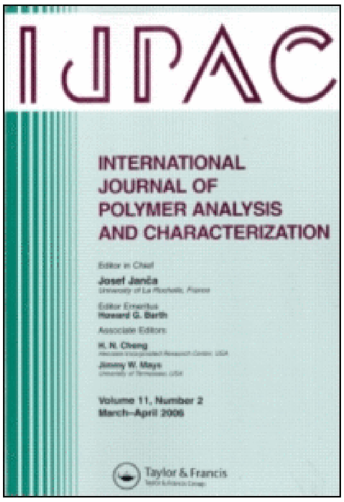

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Control of Molecular Weight for Auto-Catalyzed Poly(ortho ester) Obtained by Polycondensation Reaction

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Polycondensation of auto-catalyzed poly(ortho ester)s (POE_xLA_y) containing lactic acid units in the polymer backbone is described. The use of n-decanol during the polymerization as a chain stopper allows good control of polymer molecular weight. $POE_{70}LA_{30}$ based on 3,9-di-et-hylidene-2,4,8,10-tetraoxaspiro[5.5]undecane (DETOSU), 1,10-decanediol-lactate and 1,10-decanediol and synthesized by using 5, 10 and 15 mol % of n-decanol were characterized by ^{13}C NMR, ^1H NMR and FT-IR. The thermal and viscoelastic properties of such polymers as well as their molecular weight distribution are also reported.

Keywords: Poly(ortho esters); Bioerodible polymers; Polymer synthesis; Polymer characterization

Auto-catalyzed poly(ortho ester)s (POE_xLA_y) are bioerodible polymers containing either glycolic or lactic acid units in the polymer backbone that control the degradation rate of ortho ester linkages[1–3]. These polymers can be solids or semisolids depending on polymer structure.

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Injectable semisolid polymers are currently being extensively investigated for biomedical applications, in particular in the area of controlled release of biologically active agents[4–6]. Injectable poly(ortho esters) show good biocompatibility, in addition to their biodegradation known as erosion[7]. Poly(ortho ester)s are important bioerodible materials and have a wide range of applications such as periodontology, ophthalmology and veterinarian applications. Because drug release from low molecular weight poly(ortho ester)s depends on polymer molecular weight and molecular distribution[8,9], it is extremely important to reproducibly control molecular weight and molecular weight distribution.

A desirable goal in polymer synthesis is to produce a material with well-defined, narrow molecular weight distribution and predictable molecular weight. Since monomers with similar structures possess the same probability of reacting (equal chemical reactivity) in polycondensation, usually a wide range of polymerization products occurs during polycondensation. In order to control an AA/BB polycondensation, a monofunctional monomer that is able to condense and thus act as a "chain stopper" can be added. Indeed, during polycondensation, monofunctional impurities are known to terminate a chain and monofunctional compounds are used as a "chain stabilizer" to prevent further polycondensation in the case of polyamides, for example[10].

In this article we discuss the synthesis, properties and characterization of semisolid auto-catalyzed poly(ortho ester)s containing 30 mol % of lactic acid units ($POE_{70}LA_{30}$) synthesized using various molar percentages of decanol as the chain stopper.

EXPERIMENTAL

Materials

Triethylamine (TEA), p-toluenesulfonic acid (p-TSA) and decanol were purchased from Fluka®-Chemie AG (Buchs, Switzerland). 1,10-decanediol was purchased from Aldrich®-Chemie (Steinheim, Germany) and DL-lactide from Polyscience Inc. (Warrington, Pennsylvania). All solvents were of analytical grade and all compounds were used without further purification.

Synthesis of Monomers

The diketene acetal 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane (DETOSU) was prepared as described earlier[11]. 1,10-decanediol-lactate was synthesized by ring opening of a lactide as described previously[2].

Synthesis of Polymers

Three poly(ortho ester)s containing 30 mol % of lactic units, $POE_{70}LA_{30}$ (a), (b) and (c), were synthesized by using 5, 10 and 30 mol % of decanol, respectively. $POE_{70}LA_{30}$ (c), where LA stands for lactide, was synthesized as follows. 4.776 g of 1,10-decanediol-lactate (15×10^{-3} mol) and 3.485 g of 1,10-decanediol (20×10^{-3} mol) and 2.374 g of decanol (15×10^{-3} mol) were dissolved in 60 mL of anhydrous tetrahydrofuran (THF). The solution was stirred and gently heated until complete dissolution of the monomers took place. Then, 10.613 g of DETOSU (50×10^{-3} mol) were added under argon atmosphere and the polymerization initiated by the addition of 6 drops of p-TSA (1% w/w solution in THF). The polymerization, an exothermic reaction, produced the polymer almost instantaneously. Stirring was maintained for 1 h at room temperature. The polymer was then precipitated with methanol containing 5 drops of TEA to stabilize the polymer and recovered after 12 h at −4°C. After isolation, the polymer was dried at 40°C under vacuum (3×10^{-2} mbar) for 5 h. The vacuum was broken by introducing argon and the polymer was recovered as a transparent viscous product (yield: 61 to 87%). $POE_{70}LA_{30}$ (a) and (b) were synthesized by using 5×10^{-3} and 10×10^{-3} mol of decanol, where the proportion of 1,10-decanediol was 30×10^{-3} and 25×10^{-3} mol, respectively (yield: 89 to 96%). The reaction is shown in Figure 1.

Polymer Characterization

FT-IR spectra were recorded using a 1600 series FT-IR spectrometer (Perkin Elmer® AG, Küsnacht, Switzerland) using films cast from THF. Films were cast on sodium chloride discs and dried under vacuum.

^{1}H and ^{13}C-NMR spectra of various $POE_{70}LA_{30}$ were recorded in $CDCl_3$ using a Bruker AM 300 WB spectrometer (Dr Glaser AG, Basel, Switzerland).

Analytical high pressure size exclusion chromatography (HPSEC) was performed using a Waters® 600 E equipment with a series of four Styrogel HR® 1–4 columns as the stationary phase, a Waters 717 Plus autosampler and a Waters 410 refractometer. The mobile phase was stabilized THF (Romil Chemical, Leicestershire, England). Calibration was carried out using polystyrene standards (Tosoh Corporation, Tokyo) covering the 500 to 96,400 Dalton range.

Differential scanning calorimetry (DSC) studies were performed using a DSC 200 C microcalorimeter (Seiko, Tokyo). Glass-transition temperature (T_g) values were obtained from half-heights of the heat capacity curves using a heating rate of 6°C/min.

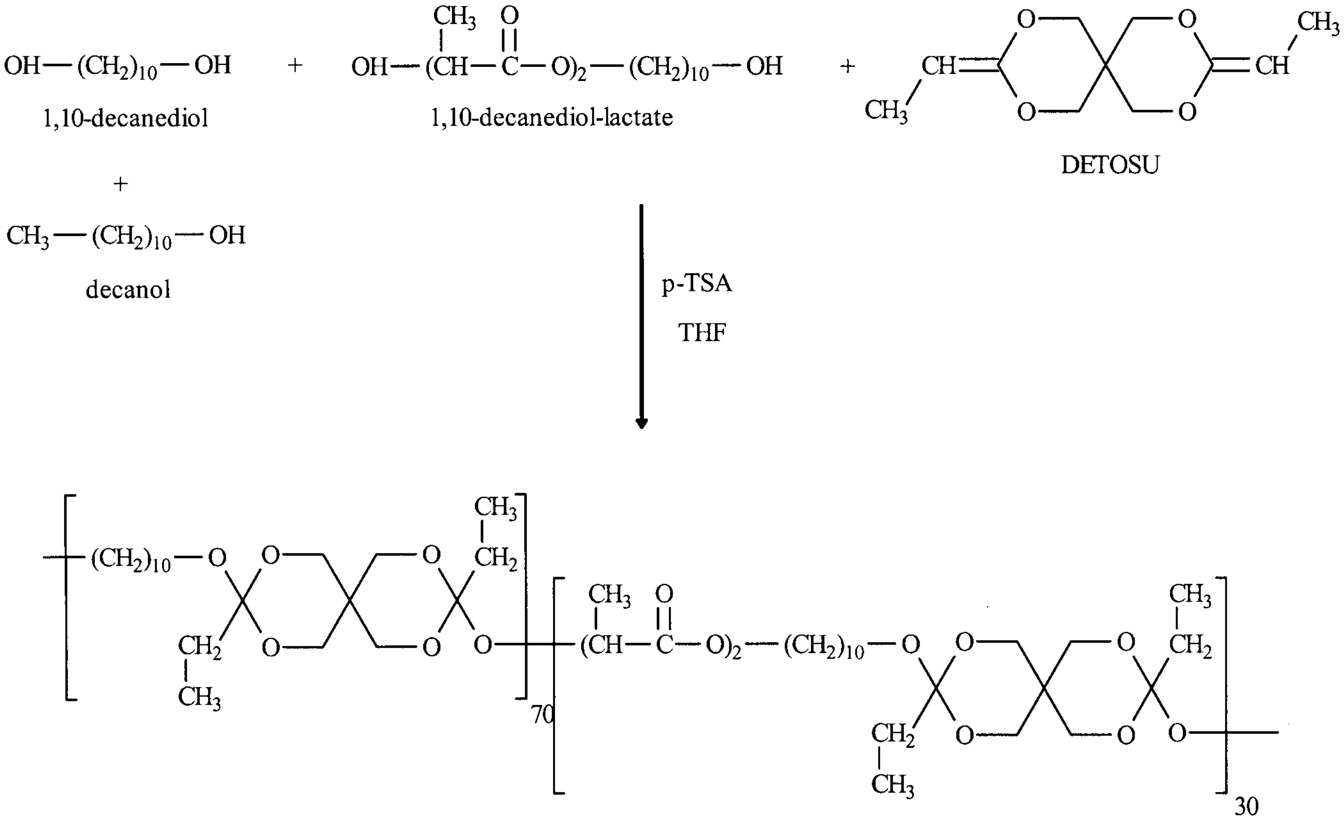

FIGURE 1 Chemical synthesis of $POE_{70}LA_{30}$ using *n*-decanol as chain stopper.

The viscoelastic behavior of $POE_{70}LA_{30}$ under forced oscillation was determined using a Bohlin® CS Rheometer (Bohlin® Rheology GmbH, Mühlacker, Germany). The temperature of the polymer samples was set at 37°C using the Bohlin® Extended Temperature Option (ETO). The sample under test was contained in a parallel plate system (PU 20). By measuring the amplitudes of stress and strain and their phase difference, G' (elastic modulus), G'' (viscous modulus) and η^* (complex viscosity) could be obtained. All the samples were examined over the frequency range from 0.002 to 7 Hz.

RESULTS AND DISCUSSION

FT-IR Analysis

The functional groups in the polymers were identified by FT-IR and the molecular composition of the polymer was established using the characteristic vibrations of the functional groups. The results are summarized in Table I.

FT-IR spectra were similar for all $POE_{70}LA_{30}$, showing that the polycondensation reaction leads to the same polymer with the same proportion of ester bands compared to ortho ester bands. Absorption arising from C–H stretching occurs in the general region of 2970–2850 cm^{-1}. The position of the C–H stretching vibrations is among the most consistent in the spectrum. An examination of this region gave the vibrations summarized in Table I.

TABLE I FT-IR characteristic vibrations and functional groups of $POE_{70}LA_{30}$.

Assignment (cm^{-1})	Characteristic bands	Functional groups
2962	ν_{as} (C-H)	$-CH_3$
2926	ν_{as} (C-H)	$>CH_2$
2872	ν_s (C-H)	$-CH_3$
2853	ν_s (C-H)	$>CH_2$
1747	ν (C=O)	R-COOR (aliphatic esters)
1480–1450	γ_{as} (C-H)	$>CH_2$ (methylene scissoring mode), $-CH_3$ (deformation)
1390–1360	γ_s (C-H)	$-CH_3$
1246–1197	ν_{as} (C-O)	C-O-C (cycle)
1170, 1140	γ (C-H)	CH_3(doublet equal intensity)
1043	ν_s (C-O)	C-O-C (cycle)
940	γ (C-O)	C-O-C (cycle)
722	γ ($-CH_2$)	$C-(CH_2)_n-C$ (for $n \geq 4$)

By comparing the intensities of the different bands in this region, it was found that the greater the molar percentage of *n*-decanol, the greater was the intensity of the characteristic band ν_{as}(C–H) at 2962 cm^{-1} corresponding to CH_3, compared to the band ν_{as}(C–H) at 2926 cm^{-1} corresponding to CH_2 (Figure 2). Indeed, 15% of chain ends in the polymer synthesized with 15 mol % of decanol were methyl groups instead of hydroxyl groups.

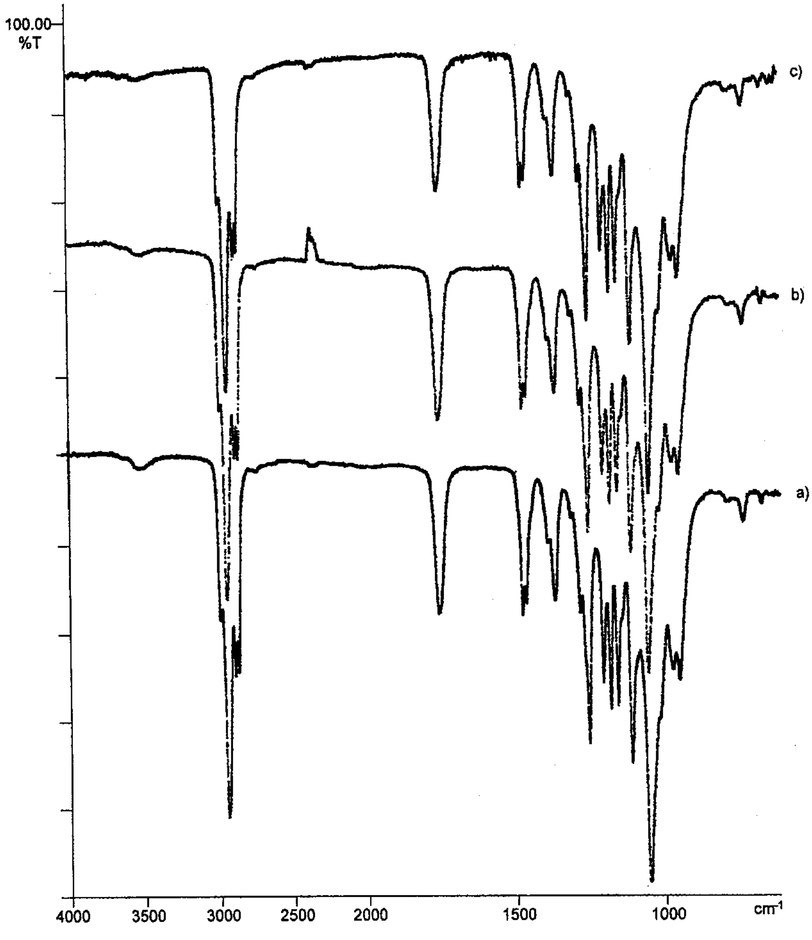

FIGURE 2 FT-IR spectra of $POE_{70}LA_{30}$ synthesized by using *n*-decanol at 5 mol % (a), 10 mol % (b) and 15 mol % (c).

^{13}C NMR Studies

The general structure of $POE_{70}LA_{30}$ was confirmed by ^{13}C NMR and ^{1}H-NMR and described earlier[2]. A more detailed analysis of some specific groups was carried out here in order to confirm the presence of more CH_3 in the polymer synthesized with the higher percent of decanol. The ^{13}C chemical shifts of the CH_3 groups and the estimated shift values are summarized in table II, and the assignments are given in Figure 3.

Experimental ^{13}C shifts were compared with those predicted by Lindeman and Adams's additivity rules[12]. Excellent agreement between experimental and calculated shifts were obtained for straight-chain hydrocarbons, and the ^{13}C-chemical shifts estimated for aliphatic hydrocarbons on the basis of the additivity rule differ by less than about 5 ppm from the experimental values. The ratio between the intensity of the end group CH_3 (C^1) and the intensity of the CH_3 (C^4) group belonging to the lactic acid units was higher for the polymer (c)

TABLE II ^{13}C NMR chemical shifts and assignments for CH_3 and CH_2.

Chemical shifts δ (ppm)	Estimated value δ (ppm)	Carbon number
	CH_3 assignments	
7.3	—	2 and 3
9.0	5.6	4′
14.1	12.9	1
16.9	14	4
20.5	15.6	4″
	CH_2 assignments	
22.7	**23.1**	**1**
26.6	26.3	3′
27.2	27.9	10
27.7	30.0	3 and 11
28.2	30.3	4 and 4′
28.4	31.6	6
29.1	32.5	2
31.9	33.2	2′
32.8	33.3	7
62.2	58.4	5
65.7	61.3	8
69.4	**63.0**	**1′**
69.5	63.1	9

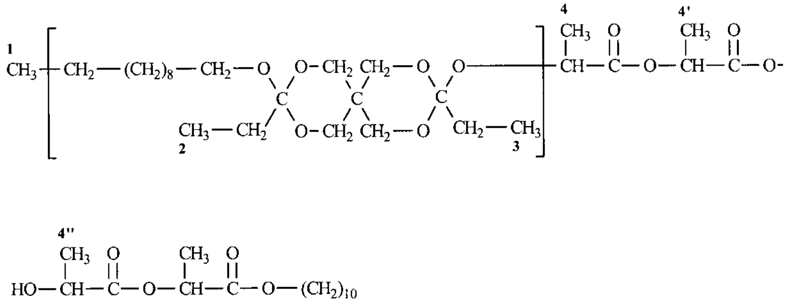

FIGURE 3 Assignments of carbon numbers belonging to CH_3 groups.

synthesized by using 15 mol % of decanol (2.59) than for other polymers (a) and (b) synthesized by using 5 and 10 mol % of decanol (1.67 and 1.25, respectively) (Figure 4). All peaks can be better visualized in the DEPT spectra (Figure 5).

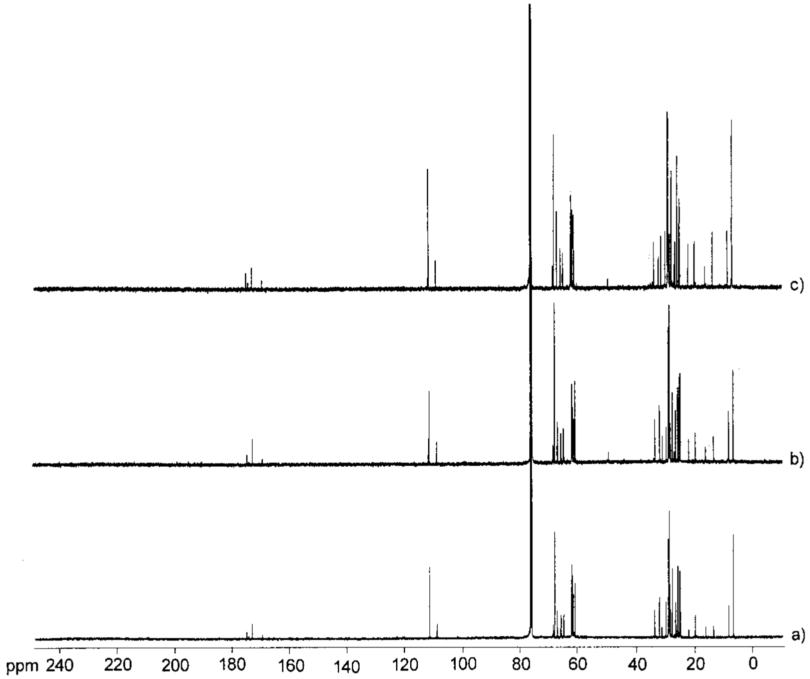

FIGURE 4 ^{13}C NMR spectra of $POE_{70}LA_{30}$ synthesized by using *n*-decanol at 5 mol % (a), 10 mol % (b) and 15 mol % (c).

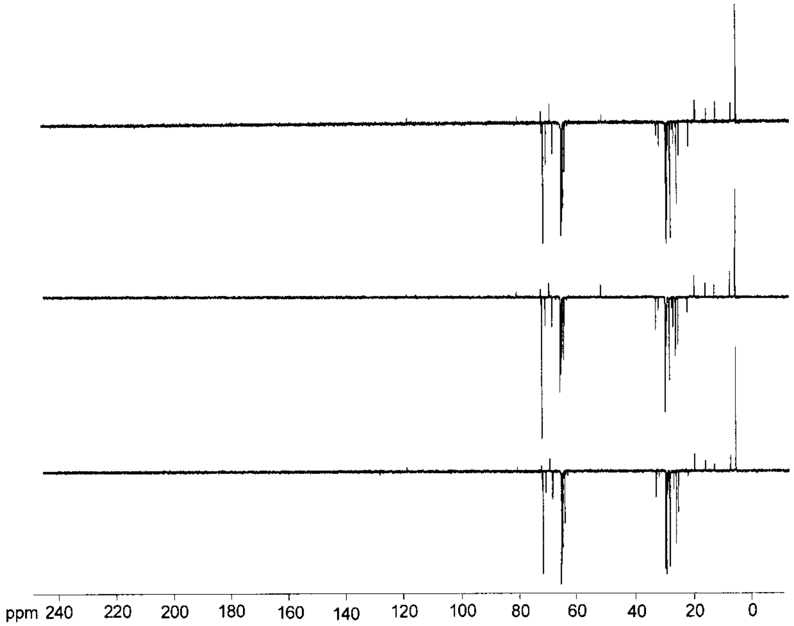

FIGURE 5 DEPT ^{13}C NMR spectra of $POE_{70}LA_{30}$ synthesized by using *n*-decanol at 5 mol % (a), 10 mol % (b) and 15 mol % (c).

Chemical shifts of carbons belonging to CH_2 groups and estimated values are summarized in Table II, and the assignments are given in Figure 6.

The ratio between the intensities of CH_2 peak ($C^{1'}$) at 69.4 ppm close to the hydroxyl end and CH_2 peak (C^1) at 22.7 ppm close to the methyl end decreased when the percent of decanol used during polymerization increased. These ratios for $POE_{70}LA_{30}$ (a), (b) and (c) were 16.4, 9.42 and 4.9, respectively. This result shows that, as expected, *n*-decanol is substituted for decanediol during the polymerization reaction and the proportion of methyl ends compared with hydroxyl ends in the polymers agrees with the initial feed concentrations.

^1H NMR Studies

^1H NMR spectra of polymer (a), (b) and (c) are shown in Figure 7, and the expansion of the region of interest between 0.8 and 1.9 ppm is shown in Figure 8. Chemical shifts and assignments for protons belonging to

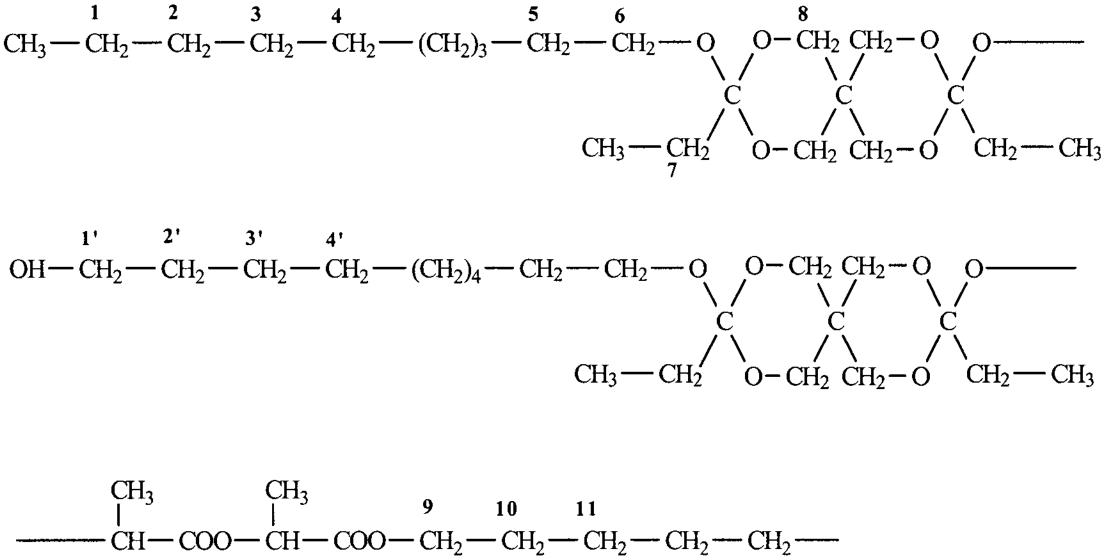

FIGURE 6 Assignments of carbon numbers belonging to CH_2 groups.

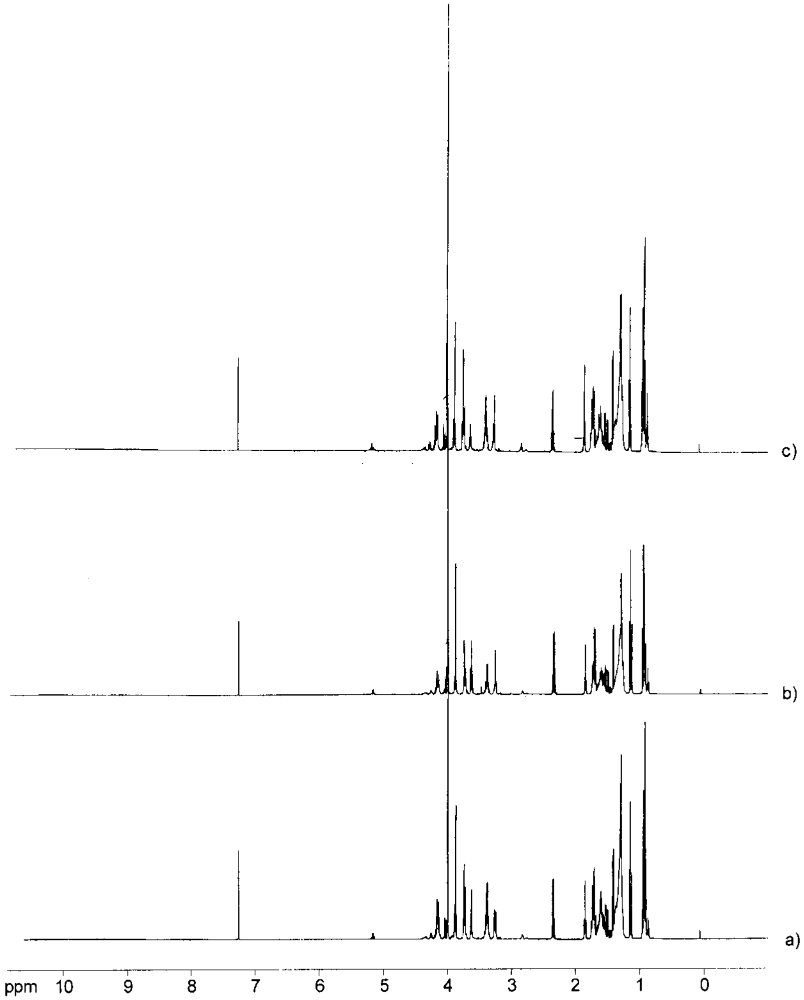

FIGURE 7 ^1H NMR spectra of $POE_{70}LA_{30}$ synthesized by using *n*-decanol at 5 mol % (a), 10 mol % (b) and 15 mol % (c).

CH_3, CH_2 and CH groups are summarized in Table III and assignments are given in Figure 9. We notice in Figure 7 that the higher the molar percent of decanol used during polymerization, the higher the intensities of proton signals belonging to CH_3 (H^1) end groups at 0.875 ppm and to CH_2 (H^2) located α to CH_3 at 1.27 ppm. Integration of all proton resonances

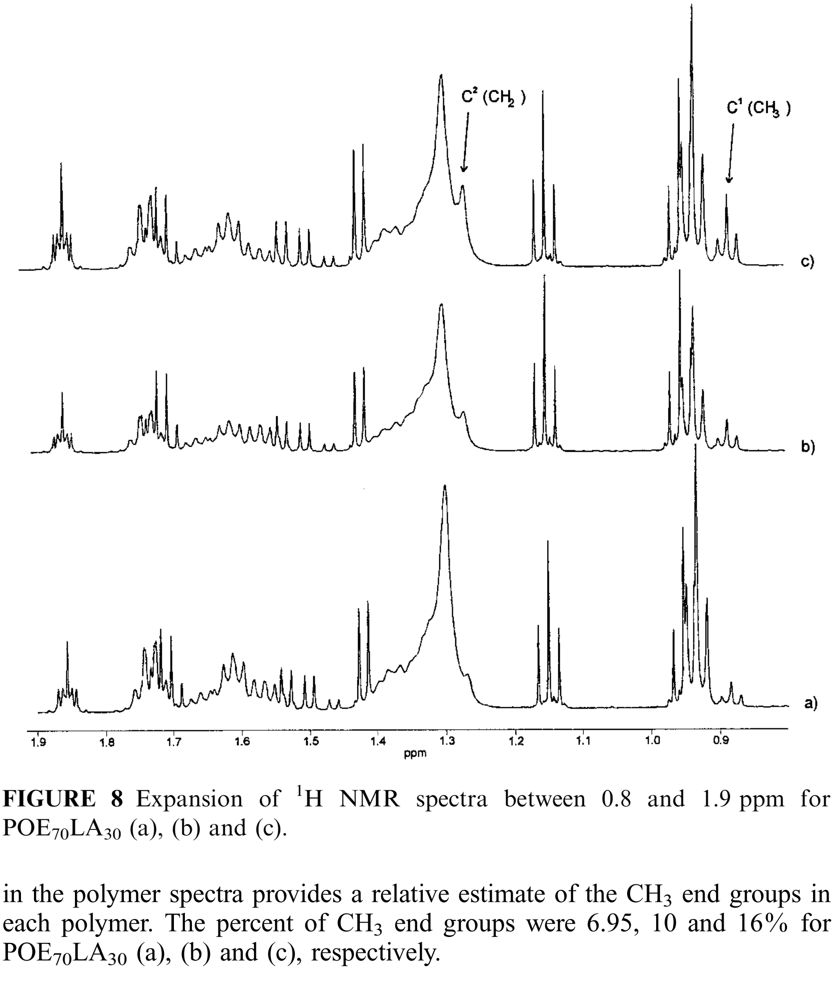

FIGURE 8 Expansion of ^{1}H NMR spectra between 0.8 and 1.9 ppm for $POE_{70}LA_{30}$ (a), (b) and (c).

in the polymer spectra provides a relative estimate of the CH_3 end groups in each polymer. The percent of CH_3 end groups were 6.95, 10 and 16% for $POE_{70}LA_{30}$ (a), (b) and (c), respectively.

SEC Analysis

$POE_{70}LA_{30}$ (a), (b) and (c) have number-average molecular weights (M_n) of 5,200, 4,500 and 3,800 Da, respectively (Table IV). This result suggests that decanol acts as a chain stopper and reproducibly decreases polymer molecular weights.

DSC Analysis

As shown in Table IV, the lower the polymer molecular weight, the lower the T_g. This is due to the increased flexibility of short chains.

TABLE III ^{1}H NMR chemical shifts and assignments for $POE_{70}LA_{30}$ spectra.

Chemical shifts δ (ppm)	Proton number	Assignment	Form
0.875	1	CH_3	triplet
0.94	12″	CH_3	triplet
0.955	12 and 12′	CH_3	triplet
1.15	12‴	CH_3	triplet
1.27	2	CH_2	singlet (medium broad)
1.32	4–9 and 4′–9′	CH_2	singlet (medium broad)
1.42	15	CH_3	doublet (sharp)
1.62	3 and 3′	CH_2	triplet (sharp)
1.72	15′	CH_3	doublet (sharp)
3.4	11 and 11′	CH_2	quadruplet (sharp)
3.87	10 and 10′	CH_2	singlet
4	13, 13′, 13″ and 13‴	CH_2	singlet
4.17	16	CH_2	triplet (well formed)
4.25	14	CH	quadruplet (sharp)
4.35	14′	CH	quadruplet (sharp)

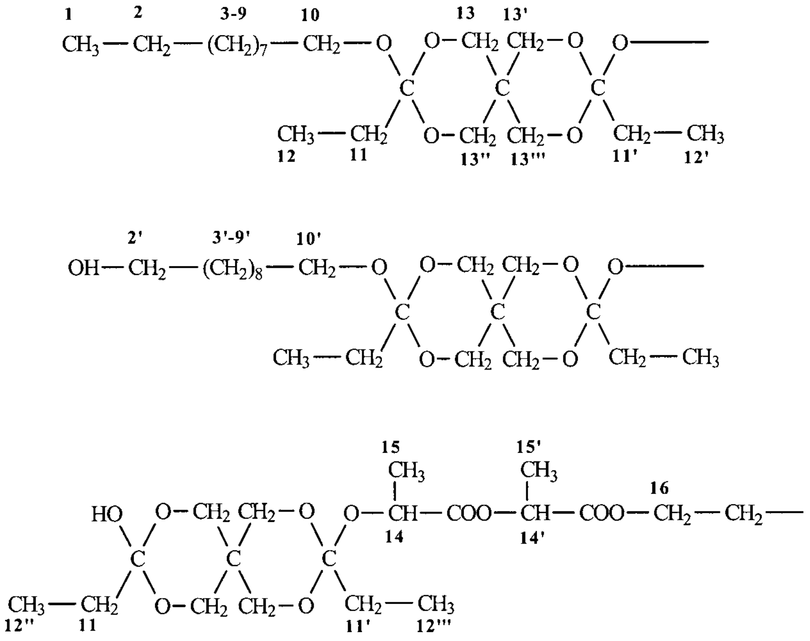

FIGURE 9 Assignments of proton numbers belonging to CH_3, CH_2 and CH groups.

TABLE IV Molecular weights and glass-transition temperatures of $POE_{70}LA_{30}$.

Percent of decanol in $POE_{70}LA_{30}$	M_n	M_w	Polydispersity $I = (M_w/M_n)$	T_g (° C)
5	5200	9700	1.86	−25
10	4500	7400	1.64	−33
15	3800	6100	1.61	−46

A linear relationship was also found between number-average molecular weights and both decanol percent and T_g (Figure 10).

Rheological Behavior

The rheological behavior of POE_xLA_y polymers has been described earlier[2]. Storage (elastic) modulus G', viscous (loss) modulus G'' and loss tangent (tan δ) were evaluated for polymers (a), (b) and (c). At a representative frequency of 0.5 Hz, as the number of CH_3 chain ends increases, G' increases and G'' decreases, leading to a decrease in tan $\delta = (G''/G')$ (Table V). A high numerical value for tan δ indicates a lower

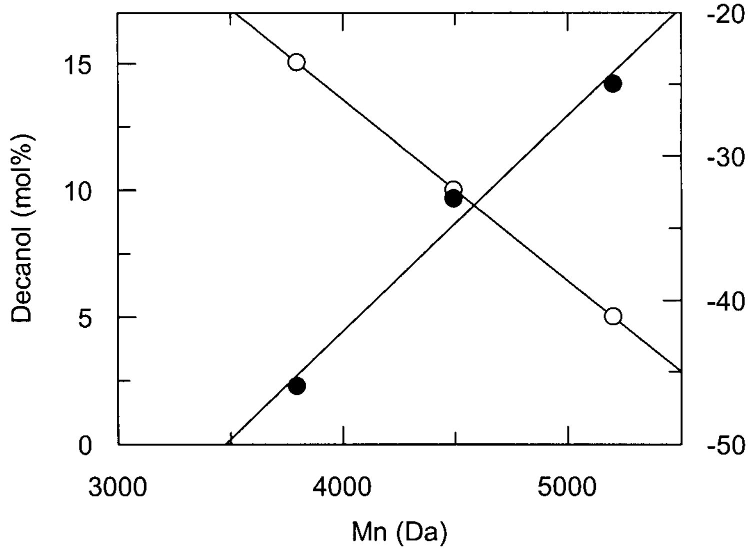

FIGURE 10 Relationship between number average molecular weights and percent *n*-decanol and T_g.

TABLE V The parameters characterizing the rheological behavior of $POE_{70}LA_{30}$ at 0.5 and 0.002 Hz.

$POE_{70}LA_{30}$	G' (Pa)	G'' (Pa)	G^* (Pa)	Complex viscosity (Pa s)	$\tan\delta = (G''/G')$
		0.5 Hz			
Decanol 5 mol %	$9.55\ 10^{-1}$	$4.65\ 10^{2}$	$4.65\ 10^{2}$	$1.48\ 10^{2}$	486.91
Decanol 10 mol %	$1.47\ 10^{1}$	$2.22\ 10^{2}$	$2.22\ 10^{2}$	$7.08\ 10^{1}$	15.10
Decanol 15 mol %	$6.05\ 10^{1}$	$1.82\ 10^{2}$	$1.91\ 10^{2}$	$6.09\ 10^{1}$	3.01
		0.002 Hz			
Decanol 5 mol %	$7.42\ 10^{-2}$	$1.36\ 10^{0}$	$1.36\ 10^{0}$	$1.44\ 10^{2}$	18.33
Decanol 10 mol %	$1.23\ 10^{-1}$	$7.02\ 10^{-1}$	$7.12\ 10^{-1}$	$7.56\ 10^{1}$	5.71
Decanol 15 mol %	$2.04\ 10^{0}$	$2.01\ 10^{0}$	$2.86\ 10^{0}$	$3.04\ 10^{2}$	0.99

degree of elasticity of the material. However, for all polymers, the tan δ values were above 1 at lower frequencies (0.5 Hz), indicating a prevalence of viscous over elastic nature.

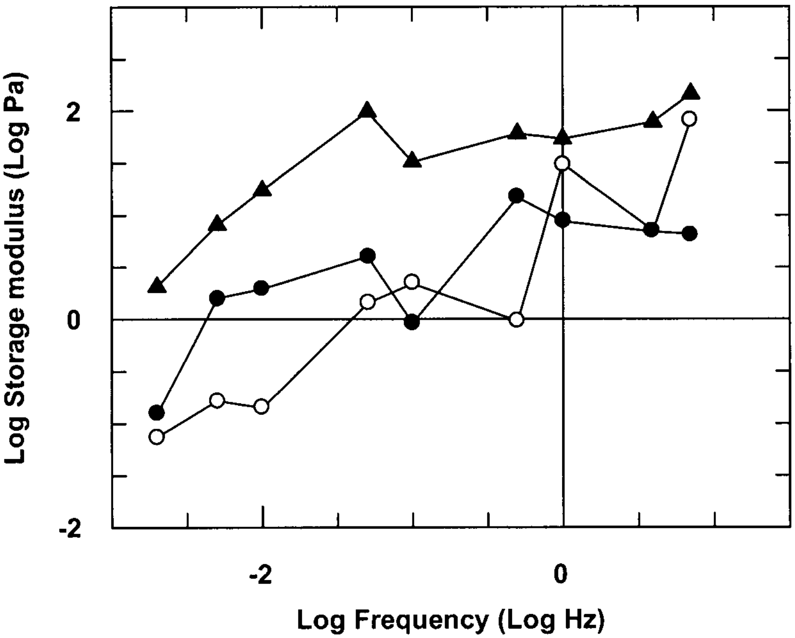

FIGURE 11 Variation of the storage modulus (G') with frequency for $POE_{70}LA_{30}$ synthesized by using *n*-decanol at 5 mol % (○), 10 mol % (●) and 15 mol % (▲).

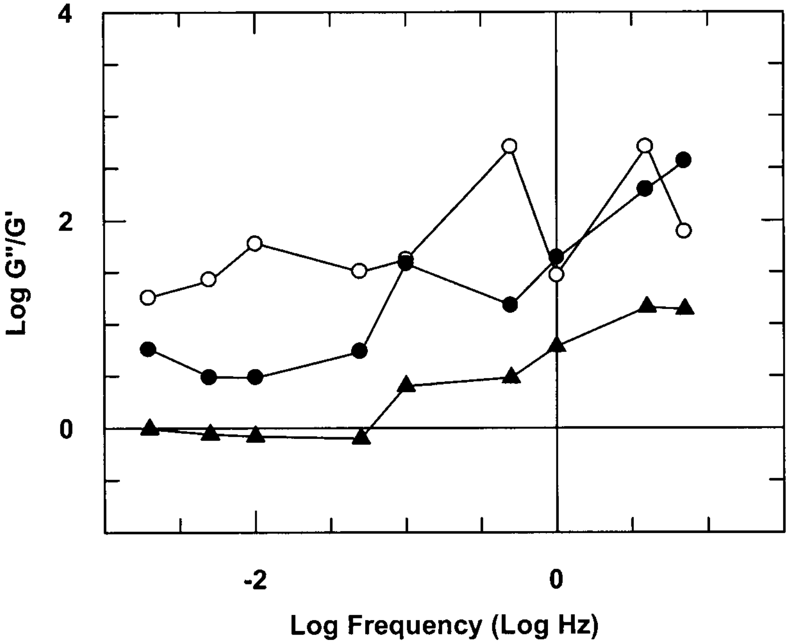

FIGURE 12 Variation of the tan δ with frequency for $POE_{70}LA_{30}$ synthesized by using *n*-decanol at 5 mol % (○), 10 mol % (●) and 15 mol % (▲).

At a lower frequency (0.002 Hz), the presence of a higher number of CH_3 chain ends also has an effect on both storage modulus G' (which increases) and tanδ value (which decreases) (Table V). At frequencies between 0.002 and 0.05 Hz, the storage moduli G' for all polymers increase with frequency; however, the tanδ values are unchanged, showing that the proportionality of the two moduli G' and G'' is maintained and that the mechanism of mechanical relaxation of such polymers is not affected at low frequencies (Figures 11 and 12).

G' and G'' for $POE_{70}LA_{30}$ (c) synthesized by using 15 mol % of decanol show a smaller variation with frequency than that observed for $POE_{70}LA_{30}$ (a) and (b). This suggests the presence of a more rigid structure in the polymer with a high percent of CH_3 chain ends.

CONCLUSION

Poly(ortho ester)s represent a versatile class of biomaterials with steadily growing applications. Injectable semisolid POE_xLA_y are currently being investigated in clinical trials in periodontology, ophthalmology and veterinarian applications. Interesting and unique properties of these polymers (such as controlled drug release) can be achieved by adjusting the molar percentage of lactic acid and the molecular weight of the polymer.

Results reported in this study have shown that the addition of decanol during polycondensation stops chain propagation and reproducibly produces low-molecular-weight polymers. The presence of CH_3 chain ends was confirmed by ^1H and ^{13}C NMR and was proportional to the percent of decanol in the monomer feed.

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