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Synthesis and Characterization of Poly(1,5-Dioxepan-2-one-*co*-L-Lactic Acid) and Poly(1,5-Dioxepan-2-one-*co*-D,L-Lactic Acid)

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SYNTHESIS AND CHARACTERIZATION OF POLY(1,5-DIOXEPAN-2-ONE-*co*-L-LACTIC ACID) AND POLY(1,5-DIOXEPAN-2-ONE-*co*-D,L-LACTIC ACID)

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ABSTRACT

Copolymers of L- or D,L-dilactide with 1,5-dioxepan-2-one (DXO) have been investigated. Statistical copolymers were obtained using stannous-2-ethylhexanoate (Sn(oct)$_2$) as catalyst in bulk. Reactivity ratios were $r_{(\mathrm{DXO})} = 0.1$ and $r_{(\mathrm{dilactide})} = 10$. ^{13}C-NMR spectroscopy indicated a more extensive block structure than expected in a totally random copolymer. Transesterification takes place and shortens the average sequence length with increased temperature. The ability of the L-lactic acid (L-LA)/DXO copolymer to crystallize seems to be retained despite substantial amounts of 1,5-dioxepan-2-one in the composition. Properties, like glass transition temperature, crystallinity, and mechanical properties, are strongly dependent on the molar composition of the copolymer. The mechanical properties of a copolymer (molar ratio: DXO/L-LA, 25/75), measured in tension, indicated a flexible, soft material. This copolymerization seems to be initiated by impurities like water present in monomers and/or Sn(oct)$_2$, giving the tin compound the role of a catalyst.

INTRODUCTION

Ring-opening polymerization of lactones and related cyclic monomers has been the major research area for the production of new hydrolyzable materials designed for medical use. There are several reasons for this. Many of these polymers give low tissue response, some have been shown to be excreted by the natural metabolism, and they possess favorable mechanical properties in many applications [1, 2].

Earlier investigations in our laboratory have dealt with degradable polyesters [3], polyether esters [4, 5], polyanhydrides [6], and polycarbonates [7]. Interesting properties of the poly(1,5-dioxepan-2-one) (poly(DXO)) described earlier [4, 5] led us to continue the research and explore the potentialities of this polymer as a component in a copolymer.

Poly(lactic acid) is perhaps the most frequently used material in biomedical applications due to its many favorable characteristics, e.g., high strength and nontoxic degradation products [8, 9]. Several commercial products are currently available in which poly(lactic acid) is a major component, either as a homopolymer or as a component in a copolymer. Surgical sutures, drug-delivery matrices, and bone grafts are examples of applications that have been developed [10]. Poly(lactic acid) can be made either by condensation polymerization or more commonly by ring-opening polymerization of the cyclic condensation product of two lactic acid molecules, known as dilactide. There are four different types of dilactide, and they give rise to polymers with different properties. The L- or D-dilactide gives a semicrystalline polymer with a glass-transition temperature (T_g) of approximately +57°C [11]. The D,L-dilactide, i.e., the racemic mixture of the two enantiomers, as well as the meso-dilactide, give rise to amorphous polymers with a T_g similar to that of their semicrystalline counterparts [12].

Poly(DXO) is also an amorphous polymer, with a T_g around −36°C [4]. The copolymerization of these corresponding monomers is easily accomplished with stannous-2-ethylhexanoate as a ring-opening catalyst, as shown in this work.

Copolymers of lactides, glycolide, and ε-caprolactone with DXO have been reported in the literature [13–16], although no detailed data were given for the lactic acid/DXO copolymer. A preliminary study of the synthesis of L- or D,L-lactic acid/DXO (LA/DXO) copolymers was reported earlier [5]. In the present work, new copolymers with higher molecular weights were obtained using a more elaborate purification of the monomers. Copolymers of different compositions were characterized in detail, including the analysis of average sequence length by quantitative ^{13}C-NMR measurement, to obtain a more thorough understanding of this copolymer system. The mechanism of ring-opening polymerization with stannous-2-ethylhexanoate is also discussed.

EXPERIMENTAL

Materials

3-Chloropropionyl chloride, aluminum trichloride (Aldrich), and ethylene gas were all obtained commercially and used without further purification. Methylene chloride was dried and distilled over anhydrous calcium chloride. Toluene was dried by reflux over CaH_2 and distilled under an inert gas atmosphere before use. Diethyl ether was dried over metallic sodium before use. 3-Chloroperoxybenzoic acid (82%) and stannous-2-ethylhexanoate were used as received. 3-Chloroperoxybenzoic acid (70%) was dissolved in dry methylene chloride. The organic layer was separated and dried with $MgSO_4$ (anhydrous) before use. 1,5-Dichloropentane-3-one was synthesized by the Friedel–Crafts acylation-type reaction of ethylene with 3-chloropropionyl chloride. Tetrahydro-4*H*-pyran-4-one was synthesized by ring closure of 1,5-dichloropentane-3-one (yield about 50%) [17]. IR and ^{1}H-NMR spectra were in accordance with earlier published work [17].

D,L- and L-Dilactide (Boehringer GmbH, Ingelheim, FRG) were in some cases recrystallized twice in dry toluene before use (as indicated in Tables 1 and 2).

1,5-Dioxepan-2-one. 20 g of tetrahydro-4*H*-pyran-4-one (THP), (0.20 mol), was added under constant stirring to a slurry of 60 g (0.28 mol) 3-chloroperbenzoic acid (82 or 70%) and 28 g (0.35 mol) sodium bicarbonate in 300 mL dry methylene chloride. The slurry was allowed to attain room temperature and stirred for 16 hours. After filtration, the methylene chloride phase was washed with sodium bisulfite and sodium bicarbonate to eliminate any remaining peracid. The methylene chloride phase was evaporated to give a slightly yellow oil. This was distilled under reduced pressure (0.1 mbar), and gave a 70% yield of DXO (60–65°C). Before polymerization, DXO was recrystallized twice in anhydrous diethyl ether to remove traces of 3-chlorobenzoic acid (purity verified by GC).

Polymerizations

A 20-mL serum bottle with a magnetic stirrer, flamed under vacuum, was used as the reaction vessel. L- or D,L-Dilactide and DXO were mixed in the bottle and the catalyst was added. The reaction vessel was closed with the rubber septum, flushed with inert gas (N_2 or Ar) through a syringe, and immersed in a thermostated oil bath (115–120°C). After the desired reaction time, the serum bottle was cooled and the contents were dissolved in chloroform and precipitated in cold methanol. The copolymer was isolated by filtration and dried at room temperature in vacuo.

The kinetics were studied using three different molar feeds: DXO/L-LA = 80/20, 50/50, and 20/80. Samples were withdrawn by syringe or spatula under a flush of inert gas (N_2 or Ar) at various times during 21 hours and analyzed by ^{1}H NMR to check the conversion and by SEC to check molecular weights. The polymerization temperature was 115°C and the monomer/catalyst ratio [M]/[C] was 600–800.

Model Study

Low molecular weight homopolymers of DXO and L-dilactide were obtained by the same procedure but with a [M]/[C] ratio of 5 and a reaction time of 15 minutes. DXO and L-dilactide were both recrystallized twice in diethyl ether and toluene, respectively, before use. The polymers were dissolved in chloroform, treated with dilute HCl solution, precipitated in cold methanol, filtered, and dried in vacuo at room temperature. The precipitation of the low molecular weight polymer (M_n = 2000–8000 g/mol) effectively removed the residual stannous-2-ethylhexanoate as verified by ^{1}H and ^{13}C NMR.

Measurements

The ^{1}H-NMR and ^{13}C-NMR spectra were obtained with a Bruker AC-250 or AC-400 FT-NMR spectrometer, using the solvent ($CDCl_3$) as the internal standard. Samples were dissolved in deuterochloroform in sample tubes 5 mm in diameter.

2D-NMR experiments were performed using standard Bruker software on an Aspect 3000 computer. For the H-C COSY long-range experiment, the F2 window (^{13}C) was set to 1.8 kHz, covering only the carbonyl region, while F1 was optimized to 1.9 kHz, corresponding to the full ^{1}H spectral region. The delay times were optimized to an average coupling constant of 7 Hz (^{2J}CH and ^{3J}CH). The relaxation delay was set to 1 second. A Gaussian multiplication was applied in the F2 dimension for better resolution. Quantitative ^{13}C NMR was carried out using the INVGATE sequence, covering the carbonyl region only. A preliminary determination of the carbonyl relaxation times ($T1$) was made by observing the relaxation behavior after a 180° pulse ($T1$ approximately 10 seconds). In the INVGATE sequence, the pulse width was set to 90°, the acquisition time was between 4 and 10 seconds, and the delay time ($D1$) + acquisition time was at least 30 seconds. To confirm that this delay was sufficient, an experiment with a $D1$ + acquisition time of 100 seconds was made and it resulted in identical intensities.

SEC measurements were made at 30°C with five μ-Styragel columns (500, 10^3, 10^4, 10^5, 100 Å). A Waters model 510 apparatus was used with a differential refractometer (Waters 410) as detector. THF was used as solvent, with a flow rate of 1 mL/min, and calibration was made with polystyrene standards. To record the data and make the calculations, a Copam PC-501 Turbo unit was used. Intrinsic viscosity measurements were made in chloroform solution at 25°C with an Ubbelohde viscometer.

Intensity light-scattering measurements were made using a photon-counting device supplied by Hamamatsu. The light source was a 3-mW He-Ne laser (633 nm). The reduced scattering intensity, Kc/R_θ, was measured on polymer-THF solutions of various concentrations at an angle of 90° and a temperature of 25°C. R_θ is the Rayleigh ratio obtained by calibration measurements with benzene. $K = 4\pi n_0^2(dn/dC)^2/N_A\lambda^4$ (optical constant for vertically polarized light), where n_0 is the solvent refractive index and dn/dC is the refractive index increment. The slope dn/dC varied with copolymer composition and thus had to be determined for each of the samples.

In the DSC analysis, a Perkin-Elmer DSC-7 with a Perkin-Elmer 7700 computer was used. ΔH values were recorded on the first scan (218-473°K) from samples of copolymer after precipitation and careful drying in vacuo at ambient temperature. The heating rate was 10°K/min.

Tensile testing was performed on an Instron model 1122. The copolymer used had a molar composition DXO/L-LA of 25/75, polymerization temperature of 115°C, $[M]/[C] = 800$, M_w (by SEC) after melt pressing = 150,700 g/mol, and $M_w/M_n = 2.10$. Parallel strips (length 100 mm, width 6 mm) were cut from a film 0.5 mm thick. The standard procedure according to ASTM D 882 was used for all of the eight samples taken from the same film. This film was made by melt-pressing the pure copolymer at 135°C for 2 to 3 minutes with a pressure of 260 N/cm^2, cooling at 40°C/min under pressure. Relative humidity during testing: 40%.

RESULTS AND DISCUSSION

Tables 1 and 2 give some details of the polymerizations and some of the results.

TABLE 1. Conditions and Results of the Copolymerizations of DXO with D,L-Dilactide in Bulk: Stannous-2-ethylhexanoate as Catalyst

Expt.	Mole ratio in feed, DXO:D,L-LA	[M]/[C]	M_w[a]	$[\eta]$[b]	Polym. time, h	Polym. temp., °C	M_w/M_n
1	90:10	600	114,000		16	110	1.7
2	80:20[c]	740	81,000		22	120	1.8
3	80:20	600	76,000		16	110	1.9
4	60:40	600	88,000		16	110	1.9
5	50:50[c]	860	85,000		22	120	1.8
6	50:50	650	89,000		16	110	2.3
7	50:50[d]	500	19,000	0.25	15	130	1.8
8	40:60	600	86,000		16	110	2.1
9	23:77[c]	1020	98,000		22	120	1.7
10	20:80	450	34,000		16	110	2.0
11	10:90	450	36,000		16	110	2.3

[a] Weight-average molecular weights obtained by SEC, polystyrene standard calibration.

[b] Intrinsic viscosity [g/dL] measured in chloroform, 25°C.

[c] D,L-Dilactide recrystallized twice in dry toluene.

[d] DXO not recrystallized before use.

TABLE 2. Conditions and Results of the Copolymerizations of DXO with L-Dilactide in Bulk: Stannous-2-ethylhexanoate as Catalyst

Expt.	Mole ratio in feed, DXO:L-LA	[M]/[C]	Polym time, h	Polym temp., °C	M_w[a]	M_w[b]	$[\eta]$[c]	M_w/M_n
1	90:10	800	9.25	113	65,000	78,000		1.8
2	80:20[d]	750	24	120	95,000			1.8
3	80:20	750	9.25	113	61,000	67,000		1.9
4	60:40	900	9.25	113	58,000	62,000		2.0
5	50:50[d]	750	24	120	109,000			1.8
6	50:50	850	9.25	113	55,000	50,000	0.63	1.7
7	40:60	450	9.25	113	64,000	90,000		1.8
8	20:80[d]	750	24	120	139,000			1.8
9	20:80	750	9.25	113	94,000	107,000		1.8

[a] Weight-average molecular weights obtained by SEC, PS standard calibration.

[b] Weight-average molecular weights obtained by light scattering of polymer solutions at room temperature.

[c] Intrinsic viscosity [g/dL] measured in chloroform, 25°C.

[d] L-Dilactide recrystallized twice in dry toluene before use.

The conversion of the lactide monomer was greater than 98% in all polymerizations. The DXO monomer, being kinetically slower, did not reach full conversion in the experiments with a polymerization time of 9.25 hours (Entries 1, 3, 4, 6, 7, and 9 in Table 2). This resulted in a copolymer composition different from that of the monomer feed. In all the other experiments, the DXO conversion was greater than 90%. Figure 1 shows that the polymerization is clearly faster in the early stages for the lactide-rich copolymerizations, indicating a higher reactivity of the lactides than the DXO.

Figure 2 shows that the molecular weight increases at a faster rate with increasing amount of L-dilactide in the monomer feed. The molecular weight reaches a maximum value at about the same time, 20 hours, for all three compositions. The reason for the difference in the final molecular weights could be an effect of a higher impurity level in the DXO monomer in this particular experiment. Dilactide is consumed at a faster rate than DXO in the copolymerization. This is true for all monomer compositions, but the most pronounced difference is observed in the DXO/L-LA = 20/80 copolymerization (Fig. 3). This is probably an effect of the crystallization of this lactide-rich copolymer. Since the polymerizations were carried out in bulk, diffusion could be a critical factor that determines the monomer diffusibility. After the onset of crystallization, the diffusion is restricted, which could explain the slow conversion of DXO in the lactide-rich copolymer. The argument proposed by Nijenhuis et al., that crystallization would concentrate catalyst and

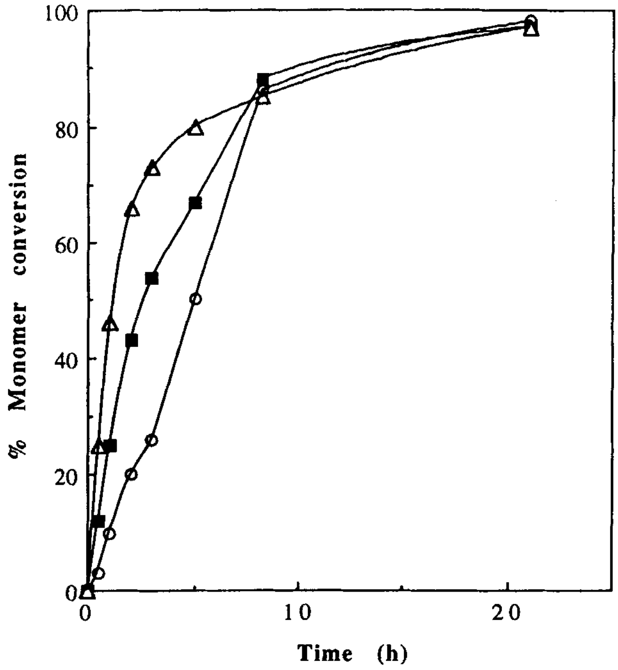


FIG. 1. Conversion as a function of time for different DXO/L-LA copolymers. Polymerization temperature: 120°C. Molar ratios: (○) DXO/L-LA, 80/20; (■) DXO/L-LA, 50/50; (△) DXO/L-LA, 20/80.

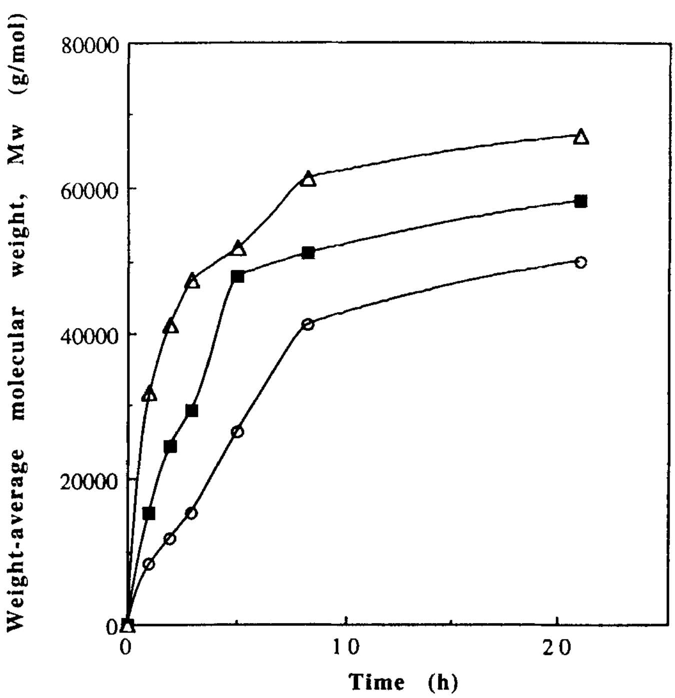


FIG. 2. Molecular weight ($\overline{M}_w$) dependence on polymerization time and copolymer composition. Polymerization temperature: 120°C. (○) DXO/L-LA, 80/20; (■) DXO/L-LA, 50/50; (△) DXO/L-LA, 20/80.

monomer to the remaining amorphous regions and thus increase the kinetics [18], does not seem to apply in this case.

Determination of the Reactivity Ratios

The reactivity ratios were determined using the method of Kelen and Tüdös [19], which is based on data obtained at high conversion. This is especially valuable when there is a large difference in reactivity between the two monomers. The reproducibility of the determination, however, indicates that the values of the reactivity ratios obtained are only approximate, and no distinction could be made between the reactivities of the two different lactides (L- and D,L-dilactide). The determination was based on ^{1}H-NMR analyses of the copolymers formed at conversion levels below 30%. Figure 4 shows a resulting plot of η against ξ for the DXO/L-LA system, where r_1 and r_2 are determined from the intercepts. $r_{(\mathrm{DXO})} = 0.1$ and $r_{(\mathrm{dilactide})} = 10$. $r_{(\mathrm{DXO})}$ is taken from the intercept at $\xi = 1$, and $-r_{(\mathrm{dilactide})}/\alpha$ from the intercept at $\xi = 0$, where α is a constant dependent on the conversion [19].

NMR Investigation of DXO/LA Copolymers

Figure 5 presents the chemical shifts of protons and carbons in the copolymer.

The difference in reactivities of the monomers plays an important role in determining the sequence distribution of the copolymers. In the beginning of a

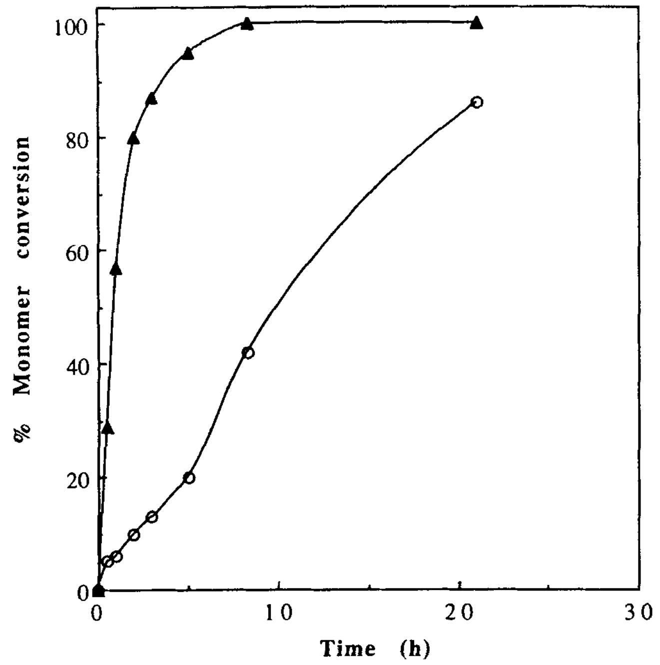


FIG. 3. Conversion of DXO and L-dilactide as a function of time in DXO/L-LA 20/80 copolymerization. Polymerization temperature: 120°C.

copolymerization, assuming no side reactions, the polymer chain formed is dominated by the more reactive lactide, forming longer sequences than expected in a totally random copolymer. As the polymerization proceeds, the lactide is depleted and DXO becomes the more abundant species and is consequently incorporated. This results in a more or less blocky or tapered copolymer. However, the tin catalyst used has been shown to cause transesterification and even racemization, especially at elevated temperatures [20, 21]. This would cause a reshuffling of the initially formed sequences to a more random structure. The side reactions are mainly due to intermolecular transesterification. Intramolecular side reactions should yield cyclic oligomers, and no such species were detected in the SEC chromatogram of crude copolymer is this study. The transesterifications take place along with the propagation and continue after full conversion as seen from the constant increase of the polydispersity with time (MWD = 1.1–2.0). A ^{13}C-NMR investigation was made on some of the DXO/L-LA copolymers. According to Kricheldorf et al., carbonyl carbons are generally the most sensitive atoms to sequence effects [22]. In order to make a quantitative determination, the carbonyl carbon relaxation times were estimated (Experimental Section).

In a binary copolymer system, eight different triads can be distinguished. The different triads were assigned by a long-range H—C COSY experiment. Observation of the coupling of carbonyl carbons with protons in the connecting units made it possible to assign the triads according to Table 3. In the triad consisting of a

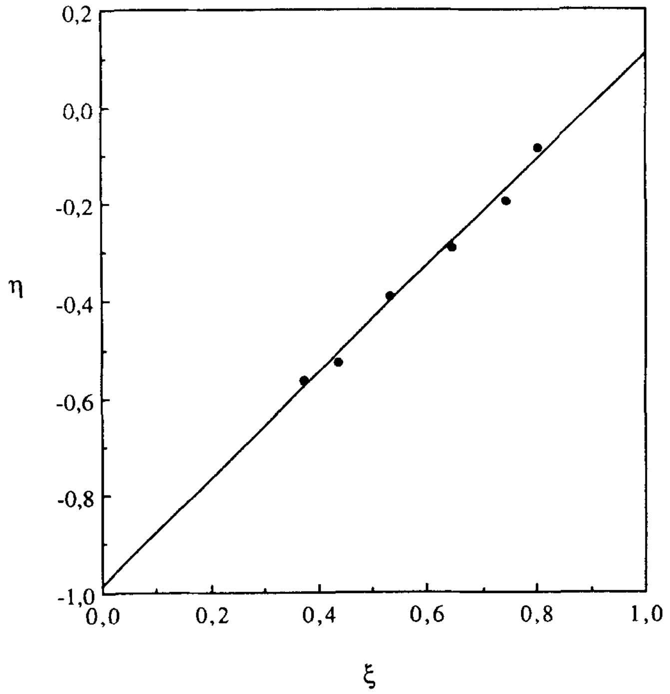


FIG. 4. Reactivity ratio evaluation of the DXO/L-LA copolymer system. $r_{(DXO)}$ = intercept at $\xi = 1$, $-r_{(dilactide)}/\alpha$ = intercept at $\xi = 0$.

half-lactide unit with a DXO unit on both sides (DLD), for example, the lactide carbonyl carbon couples to both the methyl protons in the lactide and the first methylene protons of the DXO unit, both being three bonds away from the carbonyl (see Fig. 6). The homopolymer carbonyl peaks correspond well with the peaks at the highest and lowest field in the ^{13}C-NMR spectrum in Fig. 5. The peaks in the copolymer spectrum not present in the homopolymers spectra represent the different triads listed in Table 3.

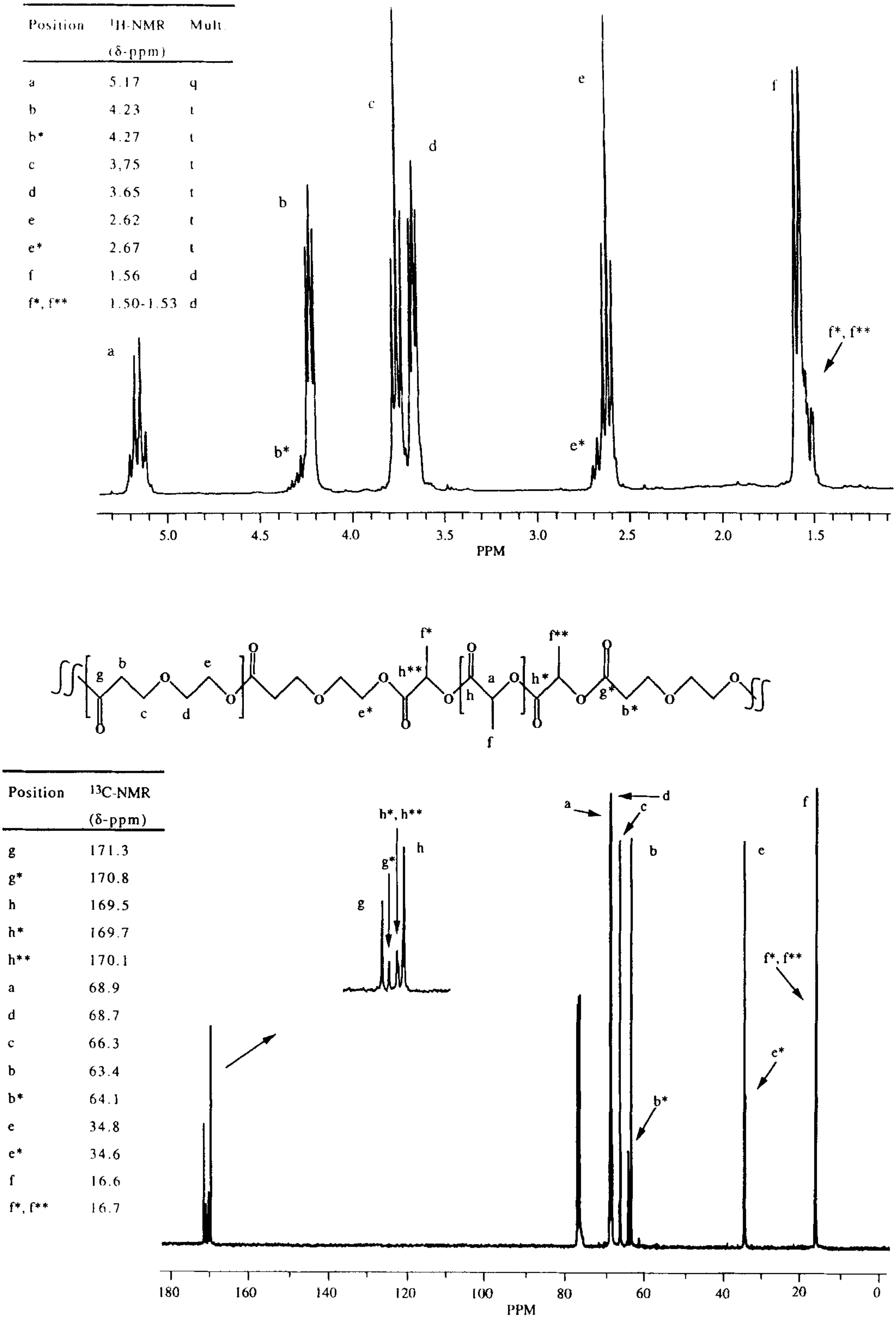
The number-average sequence lengths of monomer M_i, ($\overline{L_i}$) are determined [22] from the equation

$$\overline{L_i} = \frac{I_{iii} + I_{jii}}{I_{iij} + I_{jij}} + 1 \qquad (1)$$

where I_{iii} is the signal intensity of the M_{iii}-triad etc. The number-average sequence length for DXO ($\overline{L_D}$) and the L-lactic acid unit ($\overline{L_L}$) are thus

$$\overline{L_D} = \frac{I_{DDD} + I_{LDD}}{I_{DDL} + I_{LDL}} + 1 \qquad (2)$$

$$\overline{L_L} = \frac{I_{LLL} + I_{DLL}}{I_{LLD} + I_{DLD}} + 1 \qquad (3)$$



Position	^1H-NMR (δ-ppm)	Mult.
a	5.17	q
b	4.23	t
b*	4.27	t
c	3,75	t
d	3.65	t
e	2.62	t
e*	2.67	t
f	1.56	d
f*, f**	1.50-1.53	d

Position	^{13}C-NMR (δ-ppm)
g	171.3
g*	170.8
h	169.5
h*	169.7
h**	170.1
a	68.9
d	68.7
c	66.3
b	63.4
b*	64.1
e	34.8
e*	34.6
f	16.6
f*, f**	16.7

FIG. 5. Assignments of chemical shifts in ^1H- and ^{13}C-NMR spectra of the DXO/LA copolymer. Polymerization temperature: 115°C.

TABLE 3. Sequence Assignment of DXO/L-LA Copolymer, ^{13}C NMR, Carbonyl Region

Triad[a]	^{13}C-Carbonyl shift (ppm)
$\mathrm{L\underline{L}L}$	169.57
$\mathrm{D\underline{L}L}$	169.69
$\mathrm{L\underline{L}D}$	170.12
$\mathrm{D\underline{L}D}$	170.57
$\mathrm{L\underline{D}L}$	170.69
$\mathrm{D\underline{D}L}$	170.76
$\mathrm{L\underline{D}D}$	171.26
$\mathrm{D\underline{D}D}$	171.31

[a] D = DXO, L = L-LA.

It should be observed that the sequence length of the lactic acid unit $(\overline{L_{\mathrm{L}}})$ is defined as the half-lactide unit. A totally random chain in a 50/50 copolymer would have an average sequence length of 2.

Table 4 shows that the polymerization temperature is a very important factor determining the sequence length of the copolymers. When the polymerization temperature was increased from 120 to 140°C, transesterification reactions reshuffled the copolymer chains and thus decreased the sequence lengths of both monomers in the polymer chain. At the same time, the DLD sequence, which can only be formed by transesterification of lactide units, appeared in the carbonyl region of the ^{13}C-NMR spectrum. Generally, the DXO units had a longer sequence length than the lactic acid units. When the temperature was increased, the decrease in the LLL triad was especially significant. This indicates that the lactic acid units are more sensitive to transesterification than the DXO units. This was in agreement with the higher reactivity of the lactide monomer, as shown by the reactivity ratio determination. This is in contrast to the behavior when DXO was replaced by the similar ϵ-CL [23]. Vanhoorne et al. showed that it was the ϵ-CL that was mainly affected by transesterification reactions despite the fact that the lactide was the more reactive species. It was also concluded that the PLA/PCL hetero linkage was sensitive. Their study comprised a different initiator (aluminum isopropoxide) and was conducted in toluene [23]. Despite this, many similarities can be found between these two copolymerization systems.

Thermal Analysis of the DXO/LA Copolymers

DSC measurements were made to evaluate the glass-transition temperature (T_g) of the copolymers. The Fox equation (Eq. 4) was derived to predict glass-transition temperatures of random copolymers [24].

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}} \tag{4}$$

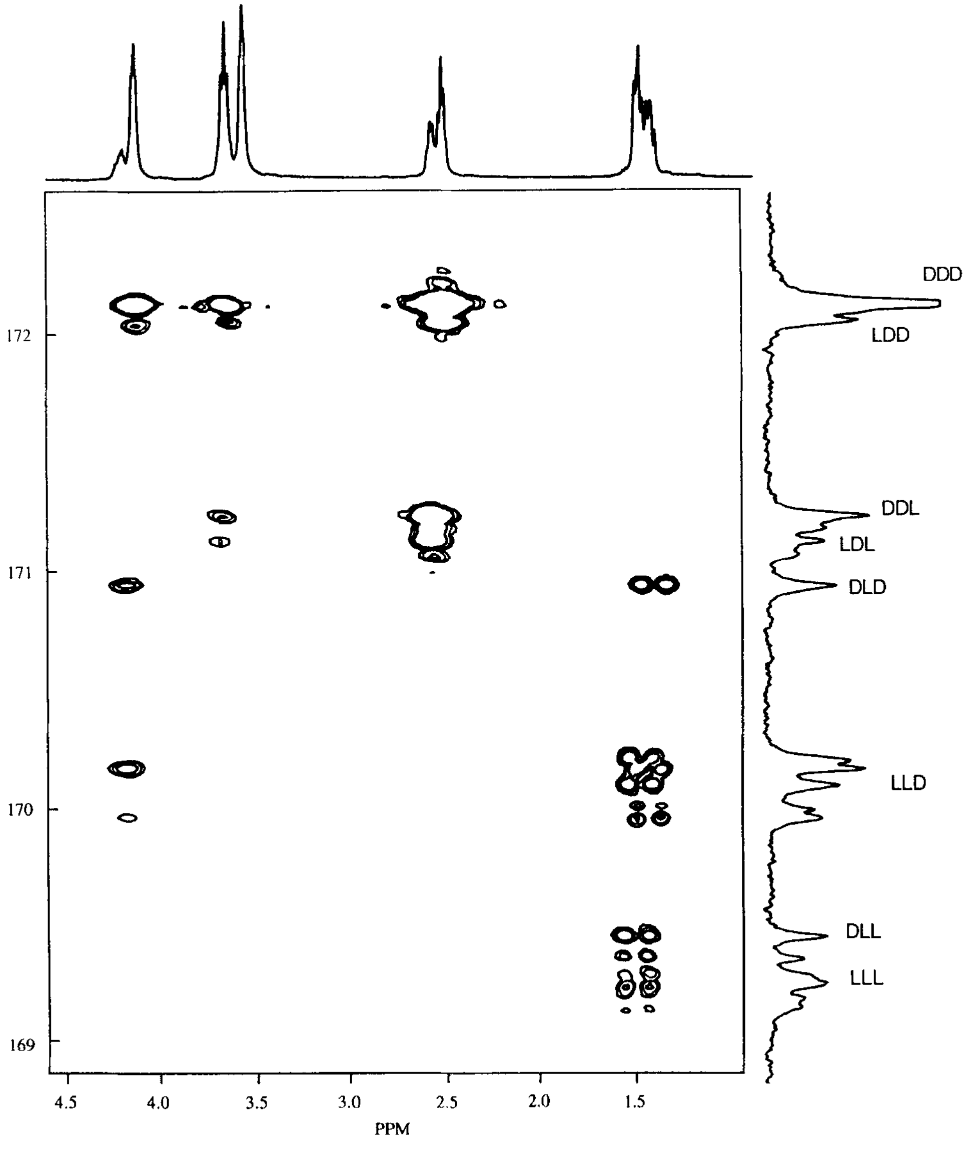


FIG. 6. H—C COSY-spectrum of 50/50 DXO/L-LA copolymer. Polymerization temperature: 140°C.

W_1 and W_2 are weight fractions of the respective monomers in the copolymer, and T_{g1} and T_{g2} are the glass-transition temperatures of the respective homopolymers.

As can be seen in Figs. 7a and 7b, there are deviations from the Fox equation, values being in general lower than predicted. Positive or negative deviations from the Fox equation are frequently encountered, since the Fox equation does not take into account factors like chemical nature, sequence effects, and polymer chain

TABLE 4. Sequence Lengths of DXO/L-LA Copolymers

Sample (DXO/L-LA)	$\overline{L_D}$[a]	$\overline{L_L}$[b]	% DLD	Polym. time, h	Polym. temp., °C
35/65	3.6	3.5	0	9.25	115
50/50	4.1	2.6	0	24	120
50/50	2.8	1.6	7	20	140
25/75	2.6	4.3	1	20	120

[a,b] Average monomer sequence length of DXO and L-LA, respectively, in copolymer as determined by ^{13}C NMR.

mobility. More sophisticated relationships have been developed to meet these shortcomings [25-27] which are able to predict some of the deviations. Because we did not have a reliable value of the glass-transition temperature corresponding to the alternating DXO/LA copolymer, no calculation of this type was done.

The crystalline melting enthalpy, ΔH, was measured for the crystalline DXO/L-LA copolymers. As can be seen in Table 5, crystalline melting was observed up to a DXO mole ratio of 50% in the copolymer (first scan). The peak melting temperature steadily decreased with increasing DXO content. This melting point depression

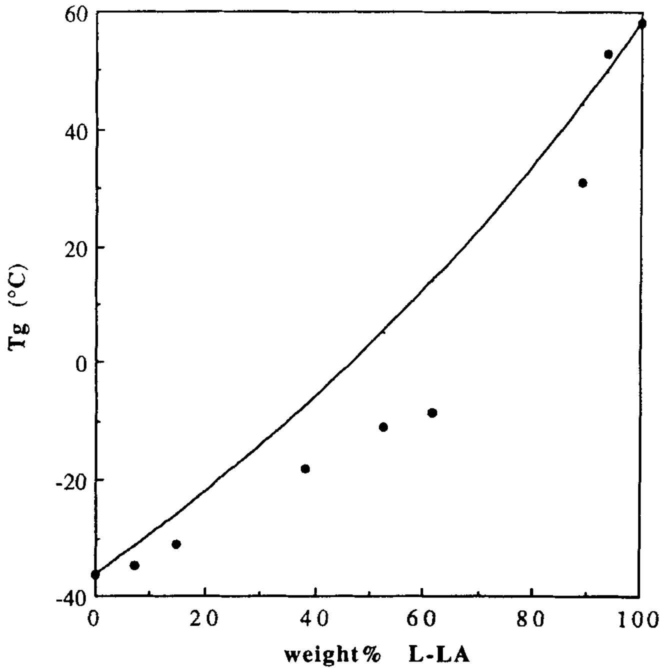


FIG. 7a. Glass-transition temperature versus L-LA content in the DXO/L-LA copolymer. The Fox equation is represented by the line.

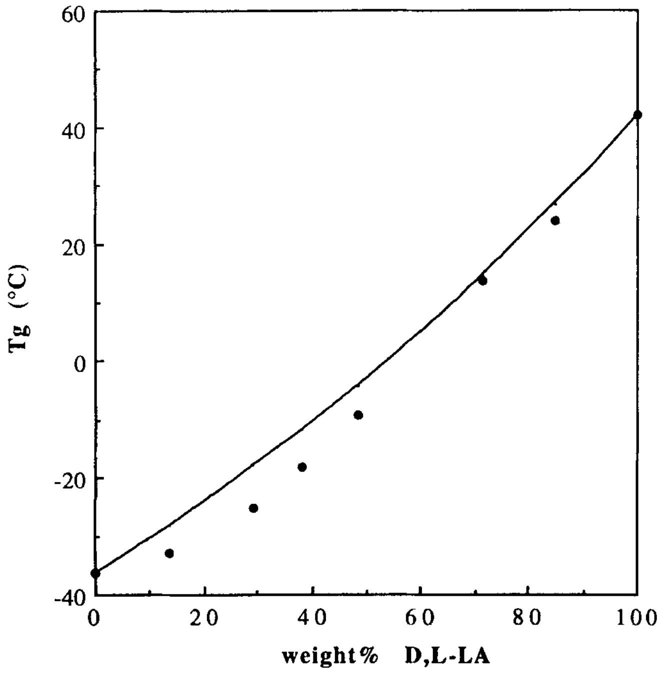


FIG. 7b. Glass-transition temperature versus D,L-LA content in the DXO/D,L-LA copolymer. The Fox equation is represented by the line.

can be described as a function of lamellar thickness using the Thomson-Gibbs relationship:

$$T_m = T_m^0(1 - 2\sigma_e/(\Delta H_f L)) \qquad (5)$$

where T_m^0 is the equilibrium melting temperature, i.e., the melting point of an infinitely thick crystal, σ_e is the fold surface free energy, ΔH_f is the heat of fusion, and L is the lamellar thickness. With values taken from literature (T_m^0 = 207 °C, σ_e = 53 erg·cm^{-2}, ΔH_f = 120 J·cm^{-3}) [28], a value of L between 28 and 103 Å is obtained (DXO/L-LA = 50/50 and 4/96 copolymers, respectively). With a length

TABLE 5. DSC Data of DXO/L-LA Copolymers. Polymerization Temperature: 113°C

Composition (DXO/L-LA)	Peak melting temperature, °C	DSC, ΔH, J/g
50/50	55	3.3
36/64	105	8.7
28/72	112	9.7
7/93	155	23.7
4/96	166	35.4

of the elementary monomer unit set to 2.78 Å [28], this corresponds to a sequence length of at least 10 to 37 units in the copolymer lamellas (without folding). These values can be compared to the overall average sequence length derived from the NMR experiment where the value of the 50/50 copolymer was 2.6. It thus seems that a sequence length of L-LA units between 3 and 10 is needed to obtain crystallization. Note that the ^{13}C-NMR measurement gives an average value of the total mass, and that the Thomson-Gibbs equation is valid for the crystalline domains only.

The crystallization can be quenched easily by heating above the melting temperature and cooling at 40°C/min. The ability of the copolymers to crystallize is related to the relatively long L-lactide sequences present, even in the 50/50 copolymer (polymerization temperature, $T_{\mathrm{polym}} < 120°\mathrm{C}$).

Mechanical Properties

Tensile measurements were made on a DXO/L-LA = 25/75 copolymer. With this composition, a very soft and flexible material was obtained. The molecular weight of the copolymer was slightly decreased due to thermal degradation during the melt-pressing of the film (M_w decrease 18%). The elastic modulus was found to be 30 ± 9% MPa, tensile strength = 21 ± 7% MPa, and elongation at break = 418 ± 15%. A DSC thermogram recorded on the melt-pressed film revealed that the fast cooling rate during film forming (40°C/min) gave an amorphous film with a T_g of +10°C. Drawing this film during tensile testing to extensions above 300% resulted in crystallization as seen from DSC thermograms. A melting peak at 130°C appeared (first scan, heating rate 10°C/min, $\Delta H = 9$ J/g). By using the Thompson-Gibbs equation as above, a lamella thickness of 55 Å was obtained, corresponding to a sequence length of 20 units ($\overline{L_L} = 4.3$ units obtained by NMR, average of total mass, see Table 4).

The small amount of material available limited the number of samples used to 8. The results show the high elastic elongation of this material. When the load was released prior to break (for example, at 300% elongation), the sample film regained its initial shape after a few seconds.

Polymerization Mechanism

Model experiments were done both with DXO and L-dilactide. In the following discussion, only L-dilactide model experiments are reported but analogous results were obtained from the DXO experiments. The mechanism by which stannous-2-ethylhexanoate ($\mathrm{Sn(oct)_2}$) operates has been debated in a number of papers [18, 29-31]. Suggested mechanisms include insertion by *endo-* and *exo*-cyclic routes as well as the idea that impurities in the monomer or initiator might be the true initiating species, giving $\mathrm{Sn(oct)_2}$ the role of a catalyst. A recent publication [18] proposes the latter version. A number of factors favor this mechanism, the most important one being the end groups of the polymer formed. The insertion of $\mathrm{Sn(oct)_2}$ at the ester bond would give rise to an energetically unfavorable anhydride end group [29]. The total lack of this end group was verified earlier [5]. The importance of impurities as initiating species has been clearly verified in the case of triphenyl tin acetate [32]. Impurities like 2-ethylhexanoic acid, stannous hydroxide,

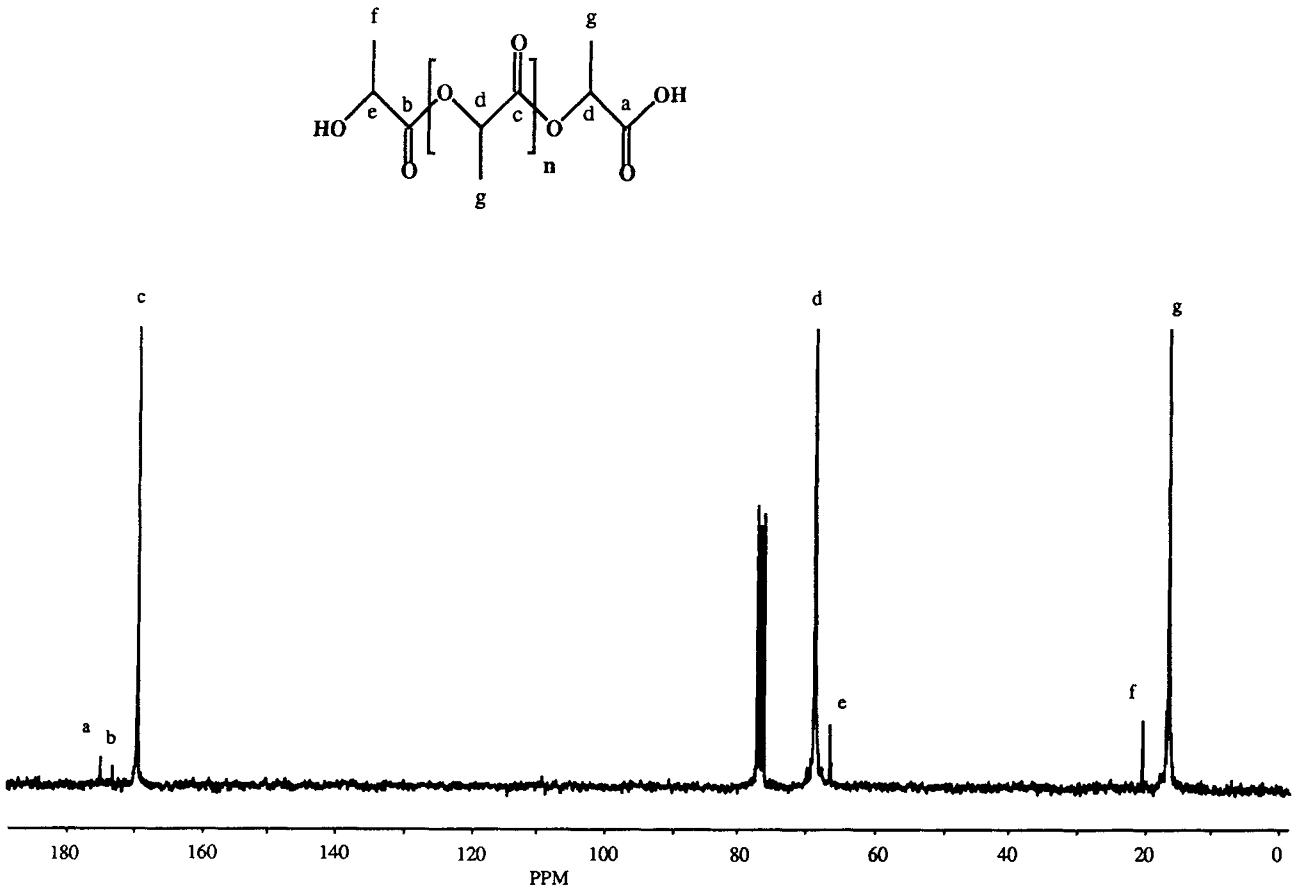


FIG. 8. ^{13}C-NMR of low molecular weight PLLA.

and water are always present in Sn(oct)$_2$ [18]. Lactic acid is a possible source of hydroxyl groups in lactide, and traces of water are also present in the monomer, even after careful purification [33]. The same authors also showed that hydroxyl-containing compounds like alcohols and water initiate lactone polymerization.

If the mechanism proposed by Nijenhuis et al. is correct, an anhydride end group (2-ethylhexanoic anhydride δ: 0.8–1.4 and 2.3 ppm) would result if the 2-ethylhexanoic acid acted as initiator and a carboxylic acid end group (δ: 10–13 ppm) if the initiating species consisted of water, lactic acid, or stannous hydroxide. In the ^{1}H-NMR spectra of the model experiments, neither of these groups is detectable. The only end group visible is hydroxyl, with the $-CH(CH_3)OH$ methine and methylene protons observed at 4.3 and 1.50 ppm, respectively. An anhydride end group should be readily visible in the ^{1}H-NMR spectrum or in an IR spectrum. Carboxylic acid end groups, however, are generally difficult to detect with ^{1}H NMR, but they can be observed in a ^{13}C-NMR spectrum where the carbonyl carbon should be displaced to a higher shift than that of the major ester carbonyl peak. In Fig. 8 two additional small peaks are observed beside the polymer peak in the carbonyl region. The peak at 175.1 ppm was assigned to the carboxyl end group, and the peak at 173.3 ppm was assigned to the ester carbonyl next to the $-CH(CH_3)OH$ end group. The assignments were based on studies of lactic acid and its dimer. It therefore seems that the initiation in our case takes place mainly by water, lactic acid, or possibly stannous hydroxide.

This mechanism explains the lack of correlation between the monomer/initiator ratio and the final molecular weight observed. It also stresses the importance of keeping impurities at a low level in order to obtain high molecular weight polymers.

CONCLUSIONS

The present work has shown that high molecular weight copolymers of 1,5-dioxepan-2-one and L- or D,L-dilactide can be made in bulk with stannous-2-ethylhexanoate as catalyst. The large difference in reactivity ratio between the DXO and the dilactides, assuming no side reactions, would lead to a microstructure with a more blocky nature than expected in a random copolymer. Transesterification reactions redistribute this structure and lead to shorter sequence lengths, especially when the polymerization temperature is raised above 120°C. The transesterification reactions are especially detrimental to the lactide sequence lengths, as shown by ^{13}C-NMR analysis. The mechanical properties of PLLA are substantially different from those of the DXO/L-LA = 25/75 copolymer, which shows a low stiffness and large elasticity compared with PLLA. The copolymerization is probably initiated preferentially by water impurities from monomers and catalyst. It is reasonable to believe that stannous-2-ethylhexanoate plays the role of catalyst, polarizing the carbon—oxygen bond of the carbonyl, thus making the carbon more susceptible to nucleophilic attack by the water molecule. It cannot, however, be ruled out that other impurities may also initiate the polymerization.

The DXO/LA copolymers are interesting materials with possible applications in the biomedical field. In-vitro/in-vivo studies have been completed, and the findings will be published elsewhere [34, 35].

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