 mmol), DCC (6 equiv, 773 mg, 3.75 mmol), DPTS (1 equiv, 186 mg, 0.63 mmol), and *N*-Fmoc-glycine (3 equiv, 562 mg, 1.89 mmol) previously dissolved in DMF (2.5 mL). After stirring at 21 °C over 48 h, the dicyclohexylurea side product was removed by filtration, and the polymer was successively precipitated in methanol (in which DPTS, DCC, and the excess of *N*-Fmoc-glycine are soluble) and pentane, and finally dried under vacuum to give **2′a** ($\bar{M}_{n,NMR}$ = 2900, 750 mg, 53%).

Synthesis and Characterization of RHNCH_2C(O){O(CH_2)$_5$C(O)}$_n$ O(CH_2)$_6$OC(O)CH_2NHR, R = *t*BuOC(O) = *t*-Boc, HN-PCL-NHR, 2′b is reported in the Supporting Information.

Synthesis of H_2NCH_2C(O){O(CH_2)$_5$C(O)}$_n$O(CH_2)$_6$OC(O)CH_2NH_2, H_2N-PCL-NH_2, 3′a from 2′a. Piperidine (large excess, 1 mL, 10 mmol) was added to a CH_2Cl_2 solution (10 mL) of **2′a** ($\bar{M}_{n,NMR}$ = 2900, 500 mg, 0.17 mmol), and the resulting solution was stirred over 24 h at 21 °C. The solution was then washed twice with a saturated NaCl aqueous solution. The organic phase containing the polymer was dried over $MgSO_4$ and the polymer, subsequently recovered by precipitation in methanol, was finally dried under vacuum to give **3′a** ($\bar{M}_{n,NMR}$ = 3100, 380 mg, 91%).

Synthesis and Characterization of H_2NCH_2C(O){O(CH_2)$_5$C-(O)}$_n$O(CH_2)$_6$OC(O)CH_2NH_2, H_2N-PCL-NH_2, 3′b, from 2′b is reported in the Supporting Information.

Synthesis of H{NHCH[(CH_2)$_2$C(O)OCH_2Ph]C(O)}$_m$NHCH_2-C(O){O(CH_2)$_5$C(O)}$_n$ O(CH_2)$_6$OC(O)CH_2NH{C(O)CH[(CH_2)$_2$-C(O)OCH_2Ph]NH}$_m$H, PBLG-*b*-PCL-*b*-PBLG, 4′, from 3′a. A CH_2Cl_2 (2.5 mL) solution of **3′a** ($\bar{M}_{n,NMR}$ = 3100, 310 mg, 0.10 mmol) was added via cannula to a CH_2Cl_2 (5 mL) solution of BLG (2.63 g, 10 mmol). The solution was then stirred over 20 h at 21 °C during which gas (CO_2) evolution and viscosity increase were observed. The triblock copolymer **4′** ($\bar{M}_{n,NMR}$ = 25 400, 2.5 g) was recovered following the same treatment as that described above for the isolation of **4**. Quantitative BLG conversion was observed. ^{1}H NMR of **PBLG$_{50}$-*b*-PCL$_{27}$-*b*-PBLG$_{50}$** (200 MHz, $CDCl_3$/TFA; 90:10): δ = 8.22 (br s, *m*H, N*H*CH[CH_2CH_2C(O)OCH_2Ph]); 7.16 (br s, 10*m*H, C(O)OCH_2C$_6H_5$ and

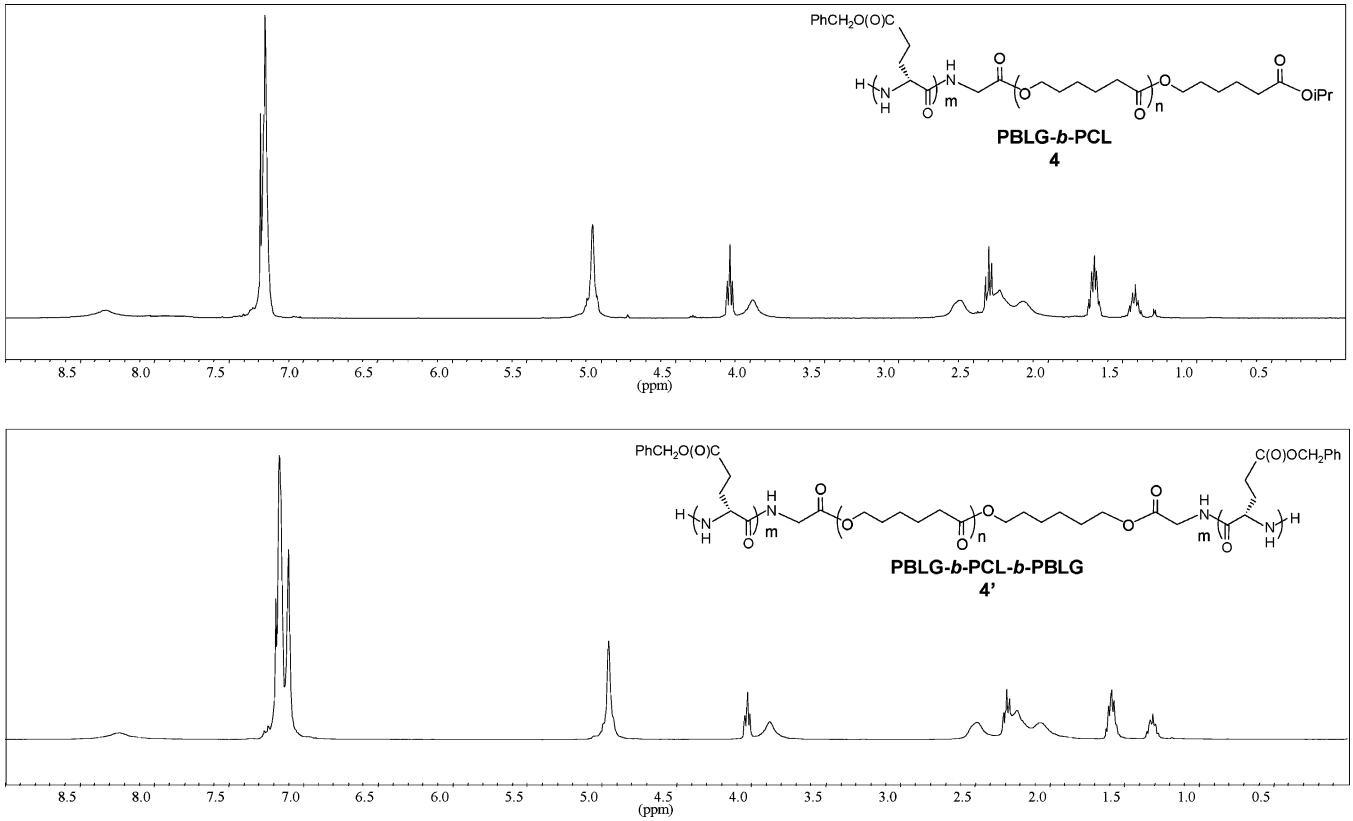


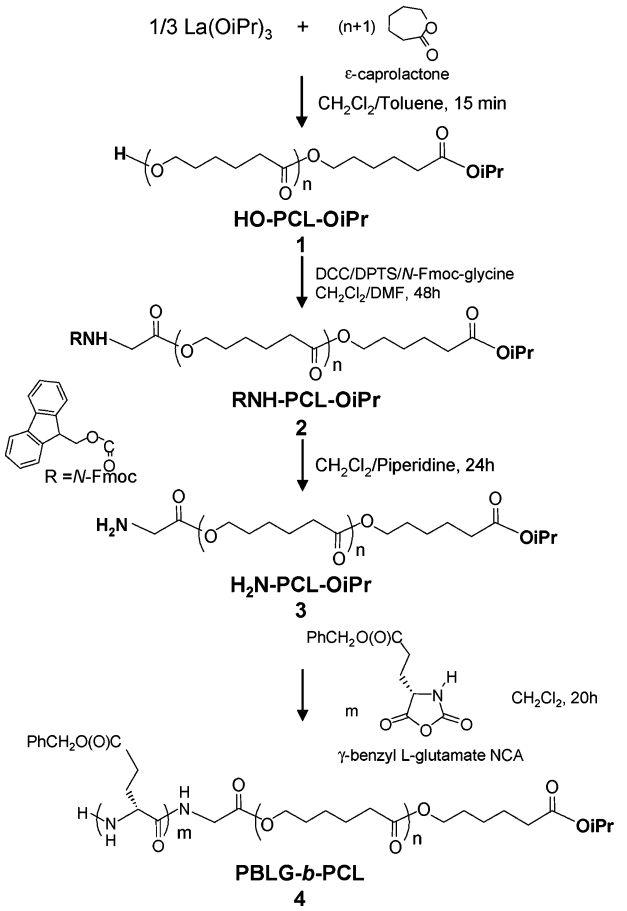
Figure 1. ^{1}H NMR spectra of $PBLG_{46}$-*b*-PCL_{100}, **4**, and $PBLG_{50}$-*b*-PCL_{27}-*b*-$PBLG_{50}$, **4′**, in $CDCl_3$/TFA (90:10).

$CDCl_3$); 4.95 (br s, 4*m*H, CH_2Ph); 4.03 (t, (2*n* + 4)H, C(O)OCH_2); 3.87 (br s, 2*m*H, NHC*H*CH_2CH_2C(O)OCH_2Ph); 2.48, 2.06, (2 br s, (2*m* + 2*m*)H, CHCH_2CH_2C(O)OCH_2Ph); 2.30 (t, 2*n*H CH_2C(O)); 2.21 (br s, 4*m*H, $CHCH_2CH_2$C(O)OCH_2Ph); 1.59 (m, (4*n* + 4)H, C$H_2CH_2CH_2$); 1.31 (m, (2*n* + 4)H, $CH_2CH_2CH_2$) (Figure 1). ^{13}C NMR (50 MHz, $CDCl_3$/TFA (90:10)): δ = 178.7, 175.5, 173.1 (NHCHCH_2CH_2C-(O)OCH_2Ph, NHCH[CH_2CH_2C(O)OCH_2Ph]*C*(O)NH, CH_2C(O)O, NHCH_2C(O)O); 128.8, 127.9 (NHCHCH_2CH_2C(O)$OCH_2C_6H_5$); 68.1 (NHCHCH_2CH_2C(O)OCH_2Ph); 65.8 (C(O)OCH_2); 53.0 (NH*C*H-[CH_2CH_2C(O)OCH_2Ph]C(O)); 33.6 (*C*H_2C(O)); 29.6 ($CHCH_2CH_2$C(O)-OCH_2Ph); 27.1 ($CH_2CH_2CH_2$); 26.4 (NHCH[CH_2CH_2C(O)OCH_2Ph]-C(O)); 24.6 ($CH_2CH_2CH_2$); 23.8 ($CH_2CH_2CH_2$). ^{1}H (especially NH*CH*CH_2CH_2C(O)OCH_2Ph and N*H*CH[CH_2CH_2C(O)OCH_2Ph]-C(O)) and ^{13}C NMR chemical shifts appeared to depend on the amount of TFA added. The triblock copolymer **4′** was prepared from **3′a** rather than from **3′b** because of the more sensitive deprotection conditions required to make **3′b**.

Results and Discussion

Both ω-secondary amide and ω-primary amine terminated PCL ({C(O)$(CH_2)_5$O}$_n$) have been reported in the literature.[9−12,23−30] Regarding RHN-PCL, upon addition of a primary amine (like *n*-butylamine) to $AlEt_3$, polymerization of CL proceeds at 40 °C to form α-*N*-*n*-butylamide,ω-hydroxyPCL, *n*-BuHN-PCL-OH.[23] Similarly to early work,[31−33] the polymerization of CL was recently initiated by the NH_2 group of an amino acid (H_2NCHRC(O)OH = L-alanine, L-leucine, L-phenylalanine, L-proline) under drastic conditions (160 °C, 40Pa) to give the corresponding [HO(O)CRHC]HN-PCL-OH.[24] The approaches developed to prepare NH_2-PCL involved various chain-end modification processes.[9−12,25−28,30] Several authors formed H_2N-terminated polymers, H_2N-$(CH_2)_{11-12}$O-PCL-X or H_2N-$(CH_2)_{10}$C(O)-PCL-X (X = OH,[10] OC(O)Ph,[26] poly(ethylene glycol)[27]), through the reduction of the bromo end-group of the corresponding Br-$(CH_2)_{10-12}$O-PCLs-X by sodium azide, combined to a hydrogenation step in the presence of ammonium formate and Pd (10%) supported on activated charcoal. The initiator used was either an aluminum (Et_2Al[O$(CH_2)_{12}$-Br]) or a tin (stannous 2-ethylhexanoate, Sn$(Oct)_2$) alkoxide, and linear as well as star-shaped amino PCLs were described.[10,25−27] With a calcium 4-nitrophenethoxide initiator, $O_2NC_6H_4(CH_2)_2$O-PCL-OH was prepared and subsequently modified into the corresponding aminophenyl-terminated polymer $H_2NC_6H_4(CH_2)_2$O-PCL-OH,[11] upon reduction by Pd/charcoal and H_2 similarly to the work cited above.[25] This NO_2/NH_2 transformation was also applied for the preparation of $H_2NC_6H_4$-$(CH_2)_2$O-terminated polycarbonate.[29] With the cyclic tin(IV) alkoxide initiator Bu_2Sn[−$O_2(CH_2)_4$−], the macrocyclic polymers Bu_2Sn[−PCL-O$(CH_2)_4$O-PCL−] were reacted in situ with 4-nitrobenzoyl chloride ($O_2NC_6H_4$C(O)Cl) ultimately resulting in α,ω-di(H_2N-C_6H_4C(O))-PCL after similar H_2(Pd/C) treatment.[9,28] The advantage in using these 4-aminobenzoyl end-groups relies in their low nucleophilicity, which prevents an aminolytic cleavage of the PCL chain during synthesis as well as upon storage.[9,28] Some HO-PCL-OiPr prepared from aluminum alkoxide were converted into $H_2N(CH_2)_x$C(O)O-PCL-OiPr upon condensation with *N*-benzyloxycarbonyl amino acid ($PhCH_2OC(O)NH(CH_2)_x$C(O)OH, x = 2, 6) followed by catalytic hydrogenation under mild conditions.[30] Finally, an ω-aminopolylactide was obtained from ROP of L-lactide initiated by a zinc alkoxide complex bearing a protected amine group, which was then deprotected.[12] This initiator was prepared in situ from the reaction of diethylzinc and *tert*-butoxycarbonylaminopropanol, a process in other respects subsequently applied.[6,34] To our knowledge, no detailed study of the stability of the PCL moiety during the chemical treatment has been reported.

Scheme 1. Synthesis of the Diblock PBLG-*b*-PCL Copolymer **4** from HO-PCL-OiPr, **1**



In the present work, we have established a new efficient and convenient synthetic route appropriate for the preparation of either the mono- or diamino-terminated PCLs H_2N-PCL-OiPr, **3**, and H_2N-PCL-NH_2, **3′**, upon chemical modification of the corresponding hydroxy-capped PCLs, HO-PCL-OiPr, **1**, and HO-PCL-OH, **1′**. This two-step procedure involves the condensation of hydroxy-terminated PCLs with a protected amino acid (*t*-Boc-VA or *N*-Fmoc-glycine) followed by the deprotection reaction of the amino group to obtain the analogous PCLs with amino chain end(s) as illustrated in Scheme 1−2. These reactions were performed under mild conditions. Indeed, selective end-functionalization of **1** and **1′** into **3** and **3′** is not obvious, for the weak aliphatic ester bonds of a PCL main chain easily react with strong acids or alkali reagents. Monitoring each step by NMR analyses allowed us to follow the appearance and disappearance of the appropriate signals.

The hydroxy-terminated prepolymers **1** and **1′** were prepared upon ROP of ϵ-caprolactone using $La(OiPr)_3$ or $Nd(BH_4)_3(THF)_3$ as initiator, respectively, as reported in our previous work (Scheme 1−2).[13,16−18] These well-established processes allow the quantitative and controlled polymerization of CL within specific conditions thereby offering, within less than 15 min at 21 °C, quite well defined polymers (Table 1). ^{1}H NMR characterization of **1** and **1′** showed in particular the typical CH_2OH signal at $\delta = 3.72-3.64$ ppm confirming the hydroxy-PCL structures.

The secondary amine terminated PCLs, RHN-PCL-OiPr, **2**, and RHN-PCL-NHR, **2′**, were easily prepared upon condensation of the hydroxy-terminated PCLs **1** and **1′** with an excess of *N*-protected amino acid at 21 °C, in CH_2Cl_2/DMF. This procedure is efficient and quantitative with both the *N*-Fmoc-glycine (**1** to **2** and **1′** to **2′a**) and the *t*-Boc-VA (**1′** to **2′b**) protective groups (Scheme 1−2) when DCC, a conventional esterification activating agent,[30] and DPTS are used as catalysts. ^{1}H NMR spectra of **2**, **2′a**, and **2′b** showed the disappearance, in comparison to the spectra of **1** and **1′**, respectively, of the end-group methylene proton signal (CH_2OH, $\delta = 3.72-3.64$ ppm) of **1** and **1′**, while typical peaks corresponding to the RHN group of the amino acid appeared; the fluorenyl ($\delta = 7.8, 7.6, 7.4, 7.3; 5.4; 4.4$ ppm) highlighted the presence of the *N*-Fmoc-$NHCH_2C(O)$ end unit in **2** and **2′a**, while the *t*-Boc-$NHCH_2C(O)$ end unit was easily identified in **2′b** with the methyl proton signal ($(CH_3)_3$; $\delta = 1.56$ ppm). Finally, the $RNHCH_2C(O)$ secondary amine and α-methylene signals came around $\delta = 5.4-4.6$ and $4.0-3.1$ ppm, respectively, in all amino-terminated polymers **2**, **2′a**, and **2′b**. On going from **1′** to **2′a** and **2′b**, no hydroxyl signal was observed in the NMR spectra of **2′a** or **2′b**, thus highlighting that both −OH (and not just one) end-groups of **1′** were indeed modified.

Quantitative cleavage of the *N*-Fmoc protective group in **2** and **2′a** to form H_2N-PCL-OiPr, **3**, and H_2N-PCL-NH_2, **3′a**, respectively, was performed under mild conditions at 21 °C over 24 h in CH_2Cl_2/piperidine without rupture of the PCL ester bonds. Deprotection of the *t*-Boc in **2′b** to form **3′b** is however more sensitive and was done with TFA at O °C over 2 h. Although this method is efficient, PCL rupture was sometimes observed, as evidenced by the reappearance of a CH_2-OH end-group signal in the NMR spectrum. To avoid this inconvenience, care should be taken to maintain the temperature below 0 °C. NMR analyses of polymers **3**, **3′a**, and **3′b** revealed the disappearance, in comparison to the spectra of **2**, **2′a**, and **2′b**, respectively, of the *N*-Fmoc and *t*-Boc characteristic peaks along with the presence of $NH_2CH_2C(O)$ (triplet, $\delta = 3.6-3.4$ ppm) signals. This clearly proved, within NMR experimental error, that a quantitative deprotection has taken place.

For all these PCLs **1**−**3** and **1′**−**3′**, a quite good agreement was observed between the calculated molar mass values and the ones determined from NMR analyses or obtained from SEC analyses (Table 1). The molar mass distributions obtained for the polymers **1′** synthesized from the rare-earth borohydride $Nd(BH_4)_3(THF)_3$ were smaller than those recorded for the polymers **1** prepared from the rare-earth alkoxide $La(OiPr)_3$, as previously noticed in lactone polymerization using these same initiators.[13,16−18] For the first time, a diaminopoly(ϵ-caprolactone), **3′a**, has been prepared upon chemical modification of a dihydroxypoly(ϵ-caprolactone). This NH_2-terminated polymer **3′a** then offered a smooth access to polypeptide−polyester−polypeptide copolymers.

The ROP of γ-benzyl L-glutamate (BLG) was then smoothly initiated by low molar mass ($\bar{M}_n < 7500$) amino-terminated PCLs **3** and **3′a** in CH_2Cl_2 at 21 °C over 20 h. The resulting diblock PCL-*b*-PBLG, **4**, and triblock PBLG-*b*-PCL-*b*-PBLG, **4′**, copolymers were isolated after precipitation in diethyl ether and diethyl ether/acetone. By adjusting the ratio of the BLG monomer to the amino-PCL initiator **3** or **3′a**, diblock and triblock copolymers of various compositions in each segment were thus synthesized (Table 2). The synthesized diblock polymers **4** exhibit a polyester chain of 46 units associated to either a longer (100 units) or shorter (25 units) polypeptide block, while the triblock polymers **4′** display a polyester chain of length varying from 23 to 64 units between two polypeptide chains of length changing from 10 to 150 units. NMR spectra of the triblock copolymers **4** and **4′** unambiguously showed the absence of the characteristic $NH_2CH_2C(O)$ triplet ($\delta = 3.6-3.4$ ppm) observed in **3** and **3′**, thereby highlighting

Scheme 2. Synthesis of the Triblock PBLG-*b*-PCL-*b*-PBLG Copolymer, **4′**, from HO-PCL-OH, **1**

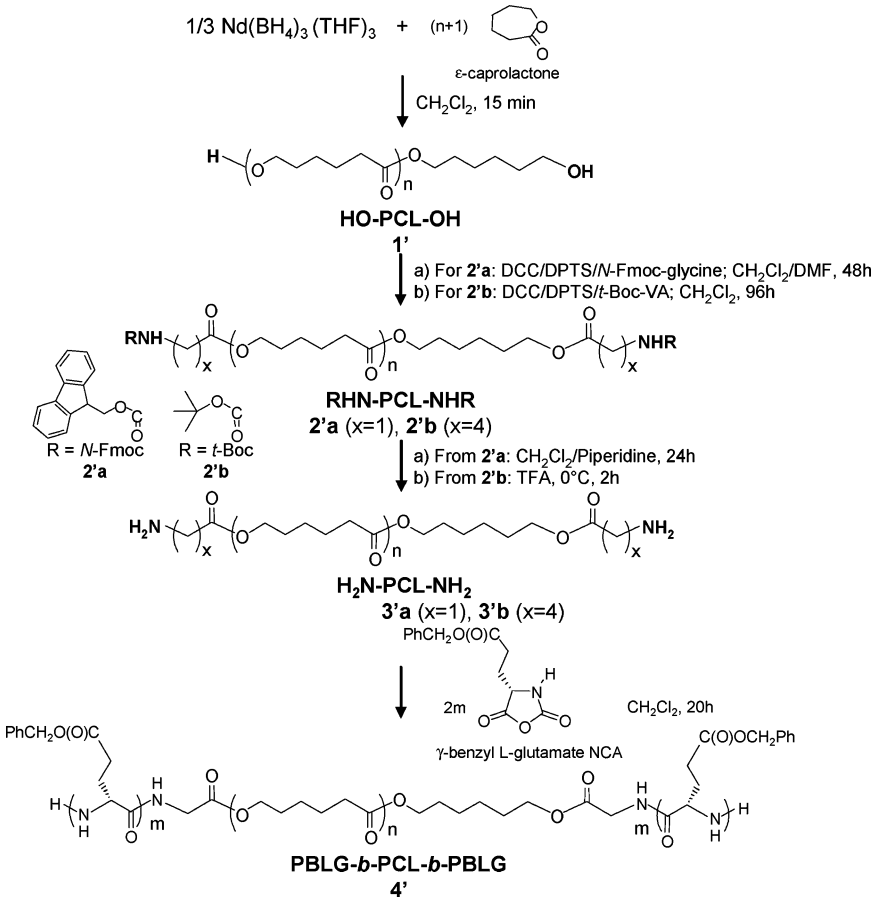


Table 1. Polymer Features of HO-PCL-OiPr, **1**; RNH-PCL-OiPr, **2**; H_2N-PCL-OiPr, **3**; HO-PCL-OH, **1′**; RNH-PCL-NHR, **2′**; and H_2N-PCL-NH_2, **3′**

PCL	$\bar{M}_{n,theo}$	$\bar{M}_{n,SEC}$[a]	$\bar{M}_w/\bar{M}_n$[b]	$\bar{M}_{n,NMR}$[c]
1	3400	4700	1.5	4600
2	4900[d]	5200	1.4	5000
3	4800[d]	5200	1.6	5500
1′	2300	1600	1.3	1400
2′a	2000[e]	2600	1.3	2900
2′b	1800[e]	2100	1.3	1600
3′a from **2′a**	2450[e]	3300	1.2	3100
3′b from **2′b**	1400[e]	2000	1.4	2400

[a] SEC values of precipitated polymer samples. [b] Molar mass distributions calculated from SEC chromatogram traces. [c] Determined from ^{1}H NMR analysis. [d] Calculated from $\bar{M}_{n,NMR}$(**1**) − H + *N*-FmocNHCH$_2$C(O) for **2**, or $\bar{M}_{n,NMR}$(**2**) − *N*-Fmoc + H for **3**. [e] Calculated from $\bar{M}_{n,NMR}$(**1′**) − 2H + 2(*N*-Fmoc/*t*-BocNH(CH$_2$)$_x$C(O)) for **2′a**(x = 1)/**2′b**(x = 4) or $\bar{M}_{n,NMR}$(**2′a/b**) − 2(*N*-Fmoc/*t*-Boc) + 2H for **3′a/3′b**.

that both **3** and **3′** polymer end-functions have actually polymerized the NCA monomer and the triblock copolymer is not contaminated by any diblock copolymer (Figure 1). While some PBLG-*b*-PCL copolymers have already been reported,[10,11] the triblock copolymers PBLG-*b*-PCL-*b*-PBLG, **4′**, represent the first isolated copolymers associating two PBLGs to a central polyester segment.[9]

The chemical compositions of the final copolymers **4** and **4′** were determined by SEC, NMR, IR, and DSC analyses. Comparison of the SEC (DMF, 20 °C) peaks of NH_2-PCLs **3** or **3′a** and of the block copolymers **4** and **4′**, respectively, confirmed an increase of the molar mass upon synthesizing the polyester−polypeptide copolymers. However, as a result of some peptide segment adsorption onto the columns,[10] the molar values observed were lower than the calculated ones. To avoid this problem, the block copolymers **4** or **4′** were analyzed by SEC in DMF/LiBr at higher temperature (60 °C; Table 2, Figure 2). The molar masses thus obtained were in good agreement with the theoretical ones, thus supporting the absence of peptide segment aggregation, a behavior otherwise often observed at ambient temperature. SEC chromatograms showed a unique monomodal peak with a relatively narrow molar mass distribution ($1.1 < \bar{M}_w/\bar{M}_n < 1.4$) highlighting first that the reactivities of **3** and **3′a**, respectively, toward the polymerization of BLG were quantitative and second that the isolated block copolymers **4** and **4′** were pure.

NMR spectra of both **4** and **4′** were recorded in $CDCl_3$/TFA (90:10) in which both the polyester and polypeptide blocks are fully soluble (Figure 1). While the analysis in pure $CDCl_3$ essentially allowed observation of the polyester block, addition of TFA permitted both the polyester and polypeptide blocks to be visualized. Both the diblock and triblock copolymers **4** and **4′** exhibited all the signals typical of the poly(amino acid) and of the polyester moieties. While the terminal −O^{i}Pr group (δ = 4.38, 1.28 ppm) of the PCL-*b*-PBLG copolymer **4** was clearly identified, H_2N− end-function(s) of copolymers **4** and **4′** were not observed. This signal (predicted at δ ($CDCl_3$) = 2.8 ppm)[35] might be covered by the PCL chain CH_2C(O) (δ = 2.42−2.30 ppm) and/or the PBLG chain NHCH[CH_2CH_2C(O)OCH$_2$Ph] (δ = 2.54−2.48, 2.33−2.21, 2.10−2.06 ppm) proton signals. Another explanation might be the modification of $-NH_2$ into $-NH_3^+$ groups in the presence of added TFA. Regarding the proton signals of the −NHCH_2C(O) copolymer junction(s) (predicted at δ ($CDCl_3$) = 8.15, 4.15 ppm),[35] these might overlap with the PBLG chain N*H*CH[$CH_2CH_2C(O)OCH_2Ph$] (δ = 8.35−8.22 ppm) and the C(O)OCH_2 PCL block (δ = 4.09−

Table 2. PCL-*b*-PBLG and PBLG-*b*-PCL-*b*-PBLG Copolymer Features

copolymer **4**, **4′**	$\bar{M}_{n,SEC}$[a] **3**, **3′a**	$\bar{M}_{n,NMR}$[b] **3**, **3′**	$[BLG]_0/[\mathbf{3}, \mathbf{3'a}]_0$	$\bar{M}_{n,theo}$[c] **4**, **4′**	$\overline{DP}_n$ (BLG)[d]	$\bar{M}_{n,SEC}$[e] **4**, **4′**	$\bar{M}_w/\bar{M}_n$[e] **4**, **4′**	$\bar{M}_{n,NMR}$[f] **4**, **4′**
PCL_{46}-*b*-$PBLG_{100}$	5200	5500	108	28 850	107	27 800	1.1	28 900
PCL_{46}-*b*-$PBLG_{25}$	5200	5500	27	11 100	35	10 900	1.3	13 200
$PBLG_{50}$-*b*-PCL_{27}-*b*-$PBLG_{50}$	3300	3100	108	27 000	102	20 600	1.4	25 400
$PBLG_{150}$-*b*-PCL_{64}-*b*-$PBLG_{150}$	7300	6900	296	72 100	300			72 600
$PBLG_{50}$-*b*-PCL_{52}-*b*-$PBLG_{50}$	6000	5700	126	33 600	126	29 400	1.2	33 300
$PBLG_{10}$-*b*-PCL_{23}-*b*-$PBLG_{10}$	2600	2900	33	9800	36	7 850	1.1	10 800

[a] SEC values of precipitated polymer samples. [b] Determined from ^{1}H NMR analysis. [c] Calculated from $\bar{M}_{n,SEC}$ **3**, **3′a** + $[BLG]_0/[\mathbf{3}$ or $\mathbf{3'a}]_0 \times 219$. [d] Number average degree of polymerization of the peptide segment determined by ^{1}H NMR analysis. [e] Determined in DMF/LiBr at 60 °C. [f] Calculated from $\bar{M}_{n,NMR}$ ***3*** *or* ***3′a*** + $\overline{DP}_n$*(BLG)* × *219.*

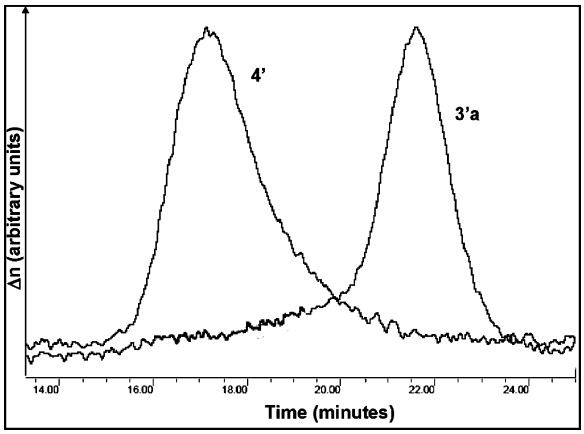


Figure 2. SEC traces of H_2N-PCL_{27}-NH_2, **3′a**, and of the corresponding $PBLG_{50}$-*b*-PCL_{27}-*b*-$PBLG_{50}$, **4′**, in DMF/LiBr at 60 °C.

4.03 ppm) signals, respectively.

The experimental apparent degrees of polymerization $\overline{DP}_n$s were in agreement with the corresponding $[monomer]_0/[macroinitiator\ \mathbf{3}$ or $\mathbf{3'a}]_0$ ratios and allowed the experimental molar mass values ($\bar{M}_{n,NMR}$) to be calculated. $\bar{M}_{n,NMR}$ values determined for **4** and **4′** were in close agreement with the molar mass values obtained from SEC measurements using universal calibration ($\bar{M}_{n,SEC}$, DMF/LiBr, 60 °C) and with the expected ones ($\bar{M}_{n,theo}$) (Table 2).

The ROP of BLG (ν_{CO} = 1770, 1865 cm^{-1})[7] has been assessed by IR spectroscopy. The spectra of copolymers **4** (PCL_{46}-*b*-$PBLG_{100}$) and **4′** ($PBLG_{50}$-*b*-PCL_{27}-*b*-$PBLG_{50}$) clearly exhibited ν_{NH} (3298, 3441/3353 cm^{-1}), ν_{CO} (1651, 1648 cm^{-1}), and a $\nu_{CO\text{-}NH}$ (1556, 1543 cm^{-1}, respectively) absorption bands typical of an amide group, thus indicating the formation of the polypeptide block.[7,9−11] The spectra also displayed ν_{CO} absorption at 1731 and 1727 cm^{-1}, respectively, characteristic of both homopolymers (PCL, 1724 cm^{-1}; PBLG, 1736 cm^{-1}).[7,17]

DSC curves of PCL-*b*-PBLG, **4**, of various compositions have been recorded (Figure 3). A melting temperature at 56.5 °C highlighting the presence of PCL (T_m = 60 °C for homoPCL) could only be detected for a copolymer having a greater polyester content, PCL_{46}-*b*-$PBLG_{25}$. A copolymer with a smaller PCL content (PCL_{46}-*b*-$PBLG_{100}$) did not give such a peak, as previously published.[11] A small endothermic peak verifying the presence of the PBLG block was recorded in the 103−122 °C range (the longer the peptide segment, the higher the temperature) with a low enthalpy (9.3−10.7 $J \cdot g^{-1}$). This irreversible transition, showing up only during the first heating run, was attributed to an irreversible change from a seven-residue two-turn (7/2) to an 18/5 α-helical conformation.[11,36,37] At higher temperatures, no other transition could be observed for the PBLG block before its degradation. DSC curves of triblock PBLG-*b*-PCL-*b*-PBLG, **4′**, copolymers richer in polypeptide fragments ($PBLG_{10}$-*b*-PCL_{23}-*b*-$PBLG_{10}$, $PBLG_{50}$-*b*-PCL_{27}-*b*-$PBLG_{50}$), only displayed the irreversible transition characteristic of the PBLG blocks at 118 °C or 124 °C, respectively, along with an increase of the enthalpy for longer polypeptide blocks (Figure 3).

Conclusion

In this contribution, we have reported on an appropriate and quantitative chemical modification of hydroxypoly(ϵ-caprolactone) HO-PCL-OiPr, **1**, and HO-PCL-OH, **1′**, into the amino-functionalized homologues, H_2N−PCL-OiPr, **3**, and H_2N−PCL-NH_2, **3′**. Along with H_2N-C_6H_4C(O)-PCL-O$(CH_2)_4$O-PCL-C(O)C_6H_4-NH_2,[9] polyesters **3′** represent, to our knowledge, the only example of α,ω-diamino telechelic poly(ϵ-caprolactone). These new macroinitiators, **3** and **3′**, first provide the

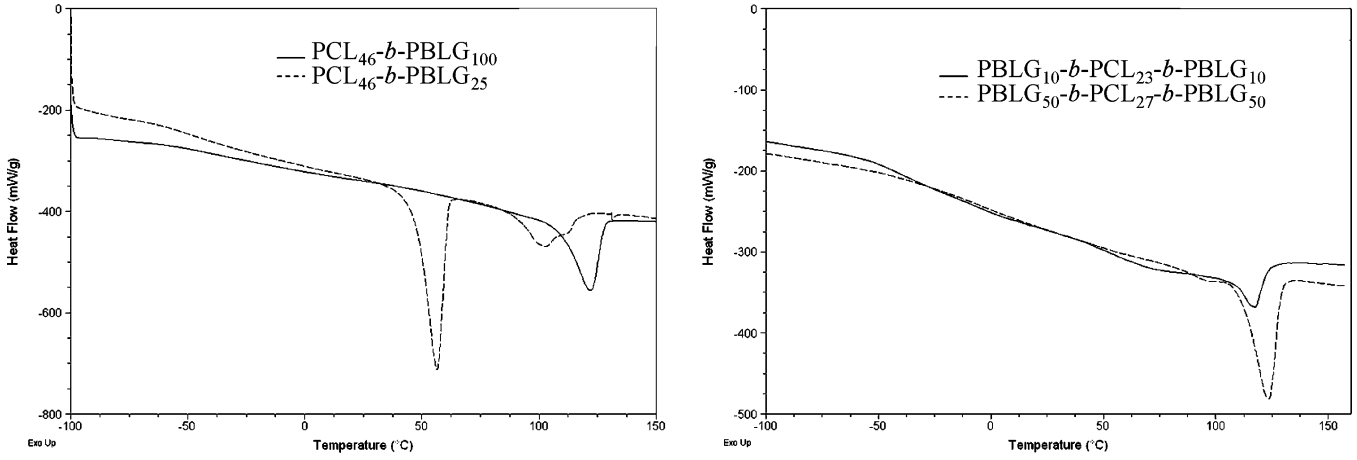


Figure 3. DSC traces of PCL_{46}-*b*-$PBLG_{25}$ and PCL_{46}-*b*-$PBLG_{100}$, **4**, and of $PBLG_{10}$-*b*-PCL_{23}-*b*-$PBLG_{10}$, and $PBLG_{50}$-*b*-PCL_{27}-*b*-$PBLG_{50}$,**4′**.

ability to polymerize α-amino acid *N*-carboxyanhydrides, and second, afford a convenient and direct route to poly(γ-benzylglutamate)-*b*-poly(ϵ-caprolactone), **4**, and poly(γ-benzylglutamate)-*b*- poly(ϵ-caprolactone)-*b*-poly(γ-benzylglutamate), **4′**, biomacromolecular architectures. The latter represent a unique class of isolated polypeptide−polyester−polypeptide triblock copolymers. These polyester−polypeptide block copolymers offer other valuable advantages. Indeed, all polymers and copolymers have been synthesized from rare-earth initiators, transition metals less toxic than the conventional ones (Al, Zn, Sn),[17] thereby making such biocompatible and biodegradable multicomponent polymers suitable for biomedical applications.[17,38] In addition, this direct and handy method is also versatile, since upon changing the ester or the amino acid, a wide range of polyester−polypeptide polymers should be prepared straightforwardly. Noticeably, the extension of this method to the synthesis of poly(trimethylene carbonate)-based copolypeptides as well as the potentiality of resulting amphiphilic polyester−polypeptide block copolymers to self-organize will be reported in a forthcoming publication.

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Supporting Information Available. Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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