Polymerization of Lactides and Lactones. 10. Synthesis, Characterization, and Application of Amino-Terminated Poly(ethylene glycol)-*co*-poly(ϵ-caprolactone) Block Copolymer

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ABSTRACT: The synthesis of hydroxy-terminated poly(ethylene glycol)-*co*-poly(ϵ-caprolactone) (MPEG−PCL) was investigated by the reaction of poly(ethylene glycol) and ϵ-caprolactone in the presence of stannous octoate. The polymerization was proved to be carried out in a controllable way. Bromo-terminated MPEG−PCL copolymer has been synthesized by macromolecular reaction as a possible method to prepare primary amino-terminated MPEG−PCL. The conversion of hydroxy-terminated MPEG−PCL to amino-terminated MPEG−PCL was detected quantitatively. The primary amino-terminated MPEG−PCL was an effective macroinitiator for the ring-opening polymerization of β-benzyl L-aspartate-*N*-carboxy anhydride. The A−B−C triblock copolymer of MPEG−PCL−PBLA thus synthesized may be used as a new potential biomaterial, which contains both a hydrophilic unit and a hydrophobic unit as well as functional groups.

Introduction

Hydrophobic aliphatic polyesters, especially bioresorbable poly(ϵ-caprolactone) (PCL) and poly(lactic acid) (PLA), have been widely studied to develop systems for sustained drug delivery.[1−3] It is well-known that poly(ethylene glycol) (PEG) presents outstanding physicochemical and biological properties, which include hydrophilicity, solubility in water and in organic solvents, lack of toxicity,[4] and absence of antigenicity and immunogenicity,[5] which allow PEG to be used for many biomedical and biotechnological applications. Recently, poly(ethylene glycol)−polyester block copolymers have been prepared using monohydroxy or dihydroxy PEG to initiate the ring-opening polymerization of lactone monomers.[6−13] Such amphilic block copolymers exhibit unique properties, i.e., permeability and degradability, which may lead to new application possibilities.

Despite the abundant literature on the studies of synthesis, characterization, degradation and properties of poly(ethylene glycol)−polyester, the synthesis of amine-terminated poly(ethylene glycol)−polyester block copolymer has not been reported. This kind of copolymers would play a desirable macroinitiator for further copolymerizaion of certain interesting monomers, such as amino acid *N*-carboxy anhydride (NCA) to prepare poly(ethylene glycol)−polyester−poly(amino acid) A−B−C triblock copolymer. In the case of amino acids that have functional groups, e.g., −COOH in aspartic acid and $-NH_2$ in lysine, this chain-extended copolymerization would offer a possibility of producing multifunctional polymers which consist of hydrophilic/hydrophobic, soft/hard chain segments, and functional groups and, thus, constituted a very attractive means to modulate the basic properties of each homopolymer.

In the present paper, we report the synthesis and characterization of amino-terminated poly(ethylene glycol)-*co*-poly(ϵ-caprolactone) copolymer and its application in chain-extended copolymerization with NCA.

Experimental Part

Materials. ϵ-Caprolactone was purchased from Aldrich and dried over calcium hydride for 48 h at room temperature, and then distilled under reduced pressure in a nitrogen atmosphere prior to use. The monomer was dried for 24 h at 25 °C under reduced pressure (5 mmHg) before polymerization. Monomethoxy−poly(ethylene glycol) with a molecular weight of 5000 (MPEG5000) was obtained from Fluka. Prior to use, MPEG5000 was dried by an azeotropic distillation in toluene. Stannous octoate (stannous 2-ethylhexanoate) [$Sn(Oct)_2$] (Fluka Co., Switzerland) was used by dissolving it in toluene under nitrogen. $CHCl_3$ and dimethylformamide (DMF) were dried by refluxing over P_2O_5 for 24 h and were distilled under nitrogen before use. 11-Bromoundecanoic acid, palladium on activated carbon (10%), triphosgene, and sodium azide were obtained from Acros Co. and used as received. Triethylamine was dried over CaH_2 for 3 days and distilled before use. $SOCl_2$, L-aspartic acid, and benzyl alcohol were used as received. β-Benzyl-L-aspartate was prepared according to literature procedures.[14] Tetrahydrofuran (THF) and 1,4-dioxane were dried and distilled from sodium immediately before use.

Synthesis of 11-Bromoundecanoyl Chloride. First, 0.1 mol of 11-bromoundecanoic acid was mixed with 0.15 mol of $SOCl_2$ in a 100 mL round-bottomed flask. The mixture was heated to 60 °C for 5 h and then left at room-temperature overnight. The crude product was obtained after removing $SOCl_2$ in excess and was purified by distilled under vacuum. The vacuum strength was not determined, but the product was collected from 80 to 90 °C to give a yield of 86%. ^{1}H NMR ($CDCl_3$), δ: 3.38 (t,2H,C**H**$_2$Br), 2.87 [t,2H,C**H**$_2$C(O)Cl], 1.2−2.0 [m,16H,(C**H**$_2$)$_8$]. IR: $\nu_{CO} = 1799\ cm^{-1}$, $\nu_{C-Cl} = 722, 680\ cm^{-1}$, $\nu_{C-Br} = 552\ cm^{-1}$. Anal. Calcd for $C_{11}H_{20}BrClO$: C, 46.6; H, 7.1; Br, 28.2; Cl, 12.5. Found: C, 46.1.2; H, 6.93; Br,27.8; Cl, 13.1. IR, ^{1}H NMR, and elemental analyses show that the prepared sample is consistent with its chemical structure of 11-bromoundecanoyl chloride..

Synthesis of Monomethoxy−Poly(ethylene glycol)-*co*-poly(ϵ-caprolactone) (MPEG−PCL). Block copolymers are easily prepared by ring-opening polymerization of CL and MPEG in the presence of stannous octoate as a catalyst. First, 5 g of CL, 5 g of MPEG, and catalyst (0.1%) were added into a 50 mL dried glass reactor, previously flamed and nitrogen-purged several times, and then sealed under reduced pressure (5 mmHg). The reaction was carried out at constant temper-

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Table 1. Synthesis of Hydroxy-Terminated MPEG−PCL[a]

no.	feed ratio (PEG %)	found ratio[b] (PEG %)	yield (%)	DP_{PCL}[b]	M_n[b] ($\times 10^4$)	M_n[c] ($\times 10^4$)	η_{inh}[d] (dL g^{-1})	M_w/M_n[c]
1	30	29.1	98.6	140	2.10	1.68	0.28	1.43
2	50	49.6	98.4	62	1.21	0.93	0.18	1.35
3	60	62.1	97	22.8	0.76	0.56	0.12	1.27
4	70	71.7	97.5	18.4	0.63	0.47	0.09	1.21
5	80	82.0	97.5	11.4	0.61	0.42	0.08	1.13

[a] Condition: 140 °C, 24 h, monomer/initiator = 1000 (w/w), in bulk. [b] Calculated from ^{1}H NMR spectra. [c] Obtained from GPC. [d] Measured at 30° with a concentration of 2 g L^{-1} in THF.

ature for a desirable period of time. The reaction mixture was terminated by cooling it in water. The reaction product was then dissolved in $CHCl_3$, and precipitated with an excess of methanol/diethyl ether to give a white product (yield: 98.4%). The purified product was dried under vacuum at 40 °C for 48 h. The polymerization degree (DP) of CL is 62. Diblock copolymers with different DP of PCL could be obtained by adjusting the feed ratio of CL to MPEG. The results are summarized in Table 1.

Synthesis of Bromo-Terminated MPEG−PCL. In a 200 mL flask, with stirring, 5 g of MPEG−PCL (DP_{MPEG} = 114, DP_{PCL} = 62) and a 3-fold molar excess of triethylamine were dissolved in 100 mL of dry $CHCl_3$ (w/v = 5%); the mixture was cooled to 0 °C. A 3-fold molar excess of 11-bromoundecanoyl chloride was added dropwise. The stirred reaction was kept at 0 °C for 30 min, and then the mixture was left at room temperature for 24 h. The reaction mixture was precipitated with an excess of methanol/diethyl ether to give a white solid. The solid was purified by dissolved in $CHCl_3$, washed with water in a separatory funnel, dried with anhydrous Na_2SO_4, filtered, and precipitated again with methanol/diethyl ether. The yield was 96%. The DP values of MPEG and PCL are 114 and 60, respectively.

Synthesis of Azide-Terminated MPEG−PCL. In a 200 mL flask, 5 g of bromo-terminated MPEG−PCL (DP_{MPEG} = 114, DP_{PCL} = 60) and a 5-fold molar excess of sodium azide was reacted in 100 mL of dry DMF (w/v = 5%) with stirring at 30 °C for 24 h. After the reaction was completed, the reaction mixture was precipitated with an excess of methanol/diethyl ether to give a white product. The yield was 92%. The DP values of MPEG and PCL are 114 and 60, respectively.

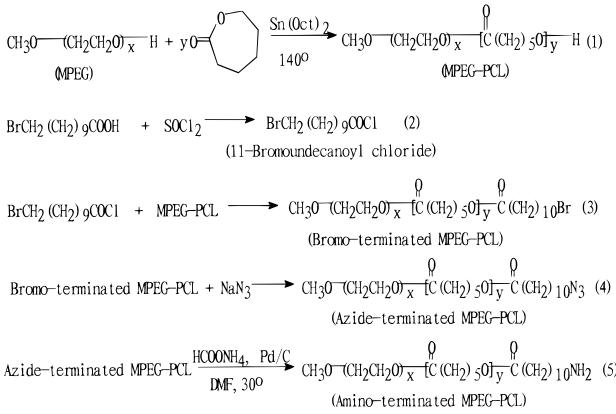
Reduction of Azide-Terminated MPEG−PCL into Amino-Terminated MPEG−PCL. Azide-terminated MPEG−PCL (10 g) (DP_{MPEG} = 114, DP_{PCL} = 60) was hydrogenated in 200 mL of dry DMF (w/v = 5%) by reaction with a 5-fold molar excess of ammonium formate and 10% Pd supported on activated carbon in a 500 mL flask. The reaction temperature was kept at 30 °C for one night. Palladium residues were recovered by centrifugation. The reaction mixture was precipitated with an excess of methanol/diethyl ether to give a white product. The yield was 95%. The DP values of MPEG and PCL are 114 and 61, respectively.

***β*-Benzyl-L-aspartate-*N*-carboxy Anhydride (BLA-NCA).** *β*-Benzyl-L-aspartate (0.05 mol) and THF (100 mL) were added into a 200 mL dried glass reactor previously flamed and nitrogen purged several times. Triphosgene (0.02 mol) was added, and the mixture was reacted at 60 °C for 3 h. After cooling, the mixture was filtered. The filtrate was concentrated under vacuum, and the solution was precipitated from hexane. The product was filtered, washed with hexane, and recrystallized from THF/hexane solution three times to give a needle-shaped crystal (yield: 90%): mp 120 °C, reported 121 °C.[19]

Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.5; N, 5.6. Found: C, 59.2; H, 4.63; N, 5.20.

A−B−C Block Copolymer of MPEG−PCL−PBLA. A 1.5 g sample of amino-terminated MPEG−PCL (DP_{MPEG} = 114, DP_{PCL} = 25) and 3 g of BLA-NCA were added into a dried 100 mL glass reactor previously nitrogen purged several times. Then, 70 mL of solvent (1,4-dioxane/$CHCl_3$ = $^3/_2$,v/v) was injected by a syringe. The mixture was stirred at 35 °C for 72 h. The mixture was precipitated with an excess of diethyl ether to give a white solid. The product was purified by dissolved in $CHCl_3$, washed with water in a separatory funnel, and precipitated again with an excess of diethyl ether. The purified product was dried under vacuum at 40 °C for 48 h (yield: 89%). The DP of PBLA is 57.

Scheme 1. Synthesis of Amino-Terminated MPEG−PCL



Characterization. ^{1}H NMR spectra of polymer were recorded in $CDCl_3$ or DMSO-d_6 with a Varian^{UNITY} INOVA-400 MHz apparatus at 25 °C. IR spectra were recorded on a NICOLET MX-1 IR apparatus. Molecular weight and molecular distribution was determined by GPC with a Waters Associates model ALC/GPC 244 apparatus, at room temperature, differential refractometer as detector, using THF as the solvent, and calibrated with polystyrene standards. As the molecular weight of PEG is known as received, the M_n of copolymer can be estimated from the relative intensities of the ^{1}H NMR spectra.

Results and Discussion

Our previous attempt proved that it is difficult to convert hydroxy-terminated MPEG−PCL into amino-terminated MPEG−PCL by the usual methods, such as the Gabriel reaction. This is because there are weak aliphatic ester bonds in the polymer chain which are easy to be break down under the strong reaction conditions. A new method should be developed to synthesize amino-terminated MPEG−PCL. It is well-known that an alkyl bromide is a potential precursor since it can be converted into a primary amine through an azidoalkyl compound.

Teyssie et al.[15] had been successfully synthesized amino-terminated CL by using functional $Br(CH_2)_{12}$-$OAlEt_2$ as initiator for the ring-opening polymerization of CL to prepare bromo-terminated PCL. But in the case of polymerization of PEG and CL, one cannot prepare the bromo-terminated PEG−PCL copolymer in this way. In our present study, we prepare the bromo-terminated MPEG−PCL copolymer by macromolecular reaction of the PEG−PCL copolymer. An outline of the synthesis of amino-terminated MPEG−PCL is provided in Scheme 1.

Synthesis of Hydroxy-Terminated MPEG−PCL. The ring-opening polymerization of CL was initiated with MPEG in the presence of stannous octoate. Polymerization was conducted in bulk with high conversion, and the synthetic conditions were carefully selected in order to minimize ester interchange. Kim et al.[16] reported the decrease of molecular weights at temperature higher than 150 °C due to the transesterification reaction. Backbiting degradation was also reported at high reaction temperature when the polymerization

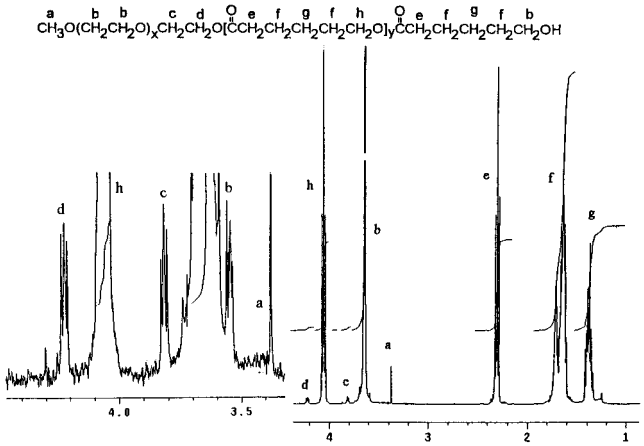


Figure 1. ^{1}H NMR spectra of hydroxy-terminated MPEG−PCL ($DP_{MPEG} = 114$, $DP_{PCL} = 62$).

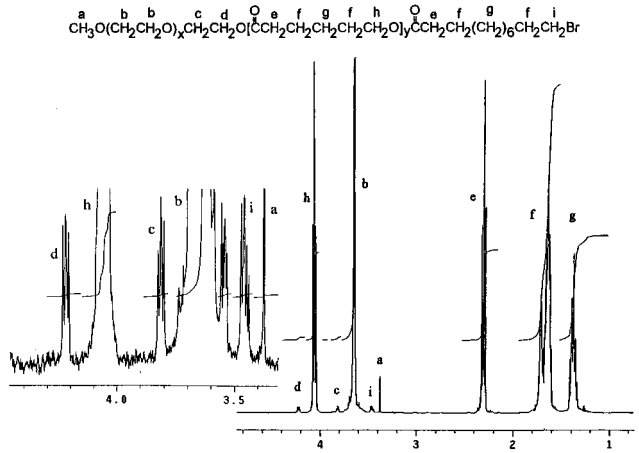


Figure 2. ^{1}H NMR spectra of bromo-terminated MPEG−PCL ($DP_{MPEG} = 114$, $DP_{PCL} = 60$).

lasted long. In our preparation, the polymerization temperature was set to 140 °C, for the overall reaction time of 24 h. The polymerization results characterized by GPC and 1H NMR are summarized in Table 1. It can be seen that hydroxy-terminated MPEG−PCL block copolymers with the expected molecular weights and compositions were obtained. The molecular weight of the copolymer could be controlled by adjusting the molar ratio of MPEG to CL according to requirements. Through strict control of the reaction conditions, a good agreement between calculated molecular weight and actual molecular weights was observed in most cases. By comparing the molecular weights of the polymers in Table 1, we can see a close agreement of the found molecular weight with the predicted molecular weight from the MPEG /CL ratio.

The copolymers were characterized by ^{1}H NMR and GPC. A typical ^{1}H NMR spectrum of MPEG−PCL was shown in Figure 1. Typical signals of both PEG and PCL units were detected. Peaks at 3.38 ppm (a), 4.2 ppm (d), and 3.8 ppm (c) confirmed the block nature of the hydroxy-terminated MPEG−PCL copolymer. The formation of block copolymer was further confirmed by GPC measurements (Figure 2), as there was no evidence of oligomers. In every case block copolymers showed sharp, unimodal distribution, indicating that the MPEG had completely reacted with CL, and no homopolymerization had occurred.

Synthesis of Bromo-Terminated MPEG−PCL. As mentioned above, bromo-terminated MPEG−PCL cannot be prepared by using functional initiator. The preferable route to make bromo-terminated MPEG−PCL is through a macromolecular reaction. The hydroxy end group of MPEG−PCL can react with an acyl chloride, which is easily obtained from an alkyl acid. 11-Bromoundecanoyl chloride was prepared in high yield and successfully used to react with hydroxy-terminated MPEG−PCL; the resulting bromo-terminated MPEG−PCL has been quantitatively isolated and purified. The ^{1}H NMR spectra of bromo-terminated MPEG−PCL is shown in Figure 3. The ^{1}H NMR spectra unambiguously shows the presence of the alkyl bromide (−C**H**$_2$Br) at a chemical shift of 3.46 ppm (i), which is in agreement with the chemical shift of the alkyl bromide (−C**H**$_2$Br) of 11-bromoundecanoyl chloride. GPC analysis (Figure 2) shows that the molecular characteristics of the polymeric backbone are kept unchanged.

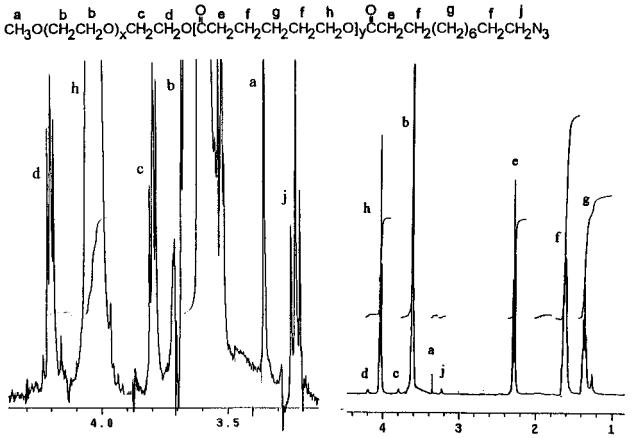


Figure 3. ^{1}H NMR spectra of azide-terminated MPEG−PCL ($DP_{MPEG} = 114$, $DP_{PCL} = 60$).

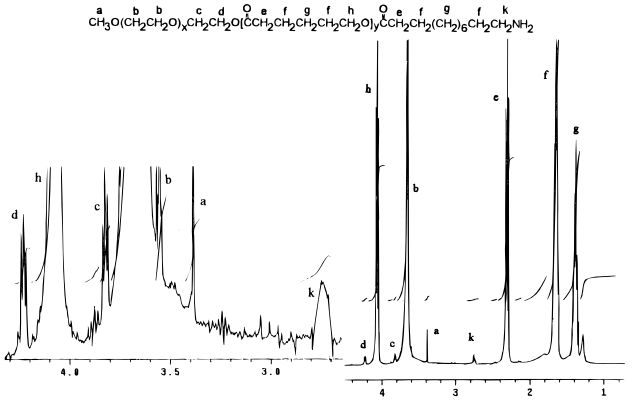


Figure 4. ^{1}H NMR spectra of amino-terminated MPEG−PCL ($DP_{MPEG} = 114$, $DP_{PCL} = 61$).

Synthesis of Azide-Terminated MPEG−PCL. Conversion of the bromo-terminated MPEG−PCL into an azide-terminated MPEG−PCL can be achieved quantitatively according to the common method based on sodium azide in DMF at 30 °C.[15,17] The ^{1}H NMR spectra of azide-terminated MPEG−PCL is shown in Figure 4, which clearly proves the existence of the azide (−CH_2N_3) due to the peak at 3.23 ppm (j) and the complete disappearance of the peak at 3.46 ppm (Figure 3, i).

Reduction of Azide-Terminated MPEG−PCL into Amino-Terminated MPEG−PCL. The reduction of azide-terminated MPEG−PCL into amino-terminated MPEG−PCL was carried out by catalytic transfer hydrogenation in the presence of ammonium formate

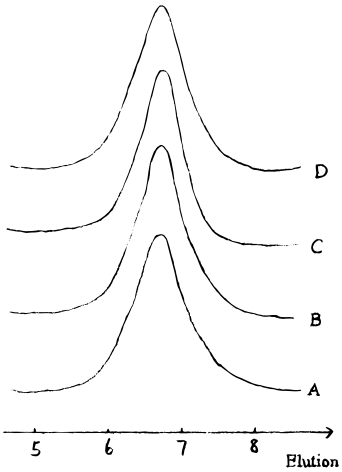
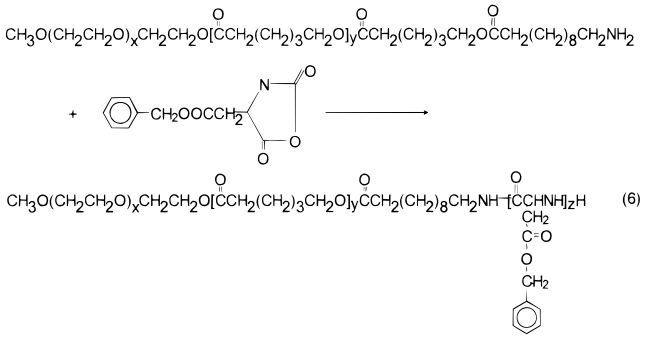


Figure 5. GPC traces of MPEG−PCL: (A) hydroxy-terminated (DP_{MPEG} = 114, DP_{PCL} = 62); (B) bromo-terminated (DP_{MPEG} = 114, DP_{PCL} = 60); (C) azide-terminated (DP_{MPEG} = 114, DP_{PCL} = 60); (D) amino-terminated (DP_{MPEG} = 114, DP_{PCL} = 61).

Scheme 2. Synthesis of MPEG−PCL−PBLA Block Copolymer



in DMF at 30 °C.[15,18] The experiment indicated that amino-terminated MPEG−PCL is synthesized successfully. The ^{1}H NMR spectrum of amino-terminated MPEG−PCL is shown in Figure 5. It can be seen from Figure 5 that the azide ($-CH_2N_3$) peak at 3.23 ppm (Figure 4, j) disappears completely, and a new peak at 2.79 ppm (k) is assigned to the methene protons of the $-CH_2NH_2$ end group.

GPC Traces of Hydroxy-, Bromo-, Azide-, and Amino-Terminated MPEG−PCL. The typical GPC traces of hydroxy-terminated MPEG−PCL, bromo-terminated MPEG−PCL, azide-terminated MPEG−PCL, and amino-terminated MPEG−PCL are shown in Figure 2. All the traces exhibit a factor so that the molecular characteristics of the polymeric backbone were kept unchanged. The molecular weights of hydroxy-terminated MPEG−PCL ranging from 6000 to 20000 have been successfully converted into amino-terminated MPEG−PCL through an original and effective method.

Application of Amino-Terminated MPEG−PCL. Homopolypeptides are generally synthesized by means of ring-opening polymerization of α-amino acid *N*-carboxyanhydrides (NCA).[14] Homopolypeptides by the NCA method generally form strong intrachain or interchain hydrogen bonds, and thus they are insoluble in almost all organic or inorganic solvents.[18] Actually, they have not been utilized so much for practical applications due to difficulty in handling, although they possess a structure related to that of proteins. It is worth recalling

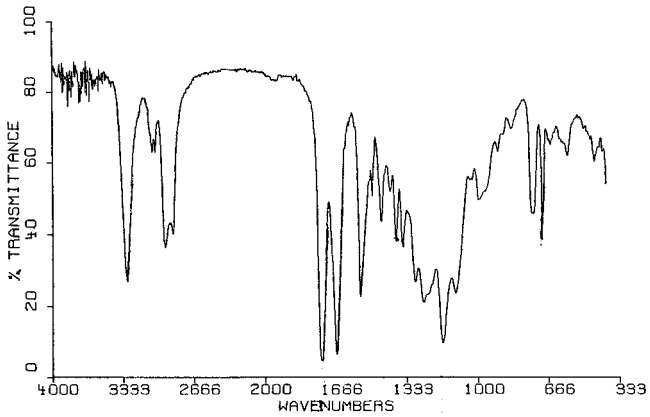
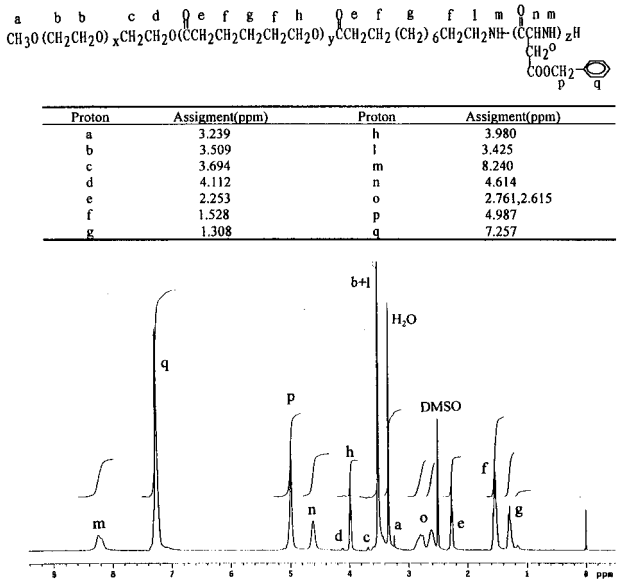


Figure 6. IR spectra of MPEG−PCL−PBLA (DP_{MPEG} = 114, DP_{PCL} = 25, DP_{PBLA} = 57).



Proton	Assigment(ppm)	Proton	Assigment(ppm)
a	3.239	h	3.980
b	3.509	l	3.425
c	3.694	m	8.240
d	4.112	n	4.614
e	2.253	o	2.761,2.615
f	1.528	p	4.987
g	1.308	q	7.257

Figure 7. ^{1}H NMR spectra of MPEG−PCL−PBLA (DP_{MPEG} = 114, DP_{PCL} = 25, DP_{PBLA} = 57).

that NCA can be polymerized by an aliphatic primary amine in such a way that the initiator is attached to the growing polypeptide chain. Combination of PEG−PCL with a polypeptide is expected to open the way to versatile original materials, such as biocompatible and biodegradable surfactants and hydrogels. Indeed, the rate of biodegradation and amphiphilicity of the related di- and triblock copolymers might be controlled by the nature and composition of each components. Amino-terminated MPEG−PCL is a desirable macromolecular initiator for the ring-opening polymerization of NCA.

In the present study, we synthesized the poly(ethylene glycol)-*co*-poly(ϵ-caprolactone)-*co*-poly(β-benzyl L-aspartic acid) (MPEG−PCL−PBLA) A−B−C block copolymer according to Scheme 2. The polymerization was carried out in a solvent mixture (1,4-dioxane/$CHCl_3$ = 3/2,v/v). Amino-terminated MPEG−PCL with a number-average molecular weight of 7800 (DP_{MPEG} = 114, DP_{PCL} = 25) was used in this study. The copolymerization product was recovered by precipitating with an excess of diethyl ether. The conversion of BLA−NCA is 89% and the degree of polymerization (DP) of PBLA is 57 (calculated from the ^{1}H NMR spectrum, Figure 7). The number-average molecular weight of MPEG−PCL−PBLA is 19000. The IR spectra of MPEG−PCL−PBLA is shown in Figure 6. Peaks at 1664 cm^{-1} (ν_{CO}) and 1551 cm^{-1}

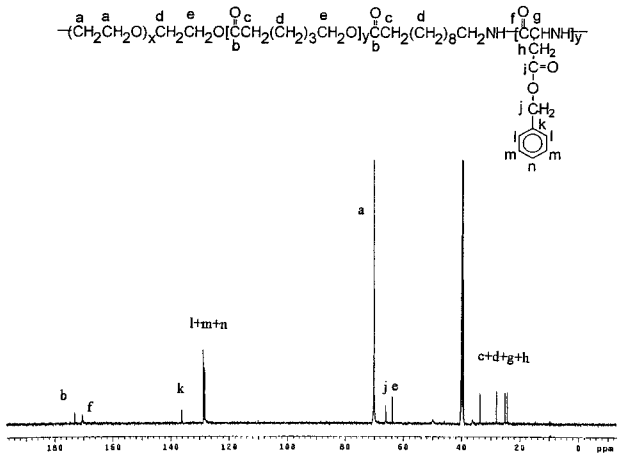


Figure 8. ^{13}C NMR spectra of MPEG−PCL−PBLA (DP_{MPEG} = 114, DP_{PCL} = 25, DP_{PBLA} = 57).

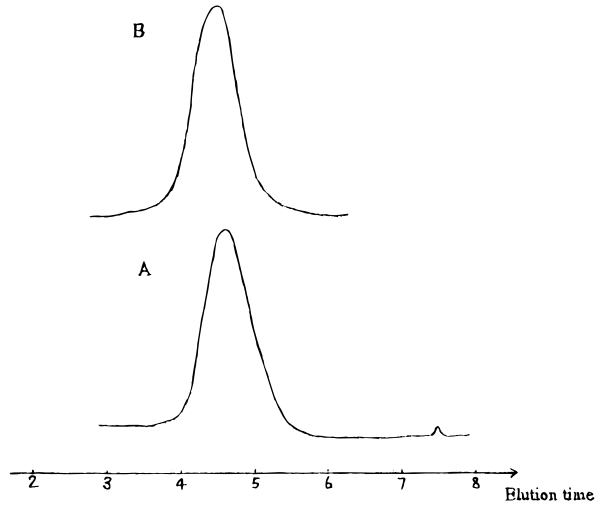


Figure 9. GPC traces of ABC triblock copolymer of MPEG−PCL−PBLA: (A) crude product, (B) purified product (DP_{MPEG} = 114, DP_{PCL} = 25, DP_{PBLA} = 57).

(ν_{CO-NH}) indicated the formation of the polypeptide block. The absorption at 699 and 745 cm^{-1} are characteristic of PBLA unit. Peak at 1735 cm^{-1} is due to the characteristic of both PCL and PBLA units. The absorption peaks at 1106 cm^{-1} belong to values characteristic of the MPEG unit.

The ^1H NMR spectra of the MPEG−PCL−PBLA block copolymer is shown in Figure 7. As the solvent is DMSO, the chemical shifts of every copolymerization unit have little differences compared with those in $CDCl_3$. Peaks at 7.26 ppm, 4.99 ppm, and 2.6−2.7, 2.62, and 8.24 ppm are assigned to protons of the PBLA unit. The peak at 3.51 ppm is assigned to a proton of the MPEG unit. Peaks at 1.2−1.6, 2.30, and 3.99 ppm are assigned to protons of the PCL unit. The ^{13}C NMR spectra of the MPEG−PCL−PBLA block copolymer is shown in Figure 8. Peaks at 24.4 ppm, 25.2 ppm, 28.1 ppm, and 33.6, 63.8, and 173 ppm are assigned to the PCL unit. The peak at 70.1 ppm is assigned to the MPEG unit. Peaks at 170.4, 136.1, and 128.3 ppm are assigned to the PBLA unit.

The GPC (Figure 9) measurements show a sharp, unimodal polydistribution which further indicates that the copolymerization proceeded completely and no homopolymerization occurred. The preliminary results reported in this paper show that primary amino-terminated MPEG−PCL is an effective macroinitiator for the ring-opening polymerization of amino acid *N*-carboxyanhydrides. After catalytic hydrogenation of the MPEG−PCL−PBLA A−B−C block copolymer, the MPEG−PCL−poly(aspartic acid) block copolymer can be prepared. Characterization and potentialities of these biocompatible and biodegradable multicomponent materials will be reported in the future.

Conclusion

This paper provided an original and well-controlled method for making bromo-terminated MPEG−PCL, which is a potential precursor to prepare primary amino-terminated MPEG−PCL. The conversion of hydroxy-terminated MPEG−PCL to amino-terminated MPEG−PCL is quantitative. The primary amino-terminated MPEG−PCL proved to be an effective macroinitiator for the ring-opening polymerization of amino acid *N*-carboxyanhydrides. The controllable copolymerization of amine-terminated MPEG−PCL with NCA offered the possibility to produce functional polymers with varying ratios of hydrophilic/hydrophobic chain segment and functional groups, and thus constituted a very attractive means to modulate the basic properties of each homopolymer.

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