Macromolecular Engineering of Polylactones and Polylactides. 7. Structural Analysis of Copolyesters of ε-Caprolactone and L- or D,L-Lactide Initiated by Al(O^iPr)$_3$

P. Vanhoorne,[†] Ph. Dubois, R. Jerome,* and Ph. Teyssie

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

Received April 4, 1991; Revised Manuscript Received July 25, 1991

ABSTRACT: Copolymerization of mixtures of ε-caprolactone (ε-CL) and D,L- or L-lactide has been initiated by aluminum isopropoxide. On the basis of the monomer reactivity ratios and assuming that no side reaction occurs, tapered copolymers should be formed particularly when D,L-lactide is the comonomer rather than L-lactide. The sequential distribution of the comonomers has been analyzed by an original method based on the quantitative measurement of the carbonyl ^{13}C signals. Comparison of the experimental and the theoretical distributions clearly shows that transesterification reactions occur during copolymerization through both intra- and intermolecular mechanisms. Gel permeation chromatography and differential scanning calorimetry data support that conclusion. The D,L-lactide-based copolymers have however a more blocky structure than those containing L-lactide, and they are also less sensitive to transesterification reactions.

Introduction

The availability of biocompatible and biodegradable polymers has promoted major advances in the biomedical field.[1-3]

A few synthetic polymers, such as poly-ε-caprolactone (PCL), polylactides (PLA), and polyglycolide (PGA) are polyesters known for their usefulness in medicine.[3,4] For example, PCL is a biocompatible polymer with a half-life time of 1 year in vivo and is permeable to many drugs. In contrast, PLA is hardly permeable to most drugs, and its half-life time is much shorter: a few weeks in vivo.[2,4] Thus, combining PCL permeability and rapid biodegradation of PLA may lead to a wide range of drug delivery devices with adjustable properties (e.g., permeability, hydrophilicity, degradation rate, ...).[2,7] Purposely, random copolymerization has been carried out to produce materials with intermediate properties between those of the parent homopolyesters. This approach has allowed permeability to be extensively controlled.[3] In contrast to random copolymers, block and graft copolymers are generally multiphase materials that provide for the additivity of the phase properties.[6] As an interesting example, block copolymerization of caprolactone and lactides is an effective way of combining the great permeability of the PCL segments and the rapid biodegradation of the PLA component.[7]

When two (or more) monomers of a comparable reactivity can be polymerized in a living manner according to the same mechanism, their sequential polymerization leads to block copolymers. It has been reported from our laboratory that bimetallic (Al, Zn) μ-oxoalkoxides are effective in the living homopolymerization and block copolymerization of unsubstituted lactones.[8-14] Interestingly enough, Stevens et al. have shown that aluminum isopropoxide (Al(O^iPr)$_3$) could be substituted for the more complex bimetallic μ-oxoalkoxides in the living (co)polymerization of ε-caprolactone (ε-CL).[27] These results have been recently extrapolated to lactides, and a living polymerization has been reported until molecular weights of ca. 100 000.[26] For both monomers (ε-CL and lactide), the polymerization mechanism corresponds to a "coordination–insertion" process. On that basis, Jacobs and Dubois[15] have synthesized perfectly controlled block copolymers of CL and lactides (L and D,L) in toluene using Al(O^iPr)$_3$ as an initiator. The key point is that ε-CL has to be the first polymerized and the average number of growing chains per Al atom must be the same for the two comonomers. However, when the reactivity ratios of CL and lactide (LA) are considered, their copolymerization initiated by Al(O^iPr)$_3$ or Sn(OBu)$_4$ should lead to copolymers with a blocky structure.[7,17,18] This paper aims at analyzing the structure of copolymers prepared from CL and LA (L,L and D,L isomers) mixtures, making block or, at least, tapered copolymers available.

Experimental Section

Chemicals. ε-CL (Janssen) and L,L- and D,L-lactides (Boehringer, Ingelheim) were used as received. ε-CL was dried over CaH_2 under nitrogen at 25 °C for 2 days and distilled under reduced pressure (10^{-2} mmHg) just before use. Lactides were 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. Aluminum triisopropoxide (Aldrich) was purified by distillation under reduced pressure and dissolved in dry toluene. Concentration of the solutions was determined by complexometric titration of Al by EDTA.

Toluene was dried by refluxing over CaH_2 and distilled under nitrogen atmosphere. Ethyl acetate was dried by refluxing over calcium chloride and distilled under nitrogen atmosphere.

Polymerization Procedure and Characterization. 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) lactide in a glovebox, under nitrogen atmosphere. Solvent was added through rubber septums using stainless steel capillaries or syringes, and lactide was dissolved at 70 °C. ε-CL and the initiator solution were successively added the same way.

Total concentration of monomers was systematically 1 mol/L, and monomer/initiator molar ratio was 1/200 in all the experiments. Polymerization was stopped by adding an excess (relative to the initiator) of 2 N HCl solution. The reaction mixture was then washed with water up to neutral pH. The polymer was recovered by precipitation in heptane and finally dried under reduced pressure at 25 °C, until constant weight.

Molecular weight and molecular weight distribution of homopolyesters were determined using a gel permeation chromatograph (HP 1090) operating in THF at 25 °C and calibrated with polystyrene standards.

[†] Aspirant of the Belgian National Found for Scientific Research (FNRS).

0024-9297/92/2225-0037$03.00/0

Table I
Determination of Reactivity Ratios in Copolymerization of ϵ-Caprolactone and D,L-Lactide: Experimental Data

M_1/M_2[a]	x, %	dM_2/dM_1
0.96	2	15.39
1.46	8	8.35
2.33	6	4.00
5.67	7	0.92

[a] 1 = CL, 2 = LA.

Copolymer composition was determined by ^{1}H NMR from the methyne ester signal (5.20 ppm) of PLA and the methylene ester signal of PCL (4.06 ppm). Spectra were recorded in $CDCl_3$ at 25 °C, using a Bruker AM400 apparatus operating at 400.13 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C, using the same Bruker AM400 apparatus operating at 100.62 MHz. The "INVGATE" sequence was used in order to investigate the comonomer distribution within copolymers. The validity of that technique was previously ascertained by analyzing samples (monomer blends and copolymers) of a well-known composition (^{1}H NMR). ^{13}C NMR measurements were proved to be quantitative with a pulse width of 30°, an acquisition time of 0.7 s, and a delay of 3 s between pulses.

Differential scanning calorimetry (DSC) measurements were carried out with a DSC Du Pont 9000 apparatus calibrated with ultrapure indium (T_m = 156.6 °C) and gallium (T_m = 28.8 °C). After their introduction in the DSC apparatus, all the samples were first cooled at 173 K for 2 min. The heat capacity/temperature curves of the nascent samples were recorded at a heating rate of 25 K/min. A second scan was recorded after the sample was cooled to 173 K and maintained at that temperature for 5 min. Melting temperatures were measured on the first scan, and glass transition temperatures on the second one.

Average theoretical composition of the copolymers and first-order Markovian sequence distribution of the comonomers[24] were calculated using an IBM compatible microcomputer. The program was based on an iterating process, splitting the reaction in n intervals. In each interval, concentrations were assumed to be constant, and composition and sequence lengths were calculated using the Mayo–Lewis equation. Concentrations were then calculated for the next interval. Composition and sequence length could be summed up at any conversion. Bernouillan statistics corresponded to the case where $r_1 = r_2 = 1$.

Results

Determination of Reactivity Ratios. ϵ-CL and LA might be copolymerized by $Al(O^iPr)_3$ since that metal alkoxide is known to homopolymerize each of these two monomers according to the same mechanism. The sequence distribution of the comonomers within the chains can be calculated provided the reactivity ratios (r_1 and r_2) are made available. r_1 and r_2 are usually determined from the experimental composition of a series of copolymers synthesized from comonomer mixtures of various compositions, the conversion degree being kept to a point where the change in the initial monomer composition is negligible.[5]

Copolymerization of ϵ-CL (M_1) and L-LA (M_2) has been previously investigated at 70 °C, with $[M_1] + [M_2] = 1$ mol/L and $[Al(O^iPr)_3] = 5 \times 10^{-3}$ mol/L. Reactivity ratios of $r_1 = 0.58 \pm 0.15$ (ϵ-CL) and $r_2 = 17.9 \pm 2.10$ (L-lactide) were reported.[18]

Under the same experimental conditions as before, the copolymerization of ϵ-CL (M_1) and D,L-LA (M_2) has been analysed. The experimental data are listed in Table I. Figure 1 illustrates the dependence of r_2 on r_1, and the intersection of the straight lines provides $r_1 = 0.92 \pm 0.07$ (ϵ-CL) and $r_2 = 26.5 \pm 0.50$ (D,L-LA). These values support that D,L-lactide also is favorably incorporated in the copolymer chains, but not exactly in the same manner as L-lactide.

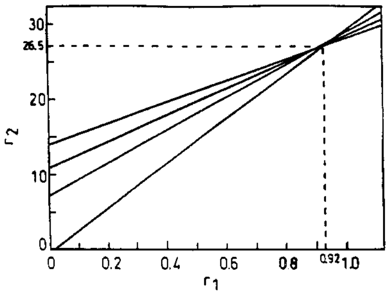


Figure 1. Determination of reactivity ratios by the Mayo–Lewis method for the D,L-lactide and ϵ-CL copolymerization.

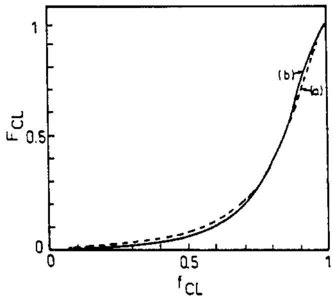


Figure 2. Instant copolymer composition (F_{CL}) versus monomer feed composition (f_{CL}) for copolymerization of (a) ϵ-CL with L-lactide and (b) ϵ-CL with D,L-lactide.

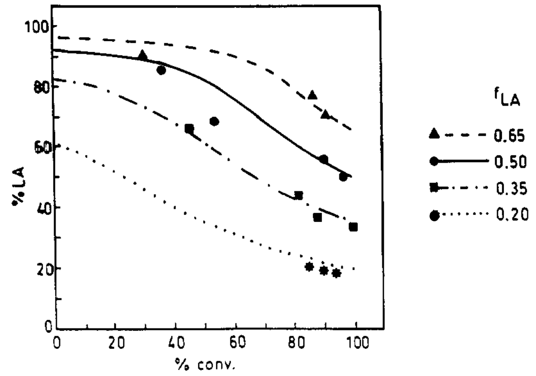


Figure 3. Dependence of the composition of the ϵ-CL and L-lactide copolymers on the comonomer conversion. Curves have been calculated from $r_L = 17.9$ and $r_C = 0.58$; dots are the experimental data.

For both lactides, r_1 (ϵ-CL) is slightly smaller than 1 and r_2 (lactide) is greater than 1, with $r_1 r_2 > 1$. These data are typical of a nonideal and nonazeotropic copolymerization. The incorporation of the two LA isomers in the copolymer is thus overwhelmingly favored as supported by the dependence of the instantaneous composition of the copolymer (F_{CL}) on the monomer feed composition (f_{CL}) (Figure 2). Accordingly, formation of tapered copolymers is expected to occur.

Although the reactivity ratios of D,L and L isomers of lactide are slightly but significantly different, Figure 2 shows that the instantaneous composition of ϵ-CL/lactide copolymers is nearly the same whatever the isomer. The same conclusion can be drawn from the change in the copolymer composition as the comonomer conversion increases (Figures 3 and 4). Theoretical curves have been calculated from the experimental r_1 and r_2 values and the Mayo–Lewis equation (see Experimental Section). Experimental compositions fit satisfactorily with theoretical curves and give credit to the experimental r_i values.

Although the Mayo–Lewis equation is not entirely satisfactory in determining the reactivity ratios,[20] that observation, together with the accuracy of r_1 (7.5%) and

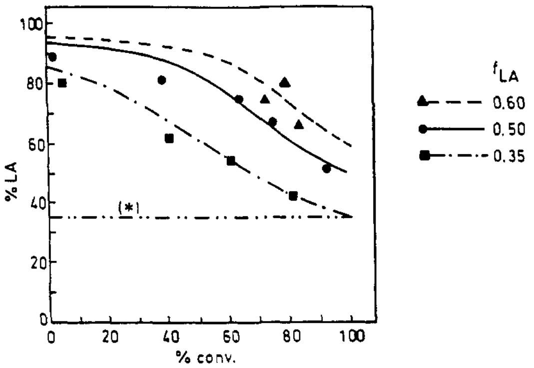


Figure 4. Dependence of the composition of the ϵ-CL and D,L-lactide copolymers on the comonomer conversion. Curves have been calculated from r_L = 26.5 and r_C = 0.92; dots are the experimental data. An asterisk refers to the Bernouillan statistics for f_{LA} = 0.35.

r_2 (2%) as determined in this work, are encouraging in view of the determination of reliable comonomer sequence lengths. That problem will be discussed in the forthcoming section.

NMR Analysis and Sequential Structure of CL/LA Copolymers. From the reactivity ratios, tapered block copolymers are expected to be formed. In order to assess that basic molecular feature, it is of prime importance to analyze the sequential distribution of the comonomers within the chains.

As reported in the Experimental Section, the first-order Markovian sequence distribution of the comonomers has been calculated for the synthesized copolymers.

^{13}C NMR spectroscopy is a method very sensitive to the chemical environment of the studied nucleus and is accordingly a powerful tool to analyze the actual average length of each type of monomer sequence. Several papers report how the sequential structure of various copolymers has been analyzed by ^{13}C NMR.[17,22,23,31,32] Kricheldorf[25] has shown that, in contrast to ^{1}H NMR, ^{13}C NMR of polyesters using the carbonyl signals turns out to be a suitable method.

In the traditional case of a binary copolymer (*i* and *j* comonomers), there are eight different triads and the average length of the *i*-type blocks ($\bar{L}_i$) is related to the triad composition of the copolymers as follows:[25]

$$\bar{L}_i = \frac{n_{iii} + n_{iij}}{n_{jii} + n_{jij}} + 1 \qquad (1)$$

where $n_{iij} = n_{jii}$ since each block of more than one *i* unit begins with a jii triad and ends up with an *iij* triad. Since the ^{13}C NMR analysis has proved to be quantitative (see Experimental Section), the integration of the triad signals can provide the average lengths. "Carbonyl" signals (between 175 and 165 ppm) have been used in the calculation of $\bar{L}_i$ because of their high sensitivity to the chemical environment. Spectra of the carbonyl region of homopolymers and a typical copolymer are shown in Figures 5 and 6. The copolymer spectrum contains obviously many more peaks than expected from the superposition of the spectrum of each homopolymer. The additional peaks are of course typical of some particular triads.

Table II summarizes the assignment of the carbonyl signals. "1" is the ϵ-CL unit and "2" is the half-lactide unit of a copolymer chain drawn with the OH end group conventionally located on the left-hand side. This assignment is in full agreement with the data published by Kricheldorf et al.[25] for the same copolymers.

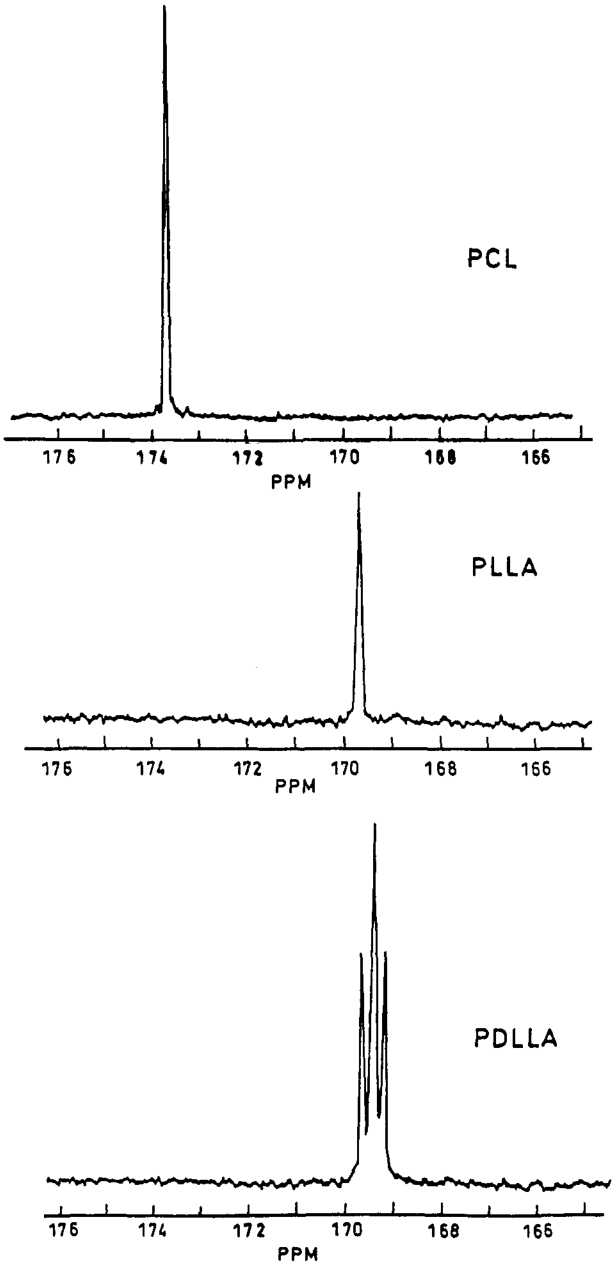


Figure 5. Carbonyl region of the ^{13}C NMR spectrum of poly-ϵ-caprolactone (top), poly-L-lactide (middle), and poly-D,L-lactide (bottom).

Relations between $\bar{L}_i$ and the integrated value (*I*) of the triads are given by eq 2. Although some pentads can be detected on the spectra, triad determination is accurate enough for the sequential analysis of the CL/LA copolymers to be reliable.

$$\bar{L}_1 = \frac{(I_{111} + I_{211})}{(I_{112} + I_{212})} + 1 \qquad (2)$$

$$\bar{L}_2 = \left[\frac{I_{222} + (I_{221} + I_{122})/2}{(I_{221} + I_{122})/2 + I_{121}} + 1\right]\frac{1}{2}$$

A series of copolymers containing L- and D,L-lactide, respectively, and synthesized from various comonomer compositions has been analyzed. Theoretical values and experimental data are listed in Table III. Bernouillan values are typical of a completely random copolyester: two values have been calculated depending on whether the lactide unit in the chain is considered as containing

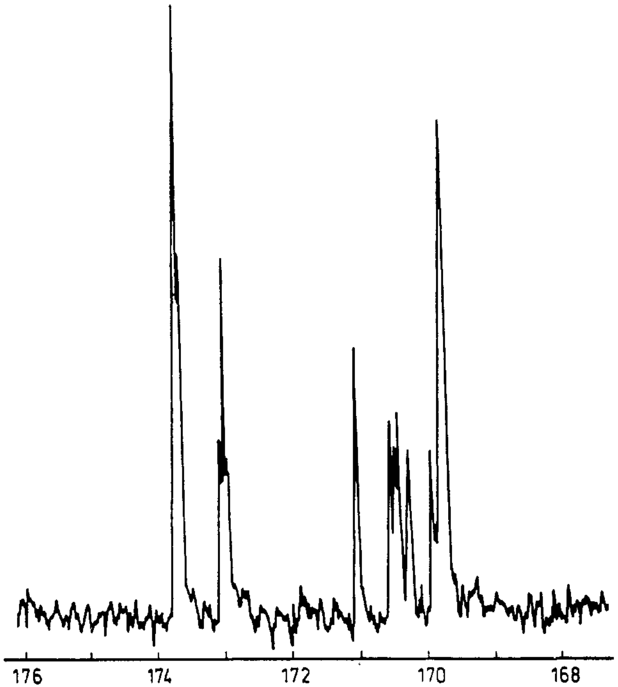
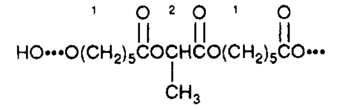


Figure 6. Carbonyl region of the ^{13}C NMR spectrum of a P(CL-*co*-L-LA) copolymer.

Table II
Assignment of "Carbonyl" Signals to Different Triads in P(CL-*co*-LA) Copolymers



$$\mathrm{HO\cdots O(CH_2)_5\overset{\overset{1}{}\;\;O}{\overset{\|}{C}}O\underset{CH_3}{\underset{|}{C}}H\overset{\overset{2}{}\;\;O}{\overset{\|}{C}}O(CH_2)_5\overset{\overset{1}{}\;\;O}{\overset{\|}{C}}O\cdots}$$

δ, ppm	triad(s)
173.6	111 + 211
173	112 + 212
171.1	121
170.2 < δ < 170.6	221 + 122
169.6[a] < δ < 170	222

[a] 169.2 for D,L-lactide.

one or two ester bond(s). The relative intensity of the 121 triad (one single "lactic" ester unit between two CL units) is also listed.

From the reactivity ratios and the rate constants, longer sequences are predicted when D,L-lactide is the comonomer rather than L-lactide. Let us note that $\bar{M}_n$ of the investigated polyesters is 10 000, ca. 80 units at total conversion. It is thus not surprising that the experimental length of the initial sequences is less than 20 units.

All the experimental lengths reported in Table III are longer than values predicted by Bernouillan statistics but smaller than those derived from the Markovian statistics (based on the reactivity ratios calculated from the Mayo–Lewis equation). Since the experimental composition curves (Figures 3 and 4) agree with the Mayo–Lewis equation, there is an obvious discrepancy between experience and theory. Actually, it might be expected that the experimental results are nothing but the consequence of transesterification reactions occuring during copolymerization and leading to shorter sequence lengths. In this respect, the ϵ-CL content in the comonomer feed has a decisive effect as supported by decreasing average lengths (compared to theoretical ones) when the ϵ-CL content increases.

It might however be argued that unaccuracy on the r_i values as calculated from the Mayo–Lewis equation might affect the calculated $\bar{L}_i$ values and be responsible for the discrepancy with the experimental data. Table IV shows that an error of ±10% on r_i is far from accounting for the experimental $\bar{L}_i$ values. Conversely, r_i values as calculated from the observed $\bar{L}_i$ data are in disagreement with those calculated by the Mayo–Lewis equation generally by several hundred percent. Clearly, transesterification reactions have a decisive effect on $\bar{L}_i$ values.

A decisive argument in favor of the occurence of transesterification reactions has to be found in the observation of the 121 triad in some copolymers. That triad cannot result from the insertion of the (di)lactide monomer into the chain but from a subsequent redistribution process.

Figure 7 shows how the relative importance of the 121 triad increases with the reaction time. The effect of the ϵ-Cl content in the feed is again obvious, as well as the nonequivalence of the two lactide isomers. D,L-lactide containing copolymers appear to be less sensitive to transesterification reactions than the L-lactide/ϵ-CL ones.

GPC Analysis of the Copolymers. GPC results are in complete agreement with the occurrence of transesterification reactions. The molecular weight distribution, which is very narrow at low monomer conversions ($\bar{M}_w/\bar{M}_n = 1.1$) increases up to nearly 2 when the reaction is complete.

Figures 8 and 9 again emphasize a difference in the sensitivity of the copolymers to secondary reactions depending on whether L-lactide or D,L-lactide has been copolymerized with ϵ-CL. The effect of the comonomer feed composition is also confirmed: the higher the ϵ-CL content, and the earlier the increase in $\bar{M}_w/\bar{M}_n$. It is worth noting that gel permeation chromatography (GPC) chromatograms reveal the presence of oligomers (Figure 10). Analyzed by ^1H NMR, these oligomers systematically contain both ϵ-CL and lactide units and consist of a mixture of cyclic and linear short chains. Indeed, oligomers recovered by precipitation in methanol clearly show methyl ester end group in the ^1H NMR spectra after hydrolysis. This phenomenon has also been reported when D,L-lactide is homopolymerized at 100 °C by aluminum isopropoxide.[26] The oligomer formation is also enhanced when L-lactide is the comonomer rather than D,L-lactide. This is another fingerprint of the greater sensitivity of the L-lactide-containing copolymers to transesterification reactions.

GPC data put clearly in evidence the occurence of both inter- (linear oligomers) and intramolecular (cyclic oligomers) transesterification reactions.

DSC Studies of the Copolyesters. Glass transition temperature (T_g) and melting point (T_m) of copolymers are physical properties that also depend on the comonomer distribution. For instance, a block copolymer usually exhibits two T_g's in contrast to a random one, the unique T_g of which is predicted by the Fox law (eq 3).

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}} \tag{3}$$

Would one component of a copolymer be able to crystallize, a melting endotherm is observed when the block length is great enough to allow crystallization to occur; this precludes crystallization in a random copolymer.

T_g and T_m have been determined for pure PCL and PLA. The experimental values are in good agreement with previously published data[2,3,28-30] and listed in Table V.

T_g of copolymers isolated at complete conversion fits the Fox equation, except for some rich D,L-lactide copol-

Table III
Theoretical and Experimental Average Sequence Lengths in P(CL-*co*-L-LA) and P(CL-*co*-D,L-LA) Copolymers

f_{LA}, init	*t*, h	% conv	F_{LA}	Markov CL/LA	exptl CL/LA	Bern CL/LA, 1 ester	Bern CL/LA, 2 esters	% 121
				P(CL-*co*-L-LA) Copolymers				
0.20	39	85	0.20	9.8/3.0	3.6/1.2	5.0/1.3	3.0/0.8	24
	162	90	0.17	10.6/3.0	4.4/1.0	5.9/1.2	3.4/0.7	23
	185	94	0.18	11.1/3.0	3.6/1.0	5.6/1.2	3.3/0.7	24
0.35	19.5	46	0.66	3.4/6.2	2.3/4.6	2.9/1.5	2.0/1.0	0
	68.5	82	0.44	6.6/4.8	2.7/2.1	2.3/1.8	1.6/1.3	9
	90	88	0.36	7.2/4.8	2.5/1.4	2.8/1.6	1.9/1.1	15
	190	100	0.33	8.7/4.7	2.5/1.7	3.0/1.5	2.0/1.0	12
0.50	24.5	41	0.74	2.0/12.1	2.8/7.9	1.4/3.9	1.2/3.4	0
	50	54	0.68	2.5/9.9	3.3/7.3	1.5/3.1	1.2/2.6	0
	170	96	0.50	6.5/7.1	2.5/3.1	2.0/2.0	1.5/1.5	4
0.65	5	31	0.90	1.4/26.7	1.8/13.0	1.1/10.0	1.1/9.5	0
	68.5	72	0.85	2.3/14.0	1.5/7.8	1.2/6.7	1.1/6.2	0
	90	87	0.77	4.0/11.4	1.9/5.4	1.3/4.4	1.2/3.9	0
	190	92	0.70	4.7/11.2	2.2/5.1	1.4/3.3	1.2/2.8	0
				P(CL-*co*-D,L-LA) Copolymers				
0.35	24	41	0.62	4.4/9.1	3.9/3.4	1.6/2.6	1.3/2.1	0
	73	61	0.54	6.4/7.4	2.7/2.8	1.9/2.2	1.4/1.7	4
	140	81	0.42	8.9/6.6	2.1/2.1	2.4/1.7	1.7/1.2	8
0.50	24	39	0.81	2.6/17.7	1.8/7.6	1.2/5.3	1.1/4.8	0
	49	64	0.75	4.4/12.0	3.2/7.4	1.3/4.0	1.2/3.5	0
	73	75	0.67	5.7/10.7	2.0/8.3	1.5/3.0	1.3/2.5	0
	144	93	0.51	8.4/9.7	1.6/2.0	2.0/2.0	1.5/1.5	2
0.60	49	53	0.75	2.4/22.3	2.8/8.4	1.3/4.0	1.2/3.5	0
	73	73	0.74	4.1/15.5	3.5/10.1	1.4/3.9	1.2/3.4	0
	140	80	0.80	5.1/14.2	2.1/8.1	1.3/5.0	1.1/4.5	0

Table IV
Discrepancy between Theoretical and Experimental $\bar{L}_i$ Cannot Be Accounted for by the Possible Inaccuracy of r_i as Determined by the Mayo–Lewis Equation

				$\bar{L}_{CL}/\bar{L}_{LA}$ based on				^{13}C NMR reactivity ratios[c]	
	f_{LA}	F_{LA}	% conv	r_{CL}; r_{LA}[a]	r_{CL} + 10%; r_{LA} + 10%[b]	r_{CL} − 10%; r_{LA} − 10%[b]	$\bar{L}_{CL}/\bar{L}_{LA}$ ^{13}C NMR	r_{LA}	r_{CL}
L-LA	0.20	0.20	85	9.8; 3.0	11.0; 3.3	9.0; 2.8	3.6/1.2	1.2	0.05
	0.65	0.70	92	4.7; 11.2	5.2; 12.4	4.2; 10.0	2.2/5.1	6.0	0.15
D,L-LA	0.35	0.62	41	4.4; 9.1	4.8; 10.0	4.0; 8.3	3.9/3.4	5.0	1.3
	0.35	0.42	81	8.9; 6.6	9.7; 7.2	8.0; 6.0	2.1/2.1	4.8	0.02

[a] Reactivity ratios determined by Mayo–Lewis method. [b] Reactivity ratios affected by a relative error of +10% and −10%, respectively. [c] Reactivity ratios calculated from the experimental (^{13}C NMR) sequence lengths ($\bar{L}_i$).

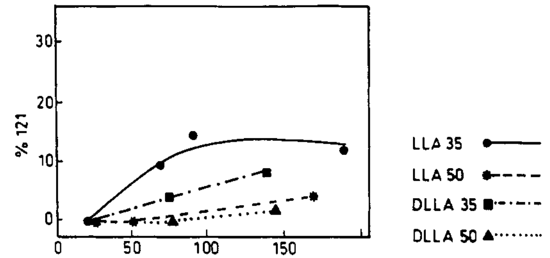


Figure 7. Relative importance of the 121 triad as a function of reaction time.

ymers. (Figures 11 and 12). A lack of crystallinity is observed when the composition ranges from 25 to 50 wt % L-lactide. For D,L-lactide containing copolymers, crystallization occurs only when the lactide weight percent does not exceed 40%.

That experimental T_g's are in agreement with eq 3 is in favor of a random structure. In some cases (high content of a crystallizable precursor (L-LA or ε-CL) and low conversion degrees), a weak melting endotherm can be observed on the first scan. This endotherm disappears on the second scan, thus after a rapid cooling.

Departure from eq 3 for some D,L-lactide-containing copolymers suggests the presence of polylactide sequences that have not been affected by transesterification reactions to the same extent as in L-lactide-containing copolymers.

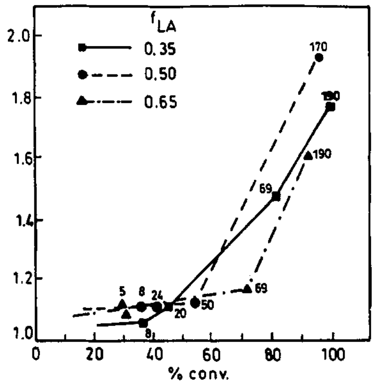


Figure 8. Polydispersity of various P(CL-*co*-L-LA) copolymers versus comonomer conversion. Dots are the reaction times (h).

This conclusion is supported by the DSC traces of the two types of copolymers when the comonomer conversion increases (Figures 13 and 14). According to Figure 13, only one T_g is observed for the L-lactide-based copolymers and that T_g changes with the PCL percent of the copolymer as predicted by the Fox's equation. In this case, transesterification should thus be effective very early in promoting a random structure.

Figure 14 refers to D,L-LA-based copolymers. In contrast to Figure 13, up to three T_g can be observed: Two are close to T_g of each homopolymer, respectively, and the third one is intermediate. When the conversion increases,

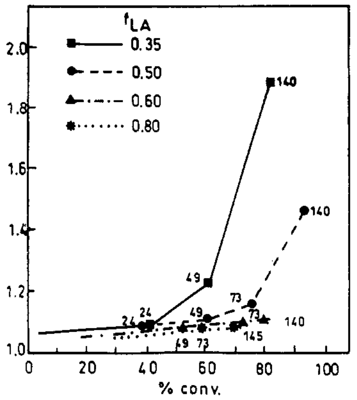


Figure 9. Polydispersity of various P(CL-*co*-D,L-LA) copolymers versus comonomer conversion. Dots are the reaction times (h).

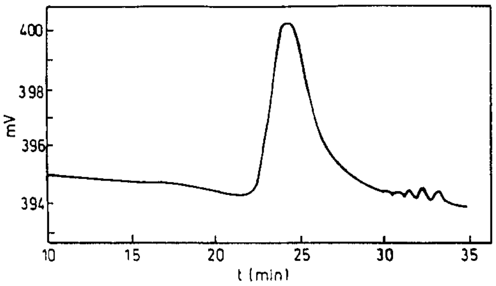


Figure 10. Typical GPC chromatogram of a P(CL-*co*-L-LA) copolymer containing oligomers.

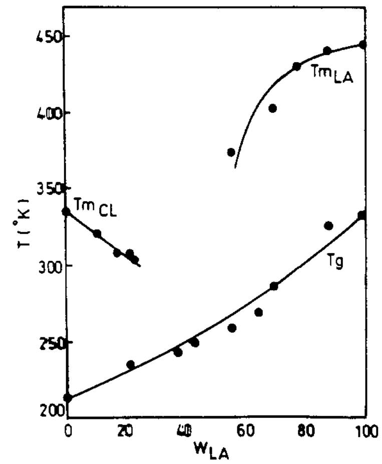


Figure 11. Phase diagram of P(CL-*co*-L-LA) copolymers.

Table V
Comparison between Experimental and Referenced Transition Temperatures of Homopolymers

polymer	T_g, °C lit.[a]	T_g, °C exptl[b]	T_m, °C lit.[a]	T_m, °C exptl[b]
PCL	-60	-60	63	60
PLLA	57	60	167	170
PDLLA	45-55	45		

[a] Published data.[2,3,28-30] [b] This work.

these T_g's tend to merge into a single broad T_g. This might be accounted for as follows: At the first stages of the reaction, the copolymer has a blocky structure and exhibits the T_g's of each homopolymer as well as an intermediate T_g characteristic of a diffuse interface. As the reaction goes on, transesterification reactions randomize the structure to the point where the T_g of each component tends to disappear in favor of one intermediate broad T_g.

DSC thus provides an additional evidence for the occurrence of transesterification reactions, particularly when L-lactide is copolymerized with ε-CL.

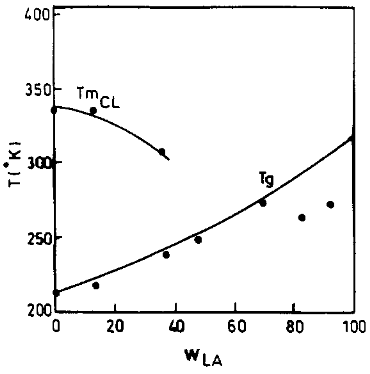


Figure 12. Phase diagram of P(CL-*co*-D,L-LA) copolymers.

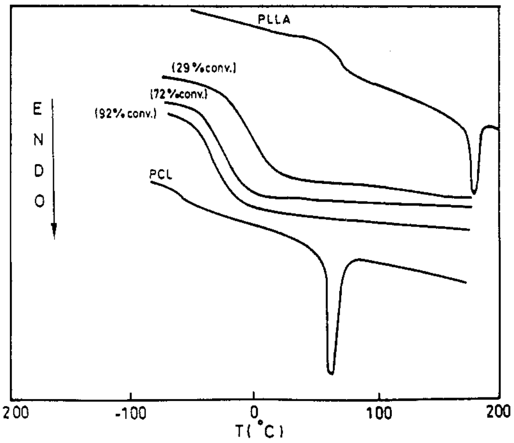


Figure 13. Typical DSC curves (second scan) of a P(CL-*co*-L-LA) copolymer at different conversions.

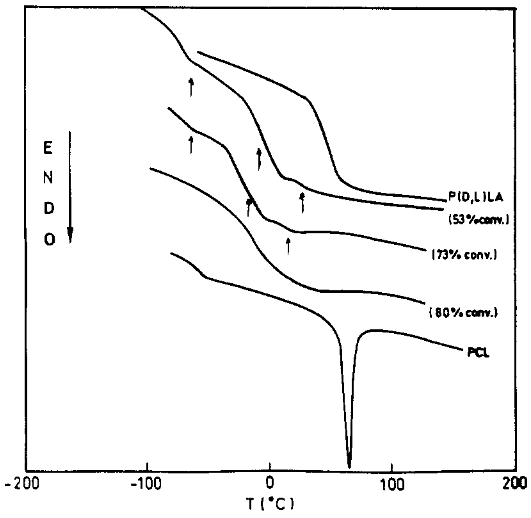


Figure 14. Typical DSC curves (second scan) of a P(CL-*co*-D,L-LA) copolymer at different conversions.

Discussion

This study has shown that ε-CL copolymerization with either L-lactide or D,L-lactide in the presence of $Al(O^iPr)_3$ in toluene at 70 °C obeys the Mayo-Lewis equation.

For both lactides, r_2 is much larger than r_1 although the rate constant of LA homopolymerization (k'_{22}) is much smaller than that of ε-CL (k'_{11}).[18,26] From r_i and k'_{ii}, k'_{ij} have been calculated (Table VI), and they show that active ε-CL units (PCL-O-AL<) are much more reactive (up to 10^5 greater) than LA ones (PLA-O-Al<). That behavior cannot be explained by the only steric hindrance of the

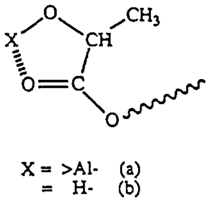


Figure 15. Coordination of the "active" lactide unit on Al propagation site (a) and H bonding in a homopolylactide chain end group (b).

Table VI
Comparison of Individual Rate Constants (k'_{ij}) in Copolymerization of ϵ-CL and L- or D,L-Lactide by Al(^{i}PrO)$_3$

	L-Lactide k'_{ij}, L/(mol·min)	D,L-lactide k'_{ij} L/(mol·min)	corresponding reaction
k'_{11}	3600	3600	PCL–O–AL< + ϵ-CL
k'_{12}	6200	3900	PCL–O–Al< + LA
k'_{21}	0.03	0.02	PLA–O–Al< + ϵ-CL
k'_{22}	0.60	0.60	PLA–O–Al< + LA

methyl group of LA. The difference in basicity of the alkoxides has also to be considered: The alkoxide derived from lactide is less basic than that conjugated to ϵ-CL because of the proximity of the carbonyl group. Furthermore, one can expect a competitive coordination to the Al atom between the comonomers and the penultimate lactide unit of the PLA growing chain (Figure 15a). This is indirectly supported by the ^{1}H NMR analysis of homopolylactide (^{i}PrO–PLA–OH) which agrees with a five-membered association of the hydroxyl end groups generated by the hydrolysis of the active species (Figure 15b). Hydroxyl protons appear as a doublet, reflecting a very slow exchange due to H bonding. Would the active alkoxide derived from ϵ-CL be cyclic, then a nine-membered ring should be formed, which is unfavorable from the entropic standpoint. Accordingly, the active lactide sites are expected to be more stable, and thus less reactive.

That k_{21} is the lowest rate constant is in good agreement with the previous observation that living PLA chains cannot initiate the ϵ-CL polymerization.[16,21] Such a low value of k_{21} could be attributed to a difference both in nucleophilicity of the living alkoxides and in conformational structure of the cyclic comonomers.

Clearly, the sequential structure of the copolymers is modified by transesterification reactions, leading to randomization of the comonomer distribution. At least two mechanisms are involved: an intermolecular mechanism (Figure 16a) accounting for modifications of average sequence length and polydispersity and an intramolecular mechanism (Figure 16b) leading to cyclic oligomers and shorter polymer chains.

These two mechanisms occur simultaneously as supported by the presence of both cyclic and linear oligomers. Formation of oligomers in lactide homopolymerization has never been reported under the conditions used in this study. Dubois et al.[26] observed that phenomenon only above 100 °C (or at 70 °C when $[LA]_0/[Al]$ is very high, i.e., >2000) when using Al(O^{i}Pr)$_3$ as an initiator in toluene. It can thus be assumed that the PCL component, rather than the PLA component, of the copolymers is at the origin of the oligomer formation. Experimental data agree with that conclusion, since homopolymerization of ϵ-CL in the toluene at 70 °C shows a rapid decrease in $\bar{M}_n$ and the formation of a large amount of oligomers after a few hours.

Sensitivity of CL/LA copolymers toward transesterification reactions has thus to be attributed to the presence of the PCL component. On that basis, it can be predicted

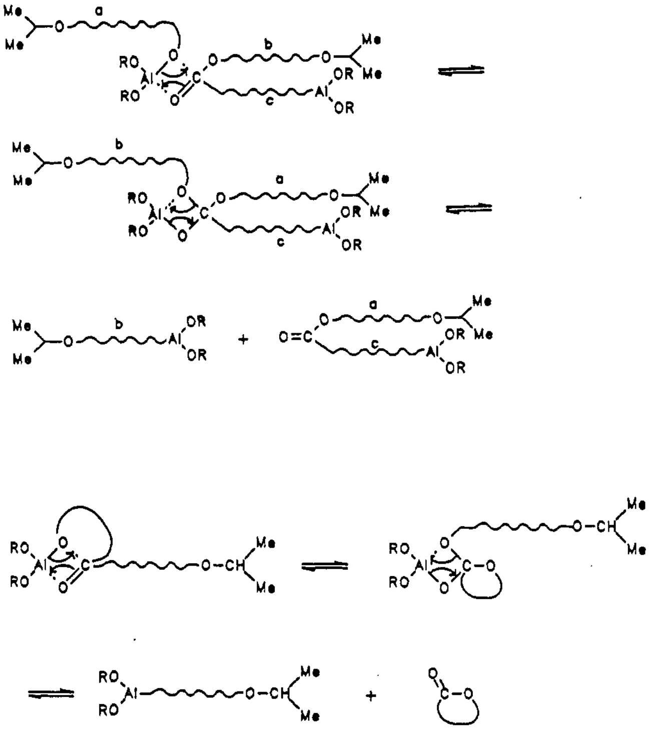


Figure 16. Mechanisms of intermolecular (top) and intramolecular (bottom) transesterification reactions.

that PCL-rich copolymers are more affected by transesterification reactions than PLA-rich ones. Since the ϵ-CL content of the monomer feed increases with conversion, chains formed at the end of the copolymerization process contain more (and/or longer) PCL segments and are expected to be more sensitive toward transesterifications. In other words, the extent of transesterification should increase with conversion, as it is experimentally observed. Of course, transesterification does not only affect PCL segments. The increased sensitivity of PLA sequences with respect to homo-PLA might be explained by a disturbing and neighboring effect of the ϵ-CL component on the conformation of PLA segments. This hypothesis is supported by the mixing of living homopolymers (P-L- or P-D,L-LA and PCL chains previously prepared in toluene at 70 and 0 °C, respectively), where no transesterification has been detected even after 200 h in toluene at 70 °C. In the same way, the sequential copolymerization (in toluene at 70 °C) of the same comonomers does not present any transesterification reactions.[15]

Moreover, this study clearly shows a difference in reactivity when L-lactide or D,L-lactide is copolymerized with ϵ-CL in the presence of Al(O^{i}Pr)$_3$ in toluene at 70 °C. That difference is reflected not only in the reactivity ratios but also in the structure of the copolymers and their sensitivity toward transesterifications. This is in contrast to the great similarity in the homopolymerization of the L and D,L isomers.[26]

A possible explanation might be found in the conformation of P-D,L-LA and P-L-LA chains. P-L-LA chains are, indeed, more rigid and more extended in toluene compared to P-D,L-LA, as supported by the Mark–Houwink exponents.[19] In the solid state, P-L-LA is a semicrystalline polymer, while P-D,L-LA is amorphous. The more extended and the more sensitive to transesterification reactions the chains should be. That explanation does not however take into account the incorporation of ϵ-CL, which modifies the structure of the chains, and makes as short as four or five units the length of polylactide segments.

When very short segments are concerned, it must be emphasized that the L- and D,L-lactide units can only be distinguished from each other when more than one lactide molecule has been incorporated in the chain. D,L-LA, indeed, is a racemic mixture of L-LA and D-LA. Insertion of only one lactide unit has no discriminating effect since aluminum alkoxide is nonchiral and the two stereoisomers D- and L-lactide behave exactly the same way. Upon insertion of a second lactide unit, differences can now be observed: L-Lactide-containing copolymers will exhibit only L–L–L–L sequences, while L–L–L–L, L–L–D–D, D–D–L–L, or D–D–D–D sequences might appear in D,L-lactide-containing copolymers.

Finally, it must be recalled that three chains are growing from a common Al atom. Due to the relatively small size of the Al atom, the insertion of one lactide molecule might be influenced by the nature of the last unit of the other growing chains. For example, the spatial organization of three L-lactide terminated chains around the Al atom is expected to be different from that of two L-lactide and one D-lactide terminated chains. These configurational effects might explain the small but significant difference observed in the reactivity ratios. Advanced theoretical calculations would be necessary in order to confirm that hypothesis.

In conclusion, the synthesis of block copolymers from a mixture of ε-CL and lactide requires experimental conditions that prevent transesterification reactions from occurring or at least cause them to be slowed down. Recent results from our laboratory indicate that the coordination of, e.g., pyridine onto Al, could be effective in reducing the extent of transesterification reactions. Studies are in progress and will be published in the near future.

Acknowledgment. We are very much indebted to IRSIA (for a fellowship to Ph.D.), to the "Fonds National de la Recherche Scientifique" (for a fellowship to P.V.), and to the "Services de la Programmation de la Politique Scientifique" (Brussels) for financial support.

References and Notes

(1) Lyman, D. J.; Rowland, S. M. Biomaterials. *Encyclopedia of Polymer Sciences and Engineering*, 2nd ed.; 1985; Vol. 2, p 267.
(2) Schindler, A.; Jeffcoat, R.; Kimmel, G. L.; Pitt, C. G.; Wall, M. E.; Zweidinger, R. In *Contemporary topics in polymer Science*; Pearce, E. M., Schaefgen, J. R., Eds.; Plenum Press: New York, 1977; Vol. 2, p 251.
(3) Pitt, C. G.; Marks, T. A.; Schindler, A. Biodegradable Drug Delivery Systems based on aliphatic Polyesters: Application to Contraceptives and Narcotic Antagonists. In *Controlled Release of Bioactive Materials*; Baker, R., Ed.; Academic Press: New York, 1980.
(4) Kopecej, J.; Ulbrich, K. *Progr. Polym. Sci.* **1983**, *9*, 12.
(5) Billmeyer, F. W. *Textbook of Polymer Science*, 3rd ed.; Wiley-Interscience: New York, 1984.
(6) Riess, C.; Hurtrez, C.; Bahadur, P. Block Copolymers. *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; 1985; Vol. 2, p 398.
(7) Song, C. X.; Sun, H. F.; Feng, X. D. *Polym. J.* **1987**, *19* (5), 485.
(8) Hamitou, A.; Ouhadi, T.; Jerome, R.; Teyssie, Ph. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 865.
(9) Ouhadi, T.; Hamitou, A.; Jerome, R.; Teyssie, Ph. *Macromolecules* **1976**, *9*, 927.
(10) Hamitou, A.; Jerome, R.; Hubert, A. J.; Teyssie, Ph. *Macromolecules* **1973**, *6*, 651.
(11) Heuschen, J.; Jerome, R.; Teyssie, Ph. *Macromolecules* **1981**, *14*, 242.
(12) Jerome, R.; Teyssie, Ph. In *Comprehensive Polymer Science*; Eastmond, G. C., Ledwith, A., Russo, S., Sigwalt, P., Eds.; Pergamon Press: New York, 1989; Vol. 3., Part 1, p 501.
(13) Hamitou, A.; Jerome, R.; Teyssie, Ph. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 1035.
(14) Heuschen, J.; Jerome, R.; Teyssie, Ph. *Macromolecules* **1981**, *14*, 242.
(15) Jacobs, C.; Dubois, Ph.; Jerome, R.; Teyssie, Ph. *Macromolecules* **1991**, *24*, 3027.
(16) Song, C. X.; Feng, X. D. *Macromolecules* **1984**, *17*, 2764.
(17) Kricheldorf, H. R.; Kreiser, I. Makromol. Chem. **1987**, *188*, 1861.
(18) Vion, J. M.; Jerome, R.; Teyssie, Ph.; Aubin, M.; Prud'homme, R. E. *Macromolecules* **1986**, *19*, 1828.
(19) Schindler, A.; Harper, D. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 2593.
(20) Kelen, T.; Tüdos, F. *J. Macromol. Sci., Chem.* **1975**, *A9* (1), 1.
(21) Dubois, Ph.; Jerome, R.; Teyssie, Ph. *Makromol. Chem., Macromol. Symp.* **1990**, *42/43*, 103.
(22) Kricheldorf, H. R.; Mang, T.; Jonte, J. M. *Makromol. Chem.* **1985**, *186*, 955.
(23) Chabot, F.; Vert, M.; Chapelle, S.; Granger, P. *Polymer* **1983**, *24*, 53.
(24) Le Borgne, A.; Spassky, N.; Chang, L. J.; Ardechir, M. *Makromol. Chem.* **1988**, *189*, 637.
(25) Kricheldorf, H. F.; Jonte, J. M.; Berl, M. *Makromol. Chem., Suppl.* **1985**, *12*, 25.
(26) Dubois, Ph.; Jacobs, C.; Jerome, R.; Teyssie, Ph. *Macromolecules* **1991**, *24*, 2266.
(27) Ouhadi, T.; Stevens, C.; Teyssie, Ph. *Makromol. Chem., Suppl.* **1975**, *1*, 191.
(28) Brode, G. L.; Koleske, J. V. *J. Macromol. Sci., Chem.* **1972**, *A6*, 1109.
(29) Vasanthakumari, R.; Pennings, A. J. *Polymer* **1983**, *24* (2), 175.
(30) Rak, J.; Ford, J. L.; Rostron, C.; Walters, V. *Pharm. Acta Helv.* **1985**, *60* (5–6), 162.
(31) Grijpma, D. W.; Zondervan, G. J.; Pennings, A. J. *Polym. Bull.* **1991**, *25*, 327.
(32) Grijpma, D. W.; Pennings, A. J. *Polym. Bull.* **1991**, *25*, 335.

Registry No. ε-CL, 502-44-3; LLA, 4511-42-6; D,L-LA, 95-96-5; ε-CL/LLA (copolymer), 65408-67-5; ε-CL/D,L-LA (copolymer), 70524-20-8; $Al(OCHMe_2)_3$, 555-31-7.