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Microstructural analysis of poly[(L,L-lactide)-*co*-(glycolide)] by ^{1}H and ^{13}C n.m.r. spectroscopy

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

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The ^{13}C nuclear magnetic resonance (n.m.r.) spectra were found to provide a means for direct observation of the structures formed along the glycolide/lactide copolymer chain upon transesterification. Nevertheless ^{1}H n.m.r. spectroscopy appeared to be more convenient and useful in the analysis of chain microstructure. The glycolide methylene group region of the proton spectra exhibits several signals which can be ascribed to longer sequences (as compared to those giving rise to ^{13}C resonances) as well as to the sequences which can appear only as a result of the second mode of transesterification. The analysis revealed that the longest blocks were in the copolymers prepared with $Al(acac)_3$ as the initiator and the shortest blocks were in the copolymers obtained with tin initiators. A decrease in temperature was found to reduce the extent of the second mode of transesterification.

(Keywords: poly[(L,L-lactide)-*co*-(glycolide)]; microstructure; transesterification)

INTRODUCTION

In recent years polyesters have been demonstrated to be extremely useful materials in controlled drug release due to their non-toxicity, good permeability of the drug and biosorption[1,2]. Copolymers of glycolide with lactide are included among the fundamental materials that have been subjected to extensive studies on degradation and release of LH–RH hormones, progesterone, antibiotics and antitumour drugs[3–6]. The microstructure of polyester chains appears to affect both the polymer biodegradation and the drug release rate. The microstructure of the obtained copolyester is influenced by the kind of applied initiator as well as by the transesterification occurring during the synthesis. The transesterification results in the redistribution of the sequences along the polymer chains leading to changes in the chain structure and the lengths of microblocks. In our previous works[7–9], ^{13}C nuclear magnetic resonance (n.m.r.) spectroscopy was successfully applied to develop a method for the determination of the microstructure of lactide/ϵ-caprolactone copolymers. However, for glycolide/lactide copolymers the problem of the microstructural analysis remains open. The structural analyses previously reported were based on ^{13}C n.m.r. spectroscopy. In the carbonyl carbon region the simplest diad sequences have been observed[10,11] which allowed the average lengths of comonomer blocks to be calculated. No detailed characterization of the copolymer chain microstructure, including expected structural changes resulting from transesterification processes, has been performed.

EXPERIMENTAL

Monomers

L,L-Lactide (Boehringer Ingelheim) was purified by distillation in vacuum and several recrystallizations from ethyl acetate and dried over P_2O_5. The glycolide used (Boehringer Ingelheim) was a commercial product.

Initiators

Tin octoate ($Sn(Oct)_2$) (Sigma), tin chloride ($SnCl_2 \cdot H_2O$) (POCh), zinc bis(acetylacetonate), $Zn(acac)_2$ (POCh), aluminium tris(acetylacetonate) ($Al(acac)_3$) (Fluka) and triethylaluminium ($AlEt_3$) (Alfa) were all commercial products.

Copolymerization procedure

The copolymerizations were carried out in chlorobenzene at 100 and 150°C with initiator to monomer molar ratio of 1 : 800 using a conventional vacuum line. Mole fractions of lactidyl and glycolydyl units in copolymers were measured by ^{1}H n.m.r.

G.p.c. measurements

The gel permeation chromatography (g.p.c.) experiments were conducted in tetrahydrofuran (flow rate 1 ml min^{-1}, at 308 K) by using the Spectra-Physics 8800 solvent delivery system with 10^4, 10^3 and 500 Å 'Styragel' columns in series and a Shodex SE 61 refractive index detector. Molecular weights were estimated according to the polystyrene calibration curve using polystyrene standards with a low polydispersity (PL Lab.).

N.m.r. measurements

The ^{13}C n.m.r. spectra of the copolymers were recorded at 75 MHz on a Varian VXR-300 spectrometer in 5 mm o.d. sample tubes in dimethyl sulfoxide d_6 as a solvent and hexamethyl disilane as external standard. Measurement temperatures were 323 and 373 K (373 K for samples with a higher amount of glycolide in the

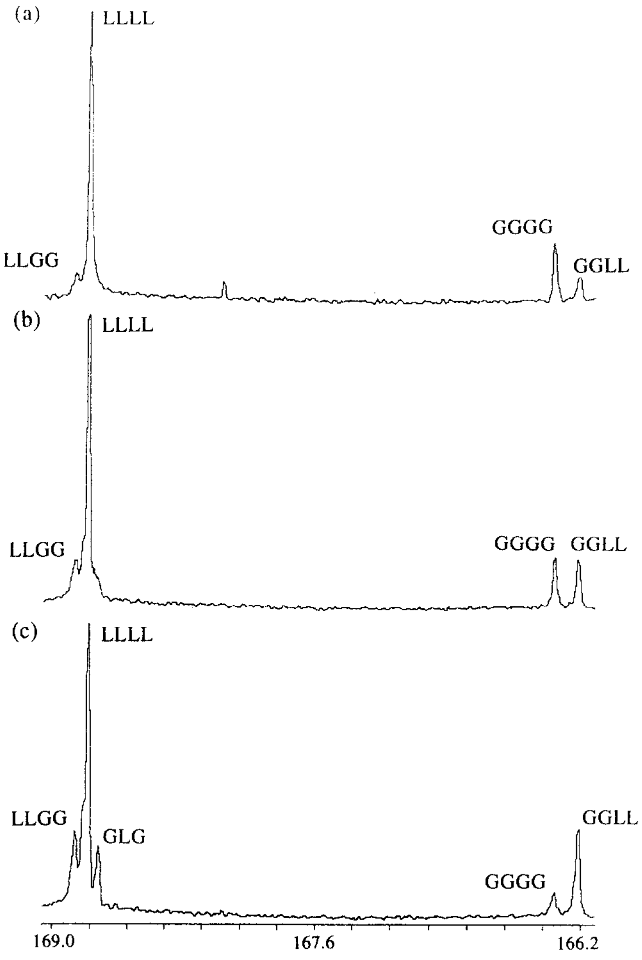

Figure 1 ^{13}C n.m.r. (75 MHz) spectra of poly[(lactide)-*co*-(glycolide)] obtained in the presence of (a) Al(acac)$_3$, $F_L = 0.79$; (b) Zn(acac)$_2$, $F_L = 0.80$; (c) Sn(Oct)$_2$, $F_L = 0.80$ as initiators (carbonyl region)

copolymers). The acquisition time was 1.8 s, pulse width 9 μs and delay between pulses 3 s; a digital resolution of 64 K data points and a spectral width of 16 500 Hz were used. A total of 10 000 transients were accumulated. The ^{1}H n.m.r. spectra of the copolymers were recorded at 300 MHz. The acquisition time was 3.74 s; a digital resolution of 32 K data points and spectral width of 4000 Hz were used, and 32 transients were accumulated.

RESULTS AND DISCUSSION

A series of glycolide/lactide copolymers were synthesized in the presence of appropriate initiators containing tin, zinc and aluminium, which allow a variety of chain microstructures to be obtained. The analysis of the copolymer microstructure was performed by means of n.m.r. spectroscopy.

The ^{13}C n.m.r. spectra of the copolymers obtained in the presence of Al(acac)$_3$ exhibit only four well resolved signals arising from the following sequences: LLGG ($\delta = 168.89$ ppm), LLLL ($\delta = 168.82$ ppm), GGGG ($\delta = 166.35$ ppm) and GGLL ($\delta = 166.21$ ppm), where L stands for the lactyl unit –CH(CH$_3$)–CO–O–, and G designates the glycolyl unit –CH$_2$–CO–O– (*Figure 1a*).

For the copolymers containing comparable amounts of comonomer units prepared with the initiators which are expected to favour transesterfication reactions, an additional signal ($\delta = 168.76$ ppm) was found to appear. This signal is due to the GLG sequence which can be formed only as a result of the transesterification (*Figures 1b* and *1c*).

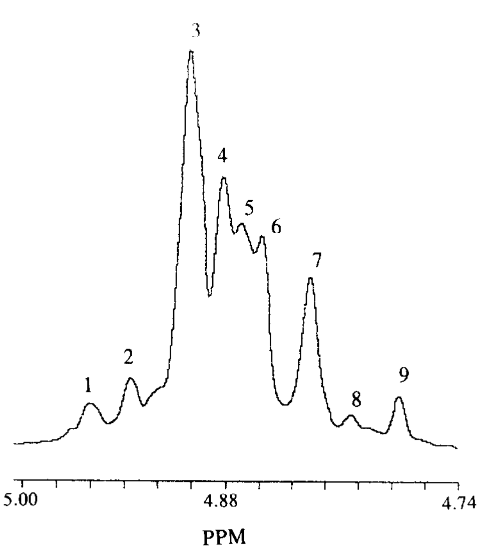

Figure 2 ^{1}H n.m.r. (300 MHz) spectrum of poly[(lactide)-*co*-(glycolide)] obtained in the presence of Sn(Oct)$_2$ as initiator, $F_L = 0.50$; region of glycolide methylene protons, for assignment of line numbers see *Table 1*

The analysis of ^{1}H n.m.r. spectra was performed using the methylene group signal of glycolide; owing to spin–spin coupling the signals in the lactide methine region are inconvenient in the analysis.

In the region of methylene protons of glycolide, well resolved signals are observed (*Figure 2*). By comparison of the spectra recorded for various copolymers the assignment of individual resonance lines to appropriate sequences was proposed (*Figure 3*, *Table 1*). A similar approach was used in the case of L,L-lactide/ϵ-caprolactone copolymers[7–9].

All pentads in line 7 (*Table 1*) consist of the LGL sequence. This sequence cannot be formed by opening of lactide and glycolide rings during the growth reaction of copolymer chain. The effect of the kind of applied initiator on the structure of the obtained copolymer can be evaluated from the changes in intensity of line 7 ascribed to the LGL sequence, which reflects the extent of the second mode of transesterification during copolymerization.

Denoting the ratio [G]/[L] as k, the concentration of lactyl units [L] and glycolyl units [G] in the copolymer chain may be expressed by the equations:

$$[\mathrm{L}] = 1/(k+1) \qquad (1)$$

$$[\mathrm{G}] = k/(k+1) \qquad (2)$$

In the case of totally random chains the intensities of the lines ascribed to individual sequences depend exclusively on the amounts of comonomers in the copolymer chain. For the LGL sequence, which can result only from the second mode of transesterification, the intensity of the line corresponding to this sequence present in the totally random chain is described by the following relation:

$$[\mathrm{LGL}]_\mathrm{R} = k/(k+1)^3 \qquad (3)$$

For the quantitative determination of the second mode

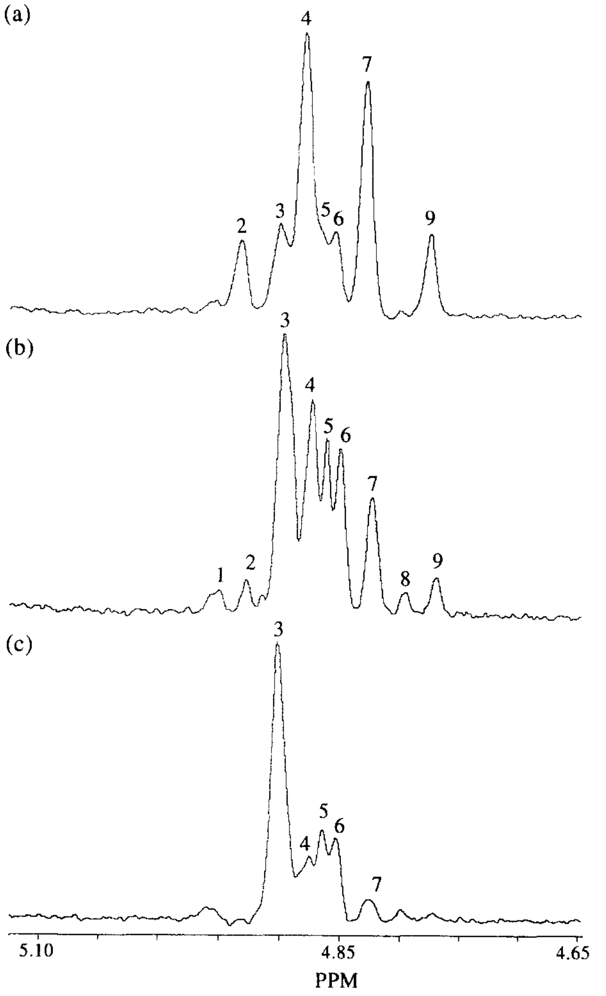

Figure 3 ^{1}H n.m.r. (300 MHz) spectra of poly[(lactide)-*co*-(glycolide)] obtained in the presence of (a) $Sn(Oct)_2$, $F_L = 0.80$; (b) $Zn(acac)_2$, $F_L = 0.80$; (c) $Al(acac)_3$, $F_L = 0.79$ as initiators; region of glycolide methylene protons. For assignment of line numbers see *Table 1*

Table 1 Assignment of resonance lines to appropriate sequences in ^{1}H n.m.r. spectrum of poly[(lactide)-*co*-(glycolide)] in the region of the glycolide methylene proton

Line number	Sequences	δ (ppm)
1	GLGGG or GGGLG	4.96
2	LGGLG or GLGGL	4.94
3	GGGGG	4.90
4	LLGGL + LGGLL	4.88
5	GGGGL + LGGGG	4.87
6	LLGGG + GGGLL	4.86
7	LLGLL + GLGLL + LLGLG + GLGLG	4.83
8	GGGLG or GLGGG	4.80
9	LGGGL + GLGGL or LGGLG	4.78

of transesterification the following expression may be applied:

$$T_{II} = [LGL]/[LGL]_R \qquad (4)$$

where [LGL] indicates the experimental concentration of LGL sequences in the copolymer chain.

The average lengths of lactidyl and glycolidyl blocks may be calculated from equations analogous to those presented in our previous work[9].

Table 2 Average lengths of blocks and yield of transesterification in poly[(lactide)-*co*-(glycolide)] obtained in the presence of initiators containing Al, Zn and Sn

Initiator	Temperature (°C)	f_L	F_L	l^e_{GG}	l^e_{LL}	T_{II}
$Sn(Oct)_2$	150	0.50	0.50	2.04	2.03	0.41
$Sn(Oct)_2$	100	0.50	0.50	2.78	2.75	0.25
$Sn(Oct)_2$	150	0.80	0.80	1.38	5.52	0.38
$SnCl_2 \cdot H_2O$	150	0.50	0.45	2.50	2.05	0.47
$Zn(acac)_2$	150	0.50	0.45	4.15	3.40	0.18
$Zn(acac)_2$	150	0.80	0.80	2.05	8.70	0.16
$Zn(acac)_2$	100	0.50	0.23	7.69	2.30	0.08
$Al(acac)_3$	150	0.50	0.36	5.15	2.90	0
$Al(acac)_3$	150	0.80	0.79	3.34	12.56	0.01
$AlEt_3$	150	0.50	0.28	5.59	2.17	0.11
$AlEt_3$	100	0.50	0.50	3.23	3.22	0.08

f_L, feed mole fractions of L,L-lactide; F_L, mole fraction of lactidyl units in copolymers; l^e_{GG}, experimental average length of glycolidyl blocks; l^e_{LL}, experimental average length of lactidyl blocks; T_{II}, yield of the second mode of transesterification

The results of our study on copolymerization of glycolide with lactide carried out in the presence of aluminium-, zinc- and tin-containing initiators are collected in *Table 2*.

The data shown in *Table 2* confirm our earlier observations concerning copolymerization of lactide with ε-caprolactone. The average length of the blocks increases and the extent of the second mode of transesterification decreases when temperature is reduced. The copolymers with the longest blocks are obtained in the copolymerization performed in the presence of aluminium initiators ($Al(acac)_3$), whereas random copolymers are produced when tin initiators are utilized ($Sn(Oct)_2$, $SnCl_2$).

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