Macromolecular Engineering of Polylactones and Polylactides. 8. Ring-Opening Polymerization of ϵ-Caprolactone Initiated by Primary Amines and Trialkylaluminum

Ph. Dubois, Ph. Degée, R. Jérôme,* and Ph. Teyssié

Laboratory of Macromolecular Chemistry and Organic Catalysis, University of Liège, Sart-Tilman, B6, 4000 Liège, Belgium

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ABSTRACT: Whenever added with triethylaluminum, primary amines have been found to be effective initiators for ϵ-caprolactone polymerization in both toluene and THF at 40 °C. The IR and NMR analysis of the polyester has supported a polymerization mechanism proceeding through a "coordination–insertion" pathway and the selective rupture of the acyl-oxygen bond of the monomer. The alkylaluminum activates the carbonyl group of the monomer and accordingly favors the nucleophilic addition of the amine, which is the actual initiation step. Propagation is typically a living process, and the molecular weight distribution is controlled by both $AlEt_3$/amine molar ratio and solvent. As an extension of that mechanism, diethylaluminum ω-amino alkoxide has been prepared on purpose and successfully used as an initiator for the synthesis of α,ω-dihydroxypoly(ϵ-caprolactone).

Introduction

The availability of biocompatible and biodegradable polymers has promoted major advances in the biomedical field.[1,2] Among them, a few aliphatic polyesters are known for their usefulness in medicine.[3] For example, poly(ϵ-caprolactone) (PCL) is very attractive due to a valuable set of properties, i.e., a high permeability, the lack of toxicity for living organisms, biodegradability, and a capacity to be blended with various commercial polymers over a wide composition range.[4,5]

Although ϵ-caprolactone (ϵ-CL) can be ring-opening polymerized by various types of initiators, living polymerization is rather an exception than a general rule.[6] Most often, the polymerization is perturbed by side intra- and intermolecular transesterification reactions leading to a mixture of linear and cyclic oligomers.[7,8] Several years ago, some of us reported that the living polymerization of ϵ-CL could be promoted by aluminum alkoxide functions such as bimetallic (Zn,Al) μ-oxo alkoxides[9] and trialkoxyaluminum.[10] Furthermore, Dubois et al. and Duda et al. have recently reported the living polymerization of ϵ-caprolactone and the selective end functionalization of PCL using aluminum alkoxides carrying functional alkoxy groups as initiators.[11-13] The functional group associated with the active alkoxy groups of the initiator is selectively attached to one chain end, whereas the second end group is systematically a hydroxyl function resulting from the hydrolysis of the living growing sites (eq 1). The functional end group derived from the initiator can be, for instance, an unsaturation, a halogen, a tertiary amine, or a methacrylic double bond, making PCL macromonomers available.[14]

$$Et_2AlOCH_2X \xrightarrow{n\epsilon\text{-CL}} Et_2Al[O(CH_2)_5C(O)]_nOCH_2X \xrightarrow{H_3O^+} H[O(CH_2)_5C(O)]_nOCH_2X \quad (1)$$

$X = CH_2Br, (CH_2)_2CH{=}CH_2, (CH_2)_2NEt_2, CH_2OCOC(CH_3){=}CH_2$

This paper aims at reporting the potentialities of primary amines added with alkylaluminum as initiators for the controlled polymerization of ϵ-CL.

Experimental Section

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. *n*-Butylamine and 3-amino-1-propanol were dried over barium oxide for 1 week at room temperature and distilled under reduced pressure just before use. Toluene and tetrahydrofuran (THF) were dried by refluxing over calcium hydride and benzophenone–Na complex, respectively.

Preparation of Diethylaluminum Alkoxides. These compounds were prepared by reaction of triethylaluminum with the corresponding alcohol (eq 1). One millimole of the required alcohol in 10 mL of toluene was slowly added to a previously 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 a vigorous stirring at room temperature. When the emission of ethane stopped, the catalyst solution was kept under stirring at room temperature for an extra hour. In this work, 3-amino-1-propanol was reacted with $AlEt_3$ to produce diethylaluminum 3-amino-1-propoxide.

Polymerization Procedure. ϵ-CL polymerization was carried out with stirring in toluene or in THF solution in a previously dried flask purged with nitrogen and kept at constant temperature during a suitable period of time. The reaction was terminated by adding a tenfold molar excess of 2 N HCl solution with respect to Al.

Characterization. ^{1}H-NMR spectra of PCL were recorded in $CDCl_3$ using either a Varian T60 (Figure 1) or a Bruker AM400 (Figures 2 and 4) apparatus. Size exclusion chromatography (SEC) was performed in tetrahydrofuran using a Hewlett-Packard 1090 liquid chromatograph equipped with a HP 1037A refractometer index detector and four columns of various pore sizes (10^5, 10^3, 500, and 100 Å). Molecular weight and molecular weight distribution were calculated by reference to a calibration curve built up by using polystyrene standards. As soon as the chain length became short enough, molecular weight ($\bar{M}_n$ < 15 000) was also determined by ^{1}H-NMR from the relative intensity of the signals of α-hydroxymethylene end groups (CH_2OH) and the ester methylene ($C(O)OCH_2$) in the chain. Molecular weight calculated by ^{1}H-NMR spectroscopy agreed very well with the value obtained by SEC. IR spectra were recorded by using a Perkin-Elmer IR 197.

Results and Discussion

Homopolymerization of ϵ-CL Initiated by $H_2N(CH_2)_3OAlEt_2$. According to a previously published

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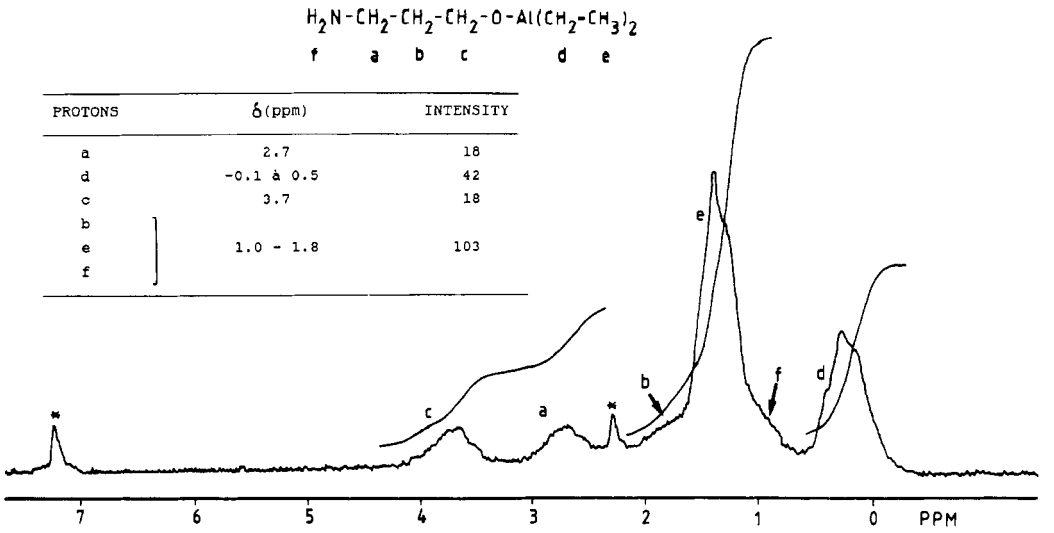


Figure 1. ^{1}H-NMR spectrum of diethylaluminum 3-amino-1-propoxide (1) in toluene-d_8 (*).

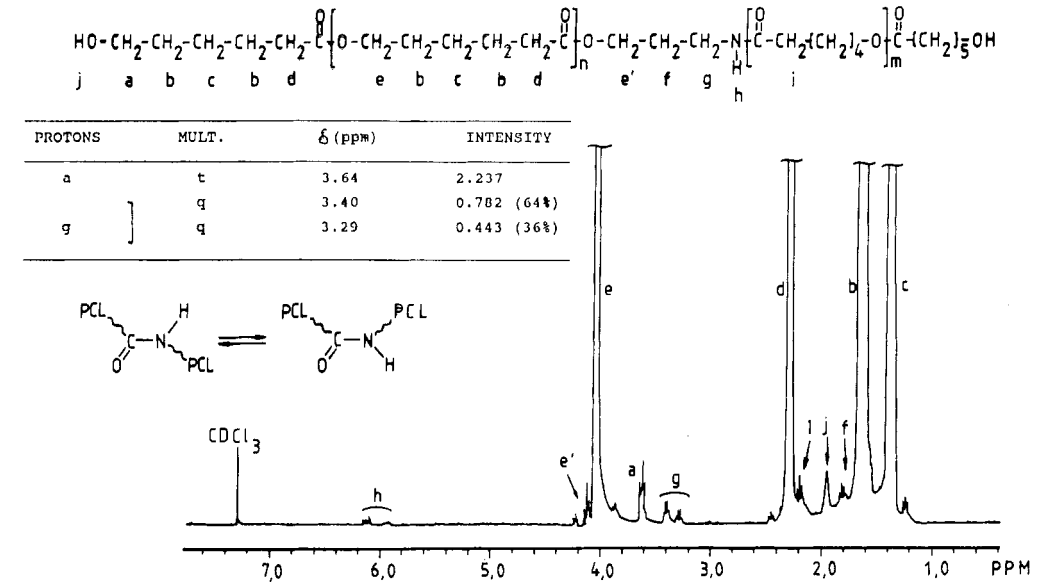
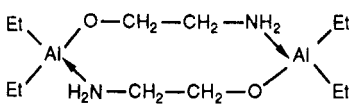


Figure 2. ^{1}H-NMR spectrum of PCL as recovered after hydrolysis of the living polymer initiated by the aluminum alkoxide 1 (solvent = $CDCl_3$).

paper,[15] diethylaluminum 3-(dimethylamino)-1-propoxide allows a quantitative attachment of a tertiary amine at one end of PCL chains. On that basis, the use of aluminum alkoxide carrying a primary amine might be recommended for the synthesis of α-amino-ω-hydroxy-PCL.

That potential initiator can be synthesized by the reaction of equimolar amounts of 3-amino-1-propanol and triethylaluminum (eq 2). In agreement with eq 2 and the volume of ethane formed as a byproduct, only one ethyl group per Al has actually reacted. The fact that $AlEt_3$ has selectively reacted with the hydroxyl group of the amino alcohol in contrast to the amino group has been assessed by ^{1}H-NMR analysis of the final product (1). Indeed, Figure 1 shows that the intensities of protons c and d (methylenes in α position with respect to the alkoxide function and aluminum atom, respectively) are in the expected 1/2 ratio. The selective reaction of the alcohol function with $AlEt_3$ is the result of the very low acidity of the amino protons. This has been confirmed by the absence of any reaction between $AlEt_3$ and *n*-butylamine under the same experimental conditions. The lack of reactivity of trialkylaluminum with different primary amines is also mentioned in the scientific literature.[16,17] Moreover, Higashi et al. have proposed a dimeric structure for $Et_2AlO(CH_2)_2NH_2$:[18]



The initiator 1 has proved to be active in the ϵ-CL polymerization in toluene at 40 °C. Indeed, the polymerization goes to completion and the molecular weight (at least in a range smaller than 20 000) is quite consistent with the actual monomer/Al molar ratio. Surprisingly enough, no amino group can be detected at the end of the polyester chains. Several observations rather suggest the formation of α,ω-dihydroxy-PCL: (i) the nonaqueous titration of the purified polyester by $HClO_4$ supports the absence of any amino group; (ii) IR spectroscopy shows absorption bands at frequencies of 1530 and 1645 cm^{-1}, respectively, which are characteristic of an amide function; (iii) ^{1}H-NMR spectroscopy (Figure 2) shows the presence of a hydroxymethylene group [$\delta(CH_2OH)$ = 3.64 ppm] at each end of the PCL chains (as deduced from the relative intensity of protons H_a). Furthermore, an *N*-methyleneamide group [$\delta(CH_2NHC(O))$ = 3.40 and 3.29 ppm; $\delta(NH(O)CCH_2)$ = 2.20 ppm] is observed. The signals at 3.40 (64%) and 3.29 ppm (36%) are evidence for the location of the amide function inside the chain. It is indeed

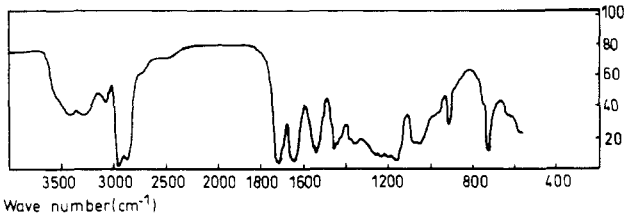


Figure 3. IR spectrum of PCL as recovered after hydrolysis of the living oligopolyester initiated by *n*-butylamine in the presence of $AlEt_3$.

well-known that the ^{1}H-NMR chemical shifts of the syn and trans conformations of sterically hindered amides are different enough to be unambiguously distinguished.[19] Furthermore, an ω-*n*-butylamide-PCL has been prepared, and only one chemical shift at 3.23 ppm has been observed (see next section).

As a whole, these data suggest that the amino group participates in the ϵ-CL polymerization in addition to the alkoxide function (eq 3).

$$Et_3Al + H_2N(CH_2)_3OH \rightarrow \underset{1}{Et_2AlO(CH_2)_3NH_2} + C_2H_6\uparrow \quad (2)$$

$$1 \xrightarrow[(2)\ H_3O^+]{(1)\ (n+m)\epsilon\text{-CL, toluene, 40 °C}} H[O(CH_2)_5C(O)]_n\text{-}O(CH_2)_3NH[C(O)(CH_2)_5O]_mH \quad (3)$$

In connection with these observations, it is worth pointing out that amino groups have been reported to initiate the polymerization of ϵ-caprolactone[20,21] and δ-valerolactone at high temperatures ($T \geq 200$ °C).[22] The nucleophilic addition of the amine on the carbonyl groups of the monomer has been proposed, directly followed by an "acyl-endocyclic oxygen" ring-opening, as the preliminary step of the initiation. That reaction should expectedly be favored by the increase in the electrophilicity of the carbonyl group as promoted by the coordination of an alkylaluminum. To support that assumption, ϵ-caprolactone has been activated by $AlEt_3$ and *n*-butylamine tested as a possible initiator of the ring-opening polymerization in toluene at 40 °C.

Homopolymerization of ϵ-CL Initiated by an Aliphatic Primary Amine. To clear up the mechanism of the ϵ-CL polymerization as initiated by a primary amine in the presence of triethylaluminum, an equimolar mixture of *n*-butylamine and $AlEt_3$ was purposely prepared and added to an ϵ-CL solution in toluene. Since no ethane evolved upon the addition of the amine/$AlEt_3$ mixture, it may be concluded that these two compounds are mutually unreactive, as reported elsewhere.[18]

When used separately in toluene at 40 °C, $AlEt_3$ and *n*-butylamine are inactive toward ϵ-CL. Under the same experimental conditions, the amine used in conjunction with $AlEt_3$ is able to initiate the polymerization of ϵ-CL and to provide an α-hydroxy-ω-*N*-*n*-butylamide PCL (**2**) after acidic hydrolysis. The IR spectrum of that polymer shows absorptions at ca. 3300, 1645, and 1540 cm^{-1}, which are quite consistent with the presence of both an *n*-butylamide group and a hydroxyl function (Figure 3). The same conclusion can be drawn from the ^{1}H-NMR chemical shifts at $\delta = 3.64$ and at $\delta = 3.23$ and 2.17, assigned to the α-hydroxymethylene protons (H_j) and the c and e protons of the amide function, respectively. On the basis of the relative intensity of these signals, there are as many *n*-butylamide end groups as hydroxyl ones within the limit of experimental error (Figure 4).

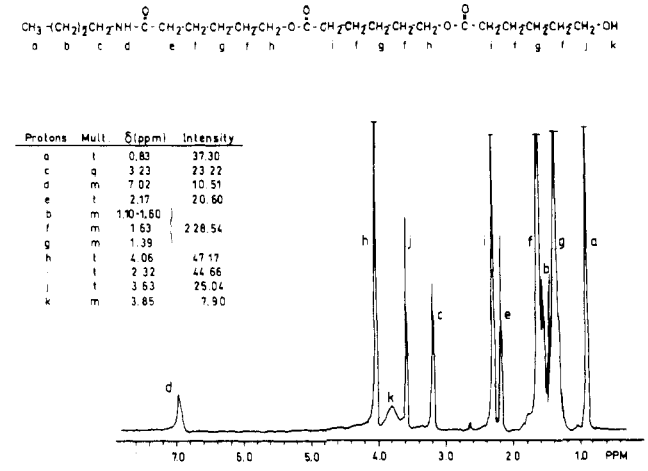


Figure 4. ^{1}H-NMR spectrum of PCL **2** as recovered after hydrolysis of the living oligopolyester initiated by *n*-butylamine in the presence of $AlEt_3$ (solvent = $CDCl_3$).

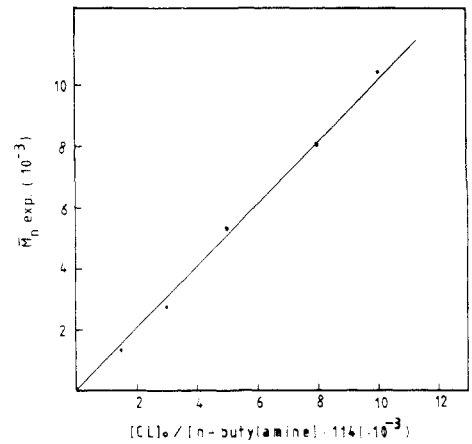


Figure 5. Dependence of $\bar{M}_n$ on the [monomer]/[*n*-butylamine] ratio in the polymerization of ϵ-CL in toluene at 40 °C initiated by *n*-butylamine in the presence of $AlEt_3$ ($[CL]_0 = 0.8$ mol·L^{-1}).

As previously reported for the ϵ-CL polymerization initiated by aluminum alkoxides,[11-13] the molecular weight of PCL increases linearly and proportionally with the monomer/amine molar ratio (Figure 5). That behavior lends credit to the living character of the polymerization.

Molecular weight distribution of the asymmetric telechelic PCL **2** was analyzed by SEC and found to be dependent on the $AlEt_3$/amine molar ratio. When that ratio is 1, the polymerization solution gelifies rapidly and the elution chromatogram of the purified PCL is bimodal, thus suggesting the presence of two distinct active sites (Figure 6a). The gelation effect becomes progressively less pronounced as the [$AlEt_3$]/[amine] ratio increases beyond 1, all other conditions (e.g., the monomer/amine molar ratio) being kept constant. Gelation cannot occur in toluene at [$AlEt_3$]/[amine] ratios of 3 and higher. In a parallel way, the bimodal molecular weight distribution disappears in favor of a unimodal distribution (Table I). That general behavior is however strongly dependent on the solvent. Although gelation of the reactive mixture is reported in toluene at 40 °C for a [$AlEt_3$]/[amine] of 2, a fluid solution is maintained when toluene is substituted by THF. As a second effect due to THF, a unimodal molecular weight distribution is observed in contrast to the bimodality in toluene. Eventually, the polymerization rate is definitely slower in THF compared to toluene. At an initial [ϵ-CL]/[amine] ratio of 43, the half-polymerization time at 40 °C is 185 min in THF ([$AlEt_3$]/[amine] = 2), in contrast to 35 min ([$AlEt_3$]/[amine] = 3) in toluene.

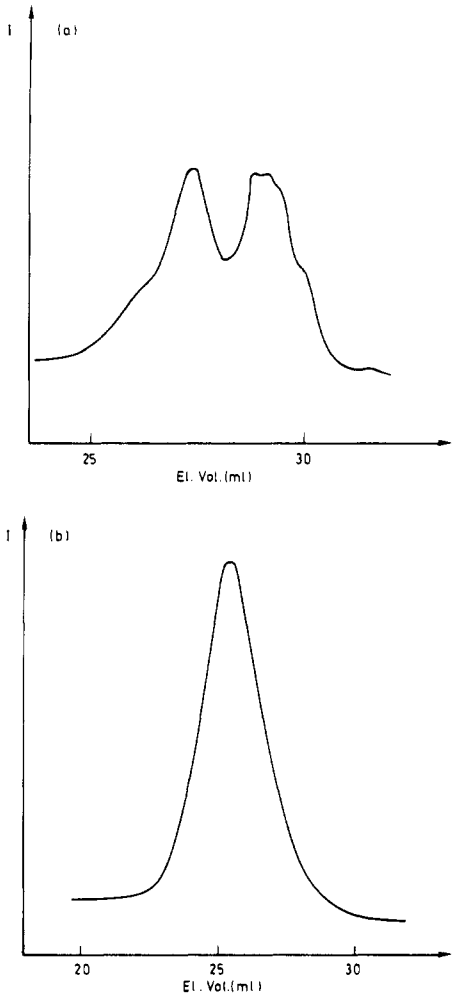
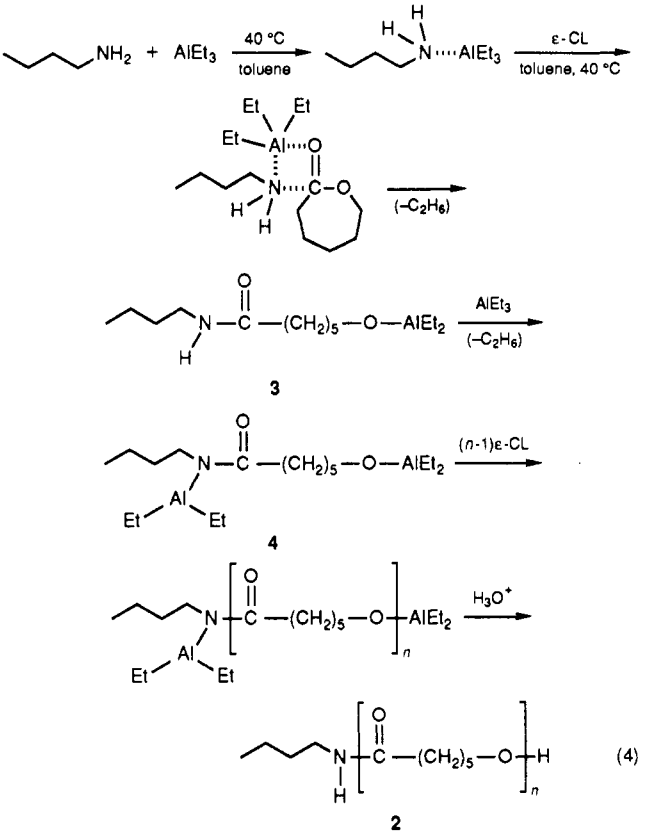


Figure 6. Size exclusion chromatograms of PCL initiated by *n*-butylamine in the presence of *n* equivalents of $AlEt_3$: (a) n = 1, in toluene (see entry 1, Table I); (b) n = 2, in THF (see entry 6, Table I).

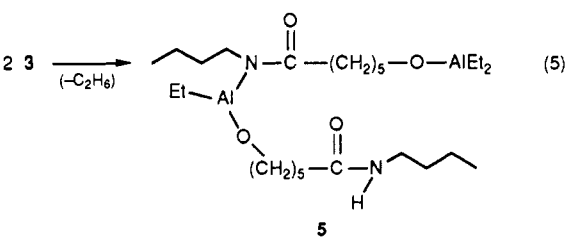
There is no evidence for a change in the opening mode of the monomer ("acyl-oxygen" rupture) when Al alkoxide is replaced by a $AlEt_3$/*n*-butylamine mixture of a ratio ranging from 1 to 4. The same is not true for the initiation step. Indeed, ethane is evolved (1.6 equiv per Al atom) when the monomer is added to the $AlEt_3$/amine mixture. It is accordingly proposed that the initiation proceeds through the nucleophilic attack of the primary amine on the carbonyl group of ε-CL, which is activated by $AlEt_3$. That attack promotes the ring-opening of the monomer and the simultaneous formation of ethane. A cleavage of the carbonyl-oxygen bond of ε-CL would occur as is usually observed in a coordination–insertion mechanism.[11,12] It is assumed that a proton from the amine then migrates to the oxygen of the opened monomer with the formation of a shortlived hydroxyl group (eq 4). Indeed, that group is very reactive toward the alkylaluminum and leads to the formation of ethane and an aluminum alkoxide responsible for the propagation step.

Together with the terminal alkoxide, a protic amide is thus formed which can react with $AlEt_3$. However, in toluene at 40 °C, this reaction is however incomplete and continues to approximately 60% as supported by the amount of ethane which is released during the whole reaction. That conclusion has been assessed by a separate reaction between $AlEt_3$ and *N*-methylacetamide in toluene (40 °C for 30 min). The formation of diethylaluminum *N*-methylacetamide was observed with a yield of 48%. According to Yasuda, the reaction of $AlEt_3$ with *N*-phenylacetamide goes to completion only at temperatures higher than 90 °C.[25]

The reaction scheme described by eq 4 allows one to account for the gelation of the polymerization medium and the bimodal molecular weight distribution of PCL when the initiation is promoted in toluene at 40 °C by an equimolar amount of amine and alkylaluminum.



When there are as many $AlEt_3$ molecules as primary amines, the protic amide **3** (eq 4) has to react preferentially with diethylaluminum alkoxide end groups, which are the main aluminum-containing species. If that reaction is intermolecular, it would rapidly lead to the cross-linking of the PCL chains. As a second effect, ~OAl(Et)N< moieties should be formed (eq 5) and then contribute to the formation of a second type of aluminum alkoxide in addition to the diethylaluminum alkoxides.



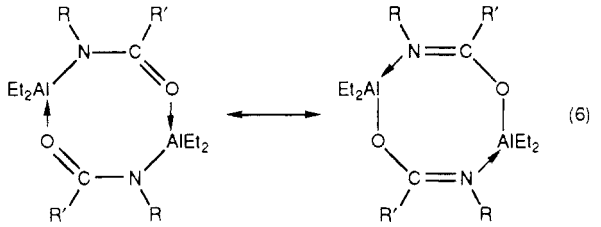
The two types of Al alkoxides could propagate the ε-CL polymerization at a specific but different rate and be responsible for a bimodal distribution. At a great enough excess of $AlEt_3$ with respect to the primary amine, reaction **5** is no longer favored, and the protonated amide reacts with $AlEt_3$ to form mainly species **4** rather than **5**. Since the excess of $AlEt_3$ required to prevent gelation from occurring depends on the polarity of the solvent, coordinative interactions also have to be considered. In addition to the well-known self-association of Al alkoxides in bulk and/or in apolar solvents,[23,24] the association of Al-

Table I
Polymerization of ϵ-CL in Toluene at 40 °C Initiated by *n*-Butylamine in the Presence of *n* Equivalents of $AlEt_3$ ($[M]_0 = 8.0 \times 10^{-1}$ mol·L^{-1})

entry	nAlEt$_3$	$[M]_0$/[amine]	time, h	conv, %	$\bar{M}_{n,GPC}$	$\bar{M}_w/\bar{M}_n$	SEC profile[a]
1	1	13	1	98[c]	1250	1.45	b
2	1	43	21	97[c]	6400	1.8	b
3	2	43	24	100[c]	4900	1.6	b
4	3	43	23	100	3800	1.45	m
5	4	43	21	100	3500	1.5	m
6	2[b]	43	22	100	3500	1.35	m

[a] Molecular weight distribution: monomodal (m) or bimodal (b). [b] Solvent = THF. [c] Gelation of solution.

substituted amides, such as species **4**, has been observed and attributed to the formation of intermolecular mesomeric structures (eq 6).[25,26]



(6)

These coordinative intermolecular interactions can of course favor the cross-linking reactions described by eq 5. The addition of a solvating agent, such as THF, is an effective way of restricting self-association of Al alkoxides and Al-substituted amides and all the consequences associated therewith.

Conclusions

Combining triethylaluminum and primary amines is an original way to generate effective initiators for the ϵ-CL polymerization. These systems allow for the quantitative control of both molecular weight and end groups. The end functionalization is actually ensured when the amine bears a functional group (e.g., 3-amino-1-propanol). That system is thus an additional way for the macromolecular engineering of PCL and particularly for the on-purpose synthesis of telechelic PCL. Variations in both the initiator composition and the monomer are under current investigation. Synthesis and the use of $H_2N(CH_2)_3OAlEt_2$ (**1**) as an initiator are also interesting, since the nucleophilic addition of the amino function on the carbonyl group of the monomer contributes to the initiation step in addition to the aluminum alkoxide itself. As a result (eqs 1 and 4), telechelic α,ω-dihydroxy-PCL are made available by a living process.

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References and Notes

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Registry No. 1, 20654-30-2; CL, 502-44-3; PCL (homopolymer), 24980-41-4; PCL (SRU), 25248-42-4; $HO(CH_2)_3NH_2$, 156-87-6; $NH_2(CH_2)_4H$, 109-73-9; $AlEt_3$, 97-93-8.