Macromolecular Engineering of Polylactones and Polylactides. XVI. On the Way to the Synthesis of ω-Aliphatic Primary Amine Poly(ε-caprolactone) and Polylactides

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SYNOPSIS

Since bromides are well-known precursors of primary amines, diethylaluminum 12-bromo-1-dodecyl oxide has been prepared and used as an initiator for the ring-opening polymerization of ε-caprolactone and L-lactide. Under strictly controlled conditions, the end-functionalization of the polyesters is quantitative and the bromo end-group is easily converted into an azide group whatever the polymeric backbone. The subsequent reduction of the azide into the expected primary amine has been investigated by catalytic transfer hydrogenation (CTH) in DMF and by hydrolysis in the presence of triphenylphosphine in THF, respectively. The hydrolysis reaction ($P\phi_3/H_2O$) is perturbed by a coupling reaction, which involves a protonated secondary amine and leads to a twofold increase in the polyester molecular weight. The CTH method gives rise to the expected ω-NH_2 poly(ε-caprolactone), in contrast to polylactide which seems to be unstable toward the nascent amine end group. Whatever the polarity of the medium (DMF or THF), aminolysis of polylactides is observed to occur and leads to the formation of an internal amide. © 1994 John Wiley & Sons, Inc.

Keywords: polycaprolactone • polylactide • ring-opening polymerization • biocompatible • co-aminopolyester

INTRODUCTION

Polymeric materials are increasingly used in a variety of medical and surgical applications, such as biomaterials and therapeutic systems.[1,2] Biodegradable polymers are of particular interest as sutures, implants, and drugs delivery systems.[3,4] Some aliphatic polyesters, e.g., polylactides (PLA) and poly(ε-caprolactone) (PCL), are widely recognized for low toxicity and hydrolytic and enzymatic biodegradability; they have accordingly potential in the controlled release of biological molecules.[4-6]
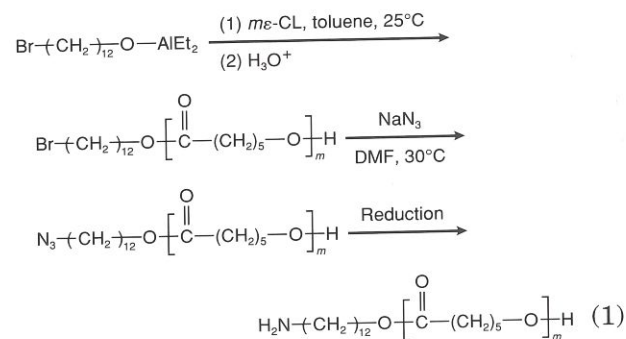
Combination of these polyesters to a polypeptide is expected to open the way to versatile original materials, such as biocompatible and biodegradable surfactants and hydrogels. Indeed, the rate of biodegradation and amphilicity of the related di- and tri-block copolymers might be controlled by the nature and composition of the two components. The ring-opening polymerization of amino acid-N-carboxy-anhydrides (NCA),[7] ε-caprolactone (ε-CL),[8] and lactides (D, L, or L-LA)[9] is nowadays under a tight control, so that the molecular characteristics and the end-functionalization of the related polypeptides and polyesters can be largely designed. It is worth recalling that NCAs can be polymerized by an aliphatic primary amine in such a way that the initiator is attached to the growing polypeptide chain and the propagation is living.[7] The availability of ω-primary amine polyesters (ω-NH_2PCL or ω-NH_2PLA), is thus a key target for the synthesis of poly(ester-b-peptide) copolymers.

In this respect, it has been recently reported that functional aluminum alkoxides, such as Et_2AlORX

(where X is a functional group), are effective initiators for the living polymerization of ε-caprolactone (ε-CL) and lactides, with formation of α-hydroxy, ω-X chains.[8-10] Although halogen atoms, tertiary amines, and double bonds (e.g., of the methacrylic type) have been successfully used as the functional group, a primary amine has failed to provide the expected amine-terminated polyesters. Indeed, diethylaluminum 3-amino, 1-propoxide has led to the formation of α,ω-hydroxy PCL.[11,12] Several alternative pathways have been considered, based either on the initiation step by an Al alkoxide bearing a protected primary amine[13] or on derivatization reactions of the hydroxy end-group.[14] At the time being, the most promising strategy is the use of an alkylbromide as the functional group of the alkyl Al alkoxide initiator. Conversion of the bromide end-group of PCL into an azide group, and its subsequent quantitative reduction leads to the expected ω-NH$_2$PCL [eq. (1)]:[15]

$$Br\text{+}CH_2\text{)}_{12}\text{O}\text{—}AlEt_2 \xrightarrow[\text{(2) }H_3O^+]{\text{(1) }m\varepsilon\text{-CL, toluene, 25°C}}$$

$$Br\text{+}CH_2\text{)}_{12}O\text{+}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}(CH_2)_5\text{—}O\text{]}_m H \xrightarrow[\text{DMF, 30°C}]{NaN_3}$$

$$N_3\text{+}CH_2\text{)}_{12}O\text{+}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}(CH_2)_5\text{—}O\text{]}_m H \xrightarrow{\text{Reduction}}$$

$$H_2N\text{+}CH_2\text{)}_{12}O\text{+}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}(CH_2)_5\text{—}O\text{]}_m H \quad (1)$$
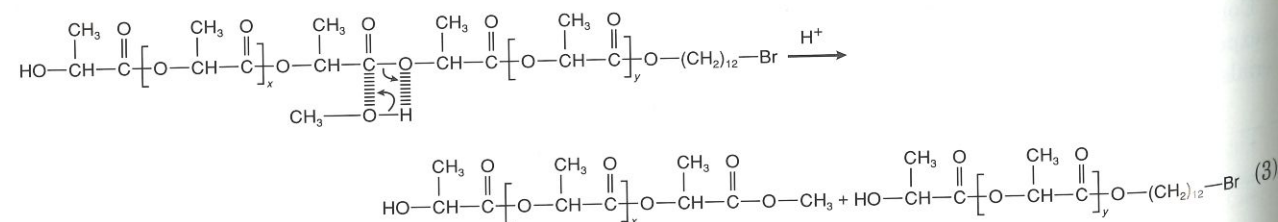
This article aims at extrapolating this route to the synthesis of ω-primary amine polylactide. An understanding of the substitution and reduction mechanisms and their effect on the length of the polyester chains will also be widely discussed.
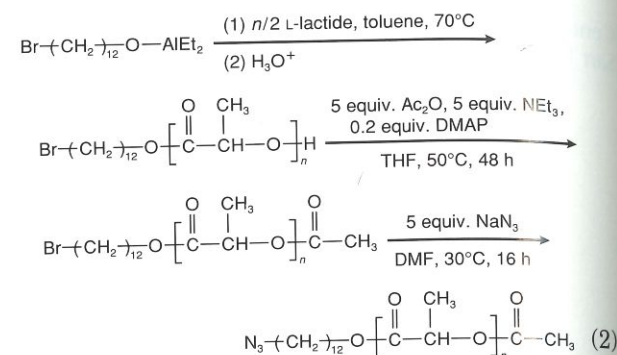
RESULTS

Synthesis of ω-Azido Polylactide (PLA)

The route previously described by Degee et al.[13] for the synthesis of ω-primary amine poly(ε-caprolac-tone) is schematized by eq. (1). The accordingly formed α-hydroxy-ω-amine PCL has been successfully used as a macroinitiator for the NCA polymerization. The hydroxyl end-group must however be protected before initiation, to avoid an additional and noncontrolled nucleophilic attack of the co-monomer.[15]

In an attempt to extent the synthesis of ω-amine PCL to polylactides, the reaction pathway summarized in eq. (2) has been followed:

$$Br\text{+}CH_2\text{)}_{12}\text{O}\text{—}AlEt_2 \xrightarrow[\text{(2) }H_3O^+]{\text{(1) }n/2 \text{ L-lactide, toluene, 70°C}}$$

$$Br\text{+}CH_2\text{)}_{12}O\text{+}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}\underset{CH_3}{CH}\text{—}O\text{]}_n H \xrightarrow[\text{THF, 50°C, 48 h}]{\text{5 equiv. Ac}_2\text{O, 5 equiv. NEt}_3,\ 0.2 \text{ equiv. DMAP}}$$

$$Br\text{+}CH_2\text{)}_{12}O\text{+}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}\underset{CH_3}{CH}\text{—}O\text{]}_n\overset{\overset{\displaystyle O}{\|}}{C}\text{—}CH_3 \xrightarrow[\text{DMF, 30°C, 16 h}]{\text{5 equiv. NaN}_3}$$

$$N_3\text{+}CH_2\text{)}_{12}O\text{+}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}\underset{CH_3}{CH}\text{—}O\text{]}_n\overset{\overset{\displaystyle O}{\|}}{C}\text{—}CH_3 \quad (2)$$

The reaction product of each step has been analyzed by ^{1}H-NMR, which shows an unexpected signal (H$_m$; Fig. 1) at $\partial = 3.73$ ppm, characteristic of a methyl ester proton [$-$O$-$C(O)$-$C$\underline{H}_3$].[16] Moreover, the intensity of this signal increases from one step to the next one as confirmed by Figure 1.

To identify the side reaction responsible for the formation of a methyl ester end-group, the effect of several experimental parameters has been investigated. The intensity of the methyl ester signal is observed to increase when the lactide is polymerized in THF instead of toluene. On completion of the monomer conversion, the active aluminum alkoxide end-group is currently hydrolyzed by addition of chlorhydric acid. When the concentration of HCl is decreased from $2N$ to $0.1N$, the side reaction does not occur anymore. Expectedly, the use of heptane as the precipitation solvent rather than methanol is the way for definitely avoiding the side reaction, which is obviously a methanolysis reaction of the polylactide chains as shown by eq. (3):
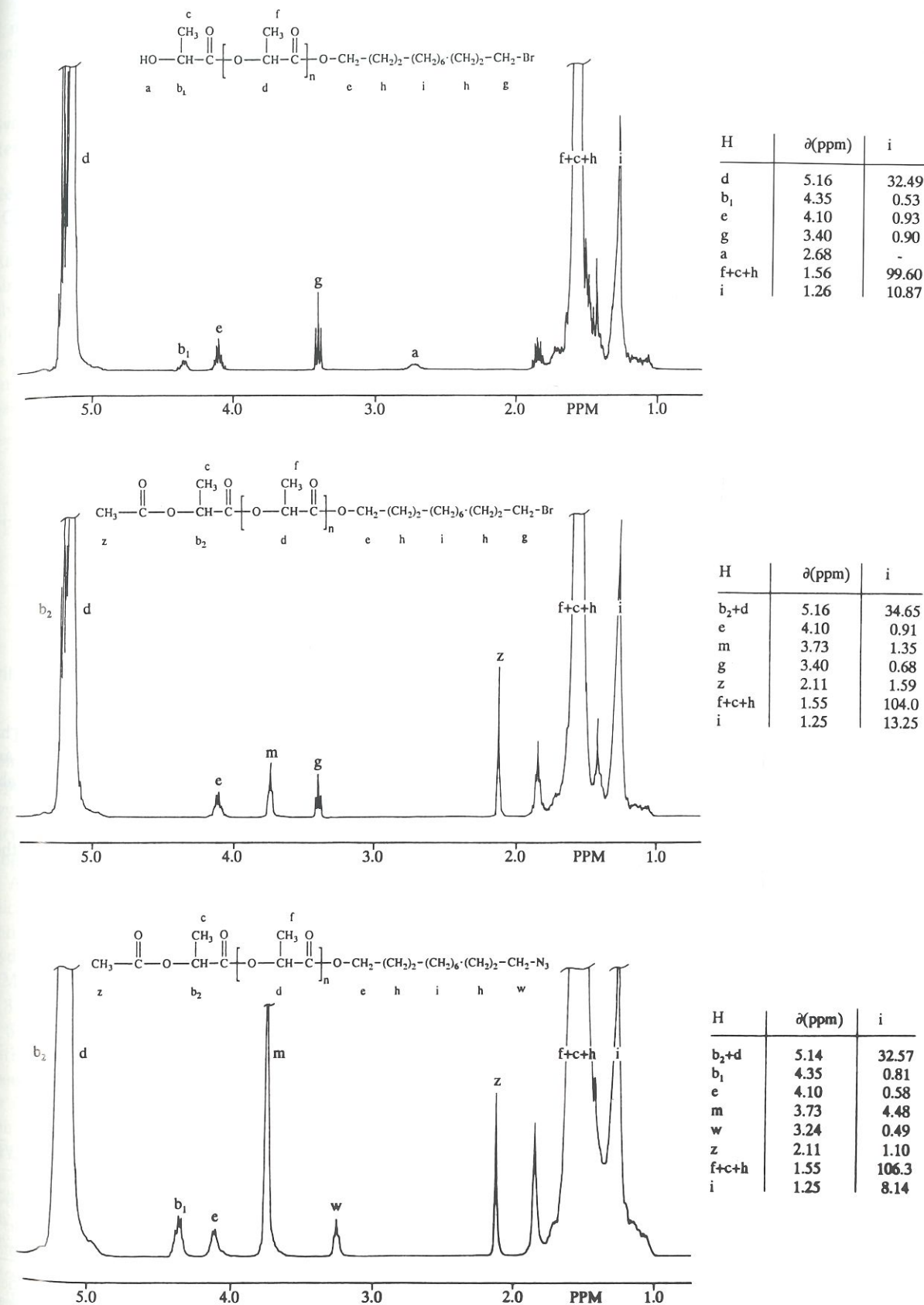
$$HO\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{+}O\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{]}_x O\text{—}\underset{\underset{\displaystyle O\text{—}H}{CH_3}}{\overset{\displaystyle CH_3}{C}}\text{—}O\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{+}O\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{]}_y O\text{—}(CH_2)_{12}\text{—}Br \xrightarrow{H^+}$$

$$HO\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{+}O\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{]}_x O\text{—}CH_3 + HO\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{+}O\text{—}\underset{CH_3}{CH}\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{]}_y O\text{—}(CH_2)_{12}\text{—}Br \quad (3)$$

H	∂(ppm)	i
d	5.16	32.49
b$_1$	4.35	0.53
e	4.10	0.93
g	3.40	0.90
a	2.68	-
f+c+h	1.56	99.60
i	1.26	10.87

H	∂(ppm)	i
b$_2$+d	5.16	34.65
e	4.10	0.91
m	3.73	1.35
g	3.40	0.68
z	2.11	1.59
f+c+h	1.55	104.0
i	1.25	13.25

H	∂(ppm)	i
b$_2$+d	5.14	32.57
b$_1$	4.35	0.81
e	4.10	0.58
m	3.73	4.48
w	3.24	0.49
z	2.11	1.10
f+c+h	1.55	106.3
i	1.25	8.14

Figure 1. ^{1}H-NMR spectra of (a) α-OH, ω-Br P(L)LA; (b) α-Acetyl, ω-Br P(L)LA; and (c) α-Acetyl, ω-N$_3$ P(L)LA. Solvent : CDCl$_3$.

H	∂(ppm)	i
b_2+d	5.16	15.05
e	4.10	0.52
w	3.24	0.43
z	2.11	0.73
f+c+h	1.55	46.92
i	1.25	3.19
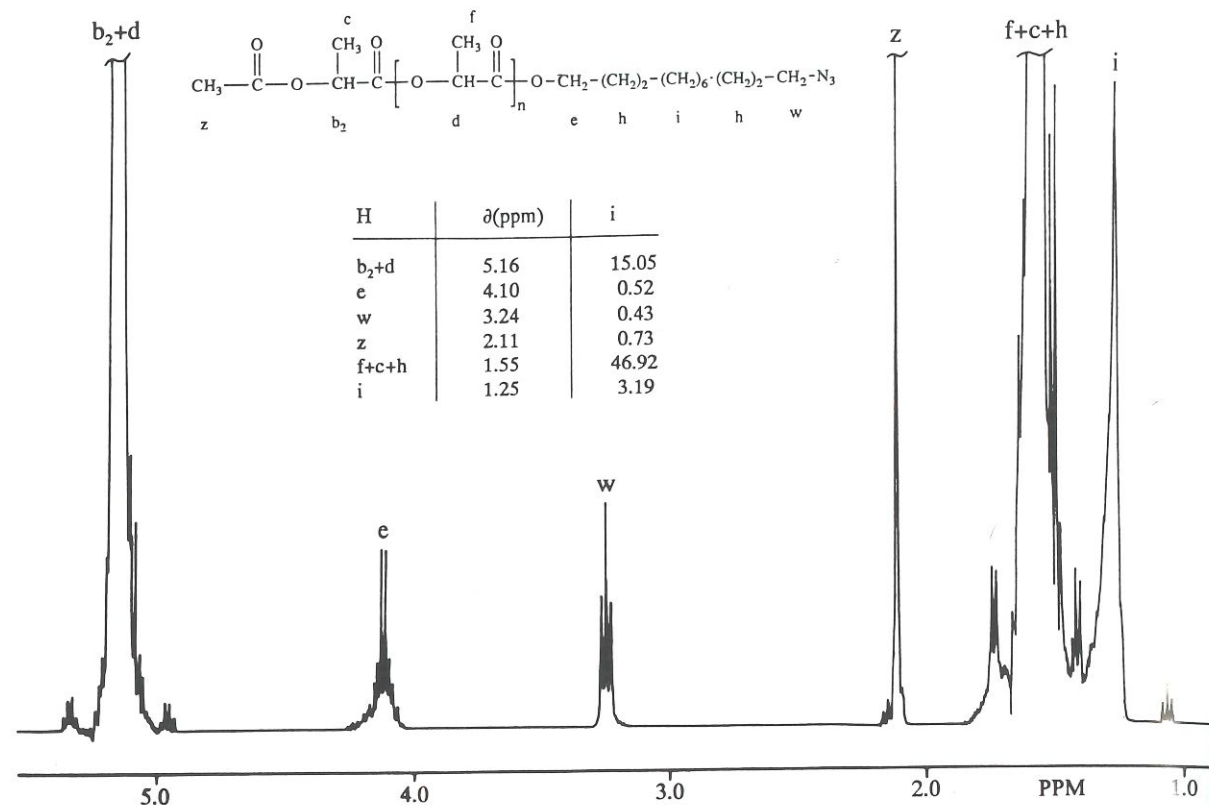
Figure 2. ^{1}H-NMR spectrum of a purified α-acetyl, ω-N$_3$ P(L)LA. $\overline{M_n}$ = 4800, $\overline{M_w}/\overline{M_n}$ = 1.20. Solvent : CDCl$_3$.

Methanolysis is more favorable in a more polar solvent and is known to be catalyzed by acids consistently with the aforementioned observations.

The experimental recipe used for PCL has thus been changed in using heptane as a nonsolvent for PLA. Since the lactide conversion is quantitative, the insolubility of the monomer in heptane is no problem. The situation is however less favorable when the esterification of the hydroxy end-group [second step, eq. (2)] is concerned. Indeed, reagents in excess (Ac$_2$O, NEt$_2$, and DMAP) are insoluble in heptane. It is the reason why they must be carefully removed by heating the crude polymer, at 50°C, under a reduced pressure. A final problem has been met in the recovery of polylactide in heptane after the substitution reaction of the bromide end-group by an azide in DMF. DMF and heptane are indeed immiscible. The addition of a large excess of THF to the reaction medium before precipitation allows that drawback to be avoided. Furthermore, the excess of NaN$_3$ becomes insoluble and is very conveniently removed by filtration before precipitation of the polymer in heptane.

The final recipe for the three steps of eq. (2) leads to the formation and recovery of well-defined ω-azide

polylactide. The polymer isolated after each step has been characterized by ^{1}H-NMR spectroscopy, and SEC analysis. As confirmed by Figure 2 and Table I, no change is observed in the molecular weight and polydispersity.

Table I. Molecular Parameters ($\overline{M_n}$, $\overline{M_w}/\overline{M_n}$) of the α-X, ω-Y P(L)LA Chains Initiated with Diethylaluminum-12-Bromododecanoxy and Chemically Modified on the Bromide End-Group

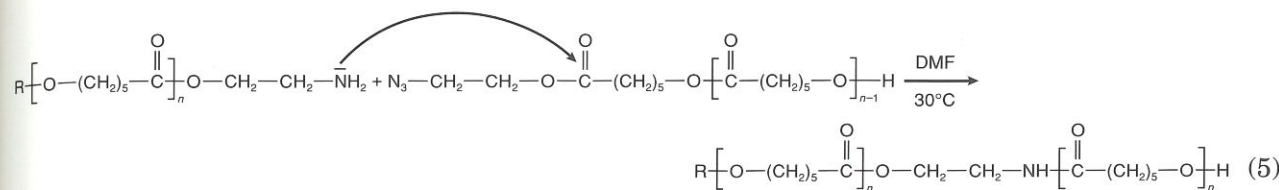|		$\overline{M_n}$		
—X	—Y	^{1}H-NMR	SEC	$\overline{M_w}/\overline{M_n}$
—Br	—OH	5300	4700	1.22
—Br	—O—C(O)CH$_3$	4900	5010	1.20
—N$_3$	—O—C(O)CH$_3$	4800	4720	1.20

^{a} $\overline{M_n}$ calculated from the signal intensities of the functional ester end-group and the methine ester groups of the polyester chains.

Synthesis of ω-Primary Amino PCL and PLA: Reduction Step

Reduction by Catalytic Transfer Hydrogenation (CTH)

As reported by Degee et al., ω-amine PCL can be obtained by reduction of the azide end-group by catalytic transfer hydrogenation (CTH) with ammonium formate in dry DMF at 30°C.[13,17] This method is efficient when the original alkyl bromide is long enough to prevent the azide from activating the nearest neighbor ester group [eq. (4)]:
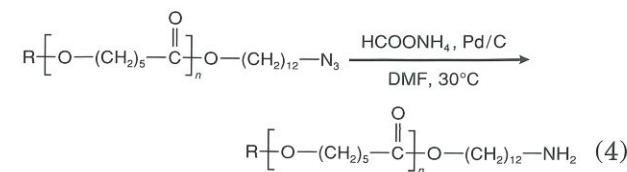

$$\text{with R = H— or CH}_3\text{—C—}$$

Actually, when diethylaluminum 2-bromoethoxide is used instead of diethylaluminum 12-bromododecanoxide, no amine end-group is observed. This has been accounted for by the attack of the azide activated ester group by the nascent amine end-group with formation of an amide [eq. (5)]:[12]

$$\text{with R = H— or CH}_3\text{—C—}$$

The set of reactions schematized in eq. (1) and completed with the catalytic transfer hydrogenation reported in eq. (4) is an original and effective strategy for the preparation of ω-amine PCL of a predictable molecular weight and able to initiate the ring-opening polymerization of NCAs.[15]

Although the method is effective for PCL, its application to PLA has systematically failed. No amine end-group has been observed by ^{1}H.NMR after the hydrogenation (CTH) of ω-azide PLA (Fig. 3). ^{1}H-NMR signals at $\partial(H_t)$ [—C(O)—NH—C$\underline{H}_2$—] = 3.25 ppm and $\partial(H_r)$ [—C(O)—N$\underline{H}$—CH$_2$—) = 6.1–6.5 ppm argue for the presence of an amide within the PLA-chain. Moreover, a hydroxyl end-group can also be observed at $\partial(H_{b1})$ [—C$\underline{H}$(Me)—OH] = 4.35 ppm. The amide likely results from the nucleophilic attack of an ester subunit of PLA by the amine end-group as soon as it is formed. This mechanism is consistent with the observation of a hydroxyl end-group. SEC analysis of the main reaction product shows no dramatic change in the chain length ($\overline{M_n}$ from 5500 to 6000) and polydispersity ($\overline{M_w}/\overline{M_n}$ from 1.20 to 1.25).

The random nucleophilic attack of ester monomer units in PLA by the nascent amine end-group is a highly probable mechanism which has been ascertained by mixing a performed PLA (e.g., ω-azido PLA) and an aliphatic amine (e.g., 3-phenyl 1-propylamine) in DMF at 30°C. As shown in Figure 4, ^{1}H-NMR analysis of the reaction product confirms the aminolysis of the polyester chain [eq. (6)]. The signal H$_{b1}$ at ∂ = 4.35 ppm accounts for a hydroxyl end-group.
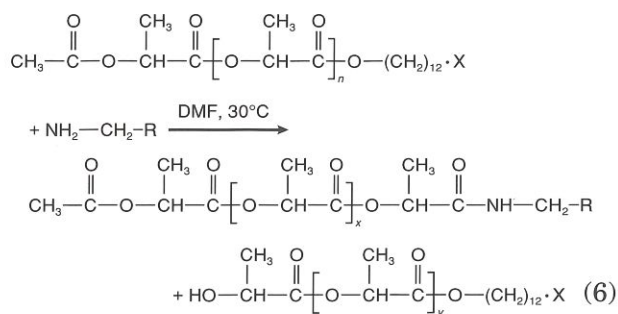
where

$$\text{—X = —Br, —N}_3$$
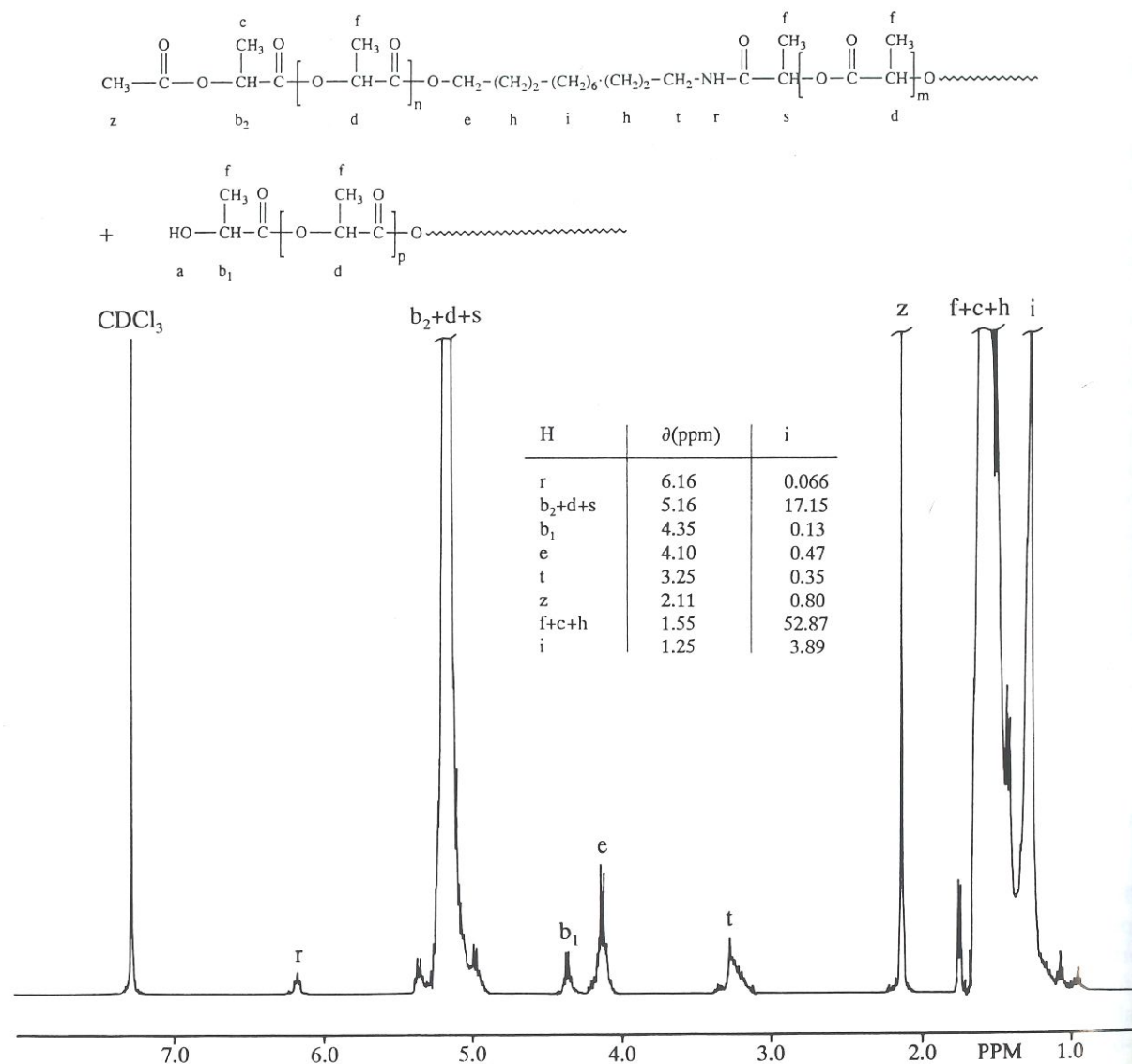$$\text{—R = —(CH}_2)_2\text{—C}_6\text{H}_5\text{, —(CH}_2)_{11}\text{—PLA—X}$$

Figure 3. ^{1}H-NMR spectrum of the polylactide chains as recovered after CTH reduction of α-acetyl, ω-N₃ P(L)LA. Solvent: CDCl₃.

Figure 4. ^{1}H-NMR spectrum of the reaction products of α-acetyl, ω-N₃P(L)LA and 3-phenyl-1-propylamine in DMF at 30°C [see eq. (6), where X = N₃]. Solvent: CDCl₃.

SEC analysis agrees with the aminolysis of PLA by 3-phenyl 1-propylamine, since the polyester $\overline{M_n}$ decreases from 5500 to 3500 while $\overline{M_w}/\overline{M_n}$ increases from 1.2 to 1.35.

In conclusion, the strategy successfully used for the synthesis of ω-amine PCL cannot be extrapolated to ω-amine PLA; another reduction way of the azide end-group into an amine function has to be considered.

Reduction by Hydrolysis in the Presence of Triphenylphosphine in THF[18,19]

It has been previously reported that the reduction of the azide end-group of N₃—(CH₂)₂—PCL—OAc, by hydrolysis with triphenylphosphine in THF leads to a coupling reaction of PCL chains.[13] The origin of this side-reaction might also be a nucleophilic attack of the ester in the β-position of the azide end-group of one chain by the nascent amine of another chain. This attack would be favored by the activation of the β-methylene ester by the azide group.

If this hypothesis is correct, the nucleophilic attack by the amine should also 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 nearest neighbor ester group. Thus, as previously discussed, diethylaluminum 12-bromo-1-dodecyloxide has been used as an initiator for the synthesis of ω-azi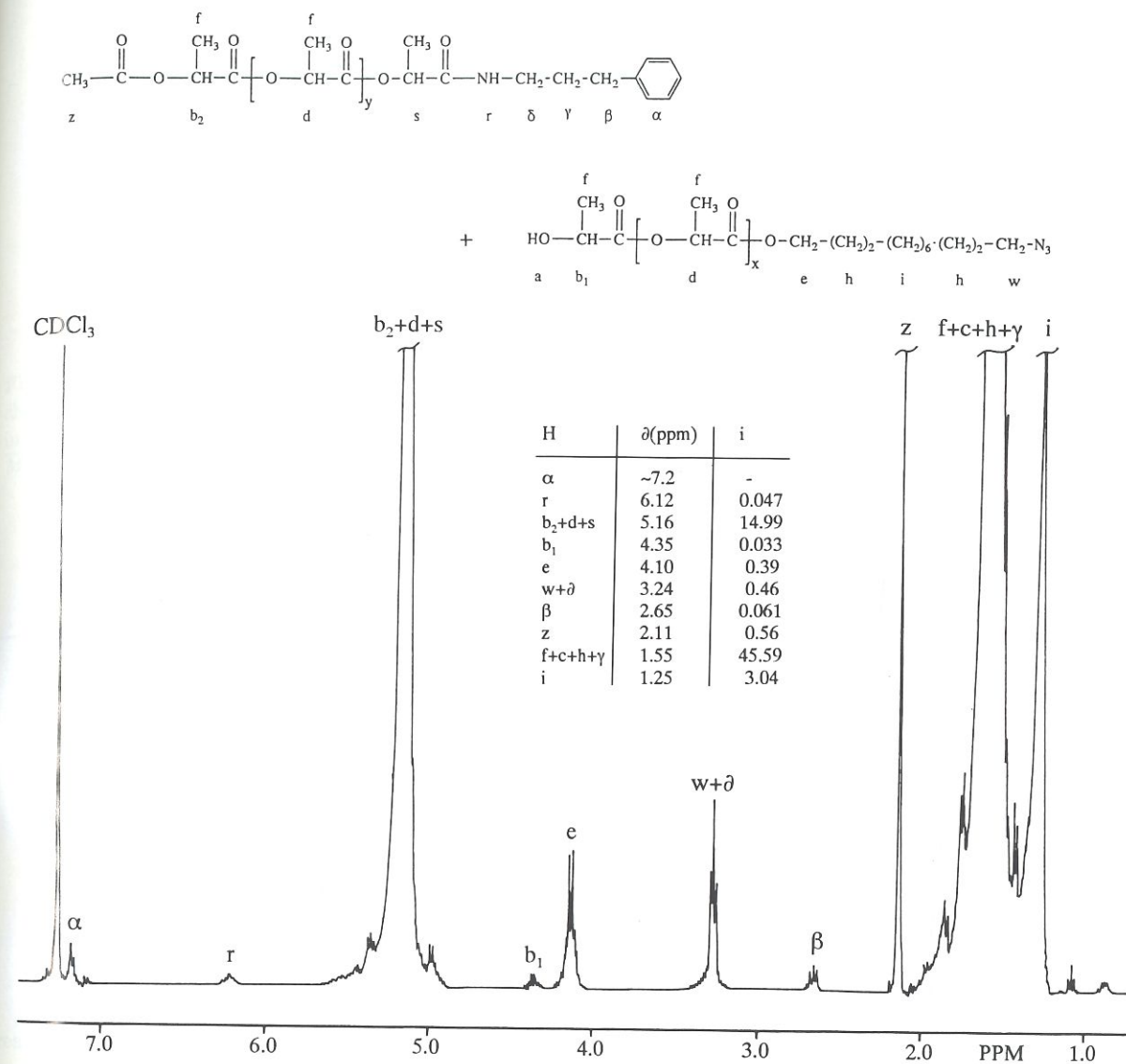de PCL. The reduction step has then been performed with tri-phenylphosphine and water in THF and the final product has been analyzed by ^{1}H-NMR (Fig. 5) and SEC (Fig. 6).

According to SEC, the coupling reaction is still effective since a second elution peak is observed in addition to that of the original PCL. The molecular weight of the additinal polymeric component is twice as high as that of the starting polymer. The ^{1}H-NMR study of the final product shows that the origin of the coupling reaction is different from the side-reaction identified when the ω-azido PCL with an ethylene spacer is hydrogenated (CTH). Indeed, no amide is observed, in contrast to some amine (Hₓ), in agreement with the potentiometric titration with HClO₄. Formation of triphenylphosphine oxide is in favor of the reduction reaction. It is however quite a problem to assign the ^{1}H-NMR signal at $\partial(H_u)$ = 3.12 ppm).

In a second step, a ω-azide polylactide has been hydrolyzed under the same experimental conditions as before. A coupling reaction takes again place, as confirmed by two elution peaks in the size excusion chromotogram (Fig. 7). Nevertheless, the ^{1}H-NMR analysis is consistent with the presence of an amide and the absence of an amine (Fig. 8). Finally, a signal at $\partial(H_u)$ = 3.12 ppm is again observed as for PCL. At first sight, two side-reactions would occur: (i) the aminolysis of PLA by the nascent amine, (ii)
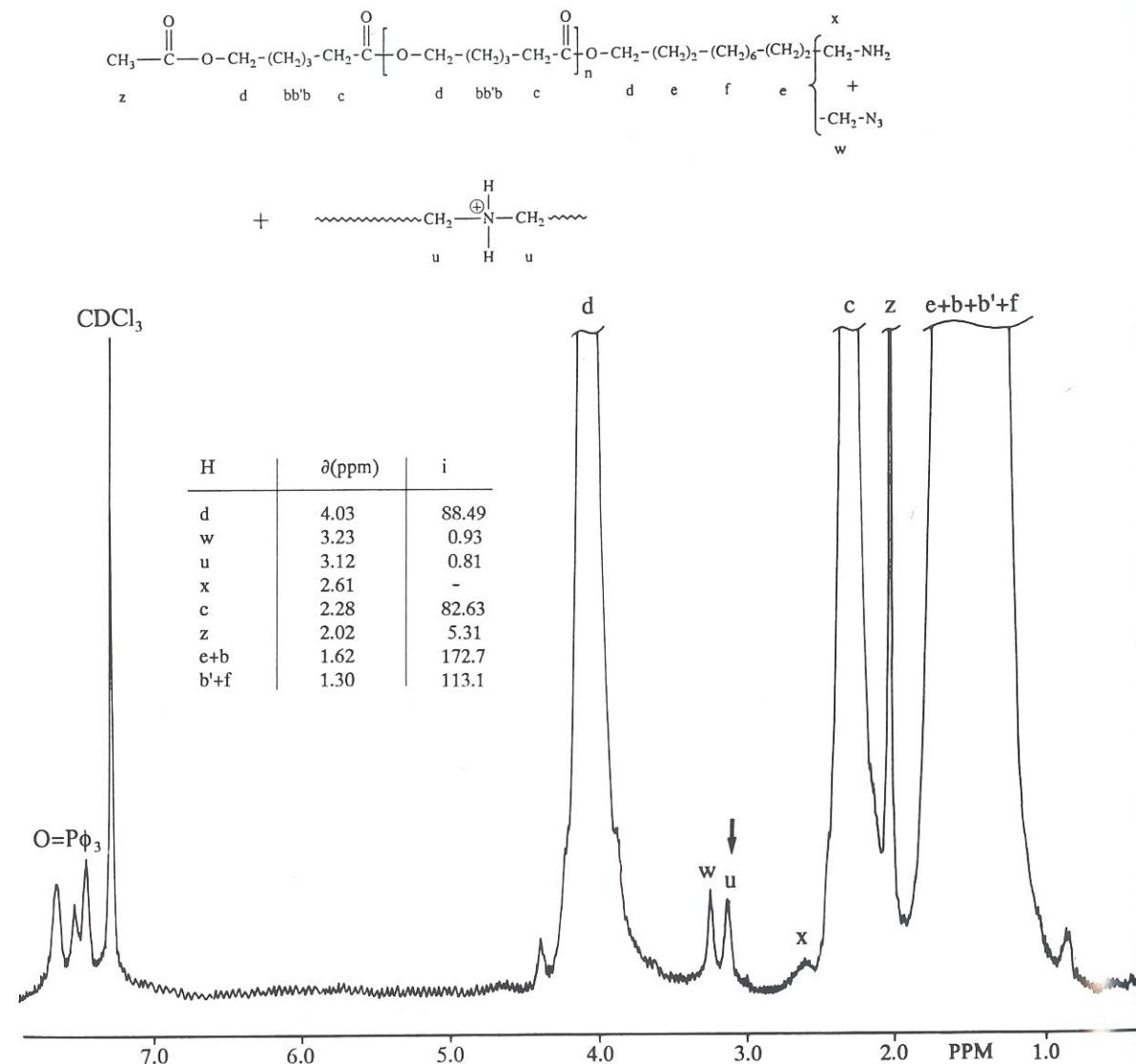
H	∂(ppm)	i
d	4.03	88.49
w	3.23	0.93
u	3.12	0.81
x	2.61	–
c	2.28	82.63
z	2.02	5.31
e+b	1.62	172.7
b'+f	1.30	113.1

Figure 5. ^{1}H-NMR spectrum of the PCL-chains as recovered after hydrolysis of α-acetyl, ω-N$_3$ PCL in the presence of P(C$_6$H$_5$)$_3$ in THF. Solvent : CDCl$_3$.

a coupling reaction which should have something to do with the ^{1}H-NMR signal at $\partial = 3.12$ ppm.

To get a better insight on the coupling reaction, several tests have been carried out:

1. In THF, i.e., the solvent for the reduction reaction, an ω-azide PLA is attacked by 3-phenyl-1-propylamine as confirmed by the ^{1}H-NMR spectrum of the final PLA which is similar to Figure 4. It is thus obvious that, as soon as an amine is formed, aminolysis of polylactide chains occurs whatever the solvent (DMF or THF) [eq. (6)].

2. When a ω-azide PLA is reacted with 3-phenyl-1-propylamine and P(C$_6$H$_5$)$_3$ in THF at 25°C, two side-reactions take place: the aminolysis in accordance to ^{1}H-NMR (Fig. 9) and the coupling reaction as shown by SEC (same chromatogram as in Fig. 7).

3. Conversely, PCL—(CH$_2$)$_{12}$—N$_3$ is stable toward 3-phenyl-1-propylamine in THF, although the coupling reaction occurs when P(C$_6$H$_5$)$_3$ is added. Indeed, two elution peaks are observed by SEC and the ^{1}H-NMR signal at $\partial = 3.12$ ppm as well.

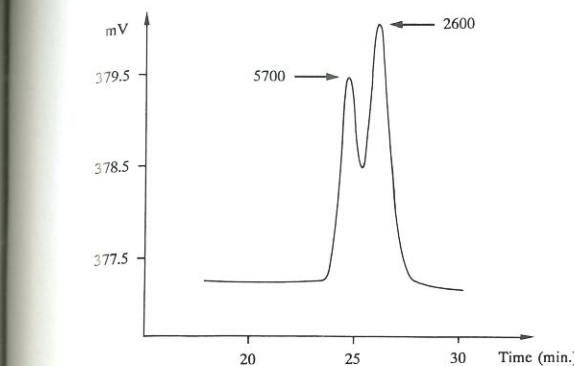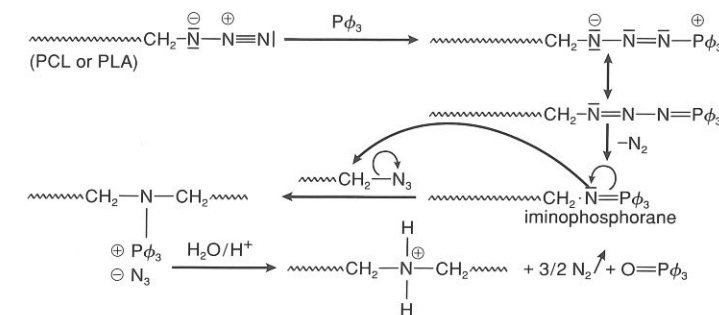From this series of experiments, three main conclusions emerge:

Figure 6. Size exclusion chromatogram of the PCL chains as recovered after hydrolysis of α-acetyl, ω-N$_3$ PCL in the presence of P(C$_6$H$_5$)$_3$ in THF. $\overline{M_n} = 3650$, $\overline{M_w}/\overline{M_n} = 1.2$.

1. Chain-ends must be involved in a coupling reaction, which leads to a twofold increase in molecular weight.

2. The chain-end reactive in the coupling reaction may not be the acetyl group, the ^{1}H-NMR signal of which remains unchanged.

3. The coupling reaction does not occur via the nascent amine end-group, since no amide signal is detected by ^{1}H-NMR analysis when polycaprolactone is concerned. A coupling reaction by aminolysis only occurs when PCL—(CH$_2$)$_2$—N$_3$ is hydrogenated (CTH) in DMF.

Thus, two distinct mechanisms are at the origin of a coupling reaction, depending on the polyester and the experimental conditions: (i) coupling of PCL—(CH$_2$)$_2$—N$_3$ by aminolysis, when hydrogenation is carried out in DMF; (ii) coupling of PCL—(CH$_2$)$_{12}$—N$_3$ and PLA—(CH$_2$)$_{12}$—N$_3$ during hydrolysis by Pϕ_3/H$_2$O in THF. Equation (7) has been proposed as the underlying mechanism of this coupling reaction:

$$(7)$$

It is reasonable to assume that the azide group reacts with triphenylphosphine with formation of our iminophosphorane. A nucleophilic substitution of the iminophosphorane by a not yet reduced azide group leads to a coupling reaction and a twofold increase in chain length, via a protonated secondary amine.

^{1}H-NMR spectra (Figs. 5 and 8) are in agreement with the postulated mecanism, particularly with the formation of triphenylphosphine oxide (O═Pϕ_3) as a byproduct. The nucleophilic behavior of an iminophosphorane toward an alcohol and an epoxy compound has already been published in the scientific literature.[20,21]

Although formation of a secondary amine is assessed by the chloranil colorimetric test, it cannot account for the not yet assigned ^{1}H-NMR signal H$_u$ at $\partial = 3.12$ ppm. Indeed, resonance of —CH$_2$—NH—CH$_2$— is currently observed at lower fields (~ 2.7 ppm). In this respect, diethylamine has been mixed in CDCl$_3$ with the polylactide chains recovered after

hydrolysis in the presence of triphenylphosphine in THF. ^{1}H-NMR analysis shows that, in addition to the signal u at 3.12 ppm, a new signal is observed

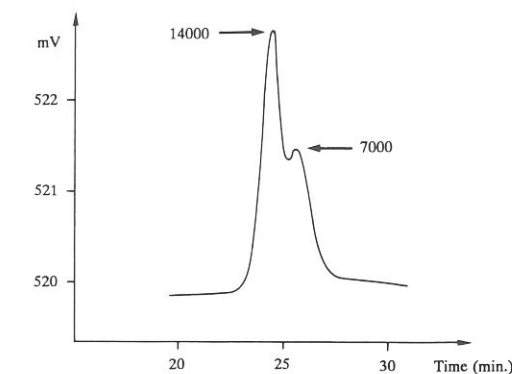**Figure 7.** Size exclusion chromatogram of the P(L)LA chains as recovered after hydrolysis of α-acetyl, ω-N$_3$ P(L)LA in the presence of P(C$_6$H$_5$)$_3$ in THF $\overline{M_n} = 8950$, $\overline{M_w}/\overline{M_n} = 1.3$.
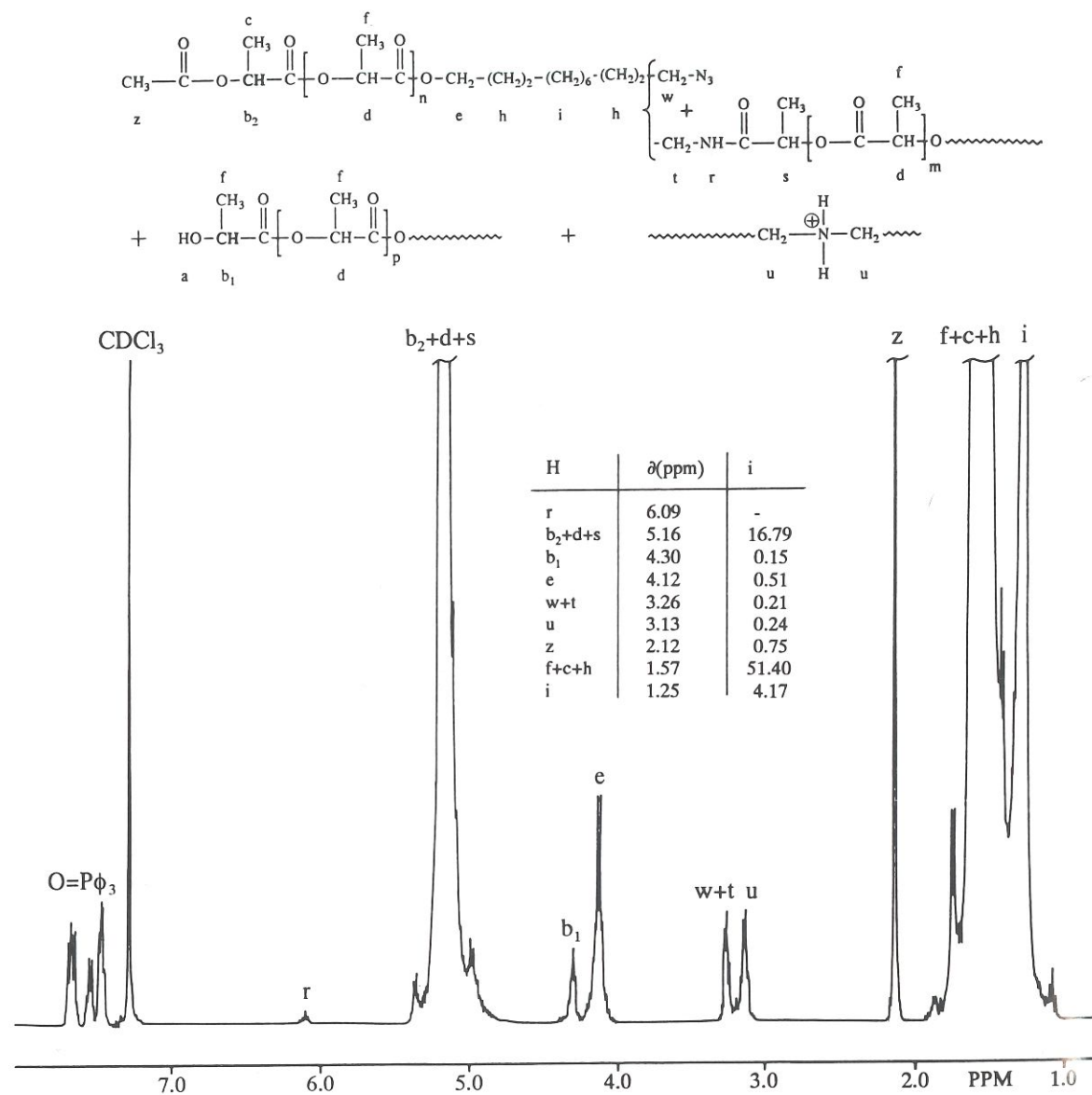
Figure 8. ^{1}H-NMR spectrum of the P(L)LA chains as recovered after hydrolysis of α-acetyl, ω-N$_3$ PLA in the presence of P(C$_6$H$_5$)$_3$ in THF. Solvent : CDCl$_3$.

H	∂(ppm)	i
r	6.09	–
b$_2$+d+s	5.16	16.79
b$_1$	4.30	0.15
e	4.12	0.51
w+t	3.26	0.21
u	3.13	0.24
z	2.12	0.75
f+c+h	1.57	51.40
i	1.25	4.17

Figure 9. ^{1}H-NMR spectrum of the reaction product of α-acetyl, ω-N$_3$ P(L)LA, P(C$_6$H$_5$)$_3$, and 3-phenyl-1-propylamine in THF at 25°C. Solvent : CDCl$_3$.

H	∂(ppm)	i
α	~7.2	0.11
r	6.12	–
b$_2$+d+s	5.16	15.53
b$_1$	4.35	–
e	4.10	0.45
w+∂	3.24	0.35
u	3.12	0.062
β	2.65	0.098
z	2.11	0.72
f+c+h+γ	1.55	47.70
i	1.25	3.063

at 2.69 ppm which is expectedly due to the α-amine methylene protons. Interestingly enough, the subsequent addition of HCl 1M leads to the upfield shift of the new signal which rapidly merges with the unknown resonance and forms a unique multiplet centered at 3.10 ppm. It is thus obvious that signal u at 3.12 ppm has to be assigned to a protonated secondary amine and particularly the —CH$_2$—$\oplus$NH$_2$—CH$_2$— protonated amino bridge within the extended PLA chains [eq. (7)]. This assignement is in agreement with data published in the scientific literature, which assign a chemical shift of 2.9–3.2 ppm to methylene protons in α position of a protonated amine, in relation to the nature of the counteranion.[22]

CONCLUSIONS

This article reports on a controlled pathway to ω-azide PLA through a route similar to that used for the synthesis of ω-azide PCL. PLA has however a greater propensity to methanolysis and degradation than PCL.

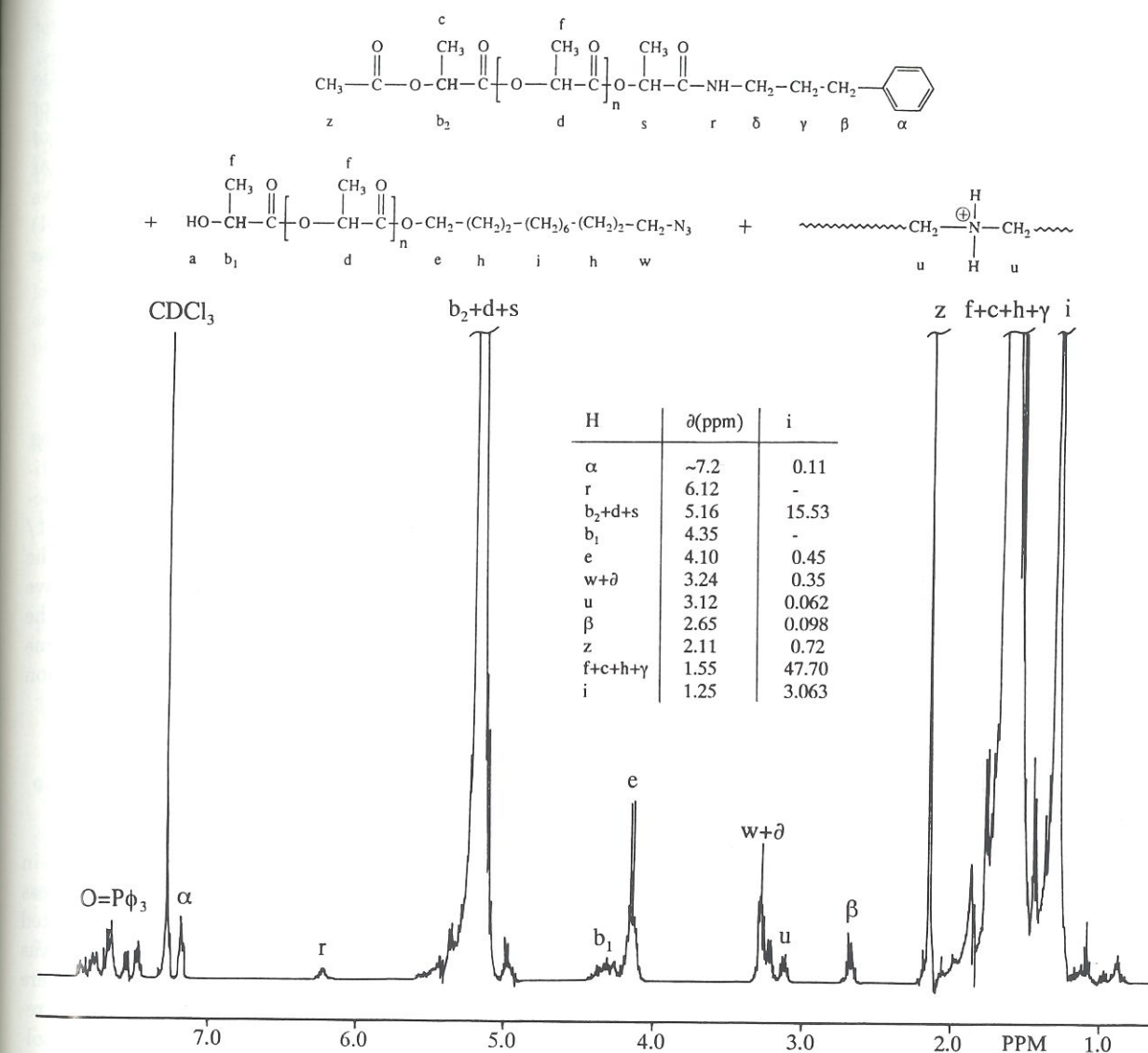Reduction of the ω-azide polyester into a ω-primary amine polyester has been considered according to two methods. Catalytic transfer hydrogenation provides the expected PCL-NH$_2$, only when the alkyl spacer between the azide group and the nearest neighbor ester is long enough. Otherwise, a coupling reaction takes place via a regiospecific aminolysis. When PLA is concerned, a random aminolysis cannot be avoided.

When the azide end-group is hydrolyzed in the presence of triphenylphosphine, a partial reduction of the azide into an amine is observed to occur. This nascent amine is however responsible for the cleavage of polylactide by aminolysis. Whatever the polyester (PCL and PLA), a coupling reaction occurs with formation of a central secondary amine. The underlying mechanism more likely results from the reaction of Pϕ_3 with the azide end-group. Then, the iminophosphorane end-group which is formed would be substituted by a still unreacted azide of another chain. The polyester coupling with formation of an internal secondary amine might accordingly be accounted for.

EXPERIMENTAL

Materials

ε-CL (Janssen Chimica) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. L-lactide

(Boehringer, Ingelheim) was recrystallized three times from dried ethyl acetate at 60°C and then dried for 24 h at 35°C under reduced pressure (10^{-2} mm Hg) before polymerization. Triethylaluminum (Fluka) was used without further purification and dissolved in dry toluene.

12-Bromododecanol (Aldrich), sodium azide (Janssen), triphenylphosphine (Janssen), ammonium formate (Janssen), and 4-(dimethylamino)-pyridine (Janssen) were dried by three azeotropic distillations of toluene before use. Triethylamine (Janssen) and 3-phenyl 1-propylamine (Janssen) were dried over barium oxide for 1 week and distilled under reduced pressure. Acetic anhydride (Aldrich) was dried over calcium chloride 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 P_2O_5 for 72 h and distilled under reduced pressure just before use. Palladium on activated carbon (10 wt %) was used as received without azeotropic distillation of toluene.

Preparation of the Initiator

Diethylaluminum alkoxides were prepared by reaction of triethylaluminum with the appropriate alcohol. A 1.0 mmol aliquot of the alcohol in 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. In this work, 12-bromododecanol was reacted with $AlEt_3$ to produce diethylaluminum 12-bromododecanoxide.

Polymerization Procedure

ε-CL polymerization and L-lactide polymerization were carried out with stirring in toluene solution in previously flamed flask purged with nitrogen and kept at 25 and 70°C, respectively, for a suitable period of time. The reaction was terminated by adding a tenfold molar excess of 0.1N HCl solution with respect to Al. Catalytic residues were removed by two successive extractions with an aqueous solution of EDTA and pure water, respectively.

Esterification of the Polyester

ω-OH PLA and ω-OH PCL were esterified by acetic anhydride (5 equiv) in dry THF, in the presence of triethylamine (5 equiv) and a catalytic amount of 4-dimethylaminopyridine (0.2 equiv), for 48 h at 50°C. The polyester was purified by three successive precipitation-dissolution cycles (THF–methanol) for PCL. PLA was simply heated at ca. 50°C for one night under reduced pressure.

Conversion of ω-Bromo Polyester into ω-Azide Polyester

A fivefold molar excess of sodium azide with respect to ω-bromo polyester was used to convert quantitatively the halogen end group into an azide function. This reaction was achieved in dry DMF (5 wt/v % of polymer in DMF), at 30°C, for 14 h. The polyester was recovered and purified by selective precipitation in methanol when PCL is used. In the case of PLA the procedure of recovering in heptane has been described in the Results and Discussion section.

Reduction of the ω-Azide Polyester into ω-Amino Polyester by CTH Method

ω-Azide polyester (5 wt/v %) was hydrogenated in dry DMF by reaction with a fivefold molar excess of ammonium formate and 10 wt % Pd supported on activated carbon. The reaction temperature was kept at 30°C for one night. Palladium residues were recovered by centrifugation. The polyester was recovered by selective precipitation in a suitable solvent.

Reduction of the ω-Azide Polyester into ω-Amino Polyester by Hydrolysis with Pφ₃

ω-Azido polyester (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 polyester was recovered by precipitation in a suitable solvent.

Polymer Characterization

^{1}H-NMR spectra were recorded in $CDCl_3$ with a Brucker AM400 apparatus at 25°C. Size exclusion chromatography was achieved in THF using a Hewlett-Packard 1090 liquid chromatograph equipped with a Hewlett-Packard 1037A refractometer index detector. Columns were calibrated with polystyrene standards. Amines were titrated with $HClO_4$ in a toluene–methanol (9 : 1) mixture (potentiometric titration).

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