Microstructure Analysis of Poly(lactic acid) Obtained by Lithium *tert*-Butoxide as Initiator

J. E. Kasperczyk

Institute of Polymer Chemistry, Polish Academy of Sciences, 41-800 Zabrze, Poland

Received July 15, 1994; Revised Manuscript Received January 10, 1995[⊗]

ABSTRACT: In the polymerization of racemic L,D-lactide by lithium *tert*-butoxide as an initiator polyesters with disyndiotactic segments in the polymer chain are obtained. The observation evidences the stereoselectivity leading to an alternating addition of enantiomers to the growing chain during polymerization. The analysis of the carbonyl and methine region in the ^{13}C NMR spectrum of obtained poly(lactic acid) allowed the calculation of the probability coefficient p_2 determining the amount of disyndiotactic structures in the polymer chain.

Introduction

During the last several years the investigations of biodegradable aliphatic polyesters as medical materials have been performed.[1,2] They found many applications in drug delivery systems and surgery as orthopedic implants and surgical sutures.[3–10]

Poly(lactic acid) appears to be a biocompatible material, hydrolitically biodegradable to nontoxic, naturally occurring metabolite. High molecular weight poly(lactic acid) can be obtained via ring-opening polymerization of lactide in the presence of initiator containing zinc, tin, and magnesium salts[11–13] various metal alkoxides,[14,15] cationic catalysts such as BF_3 and triflic acid,[16,17] and anionic potassium methoxide.[18,19] Lithium alkoxide-initiated polymerizations of L-lactide were also performed.[20]

A study concerning the influence of tranesterification on the microstructure of obtained poly(lactic acid) showed the strongest transesterification activity for zinc chloride initiator, medium activity for diethylzinc and diethylzinc/aluminum isopropoxide complex, and lack of transesterification for aluminum tris(acetylacetonates).[21] Because the lactide molecule possesses two equivalent asymmetric carbon atoms, in the polymerization without transesterification a polyester chain which obeys the pair-addition statistics is obtained.[21,22] For example from racemic D,L-lactide "prediminantly isotactic" polymer chain (using Vert's terminology[22]) by pair-addition Bernoullian statistics is formed. Transesterification determines the changes of the chain microstructure to atactic polymer.[21] In crude racemic lactide, a small amount of *meso*-lactide is present. Separation of *meso*-lactide and its polymerization lead to partly syndiotactic polyester, but it results from the monomer structure.[23]

During the synthesis of block copolymers of lactide and ϵ-caprolactone in the presence of lithium *tert*-butoxide,[24] nontypical distribution of intensity of the lines due to lactydyl segment in the ^{13}C NMR spectrum was observed. It suggested a diverse structure of the lactydyl segment in comparison to that of the polyesters described in the literature to date. This work contains microstructure analysis of poly(lactic acid) obtained from racemic D,L-lactide in the presence of lithium *tert*-butoxide.

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1995.

Experimental Part

Monomers. Racemic L,D-lactide [Boehringer Ingelheim] was purified by distillation (1 mmHg) and three times recrystallized from dry ethyl acetate and dried over P_2O_5 in vacuo.

Solvent. THF was purified according to the method described[25] and then was distilled over a sodium–potassium alloy in an atmosphere of dry argon.

Initiator: The commercial grade lithium *tert*-butoxide [Fluka] was used.

Polymerization Procedure. In the closed flask equipped with magnetic stirrer and dry argon supply a 1.4 M solution of racemic lactide in dry THF was introduced. The content of the flask was cooled using liquid nitrogen. Then a solution of lithium *tert*-butoxide in dry THF (initiator-to-monomer mole ratio 1:400) was added. A conventional vacuum line method was used for degassing and sealing the flask. The flask was cut and placed in magnetic stirrer and polymerization was conducted for 60 min at 293 K. Finally, the reaction mixture was poured into *n*-hexane to precipitate the polymer. In order to remove residual amounts of the monomer, the polymer was purified by dissolving in THF and precipitated into cold methanol. The obtained product was dried in vacuum at 323 K. The yield of obtained polymers was 80%.

GPC Measurements. The gel permeation chromatography experiments were conducted in THF (flow rate 1 mL/min, at 308 K) by using the ALC GPC 3M Waters apparatus. The column configuration consists of two PL gel-packed columns (2×Mixed C). Molecular weights were estimated according to the Polystyrene calibration curve using polystyrene standards with a low polydispersity.

^{13}C NMR Measurements. The ^{13}C NMR (75 MHz) spectra were performed on a Varian VXR-300 spectrometer in 5 mm o.d. sample tubes in $CDCl_3$ as a solvent and TMS as internal standard. A measurement temperature of 303 K, acquisition time of 1.8 s, pulse width of 9 μs and delay of 3 s between pulses, and digital resolution of 64K data points/16 500 Hz spectral width were used. A total of 3000 transients were accumulated. The quantitativity of the ^{13}C NMR measurements was previously ascertained. For the syntheses of poly(lactic acid) nonequimolar mixtures of enantiomers were used which were obtained by adding L,L-lactide to the known amount of racemic lactide. Several mixtures with various ratios of enantiomers were polymerized, yielding polyesters in which the distribution of monomer units obeys pair-addition Bernoullian statistics. The experimental intensities of lines (methine and carbonyl regions) in the ^{13}C NMR spectra were compared with theoretical intensities calculated from appropriate equations presented in our previous paper,[21] and good agreement of the line intensities was found.

Results and Discussion

In the homopolymerization of racemic lactide using lithium *tert*-butoxide as an initiator a high molecular

0024-9297/95/2228-3937$09.00/0

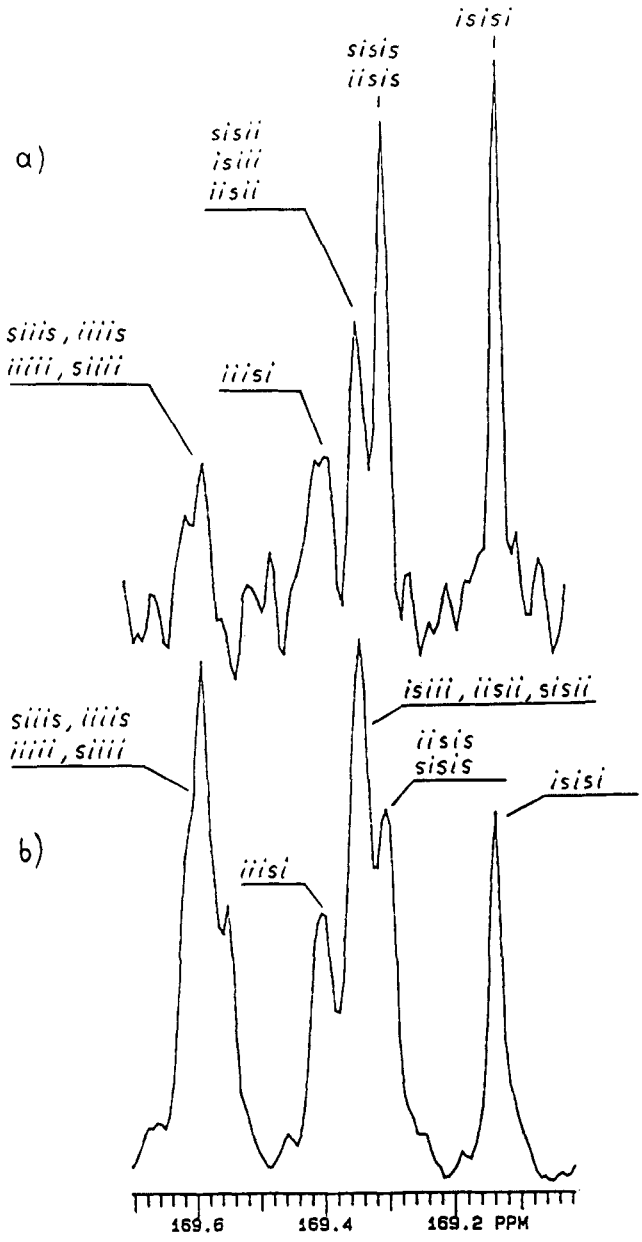

Figure 1. ^{13}C NMR spectra of the carbonyl region of the racemic poly(lactic acid) obtained in the presence of (a) lithium *tert*-butoxide and (b) aluminum tris(acetylacetonate) as initiators.

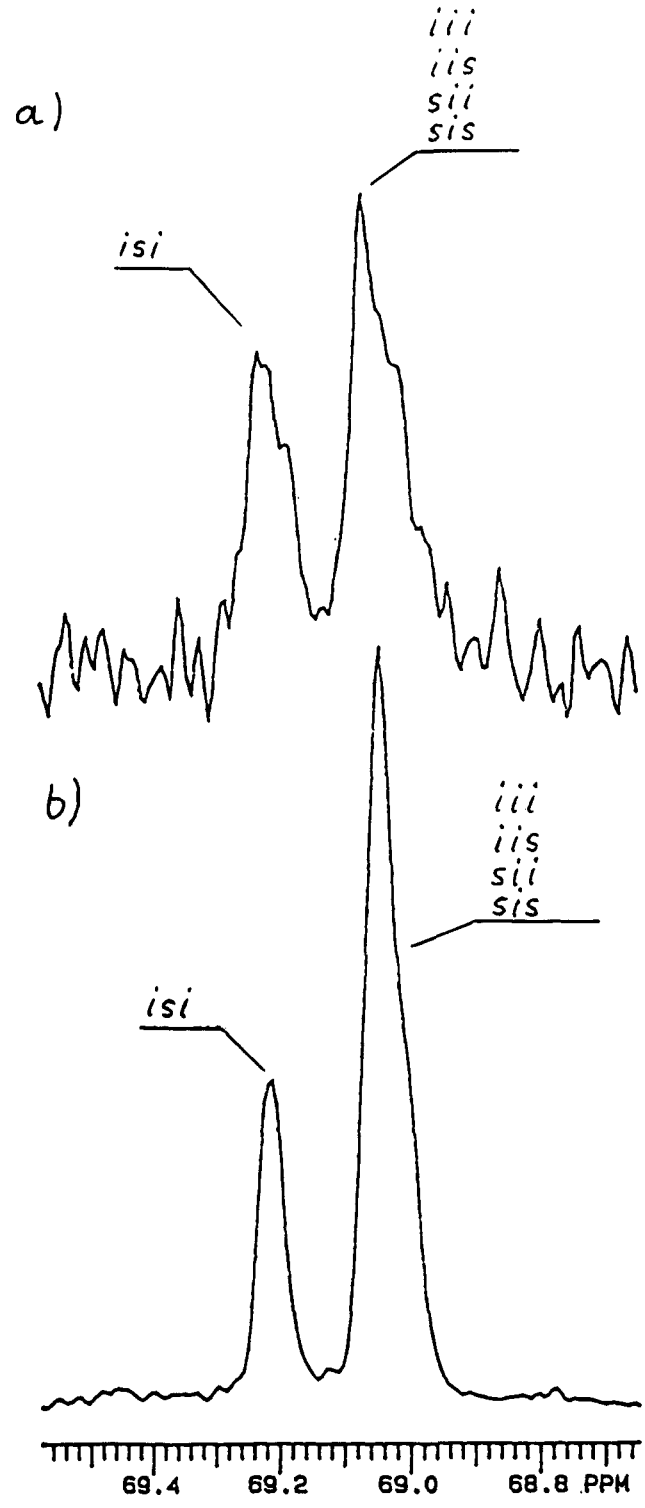

Figure 2. ^{13}C NMR spectra of the methine region of the racemic poly(lactic acid) obtained in the presence of (a) lithium *tert*-butoxide and (b) aluminum tris(acetylacetonate) as initiators.

weight polyester was obtained (M_n = 40 000). The ^{13}C NMR spectrum of this polymer is presented in Figure 1a. The carbonyl carbon region exhibits several lines which correspond to 11 hexads resulting from pair addition of enantiomers of lactide molecules. There are no lines due to the remaining hexads which would be formed via transesterification. (When the transesterification occurs during polymerization, in the spectrum of the carbonyl region new lines are observed as a combination of 21 hexads containing an ss segment.) Likewise, in the methine region the resonance lines due to iss, sss, and ssi tetrads, which could also be formed exclusively by the transesterification, are not observed.

However in the carbonyl carbon region of the NMR spectrum (Figure 1a) an increase in intensities of two lines is seen as compared to those observed in polylactide where the sequence distribution obeys pair-addition Bernoullian statistics (Figure 1b). Similarly, in the methine carbon region an increase in intensity of the alternating isi tetrad is also observed (Figure 2).

In the previous work[21] the equations describing intensity values of the individual sequences obey pair-addition Bernoullian statistics and various ratios of enantiomers k were presented. A nontypical increase in the intensities of two lines in the carbonyl region of the ^{13}C NMR spectrum (Figure 1a) suggests a possibility of non-Bernoullian statistics and stereoselection during the polymerization of racemic lactide in the presence of lithium *tert*-butoxide as initiator.

In that case it is necessary to derive the equations which will describe such processes. In the studied polymerizations a racemic mixture is used. Therefore the ratio of enantiomers $k = 1$. It is possible to assume that the probabilities of the enantiomer addition to the growing chain terminated with the same enantiomer are equal $p_{LL/LL} = p_{DD/DD} = p_1$. Because $p_{DD/DD} + p_{LL/DD} = 1$ and $p_{LL/LL} + p_{DD/LL} = 1$, the probabilities of the enantiomer addition to the growing chain terminated with opposite enantiomers are equal too, e.g. $p_{LL/DD} = p_{DD/LL} = p_2$. Thus it is then possible to calculate the intensity values of the individual sequences.

$$\text{diads: (i)} = p_1^3 + 2.5p_1^2p_2 + 2p_1p_2^2 + 0.5p_2^3 \quad (1)$$

$$\text{(s)} = 0.5p_1^2p_2 + p_1p_2^2 + 0.5p_2^3 \quad (2)$$

$$\text{triads: (ii)} = p_1^3 + 2p_1^2p_2 + p_1p_2^2 \quad (3)$$

$$\text{(is)} = \text{(si)} = 0.5p_1^2p_2 + p_1p_2^2 + 0.5p_2^3 \quad (4)$$

$$\text{tetrads: (iii)} = p_1^3 + 1.5p_1^2p_2 + 0.5p_1p_2^2 \quad (5)$$

$$\text{(iis)} = \text{(sii)} = 0.5p_1^2p_2 + 0.5p_1p_2^2 \quad (6)$$

$$\text{(isi)} = 0.5p_1^2p_2 + p_1p_2^2 + 0.5p_2^3 \quad (7)$$

$$\text{(sis)} = 0.5p_1p_2^2 + 0.5p_2^3 \quad (8)$$

$$\text{pentads: (iiii)} = p_1^3 + p_1^2p_2 \quad (9)$$

$$\text{(iiis)} = \text{(iisi)} = \text{(isii)} = \text{(siii)} = 0.5p_1^2p_2 + 0.5p_1p_2^2 \quad (10)$$

$$\text{hexads: (iiiii)} = p_1^3 + 0.5p_1^2p_2 \quad (11)$$

$$\text{(iiiis)} = \text{(siiii)} = \text{(iisii)} = 0.5p_1^2p_2 \quad (12)$$

$$\text{(iiisi)} = \text{(isiii)} = 0.5p_1^2p_2 + 0.5p_1p_2^2 \quad (13)$$

$$\text{(iisis)} = \text{(siiis)} = \text{(sisii)} = 0.5p_1p_2^2 \quad (14)$$

$$\text{(isisi)} = 0.5p_1p_2^2 + 0.5p_2^3 \quad (15)$$

$$\text{(sisis)} = 0.5p_2^3 \quad (16)$$

From the equations presented above using intensities of signals in the ^{13}C NMR spectrum we may calculate coefficient probabilities p_1 and p_2. The structures of the polymer chain resulting from extreme p values are shown in Scheme 1.

Scheme 1

D,D + L,L ($p_1 = 1, p_2 = 0$) ⟹ ...LLLLLL... + ...DDDDD...
isotactic

D,D + L,L ($p_1 = p_2 = 0.5$) ⟹ ...LLLDDLLLLDDD...
"predominantly isotactic"

D,D + L,L ($p_1 = 0, p_2 = 1$) ⟹ ...LLDDLLDDLLDD...
disyndiotactic

From eqs 11−16 describing hexads only one line is expected in the spectrum of isotactic polymer; however in the spectrum of completely disyndiotactic polymer two lines with equal intensities should be seen. The same conclusions can be drawn from the equations describing tetrads.

In the ^{13}C NMR spectrum of poly(lactic acid) obtained by lithium *tert*-butoxide as an initiator, a considerable increase in the intensities of two lines (δ = 169.1, 169.3 ppm) is seen accompanied by the decrease in the intensities of the lines due to the remaining hexads. The calculated coefficients of probability were found to be $p_1 = 0.24$ and $p_2 = 0.76$. It indicates a preference in alternating D,D and L,L enantiomer addition to the growing chain end leading to an enhanced contribution of disyndiotactic segments in poly(lactic acid) molecules. Therefore it shows that in the growing step of a polyester chain a partial stereoselection occurs.

Acknowledgment. The study has been supported by the research programs (Project 4-17439101 of the Committee of Scientific Research in Poland).

References and Notes

(1) Kulkarni, R. K.; Moore, E. G.; Hegyeli, A. F.; Leonard, F. *J. Biomed. Mater. Res.* **1971**, *5*, 169.
(2) Cutright, D. E.; Hunsuck, E. E.; Beasley, J. D. *J. Oral Surg.* **1971**, *29*, 393.
(3) Vert, M.; Chabot, F.; Lewvay, J.; Christel, P. *Makromol. Chem. Suppl.* **1981**, *5*, 30.
(4) Vert, M.; Christel, P.; Garreau, H.; Audion, M.; Charanaz, M.; Chabot, F. *Polym. Sci. Technol.* **1986**, *34*, 263.
(5) Leenslag, J. W.; Pennings, A. J.; Boss, R. R. M.; Rozerna, F. R.; Boering, G. *Biomaterials* **1987**, *8*, 70.
(6) Younes, H.; Cohn, D. *Eur. Polym. J.* **1988**, *24*, 765.
(7) Cohn, D.; Younes, H. *Biomaterials* **1989**, *10*, 466.
(8) Song, C. X.; Feng, X. D. *Macromolecules* **1984**, *17*, 2764.
(9) Pitt, C. G.; Jeffcoat, A. R.; Zweidinger, R. A.; Schindler, A. *J. Biomed. Mater. Res.* **1979**, *13*, 497.
(10) Tunc, D. C. *Clin. Mater.* **1991**, *8*, 119.
(11) Ditrich, W.; Schulz, R. C. *Angew. Makromol. Chem.* **1971**, *15*, 109.
(12) Kulharni, K. K.; Pani, K. C.; Neuman, C.; Leonard, F. *Arch. Surg.* **1966**, *93*, 859.
(13) Dunsing, R.; Kricheldorf, H. R. *Polym. Bull.* **1985**, *14*, 491.
(14) Gilding, D.; Reed, A. *Polymer* **1979**, *20*, 1459.
(15) Kricheldorf, H. R.; Berl, M.; Scharnagl, N. *Macromolecules* **1988**, *21*, 286.
(16) Kricheldorf, H. R.; Dunsing, R. *Makromol. Chem.* **1986**, *187*, 1611.
(17) Kricheldorf, H. R.; Kreiser, I. *Makromol. Chem.* **1987**, *188*, 1861.
(18) Jedlinski, Z.; Walach, W.; Kurcok, P.; Adamus, G. *Makromol. Chem.* **1991**, *192*, 2051.
(19) Kricheldorf, H. R.; Kreiser, I. *Makromol. Chem.* **1990**, *191*, 1057.
(20) Kricheldorf, H. R.; Boettcher, C. *Makromol. Chem.* **1993**, *194*, 1665.
(21) Bero, M.; Kasperczyk, J.; Jedlinski, Z. *Makromol. Chem.* **1990**, *191*, 2287.
(22) Chabot, F.; Vert, M. *Polymer* **1983**, *24*, 53.
(23) Kricheldorf, H. R.; Boettcher, C.; Tonnes, K. *Polymer* **1992**, *33*, 2817.
(24) Bero, M.; Adamus, G.; Kasperczyk, J.; Janeczek, H. *Polym. Bull.* **1993**, *31*, 9.
(25) Wiessberger, A. *Organic Solvents*; Wiley-Interscience: New York, 1970; p 794.

MA945055Y