BUTTERWORTH HEINEMANN

Polymer Vol. 36 No. 4, pp. 857–866, 1995

0032-3861/95/$10.00 + 0.00

Synthesis and study of novel biodegradable oligo(ester amide)s based on sebacic acid, octadecanedioic acid, 1,6-hexanediamine and ε-caprolactone: 2

Ioannis Arvanitoyannis*, Atsuyoshi Nakayama, Norioki Kawasaki and Noboru Yamamoto

Osaka National Research Institute, AIST, Organic Materials Department, Functional Polymer Section, 1-8-31 Midorigaoka, Ikeda, 563 Osaka, Japan
(Received 15 April 1994; revised 10 June 1994)

Two series of novel oligo(ester amide)s based on sebacic acid/1,6-hexanediamine/ε-caprolactone and octadecanedioic acid/1,6-hexanediamine/ε-caprolactone were synthesized. The determination of the molecular weights with both gel permeation chromatography and ^1H nuclear magnetic resonance (n.m.r.) showed that they vary from 1000 to 6000. Differential scanning calorimetry and thermogravimetric analysis were employed for determining glass transitions, melting points, heats of melting and decomposition temperatures of the oligo(ester amide)s. Fourier-transform infra-red and ^1H–^{13}C n.m.r. spectra were taken to confirm the composition of the novel oligo(ester amide)s. The test of enzymatic hydrolysis was employed to assess the potential biodegradability of these oligomers.

(Keywords: biodegradable oligomers; oligo(ester amide)s; synthesis)

INTRODUCTION

Degradation of components made from polymeric materials occurs in a wide variety of environments and service conditions and occasionally limits the service lifetime[1]. The biodegradation of synthetic polymers is of considerable interest to environmentalists and industrialists, as well as academic researchers[2]. Although several series of aliphatic polyesters based on L-lactide[3–8], glycolic acid[9,10], L-lactic acid[11,12], ε-caprolactone[13–22], β-methyl-δ-valerolactone[23] and their copolymers[24–31] have often been successful in biomedical applications[30–33] such as drug release, implants, bone fixation and bioabsorbable sutures, they still lack certain optimum properties, i.e. mechanical, thermal and processing[3]. On the other hand, synthetic poly(amino acid)s and polyamides, though regarded as the analogues of protein and natural peptides, have not yet found the extent of expected applications, mainly because of preparation difficulties[34,35]. Therefore the aliphatic copoly(ester amide)s have been suggested, and only recently investigated to a limited extent, as a potential family of polymers endowed with optimum mechanical and thermal properties, processability and susceptibility to degradation[36–48]. In the first paper of this series the synthesis and some properties of biodegradable oligo(ester amide)s based on nylon-6,6 and ε-caprolactone were reported[49]. The aim of this paper is to investigate the synthesis and properties of two novel series of biodegradable oligo(ester amide)s based on sebacic acid (SA), octadecanedioic acid (ODA), 1,6-hexanediamine (1,6-HD) and ε-caprolactone (ε-CL), which could find applications either in reactive blending with polymers or as comonomer units (prepolymers) for synthesizing 'tailor-made' polymers.

*To whom correspondence should be addressed

EXPERIMENTAL PROCEDURES

Synthesis of oligomers from 1,6-hexanediamine, octadecanedioic acid, sebacic acid and ε-caprolactone

The reagents 1,6-HD (twice distilled), ODA and SA (recrystallized from acetone and ethyl acetate) and ε-CL (distilled under reduced pressure) were added to the polymerization apparatus consisting of two tubes, the polymerization tube and a three-necked tube (adapted at the top of the former) used for feeding the monomers, as inlet of nitrogen and for connecting a condenser in order to avoid loss of the volatile components (i.e. 1,6-HD and ε-CL) at an early stage. The molar ratio of 1,6-HD to SA or ODA was 1:1 and a 1% surplus of 1,6-HD was added to make up for losses due to the volatility of 1,6-HD. Initially the temperature was kept at 120°C for 2 h and then was increased to 180°C for 2 h and finally for 30 min to 250°C. At this stage vacuum was applied in order to remove the water formed during the condensation reaction or any residual volatile components such as monomers or oligomers. The final product, the texture of which varied from hard and tough to soft and weak depending on the molar composition of comonomer units (amide- and ester-rich), was dissolved/extracted with $CHCl_3$ and/or CH_3OH and finally precipitated with diethyl ether.

Thermal analysis

The thermal behaviour of the oligo(ester amide)s was studied by using a differential scanning calorimeter (DSC-10A Rigaku, Thermoflex) connected with a chart recorder (Rigaku) and a temperature controller 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 for both melting point T_m and heat of melting ΔH_m (for indium, T_m = 156.7°C and ΔH_m = 28.36 J g^{-1}). The glass transition temperature (T_g) was determined as the middle of the recorded step change in heat capacity and the melting point (T_m) was defined as the maximum of the endothermic peak.

Thermogravimetric analysis

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

FT*i.r. spectroscopy*

The *FT*i.r. spectra were recorded with a spectrometer (Nicolet, model 710 FT-IR) connected with a PC computer (Nicolet) and a colour pro plotter (Fujitsu, model FPG 315-101). The amide-rich samples were recorded as KBr discs (1% w/w polymer/KBr) whereas the ester-rich were recorded as films since they were soluble in $CHCl_3$.

Nuclear magnetic resonance spectroscopy

^1H 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°, acquisition time 3.276 s, pulse interval time 1.00 s. The ^1H–^{13}C COSY (correlation spectroscopy) experiments were recorded on a JEOL GX-500 spectrometer with a frequency of 500 MHz for ^1H and 125 MHz for ^{13}C and employed a recycle time of 1.5 s. A total of 256 spectra, each consisting of 512 data points, were accumulated. The frequency range for ^1H and ^{13}C was 4.5 and 26.25 kHz, respectively. In this work, a sine bell window function was employed in the Fourier transform of 2d n.m.r. data matrices in order to suppress peak broadening.

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 TSK gel G3000 HXL with limited exclusion molecular weight 4×10^5. The eluent was $CHCl_3$ (ester-rich) or hexafluoroisopropanol (amide-rich) and the flow rate was 0.6 ml min^{-1}.

Enzymatic hydrolysis[50]

First, 25 mg of oligo(ester amide) samples and 2 ml of phosphate buffer (KH_2PO_4/NaH_2PO_4, pH = 7.00) were added to each of three tubes. Then, 200 units of enzyme were added to two tubes and the third was for a blank test. The enzyme used was lipase from *Rhizopus arrhizus*. The enzymatic hydrolysis was carried out at 37°C for 42 h. After filtration (0.2 mm 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 with the blank levels.

Enzymatic hydrolysis for studying the degradation products

First, 100 mg of oligo(ester amide) sample and 2 ml of phosphate buffer (KH_2PO_4/NaH_2PO_4, pH = 7.00) were added to each of three tubes. Then, 2000 units of enzyme were added to two tubes and the third was for a blank test. The enzyme used was 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 extracted with $CHCl_3$ and dried with Na_2SO_4 in order to remove residual moisture from the phosphate buffer. After filtration for removing Na_2SO_4 the chloroform was evaporated and the remaining sample was used for n.m.r. and g.p.c. measurements.

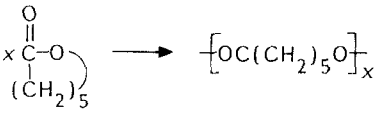
Alkali hydrolysis (10% NaOH w/v, 80°C)—weight-loss experiments

In view of the friability of our oligomers and their inadequate strength, no films could be formed. Therefore, bars of the following 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 our samples were followed by weighing them every day. Our results give the average of three measurements.

RESULTS AND DISCUSSION

The yields of oligomer syntheses after extraction with CH_3OH and $CHCl_3$ (for removing oligomers and/or residual monomers) are given in *Tables 1* and *2*. The oligomer yields *versus* the comonomer feed ratio show eutectic curves within the minima at 60 and 50% ε-CL content for the oligo(ester amide)s based on SA/1,6-HD/ε-CL and ODA/1,6-HD/ε-CL, respectively. These minima could probably be attributed to the fact that at such intermediate compositions the antagonizing effect of the two incompatible structures, that is orthorhombic[51] and triclinic[51] for P(ε-CL) and nylon-6,18 or nylon-6,10, respectively, is much more intense than at compositions where one of the two comonomer units prevails over the other.

The mechanism of terpolymerizations SA/1,6-HD/ε-CL and ODA/1,6-HD/ε-CL is thought to proceed according to the following general scheme:



(1)

$$\text{–[OC(CH}_2\text{)}_5\text{O]}_x\text{–} + \text{HOOC(CH}_2\text{)}_4\text{COOH} \rightarrow \text{HOOC(CH}_2\text{)}_4\text{CO–[O(CH}_2\text{)}_5\text{CO]}_x\text{–} \quad (2)$$

$$\text{HOOC(CH}_2\text{)}_4\text{CO–[O(CH}_2\text{)}_5\text{CO]}_x\text{–} + \text{H}_2\text{N(CH}_2\text{)}_6\text{NH}_2 \rightarrow \text{H}_2\text{N(CH}_2\text{)}_6\text{NH–OC(CH}_2\text{)}_4\text{OC–[O(CH}_2\text{)}_5\text{CO]}_x\text{–} \quad (3)$$

However, in view of the high temperature at which the polymerization is carried out, it is also possible that 1,6-hexanediamine reacts first with the diacid (SA or ODA), thus forming the salt via reaction (4), and then

Table 1 Sebacic acid/1,6-hexanediamine/ε-caprolactone (SA/1,6-HD/ε-CL) oligomers: percentage yields, molecular-weight determination (g.p.c. and n.m.r.) and *TOC* results

Monomer feed ratio (mol%)			Yield (%) after extraction with solvent	G.p.c.		N.m.r.	
SA	1,6-HD	ε-CL		M_n	M_w	M_n	*TOC* (ppm)
50.00	50.00	0.00	96	6.1×10^3	14.5×10^3		0
43.75	43.75	12.50	96	2.8×10^3	4.7×10^3		0
40.00	40.00	20.00	89	2.3×10^3	3.3×10^3		25
33.30	33.30	33.30	85	2.2×10^3	3.1×10^3		60
25.00	25.00	50.00	82	2.0×10^3	3.0×10^3		300
20.00	20.00	60.00	75	1.5×10^3	3.2×10^3	1100	1300
16.66	16.66	66.68	84	1.7×10^3	3.6×10^3	1900	1700
14.29	14.29	71.42	89	2.2×10^3	4.8×10^3	2000	1900
12.50	12.50	75.00	88	2.5×10^3	5.3×10^3	2500	2200
10.00	10.00	80.00	95	2.6×10^3	5.0×10^3	2600	2300

Table 2 Octadecanedioic acid/1,6-hexanediamine/ε-caprolactone (ODA/1,6-HD/ε-CL) oligomers: percentage yields, molecular-weight determination (g.p.c. and n.m.r.) and *TOC* results

Monomer feed ratio (mol%)			Yield (%) after extraction with solvent	G.p.c.		N.m.r.	
ODA	1,6-HD	ε-CL		M_n	M_w	M_n	*TOC* (ppm)
50.00	50.00	0.00	97	3.3×10^3	7.5×10^3		0
43.75	43.75	12.50	84	1.1×10^3	2.7×10^3		8
40.00	40.00	20.00	77	1.0×10^3	2.5×10^3		40
33.30	33.30	33.30	71	1.2×10^3	2.2×10^3		90
25.00	25.00	50.00	60	1.5×10^3	3.5×10^3		400
20.00	20.00	60.00	66	4.3×10^3	7.6×10^3	2140	1250
16.66	16.66	66.68	73	3.0×10^3	6.4×10^3	2950	2100
14.29	14.29	71.42	79	4.4×10^3	8.6×10^3	2720	2400
12.50	12.50	75.00	82	3.2×10^3	6.9×10^3	3050	2800
10.00	10.00	80.00	84	3.0×10^3	6.7×10^3	3270	2800

Table 3 Comparison of comonomer compositions in four representative oligomers

Polymer	Molar feed ratio	Determined with n.m.r.
SA/1,6-HL/ε-CL[a]	12.5/12.5/75.0	12.5/12.5/75.0
SA/1,6-HD/ε-CL	14.3/14.3/71.4	16.25/16.25/67.5
SA/1,6-HD/ε-CL	20.0/20.0/60.0	21.4/21.4/57.2
ODA/1,6-HD/ε-CL[b]	12.5/12.5/75.0	14.3/14.3/71.4

[a]See *Figure 1*
[b]See *Figure 2*

reacting with ε-caprolactone (ε-CL) via reaction (5):

$$H_2N(CH_2)_6NH_2 + HOOC(CH_2)_4COOH \rightarrow \{HN(CH_2)_6NH\text{–}CO(CH_2)_4CO\} \quad (4)$$

$$\{HN(CH_2)_6NH\text{–}CO(CH_2)_4CO\} + \{OC(CH_2)_5O\}_x \rightarrow \{HN(CH_2)_6NHCO(CH_2)_4CO\text{–}\{O(CH_2)_5CO\}_x\} \quad (5)$$

The comonomer compositions (SA or ODA, 1,6-HD and ε-CL) in several oligomers were determined with n.m.r. and found to be in satisfactory agreement with the initial feed ratios. Four polymers that could be referred to as representative examples are shown in *Table 3*. The assignments of ^1H n.m.r. spectra of SA/1,6-HD/ε-CL (12.5/12.5/75.0, molar ratio) and ODA/1,6-HD/ε-CL (12.5/12.5/75.0, molar ratio) oligo(ester amide)s after the examination of all available combinations are as shown in *Figures 1* and *2*.

Two-dimensional (2d) n.m.r. was also recorded (^{13}C and ^1H) in order to ensure a more rigorous and detailed assignment in terms of coupling/decoupling among the nuclei as shown in *Figure 3*. A detailed assignment of ^{13}C n.m.r. trace of SA/1,6-HD/ε-CL (12.5/12.5/75.0, molar ratio) is given in *Table 4*. A previous paper by Iyoda *et al.*[52] on P(ε-CL) and SA/ODA in conjunction with the *Aldrich Library of NMR Spectra*[53] were taken into consideration for confirming our assignment.

The assignment of hydroxyl end-groups at 3.6 ppm (^1H) to ε-CL is also supported by similar assignment by *Aldrich Library of NMR Spectra*[53]. At this instance, it should be mentioned that this assignment is also valid for the oligo(ester amide) series of ODA/1,6-HD/ε-CL, since the only difference between the two series is related to the chain length of the aliphatic diacid.

Assuming that x = ε-CL mol%, y = SA mol% and z = 1,6-HD mol% in the oligomer and taking into account the assignment given in *Figure 1*, a system with four equations containing three unknown parameters (x, y, z) is derived as follows:

$$2x = (P_1) + (P_2) \quad (6)$$

$$4z = (P_3) \quad (7)$$

$$2x + 4y = (P_4) + (P_5) \quad (8)$$

$$6x + 12y + 8z = (P_6) \quad (9)$$

where (P_1), (P_2), (P_3), (P_4), (P_5) and (P_6) are the signal intensities. Thus x = 75 mol% ε-CL, y = 12.5 mol% SA,

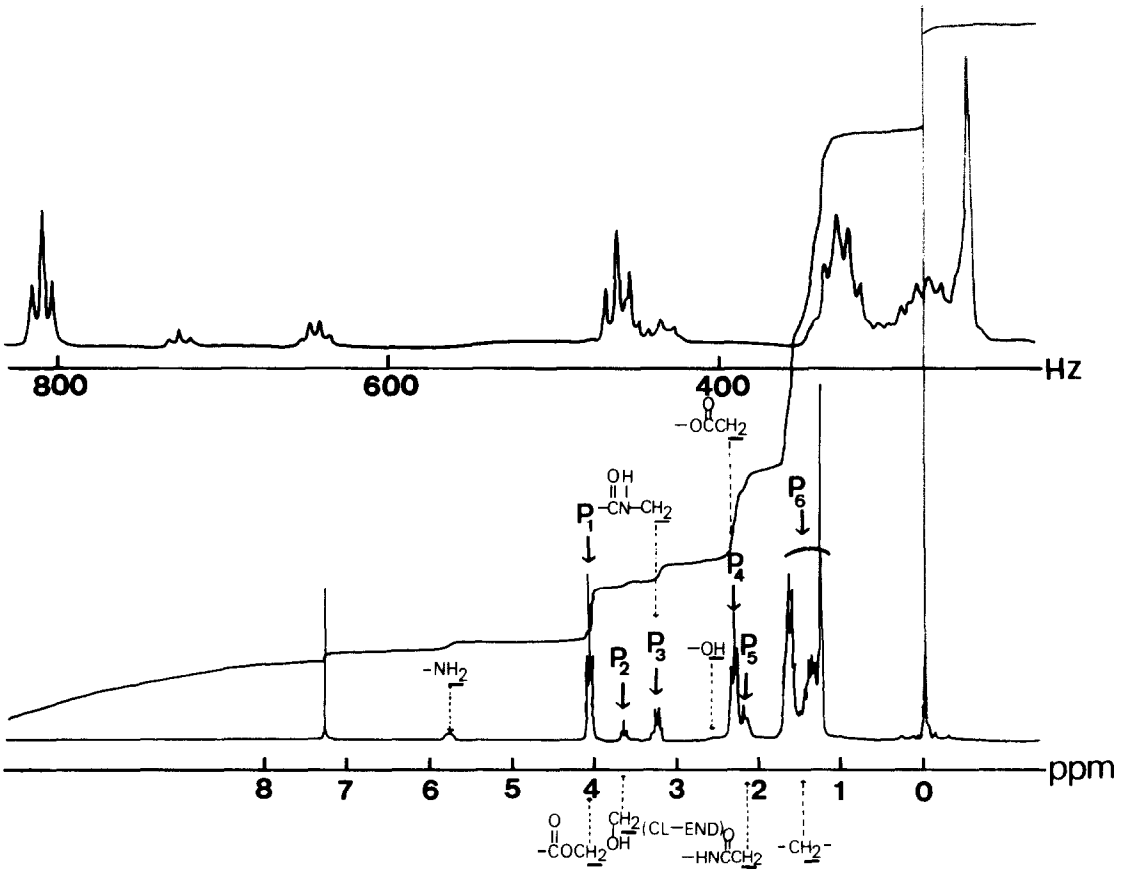


Figure 1 Assignment of ^{1}H n.m.r. trace of oligo(ester amide) SA/1,6-HD/ε-CL (12.5/12.5/75.0 in mol%)

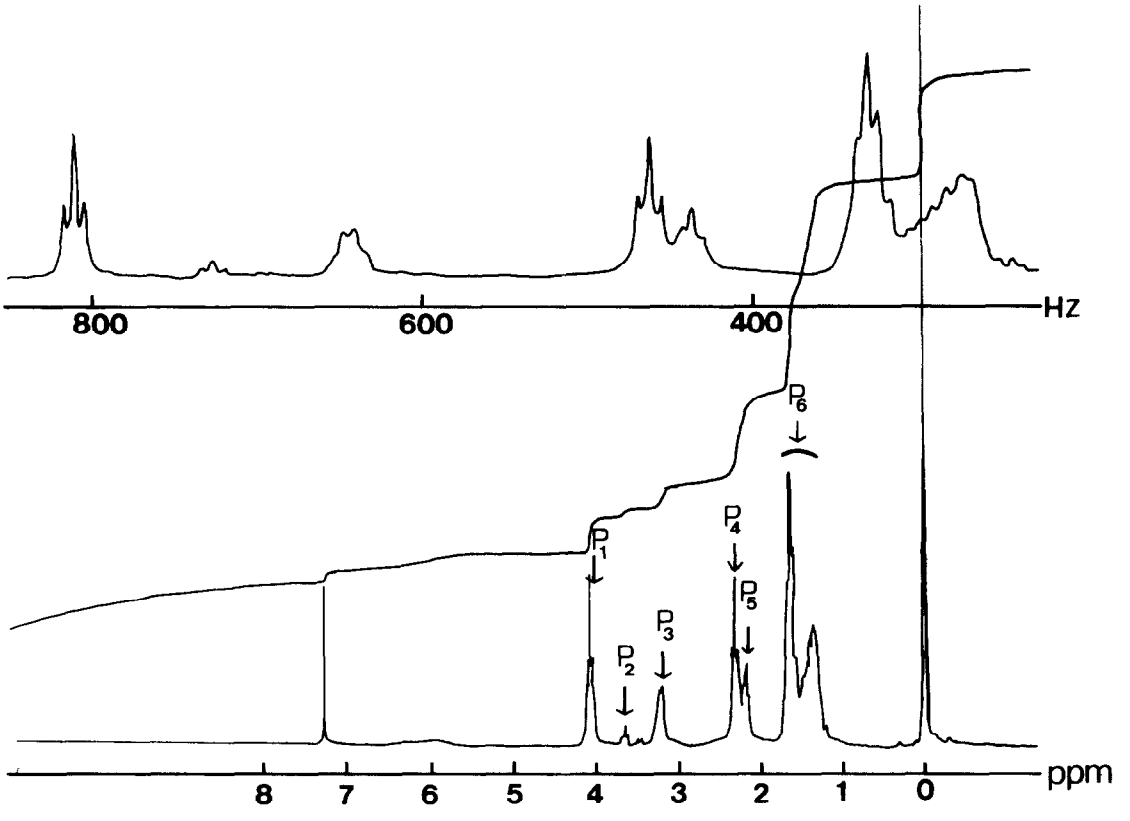


Figure 2 Assignment of ^{1}H n.m.r. trace of oligo(ester amide) ODA/1,6-HD/ε-CL (12.5/12.5/75.0 in mol%)

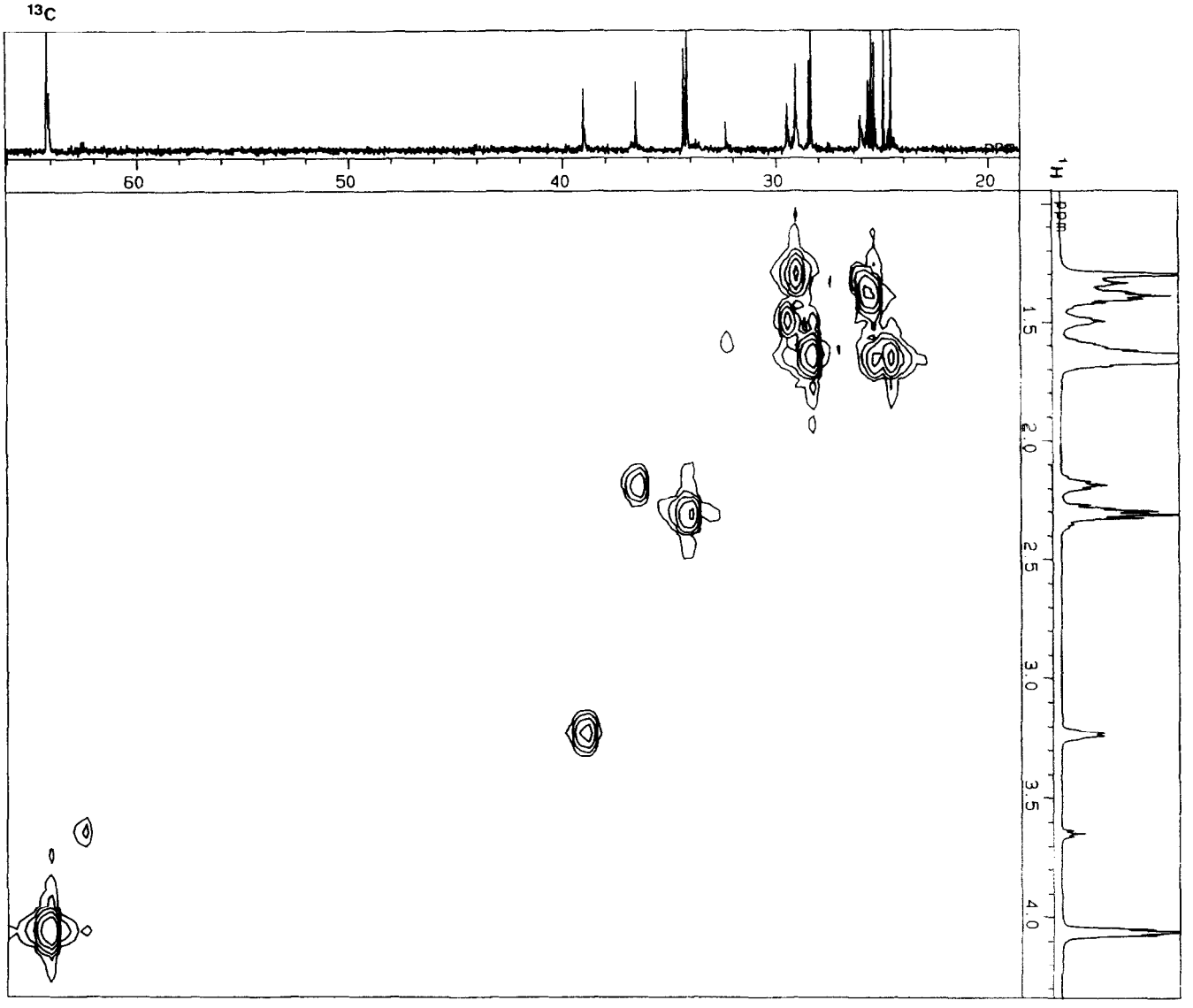


Figure 3 Two-dimensional (2d) n.m.r. spectrum (^1H and ^{13}C) of oligo(ester amide) SA/1,6-HD/ε-CL (12.5/12.5/75.0)

Table 4 Assignment of ^{13}C n.m.r. spectrum of SA/1,6-HD/ε-CL (12.5/12.5/75.0) oligo(ester amide) (see *Figure 3*)

	δ (ppm)										Source
P(ε-CL)	–O–	CH_2	CH_2	CH_2	CH_2	CH_2	C=O				
		64.1	28.4	25.5	24.6	34.1	173.5				Ref. 52
		64.2	28.4	25.5	24.6	34.1	–				Our sample
ε-CL (end-group)	HO–	CH_2	CH_2	CH_2	CH_2	CH_2	C=O				
		62.1	32.1	25.4	24.8	34.2	173.6				Ref. 52
		61.1	32.2	25.2	24.4	34.2	173.9				Ref. 53 (see 1040C)
		60.2	32.3	25.4	24.5	34.2	–				Our sample
(SA)–(ε-CL)	O=C	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	C=O	
ester bond	174.2	34.1	29.2	29.2	24.9	24.9	29.2	29.2	34.1	174.2	Ref. 53 (see 945C)
		34.3	29.5	25.4	24.9	24.9	29.5	29.5	34.3		Our sample
(SA)–(1,6-HD)	O=C	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	C=O	
amide bond	185.7	35.9	30.3	30.3	27.1	27.1	30.3	30.3	35.9	185.7	Ref. 53 (see 1253B)
	–	36.6	32.3	28.4	25.7	25.7	28.4	32.3	36.6	–	Our sample
(SA)–(1,6-HD)	–NH–	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	–NH–			
amide bond		38.8	29.2	26.3	26.3	29.2	38.8				Ref. 53 (see 1231A)
		39.0	29.1	26.0	26.0	29.1	39.0				Our sample

$z = 12.5$ mol% 1,6-HD, or $x' = 6$, $y' = 1$ and $z = 1$ (molar ratio).

Determination of oligomer molecular weight (MW) from n.m.r. can be carried out after the exact contribution of the three comonomer units to the polymer is found:

$$\varepsilon\text{-CL units} \qquad c = x' \frac{(P_1)}{(P_1) + (P_2)} = 6 \frac{34.6}{34.6 + 8.8} = 5$$

Since both SA and 1,6-HD participate in the polymeric structure with only one unit ($a = 1, b = 1$) and $c = 5$ (+2 as terminal groups), there should be a total of seven units having:

$$MW = 1 \times MW_{SA} + 1 \times MW_{1,6\text{-HD}} + 7 \times MW_{\varepsilon\text{-CL}} = 1133$$

which is in satisfactory agreement with the g.p.c. results ($M_n = 1500$).

*FT*i.r. spectroscopy was used for the identification of the oligo(ester amide) structure:

amide A and B	~3310 and 1085 cm^{-1}
amide I	~1640 cm^{-1}
amide II	~1550 cm^{-1}
aliphatic ester groups $\nu_{C=O}$	~1730 cm^{-1}
aliphatic ester groups ν_{C-O}	~1150 cm^{-1}

Their relative intensities varied in the expected way with change in amide/ester comonomer feed ratio for both series of oligomers, which is in agreement with previous publications on several copoly(ester amide)s[38-43,49].

If the g.p.c. values are presented schematically *versus* the composition of the two novel series of oligo(ester amide)s, two eutectic curves are produced with minima at ODA/1,6-HD/ε-CL (33.3/33.3/33.3) and SA/1,6-HD/ε-CL (20/20/60) comonomer feed, respectively. The low molecular weights should be rather attributed as previously[49] to extreme synthesis conditions, which have an adverse effect on the polymerizability of ε-CL[54].

Tables 5 and *6* give synoptically all the determined thermal properties for the two novel series of oligo(ester amide)s. Although the melting points (T_m) *versus* ε-CL content were found to give straight lines, the heats of fusion *versus* ε-CL content show eutectic curves with minimum at 20/20/60 composition for both SA/1,6-HD/ε-CL and ODA/1,6-HD/ε-CL as described in previous publications on poly(octanelactam/dodecanelactam) (POL/PLL) copolymers[55]. The observed substantial difference in the heats of fusion between the ester-rich and the amide-rich copolymers could be attributed to the incompatibility of crystal structures (monoclinic or triclinic for nylons, but orthorhombic for PCL)[49], which results in intermediate (probably modified) crystal structures, in particular, for the copolymers of intermediate compositions[55]. *Figures 4* and *5* show typical d.s.c. curves for the two novel series of oligo(ester amide)s. An increase in ε-CL content resulted in broadening of peaks and in lower T_m and T_g values owing to the higher flexibility of the polymeric chain imparted by the incorporation of ε-CL similarly to AA/1,6-HD/ε-CL copolymers[49] (AA = adipic acid).

The terms 'initial' ($T_{d,0}$) and 'half' ($T_{d,1/2}$) decomposition temperatures are usually employed for characterizing the

Table 5 Sebacic acid/1,6-hexanediamine/ε-caprolactone oligomers: thermal properties from d.s.c. and t.g.a. measurements

Monomer feed ratio (mol%)			D.s.c.[a]					T.g.a.	
SA	1,6-HD	ε-CL	T_g (°C)	^1T_m (°C)	$^2T'_m$ (°C)	$^1\Delta H_m$ (J g^{-1})	$^2\Delta H'_m$ (J g^{-1})	$T_{d,0}$ (°C)	$T_{d,1/2}$ (°C)
50.00	50.00	0.00	48	218	216	100	93	330	481
43.75	43.75	12.50	26	212	211	92	89	328	459
40.00	40.00	20.00	22	202	202	85	80	326	464
33.30	33.30	33.30	16	176	173	72	66	286	445
25.00	25.00	50.00	7	139	135	35	31	283	436
20.00	20.00	60.00	−2	104	98	28	24	281	425
16.66	16.66	66.68	−7	79	75	32	29	278	420
14.29	14.29	71.42	−14	76	80	37	33	280	417
12.50	12.50	75.00	−19	73	77	44	38	262	415
10.00	10.00	80.00	−24	64	70	53	48	259	423

[a]Notation: ^1T_m (°C) and $^1\Delta H_m$ stand for melting point and heat of fusion from first run; $^2T'_m$ and $^2\Delta H'_m$ are values from second run

Table 6 Octadecanedioic acid/1,6-hexanediamine/ε-caprolactone oligomers: thermal properties from d.s.c. and t.g.a. measurements

Monomer feed ratio (mol%)			D.s.c.[a]					T.g.a.	
ODA	1,6-HD	ε-CL	T_g (°C)	^1T_m (°C)	$^2T'_m$ (°C)	$^1\Delta H_m$ (J g^{-1})	$^2\Delta H'_m$ (J g^{-1})	$T_{d,0}$ (°C)	$T_{d,1/2}$ (°C)
50.00	50.00	0.00	36	185	183	95	88	391	477
43.75	43.75	12.50	20	180	180	89	84	343	477
40.00	40.00	20.00	13	178	176	81	79	309	475
33.30	33.30	33.30	9	172	169	68	63	308	473
25.00	25.00	50.00	3	148	132	36	32	295	445
20.00	20.00	60.00	−5	112	107	25	21	293	428
16.66	16.66	66.68	−10	96	94	30	26	274	423
14.29	14.29	71.42	−17	78	75	35	30	261	422
12.50	12.50	75.00	−21	76	73	41	39	248	420
10.00	10.00	80.00	−24	74	74	50	46	231	420

[a]Notation: see footnote to *Table 5*

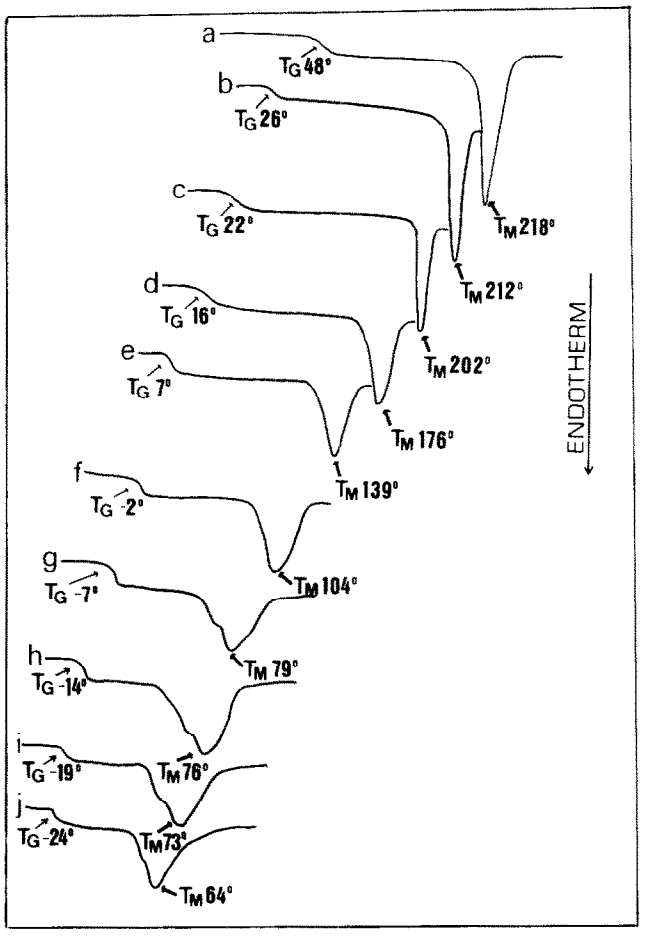


Figure 4 D.s.c. curves of oligo(ester amide) series based on SA/1,6-HD/ε-CL: (a) 50.0/50.0/0.0, (b) 43.75/43.75/12.50, (c) 40.0/40.0/20.0, (d) 33.3/33.3/33.3, (e) 25.0/25.0/50.0, (f) 20.0/20.0/60.0, (g) 16.66/16.66/66.68, (h) 14.3/14.3/71.4, (i) 12.5/12.5/75.0 and (j) 10.0/10.0/80.0 expressed in mol%

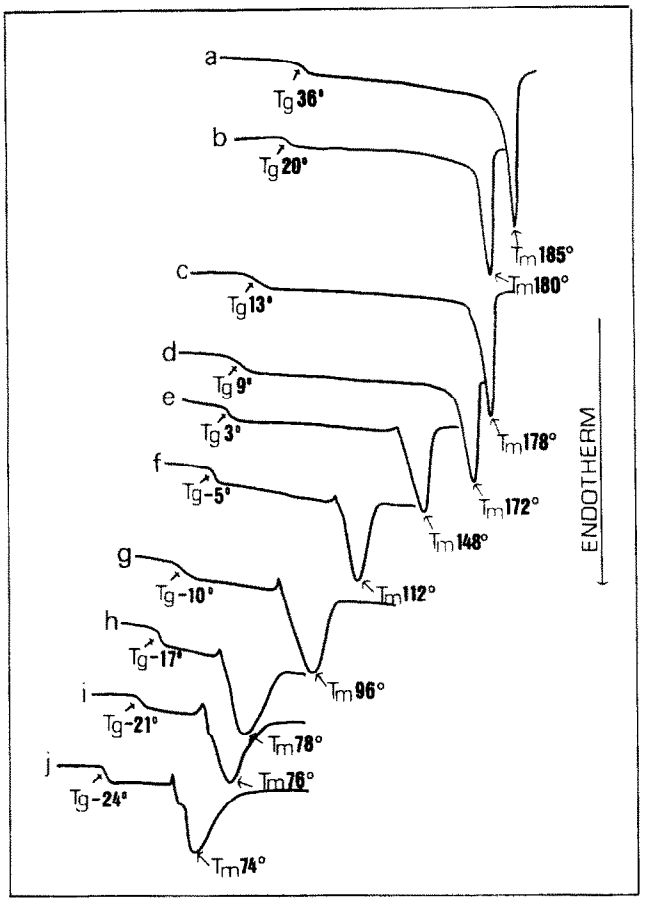


Figure 5 D.s.c. curves of oligo(ester amide) series based on ODA/1,6-HD/ε-CL: (a) 50.0/50.0/0.0, (b) 43.75/43.75/12.50, (c) 40.0/40.0/20.0, (d) 33.3/33.3/33.3, (e) 25.0/25.0/50.0, (f) 20.0/20.0/60.0, (g) 16.66/16.66/66.68, (h) 14.3/14.3/71.4, (i) 12.5/12.5/75.0 and (j) 10.0/10.0/80.0 expressed in mol%

Table 7 Sebacic acid/1,6-hexanediamine/ε-caprolactone oligomers: weight losses and molecular weights (M_n, M_w from g.p.c. measurements) against time of alkali hydrolysis (10% NaOH w/v, 80°C)

Monomer feed ratio (mol%)			Weight loss (wt%)					G.p.c.			
SA	1,6-HD	ε-CL	2 h	5 h	10 h	20 h	40 h	M_n (5 h)	M_w (5 h)	M_n (40 h)	M_w (40 h)
50.00	50.00	0.00	0.0	0.0	0.0	0.0	0.0	6.0×10^3	14.2×10^3	6.2×10^3	14.6×10^3
43.75	43.75	12.50	2.1	2.8	3.5	8.4	18.3	2.1×10^3	3.9×10^3	1.4×10^3	2.5×10^3
40.00	40.00	20.00	2.6	3.4	4.3	10.7	21.5	1.8×10^3	2.8×10^3	1.2×10^3	2.2×10^3
33.30	33.30	33.30	3.0	4.0	5.2	13.0	24.8	1.7×10^3	2.8×10^3	1.0×10^3	2.3×10^3
25.00	25.00	50.00	3.8	4.5	6.5	14.8	27.2	1.5×10^3	2.6×10^3	1.0×10^3	2.0×10^3
20.00	20.00	60.00	5.0	6.2	7.3	16.7	30.0	1.3×10^3	2.4×10^3	0.9×10^3	1.9×10^3
16.66	16.66	66.68	5.4	6.5	7.5	19.5	33.5	1.6×10^3	3.0×10^3	1.1×10^3	2.7×10^3
14.29	14.29	71.42	5.5	6.7	8.0	22.4	36.7	1.9×10^3	4.0×10^3	1.3×10^3	3.0×10^3
12.50	12.50	75.00	6.0	7.1	9.2	24.0	38.9	2.1×10^3	4.8×10^3	1.4×10^3	2.9×10^3
10.00	10.00	80.00	6.7	7.8	10.3	26.3	42.4	2.4×10^3	4.6×10^3	1.6×10^3	3.2×10^3

thermal resistance of a polymer. $T_{d,0}$ is the temperature at which the loss of weight during heating can be just measured and is defined as the inclination point of the loss of weight vs. temperature curve. The temperature at which the loss of weight of the oligomer has reached 50% is considered to be the $T_{d,1/2}$ (ref. 56). Since the t.g.a. measurements gave $T_{d,0}$ values always higher than 200°C, the applicability of these novel oligo(ester amide)s is not impaired (*Tables 5* and *6*).

The *TOC* results indicated that only the ester-rich oligo(ester amide)s (>50% ester content) could be considered biodegradable because the *TOC* values for the amide-rich copolymers were very low (*Tables 1* and *2*). The *TOC* values are proportional to the concentration of the water-soluble products, which in our case could be due to ε-caprolactone (monomer or oligomeric units) or to diacid (SA or ODA). These results are in agreement with previous investigations on the biodegradability of copoly(ester amide)s where it was stated that high ester contents promote biodegradability[13-15,49]. Although the effect of M_n upon the potential degradability of the polymer has been previously investigated[57-59], in this

publication the molecular-weight range was limited to under 6000 so that the *TOC* results could reflect mainly structural differences (i.e. ester-rich or amide-rich) in these oligo(ester amide)s. However, the *TOC* results did not indicate any degradation for the amide-rich oligo(ester amide)s even at $MW < 3000$.

Tables 7 and *8* give the weight-loss percentages of the SA/1,6-HD/ε-CL and ODA/1,6-HD/ε-CL oligo(ester amide)s after their immersion in alkali solution against time. The higher the ε-CL content in the oligo(ester amide), the higher is the weight loss. After the first 10 h of exposure of oligomers to alkali solution, the weight losses proceeded at a considerably higher rate, reaching values 4–6 times higher within the next 30 h: for example, we could refer to the weight loss of SA/1,6-HD/ε-CL (10/10/80) from 10.3% to 42.4% (for 10 and 30 h,

Table 8 Octadecanedioic acid/1,6-hexanediamine/ε-caprolactone oligomers: weight losses and molecular weights (M_n, M_w from g.p.c. measurements) against time of alkali hydrolysis (10% NaOH w/v, 80°C)

Monomer feed ratio (mol%)			Weight loss (wt%)					G.p.c.			
ODA	1,6-HD	ε-CL	2 h	5 h	10 h	20 h	40 h	M_n (5 h)	M_w (5 h)	M_n (40 h)	M_w (40 h)
50.00	50.00	0.00	0.0	0.0	0.0	0.0	0.0	3.4×10^3	7.4×10^3	3.3×10^3	7.6×10^3
43.75	43.75	12.50	2.5	3.3	4.0	10.0	21.4	0.9×10^3	2.4×10^3	0.7×10^3	1.8×10^3
40.00	40.00	20.00	3.5	4.2	5.6	13.2	24.9	0.8×10^3	2.0×10^3	0.7×10^3	1.5×10^3
33.30	33.30	33.30	4.8	6.5	8.8	16.1	27.5	1.0×10^3	2.1×10^3	0.8×10^3	1.7×10^3
25.00	25.00	50.00	5.9	7.7	9.4	18.0	31.2	1.2×10^3	3.0×10^3	0.9×10^3	2.3×10^3
20.00	20.00	60.00	6.6	8.5	11.0	19.2	32.3	3.4×10^3	6.2×10^3	2.7×10^3	5.3×10^3
16.66	16.66	66.68	6.8	9.0	11.8	20.4	34.0	2.6×10^3	5.4×10^3	2.0×10^3	3.5×10^3
14.29	14.29	71.42	7.5	10.2	12.7	22.0	35.7	4.0×10^3	7.5×10^3	2.6×10^3	5.4×10^3
12.50	12.50	75.00	8.0	11.0	15.1	23.9	38.0	2.8×10^3	6.0×10^3	1.9×10^3	4.0×10^3
10.00	10.00	80.00	8.7	12.3	16.0	25.1	39.5	2.5×10^3	6.0×10^3	1.5×10^3	3.4×10^3

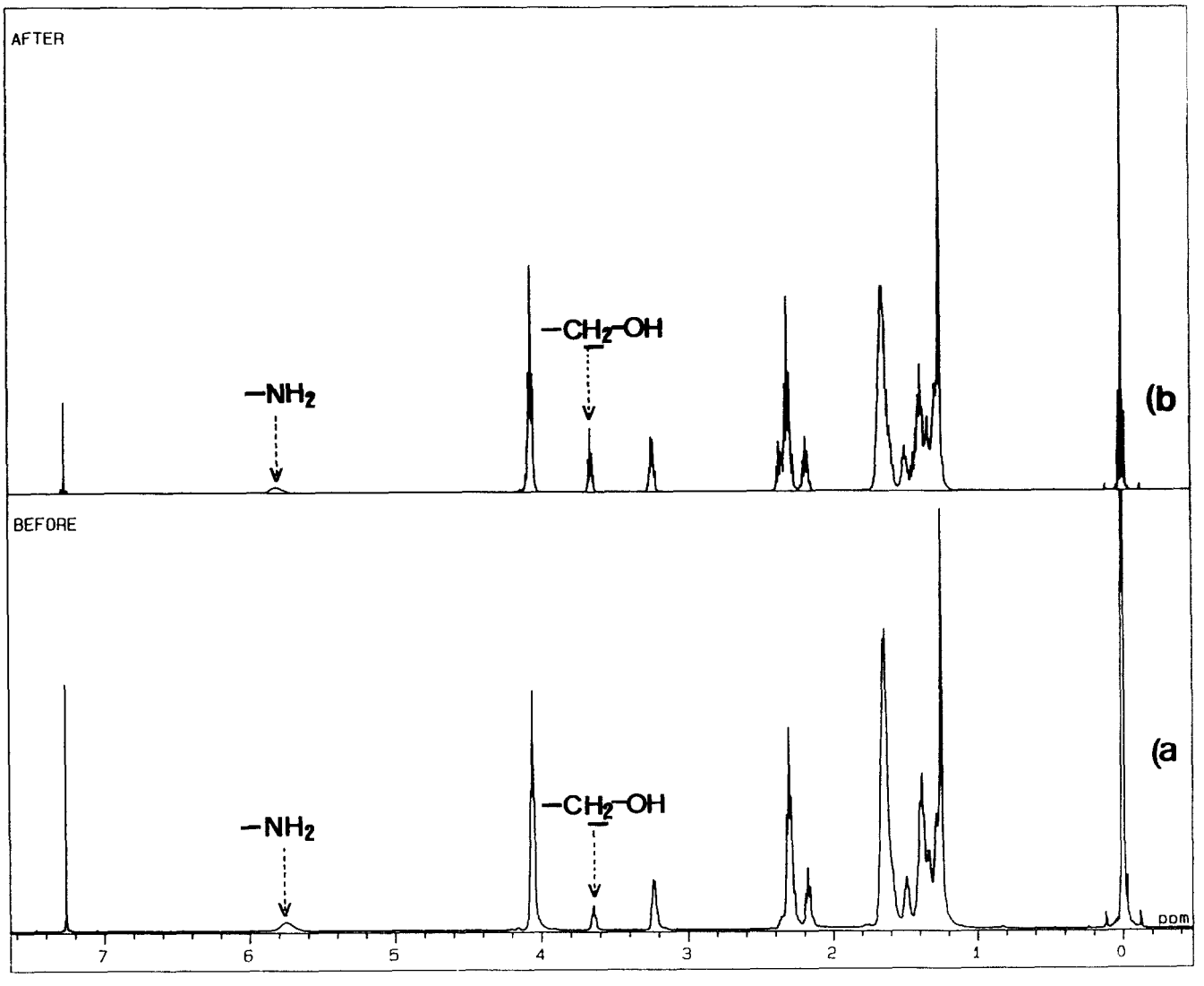
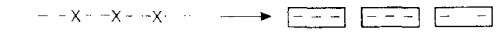


Figure 6 ^{1}H n.m.r. spectra of oligo(ester amide) ODA/1,6-HD/ε-CL (10.0/10.0/80.0 in mol%) (a) before and (b) after enzymatic hydrolysis

respectively). At the same time the M_n and M_w (determined with g.p.c.) decreased substantially, thus finally reaching values equal to approximately 50% of the initial M_n and M_w values before the alkali hydrolysis. In the absence of hydrophobic side groups and crosslinks it should be suggested that the oligomer degradation in alkali solution is 'homogeneous' (through the entire mass) and proceeds via the cleavage of labile bonds in the polymer backbone, which results in lower molecular weight and water-soluble products according to the following scheme:



where × represents the labile backbone bonds. Since according to the g.p.c. experiments (*Tables 7* and *8*) the most substantial decrease in the molecular weights (with alkali hydrolysis) was recorded for the ε-CL-rich oligomers, the × points should probably be the bonds between ε-CL and SA or ODA.

The test of enzymatic hydrolysis was also carried out in order to study the degradation products of the ODA/1,6-HD/ε-CL (10/10/80, molar ratio) oligo(ester amide), and *Figure 6* shows its ^{1}H n.m.r. spectra before and after its enzymatic hydrolysis (5 days). Although there is a peak (assigned to $-NH_2$ end-group, *Figure 2*) at 5.7 ppm, its intensity does not increase, as expected, thus showing that no further cleavage in the amide-type bonds (O=C–NH–) occurs (*Figures 6a* and *6b*), in agreement with our previous observation for adipic acid/1,6-hexanediamine/ε-caprolactone oligo(ester amide)s[49]. However, the peak at 3.6 ppm, previously attributed to hydroxyl end-groups of ε-CL, has gained considerably in intensity (compare *Figures 6b* and *6a*) probably due to cleavage of CL–CL labile bonds. The g.p.c. analysis gave values 2.0×10^3 and 4.4×10^3 for M_n and M_w, respectively, which agree satisfactorily with the above-mentioned g.p.c. results from alkali hydrolysis.

CONCLUSIONS

The presence of ε-CL units in these model oligo(ester amide)s lowers their hydrogen-bond density, thus resulting in low crystallinities (heats of fusion), in particular for the oligomers of intermediate composition. The T_m and T_g values *versus* the ester content percentage show a linear decrease whereas the *TOC* values increase, thus confirming the high susceptibility of the ester-rich oligomers to degradation. Although no degradation was observed for the amide-rich oligomers according to the *TOC* measurements despite their low molecular weights, their alkali hydrolysis tests showed a weight loss (20–40% of the initial weight) accompanied by a decrease in their molecular weights.

ACKNOWLEDGEMENTS

I. Arvanitoyannis is grateful to Mr Takashi Higashi (Sekisui Plastics Co. Ltd) and to Dr Yuko Tanaka (ONRI, AIST) for their help with g.p.c. and d.s.c./t.g.a. measurements, respectively.

REFERENCES

1 Chen, X., Gonsalves, K. E. and Cameron, J. A. *J. Appl. Polym. Sci.* 1993, **50**, 1999
2 White, J. R. and Turnbull, A. *J. Mater. Sci.* 1994, **29**, 584
3 Vert, M., Li, M. S., Spenlehauer, G. and Guerin, P. *J. Mater. Sci.-J. Mater. Med.* 1992, **3**, 432
4 Satyanarayana, D. and Chaterji, P. R. *J. Mater. Sci.-Rev. Macromol. Chem. Phys. (C)* 1993, **33(3)**, 349
5 Kim, S. H., Han, Y. K., Ahn, K. D., Kim, Y. H. and Chang, T. *Makromol. Chem.* 1993, **194**, 3229
6 Kim, S. H., Han, Y. K., Kim, Y. H. and Hong, S. I. *Makromol. Chem.* 1992, **193**, 1623
7 Gogolewski, G., Jovanovic, M., Perren, S. M., Dillon, J. G. and Hughes, M. K. *J. Biomed. Mater. Res.* 1993, **27**, 1135
8 Reeve, M. S., McCarthy, S. P., Downey, M. J. and Gross, R. A. *Macromolecules* 1994, **27**, 825
9 Storey, R. F. and Shoemake, K. A. *Polym. Bull.* 1993, **31**, 331
10 Ouchi, T., Shiratani, M., Jinno, M., Hirao, M. and Ohya, Y. *Makromol. Chem., Rapid Commun.* 1993, **14**, 825
11 Barrera, D. A., Zylstra, E., Lansbury, P. T. Jr and Langer, R. *J. Am. Chem. Soc.* 1993, **115**, 11010
12 Helder, J., Feijen, J., Lee, S. J. and Kim, S. W. *Makromol. Chem., Rapid Commun.* 1986, **7**, 193
13 Tokiwa, Y., Suzuki, T. and Takeda, K. *Agric. Biol. Chem.* 1988, **52(8)**, 1937
14 Tokiwa, Y., Suzuki, T. and Takeda, K. *Agric. Biol. Chem.* 1983, **50(5)**, 1323
15 Benedict, C. V., Cameron, J. A. and Huang, S. J. *J. Appl. Polym. Sci.* 1983, **28**, 335
16 Benedict, C. V., Cook, W. J., Jarrett, P., Cameron, J. A., Huang, S. J. and Bell, J. P. *J. Appl. Polym. Sci.* 1983, **28**, 327
17 Cook, W. J., Cameron, J. A., Bell, J. P. and Huang, S. J. *J. Polym. Sci., Polym. Lett. Edn.* 1981, **19**, 159
18 Jarrett, P., Cook, W. J., Bell, J. P., Huang, S. J. and Cameron, J. A. *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.* 1981, **22**, 381
19 Tokiwa, Y. and Suzuki, T. *Nature* 1977, **270**, 76
20 Tokiwa, Y., Ando, T. and Suzuki, T. *J. Ferment. Technol.* 1976, **8**, 603
21 Fields, R. D., Rodriguez, F. and Finn, R. K. *J. Appl. Polym. Sci.* 1974, **18**, 3571
22 Nakayama, A., Kawasaki, N., Iyoda, J., Ukita, M., Hayashi, K. and Yamamoto, N. *Chem. Express* (Kinki Chem. Soc. Japan) 1993, **8(3)**, 181
23 Nakayama, A., Kawasaki, N., Arvanitoyannis, I. and Yamamoto, N. Proc. 3rd Int. Scientific Workshop on Biodegradable Plastics and Polymers (Eds Y. Doi and K. Fukuda), Elsevier, Amsterdam, 1994, pp. 557–561
24 de Olivierra, W. and Glasser, W. G. *Macromolecules* 1994, **27**, 5
25 Zhang, X., Wyss, U. P., Pichora, D. and Goosen, M. F. A. *J. Mater. Sci.-Pure Appl. Chem. (A)* 1993, **30(12)**, 933
26 Mikos, A. G., Bao, Y., Cima, L. G., Ingber, D. E., Vacanti, J. P. and Langer, R. *J. Biomed. Mater. Res.* 1993, **27**, 183
27 Verheyen, C. C. P. M., de Wijn, J. R., van Blitterswijk, C. A., de Groot, K. and Rozing, P. M. *J. Biomed. Mater. Res.* 1993, **27**, 433
28 Grijpma, D. W., Joziasse, C. A. P. and Pennings, A. J. *Makromol. Chem., Rapid Commun.* 1993, **14**, 155
29 Cerrai, P. and Tricoli, M. *Makromol. Chem., Rapid Commun.* 1993, **14**, 529
30 Shen, Z. R., Zhu, J. H. and Ma, Z. *Makromol. Chem., Rapid Commun.* 1993, **14**, 457
31 Hu, D. S. G. and Liu, H. J. *J. Appl. Polym. Sci.* 1994, **51**, 473
32 Ratner, B. D. *J. Biomed. Mater. Res.* 1993, **27**, 837
33 Ali, A. M., Doherty, P. J. and Williams, D. F. *J. Biomed. Mater. Res.* 1993, **27**, 1409
34 Yang, J. Z., Wang, M. and Otterbrite, R. L. *J. Mater. Sci.-Pure Appl. Chem. (A)* 1993, **30(8)**, 503
35 Kumar, G. S. 'Biodegradable Polymers: Prospects and Progress', Marcel Dekker, New York, 1987, pp. 1–40
36 Akcatel, P. and Jasse, B. *J. Polym. Sci., Polym. Chem. Edn.* 1976, **14**, 1537
37 Castaldo, L., De Candia, F., Maglio, G., Palumbo, R. and Strazza, G. *J. Appl. Polym. Sci.* 1982, **27**, 1809
38 Goodman, I. and Valavanidis, A. *Eur. Polym. J.* 1984, **20**, 241
39 Goodman, I. and Vachon, R. N. *Eur. Polym. J.* 1984, **20**, 529
40 Goodman, I. *Eur. Polym. J.* 1984, **20**, 549
41 Goodman, I. and Sheahan, R. J. *Eur. Polym. J.* 1990, **26**, 1081
42 Goodman, I. and Sheahan, R. J. *Eur. Polym. J.* 1990, **26**, 1089
43 Goodman, I. and Rodriguez, M. T. *Macromol. Chem. Phys.* 1994, **195**, 1075

44 Wang, C. and Nakamura, S. *J. Polym. Sci. Part A Polym. Chem.* 1994, **32**, 413
45 Izu, P., Munoz, M. E., Pena, J. J. and Santamaria, A. *Makromol. Chem., Rapid Commun.* 1993, **14**, 539
46 Bera, S. and Jedlinski, Z. *J. Polym. Sci. (A) Polym. Chem.* 1993, **31**, 731
47 Gaymans, R. J. and de Haan, J. L. *Polymer* 1993, **34**, 4360
48 van Hutten, P. F., Magnus, R. M. and Gaymans, R. J. *Polymer* 1993, **34**, 4193
49 Arvanitoyannis, I., Nakayama, A., Kawasaki, N. and Yamamoto, N. *Angew. Makromol. Chem.* in press
50 Tokiwa, Y., Suzuki, T. and Ando, T. *J. Appl. Polym. Sci.* 1979, **24**, 1701
51 Miller, R. L., 'Crystallographic data for various polymers' in 'Polymer Handbook', 3rd Edn. (Eds J. Brandrup and E. H. Immergut), Wiley, New York, 1989, pp. VI 1–208
52 Iyoda, J., Nakayama, A. and Yamamoto, N. *Bull. Gov. Ind. Res. Inst., Osaka* 1993, **44(1)**, 1
53 'The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra' (Eds C. J. Pouchert and J. Behnke), Aldrich Co. Inc., USA 1993, Vol. 1, pp. 945, 1040, 1231, 1253
54 Dubois, Ph., Barakat, I., Jerome, R. and Teyssie, Ph. *Macromolecules* 1993, **26**, 4407
55 Kchayoglou, A. H. and Arvanitoyannis, I. *Eur. Polym. J.* 1990, **26**(3), 261
56 van Krevelen, D. W., 'Properties of Polymers', 3rd Edn. Elsevier, Amsterdam, 1990, pp. 641–53
57 Arvanitoyannis, I., Nikolaou, E. and Yamamoto, N. *Angew. Makromol. Chem.* 1994, **221**, 67
58 Arvanitoyannis, I., Nikolaou, E. and Yamamoto, N. *Polymer* 1994, **35**, 4678
59 Arvanitoyannis, I., Nikolaou, E. and Yamamoto, N. *Macromol. Chem. Phys.* in press