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Anionic polymerization of D,L-lactide initiated by lithium diisopropylamide

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Abstract

The anionic polymerization of D,L-lactide initiated by lithium diisopropylamide.monoTHF complex was performed in different solvents and at various temperatures. No polymerization took place in THF solution. In dioxane at 25°C the polymerization is fast and goes up to completion in few minutes. In toluene, due to solubility requirements, polymerizations were run at 70°C. At initial stage of polymerization M_w/M_ns were quite narrow, but at higher conversion a significant broadening occurred due to transesterification reactions. The latter were identified by ^{13}C NMR analysis, while MALDI-TOF spectra revealed the simultaneous presence of cyclic and linear oligomers substantiating the occurrence of both intra and inter ester exchange processes. At low conversion, polymers exhibited a highly syndiotactic microstructure.

Keywords: Polylactides; Anionic polymerization; Disyndiotacticity

1. Introduction

The synthesis and characterization of well-defined polylactides resulting from ring-opening polymerization (ROP) of the corresponding lactide monomers (L-, D,L- and meso) has attracted considerable interest since the 1970s. A major part of the research efforts has been devoted to the ROP by metal complexes (tin(II) octanoate, Zn alkoxides, $Al(OiPr)_3$, Al-Schiff's base alkoxides, rare earth metal alkoxides based on La or Y), which generally proceeds by insertion of monomer into the metal-alkoxide bond. Some of these initiators have proved to be very attractive since they give rise to controlled polymerization of lactides. On the other hand, the anionic polymerization of lactides has been studied to a much lesser extent probably because earlier studies [1,2] were not fully detailed or rather inconclusive. Recently, a number of research groups have reported on the ROP of lactides using anionic initiators as summarized in Table 1. These initiators proceed either by direct nucleophilic attack on the carbonyl group of the lactide molecule or by monomer deprotonation via an acid-base reaction. In both cases however, propagation occurs by an alkoxide anion.

Kricheldorf et al. [3,4] reported that the yield of L-lactide polymerization initiated with potassium tert-butoxide and butyllithium in toluene or dioxane at variable temperatures did not exceed about 75%. They also observed partial racemization of lactidyl units from optical rotation measurements. The polylactides showed broad molar mass distribution which was attributed to the occurrence of side transesterification reactions. The same group achieved better results with lithium alkoxides derived from butyllithium and primary alcohols [5]. High yields and high molar masses of poly(L-lactides) were reported. Relatively high optical purity of the polymers indicated that racemization was minimized. However, the polymerization does not exhibit living characteristics as evidenced by an important discrepancy between experimental and calculated degrees of polymerization.

Jedlinski et al. [6] investigated the polymerization of L- and D,L-lactides using potassium methoxide in THF at room temperature. The polymerization was found to be quite fast and quantitative yields were obtained. In contrast to the lithium alkoxides, narrow molar mass distributions as well as a good correlation between experimental and predicted molar masses were reported. Analysis of the microstructure of the polymers by ^{13}C NMR indicated the minimization of transesterification reactions. Sipos and Zsuga [7] observed a very fast polymerization of L-lactide ($k_{app} = 0.01870\ \mathrm{l\,mol^{-1}s^{-1}}$ at $M/I = 100$) with lithium tert-butoxide. However, they reported that the molar mass of the polymers did not increase linearly with conversion

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Table 1
Anionic initiators used for L- and D,L-lactide polymerization

Lactide	Solvent	Temperature (°C)	Mechanism	Initiator
L	Toluene or dioxane	20, 80	Deprotonation	tBuOK [3] and analogues [4]
L	Toluene	50	Nucleophilic attack	ROLi [5]
L and D,L	THF	20	Nucleophilic attack	CH_3OK [6]
L	THF	Ambient	Deprotonation	tBuOLi (K) [7,8]
D,L	THF	20	Nucleophilic attack	tBuOLi [9,10]
L,D,L, meso	Bulk	120		Bu_2Mg [11]
D,L	THF	20		Bu_2Mg [12]
L	Toluene or dioxane	20, 80	Deprotonation	BuLi [3]
D,L	THF	20		BuLi [12]

but is above calculated values. Although monomodal SEC chromatograms were obtained, the molar mass distributions were quite broad ranging from 1.3 to 3.0. This was attributed to the presence of both inter- and intra-molecular transesterification reactions. The authors also showed that the presence of crown ethers lead to a lowering of the rate of polymerization of L-lactide in presence of lithium alkoxides substantiated by the formation of a 1:1 complex between monomer and lithium ion in THF [8].

The use of lithium tert-butoxide as initiator for D,L-lactide polymerization by Kasperczk [9,10] also proved to be interesting from a structural aspect. Indeed, analysis of the tetrads and hexads in the methine and carbonyl regions respectively revealed the presence of enhanced disyndiotactic structures indicating preferential alternating addition of monomers.

Other initiators such as Bu_2Mg and BuLi were also used to polymerize lactides either in bulk [11] or in solution [12].

In this article, we present the anionic polymerization of D,L-lactide initiated by lithium diisopropylamide (LDA).monoTHF which is recognized in organic syntheses as a sterically hindered non-nucleophilic strong base. It was used in the presence of amine for the polymerization of divinylbenzene [13,14] and it was reported to be an efficient initiator for the living anionic polymerization of methyl methacrylate [15]. To the best of our knowledge, LDA has not been used before for polymerizing lactides. A study of the polymerization in different solvents will be presented in this paper. The occurrence of side reactions and the tacticity of the polymers will be discussed as well.

2. Experimental

2.1. Materials

Monomer — D,L-lactide was purchased from Purac-Biochem. It was recrystallised three times from dry ethyl acetate, dried under vacuum and kept under argon.

Solvent — Toluene was first refluxed and then distilled over sodium under nitrogen and kept under argon. Tetrahydrofuran was refluxed, then distilled over CaH_2 and kept under argon. Anhydrous dioxane sealed under nitrogen was obtained from Aldrich and used without further purification.

Initiator — Lithium diisopropylamide mono(tetrahydrofuran) was obtained from Aldrich as a 1.5 M solution in cyclohexane and used as received.

2.2. Polymerization procedure

All polymerizations were conducted under argon in glass tubes sealed with septums. When dioxane or THF was used, the monomer was first dissolved in the solvent inside the glove box at ambient temperature followed by addition of LDA.monoTHF using a gas-tight micro-syringe, at the required polymerization temperature.

The procedure is slightly different in toluene since lactide is insoluble in the latter at ambient temperature. Both lactide and solvent were introduced in the tubes inside the glove box and heated to 70°C until all the lactide is completely dissolved. The initiator is then added and polymerization is allowed to proceed at 70°C.

After the desired time of polymerization, the reaction was stopped by opening the tube to air followed by dilution with dichloromethane. The solvent was removed under vacuum at room temperature and the percentage conversion was determined by ^1H NMR. Then the reaction mixture was dissolved in chloroform and the polymers were isolated by precipitation in methanol and finally dried under vacuum at 40°C.

2.3. Measurements

^1H and ^{13}C NMR spectra were recorded in 5 mm sample tubes in $CDCl_3$ using an FT Bruker 250 MHz spectrometer at 25°C.

SEC measurements were carried out in THF as eluent using a Waters 510 pump, an LDC analytical refractometer and four PL gel columns (10^4, 10^3, 500 and 100 Å). Calibration was effected with polystyrene standards. Molar masses were determined according to the universal calibration method.

MALDI-TOF-MS was performed using a PerSeptive Biosystems Voyager Elite (Framingham, MA) time-of-flight mass spectrometer. This instrument is equipped with a nitrogen laser (337 nm), a delayed extraction and a reflector.

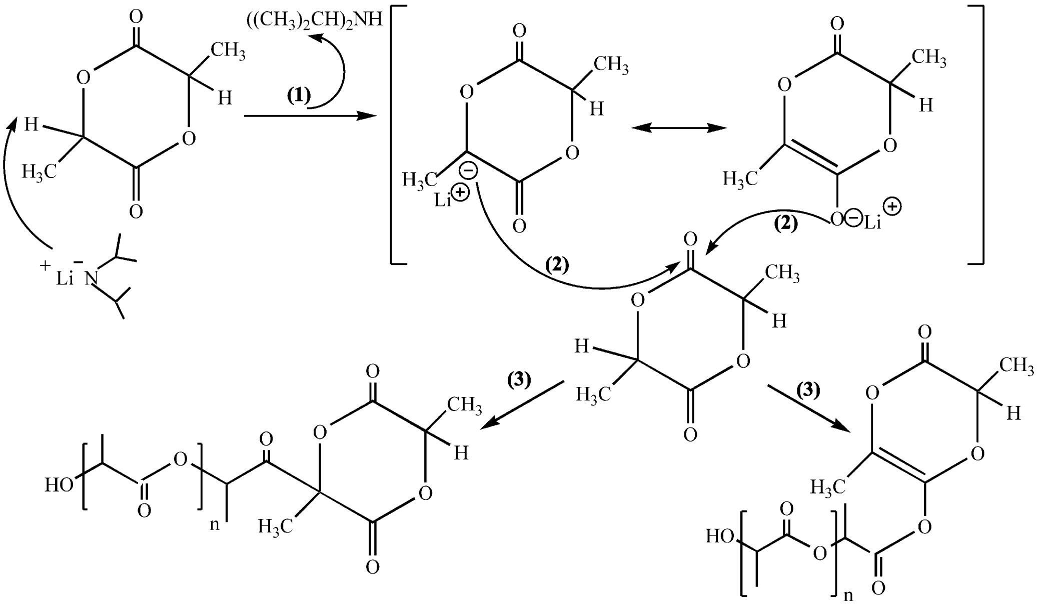

Fig. 1. Proposed mechanism of polymerization using LDA.monoTHF.

It was operated at an accelerating potential of 20 kV in both linear and reflector modes. The MALDI mass spectra represent averages over 256 consecutive laser shots (3 Hz repetition rate). The poly(D,L-lactide) solutions (1 $\mathrm{g\,l^{-1}}$) were prepared in THF. The matrix, 2,5-dihydroxybenzoic acid (DHB), was also dissolved in THF (20 $\mathrm{g\,l^{-1}}$). The poly(D,L-lactide) solution (5 μl) was mixed with 30 μl of the matrix solution. A 1 μl portion of the final solution was deposited onto the sample target and allowed to dry in air at room temperature. Internal standards (peptides or porphyrin derivatives) were used to calibrate the mass scale using the two-point calibration software 3.07.1 from PerSeptive Biosystems.

3. Results and discussion

3.1. Mechanism of polymerization

The polymerization of D,L-lactide in the presence of lithium diisopropylamide.mono tetrahydrofuran is found to proceed quite fast and quantitative yields can be obtained irrespective of the nature of the solvent. The results are comparable with the polymerization initiated by other anionic initiators such as potassium methoxide [5] and tBuOLi [9]. The absence of diisopropylamino signals (2 C*H*, multiplet, 2.75 ppm as given in Ref. [15]) in the ^{1}H NMR suggests that LDA reacts with D,L-lactide by deprotonation

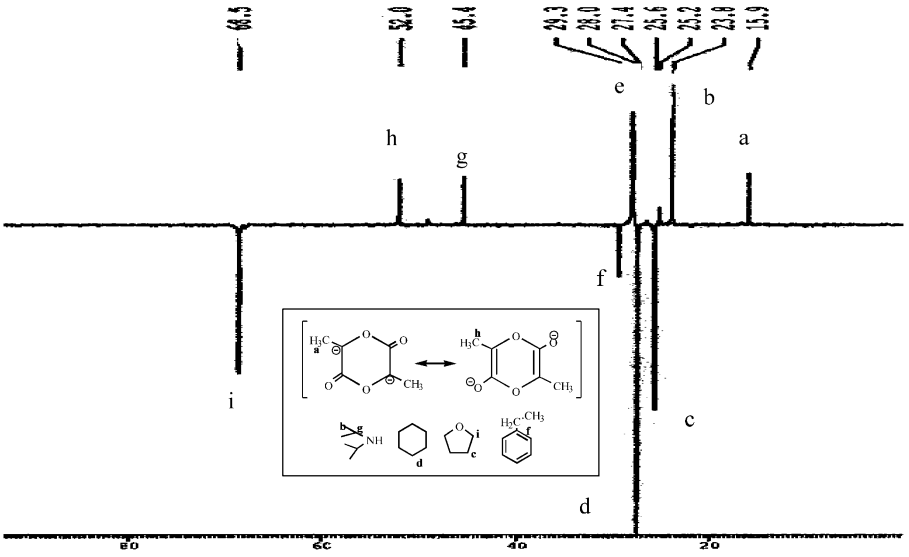

Fig. 2. ^{13}C DEPT NMR spectrum of the product resulting from reaction between D,L-lactide and LDA (ratio 1:2).

Table 2
Polymerization of D,L-lactide in presence of LDA.monoTHF in either dioxane or toluene

Polymer	$[M]_0/[I]_0$	Temperature (°C)	Time (min)	X^a (%)	M_n (calc)[b]	M_n (SEC)[c]	M_n (correc.)[d]	M_w/M_n
P1[e]	50	25	5	98	7056	13 200	7650	1.86
P2		0	180	99	7128	14 500	8400	1.71
P3		−10	200	100	7200	11 700	6800	1.74
P4	100	25	3	32	4608	7285	–	1.16
P5			7	87	12 528	21 900	12 700	1.69
P6		0	150	98	14 112	21 100	12 200	1.89
P7		−10	230	70	10 080	13 600	7900	1.48
P8[f]	50	70	2	25	1800	4583	–	1.12
P9			5	97	6984	24 000	13 900	1.66
P10	100		5	44	6338	8250	–	1.52
P11			9	87	12 528	22 100	12 800	1.7
P12			15	93	13 392	20 400	11 800	1.9

[a] X: % conversion.
[b] $M_n(\text{calc}) = [M]_0/[\text{LDA}]_0 \times 144 \times X\%$.
[c] Determined using polystyrene as standards.
[d] $M_n \times 0.58$ (correction factor applied for $M_n(\text{SEC}) > 10^4$).
[e] P1–P7: polymerization in dioxane.
[f] P8–P12: polymerization in toluene.

to give the enolate (reaction 1 in Fig. 1). The formation of the enolate was confirmed in a model reaction where lactide was made to react with LDA.monoTHF in 1:2 molar ratio. The reaction was carried out in deuterated benzene at ambient temperature and it was monitored by ^{13}C NMR (Fig. 2). A peak at 52 ppm corresponding to a methyl group adjacent to a C=C was observed in addition to the signal at 16 ppm assigned to CH_3 of the carbanion. The signal at 68 ppm corresponding to CH of lactide is also absent.

The enolate then reacts with another lactide molecule with acyl-bond cleavage and subsequent formation of an alkoxide anion (reaction 2). The latter is most probably the active species in the propagation step (reaction 3).

The polymerization was studied at various temperatures in cyclic ethers such as dioxane and THF and in a less polar solvent, namely toluene. The percentage conversion was monitored by ^{1}H NMR and determined from the integration of the methine signals of lactide monomer ($\delta = 5.01 - 5.11$) and polymer ($\delta = 5.11 - 5.27$).

3.2. Synthesis of poly(D,L-lactides)

The polymerization of D,L-lactide using LDA.monoTHF was first investigated in dioxane and tetrahydrofuran. No polymerization took place in THF at $[M]/[I] = 50$ even at higher temperatures and after prolonged reaction time (24 h). Kricheldorf and Lee [11] reported a rather similar behaviour concerning the polymerization of L-lactide using dibutylmagnesium in THF in contrast with other solvents. In our case, the absence of polymerization may be explained possibly by the presence of only dimeric LDA aggregates in THF. The existence of such species has been described in previous studies [16] and they can be considered as being inactive towards polymerization.

On the other hand, the synthesis of poly(D,L-lactides) initiated by LDA.monoTHF, has been successful in dioxane and toluene under different experimental conditions of temperature and initiator concentrations (Table 2).

As can be seen, the polymerization goes to completion in a few minutes to a few hours depending mainly on the temperature. The polymerization kinetics were monitored in both solvents at a monomer to initiator ratio equal to 100 (Fig. 3). We observe an induction period in both cases on account of the aggregation of the initiator followed by a slightly faster polymerization in dioxane although a lower temperature is used. This is probably due to a lesser extent of aggregation in the latter solvent as compared to the aromatic hydrocarbon.

The M_n of the polymers determined by SEC after applying the correction factor 0.58 [17] are in most experiments in satisfactory agreement with the calculated molar masses (Table 2). The molar mass distribution is quite narrow (1.1–1.2) in both solvents in the initial stage of

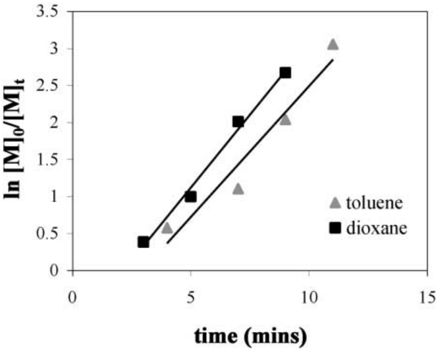

Fig. 3. Plot of $\ln[M]_0/[M]_t$ vs. time in (▲) toluene at 70°C and (■) dioxane at ambient temperature; $[M]/[I] = 100$.

Table 3
Polydispersity indices of poly(lactides) obtained with other anionic initiators in THF at ambient temperature

Monomer	Initiator	$[M]/[I]$	Conversion (%)	M_w/M_n
L-lactide	tBuOK [7]	100	90	2.4
	tBuOLi [7]	100	90	3.0
D,L-lactide	BuLi [12]	50	93	3.2
		100	81	1.8
	Bu_2Mg [12]	50	94	3.1
		100	80	1.7

Table 4
Assignment of peaks for MALDI-TOF spectrum of P4

Peak	M_{peak}	Assignment	M_{cal} [a]
1	5068	Cyclic $[OCH(CH_3)CO]_{70}\ldots Na^+$	5067.4
2	5086	$H{-}[OCH(CH_3)CO]_{70}{-}OH\cdots Na^+$	5085.4
3	5102	$H{-}[OCH(CH_3)CO]_{70}{-}OH\cdots K^+$	5101.6
4	5140	Cyclic $[OCH(CH_3)CO]_{71}\ldots Na^+$	5139.5
5	5158	$H{-}[OCH(CH_3)CO]_{71}{-}OH\cdots Na^+$	5157.5
6	5174	$H{-}[OCH(CH_3)CO]_{71}{-}OH\cdots K^+$	5173.6

[a] M_{cal}: average molar mass.

polymerization as evidenced by P4 and P8 while a significant broadening is observed at higher conversion (1.5–1.9). It can be noted that in general, the polydispersity index decreases as the polymerization temperature is lowered and increases with conversion (P8 and P9 or P10–P12). Both trends can be explained by the occurrence of transesterification reactions. As indication, previously reported values of polydispersity indices of poly(D,L-lactides), obtained under comparable experimental conditions using other anionic initiators, are listed in Table 3 and are quite broad ranging from 1.7 to 3.2.

^{13}C NMR analyses indeed confirm the presence of transesterification reactions. This is the case of polymers P1, P2, P6 and P9, P11 P12. However, it is important to note that the NMR spectra of the other polymers (P3, P4, P5, P7, P8, P10) which do not show the forbidden tetrads *iss* and *sss* at 69.3 and 69.4 ppm respectively, do not allow one to conclude on the incidence or not of side reactions. Indeed, a better insight is obtained by further characterization of the polylactides by MALDI-TOF-MS. It is important to point out that the spectra were recorded on crude polymer samples without prior precipitation. In addition, care has been taken to avoid hydrolysis of the polylactides by keeping the samples under argon. For example, the MALDI-TOF spectrum of P4 (Fig. 4) and the corresponding assignment of the various peaks summarized in Table 4, indicate the presence of linear chains (even and odd-membered) as well as cycles. From the relatively low polydispersity of the polymer ($I = 1.16$), it can be inferred that intramolecular transesterification is also occurring at low conversion but are not detectable by NMR. As compared to P4, the MALDI-TOF spectrum of P8 shows a slightly higher percentage of cycles and odd-membered polymer chains, which is an indication of enhanced transesterification and racemization in toluene.

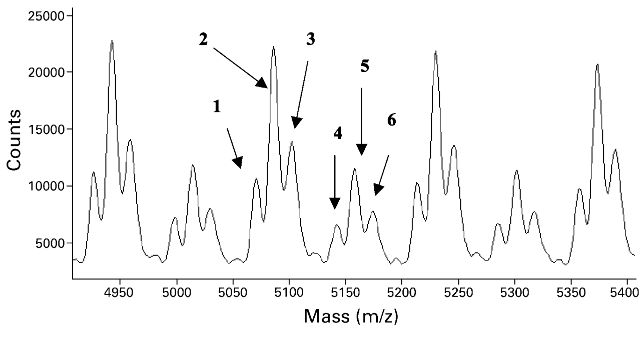

Fig. 4. Part of MALDI-TOF spectrum of P4.

3.3. Microstructure of polymers

The microstructure of all polymers (P1–P12) were studied by ^{13}C NMR (Table 5) and important parameters such as the coefficients of probability or stereoselectivity, p_1 and p_2 as well as the average length of the isotactic blocks (L-lactyl units, L_i) were evaluated using the intensities of tetrads. The coefficients of probability in fact correspond respectively to addition of the growing chain with the same enantiomer and with the opposite enantiomer. Calculations of p_1 and p_2 were based on the equations developed by Kasperczyk [9] in case of a non-Bernouillian statistics and in the absence of transesterification reactions, while L_i were determined using the method described by Coudane et al. [18]. The values of the coefficients p_1 and p_2 give a good indication of the structure of the polymer. For instance, in a perfectly disyndiotactic structure, $p_1 = 0$ and $p_2 = 1$ while $L_i = 2$. The occurrence of racemization will probably alter the syndiotactic stereosequences in direction of random ones and, consequently, will lead to a decrease of p_2 and an increase of L_i value.

As can be noted from Table 5, polymers P4 and P7 which were obtained in dioxane exhibit a highly syndiotactic structure ($p_2 \geq 0.8$; L_i close to 2). However, at very high conversion (P3 and P5), this predominant syndiotactic tendency decreases due to tranesterification reactions and probable racemization of monomer and lactidyl units. Moreover, a comparison of polymers prepared in dioxane and in toluene show that in the latter solvent, significantly lower values of p_2 are obtained although the molar mass distribution is quite narrow as in the case of P8 for instance. These results suggest that intramolecular transesterification reactions and racemization probably occur in toluene even at low conversion but are much less pronounced in dioxane. In conclusion, the poly(D,L-lactides) synthesized in dioxane even at high conversion contain an enhanced percentage of disyndiotactic structure. A similar tendency was reported previously [9,10,12] for polymerizations of D,L-lactide in

Table 5
Tetrad intensities and calculated values of p_1, p_2 and L_i of poly(D,L-lactides)

Polymer	Solvent	$[M]/[I]$	X(%)	Tetrads (%)					p_1 [a]	p_2 [b]	L_i [c]
				ssi	sss	isi	iss	sis,iis,sii,iii			
P1	Dioxane	50	98	5.7	2.6	25	6.7	60.0	–	–	–
P2			99	8.5	6.7	16.7	9.2	58.9	–	–	–
P3			100	–	–	36.0	–	64.0	0.28	0.72	2.78
P4		100	32	–	–	42.0	–	58.0	0.16	0.84	2.38
P5			87	–	–	39.0	–	61.0	0.22	0.78	2.56
P6			98	3.6	1.9	29.7	5.5	59.3	–	–	–
P7			70	–	–	40.0	–	60.0	0.20	0.80	2.50
P8	Toluene	50	25	–	–	33.0	–	67.0	0.34	0.66	3.03
P9			97	5	3.1	24.1	8.5	59.3	–	–	–
P10		100	44	–	–	33.0	–	67.0	0.34	0.66	3.03
P11			87	3.9	2.5	28.3	6.0	59.3	–	–	–
P12			93	5.0	3.6	25.4	7.8	58.2	–	–	-

[a] p_1,p_2: probability coefficients.
[b] $p_2 = \text{isi}/50$.
[c] $L_i = 2/p_2$.

Table 6
Poly(D,L-lactides) obtained with other anionic initiators, showing disyndiotactic structure

Initiator	$[M]/[I]$	Yield (%)	p_1	p_2	L_i
BuLi [12]	200	79	0.28	0.72	2.77
Bu_2Mg [12]	100	80	0.37	0.63	3.17
tBuOLi [9,10]	250	35	0.10	0.90	2.22

THF at 20°C with other initiators such as tBuOLi, BuLi and Bu_2Mg used mostly at lower concentrations. The corresponding values of p_1, p_2 and L_i are summarized in Table 6 and are found to be quite close to those we have calculated for LDA.monoTHF.

4. Conclusions

Lithium diisopropylamide.monoTHF complex is a quite efficient initiator for ring-opening polymerization of D,L-lactide, exhibiting a reactivity comparable to that of other anionic type lithium containing initiators. Similar trends, such as occurrence of transesterification reactions and probably racemization as well as a tendency to high predominance of disyndiostructure, were observed. MALDI-TOF analysis confirmed the incidence of intramolecular transesterification reactions in addition to intermolecular ones.

A study of the polymerization of L-lactide using LDA.monoTHF is underway and will help shed more light into the occurrence of transesterification and racemization reactions. The results of this study will be the object of a further paper.

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