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Novel star-shaped polylactide with glycerol using stannous octoate or tetraphenyl tin as catalyst: 1. Synthesis, characterization and study of their biodegradability

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Novel star-shaped polyesters were synthesized by reacting L-lactide (LLA) with glycerol (GL) in the presence of stannous octoate or tetraphenyltin as catalyst. These polymers were characterized by nuclear magnetic resonance, Fourier-transform infra-red spectroscopy, differential scanning calorimetry (d.s.c.) and thermogravimetric analysis. D.s.c. curves showed that these polymers are semicrystalline when the ratio LLA/GL is higher than 20/1 (mol/mol). When this molar ratio falls below 20/1, the polymers are amorphous. The molecular-weight distribution of these polymers was studied with gel permeation chromatography measurements, which showed that the M_n decreased proportionally to the glycerol content in the polymer. The potential biodegradability of these polymers was assessed with the aid of enzymatic and alkali hydrolysis.

(Keywords: L-lactide/glycerol; star-shaped polyesters; biodegradability)

INTRODUCTION

Broad interest in the possible biodegradation of synthetic polymers has developed only in recent years and primarily in response to the growing problem of the waste disposal of plastics[1]. The most widely evaluated and the first systematically studied type of synthetic polymer for biodegradability were the polyesters. Among the polyesters, poly(ϵ-caprolactone) (PCL) and poly(L-lactide) (PLLA) were found to be the most responsive to biodegradation with *in vitro*[1–8] and *in vivo*[9–11] experiments.

Apart from the above-mentioned homopolymers PCL and PLLA, numerous copolymers (based on one[12,13] or both components[14–17]) have been synthesized in order to improve the properties of homopolymers in view of their various applications. The introduction of a soft segment, usually poly(ethylene glycol), in PLLA has recently attracted a significant amount of research work[17–21] in an attempt to produce novel biomaterials that could be shaped *in situ* and would also be endowed with higher adhesion to living tissues. Although PLLA has been widely regarded as one of the most popular biocompatible and biodegradable polymers, especially for biomedical applications, i.e. surgical sutures[22], implants for fixation of fractures[23,24] and drug delivery systems[25], the difficulties encountered in its processing were always its major shortcomings[26]. Although orthopaedic applications of PLLA require a high *MW*, its high melt viscosity (for linear PLLA) results in degradation during melt processing for fibres, bone plates and screws[26]. The imperative for overcoming this problem was already acknowledged in several previous publications[26–29], where it was suggested that branched (star-shaped) polymers could yield high-molecular-weight PLLA but with significantly lower melt viscosities than the linear PLLA[30–33]. In our case, glycerol was preferred to the previously used pentaerythritol because of its higher availability in nature and because lipases are known to hydrolyse readily the fatty acid esters of glycerol (triacyl glycerides[1]). Therefore, it could be anticipated that these novel polyesters should exhibit higher rates of solubilization followed by degradation as suspensions in aqueous media containing lipases. The aim of this research work was to synthesize a novel series of polyesters based on L-lactide and glycerol in the presence of two of the most effective catalysts, tetraphenyl tin (powder) and stannous octoate (liquid), which has the edge over the former because of its acceptance by the US FDA as a food additive[34], to compare their properties with other copolymers (with structural similarities) and to carry out preliminary biodegradability tests with the aid of enzymatic and alkali hydrolysis.

EXPERIMENTAL

Synthesis of polymers from L-lactide and glycerol in the presence of tetraphenyl tin and tin octoate

L-Lactide (LLA) was purified by recrystallization from

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dried toluene under nitrogen atmosphere and then dried for 24 h in vacuum at 30°C. Both tin 2-ethylhexanoate (stannous octoate, Sn oct) and tetraphenyl tin (TPhT) were purchased from Wako Chemicals (Japan) and used without further purification. Glycerol (GL) was purified by distillation under reduced pressure and treated with sodium sulfate to remove any residual moisture traces. Polymerization of LLA was carried out in a glass ampoule. Freshly recrystallized LLA and various amounts of GL were transferred into the ampoule. Sn oct or TPhT were added under nitrogen atmosphere. The ampoule was sealed in vacuum after three times purging with nitrogen. The ampoule was heated up to 130°C in an oil bath for 4 days. After this time had elapsed, the ampoule was broken and the products were dissolved in chloroform, followed by microfiltering through a 0.45 μm pore membrane filter. The polymers whose comonomer molar feed was higher than 20/1 (LLA/GL) were precipitated dropwise into methanol, whereas those with molar composition lower than 20/1 (LLA/GL), that is richer in GL, were evaporated to yield low-molecular-weight PLLA. Both high- and low-molecular-weight PLLA were dried in a vacuum desiccator at 50°C for 24 h.

Thermal analysis

The thermal behaviour of the polyesters was studied by using a differential scanning calorimeter (DSC-10A, Rigaku, Thermoflex) connected with a chart recorder (Rigaku) and a temperature control unit (PTC 10D, Rigaku). The heating rate was 10°C min^{-1} and an empty aluminium pan was used as reference. Indium metal was used for calibration purposes both for T_m and ΔH_m (T_m (In) = 156.7°C and ΔH_M(In) = 28.36 J g^{-1}). The glass transition (T_g) was determined as the middle of the recorded step change in heat capacity, and melting points (T_{m1}, T_{m2}) were defined as the peaks of the endotherm curve.

Thermogravimetric analysis

T.g.a. measurements were carried out with Shimadzu model DT-30 TGA thermogravimetric analyser at a heating rate of 5°C min^{-1} under a stream of N_2.

Fourier-transform infra-red spectroscopy

The *FT*i.r. spectra were recorded with a spectrometer (Nicolet, Model 710 FT-IR) connected with a PC computer (Nicolet) and a Color Pro plotter (Fujitsu, model FPG 315-101). The samples were recorded as films since they were soluble in $CHCl_3$.

Nuclear magnetic resonance spectroscopy

^{1}H n.m.r. (200 MHz) and ^{13}C n.m.r. (50 MHz) spectra were recorded on a JEOL-FX200 spectrometer. All spectra were obtained from chloroform-d solutions at room temperature with tetramethylsilane (TMS) as internal standard and according to the following specifications: pulse width, 30°; aquisition time, 3.276 s; pulse interval time, 1.00 s.

Gel permeation chromatography

The molecular-weight distributions (M_n, M_w and polydispersity indices) were measured with g.p.c. (Tosoh, model HLC-8020) using polystyrene standards. The columns were TSK gel G4000 HXL and a TSK gel G3000 HXL with limited exclusion molecular weight 4×10^5. The eluent was $CHCl_3$ and the flow rate was 0.6 ml min^{-1}.

Enzymatic hydrolysis

Polyester samples (25 mg) and 2 ml of phosphate buffer (KH_2PO_4/Na_2HPO_4, pH 7.00) were added to three tubes. Then 200 units of enzyme were added to two tubes and the third was for a blank test. The enzyme used was the lipase from *Rhizopus arrhizus*. The enzymatic hydrolysis was carried out at 37°C for 24 and 72 h, respectively. After filtration (0.2 μm membrane filter), a small amount of 1 N hydrochloric acid was dropped onto the filtrate and *TOC* (total organic carbon) was measured. The *TOC* values were the average of two measurements and corrected appropriately by subtracting the blank levels.

Enzymatic hydrolysis for studying the degradation products. Polyester sample (100 mg) and 2 ml of phosphate buffer (KH_2PO_4/Na_2HPO_4, pH 7.00) were added to three tubes. Then 2000 units of enzyme were added to two tubes and the third was for a blank test. The enzyme used was the lipase from *Rhizopus arrhizus*. The enzymatic hydrolysis was carried out at 37°C for 120 h. After the end of enzymatic hydrolysis, the suspension was first extracted with $CHCl_3$ and then dried with Na_2SO_4 in order to remove residual moisture from the phosphate buffer. After filtration (removal of Na_2SO_4) the chloroform was evaporated and the remaining sample was used for n.m.r. and g.p.c. measurements. The water-soluble fraction (mainly glycerol) was dissolved in D_2O for n.m.r. measurement.

Alkali hydrolysis (10% NaOH w/v, 80°C)–weight loss experiments

In view of the friability of our polyesters and their inadequate strength, no films could be formed. Therefore, bars of dimensions 40 mm length, 7 mm width and 2.0 mm thickness were moulded and immersed in alkali solutions (10% NaOH w/v) at 80°C. The weight losses of the samples were followed by weighing them every day. Our results give the average of three measurements.

RESULTS AND DISCUSSION

The two primary hydroxyl groups of GL are expected to initiate the polymerization of LLA, while it is rather debatable whether the secondary –OH will act similarly in view of its stereochemical inhibition. Whether or not all three hydroxyl groups reacted can be investigated with the aid of n.m.r. provided, however, that the molecular weights of synthesized PLLA are not too high. The general scheme for the conversion of the involved monomers to polymer is as shown in *Figure 1*.

The yields of polymer syntheses after precipitation with CH_3OH or evaporation of $CHCl_3$ (for GL-poor and –rich polymers, respectively) and the n.m.r. determination of the LLA/GL (molar ratio) in the polymer are given in *Table 1*.

Relatively high amounts of GL and catalyst (Sn oct or TPhT) were used in order to obtain low-molecular-weight polymers. Bearing in mind previous publications[26,27], where it was clearly shown that the selected polymerization temperatures (for pentaerythritol and

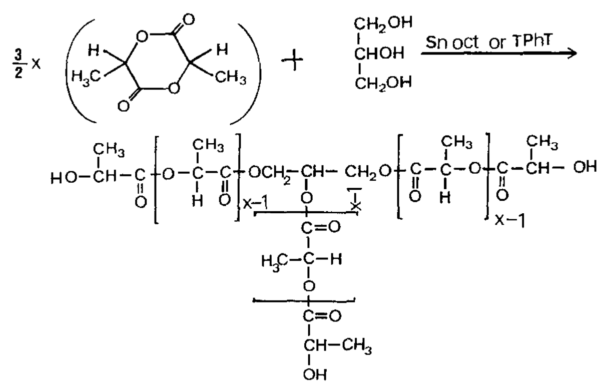

Figure 1 Reaction mechanism of LLA/GL polycondensation polyesters

Table 1 Percentage yields and n.m.r. evaluation of LLA/GL molar ratio for bulk polymerizations of LLA/GL at 130°C for 96 h

Monomers: LLA/GL feed molar ratio	Catalyst[a]	Method[b]	Yield (%)	N.m.r.: LLA/GL polymer molar ratio
100/0	Sn oct	XP	99	–
100/1		XP	99	–
70/1		XP	98	–
40/1		XP	96	38/1
20/1		EV	97	20/1
10/1		EV	95	10/1
3/1		EV	94	5/1
100/0	TPhT	XP	100	–
100/1		XP	100	–
70/1		XP	99	–
40/1		XP	98	43/1
20/1		EV	98	24/1
10/1		EV	96	12/1
3/1		EV	94	9/1

[a] Tin octoate, 0.5% mol/mol (top half of table) or tetraphenyltin, 0.5% mol/mol (bottom half)

[b] XP = after extraction ($CHCl_3$) and precipitation (CH_3OH); EV = after evaporation of $CHCl_3$

LLA) are in the range of 110–190°C, in conjunction with our preliminary experiments, which showed that below 110°C no polymerization occurred whereas above 160°C the reaction proceeded at an uncontrollable rate (browning of products due to decomposition), a temperature of 130°C was selected. The polymer yields *versus* the GL feed ratios show a linear relationship and, in particular, high GL contents are associated with lower polymer yields.

The *FT*i.r. spectra of these polyesters show a broad absorption at ca. 3500 cm^{-1} indicating the presence of –OH groups. In addition, an absorption band at 1750 cm^{-1} confirms the formation of –O–C=O ester bonds. *Figure 2* shows a series of representative traces of polyesters (LLA/GL) where it is obvious that, the higher the glycerol content in the polymer, the more pronounced the intensity of the hydroxyl group absorption becomes.

Although the n.m.r. spectra of our polyesters show the resonance signals for methyl and methine protons at 1.4 and 5.1 ppm, respectively (in agreement with previous publications for both linear[35] and star-shaped[26] PLLA), there are several other peaks, occasionally overlapped, due to the incorporation of glycerol. The assignment of the peak at 4.2 ppm to the methylene groups of GL is supported by its proportional decrease in resonance intensity with an increase in the LLA/GL molar ratio. The presence of a secondary –OH group at the chain end and/or an unreacted –OH group of GL could be at 2.8 ppm. The hydroxyl group shows a relative mobility concerning its position, that is from 2.4 to 3.5 ppm.

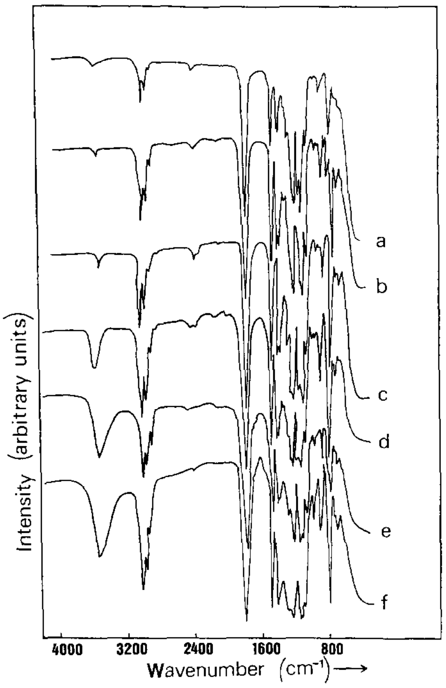

Figure 2 *FT*i.r. spectra of a series of LLA/GL polyesters synthesized using TPhT (mol/mol): (a) PLLA, (b) LLA/GL (100/1), (c) LLA/GL (70/1), (d) LLA/GL (40/1), (e) LLA/GL (10/1) and (f) LLA/GL (3/1)

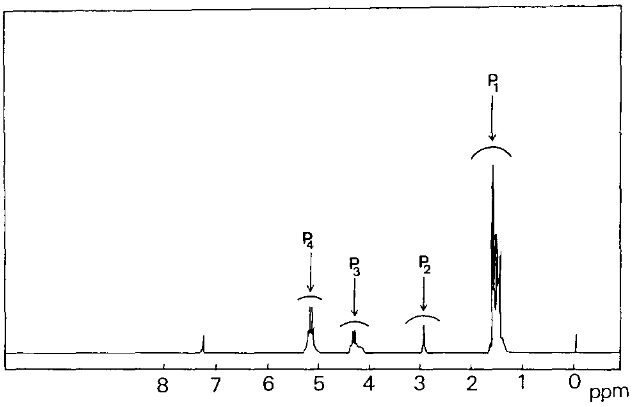

Figure 3 ^1H n.m.r. spectrum of LLA/GL (10/1) polyester (mol/mol)

Figure 3 shows a representative n.m.r. trace for LLA/GL 10/1 (mol/mol). *Figure 4* shows the peak assignments for LLA/GL polyesters. Bearing in mind the assignments of peaks from n.m.r. traces, the following equations were suggested for determining the LLA/GL molar ratio in the polymers:

$$3x = (P_1) \quad (1)$$

$$x + y = (P_4) \quad (2)$$

$$4y = (P_3) \quad (3)$$

where (P_1), (P_4) and (P_3) equal the integration intensities

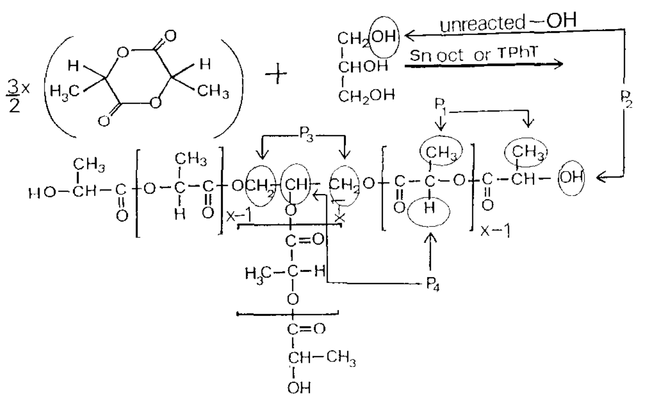

Figure 4 Assignment of ^{1}H n.m.r. spectrum of LLA/GL of *Figure 3*

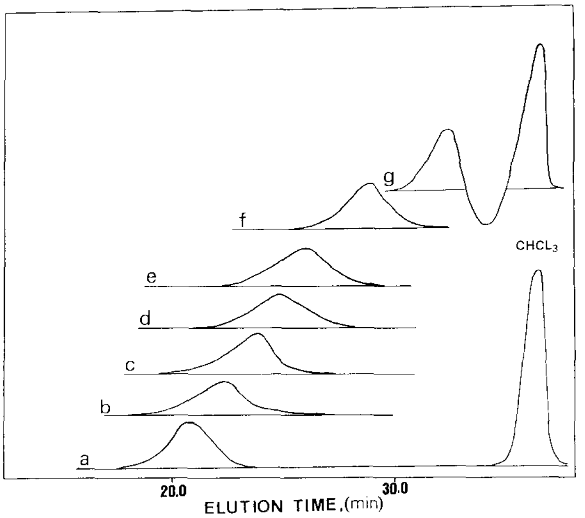

Figure 5 G.p.c. elution curves of a series of LLA/GL polyesters synthesized using Sn oct (mol/mol): (a) PLLA, (b) LLA/GL (100/1), (c) LLA/GL (70/1), (d) LLA/GL (40/1), (e) LLA/GL (20/1), (f) LLA/GL (6/1) and (g) LLA/GL (3/1)

and (x/y) the LLA/GL molar ratio. As an example we could refer to LLA/GL 10/1 (comonomer molar feed ratio):

$$(1) \Rightarrow 3x = 25.9 \qquad \Rightarrow x = 8.6$$

$$(2) \Rightarrow x + y = 7.3 \qquad \Rightarrow x = 6.6$$

$$(3) \Rightarrow 4y = 2.9 \qquad \Rightarrow y = 0.73$$

By taking the average of the x values found from equations (1) and (2), we find $x = 7.6$. Hence:

$$\frac{x}{y} = \frac{7.6}{0.73} = 10$$

The g.p.c. traces of the LLA/GL polyesters (synthesized using Sn oct as catalyst) give monodisperse curves, thus excluding the possibility that more than one mechanism is in action (*Figure 5*). In fact, this is in agreement with a previous publication where Sn oct was used as catalyst for the LLA/pentaerythritol system[26]. Therefore it could be suggested that initiation of polymerization occurs via the alcohol and, in particular, GL, similarly to the polymerization of ϵ-caprolactone in the presence of alcohol[36].

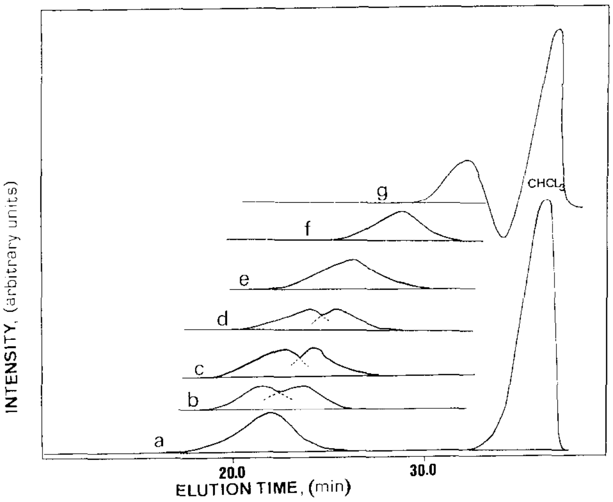

Figure 6 G.p.c. elution curves of a series of LLA/GL polyesters synthesized using TPhT (mol/mol): (a) PLLA, (b) LLA/GL (100/1), (c) LLA/GL (70/1), (d) LLA/GL (40/1), (e) LLA/GL (20/1), (f) LLA/GL (6/1) and (g) LLA/GL (3/1)

However, when TPhT was used as catalyst, several bimodal g.p.c. traces were obtained, as shown in *Figures 6b–d*, which favour the assumption that two initiation mechanisms occur; that is one via the glycerol (GL) and the other via the TPhT. An increase in GL content (LLA/GL< 20/1) resulted in monodisperse g.p.c. curves (*Figures 6e–g*), probably because the high GL concentration promoted mainly the polymerization via GL and not via the catalyst.

Table 2 summarizes all the g.p.c. data obtained for the polyesters. The star-shaped PLLAs (synthesized with LLA/GL in the presence of Sn oct or TPhT) are viscous liquids at LLA/GL< 20/1 (mol/mol), whereas they become white solids for LLA/GL> 20/1 (mol/mol).

Table 3 summarizes the thermal properties of these novel polyesters and in particular their glass transitions (T_g), crystallization temperatures (T_{cr}), melting peaks (T_m), heats of fusion (ΔH_m) and percentage crystallinities (X_c) obtained from d.s.c. analysis.

Some typical d.s.c. traces are shown in *Figure 7*. The traces b, c, d and e show bimodal peaks, which may be due to the existence of two different mechanisms initiating the polymerization and resulting both in different molecular distributions and probably in different spherulite morphologies and sizes as previously confirmed with SEM measurements[37,38].

Therefore, our previously formulated suggestion with regard to the observed differences governing the initiation of polymerization of the LLA/GL system with two different catalysts seems to be further corroborated. However, additional experimentation with microscopy is required in order to determine the presence or not of different spherulite morphologies apart from their different sizes. *Figure 8* shows the effect of cooling and reheating the LLA/GL 40/1 (mol/mol) polymer. The initially existing 'shoulder' in the first run becomes a distinct peak in the second run, whereas the major peak further splits into two peaks in the third run, thus giving a total of three peaks. These results support the above expressed suggestion concerning the induction of several crystallite sizes (formed on heating) and probably differences in molecular weights as well[37].

Table 2 Determination of number and weight-average molecular weights (M_n, M_w) and polydispersity indices (n) from gel permeation chromatography measurements

Monomers: LLA/GL molar ratio	Catalyst[a]	M_n	M_w	$n = M_w/M_n$
100/0	Sn oct	4.2×10^4	8.1×10^4	1.9
100/1		1.4×10^4	2.0×10^4	1.4
70/1		1.4×10^4	2.1×10^4	1.5
40/1		9.8×10^3	1.4×10^4	1.4
20/1		7.6×10^3	1.1×10^4	1.4
10/1		5.4×10^3	6.7×10^3	1.2
3/1		1.4×10^3	1.5×10^3	1.1
100/0	TPhT	4.7×10^4	1.6×10^5	3.4
100/1		4.3×10^4	2.3×10^5	5.3
70/1		1.5×10^4	2.0×10^4	1.4
40/1		1.3×10^4	1.5×10^4	1.2
20/1		3.9×10^3	5.5×10^3	1.4
10/1		4.3×10^3	4.8×10^3	1.1
3/1		2.2×10^3	2.5×10^3	1.1

[a] See *Table 1*

The effect of GL content on the crystallization of LLA/GL polymers was investigated by studying the isothermal crystallization of LLA/GL polyesters. The development of relative crystallinity at time t was calculated from the following equation:

$$X_c = A(t')/A(\infty) \tag{4}$$

where $A(t')$ is the area under the d.s.c. curve from $t = 0$ to $t = t'$, and $A(\infty)$ is the maximum area (for $t \rightarrow \infty$) under the crystallization temperature curve. Plots of the non-crystallized material $(1 - x_t)$ *versus* $\log t$ for a polyester at various temperatures gave isotherms of a characteristic sigmoid shape and superposable by translation along the t axis (*Figure 9*). This tendency should be attributed to similar mechanisms of nucleation and crystal growth for each polyester similarly to previously reported copolyamides[39,40].

Although at the very beginning of the crystallization process nucleation is the dominating factor, at a later stage the crystallization rate drops significantly, probably due to radical impingement of spherulites because of decrease in the amount of sample available for crystallization.

The classical Avrami equation in both its exponential (5) and its logarithmic version (6) was used for the analysis of the isothermal crystallization of polyesters:

$$1 - x_t = \exp(-kt^n) \tag{5}$$

$$\log(-\ln x_t) = \log k + n \log t \tag{6}$$

where x_t is the fraction crystallized at time t, n is the Avrami constant depending both on the nucleation mechanism and on the crystal geometry, and k is a crystallization rate constant related to nucleation and growth parameters. The Avrami parameters n and k are estimated from the slope and intercept, respectively, in plots of $\log(-\ln x_t)$ *versus* $\log t$ as shown in *Figure 10*. These plots produced straight parallel lines, thus confirming the validity of the Avrami equation for the polyesters under the measurement conditions of this study. The Avrami parameters n and k determined by taking into account only the primary crystallization process under the assumption that it proceeds independently of the secondary crystallization process are given in *Table 4*.

The bulk crystallization rate of the LLA/GL polyesters decreases with increasing GL if the $t_{1/2}$ (half crystallization times) for various LLA/GL polyesters are compared. The lower mobility and lower crystallization rates of these novel polymers could be due to insufficient flexibility and mobility of GL whose action is similar to that of compatibilizing agents, which were found to delay considerably the crystallization process in previous publications[41–43]. The values of Avrami index were found to be practically independent of the temperature of isothermal crystallization for each LLA/GL polyester. Furthermore, the Avrami parameter n shows a considerable decrease from $n = 3.3$ for

Table 3 Glass transitions (T_g), crystallization temperatures (T_{cr}), melting points (T_{m1}, T_{m2}), heats of fusion (ΔH_m) and percentage crystallinities (X_c) of LLA/GL polyesters

Monomers: LLA/GL		T_g (°C)		T_{cr} (°C)	T_{m1} (°C)		T_{m2} (°C)		ΔH_m (J g^{-1})		X_c (%)	
molar ratio	Catalyst[a]	1st run	2nd run	2nd run	1st run	2nd run	1st run	2nd run	1st run	2nd run	1st run	2nd run
100/0	Sn oct	–	57	107	176	178	–	–	60.2	58.0	64.3	61.9
100/1		47	49	104	158	158	150(sh)	145	55.2	52.5	58.9	56.0
70/1		42	47	98	151	152	–	138	47.8	44.2	51.0	47.2
40/1		40	45	102	138	140	–	128	30.0	27.7	32.0	29.6
20/1		42	44	92	131	127	112(sh)	–	15.5	12.0	16.5	12.8
10/1		15	18	–	–	–	–	–	–	–	–	–
3/1		-10	-13	–	–	–	–	–	–	–	–	–
100/0	TPhT	–	58	104	177	176	–	–	58.7	56.2	62.7	60.0
100/1		–	55	100	170	172	–	–	52.3	49.3	55.8	52.6
70/1		–	51	101	164	165	–	–	44.7	41.0	47.7	43.8
40/1		40	42	–	128	130	–	121	24.8	20.6	26.5	22.0
20/1		–	37	–	120	122	–	–	12.2	9.1	13.0	9.7
10/1		14	17	–	–	–	–	–	–	–	–	–
3/1		-13	-15	–	–	–	–	–	–	–	–	–

[a] See *Table 1*

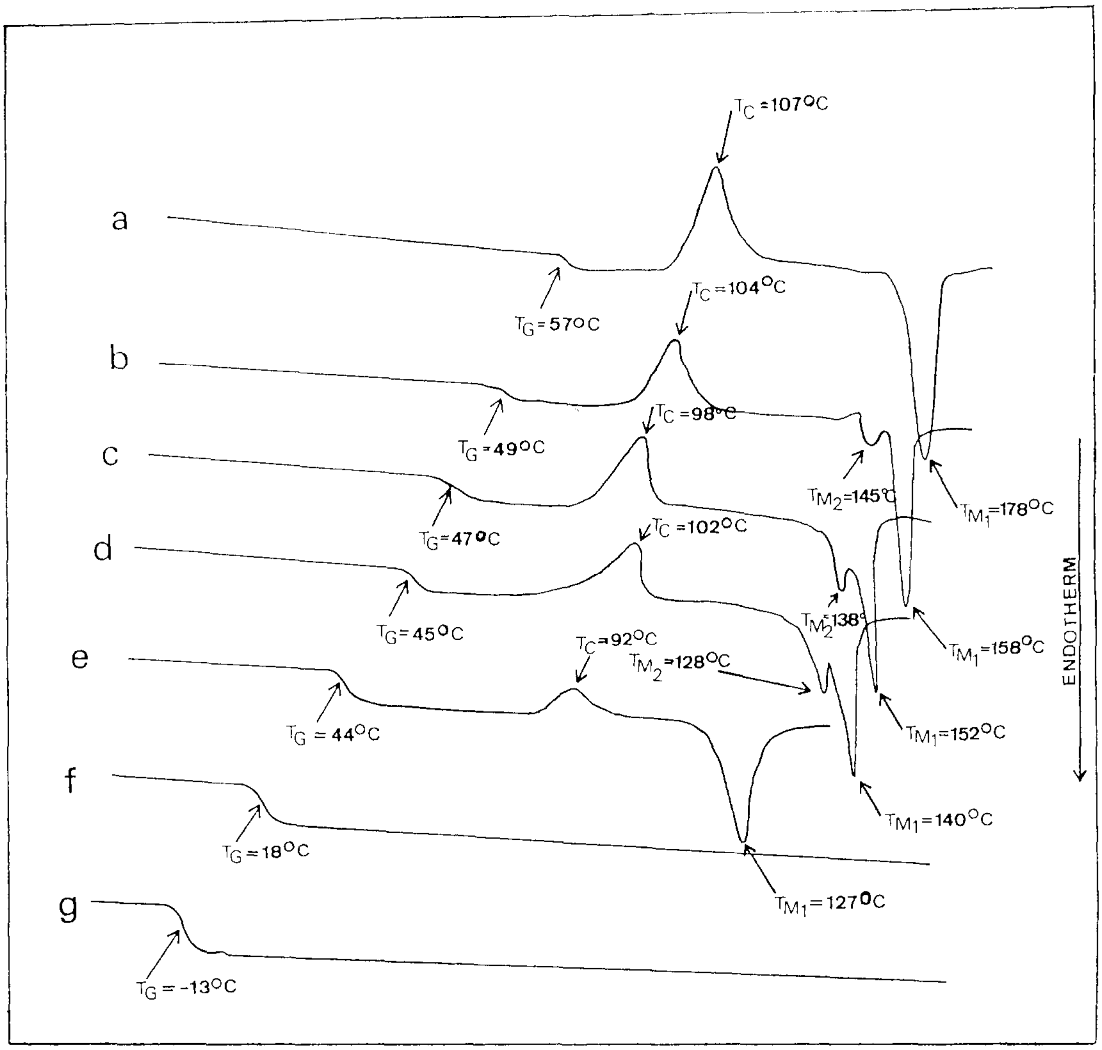

Figure 7 Second-run d.s.c. curves of LLA/GL polyesters synthesized using Sn oct (mol/mol): (a) PLLA, (b) LLA/GL (100/1), (c) LLA/GL (70/1), (d) LLA/GL (40/1), (e) LLA/GL (20/1), (f) LLA/GL (10/1) and (g) LLA/GL (3/1)

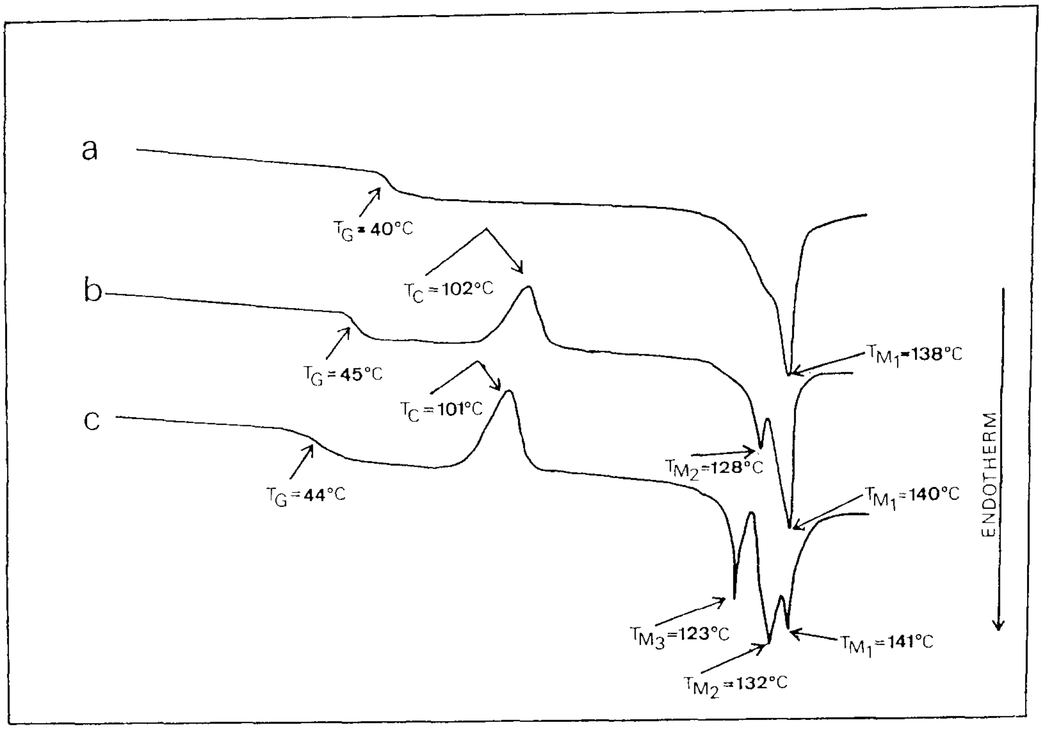

Figure 8 D.s.c. curves of LLA/GL (40/1, mol/mol) polyesters synthesized using Sn oct: (a) first run, (b) second run and (c) third run

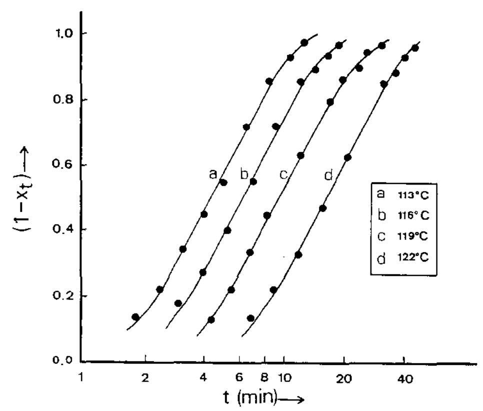

Figure 9 Non-crystallized part $(1 - x_t)$ *versus* crystallization time according to equation (5) for the isothermal crystallization of LLA/GL (20/1) (mol/mol) at various crystallization temperatures

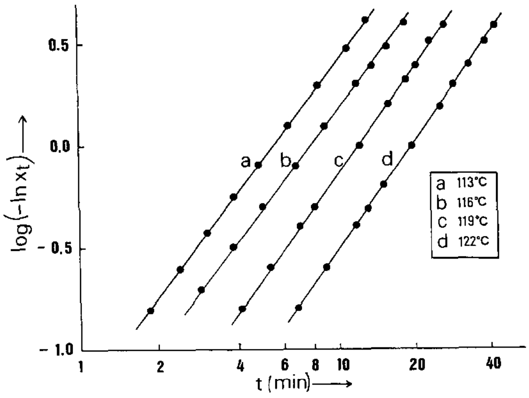

Figure 10 Plot of $\log(-\ln x_t)$ *versus* $\log t$ according to equation (6) for the isothermal crystallization of LLA/GL 20/1 (mol/mol) at various crystallization temperatures

Table 4 Kinetic parameters of isothermal crystallization, obtained by d.s.c. measurements for the LLA/GL polyesters

Polyester: LLA/GL molar ratio	T_c (°C)	ΔT (°C) (T_m, T_c)	$t_{1/2}$ (min)	n	k (min^{-1})	R^a (%)
	113	18	4.3	2.2	2.7×10^{-2}	9.8
(20/1)	116	15	6.5	1.8	2.9×10^{-2}	7.1
T_{ml} = 131°C	119	12	10.1	1.9	1.0×10^{-2}	4.8
	122	9	16.5	1.8	8.9×10^{-3}	2.8
	140	18	3.5	3.2	1.8×10^{-2}	24.8
(100/1)	143	15	5.0	3.3	3.9×10^{-3}	18.9
T_{ml} = 158°C	146	12	7.0	3.2	1.2×10^{-3}	12.7
	149	9	10.2	3.3	5.3×10^{-4}	9.5
	158	18	2.5	3.3	3.0×10^{-2}	38.3
(100/0)	161	15	2.8	3.2	2.1×10^{-2}	29.2
T_{ml} = 176°C	164	12	3.5	3.4	9.1×10^{-3}	25.9
	167	9	5.3	3.3	2.8×10^{-3}	18.3

[a] *R* is the crystallization rate

PLLA and LLA/GL 100/1 down to $n = 1.9$ for LLA/GL 20/1 (mol/mol). This drop indicates the occurrence of a change in the nucleation mechanism of LLA/GL polyesters at high GL contents.

Table 5 Initial decomposition ($T_{d,0}$) and half decomposition temperatures ($T_{d,1/2}$) of the LLA/GL polyesters determined from t.g.a. measurements

Monomers: LLA/GL molar ratio	Catalyst^a	T.g.a $T_{d,0}$ (°C)	T.g.a $T_{d,1/2}$ (°C)
100/0	Sn oct	241.1	300.5
100/1		238.9	304.7
70/1		233.4	306.9
40/1		228.0	310.2
20/1		221.3	311.8
10/1		215.0	313.0
3/1		204.8	315.7
100/0	TPhT	243.0	298.7
100/1		238.5	301.6
70/1		235.1	309.8
40/1		227.4	315.7
20/1		219.1	318.6
10/1		213.4	320.3
3/1		204.5	319.8

[a] See *Table 1*

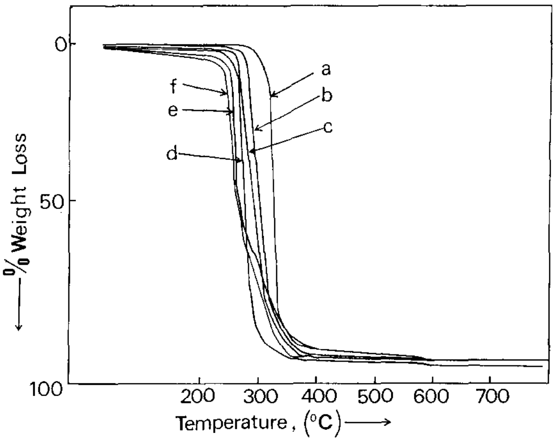

Figure 11 Some representative t.g.a. traces of the series of LLA/GL polyesters synthesized using TPhT (mol/mol): (a) PLLA, (b) LLA/GL (100/1), (c) LLA/GL (70/1), (d) LLA/GL (40/1), (e) LLA/GL (20/1) and (f) LLA/GL (6/1)

The t.g.a. measurements of the polyesters (*Table 5, Figure 11*) are expressed in terms of 'initial' ($T_{d,0}$) and 'half' decomposition ($T_{d,1/2}$) temperature[44]. $T_{d,0}$ is defined as the inclination point of the weight loss *versus* temperature curve and $T_{d,1/2}$ as the temperature at which the loss of weight of a polymer during pyrolysis reaches 50% of its final value. Although, the $T_{d,0}$ decreased on increasing the ratio of GL, the $T_{d,1/2}$ did not follow exactly the same tendency. In fact, the GL-rich polyesters showed a degradation pattern consisting of two stages as shown in *Figure 11e*. A similar decomposition pattern was also reported in a previous publication on annealed nylon-6,6 samples[45]. This 'two-stage' decomposition pattern was previously attributed to post-condensation/crosslinking reactions mainly induced by the presence of –OH (either GL or chain ends of LLA)[46].

The biodegradability of these novel polyesters was assessed in terms of their susceptibility to enzymatic hydrolysis. *Table 6* gives the *TOC* (total organic carbon, soluble products) results for the two series of polyesters after the samples were exposed to hydrolysis for 24 and 72 h, respectively.

Table 6 Results of enzymatic hydrolysis with lipase (*Rhizopus arrhizus*) in phosphate buffer (25 mg of polyester in 2 ml of buffer KH_2PO_4/Na_2HPO_4,pH 7.0) of LLA/GL copolyesters expressed in *TOC* (ppm)

Monomers: LLA/GL molar ratio	Catalyst[a]	*TOC* (ppm) 1 day	3 days
100/0	Sn oct	3	7
100/1		20	30
70/1		50	50
40/1		70	90
20/1		90	130
10/1		120	170
3/1		140	180
100/0	TPhT	2	5
100/1		30	40
70/1		60	80
40/1		75	100
20/1		100	150
10/1		130	175
3/1		155	210

[a] See *Table 1*

Table 7 Alkali hydrolysis (10% NaOH w/v, 80°C) of LLA/GL polyesters: percentage weight loss (wt %) against hydrolysis time. The results give the average of three measurements

Monomers: LLA/GL molar ratio	Catalyst[a]	Weight loss (%) 2 h	5 h	10 h	20 h	40 h
100/0	Sn oct	1.2	2.6	4.4	7.9	13.0
100/1		2.0	3.9	6.3	10.5	19.6
70/1		3.3	5.5	8.0	17.8	33.9
40/1		4.5	6.4	10.7	23.9	45.8
20/1		6.7	10.3	18.8	30.5	56.2
10/1		8.4	13.0	25.4	48.0	63.5
3/1		10.0	19.6	36.2	57.5	78.0
100/0	TPhT	1.0	2.1	4.3	6.9	11.7
100/1		1.8	3.5	7.0	13.2	20.8
70/1		2.7	5.0	8.4	16.1	32.0
40/1		4.3	6.8	13.0	25.4	42.3
20/1		7.0	13.6	20.1	32.8	55.4
10/1		8.1	14.8	21.5	34.0	57.1
3/1		10.5	21.9	40.7	61.8	80.5

[a] See *Table 1*

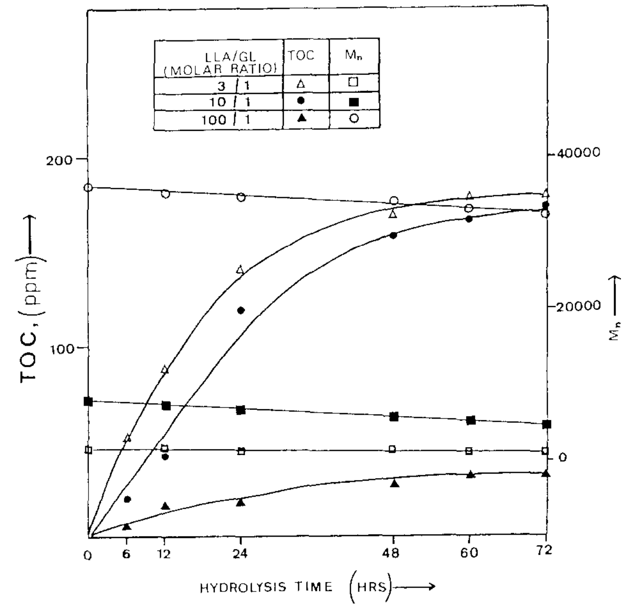

Figure 12 *TOC* and M_n (g.p.c.) values *versus* exposure time to enzymatic hydrolysis for several LLA/GL polyesters synthesized using Sn oct

The degradation rates of polyesters were investigated in terms of change in both *TOC* and M_n (g.p.c.) *versus* their exposure time to lipase (*Rhizopus arrhizus*). *Figure 12* shows typical curves of *TOC* and M_n values of LLA/GL polyester (3/1, 10/1 and 100/1 expressed in mol/mol) against enzymatic hydrolysis time. *TOC* values increase whereas M_n decrease slightly but steadily because of cleavage of hydrolysable bonds. Finally, the n.m.r. spectrum of polyester LLA/GL 3/1 (*Figures 13a* and *13b*) before and after its enzymatic hydrolysis (5 days) showed the appearance of a distinct new peak at 3.4 (–OH, end-group of PLLA) and proportionally stronger peak at 5 ppm (–OH of GL)[47], which confirm the degradation of the polyesters by releasing GL.

Table 7 gives the weight-loss percentages of the LLA/GL polyesters after their alkali hydrolysis (10% NaOH w/v, 80°C) against time. High GL contents resulted in high weight-loss rates similarly to enzymatic hydrolysis. The weight losses of polymers were proportional to their exposure time to alkali hydrolysis. The percentage crystallinities (X_c) and the molecular-weight distributions (M_n, M_w) were investigated with d.s.c. and g.p.c.

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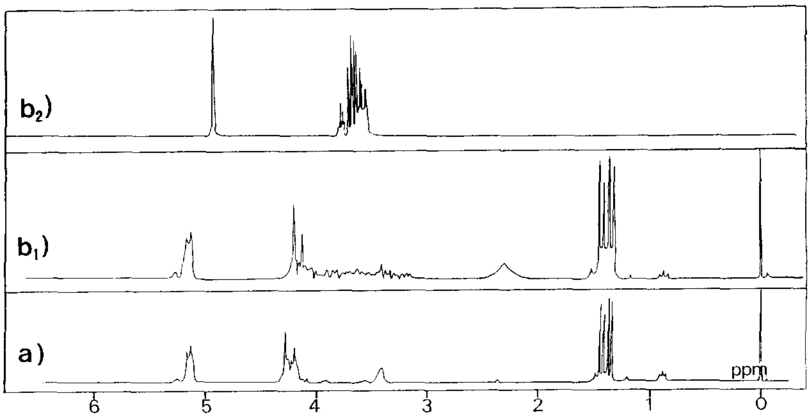


Figure 13 ^1H n.m.r. of LLA/GL 3/1 (mol/mol) polyester before (a) and after (b) exposure for 5 days to enzymatic hydrolysis. (b_1) Soluble in $CHCl_3$ ($CDCl_3$ for n.m.r.) PLLA fraction; (b_2) soluble in H_2O (D_2O for n.m.r.) APD fraction after enzymatic hydrolysis

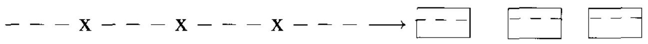
Table 8 Alkali hydrolysis (10% NaOH w/v, 80°C) of LLA/GL polyesters: percentage crystallinities (d.s.c.) and g.p.c. results (M_n, M_w) against their hydrolysis time. The results give the average of three measurements

Monomers: LLA/GL molar ratio	Catalyst[a]	X_c (%) 5 h	X_c (%) 40 h	5 h M_n	5 h M_w	40 h M_n	40 h M_w
100/0	Sn oct	61.6	59.2	4.1×10^4	8.3×10^4	4.0×10^4	8.5×10^4
100/1		55.0	48.6	1.2×10^4	2.1×10^4	0.9×10^4	2.0×10^4
70/1		47.1	39.0	1.1×10^4	2.3×10^4	0.9×10^4	2.2×10^4
40/1		26.3	17.1	8.6×10^3	1.5×10^4	7.2×10^3	1.3×10^4
20/1		11.0	5.2	6.8×10^3	1.0×10^4	5.3×10^3	1.1×10^4
10/1		–	–	4.9×10^3	6.7×10^3	3.8×10^3	6.5×10^4
3/1		–	–	1.3×10^3	1.6×10^3	1.0×10^3	1.8×10^4
100/0	TPhT	61.0	58.9	4.7×10^4	1.8×10^5	4.6×10^4	1.7×10^5
100/1		52.1	46.8	4.2×10^4	2.3×10^5	4.0×10^4	2.4×10^5
70/1		39.7	30.4	1.5×10^4	2.4×10^5	1.2×10^4	2.5×10^4
40/1		20.6	13.2	1.2×10^4	1.6×10^4	1.0×10^4	1.8×10^4
20/1		8.3	3.5	3.6×10^3	6.0×10^3	2.5×10^3	7.2×10^3
10/1		–	–	4.1×10^3	5.6×10^3	2.6×10^3	6.4×10^3
3/1		–	–	2.0×10^3	2.9×10^3	1.3×10^3	3.2×10^3

[a] See *Table 1*

measurements, before and after the hydrolysis of polyesters (*Table 8*).

An increase in X_c of polymers against time of alkali hydrolysis shows that, at least at an early stage, the amorphous regions of the LLA/GL are more susceptible to hydrolysis and thus their gradual removal by degradation results in higher X_c values. The g.p.c. measurements indicated slightly lower M_n and M_w after 5 h whereas this decrease was accentuated (reaching as low as 40–50% of the initial values) after 40 h. Since the degradation does not occur only at the surface but through the entire mass of the LLA/GL polymer, in view of its impregnation by alkali solution, it could be described as 'homogeneous'. Despite the presence of GL, which theoretically could act as a crosslinking agent (solubility experiments with $CHCl_3$ did not confirm any crosslinking), it is only fair to suggest that the degradation mechanistic scheme is promoted by the cleavage of labile bonds along the polymer backbone, thus resulting in even lower weights and eventually water-soluble products as follows:



where x stands for the labile backbone bonds. Bearing in mind that an increase in GL content of the LLA/GL copolymers promoted higher degradation rates, the x parts should probably be the bonds between LA–GL units as shown in *Figure 1*.

CONCLUSIONS

Two novel series of biodegradable star-shaped polyesters were synthesized based on LLA/GL and using TPhT and Sn oct as catalysts, respectively. G.p.c. and d.s.c. usually showed bimodal curves for the TPhT and monodisperse for the Sn oct initiated polymers. The susceptibility of polyesters to biodegradation was tested by means of enzymatic hydrolyis (*TOC* measurements) *versus* their exposure time. High GL content and low percentage crystallinity (d.s.c.) promoted polyester degradation substantially. Alkali hydrolysis tests also showed substantial weight losses and resulted in lower molecular weights (g.p.c.) for the GL-rich polyesters.

REFERENCES

1 Lenz, R. W. in 'Biopolymers I' (Eds N. A. Peppas and R. S. Langer), Advances in Polymer Science, Vol. 107, Springer-Verlag, Berlin, 1993, pp. 1–41
2 Nishida, H. and Tokiwa, Y. *J. Appl. Polym. Sci.* 1992, **46,** 1467
3 Nishida, H. and Tokiwa, Y. *Envir. Polym. Degrad.* 1993, **1,** 65
4 Nishida, H. and Tokiwa, Y. *Envir. Polym. Degrad.* 1993, **1,** 227
5 Nishida, H. and Tokiwa, Y. *Kobunshi Ronbunshu* 1993, **50,** 739
6 Komatsu, S. and Tokiwa, Y. *Kobunshi Ronbunshu* 1993, **50,** 785
7 Iwamoto, A. and Tokiwa, Y. *Kobunshi Ronbunshu* 1993, **50,** 789
8 Reeve, M. S., McCarthy, S. P., Downey, M. J. and Gross, R. A. *Macromolecules* 1994, **27,** 825
9 Nakamura, T., Hitomi, S., Watanabe, S., Shimizu, Y., Jamshidi, K., Hyon, S. H. and Ikada, Y. *J. Biomed. Mater. Res.* 1989, **23,** 1115
10 Gogolewski, S., Jovanovic, M., Perren, S. M., Dillon, J. G. and Hughes, M. K. *J. Biomed. Mater Res.* 1993, **27,** 1135
11 Verheyen, C. C. P. M., de Wijn, J. R., van Blitterswijk, C. A. and de Groot, K. *J. Biomed. Mater Res.* 1993, **27,** 433
12 Jedlinski, Z. *J. Mater. Sci.–Pure Appl. Chem. (A)* 1993, **30**(9&10), 689
13 Mikos, A. G., Bao, Y., Cima, L. G., Ingber, D. E., Vacanti, J. P. and Langer, R. *J. Biomed. Mater. Res.* 1993, **27,** 183
14 Kricheldorf, H. R., Berl, M. and Scharnagl, N. *Macromolecules* 1988, **21,** 286
15 Vanhoorne, P., Dubois, Ph., Jerome, R. and Teyssie, Ph. *Macromolecules* 1992, **25,** 37
16 Zhang, X., Wyss, U. P., Pichora, D. and Goosen, M. F.A. *J. Mater. Sci.–Pure Appl. Chem. (A)* 1993, **30**(12), 933
17 Bero, M., Adamus, G., Kasperczyk, J. and Janeczek, H. *Polym. Bull.* 1993, **31,** 9
18 Kobayashi, H., Hyon, S.-H. and Ikada, Y. *J. Biomed. Mater. Res.* 1991, **25,** 1481
19 Cerrai, P. and Tricoli, M. *Makromol. Chem., Rapid Commun.* 1993, **14,** 529
20 Hu, D. S.-G. and Liu, H.-J. *Polym. Bull.* 1993, **30,** 669
21 Hu, D. S.-G., Liu, H.-G. and Pan, I.-L. *J. Appl. Polym. Sci.* 1993, **50,** 1391
22 Leenslag, J. W., Gogolewski, S. and Pennings, A. J. *J. Appl. Polym. Sci.* 1984, **29,** 2829
23 Getter, L. and Cutright, D. E. *J. Oral Surg.* 1972, **30,** 344
24 Hofmann, G. S. *Clin. Mater.* 1992, **10,** 75
25 Pitt, C. G. *Int. J. Pharmacol.* 1990, **59,** 173
26 Kim, S. H., Han, Y.-K., Ahn, K.-D., Kim, Y. H. and Chang, T. *Makromol. Chem.* 1993, **194,** 3229

27 Kim, S. H., Han, Y.-K., Kim, Y.-H. and Hong, S. I. *Makromol. Chem.* 1992, **193**, 1623

28 Grijpma, D. W., Joziasse, C. A. P. and Pennings, A. J. *Makromol. Chem., Rapid Commun.* 1993, **14**, 155

29 Gorda, K. R. and Peiffer, D. G. *J. Appl. Polym. Sci.* 1993, **50**, 1977

30 Grijpma, D. W. and Pennings, A. J. *Macromol. Chem. Phys.* 1994, **195**, 1633

31 Grijpma, D. W. and Pennings, A. J. *Macromol. Chem. Phys.* 1994, **195**, 1649

32 Aragade, A. B. and Peppas, N. A. *Polym. Bull.* 1993, **31**, 401

33 Zhu, K. J., Bihai, S. and Shilin, Y. *J. Polym. Sci., Polym. Chem. Ed.* 1982, **20**, 319

34 Gilding, D. K. and Reed, A. M. *Polymer* 1979, **20**, 1459

35 Kricheldorf, H. R. and Sumbel, M. *Eur. Polym. J.* 1989, **25**, 585

36 Schindler, A., Hibionada, Y. M. and Pitt, C. G. *J. Polym. Sci., Polym. Chem. Edn.* 1982, **20**, 319

37 Li, S., Garreau, H. and Vert, M. *J. Mater. Sci.; Mater. Med.* 1990, **1**, 198

38 Li, S., Garreau, H. and Vert, M. *J. Mater. Sci.; Mater. Med.* 1990, **1**, 131

39 Mandelkern, L. 'Crystallization of Polymers', McGraw-Hill, New York, 1964

40 Arvanitoyannis, I. and Kehayoglou, A. H. *Angew. Makromol. Chem.* 1993, **204**, 91

41 Hu, D. S. G. and Liu, H. J. *Macromol. Chem. Phys.* 1994, **195**, 1213

42 Arvanitoyannis, I., Blanshard, J. M. V. and Kolokuris, I. *Polym. Int.* 1992, **27**, 297

43 Parrini, P. and Corrieri, G. *Makromol. Chem.* 1965, **86**, 271

44 van Krevelen, D. W. 'Properties of Polymers', 3rd Edn., Elsevier, Amsterdam, 1990, pp. 641–653

45 Mitomo, H. *Sen-i Gakkaishi* 1989, **45**, 84

46 Arvanitoyannis, I., Psomiadou, E., Yamamoto, N., Nikolaou, E. and Blanshard, J. M. V. *Polymer* 1995, **36**, 2945

47 'The Aldrich Library of ^{13}C and ^{1}H FT NMR spectra' (Eds C. J. Pouchert and J. Behnke), Edn. 1, Aldrich Company, 1993, Vol. 1, p. 283