Macromolecular Engineering of Polylactones and Polylactides. 9. Synthesis, Characterization, and Application of ω-Primary Amine Poly(ε-caprolactone)

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Received January 16, 1992; Revised Manuscript Received April 22, 1992

ABSTRACT: The synthesis and use of functional diethylaluminum alkoxides (Et_2AlORX) as initiators for the ring-opening polymerization of ε-caprolactone have been investigated as a possible strategy to prepare ω-primary amino poly(ε-caprolactone) (PCL). In a first approach, an initiator containing ethylphthalimide as the functional -RX group has been synthesized. That protected amino group has been successfully attached at the end of PCL chains. The conversion of the phthalimide end group into a primary amine has however failed, whatever the experimental conditions. In an alternative approach, an alkyl bromide has been considered as the functional group to be attached to PCL chains, via the appropriate initiator. The end functionalization was quantitative and the bromo end group converted into an azido group which was subsequently reduced to the expected primary amine. ω-primary amino PCL has proved to be an effective macroinitiator for the ring-opening polymerization of γ-benzylglutamate *N*-carboxy anhydride with the formation of a poly(caprolactone-*b*-peptide) diblock copolymer.

Introduction

Sustained drug release systems are widely investigated in view of improving the biological and pharmaceutical efficiency of drugs.[1,2] Cross-linked hydrophilic polymers, hydrogels, are systems of great interest for the release of biological macromolecules at a constant rate over long periods of time.[3,4] Small bioactive molecules are usually released from microparticles of biocompatible aliphatic polyesters, such as polylactide (PLA) and poly(ε-caprolactone) (PCL).[5] The production of these microparticles requires the use of surfactants, which should ideally be biocompatible and biodegradable.

The successful block polymerization of ε-caprolactone (ε-CL), or lactide, and amino acid *N*-carboxy anhydrides (NCA's) might be a major step toward the availability of biocompatible and biodegradable hydrogels and surfactants. Since the ring-opening polymerization of amino acid *N*-carboxy anhydride is known to be living when initiated by a primary amine,[6] the main target to be reached is the availability of ω-primary amine poly(ε-caprolactone) (PCL) or polylactides (PLA). In that respect, it has been reported recently that functional aluminum alkoxides, such as Et_2AlORX (where X is a functional group), are effective initiators for the living polymerization of ε-CL and lactides.[7,8] Moreover, α-hydroxy-ω-X functional alkoxy groups (-ORX) are actually attached to the growing polyester chains.[7,9] Although halogen atoms, tertiary amines, and double bonds (e.g. of the methacrylic type) have been successfully used as the X functional group, a primary amine failed to provide the expected amino-terminated polyester. Indeed, diethylaluminum 3-amino-1-propoxide led to the formation of α,ω-dihydroxy PCL.[10]

This paper aims at using functional diethylaluminum alkoxides Et_2AlORX, where -RX is (i) ethylphthalimide, i.e. a protected amino group, and (ii) alkyl bromide, i.e. a primary amine precursor via an azide function, in order to prepare ω-amino PCL.

Experimental Part

Materials. ε-CL (Janssen Chimica) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. Triethylaluminum (Fluka) was used without further purification and dissolved in dry toluene. Phosgene solution in toluene (1.93 M) and methylamine solution in water (40%) were purchased from Fluka and Janssen, respectively. 2-Bromoethanol (Aldrich) was repeatedly treated with saturated aqueous K_2CO_3, dried over phosphorus pentoxide, and freshly distilled under reduced pressure.

Solid Derivatives. Palladium on activated carbon (10 wt %), *N*-(hydroxyethyl)phthalimide (Fluka), 12-bromododecanol (Aldrich), sodium azide (Janssen), triphenylphosphine (Janssen), ammonium formate (Janssen), γ-benzylglutamate (Aldrich), and 4-(dimethylamino)pyridine (Janssen) were dried by three azeotropic distillations of toluene before use. Triethylamine (Janssen) and acetic anhydride (Aldrich) were dried over BaO and $CaCl_2$, respectively, for 1 week and distilled under reduced pressure. Toluene and tetrahydrofuran (THF) were dried by refluxing over calcium hydride and benzophenone Na complex, respectively. Dimethylformamide was dried over KOH for 1 day, stored over molecular sieves (4 Å), and distilled under reduced pressure just before use. Chloroform was successively dried over $CaCl_2$ and P_2O_5 and distilled under reduced pressure.

Preparation of Initiator. Diethylaluminum alkoxides were prepared by reaction of triethylaluminum with the appropriate alcohol. A 1.0-mmol aliquot of the alcohol of 10 mL of toluene was slowly added into a carefully flamed Pyrex flask equipped with a rubber septum, connected through an oil valve to a gas buret and containing an equimolar amount of $AlEt_3$ in 90 mL of toluene. The reaction proceeded under nitrogen and stirring at room temperature. When the emission of ethane stopped, the catalyst solution was kept under stirring at room temperature for an extra 1 h.

Polymerization Procedure. ε-CL polymerization was carried out under stirring in toluene in a flask previously flamed, purged with nitrogen, and kept at 25 °C for 10 h. The reaction was stopped by adding a 10-fold excess of 2 N HCl solution with respect to Al. Catalytic residues were removed by two successive extractions with an aqueous solution of EDTA and pure water, respectively.

Deprotection of the Phthalimide Group. ω-Phthalimide PCL (10 wt/v %) was converted into the parent amine in an ethanol:THF (3:2) mixture at 30 °C. A 100-fold molar excess of methylamine in water with respect to the phthalimide chain end group was used. After reaction times from 0.5 to 5 h, the polyester was recovered by precipitation in methanol.

Conversion of ω-Bromo PCL into ω-Amino PCL. A 5-fold molar excess of sodium azide with respect to ω-bromo PCL was used to convert quantitatively the halogen end group into an azide function. This reaction was achieved in dry DMF (10 wt/v % of PCL in DMF), at 30 °C, for 14 h. The polyester was recovered and purified by selective precipitation in methanol.

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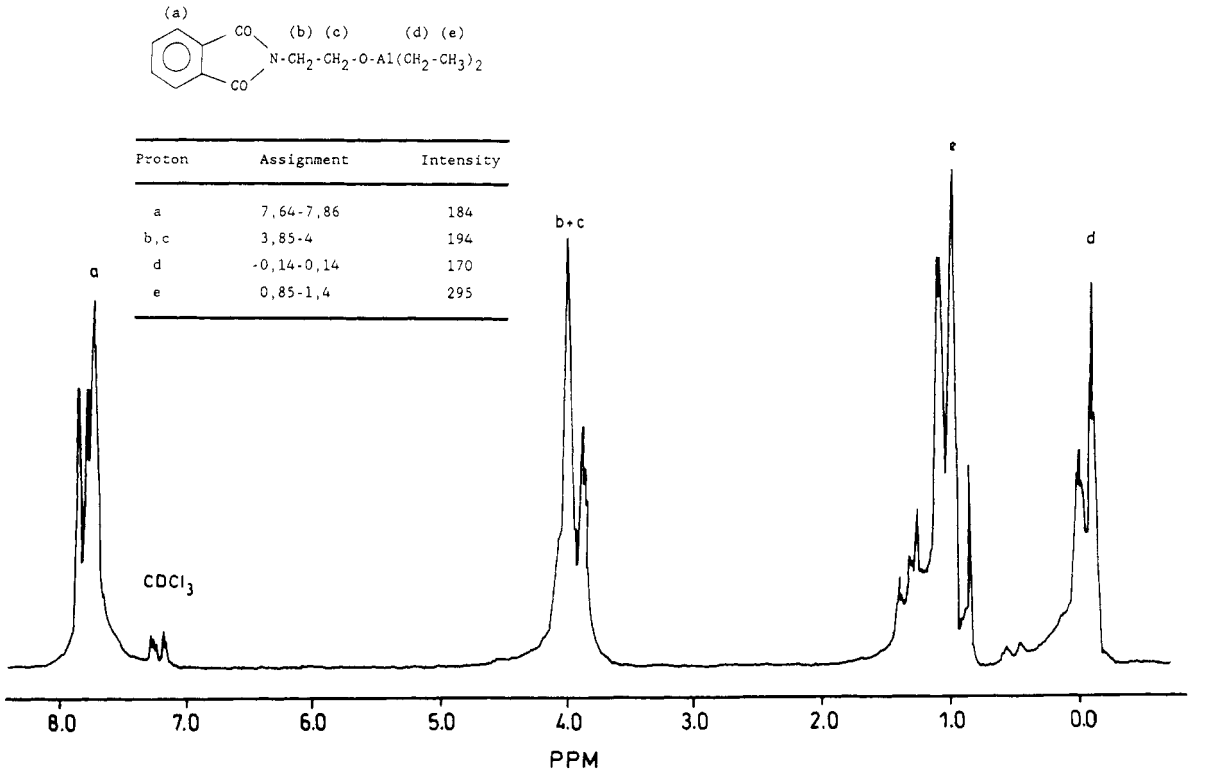


Figure 1. ^{1}H NMR spectrum of diethylaluminum (*N*-phthalimido)ethoxide (solvent: $CDCl_3$).

ω-Azido PCL (10 wt/v %) in THF was hydrolyzed by reaction with 5 equiv of triphenylphosphine and an equimolar amount of water with respect to the azido end groups, for 12 h at 25 °C. The solution was then filtered and the polymer recovered by precipitation in methanol.

ω-Azido PCL (10 wt/v %) was also hydrogenated in dry DMF by reaction with a 5-fold molar excess of ammonium formate and 10 wt % Pd supported on activated carbon. The reaction temperature was kept at 30 °C for at least 150 min. Palladium residues were recovered by filtration. The polyester was recovered by selective precipitation in methanol.

Esterification of PCL-OH. PCL-OH (10 wt/v %) was esterified by acetic anhydride (5 equiv) in dry THF, in the presence of triethylamine (5 equiv) and a catalytic amount of 4-(dimethylamino)pyridine (0.2 equiv), for 48 h at 50 °C. The polyester was purified by three successive precipitation–dissolution cycles (THF–methanol).

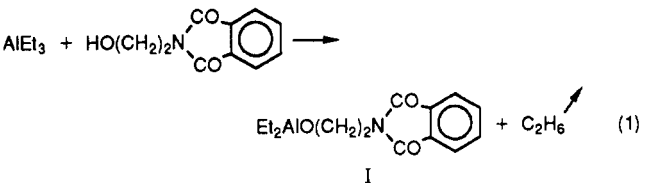
Copolymerization of γ-Benzylglutamate *N*-Carboxy Anhydride (BG-NCA). ω-Amino PCL was used as an initiator and previously dried by two azeotropic distillations of toluene and finally dissolved in $CHCl_3$. Copolymerization was carried out in dry $CHCl_3$ under nitrogen in a previously flamed glass reactor connected to an oil valve ([BG-NCA] = 0.15 M, [M]/[C] = 46). After a 1-h reaction time at 20 °C, the copolymer was recovered by precipitation in diethyl ether.

Polymer Characterization. ^{1}H NMR spectra were recorded with a Bruker AM 400 apparatus at 25 °C. Size exclusion chromatography was achieved in THF by using a Hewlett Packard 1090 liquid chromatograph equipped with a Hewlett Packard 1037 A refractometer index detector. Columns were calibrated with polystyrene standards. Amines were titrated with $HClO_4$ (2×10^{-2} N) in a toluene–methanol (9:1) mixture (potentiometric titration). IR spectra were recorded by using a Perkin-Elmer 160 FTIR.

Results and Discussion

Since the initiation of ε-CL polymerization by diethylaluminum aminoalkoxide failed to provide the expected ω-amino PCL,[10] two potential indirect pathways to that functional polyester have been considered, i.e. protection of the amino group of the initiator and substitution of that amino group by a precursor which would not interfere with the polymerization process.

Diethylaluminum (*N*-phthalimido)ethoxide as an Initiator for ε-CL Polymerization. That initiator has been prepared by the equimolar reaction of $AlEt_3$ and *N*-(hydroxyethyl)phthalimide in toluene at 25 °C (eq 1).

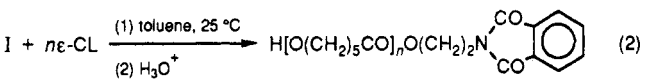


(1)

I

In the limits of experimental error, the expected volume of ethane was emitted and structure I has been ascertained by ^{1}H NMR spectroscopy (Figure 1).

Similarly to the previously investigated functional aluminum alkoxides,[7,8] compound I has proved to be very efficient for the ring-opening polymerization of ε-CL. For instance, ^{1}H NMR analysis of the recovered PCL clearly supports that the chain end groups are a hydroxyl and an *N*-phthalimide function, respectively (Figure 2). That observation is in agreement with the accepted mechanism for ε-CL polymerization in the presence of an aluminum alkoxide, i.e. insertion of ε-CL into the Al–O bond of the initiator through the selective cleavage of the acyl–oxygen bond of the monomer (eq 2).[11,12]



(2)

Furthermore, the linear dependence of the average number molecular weight at complete conversion ($\bar{M}_{n\ exp}$) of the monomer over initiator molar ratio is evidence for a living polymerization (Figure 3). Finally, the chain length distribution is narrow ($\bar{M}_w/\bar{M}_n = 1.1$) in the investigated range of molecular weight ($\overline{DP} \leq 100$).

Although hydrazine is a reagent commonly used to convert phthalimide into primary amine, its nucleophilicity is detrimental to the integrity of PCL chains. Hy-

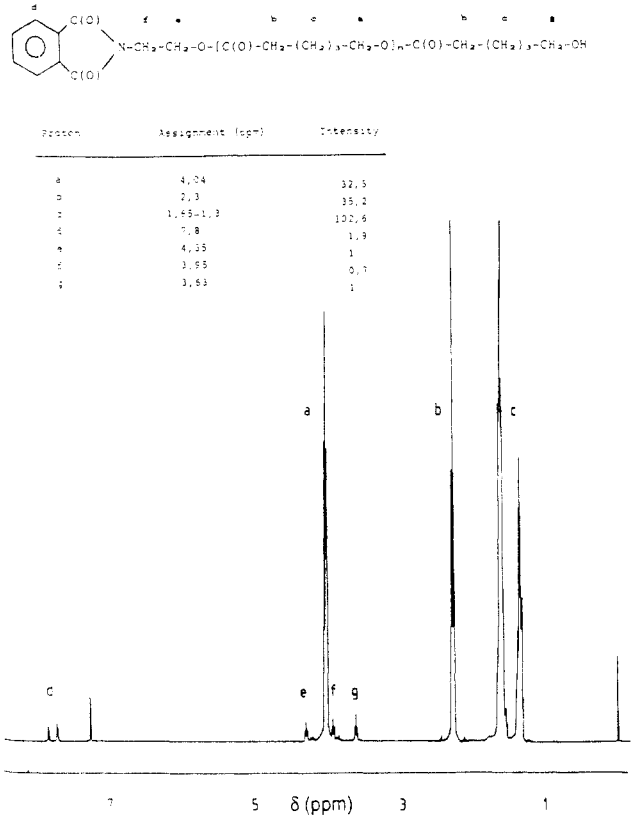


Figure 2. ^{1}H NMR spectrum of PCL as recovered after hydrolysis of the living polymer initiated by aluminum alkoxide (I) (solvent $CDCl_3$; reference TMS).

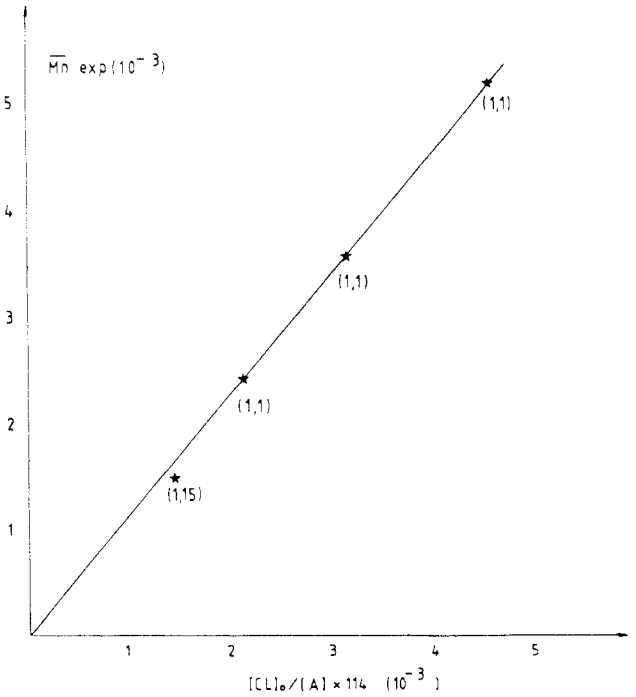


Figure 3. Dependence of $\bar{M}_{n\,exp}$ on [monomer]/[initiator] molar ratio for the polymerization of ϵ-CL initiated by aluminum alkoxide (I) in toluene at 25 °C ($[\epsilon\text{-CL}]_0$ = 1.0 mol L^{-1}).

drazine can however be substituted by an aqueous solution of methylamine at room temperature.[13] PCL (10 wt/v %) has proved to be stable when added with a 100-fold molar excess of methylamine in a 3:2 THF–ethanol mixture, at 30 °C, for 5 h. These experimental conditions have thus been selected for the deprotection of α-hydroxy-ω-ethylphthalimide PCL. As a result of that treatment some disappointing observations have been reported. Indeed, the amine functionality as determined by nonaqueous ti-

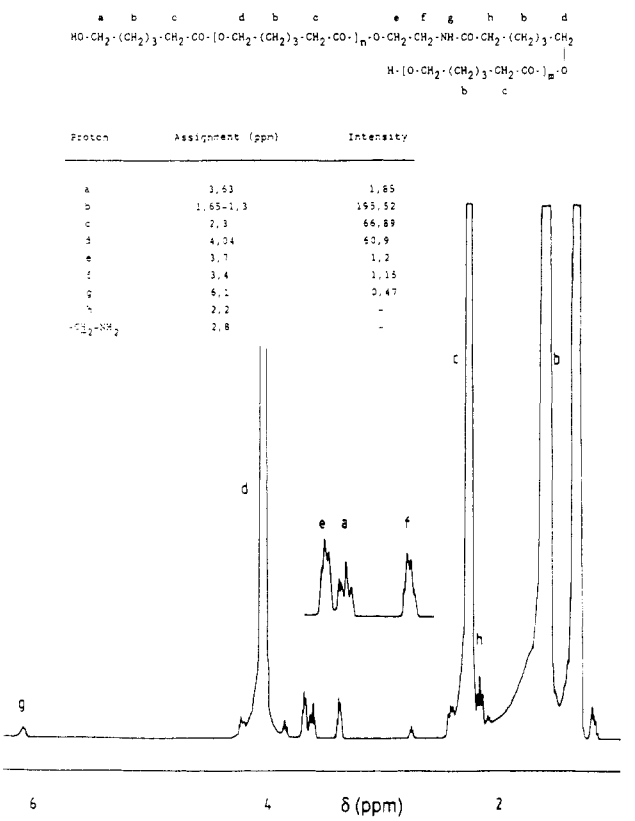
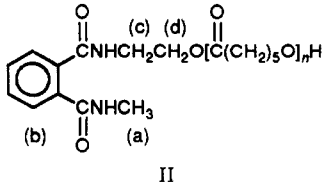


Figure 4. ^{1}H NMR spectrum of deprotected α-hydroxy-ω-ethylphthalimide PCL. The reaction was with methylamine for 90 min, at 30 °C, in a 3:2 ethanol:THF mixture (solvent:$CDCl_3$).

Table I
Number Average Molecular Weight ($\bar{M}_n$) and Polydispersity ($\bar{M}_w/\bar{M}_n$) of PCL When Reacted with Methylamine in Ethanol–THF (3:2) at 30 °C

reaction time (min)	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$
0	4200	1.05
60	4200	1.40
90	4200	1.45

tration of the amino groups has been found to be as small as 5% of the theoretical value whatever the reaction time (≤5 h). Moreover, the ^{1}H NMR spectrum of PCL chains treated for 90 min and purified by repeated precipitations shows a signal of a weak intensity at 2.8 ppm, which can be assigned to an aminomethylene group. The complete analysis of the ^{1}H NMR spectrum (Figure 4) evidences the presence of mainly α,ω-dihydroxy PCL containing an amide function inside the chain. Finally, depending on reaction time, formation of an intermediate compound was noted and assigned to structure II on the basis of ^{1}H NMR spectroscopy.



protons	δ (ppm)
a	2.95
b	7.65–7.45
c	3.2
d	3.7

II

Intermediate II clearly results from the nucleophilic attack of methylamine on the phthalimide end group (eq 3). Its relative importance decreases as the reaction time increases and it completely disappears after 90 min.

Although eq 3 predicts the formation of the expected α-hydroxy-ω-amino PCL, an amide-containing α,ω-dihydroxy PCL is actually recovered. In order to account for that result, it has to be assumed that a reaction occurs

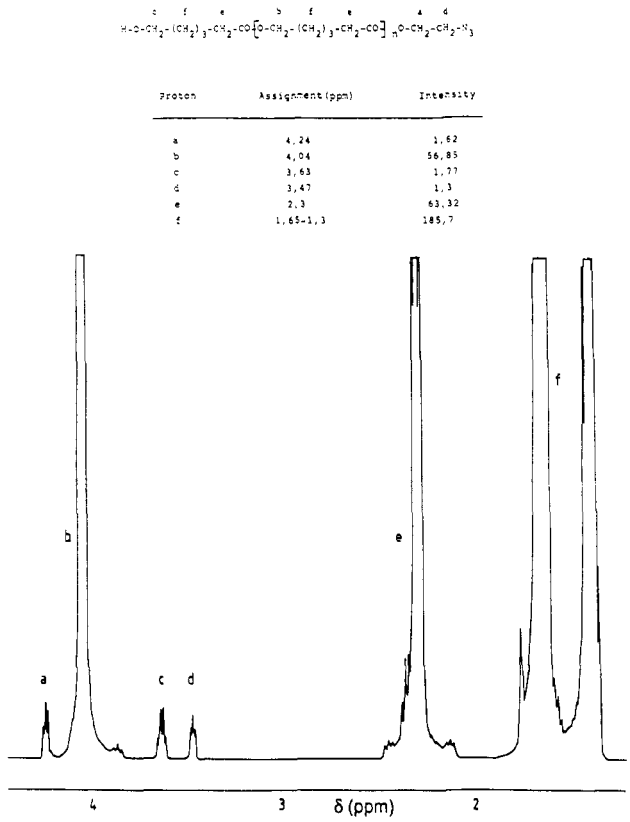
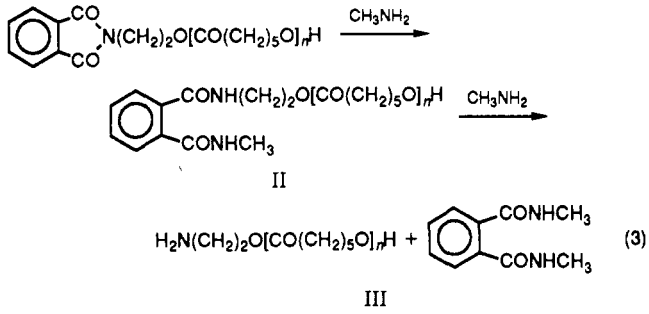
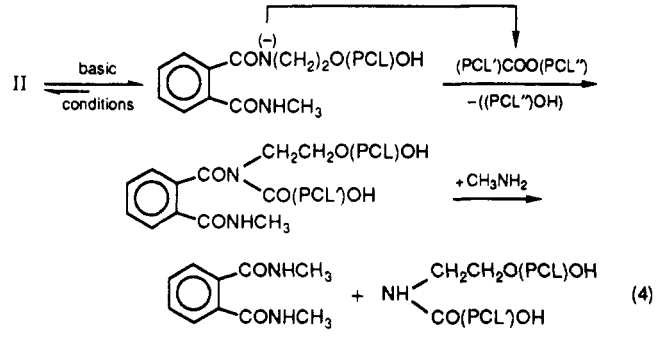


Figure 5. ^{1}H NMR spectrum of α-hydroxy-ω-ethyl bromide PCL as recovered after reaction with sodium azide (solvent: $CDCl_3$).



between an aromatic amide of the intermediate compound II and an ester unit of the PCL chains (eq 4).



That hypothesis is supported by the well-known nucleophilicity of amides and their reactivity toward the carbonyl group of esters under basic conditions.[14,15] The size exclusion chromatogram of PCL changes versus the deprotection time in such a way that the reaction described by eq 4 is an intermolecular rather than an intramolecular process. Indeed, no formation of a cyclic oligomer is observed, whereas the number average molecular weight ($\bar{M}_n$) remains unchanged in contrast to the polydispersity ($\bar{M}_w/\bar{M}_n$) which increases together with reaction time (Table I).

A modification in the molar excess of methylamine does not improve the experimental content of amino end groups. The use of an *N*-phthalimide group as a protected amine is thus unsuitable in order to prepare ω-amino PCL.

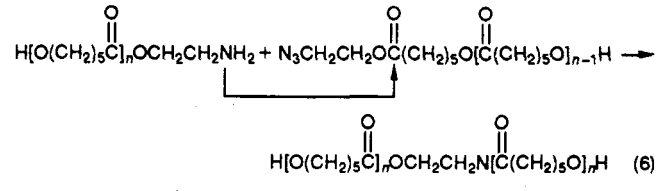
An Alkyl Bromide as a Potential Precursor of a Primary Amine End Group. Instead of initiating the ϵ-CL polymerization with an aluminum alkoxide containing a protected amine, ω-amino PCL might be prepared from an initiator that contains a precursor of the primary amine. An alkyl bromide is a potential candidate since it can be converted into a primary amine through an azidoalkyl compound, as shown by eq 5.

$$RBr \xrightarrow{NaN_3} RN_3 \xrightarrow[-N_2]{\text{reduction}} RNH_2 \qquad (5)$$

Diethylaluminum 2-bromoethoxide has already been prepared and successfully used in the initiation of ϵ-CL polymerization, which has proved to be living.[7]

Conversion of the bromo end group into an azido function has been achieved according to the common method based on sodium azide in dry DMF at 30 °C.[16] After a 14-h reaction time, the expected ω-azido PCL has been quantitatively isolated and purified. ^{1}H NMR analysis unambiguously shows the presence of the azide ($-CH_2N_3$) at a chemical shift of 3.47 ppm and the complete disappearance of the alkyl bromide [$\delta(-CH_2Br)$ = 3.52 ppm] (Figure 5). This is confirmed by the observation of an additional IR absorption at 2105 cm^{-1} compared to the bromoethyl-terminated precursor, which is characteristic of the azido group (Figure 6). It is worth noting that the molecular characteristics of the polymeric backbone are kept unmodified (SEC analysis).

The azido end group can be reduced into a primary amine by either hydrolysis in the presence of triphenylphosphine in THF at 25 °C[17,18] or catalytic transfer hydrogenation (CTH) in the presence of ammonium formate in dry DMF at 30 °C.[19] Whichever method employed the integrity of PCL is maintained and the azido group completely disappears, but no amino group can be detected by IR and ^{1}H NMR analysis (Figure 6 and 7). In fact, both NMR signals at $\delta(-CH_2C(O)NH-)$ = 2.21 ppm and $\delta(-C(O)NHCH_2-)$ = 3.40 ppm and the IR band at 1540 cm^{-1} (NH amide) argue for the presence of an amide inside the PCL chains. That amide might result from the nucleophilic attack of an ester subunit of PCL by the amine end group as soon as it is formed. However, SEC analysis of the main reaction product shows a 2-fold increase in PCL $\bar{M}_n$ (from 4300 to 8600) and the constancy of $\bar{M}_w/\bar{M}_n$. Accordingly, a nucleophilic attack by the nascent amino group should occur on the ester in the β-position of the azido end group of a second chain (eq 6). That specific



attack is more likely promoted by the activation of the β-methylene ester by the azido group, as can be inferred from ^{1}H NMR chemical shifts: $\delta(-C(O)OCH_2CH_2N_3)$ = 4.24 ppm compared to $\delta((PCL)C(O)OCH_2(PCL))$ = 4.06 ppm.

If that hypothesis is correct, the nucleophilic attack of the amine should be prevented from occurring by increasing the length of the original alkyl bromide to such an extent that the azide is no longer able to activate the

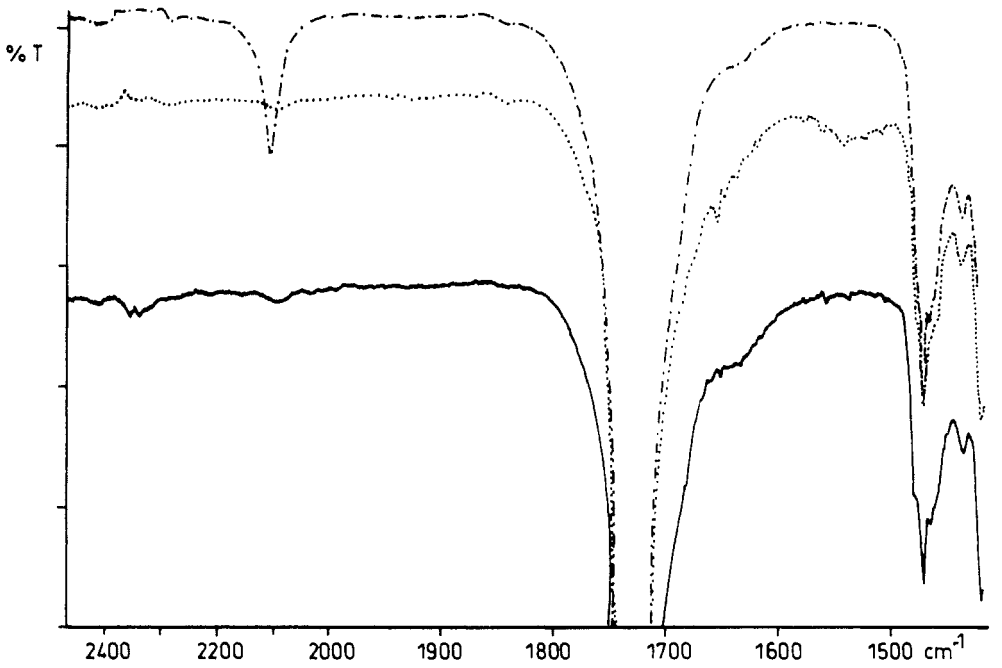


Figure 6. Cumulative IR spectrum of bromoethyl PCL, azidoethyl PCL and the reduction product of azidoethyl PCL: (—) bromoethyl PCL; (– · –) azidoethyl PCL ($\nu(N_3)$ = 2105 cm^{-1}); (···) PCL reduced (δ(NH amide) = 1540 cm^{-1}).

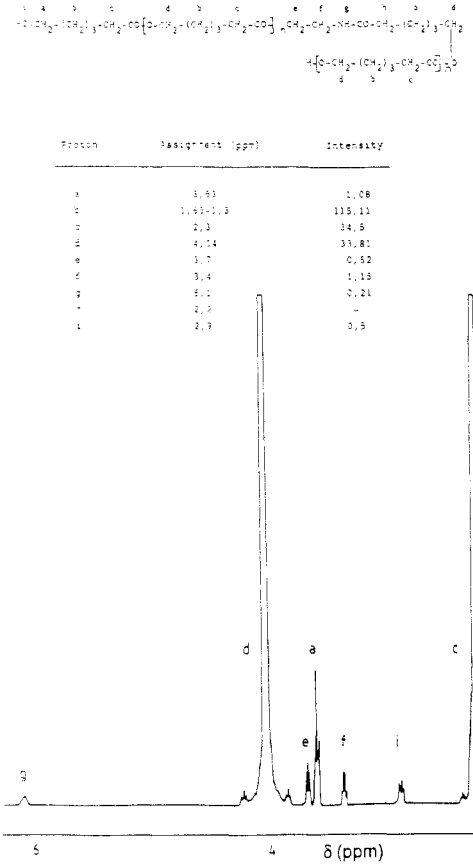


Figure 7. ^{1}H NMR spectrum of α-hydroxy-ω-azido PCL after reduction by CTH (solvent: $CDCl_3$).

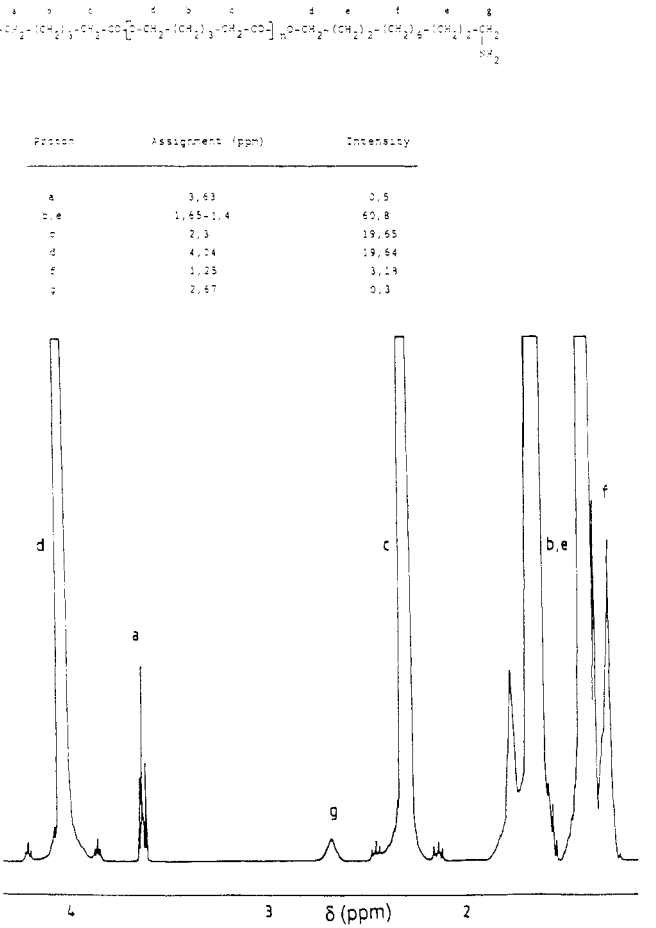


Figure 8. ^{1}H NMR spectrum of ω-primary amino PCL synthesized according to eq 7 (solvent: $CDCl_3$).

next ester group. Purposely, diethylaluminum 12-bromo-1-dodecyl oxide has been prepared and used as an initiator for the synthesis of α-hydroxy-ω-amino PCL, as schematized by eq 7.

As illustrated by Figure 8, ^{1}H NMR analysis shows indeed that a primary amino group has been attached to the end of the PCL chains [$\delta(-CH_2NH_2)$ = 2.67 ppm]. According to the intensity of protons a and g, there are as many hydroxy as amino end groups. IR spectroscopy is also in agreement with the formation of a primary amino end group (Figure 9).

The nonaqueous titration leads to the quantitative amino functionalization of one chain end.

The set of reactions described by eq 7 is thus an original and effective strategy in preparing α-hydroxy-ω-amino PCL with a predictable molecular weight and the ability of initiating the ring-opening polymerization of NCA's.

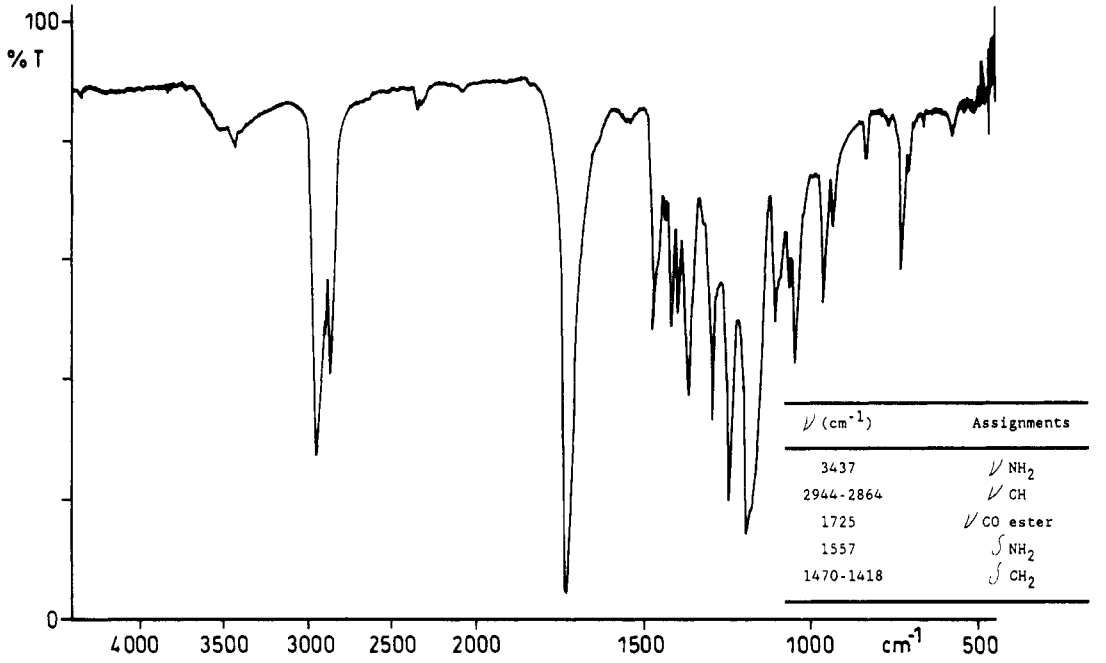
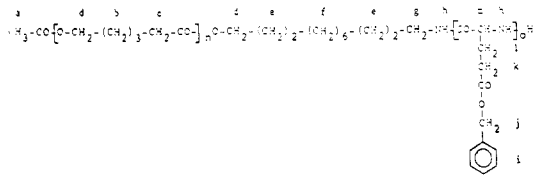


Figure 9. IR spectrum of ω-aminododecanyl PCL.



Proton	Assignment (ppm)	Intensity
h	8,3	13,34
i	7,25	170,54
j	5,04	61,41
d,m	4,05	112,75
a,c,k	2-3	213,2
b,e,l	1,9-1,3	285,91
f	1,26	19,86
g	3,46	1,32

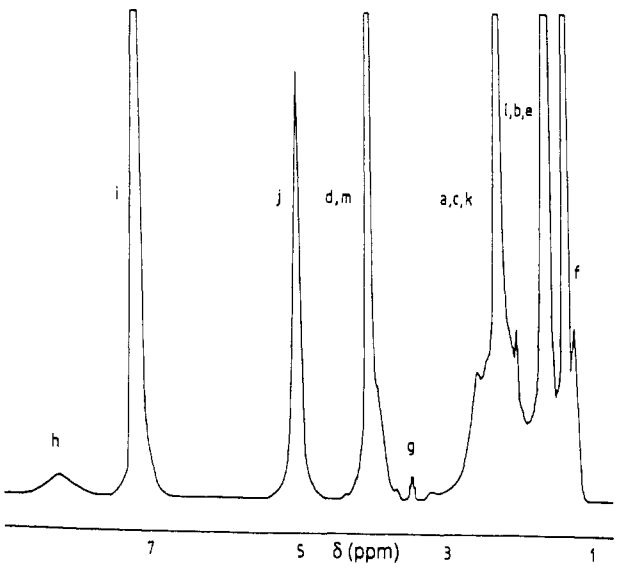
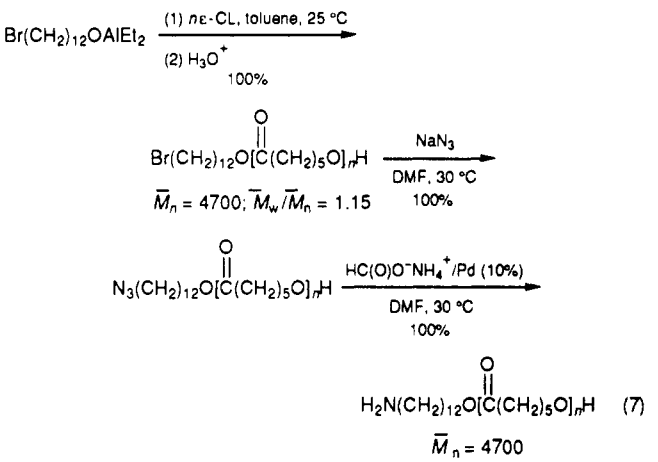


Figure 10. ^{1}H NMR spectrum of the copolymer resulting from the polymerization of BG-NCA initiated with a α-acetyl-ω-amino PCL.

Block Copolymerization of ε-CL and BG-NCA. *N*-Carboxy anhydrides (NCA's) are known to be polymerized by primary amines in such a way that the initiation is attached to the growing chain and the propagation is living.[6] ω-Amino PCL is thus a potential macroinitiator for the γ-benzylglutamate NCA (BG-NCA), that opens



the way to poly(ε-CL-*b*-peptide) copolymers. BG-NCA has the advantage of being synthesized within a very high yield (≥95%) by a direct phosgenation of the benzyl ester of the parent amino acid.[20]

Furthermore, the poly(benzylglutamate) can be easily hydrogenated with the formation of poly(glutamic acid), i.e. a hydrophilic polypeptide. Poly(ε-CL-*b*-glutamic acid) is thus a potential surfactant, whereas poly(ε-CL-*b*-glutamic acid–*b*-ε-CL) might be swollen by water and give rise to a hydrogel.

Before it can initiate the BG-NCA polymerization, the hydroxyl end group of α-hydroxy-ω-amino PCL has to be protected in order to avoid an additional (and noncontrolled) nucleophilic attack of the monomer. It is actually the hydroxyl end group of α-hydroxy-ω-bromo PCL which has been protected by a quantitative reaction with acetic anhydride under basic conditions. Of course, the resulting acetate end group is not expected to perturb the derivatization of the amine from the alkyl bromide end group.

Copolymerization of BG-NCA has been initiated by a short length of α-acetyl-ω-amino PCL ($\bar{M}_n$ = 5700) in dry chloroform at 25 °C for 1 h. The copolymerization product has been precipitated into diethyl ether, recovered within a ca. 90% yield and analyzed by ^{1}H NMR spectroscopy (Figure 10). The relative intensities of the aromatic protons (i) and protons (d + m) at 4.05 ppm allow the

molecular weight of the polypeptide block to be estimated at 9200, which is in close agreement with the theoretical $\bar{M}_n$ (10^4). The most decisive observation in favor of the block copolymerization is certainly the signal at 3.46 ppm (protons g; see Figure 10), which is characteristic of an amide linkage between PCL and polypeptide components. Moreover, the intensity of the *N*-amide methylene protons ($I(H_g) = 1.32$) compared to the intensity of the benzyl protons ($I(H_i) = 2.5\overline{DP}_{PP}I(H_g) \rightarrow I(H_g) = 1.6$) and the PCL protons ($I(H_{d,m}) = (\overline{DP}_{PCL} + \overline{DP}_{PP}/2)I(H_g) \rightarrow I(H_g) = 1.55$), respectively, is in favor of the blocky structure of the copolymer and precludes formation of homopolymers, within the limits of the NMR experimental error.

Conclusion

This paper provides an original and highly controlled pathway to ω-primary amino PCL. Although conversion of an alkyl bromide into the related primary amine is required, the functionalization appears to be quantitative within the limits of experimental error. The NH_2-terminated PCL is actually an effective macroinitiator for the ring-opening polymerization of NCA's with formation of a diblock copolymer. Since that diblock copolymer bears a primary amine at the end of the polypeptide component, a coupling reaction could lead to poly(CL-*b*-peptide-*b*-CL) triblock molecules. Synthesis and characterization of these potentially biocompatible and biodegradable multicomponent materials will be extensively reported in the near future.

Acknowledgment. We are indebted to IRSIA for a fellowship to Ph. Degée and Ph. Dubois, respectively, and the "Services de la Programmation de la Politique Scientifique" for financial support.

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Registry No. I, 142067-38-7; II (SRU), 142067-41-2; (I)(ε-CL), 142102-23-6; (PCL)(BG) (block copolymer), 142067-40-1; $HO((CH_2)_5COO)_nCONH(CH_2)_2(OCO(CH_2)_5)_nOH$, 142067-42-3; $Br(CH_2)_{12}OAlEt_2$, 142067-39-8; $Br(CH_2)_{12}(OCO(CH_2)_5)_nOH$, 142067-43-4; $N_3(CH_2)_{12}(OCO(CH_2)_5)_nOH$, 142067-44-5; $H_2N(CH_2)_{12}(OCO(CH_2)_5)_nOH$, 142067-45-6.