Macromolecules **1996,** *29,* 6461−6465

Evidence for Ester-Exchange Reactions and Cyclic Oligomer Formation in the Ring-Opening Polymerization of Lactide with Aluminum Complex Initiators

Giorgio Montaudo*

Dipartimento di Scienze Chimiche, Universita' di Catania, Viale A. Doria, 6-95125 Catania, Italy

Maurizio S. Montaudo, Concetto Puglisi, and Filippo Samperi

Istituto per la Chimica e la Tecnologia dei Materiali Polimerici, Consiglio Nazionale delle Ricerche, Viale A. Doria, 6-95125 Catania, Italy

N. Spassky, Alain LeBorgne, and Muriel Wisniewski

Laboratoire de Chimie Macromoleculaire, Universite' Pierre et Marie Curie, 4 Place Jussieu, 752552 Paris Cedex 05, France

Received April 10, 1996; Revised Manuscript Received July 2, 1996[⊗]

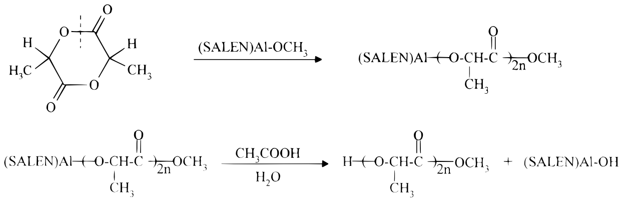
ABSTRACT: Four polylactide samples, obtained by ring-opening polymerization with an aluminum alkoxide initiator derived from a Schiff's base, were characterized by MALDI-TOF mass spectrometry. The MALDI mass spectra of these polylactides show well-resolved signals that can be reliably assigned to polylactide oligomers. Remarkably, both even-membered and odd-membered oligomers are present in these MALDI spectra. The presence of odd-membered oligomers cannot be explained on the basis of the lactide ring-opening polymerization, and one must admit that ester-exchange reactions do occur parallel to the polymerization process, causing a random cleavage of the polylactide chain. Furthermore, evidence for the presence of cyclic lactides was found in the MALDI-TOF spectrum of a low molecular weight polylactide fraction, indicating that ester exchange occurs also in polylactides by intramolecular end-biting reactions (ring−chain equilibration), with formation of cyclic oligomers.

Introduction

Polylactides are interesting materials due to their biodegradable, biodesorbable, biocompatible, and mechanical properties leading to biomedical and pharmacological application.[1,2] The most efficient way of preparing of polylactides is the ring-opening polymerization by anionic, cationic, and coordination initiators. The coordination initiation usually allows a controlled living type synthesis leading to polymers with narrow molecular weight distributions (MWD). Typical coordination initiators are aluminum alkoxides such as $Al(O\text{-}i\text{-}Pr)_3$,[3,4] $Zn(OAl(OR)_2)_2$,[5] and tetraphenylporphinate AlOR.[6] Most of the lactide polymerization were found to be accompanied by ester-exchange reactions which produce a broadening of the MWD and a reshuffle of the configurational units. Transesterification reactions may be identified by ^{13}C NMR analysis[7,8] and by SEC.[4,9] However, up to now it has not been clearly established if the ester-exchange reactions occur during or after the polymerization and if transesterification reactions are intermolecular or intramolecular.

In a recent study,[10−12] we followed the ring-opening polymerization of a racemic lactide as a function of time and conversion, using as initiator an aluminum alkoxide derived from a Schiff's base, namely, {2,2′-[ethylenebis-(nitrilomethylidine)]diphenolate}aluminum methoxide, which will be denoted as $(SALEN)AlOCH_3$.[13] With this initiator the ring opening of the lactide occurs via O-acyl scission leading to a polymer with methoxy ester ($-COOCH_3$) and hydroxy alcohol (−OH) end groups (Scheme 1).

Scheme 1



This system presents some features of a living type polymerization (e.g., narrow MWD) up to 70% conversion, but after this value the MWD broadens. However, the typical peaks of transesterification[7,8] were absent in ^{13}C NMR, and they could be detected only for polymer samples which were allowed to react for several months. In that case the molecular weight (MW) of polymer was found to decrease, and an oligomeric fraction soluble in methanol was isolated.

To further the study, we have now performed the structural characterization of polylactide by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Mass spectrometry is able to look at the mass of individual molecules in a mixture of homologues, and therefore it is specifically suited both for structural and end-group analysis. MALDI-TOF mass spectrometry is a recently introduced[14] soft ionization technique that possesses unprecedented high sensitivity and allows desorption and ionization of very large molecules even in complex mixtures, such as the wide molecular weight distribution (MWD) present[15−19] in synthetic and natural macromolecules. MALDI-TOF spectra, which have the advantage of being obtained from intact (and even crude) polymer samples, allow the identification of mass-resolved polymer chains, i.e., the direct determination[15−19] of the species contained in a polymer sample.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

S0024-9297(96)00538-4 CCC: $12.00

Scheme 2

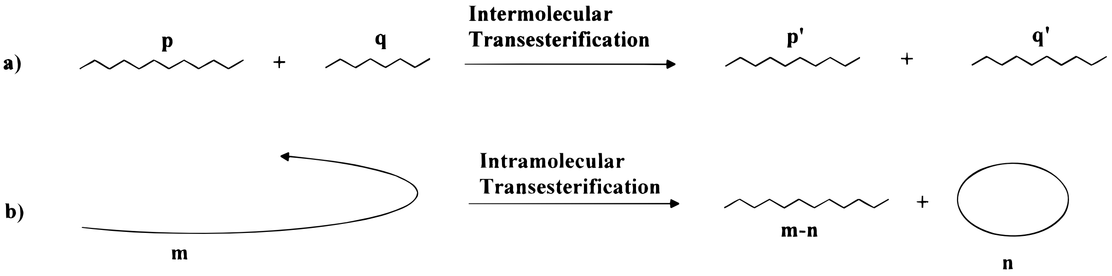


Table 1. Condition of Synthesis and Characteristic of Polylactide Samples

sample	mon[a]	[M]/[I][b]	solv[c]	time[d] (h)	temp (°C)	conv[e] (%)	M_n[f]	MWD[g]	M_n[h]	MWD[i]
PLA1	D,L	243	CH_2Cl_2	90	70	29.5	4500	1.07	3800	1.08
PLA2	D,L	243	CH_2Cl_2	235	70	62.5	11800	1.16	7800	1.22
PLA3	L	29	toluene[j]	15	70	96.0	3100	1.2	3000	1.36
PLA4	D,L	75	CH_2Cl_2	3240	70	98.0	1400[k]	3.1	3300	1.5

[a] Type of monomer. [b] [monomer]/[initiator] moles ratio. [c] Solvent used. [d] Reaction time in hours. [e] Percent of conversion. [f] Calculated number average molecular weight using the SEC calibration curves (log M vs volume eluted) obtained with polystyrene (PS) standards in THF as eluent at 35 °C. [g] Calculated polydispersity index (M_w/M_n) as resulting from the SEC curve. [h] Calculated number average molecular weight from the analysis of MALDI-TOF mass spectra. [i] Calculated polydispersity index (M_w/M_n) as resulting from the analysis of MALDI-TOF mass spectra. [j] Pyridine was added in stoichiometric amount to the initiator. [k] Calculated as in f. However, this sample contains a large amount of cyclic oligomers and the SEC calibration curve obtained with PS standards is likely to be somehow inaccurate.[23]

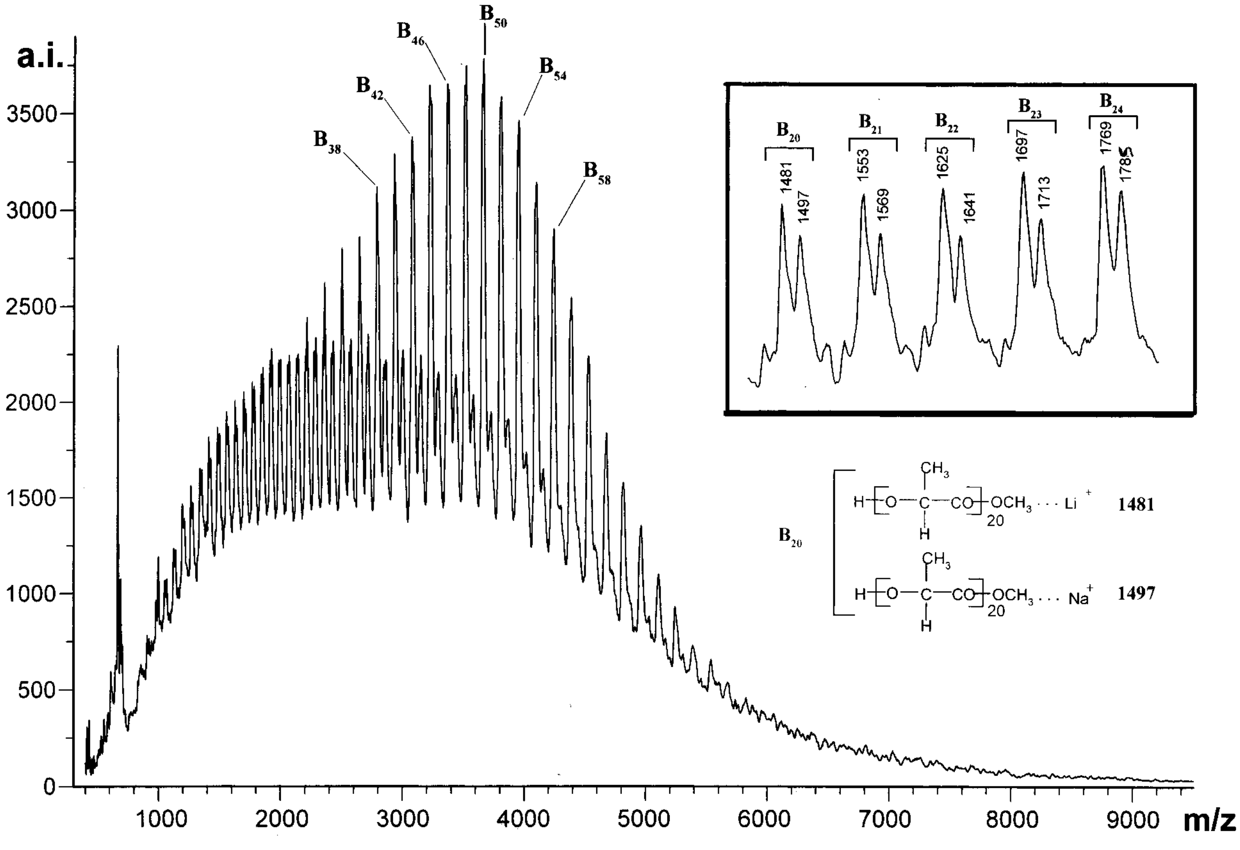


Figure 1. MALDI-TOF Mass Spectrum, recorded in linear mode using DHBA as matrix, of the a low conversion (29.5%) poly-(D,L)lactide sample (PLA1).

The MALDI mass spectra of the polylactides analyzed here show that both even-membered and odd-membered oligomers are present even in low conversion samples. The presence of odd-membered oligomers cannot be explained on the basis of the lactide ring-opening polymerization, and one must admit that ester-exchange reactions do occur parallel to the polymerization process, causing a random cleavage of the polylactide chain (Scheme 2).

Furthermore, evidence for the presence of cyclic lactides was found in the MALDI-TOF spectrum of a low molecular weight polylactide fraction, isolated from the crude polymer after a very long period of polymerization.

Experimental Section

Synthesis. The details of the synthetic conditions are given in Table 1, along with an estimate of the molecular weight of the resulting polymer. The synthesis of (SALEN)$AlOCH_3$ was described elsewhere.[13]

PLA1 and PLA2 are two samples from a kinetical study of racemic lactides.[10–12] The polymerization was run under vacuum in CH_2Cl_2 at 70 °C. At given times aliquots were withdrawn from the polymerization mixture and after remov-

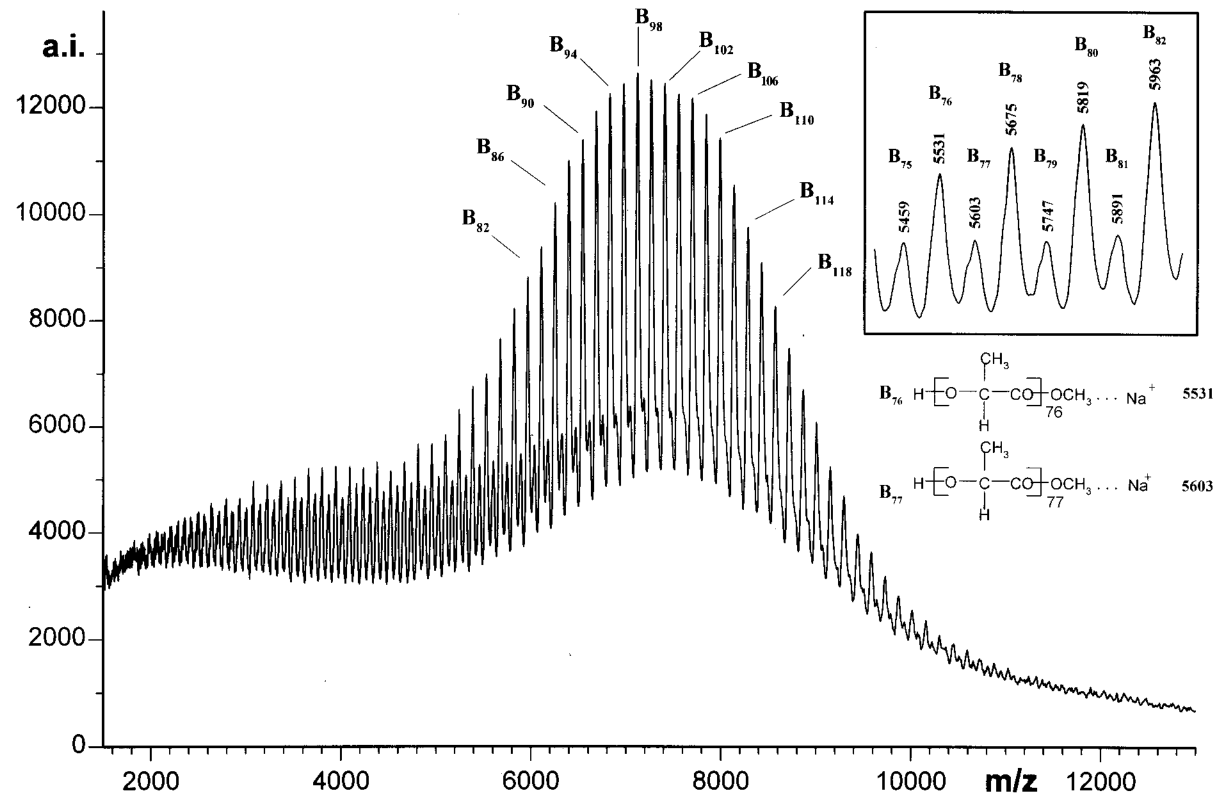


Figure 2. MALDI-TOF Mass Spectrum, obtained in linear mode using HABA as matrix, of the a medium conversion (62.5%) poly(D,L)lactide sample (PLA2).

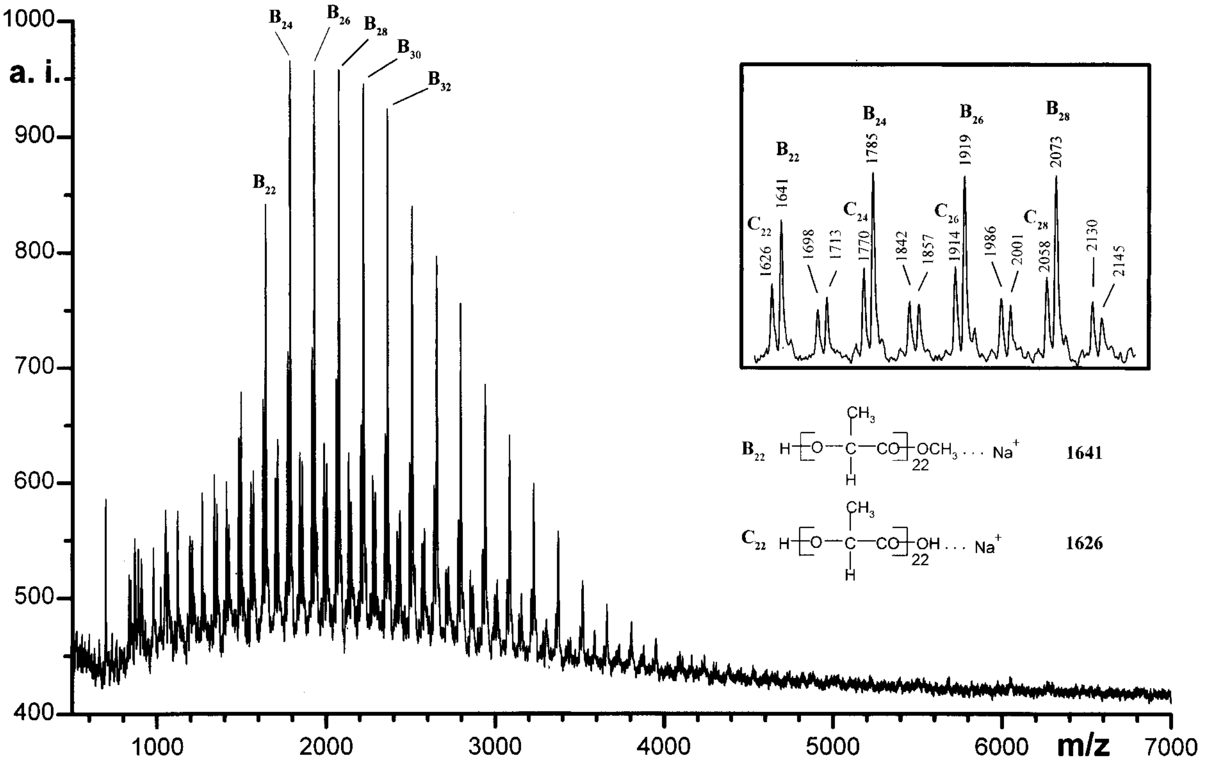


Figure 3. MALDI-TOF Mass Spectrum, recorded in reflectron mode using DHBA as matrix, of the high conversion (96.0%) poly(L)lactide sample (PLA3),.

ing solvent and drying, the conversion was determined by ^{1}H NMR from monomer and polymer signals. The molecular weight (MW) and the molecular weight distribution (MWD) are determined from SEC analysis using THF as solvent at 35 °C.

In another kinetic run the polymerization was prolonged a long time (18 weeks). After removal of solvent from the reaction mixture, the raw polymer was dried, the conversion (98%) was determined by ^{1}H NMR. Then the polymer was worked up several times with methanol, and from the soluble in methanol part after removal of the solvent oligomers (PLA4) were isolated and examined by SEC in THF and by ^{1}H NMR.

PLA3 is a low molecular weight polymer prepared from (L)-lactide in toluene at 70 °C. Pyridine was added in stoichiometric amount to the initiator. It was reported in the literature[13,20] that the addition of Lewis bases such as pyridine limits the transesterification reactions. The combined effects

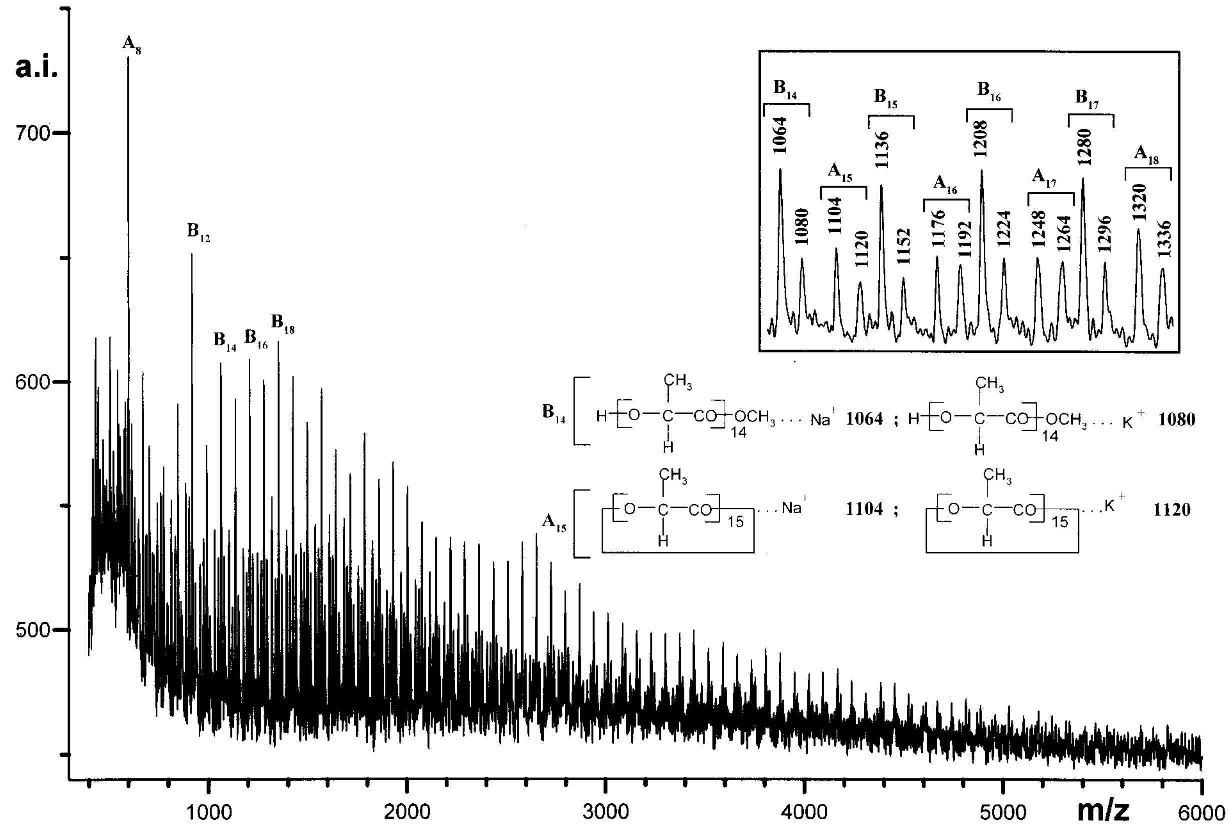


Figure 4. MALDI-TOF Mass Spectrum, recorded in reflectron mode using DHBA as matrix, of the low molecular weight methanol soluble fraction (PLA4) from a high conversion (98.0%) poly(D,L)lactide sample.

of low [M]/[I] ratio, use of toluene as solvent, and addition of pyridine greatly increase the rate of polymerization.

MALDI-TOF Mass Spectra. The matrix and solvent used in the MALDI experiments were supplied from Aldrich Chemical Co (MI, Italy) and LAB-SCAN (Italy), respectively. A Bruker Reflex mass spectrometer was used to obtain the matrix-assisted laser desorption/ionization time-of-flight mass spectra. The spectrometer was equipped with a nitrogen laser (337 nm, 5 ns), a double-plate microchannel detector, and a flash ADC (time base 4 ns). Accelerating voltage was 30 kV. The laser irradiance was not measured. However, it was slightly above threshold (10^6–10^7 W/cm^2). The detection was in the reflectron and linear mode. Ions below *m/z* 350 were removed with pulsed deflection, and 100 transients were summed. The resolution was about 400 at 5000 Da. Either 2,5-dihydroxybenzoic acid (DHBA) or [2-(4-hydroxyphenylazo)-benzoic acid] (HABA) were used as the matrix and tetrahydrofuran was used as a solvent. Probe tips were loaded with about 20 pmol of polymer and 100 nmol of matrix. Time-to-mass conversion of the time-of-flight mass spectra was achieved using a self-calibration method.[19]

Results and Discussion

The ionization process of a neutral macromolecule in MALDI-TOF proceeds through the capture of a proton or a metal ion (usually lithium, sodium, potassium), which forms a charged adduct with the molecular species.[14–19]

In Figure 1 is reported the MALDI-TOF mass spectrum, recorded in linear mode, of a low conversion (29.5%) poly(D,L)-lactide sample (PLA1). The spectrum shows well resolved signals approximately in the 1000–5500 Da region, which are due to polylactide oligomers. The inset in Figure 1 shows an expanded portion of the spectrum with two distinct mass series, due to open-chain oligomers clustered to Li^+ and Na^+ ions, and terminated by methoxy ester and hydroxy end groups. Remarkably, both even-membered and odd-membered oligomers are present in this MALDI spectrum. The odd- and even-membered oligomers have a comparable abundance in the lower mass region (with a MW distribution centered around 2000 Da), whereas the even-membered oligomers appear more abundant at higher masses, with a MW distribution centered around 3500 Da. The presence of odd-membered oligomers in this low conversion (29.5%) polylactide sample cannot be explained on the basis of the lactide ring-opening polymerization, which should produce only even-membered oligomers (Scheme 1). Therefore, one must admit that ester-exchange reactions do occur parallel to the polymerization process, causing a random cleavage of the polylactide chain (Scheme 2a) with consequent production of even-membered and odd-membered oligomers.

To ascertain which of the two processes depicted in Scheme 2 actually occurs, it should be noted that ester exchange is known[21,22] to proceed in polyesters by intermolecular and intramolecular reactions occurring through active chain ends. The intramolecular process (Scheme 2b) occurs by a partial depolymerization reaction leading to the formation of cyclic oligomers. The latter process (ring–chain equilibration reactions)[23] may be thermodynamically or kinetically controlled and produce cyclic oligomers of relatively low MW.[22–24]

However, the presence of cyclic lactides, diagnostic for direct proof of an intramolecular exchange reaction (Scheme 2b), was not found in the Maldi spectrum in Figure 1, and therefore further evidence must be sought.

Higher conversion polylactide samples were therefore analyzed by MALDI-TOF in order to obtain evidence for the presence of cyclic oligomers.

In Figure 2 is reported the MALDI-TOF mass spectrum, recorded in linear mode, of a medium conversion (62.5%) poly-(D,L)-lactide sample (PLA2). The spectrum shows well-resolved signals approximately in the 2000–10 000 Da region, due to lactide oligomers. The inset in Figure 2 shows an expanded portion of the spectrum with a single mass series, due to open-chain oligomers clustered to Na^+ ions and terminated by methoxy ester and hydroxy end groups as observed in the case of the PLA1 sample. Also in this case both even-membered and odd-membered oligomers are present in the MALDI spectrum. As in the case of PLA1 sample, in the PLA2 sample the odd- and even-membered oligomers have a comparable abundance in the lower mass region (with a MW distribution centered around 4000 Da), whereas the even-membered oligomers appear more abundant at higher masses, with a MW distribution centered around 7000 Da. Therefore, the inspection of the MALDI spectrum in Figure 2 confirms the above observation but does not add new evidence.

Essentially, the same result was obtained by analyzing a high conversion (96.0%) poly-(L)-lactide sample (PLA3, see Figure 3). This sample was prepared from pure L enantiomer, at low [M]/[I] ratio (Table 1) and with addition of pyridine in order to decrease the transesterification reactions. Starting from a pure enantiomer, it is not possible to determine by NMR the amount of transesterification, since the “forbidden” modes do not exist.[7,8] The MALDI-TOF mass spectrum of the PLA3 sample reported in Figure 3 was recorded in reflectron mode (allowing a higher resolution with respect to the linear mode) and shows well-resolved signals approximately in the 1000−4000 Da region. The inset in Figure 3 shows an expanded portion of the spectrum with two distinct mass series, due to open-chain oligomers clustered to Na^+ ions and terminated by methoxy ester and carboxylic end groups, respectively. The carboxylic end group may be formed by hydrolysis of ester groups, owing to the presence of a trace of water in the synthesis mixture.

Since the unfractionated poly-(D,L)-lactide samples (PLA1 and PLA2) failed to show the presence of cyclic oligomers, as well as the high conversion (96.0%) poly-(L)-lactide sample (PLA3) prepared in the presence of pyridine, a high conversion (98%) poly-(D,L)-lactide sample obtained after a long period of polymerization (18 weeks) was examined and more particularly the oligomer part obtained by treating the raw unfractionated polymer with methanol. This low MW fraction (PLA4) was then analyzed by MALDI-TOF.

The spectrum in Figure 4, obtained in reflectron mode, shows well-resolved signals approximately in the 500−5000 Da region. The most intense peak is at 599 Da, and it corresponds to the sodium adduct of the cyclic octamer of lactic acid. The inset in Figure 4 shows an expanded portion of the spectrum with four distinct mass series, due to open-chain and cyclic oligomers clustered to Na^+ and K^+ ions, respectively. Therefore, the MALDI spectrum in Figure 4 shows without ambiguity the presence of open-chain and cyclic oligomers (approximately in 60/40 molar ratio), and this result indicates the occurrence of intramolecular exchange reactions (Scheme 2b).

These preliminary results obtained on polylactides prepared using the $SALENAlOCH_3$ initiator system indicate that polymerization and transesterification reactions are occurring in parallel from the beginning (as indicated by the results on the low conversion PLA1 sample).

A more careful examination of different polymers obtained with this particular initiator and with other initiators is necessary to substantiate a general scheme of transesterification reactions occurring in the course of ring-opening lactide polymerization.

In conclusion, we have obtained evidence for the occurrence of an intermolecular and intramolecular ester exchange in the ring-opening polymerization of lactide. It was also shown that transesterification reactions occur from the beginning of the polymerization reaction. Further studies will concern the influence of different parameters (medium, temperature, time of polymerization, nature of the initiator) on the development of transesterification reactions.

It is believed that the possibility of detecting both linear and cyclic lactide oligomers by MALDI analysis shall be of help in further studies concerning the control of lactide polymerization conditions.

Acknowledgment. Partial financial support from the Italian Ministry of University and Technological Research (MURST), from Progetto Strategico Tecnologie Chimiche Innovative, and from National Council of Research (Rome) is gratefully acknowledged

References and Notes

(1) Kharas, G. B.; Sanchez-Riera, F.; Sevenson, D. K. In *Plastics from microbes*; Mobley, D. P., Ed.; Hanser Publishers: Munich, 1994; Chapter 4, p 93.
(2) Vert, M.; Li, S. M.; Spenlehauer, G.; Guerin, P. *J. Mater. Sci., Mater. Med.* **1992**, *3*, 432.
(3) Kricheldorf, M. R.; Berl, M.; Scharnagl, N. *Macromolecules* **1988**, *21*, 286.
(4) Dubois, P.; Jacobs, C.; Jerome, R.; Teyssié, P. *Macromolecules* **1991**, *24*, 2266.
(5) Song, C. X.; Feng, X. D. *Macromolecules* **1984**, *17*, 2764.
(6) Trofimoff, L.; Aida, T.; Inoue, S. *Chem. Lett.* **1987**, 991.
(7) Chabot, F.; Vert, M.; Chapelle, S.; Granger, P. *Polymer* **1983**, *24*, 53.
(8) Bero, M.; Kasperczyk, J.; Jedlinski, Z. *Makromol. Chem.* **1988**, *191*, 2287.
(9) Penczek, S.; Duda, A.; Szymanski, R. *Polym. Prepr., Div. Polym. Sci. Am. Chem. Soc.* **1996**, *37*, 219.
(10) LeBorgne, A.; Wisniewski, M.; Spassky, N. *Polym. Prepr., Div. Polym. Sci. Am. Chem. Soc.* **1995**, *36*, 217.
(11) LeBorgne, A.; Wisniewski, M. *Macromolecules*, in press.
(12) Wisniewski, M. Doctoral Thesis, Paris, 1995.
(13) LeBorgne, A.; Vincens, V.; Jouglard, M.; Spassky, N. *Makromol. Chem., Macromol. Symp.* **1993**, *173*, 37.
(14) Karas, M.; Hillenkamp, F. *Anal. Chem.* **1988**, *60*, 2299.
(15) Bahr, U.; Deppe, A.; Karas, M.; Hillenkamp, F.; Giessman, U. *Anal. Chem.* **1992**, *64*, 2866.
(16) Danis, P. O.; Karr, D. E.; Mayer, F.; Holle, A.; Watson, C. H. *Org. Mass Spectrosc.* **1992**, 27, 843. Danis, P. O.; Karr, D. E. *Org. Mass Spectrom.* **1993**, *28*, 923.
(17) Montaudo, G.; Montaudo, M. S.; Puglisi, C.; Samperi, F. *Anal. Chem.* **1994**, *66*, 4366; *Rapid Commun. Mass Spectrom.* **1994**, *8*, 981; **1994**, *8*, 1011; **1995**, *9*, 453; *Macromolecules* **1995**, *28*, 4562.
(18) Montaudo, G.; Montaudo, M. S.; Puglisi, C.; Samperi, F. *Rapid Commun. Mass Spectrom.* **1995**, *9*, 1158; *Macromolecules* **1995**, *28*, 7983; *J. Polym. Sci., Polym. Chem. Ed.* **1996**, *34*, 439.
(19) Montaudo, G. *Trends Polym. Sci.* **1996**, *4*, 81.
(20) Dubois Ph.; Jerome R.; Teyssié Ph. *Polym. Prepr. Div. Polym. Sci., Am. Chem. Soc.* **1994**, *35*, 596.
(21) Montaudo, G.; Montaudo, M. S.; Scamporrino, E.; Vitalini, D. *Macromolecules* **1992**, *25*, 5099.
(22) Montaudo, G. *Macromolecules* **1991**, *24*, 5829.
(23) Semlyen, J. A In *Cyclic Polymers*; Elsevier: New York, 1986.
(24) Maravigna, P.; Montaudo, G. In *Comprehensive Polymer Science*; Allen, G.; Bevington, J. C., Eds.; Pergamon Press: New York, 1989; Vol. 5.

MA960538I