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Macromolecular Engineering of Polylactones and Polylactides. 5. Synthesis and Characterization of Diblock Copolymers Based on Poly-ϵ-caprolactone and Poly(L,L or D,L)lactide by Aluminum Alkoxides

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ABSTRACT: Aluminum isopropoxide is known to be an effective initiator for the ring-opening polymerization of lactides (D,L and L,L) and ϵ-caprolactone (ϵ-CL). For a question of mutual reactivity, the sequential polymerization of these two comonomers can only be achieved when ϵ-CL is first polymerized followed by the lactide. Formation of a large amount of homo PLA is however observed and has been attributed to a great difference in the mean degree of association of aluminum alkoxides in toluene in the presence of ϵ-CL and LA. In toluene, the mean number (n) of active sites per $Al(O^iPr)_3$ molecule jumps from 1 to 3 when ϵ-CL is substituted by LA. The addition of a small amount of an alcohol, like 2-propanol, is effective in preventing the aluminum alkoxide from associating, and n is then 3 whatever the monomer used. 2-Propanol participates in the polymerization of ϵ-CL and LA as supported by a decrease in the molecular weight of the final polymer in relation to the molar amount of added alcohol. This means that the alcohol molecules are rapidly exchanged with the alkoxide groups on Al. Under such conditions, the formation of pure diblock copolymers P(ϵ-CL-*b*-LA) is reported. Another successful strategy for the synthesis of the diblock copolymer consists in using an Al derivative that bears only one alkoxide group to initiate the polymerization of the two cyclic esters. In this regard, a diethylaluminum alkoxide is of great value, particularly the ethoxide one. A third, conceptually similar, approach to the synthesis of P(ϵ-CL-*b*-LA) copolymers relates to the reaction of a preformed hydroxy-terminated PCL with triethylaluminum and the use of that macroinitiator in the ring-opening polymerization of the lactide.

Introduction

A few synthetic polymers, particularly linear polyesters such as poly-ϵ-caprolactone (PCL), polylactides (PLA), and polyglycolide (PGA) are of great interest for medical applications. Biocompatibility, biodegradability, and permeability to many drugs are properties that justify the potentialities of these polyesters in surgery (biodegradable sutures, artificial skin, resorbable protheses), chemotherapy, and galenic formulations.[1-6]

Random copolymerization is known to provide new materials with properties intermediate between those of the parent homopolymers.[2] This is a valuable method to finely adjust one property to the required value. Biodegradable sutures, commerciallized under the trademark name of Vicryl are for instance based on a random copolymer of PGA and PLA.

In contrast to random copolymers, block and graft multicomponent systems are most often multiphase materials that provide for additivity of the phase properties.[7] As an example, block copolymerization of ϵ-caprolactone (ϵ-CL) and lactides (LA) allows the great permeability of the PCL to be combined with the rapid biodegradation of PLA.[8] Furthermore, these types of diblock copolymers are potential emulsifiers for the related homopolymer blends. That strategy is useful to improve the phase morphology, the interfacial adhesion and, accordingly, the ultimate mechanical properties of immiscible polymer blends.[9,10]

When two (or more) monomers can be polymerized in a living manner according to the same mechanism, their sequential polymerization generally leads to related block copolymers. It has been reported from our laboratory that bimetallic (Al, Zn) μ-oxo alkoxides[11-15] were effective in the living polymerization of unsubstituted lactones. Using these initiators, Hamitou et al. succeeded in the block copolymerization of ϵ-caprolactone and β-propiolactone.[16] Another interesting approach was pioneered by Heuschen et al.,[17] who substituted some of the alkoxide groups of the initiator with a hydroxy-terminated prepolymer (i.e., polystyrene or polybutadiene), whereas the exceeding alkoxides were replaced by inactive carboxylate groups. These macroinitiators were active in the ϵ-CL polymerization and provided the related diblock copolymers with high yield and purity. Block copolymerization of ϵ-CL and (D,L)LA was also reported by Feng and Song using the same bimetallic initiators.[18,19] However, they observed the formation of homopolyesters to an extent that was not disclosed. Interestingly, Stevens et al. demonstrated that aluminum isopropoxide ($Al(O^iPr)_3$) could have the same

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activity as the more complex bimetallic μ-oxo alkoxides in the living copolymerization of ϵ-CL.[20] These results were recently extrapolated to lactides and a living polymerization was maintained until a molecular weight of ca. 100 000.[21] For both monomers (ϵ-CL and LA), the polymerization mechanism is identical and corresponds to a "coordination-insertion" process. This paper reports an original method for the synthesis of perfectly controlled block copolymers of ϵ-CL and lactides (L,L and D,L) by means of the commercially available $Al(O^iPr)_3$.

Experimental Section

Monomers. ϵ-CL (Janssen Chimica) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. Lactides (D,L and L,L) were purchased from Boehringer, recrystallized three times from dried ethyl acetate at 60 °C, and then dried for 24 h at 35 °C under reduced pressure (10^{-2} mmHg) before polymerization.

Initiators. Triethylaluminum (Fluka) and aluminum triisopropoxide (Aldrich) were purified by distillation under reduced pressure. Concentration of the initiator solutions was determined by complexometric titration of Al by EDTA. Diethylaluminum alkoxides (Et_2AlOR with R = ^iPr, Et, PCL) resulted from the reaction of equimolar amounts of triethylaluminum and the corresponding alcohol.[26] Aluminum trialkoxides ($^iPrOAl(OR)_2$ with R = $CH(CH_2Cl)_2$ and $C_6H_4{}^pNO_2$) and 2,2-diethylhexanoylaluminum isopropoxide were prepared by reacting aluminum triisopropoxide with 2 equiv of the appropriate alcohol or carboxylic acid. All these reactions were carried out with carefully dried reagents under anhydrous nitrogen at 25 °C. The 2-propanol formed was removed from the reaction medium by azeotropic solvent distillation.[26] The aluminum alkoxides were characterized by ^1H NMR spectroscopy.

Solvents. Toluene and dichloromethane were dried by refluxing over CaH_2 and distilled under nitrogen atmosphere. THF and ethyl acetate were dried by refluxing over benzophenone–sodium complex and calcium chloride, respectively, and distilled under nitrogen atmosphere. All the alcohols (Aldrich) were dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use.

Polymerization Procedure. ϵ-CL and lactides were polymerized in solution under stirring, in a previously flamed and nitrogen-purged glass reactor. The reactor was charged with the solid (L,L or D,L)LA in a glovebox, under nitrogen atmosphere. As a liquid, ϵ-CL was introduced into the reactor with a syringe and rubber septums. Solvent and initiator solution were then added through stainless steel capillaries. In order to prepare block copolymers, a living PCL solution was added into a (L,L or D,L) lactide solution under strictly anhydrous conditions. The reaction was stopped by adding an excess (relative to the initiator) of 2 N HCl solution. The reaction mixture was then washed with water to a neutral pH. Two-thirds of the initial solvent was distilled off under reduced pressure and the polymer recovered by precipitation in heptane (homopoly-ϵ-caprolactone) or in methanol (homopolylactides and block copolyesters P(CL-*b*-LA)). Polymers were finally dried under reduced pressure at 25 °C, until a constant weight.

NMR Measurements. ^1H and ^{13}C NMR spectra of the polyesters were recorded in $CDCl_3$ with a Bruker AM 400 apparatus at 25 °C.

Molecular Weight Determination. Molecular weight and molecular weight distribution of homopolyesters were determined by using a gel permeation chromatograph (Waters 200) operating in THF and calibrated with polystyrene standards. The universal calibration method was applied for P(D,L)LA and PCL, using the previously reported viscometric relationships.[14,31]

When low ($\bar{M}_n < 15\,000$), the molecular weights were also estimated by ^1H NMR from the relative intensity of signals of the isopropyl ester end group and methine (PLA) or methylene (PCL) ester group, respectively.

Block copolyesters were also characterized by GPC and their composition determined by ^1H NMR from the signal intensities of the PLA methine ester group (δ = 5.20 ppm) and the PCL methylene ester group (δ = 4.06 ppm). From the overall composition and $\bar{M}_n$ of the first polymerized PCL block (GPC and/or ^1H NMR), the molecular weight of the second block was easily calculated.

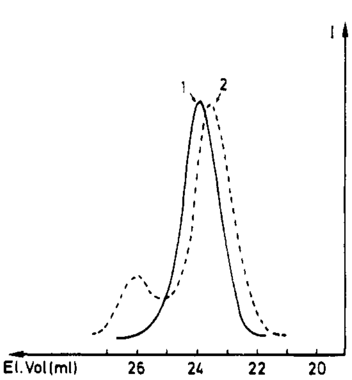


Figure 1. Size exclusion chromatograms of a P(CL-*b*-(D,L)LA) copolymer (+ homo PLA) (curve 2) and of the PCL block prepared in the first stage (curve 1). Initiator, $Al(O^iPr)_3$; solvent, toluene.

Table I
Kinetic Constants Characteristic of the Polymerization of Mixtures of ϵ-CL (*i*) and (L,L)(LA) (*j*)[22]

polymerization type	k, L mol^{-1} min^{-1}
PCL-O-Al< + ϵ-CL	k_{ii} = 3600
PCL-O-Al< + (L,L)LA	k_{ij} = 6300
P(L,L)LA-O-Al< + ϵ-CL	k_{ji} = 0.03
P(L,L)LA-O-Al< + (L,L)LA	k_{jj} = 0.60

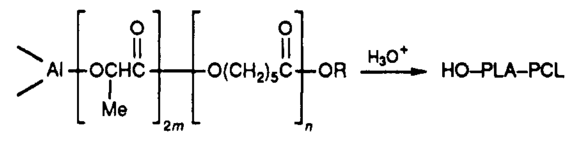
Table II
Effect of Temperature on the Polymerization of ϵ-CL by $Al(O^iPr)_3$

$[\epsilon\text{-CL}]_0/[Al]$	T, °C	$\bar{M}_n$ PCL (GPC)	$\bar{M}_w/\bar{M}_n$	n^a	yield (x), %
482	0	59 000	1.1	0.93	100
438	25	48 000	1.2	1.04	99
880	50	80 000	1.3	1.25	100
590	100	47 500	1.35	1.40	100
590[b]	170	13 000	2.1	4.10	80

[a] Average number of active sites per Al molecule, $n = (x/100)[([\epsilon\text{-CL}]_0/[Al])/\bar{M}_{n\,\mathrm{GPC}}]\mathrm{MM}\ \epsilon\text{-CL}$. [b] In bulk; otherwise $[\epsilon\text{-CL}]_0$ = 1 mol L^{-1} in toluene.

Results and Discussion

Mutual Reactivity of ϵ-CL and LA. Equation 1 schematizes the sequential polymerization of ϵ-CL and lactides as initiated by aluminum isopropoxide in toluene.



$$\mathrm{{>}AlOR} + \varepsilon\text{-CL} \longrightarrow \mathrm{{>}Al}\left[\mathrm{O(CH_2)_5\overset{\overset{\displaystyle O}{\|}}{C}}\right]_n\mathrm{OR} \xrightarrow{m\mathrm{LA}} \mathrm{{>}Al}\left[\mathrm{O\underset{\underset{\displaystyle Me}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}}\right]_{2m}\left[\mathrm{O(CH_2)_5\overset{\overset{\displaystyle O}{\|}}{C}}\right]_n\mathrm{OR} \xrightarrow{\mathrm{H_3O^+}} \mathrm{HO{-}PLA{-}PCL} \quad (1)$$

The nature of the monomer first polymerized in the sequential process is of critical importance. In agreement with some previously published data,[18] it has been observed that the block copolymerization is successful only when ϵ-CL is the first monomer to be polymerized. In contrast, ϵ-CL does not polymerize at all, when added to living PLA chains. This is consistent with the reactivity ratios characteristic of the ϵ-CL and (L,L)LA copolymerization initiated by aluminum isopropoxide in toluene at 70 °C, i.e., r((L,L)LA) = 17.9 and r(ϵ-CL) = 0.58.[22]

From $r_i = k_{ii}/k_{ij}$ and the polymerization rate constants of ϵ-CL (k_{ii}) and (L,L)LA (k_{jj}), the cross-propagation rate constants k_{ij} and k_{ji} (global) have been calculated and are

Table III
Effect of Solvent on the Homopolymerization of ϵ-CL at 0 °C in the Presence of $Al(O^iPr)_3$[a]

solvent	dielec const ϵ	half-life $t_{1/2}$, min	no. of active sites n
toluene	2.44	3.5	0.9
THF	7.60	8.7	1.0
CH_2Cl_2	9.08	47	0.9

[a] [ϵ-CL] = 1 mol L^{-1}. $[\epsilon\text{-CL}]_0/[Al] = 200$.

reported in Table I. It is clear that the propagating species derived from LA are poorly reactive toward ϵ-CL; actually, they are 2×10^5 times less reactive than the species of the ϵ-CL type toward (L,L)LA. The same behavior is observed when (D,L)LA is substituted for the L,L isomer.

Average Number of Active Sites (*n*). In preliminary block copolymerization experiments, the ϵ-CL polymerization was first initiated by $Al(O^iPr)_3$ in toluene at 0 °C. After 23 h of polymerization, a small sample was withdrawn from the reactor, the PCL formed was recovered, and its molecular weight was determined by GPC ($\bar{M}_n$ = 51 000). The living polyester solution was then added to a strictly dry (D,L)LA solution and the temperature raised to 70 °C. After 72 h, the polymerization medium was acidified and the crude copolymerization product analyzed by GPC and ^{1}H NMR. The polymerization yield was 100% for ϵ-CL and 86% for (D,L)LA. The size exclusion chromatogram (Figure 1) showed two well-resolved elution peaks. By fractionation of the crude copolymer based on the selective solubility of P(D,L)LA in cold acetone ($T < 10$ °C) and the use of $CHCl_3$ as a common solvent, a homo P(D,L)LA of 16 000 $\bar{M}_n$, as determined by ^{1}H NMR and GPC was separated from the P(ϵ-CL-*b*-(D,L)LA) block copolymer ($\bar{M}_{n\ \mathrm{PCL\ block}}$ = 51 000; $\bar{M}_{n\ \mathrm{PLA\ block}}$ = 14 000 as determined by ^{1}H NMR). No homo PCL was detected. The partial homopolymerization of (D,L)LA expectedly results from a decrease in the association degree of the active alkoxide groups upon addition of the second comonomer. Actually, the average number of active alkoxide groups per Al has been shown to be very different in toluene for the ϵ-CL polymerization at 0 °C (n = 0.9) and for the (D,L)LA polymerization at 70 °C (n = 3).[21] Thus, after the first copolymerization step, the increase of temperature and/or the addition of the (D,L)LA comonomer should promote a modification in the association of the active species, such as the average number of active sites increasing from 0.9 (for ϵ-CL at 0 °C) to 3 (for (D,L)LA at 70 °C). This means that the isopropoxide groups inactive in the ϵ-CL polymerization are made available for the conversion of second comonomer.

In order to solve that problem, two approaches have been considered. First, $Al(O^iPr)_3$ should be completely dissociated as to make all the potential polymerization sites (Al–O bonds) active whatever the comonomer (n = 3). Second, it would be of great interest to synthesize an initiator bearing only one alkoxide group per Al in order to prevent the coordinative association of the initiator to interfere whatever the monomer used.

Dissociation of $Al(O^iPr)_3$. Coordinative association of aluminum isopropoxide is a dynamic process[23,24] expectedly sensitive to temperature, solvent, and addition of a competing agent.

Effect of Temperature. The effect of temperature on the association of $Al(O^iPr)_3$ in toluene and, as a result, on the ϵ-CL polymerization is summarized in Table II.

The average number of active sites per aluminum (n) in toluene (Table II) increases moderately from 0.9 to 1.4 when temperature is raised from 0 to 100 °C. When the ϵ-CL polymerization is performed in bulk at 170 °C, the value of n increases sharply until 4.1, indicating that secondary reactions occur, accounting for the formation of more than one chain per potential Al–O insertion site. It is thus clear that temperature is not an effective parameter to promote the complete dissociation of the initiator in toluene, whereas, in bulk, secondary reactions occurring at high temperatures prevent any controlled polymerization to be carried out.

Effect of Solvent. Increasing the solvent polarity should expectedly depress the association of $Al(O^iPr)_3$. That is the reason why toluene (ϵ = 2.44) has been substituted by more polar solvents such as THF (ϵ = 7.60) and dichloromethane (ϵ = 9.08). The results, summarized in Table III, support the coordinative character of the ring-opening polymerization of cyclic esters. Indeed, when the dielectric constant of the solvent increases from 2.44 to 9.08, the polymerization rate significantly decreases. The solvent is however unable to perturb the coordinative association of the initiator itself since n remains constant.

Effect of Dissociating Agent. The association of $Al(O^iPr)_3$ in toluene can be accounted for by a dynamic coordination of the Al atoms to isopropoxide functions. The addition of any compound able to compete with alkoxides for coordination to Al is a possible way to prevent the initiator from associating. Purposely well defined amounts of 2-propanol have been added to the polymerization medium and their effect on the ϵ-CL polymerization has been analyzed, as reported in Table IV.

Expectedly, the addition of 2-propanol has a deleterious effect on the polymerization rate. Although, the reaction was complete after 4 h at a monomer to initiator molar ratio of 370, in toluene at 25 °C, a much longer period of time was required in the presence of 2-propanol. For instance, a yield close to 100% is only observed after 48 h, when the amount of ^{i}PrOH does not exceed 4 times that of the Al initiator. When a 16-fold molar excess of alcohol with respect to Al is used, the polymerization is not yet complete even after 88 h (77%). As a second effect, $\bar{M}_n$ decreases regularly as the amount of ^{i}PrOH increases. From the experimental molecular weight and monomer conversion, the average number of active sites has been calculated for a living process, n_{exp} (see Table IV). For the sake of comparison, the total number of potential isopropoxide groups (i.e., n_{th} = 2-propanol + isopropoxide) has also been reported in Table IV. There is a very close agreement between n_{th} and n_{exp}, at least until a 4-fold molar excess of 2-propanol with respect to Al. When the excess is higher (>11 times), the experimental molecular weight is too high and n_{exp} too small. A fast exchange between the isopropoxide groups and 2-propanol molecules is more likely responsible for the decrease in $\bar{M}_n$ upon the addition of increasing amounts of alcohol. In the presence of a large excess of 2-propanol (16 times), the disagreement between n_{exp} and n_{th} might indicate that all the alcohol molecules cannot participate to that exchange process.

In order to prove that an alkoxide–alcohol exchange actually occurs, isopropyl alcohol has been substituted by 1-phenyl 2-propanol. Although of approximately the same reactivity as 2-propanol, the phenyl-substituted propanol has the advantage of being easily detected by ^{1}H NMR spectroscopy.

When carried out in toluene at 25 °C in the presence of $Al(O^iPr)_3$ and 3 equiv of 1-phenyl-2-propanol, ϵ-CL polymerization provides a polyester that has been analyzed by ^{1}H NMR after purification (Figure 2). This indicates the presence of aromatic protons, i.e., the participation of 1-phenyl-2-propanol in the initiation of ϵ-CL polymerization. The relative importance of this participation has

Table IV
Effect of ^iPrOH on the Ring-Opening Polymerization of ϵ-CL Initiated by $Al(O^iPr)_3$ in Toluene at 25 °C[a]

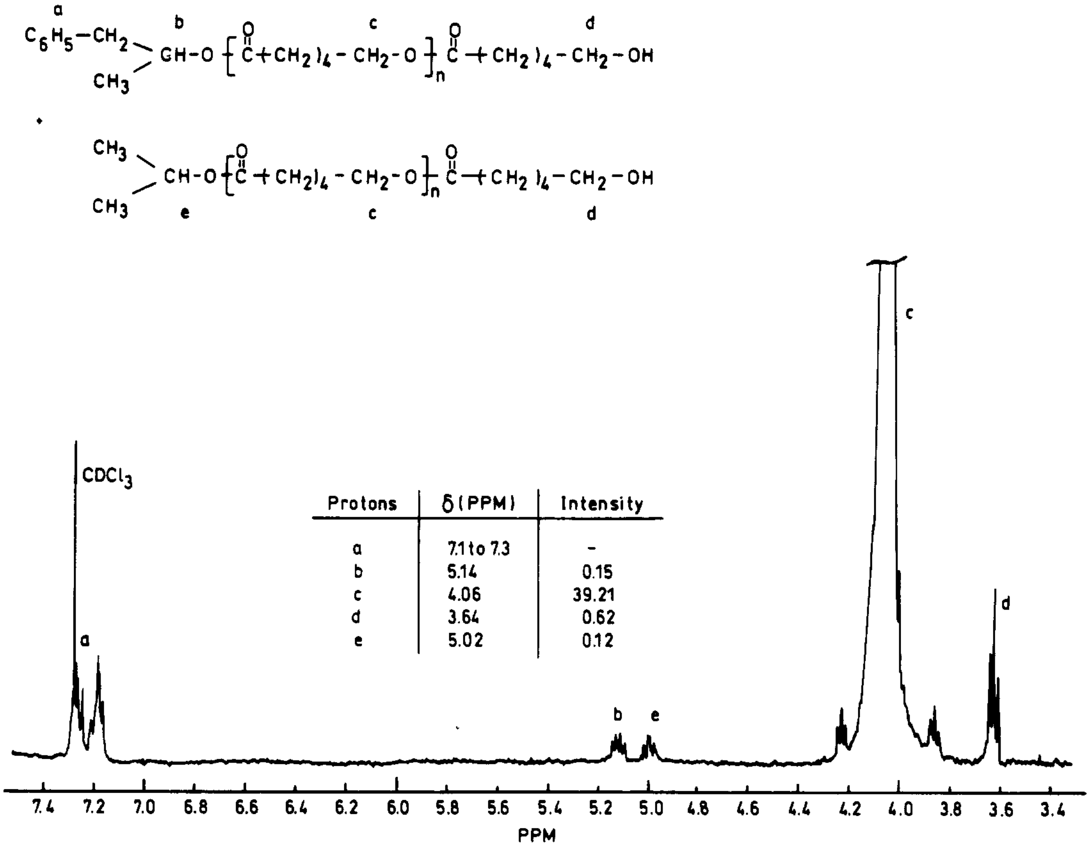
entry	n^iPrOH, mol	t, h	yield (x), %	$\bar{M}_n$ (GPC)	$\bar{M}_w/\bar{M}_n$	n_{th}[b]	n_{exp}[c]
1	0	4	100	40500	1.20	3.0	1.04
2	7.12×10^{-5}	48	97	12300	1.34	4.0	3.3
3	1.42×10^{-4}	48	98	9100	1.22	5.0	4.5
4	2.84×10^{-4}	48	97	6200	1.12	7.0	6.6
5	5.68×10^{-4}	48	92	4300	1.13	11.0	9.1
6	1.16×10^{-3}	88	77	2900	1.36	19.0	11.3

[a] $[\epsilon\text{-CL}]_0/[Al] = 370$. $[\epsilon\text{-CL}]_0 = 1$ mol L^{-1}. [b] n_{th} is the total number of "O^iPr" functions per Al molecule. $n_{th} = (n^iPrOH + 3nAl(O^iPr)_3)/nAl(O^iPr)_3$. [c] n_{exp} is the average number of active sites per Al molecule. $n_{exp} = (x/100)[(n\epsilon\text{-CL}/nAl(O^iPr)_3 \times MM\,\epsilon\text{-CL})/\bar{M}_{n\,exp}] = (x/100)(42000/\bar{M}_{n\,exp})$ for $[\epsilon\text{-CL}]_0/[Al] = 370$).

Table V
Effect of ^iPrOH on the Ring-Opening Polymerization of (D,L)LA Initiated by $Al(O^iPr)_3$ in Toluene at 70 °C ((D,L)LA = 1 mol L^{-1})

entry	n(D,L)LA, mol	$nAl(O^iPr)_3$, mol	n^iPrOH, mol	time, h	yield (x), %	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$	n_{th}[a]	n_{exp}[b]
1	2.83×10^{-1}	4.53×10^{-4}	0	70	98	29800	1.2	3.00	2.95
2	3.27×10^{-2}	5.24×10^{-5}	5.24×10^{-5}	76	89	21500	1.35	4.00	3.74
3	2.91×10^{-2}	4.66×10^{-5}	9.30×10^{-5}	76	84	19300	1.4	5.00	4.67
4	2.08×10^{-2}	4.48×10^{-5}	1.42×10^{-4}	113	90	10250	1.2	6.17	5.87
5	2.43×10^{-2}	3.89×10^{-5}	2.72×10^{-4}	76	70	7650	1.1	10.00	8.24

[a] n_{th} is the total number of "O^iPr" functions per Al molecule. $n_{th} = (n^iPrOH + 3nAl(O^iPr)_3)/nAl(O^iPr)_3$. [b] n_{exp} is the average number of active sites per Al molecule. $n_{exp} = (x/100)[((n(\text{D,L})LA/nAl(O^iPr)_3)\ MM\ LA)/\bar{M}_{n\,GPC}]$.



Protons	δ (PPM)	Intensity
a	7.1 to 7.3	-
b	5.14	0.15
c	4.06	39.21
d	3.64	0.62
e	5.02	0.12

Figure 2. ^1H NMR spectrum of a PCL synthesized in toluene at 25 °C in the presence of $Al(O^iPr)_3$ and 3 equiv of 1-phenyl-2-propanol. Solvent, $CDCl_3$.

been calculated by comparison of the signal intensities at $\delta(Me_2CHO) = 5.02$ ppm and $\delta(PhCH_2CH(Me)O) = 5.11$ ppm and found to be ca. 55%. It is thus obvious that the polymerization of ϵ-CL is not only initiated by the isopropoxide groups of the initial $Al(O^iPr)_3$ molecules but also by the alcohol added purposely to prevent the initiator from coordinative association. An alcohol–alkoxide exchange thus occurs in toluene at 25 °C, which is faster than the propagation event of ϵ-CL proceeding through a coordination–insertion mechanism. Inoue reported the same exchange process when ϵ-CL was polymerized by (tetraphenylporphinato)aluminum alkoxides in the presence of methanol.[25]

The next question that has been addressed is to know whether the (D,L)LA polymerization is also affected by the addition of an alcohol to the initiator. (D,L)-Lactide has been polymerized in toluene at 70 °C in the presence of $Al(O^iPr)_3$ and various amounts of 2-propanol. The results are summarized in Table V.

As previously reported,[21] the three alkoxide functions of $Al(O^iPr)_3$ initiate (D,L)LA polymerization even in the absence of ^iPrOH. The addition of increasing amounts of that alcohol with respect to the initiator promotes a decrease in the number-average molecular weight, stating

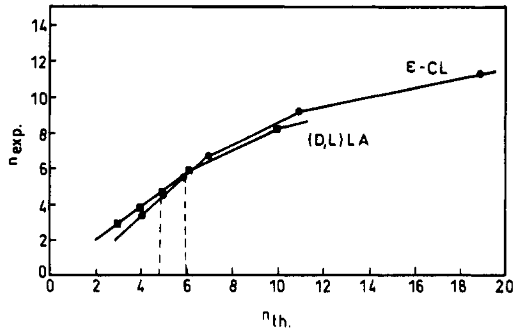


Figure 3. Dependence of the average number of active sites per Al molecule (n_{exp}) versus the total number of "O^{i}Pr" groups (n_{th}) in the polymerization of ε-CL and (D,L)LA, respectively. Initiator, Al(O^{i}Pr)$_3$ added with various amounts of 2-propanol; solvent, toluene.

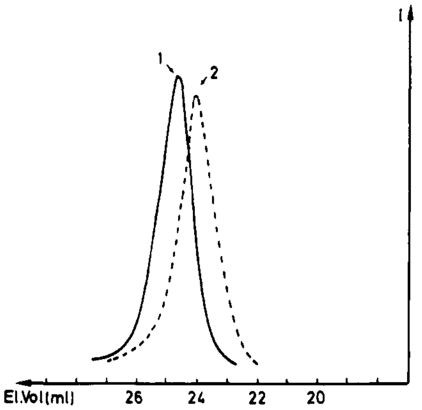
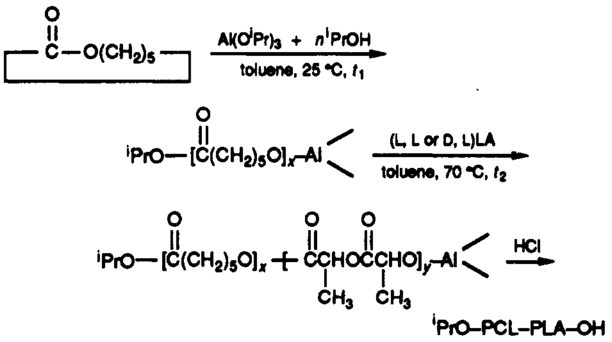


Figure 4. Size exclusion chromatograms of a P(CL-*b*-(D,L)LA) copolymer (curve 2) and the PCL block prepared in the first stage (curve 1). Initiator, Al(O^{i}Pr)$_3$ + ^{i}PrOH; solvent, toluene.

again that the added alcohol participates in the polymerization of (D,L)LA. Similarly to ε-CL polymerization, it appears that when the alcohol/Al molar ratio exceeds 6, n_{exp} is smaller than n_{th}. This indicates that some alcohol molecules do not exchange and so do not initiate (D,L)-lactide polymerization.

According to the data gathered in Figure 3, when the ^{i}PrOH/Al molar ratio is at least 1 or higher, the number of active sites is the same for the two comonomers. These conditions should favor the formation of P(CL-*b*-(L,L)LA) and P(CL-*b*-(D,L)LA) copolymers excluding homopolymers. Equation 2 schematizes the block copolymerization of ε-CL and lactides.



(2)

In order to assess the effectiveness of a completely dissociated initiator in the sequential polymerization of ε-CL and (L,L or D,L)LA, ε-CL was first polymerized in toluene at 25 °C by Al(O^{i}Pr)$_3$ added with a 2-fold or a 3-fold molar excess of 2-propanol. The solution of the "living" PCL was then transferred to a lactide (L,L or D,L) solution in toluene and the temperature increased to 70 °C. The crude copolymerization product was purified (see Experimental Section), and characterized by GPC and NMR. Results reported in Table VI show that, in all the cases, the whole yield is higher than 90%. Size exclusion chromatography (Figure 4) confirms the absence of any detectable amount of homopolymers. Furthermore, the molecular weight of the diblock calculated from the $\bar{M}_n$ of the PCL block (GPC, universal calibration) and composition of the copolymer (^{1}H NMR) is in a close agreement with the expected values.

As an example, Figure 5 shows the ^{1}H NMR spectrum of a copolyester mentioned in Table VI (first entry). $\bar{M}_n$ of the PCL segment is 13 300 as measured by GPC. From the comparison of the PLA methine ester group signal at δ = 5.20 ppm and that of the PCL methylene one at δ = 4.06 ppm, $\bar{M}_n$ of the PLA segment is found to be ca. 8600 ± 10%. The values are in good agreement with theoretical molecular weights taking conversion into account ($\bar{M}_n$ = 12 000 and 7700 for PCL and PLA segments, respectively).

Modification of the Initiator. Data of Table VI have unambiguously shown that the sequential polymerization of ε-CL and lactides is perfectly controlled provided that the aluminum alkoxide is unassociated. Instead of using a trialkoxide together with a dissociation agent, another strategy could consist of synthesizing an aluminum monoalkoxide, the two other substituents of which would prevent any coordinative association to occur.

In a first step, two potentially active isopropoxide groups of Al(O^{i}Pr)$_3$ have been substituted by more acidic and bulky alcohols, i.e., 1,3-dichloro-2-propanol or *p*-nitrophenol, and by 2-ethylhexanoic acid. These aluminum monoisopropoxide compounds have been used as initiators in the ε-CL polymerization in toluene at 25 °C. Table VII shows that substituents derived from acid compounds decrease the general reactivity of the Al initiator. The half-polymerization time increases substantially when *p*-nitrophenolate groups are attached to Al, whereas 2-ethylhexanoate substituents completely deactivate the aluminum monoisopropoxide. The 1,3-dichloro-2-propanolate groups have the less depressive effect on the polymerization kinetics (2-fold increase of $t_{1/2}$), but they participate partly to the polymerization since n = 2.1 instead of 1.0 as expected.

In a second approach, two of the three isopropoxide groups of Al(O^{i}Pr)$_3$ have been replaced by electronically poor and totally inactive alkyl groups.[26,27] The Et$_2$AlO^{i}Pr compound can be synthesized in a very easy and direct way by reacting equimolar amounts of 2-propanol (^{i}Pr-OH) with triethylaluminum (eq 3).

$$\mathrm{AlEt_3} + {}^i\mathrm{PrOH} \xrightarrow{\text{toluene}} \mathrm{Et_2AlO^iPr} + \mathrm{EtH} \qquad (3)$$

That technique has been used successfully to prepare functional aluminum alkoxides.[26,28,29] Table VIII shows that diethylaluminum monoisopropoxide and diethylaluminum monoethoxide are very effective initiators in the sequential polymerization of ε-CL and LA (eq 4).

$$\mathrm{RO\text{-}AlEt_2} \xrightarrow[\text{toluene, 25 °C, } t_1]{n\epsilon\text{-CL}} \mathrm{RO\text{-}[C(O)(CH_2)_5O]_{\mathit{n}}\text{-}AlEt_2} \xrightarrow[\text{toluene, 70 °C, } t_2]{m(\mathrm{D,L})\mathrm{LA}} \mathrm{RO\text{-}[C(O)(CH_2)_5O]_{\mathit{n}}\text{-}[C(O)\text{-}}$$

$$\mathrm{C(CH_3)HO]_{2\mathit{m}}\text{-}AlEt_2} \xrightarrow{\mathrm{HCl}} \mathrm{RO\text{-}PCL\text{-}P(D,L)LA\text{-}OH} \qquad (4)$$

There is indeed a good agreement between the theoretical and the experimental molecular weight and composition. GPC analysis shows the formation of a P(CL-*b*-LA)

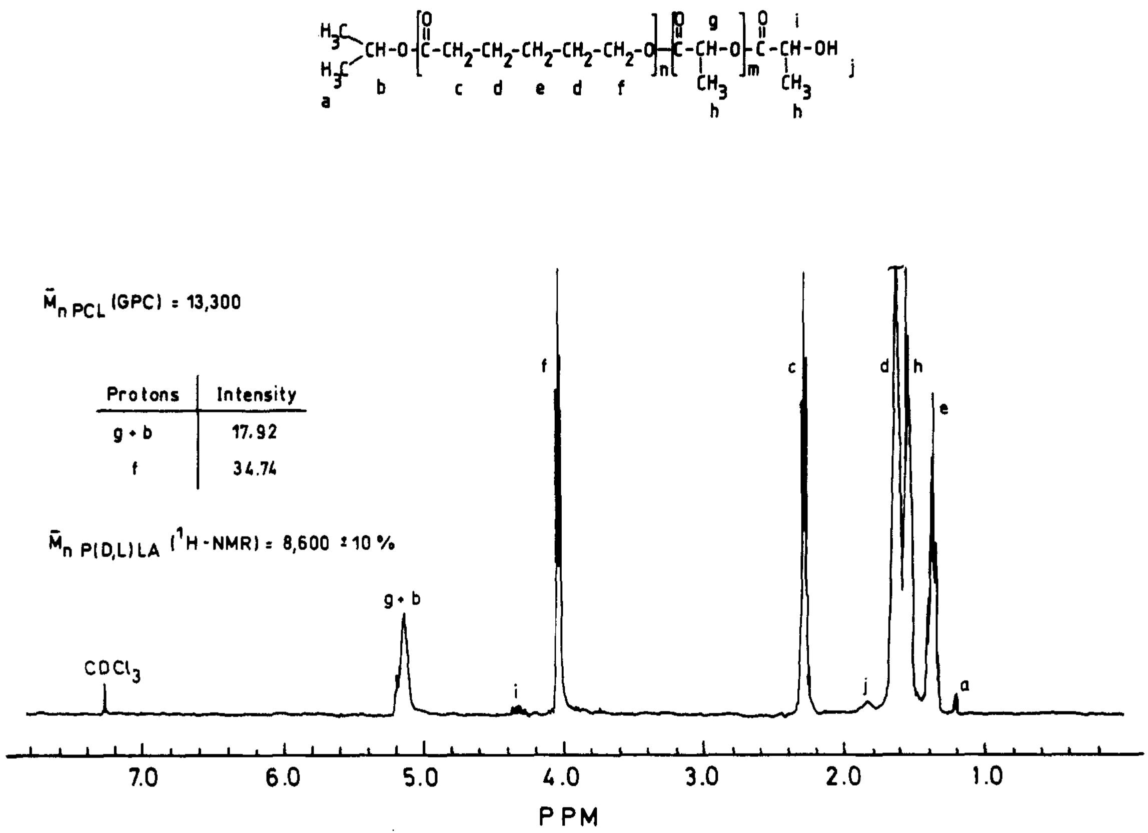


Figure 5. ^{1}H NMR spectrum of a poly(ε-CL-*b*-(D,L)LA) copolymer synthesized in toluene in the presence of Al(O^{i}Pr)$_3$ and ^{i}PrOH (see Table VI, first entry). Solvent, CDCl$_3$.

Table VI
Block Copolymerization of ε-CL and Lactides in Toluene in the Presence of Al(O^{i}Pr)$_3$ Added with a Twofold (n_{th} = 5) or Threefold (n_{th} = 6) Molar Excess of 2-Propanol

n_{th}[a]	LA	$\bar{M}_{n\,th}$ PCL[b]	$\bar{M}_{n\,th}$ PLA[c]	$t_{1\,CL}$,[d] h	$t_{2\,LA}$,[d] h	LA convrsn,[e] %	$\bar{M}_{n\,PCL}$ (GPC)	$\bar{M}_{n\,PLA}$ (^{1}H NMR)	$\bar{M}_w/\bar{M}_n$
5	D,L	1200	9300	47	142	81	13300	8600	1.35
6	D,L	5500	4500	25	88	87	6000	4400	1.25
6	L,L	11200	8600	24	90	80	12000	7500	1.3

[a] n_{th} is the total number of "O^{i}Pr" functions per Al molecule. [b] $\bar{M}_{n\,th}$ PCL = $m_{\epsilon\text{-CL}}/(n_{th} \times n\text{Al(O}^i\text{Pr)}_3)$ (at 100% conversion). [c] $\bar{M}_{n\,th}$ PLA = $m_{LA}/(n_{th} \times n\text{Al(O}^i\text{Pr)}_3)$ (at 100% conversion). [d] t_1 and t_2 are the polymerization time for ε-CL and LA, respectively. [e] Note thate ε-CL conversion is complete in each experiment.

Table VII
Polymerization of ε-CL in Toluene at 25 °C, in the Presence of Al(O^{i}Pr)(OR)$_2$[a]

OR	p$K_{a\,(ROH)}$	half-life $t_{1/2}$, s	n
$OCH(CH_3)_2$	17.1	24	1.0
$OCH(CH_2Cl)_2$	7.15 < pK_a < 17.1	45	2.1
OC_6H_4-*p*-NO_2	7.15	36000	
$OCOCH(Et)C_4H_9$	4.85	no reaction	

[a] [ε-CL]$_0$/[Al] = 140. [ε-CL]$_0$ = 1 mol L^{-1}.

copolymer free from any homopolymer. It is worth noting that the polymerization rate of ε-CL is seemingly slower (ca. 80×) when diethylaluminum monoalkoxide (isopropoxide or ethoxide) is used as the initiator instead of aluminum triisopropoxide. This kinetic depression of the ε-CL polymerization was also observed when functional diethylaluminum alkoxide was used as an initiator instead of the corresponding functional aluminum trialkoxide. All the kinetic effects reported in this section will be discussed in a separate paper.

$$\text{PCL-OH} \xrightarrow[\text{toluene, 25 °C}]{\text{AlEt}_3} \text{PCL-O-AlEt}_2 \xrightarrow[\text{(2) H}_3\text{O}^+]{\text{(1) (D,L)LA}} \text{P(CL-}b\text{-LA)} \tag{5}$$

As an alternative way to aluminum monoalkoxide derivatives (eq 3), triethylaluminum can possibly be reacted with 1 equiv of a hydroxy-terminated PCL (eq 5). A diethyl Al(O-PCL) compound has been prepared by using a carefully dried solution of ω-hydroxy PCL ($\bar{M}_n$ = 8000) in toluene. That macroinitiator has been used to polymerize (D,L)LA in toluene at 70 °C. After 54 h, the yield is 80% and, taking into account of the [LA]$_0$/[Al] ratio and the (D,L)LA conversion, the experimental $\bar{M}_n$ of the PLA block (10 000) corresponds satisfactorily to the expected value (9000).

Characterization of the Diblock Copolymers. P(CL-*b*-LA) copolymers have been analyzed by GPC, ^{1}H NMR, and ^{13}C NMR. As already pointed out, GPC does not show any detectable amount of homopolyesters (PCL or PLA) (Figure 4). ^{1}H NMR of the block copolyesters has been previously discussed (Figure 5).

^{13}C NMR indicates the block copolymerization of ε-CL and LA is free from any transesterification reactions under the experimental conditions used in this study. Indeed, the sequential analysis of the copolymers as described by Kricheldorf et al.[30] allows demonstration of the absence of any transesterification reactions. These authors copolymerized ε-caprolactone and (L,L)-lactide in bulk at 100 °C by means of tributyltin methoxide and ^{13}C NMR reported shows, between the peaks of the homogeneous block (e.g., Cap–Cap bonds), different signals characteristic of a more random distribution of the comonomers and

Table VIII
Block Copolymerization of ϵ-CL and (D,L)LA in Toluene in the Presence of Et$_2$AlOR

R	$\bar{M}_{n\ PCL}$(th)^a	$\bar{M}_{n\ PLA}$(th)^b	(D,L)LA convrsn,^{c} %	$t_{1\ CL}$, h	$t_{2\ LA}$, h	$\bar{M}_{n\ PCL}$ (GPC)	$\bar{M}_{n\ PLA}$ (^{1}H NMR)	$\bar{M}_w/\bar{M}_n$
^{i}Pr	9100	7600	79	76	168	8500	6000	1.6
^{i}Pr	4000	5000	80	55	93	4200	4000	1.4
Et	10000	12000	83	19	96	9800	9300	1.3

^{a} $\bar{M}_{n\ PCL}$(th) = $m_{\epsilon\text{-CL}}/n\text{Et}_2\text{AlOR}$ (at 100% conversion). ^{b} $\bar{M}_{n\ PLA}$(th) = $m_{LA}/n\text{Et}_2\text{AlOR}$ (at 100% conversion). ^{c} Note that ϵ-CL conversion is complete in each experiment.

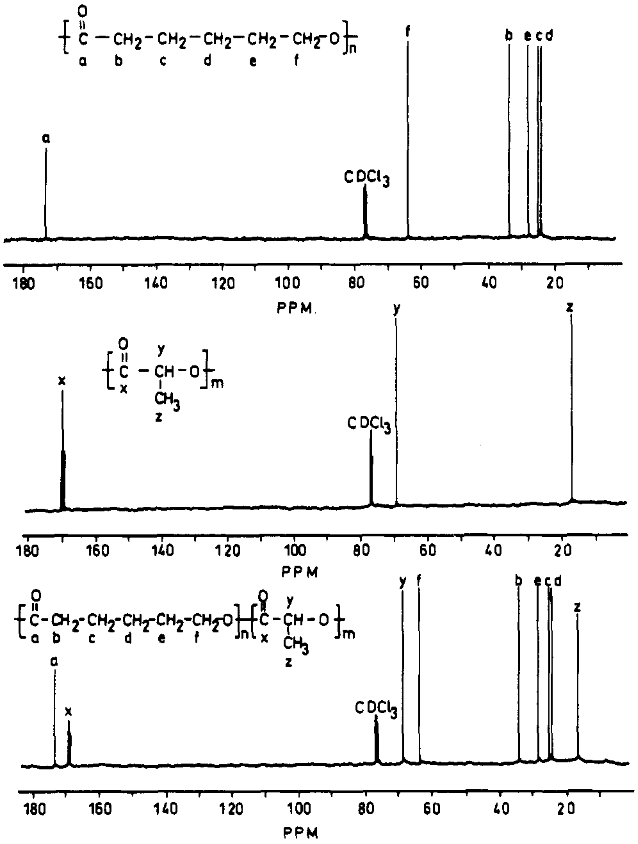


Figure 6. ^{13}C NMR spectra of PCL, P(D,L)LA and poly(ϵ-CL-*b*-(D,L)LA) copolymer in CDCl$_3$.

one peak at δ = 170.8 ppm assigned to the "Cap–Lac–Cap" triad due to the transesterification reactions.

As shown in Figure 6, the copolyesters P(CL-*b*-LA) we have synthesized do not present any intermediate signals between the two carbonyl ones of each homopolyesters (PCL and P(D,L)LA) and so clearly demonstrate the pure diblock structure of the copolymer.

Conclusions

Thanks to the similarity of the polymerization mechanism initiated by aluminum isopropoxide, ϵ-CL and lactides (D,L or L,L) can possibly be polymerized in a sequential way with formation of the related block copolymers. However, the mutual reactivity of these two comonomers dictates the order of their addition: ϵ-CL must be first polymerized followed by the lactide.

The average number of active sites per aluminum molecule increases from one to three when LA is added to the solution of living PCL in toluene. This is responsible for the formation of homo PLA besides the expected block copolymer.

The complete dissociation of Al(O^{i}Pr)$_3$ by 2-propanol ($n \geqslant 3$) from the very beginning of the sequential polymerization or the use of a diethylaluminum monoalkoxide ($n = 1$) has allowed P(CL-*b*-LA) copolymers to be prepared with the exclusion of any homopolymer.

Let us point out that the monoalkoxide function can be either a traditional isopropoxide or a polymeric group. If the polymeric substituent of the alkoxide is PCL, a macroinitiator is available for lactide polymerization and the synthesis of the (PCL-*b*-PLA) copolymer.

In all cases, the molecular weight of each block matches the expected value. Furthermore, ^{13}C NMR spectroscopy has shown that no transesterification reaction occurs to a significant extent during block copolymerization processes.

Morphology and mechanical properties of P(CL-*b*-LA) copolyesters will be characterized in the near future as well as their potential interfacial activity in the immiscible blends of PCL and PLA.

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Registry No. PCL-*b*-(D,L)LA, 109351-64-6; THF, 109-99-9; PCL-*b*-(L,L)LA (block copolymer), 111821-20-6; Al(O-*i*-Pr)$_3$, 555-31-7; PhCH$_2$CH(OH)CH$_3$, 698-87-3; CH$_3$Ph, 108-88-3; CH$_2$Cl$_2$, 75-09-2; *i*-PrOH, 67-63-0; Al(OPr-*i*)(OCH(CH$_2$Cl)$_2$)$_2$, 32013-90-4; Al(OPr-*i*)(OC$_6$H$_4$-*p*-NO$_2$)$_2$, 132750-03-9; Et$_2$AlOPr-*i*, 6063-60-1; Et$_2$AlOEt, 1586-92-1.