

# Synthesis and degradability of a novel aliphatic polyester: poly( $\beta$ -methyl- $\delta$ -valerolactone-co-L-lactide)

Atsuyoshi Nakayama\*, Norioki Kawasaki, Ioannis Arvanitoyannis,  
Jun Iyoda and Noboru Yamamoto

Osaka National Research Institute, AIST, 1-8-31 Midorigaoka, Ikeda, Osaka 563, Japan  
(Received 1 April 1994; revised 9 September 1994)

Biodegradable polyesters were synthesized by ring-opening copolymerization of L-lactide (LA) with DL- $\beta$ -methyl- $\delta$ -valerolactone (MV).  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance analyses showed that these copolymers were statistical and that their number-average molecular weights were within the range of  $(3\text{--}5) \times 10^4$ . The melting temperatures of these polyesters were dependent upon the LA content in the copolymers, thus showing that high LA composition resulted in higher  $T_m$ . The copolymers containing more than 90 mol% LA formed tough and hard films, whereas those with less than 80 mol% LA formed flexible films similar to natural rubber. Accelerated hydrolysis was carried out with copolymers of various compositions at  $70^\circ\text{C}$  for 18 days. The hydrolysis rates were much faster than that of poly(LA), which is well known to be a hydrolysable polymer. The copolymers were easily hydrolysed with lipases from *Rhizopus arrhizus*, *R. delemar*, *Pseudomonas* sp. and *Candida cylindracea*. In particular, the lipases from *R. arrhizus* and *R. delemar* proved to be very effective in promoting hydrolysis.

(Keywords: biodegradable copolyester; methylvalerolactone-lactide; hydrolysis)

## INTRODUCTION

The extensive use of bioresistant synthetic polymers is considered to be one cause of environmental pollution. The current demand for easy disposal of polymers has instigated many investigations on the synthesis and evaluation of novel biodegradable polymers. These polymers are expected to find applications in medicine (sutures, implants), pharmacy (drug release) and agriculture (mulch, food packaging)<sup>1</sup>. Although several polymers have been identified as degradable in model aqueous media or in animal bodies, the family of aliphatic polyesters appears at the moment to be the most attractive and promising<sup>2–5</sup>.

A long methylene chain promotes biodegradability by imparting flexibility to the polymeric chain. Therefore, poly( $\delta$ -valerolactone) and poly( $\epsilon$ -caprolactone), with four and five methylene units, respectively, in their backbones, are more biodegradable than poly( $\beta$ -propiolactone), with two methylene units<sup>6</sup>. However, a much longer methylene chain might cause a decrease in biodegradability<sup>7</sup> because of a decrease in the density of ester bonds in the main chain. Furthermore, substituent groups were also found to decrease the susceptibility of polymers to biodegradation<sup>6</sup>.

To the best of our knowledge, poly(DL- $\beta$ -methyl- $\delta$ -valerolactone) (poly(MV)) has not been reported except for its oligomer as a raw material of polyurethane. Poly(MV) is expected to be biodegradable, and the interest for its current study lies in its structure, which reflects two antagonistic tendencies with regard

to biodegradability: the methylene chain promotes biodegradability, whereas the methyl pendent group has an adverse effect upon the susceptibility of a polymer to degradation.

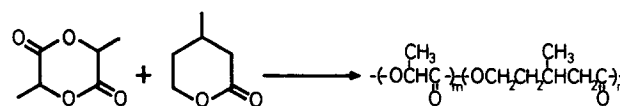
On the other hand, L-lactide (LA) is a well known monomer used extensively for the synthesis of bioabsorbable polymers for biomedical applications<sup>8–16</sup>. Since poly(LA) has a rigid macromolecular structure, various approaches to increase its flexibility have been devised, among which its copolymerization with other monomers is a promising one. Copolyesters<sup>8,17–19</sup>, copoly(ester ether)s<sup>20–24</sup> and copoly(ester amide)s<sup>11,25</sup> are the polymer families that have been more thoroughly investigated. The copolymer of  $\epsilon$ -caprolactone and LA has been repeatedly studied by several researchers because of its appealing mechanical properties<sup>9,26–29</sup>.

The aim of this investigation is to synthesize by ring-opening polymerization (Scheme 1) novel copolyesters combining the attractive features of MV (flexibility) and LA (hydrolysability) and to study their thermal and mechanical properties and biodegradability.

## EXPERIMENTAL

### Reagents

DL- $\beta$ -Methyl- $\delta$ -valerolactone (Kuraray) was purified by distillation under vacuum. L-Lactide (Boehringer,



Scheme 1

\* To whom correspondence should be addressed

Ingelheim) was purified by recrystallization from ethyl acetate. Tetraphenyltin (Wako), 15% triethylaluminium toluene solution (Tokyo Kasei), titanium tetrabutoxide monomer (Wako), 15% n-butyllithium hexane solution (Tokyo Kasei) and anhydrous iron(III) chloride (Nakarai) were used as initiators without further purification. Zinc dibutoxide and  $\mu$ -oxo-aluminium-zinc complex ((n-butoxy)<sub>4</sub>Al<sub>2</sub>O<sub>2</sub>Zn) were prepared by reported methods<sup>30</sup>. The enzymes for biodegradation tests were lipases from *Rhizopus arrhizus*, *Pseudomonas* sp. and *Candida cylindracea* of Boehringer, Mannheim, and from *Rhizopus delemar* of Seikagaku Kogyo.

#### Measurements

I.r. spectra were recorded on a Perkin–Elmer 1600 FTi.r. spectrometer, using film samples cast on a sodium chloride plate from chloroform solutions. <sup>1</sup>H n.m.r. (200 MHz) and <sup>13</sup>C n.m.r. (50 MHz) spectra were recorded on a JEOL JNM-FX200 spectrometer. All spectra were obtained from chloroform-d solutions at room temperature with tetramethylsilane (TMS) as internal standard. Thermal analyses were performed on a Rigaku model 10A differential scanning calorimeter. Samples of 2–8 mg (weighed into aluminium pans) were measured from room temperature to 200°C at a heating rate of 5°C min<sup>-1</sup>. Molecular-weight distributions were measured with a Tosoh g.p.c. system (HLC-8020), using polystyrene standards. The columns were a TSKgel G4000HXL and a TSKgel G3000HXL with limited exclusion molecular weight of 4 × 10<sup>5</sup>. Mechanical properties were measured on a Toyo Baldwin tensile tester (TMI UTM-4). For measurements of mechanical properties and biodegradation tests, film samples were prepared by a solvent casting method using chloroform at room temperature.

#### Polymerizations

The polymerization of MV was carried out in bulk. MV and catalyst (0.3–1.5 mol%) were charged on a dried ampoule. The catalysts used were tetraphenyltin,  $\mu$ -oxo-aluminium-zinc complex ((n-butoxy)<sub>4</sub>Al<sub>2</sub>O<sub>2</sub>Zn), triethylaluminium, zinc dibutoxide, titanium tetrabutoxide monomer, n-butyllithium and iron(III) chloride. After the mixture was degassed by three freeze–thaw cycles, the ampoules were sealed under vacuum and heated with the aid of an oil bath at 120°C for 2–5 days. The polymerization products were viscous oils. They were allowed to cool down to room temperature and then dissolved in chloroform after the addition of a few drops of methanol in order to stop the polymerization. Poly(MV) was obtained by precipitation in methanol.

#### Copolymerizations

LA, MV and tetraphenyltin (0.3 mol% vs. total monomers) were added to a dried ampoule. The copolymerization was carried out following the same method as for the polymerization of MV. The copolyester was purified by repeated precipitation. A series of copolymers with different compositions were synthesized by changing the feed ratio of MV/LA from 20/80 to 80/20. The molar composition and the sequence distribution of the copolyesters were determined from <sup>1</sup>H n.m.r. and <sup>13</sup>C n.m.r. spectra.

#### Hydrolysis

First, 25 mg of polyester samples and 2 ml of distilled water were added to each of three tubes. The first two tubes were used for accelerated hydrolysis tests at 70°C and the third one for a blank test at room temperature. The water-soluble hydrolysis products were measured by TOC (total organic carbon concentration) analyser. The TOC values were averaged from the recorded data of the first two tubes after having subtracted the blank levels.

#### Enzymatic hydrolysis<sup>31</sup>

First, 25 mg of polyester samples and 2 ml of phosphate buffer (KH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, pH 7.0) were added to each of three tubes. Then 200 units of enzymes were added to two tubes and the third was a blank test. The enzymes used were lipases from *Rhizopus arrhizus*, *R. delemar*, *Pseudomonas* sp. and *Candida cylindracea*. The enzymatic hydrolysis was carried out at 37°C for 24 h. After filtration (0.2  $\mu$ m membrane filter), a small amount of 1 N hydrochloric acid was dropped onto the filtrate and TOC was measured. The TOC data were the average of two measurements and corrected appropriately with the blank levels.

## RESULTS AND DISCUSSION

#### Polymerization of DL- $\beta$ -methyl- $\delta$ -valerolactone

Poly(MV) was synthesized by using several coordinated polymerization catalysts, a cationic and an anionic polymerization catalyst (Table I). The synthesized polymers were colourless and transparent except for No. 11. It should be mentioned that the number-average molecular weights ( $M_n$ ) were (2.0–8.0) × 10<sup>4</sup> and the polymers were amorphous.

Using tetraphenyltin, both yield and  $M_n$  were very low, and failed to increase despite the change in the amount of catalyst used. However, the use of coordinated polymerization catalysts, such as triethylaluminium, zinc dibutoxide,  $\mu$ -oxo-aluminium-zinc complex and titanium tetrabutoxide monomer at 60°C, promoted the polymerizations, thus resulting in yields of 50–70%, and  $M_n$  values higher than 2.0 × 10<sup>4</sup>. Using anionic catalyst, n-butyllithium, similar results to the polymerization with coordinated polymerization catalysts were obtained. On

Table I Polymerization of DL- $\beta$ -methyl- $\delta$ -valerolactone

Run No.	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)	$M_n \times 10^{-3}$	$M_w/M_n$
1	Ph <sub>4</sub> Sn (0.06)	120	48	4	3.6	2.1
2	Ph <sub>4</sub> Sn (0.3)	120	48	6	3.7	5.2
3	Ph <sub>4</sub> Sn (1.5)	120	48	2	3.4	2.0
4	Ph <sub>4</sub> Sn (0.3)	60	48	0.2	0.3	1.0
5	AlEt <sub>3</sub> (0.3)	60	36	65	30.0	1.9
6	ZnEt <sub>2</sub> (0.3)	60	36	65	78.8	1.3
7	AZ <sup>a</sup> (0.3)	60	48	72	22.2	1.4
8	Zn(tBuO) <sub>2</sub> (0.3)	60	36	61	36.8	1.8
9	Ti(nBuO) <sub>4</sub> (0.3)	60	36	66	24.6	1.9
10	n-BuLi (0.3)	60	36	68	25.7	1.9
11	FeCl <sub>3</sub> (0.3)	60	36	55	8.1 <sup>b</sup>	4.4 <sup>b</sup>

<sup>a</sup> AZ = (n-BuO)<sub>4</sub>Al<sub>2</sub>O<sub>2</sub>Zn

<sup>b</sup> This was composed of two peaks: high-molecular-weight part,  $M_n = 29.9 \times 10^3$ ,  $M_w/M_n = 1.5$ ; low-molecular-weight part,  $M_n = 2.31 \times 10^3$ ,  $M_w/M_n = 1.4$

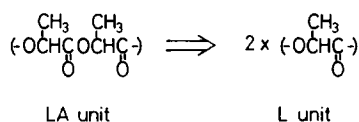
**Table 2** Copolymerization of  $\beta$ -methyl- $\delta$ -valerolactone with L-lactide using various catalysts at 60 °C (feed ratio MV/LA = 50/50, i.e. MV/L = 33/67; see text)

Catalyst	Composition, MV:L (mol%)	G.p.c.		D.s.c.		Block length	
		$M_n \times 10^{-3}$	$M_w/M_n$	$T_g$ (°C)	$T_m$ (°C)	L	MV
AlEt <sub>3</sub>	14.86	27.5	1.4	24	143	6.7	1.7
ZnEt <sub>2</sub>	9.91	35.8	1.4	31	152	9.7	2.0
AZ <sup>a</sup>	6.94	35.6	1.3	39	158	17.0	1.6
Ti(nBuO) <sub>4</sub>	6.94	66.1	1.1	34	123, 130	8.7	NC <sup>c</sup>
FeCl <sub>3</sub>	25.75	89.4	1.2	-5	112, 126	NC <sup>c</sup>	NC <sup>c</sup>
nBuLi	3.97	25.6	1.8	45	155	NC <sup>c</sup>	NC <sup>c</sup>
Sn(oct) <sub>2</sub> <sup>b</sup>	27.73	23.2	1.6	2	159	3.0	1.5
Mg(OEt) <sub>2</sub>	2.98	33.3	1.3	51	166	NC <sup>c</sup>	NC <sup>c</sup>
Al(iPrO) <sub>3</sub>	11.89	31.4	1.4	30	150	11.9	1.8
SnPh <sub>4</sub> <sup>b</sup>	20.80	99.7	1.6	13	-	4.2	1.5

<sup>a</sup> AZ = (n-BuO)<sub>4</sub>Al<sub>2</sub>O<sub>2</sub>Zn

<sup>b</sup> Polymerizations were carried out at 120 °C

<sup>c</sup> Not calculated



Scheme 2

the other hand, when anhydrous iron(III) chloride was used as a cationic catalyst, the obtained polymer was dark brown. Its g.p.c. trace was bimodal, showing that its high-molecular-weight part was substantially smaller than the low-molecular-weight one.

<sup>1</sup>H n.m.r. ( $\delta$ , CDCl<sub>3</sub>): 4.12 ppm (t,  $J$  = 6.6 Hz, 2H), 2.4–1.9 ppm (m, 3H), 1.8–1.4 ppm (m, 2H), 0.98 ppm (d,  $J$  = 6.1 Hz, 3H).

### Copolymerization

The copolymerizations were carried out with 50/50 mol% of the feed ratio (MV/LA) using several catalysts (Table 2). In this table, the L-lactide unit (LA) is replaced by the L-lactic acid unit (L), which is a half-unit of L-lactide (Scheme 2).

Several catalysts were used in order to elucidate the effect of catalyst on the final product. However, in most cases the catalysts gave similar results, that is lactide-rich polymers (L ~ 90 mol%). Use of iron(III) chloride and tin octoate resulted in polymers of similar MV/L compositions to that of tetraphenyltin. It should be noted, however, that the copolymer with iron(III) chloride has two  $T_m$  values at 112 and 126 °C and also shows the existence of a long L–L chain. In contrast, tin octoate, though known to be a transesterification catalyst for lactide polymers characterized by comparatively short average L block lengths, produced the copolymer (MV/L = 27/73) of a high  $T_m$  at 159 °C, which corresponds to the 6/94 copolymer with tetraphenyltin. As for tetraphenyltin, it was found to produce the statistical copolymer of MV with LA despite its generally acknowledged low activity for homopolymerization of MV. These results could probably be explained as follows:

(i) Most catalysts in Table 2 activate not only MV but

**Table 3** Copolymerization of  $\beta$ -methyl- $\delta$ -valerolactone with L-lactide using Ph<sub>4</sub>Sn at various polymerization times at 120 °C<sup>a</sup>

Time (h)	Composition, MV:L (mol%)	G.p.c.		D.s.c.	
		$M_n \times 10^{-3}$	$M_w/M_n$	$T_g$ (°C)	$T_m$ (°C)
6	10/90	3.6	1.1		
12	10/90	12.9	1.1	34	106, 114
24	15/85	24.7	1.3	21	90, 103
48	16/84	35.9	1.5	21	93, 103
84	20/80	59.8	1.6	13	ND <sup>b</sup>
144	25/75	50.8	1.7	7	ND <sup>b</sup>

<sup>a</sup> Feed ratio: MV/L = 33/67

<sup>b</sup> Not detected

also highly LA because the produced polymers were L-rich.

(ii) Both polymerizations proceed individually and mainly the homopolymers are produced.

(iii) Only L-rich polymers remain because MV-rich polymers are removed as a soluble part in the reprecipitation operation using methanol.

When tetraphenyltin is used as catalyst, the polymerization of LA proceeds rapidly whereas that of MV is rather slow. Furthermore, tetraphenyltin inserts the synthesized MV chains in L chains owing to its ability to transesterify lactide polymers. Therefore, copolymerizations catalysed by tetraphenyltin were far more successful than those with any other catalyst, as can be seen from Table 2. Table 3 gives the results of the copolymerization of MV with LA whose feed ratio is 50/50 mol/mol (MV/L = 33/67) for various reaction times. These results are in agreement with the above presented interpretation of catalyst activity. The MV content and molecular weights increased from 10 to 25 mol% and from monomer to  $50 \times 10^3$  versus reaction time. Although up to 48 h of reaction time some  $T_m$  values persisted, confirming the presence of several long L–L chains, further prolongation of reaction time resulted in disappearance of the  $T_m$  probably because of transesterification of L and MV chains.

**Table 4** Copolymerization of  $\beta$ -methyl- $\delta$ -valerolactone with L-lactide using  $\text{Ph}_4\text{Sn}$  at various feed ratios

Monomer feed, MV/L (mol%)	Copolymer						
	Composition, MV/L (mol%)	Yield (%)	$M_n \times 10^{-3}$	$M_w \times 10^{-3}$	$M_w/M_n$	Block length	
						MV	L
11/89	10/90	87	30.9	59.3	1.9	1.2	13.1
20/80	9/91	81	49.9	87.5	1.8	1.2	14.0
33/67	21/79	75	45.7	75.1	1.7	1.6	6.4
50/50	36/64	60	40.4	72.6	1.8	2.2	4.1
67/33	42/58	54	47.5	72.6	1.5	2.1	3.1

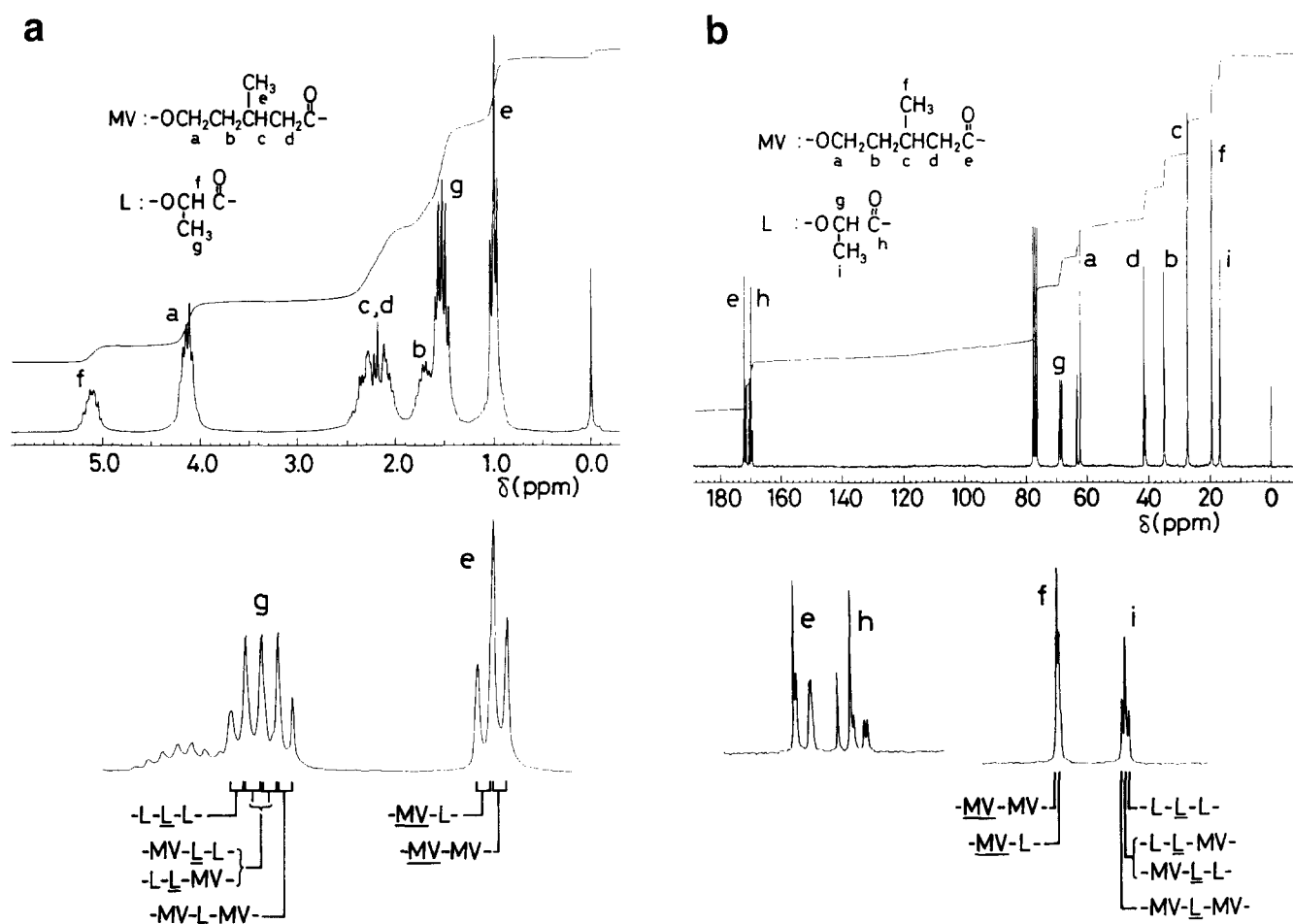
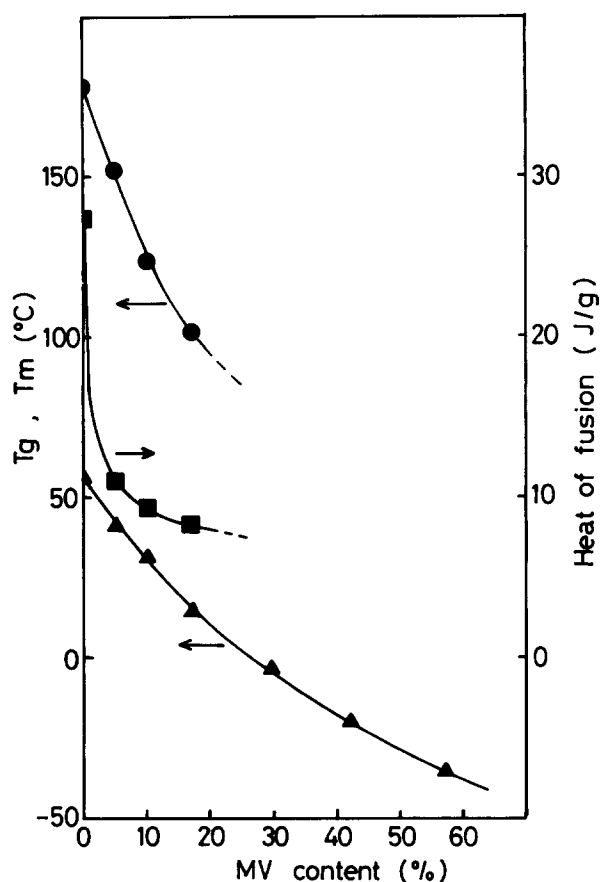

**Figure 1**  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra of the copolyester with MV/L=42/58 measured in  $\text{CDCl}_3$  at room temperature: (a) 200 MHz  $^1\text{H}$  n.m.r.; (b) 50 MHz  $^{13}\text{C}$  n.m.r.

Table 4 shows the results of the bulk copolymerization with various monomer feed ratios of MV and LA using  $\text{Ph}_4\text{Sn}$  at  $120^\circ\text{C}$ . The polymerization yield rose with an increase in the LA feed ratio. The results from  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. showed that the copolymer composition was in satisfactory agreement with the comonomer feed ratio. The molecular weights were  $(3.0\text{--}5.0) \times 10^4$  and  $M_w/M_n$  were from 1.5 to 1.9.

$^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra of the copolymers were assigned to monomer sequence as shown in Figure 1. The assignments of the methyl groups were determined by the chemical shifts of both homopolymers, correlation of signal integrals and copolymer composition, and

$^{13}\text{C}\{^1\text{H}\}$  selective decoupling method. There are four kinds of doublet in L methyl region (1.5 ppm), which suggests the following four kinds of triad monomer sequence:  $-\text{L}-\text{L}-\text{L}-$ ,  $-\text{MV}-\text{L}-\text{L}-$ ,  $-\text{L}-\text{L}-\text{MV}-$  and  $-\text{MV}-\text{L}-\text{MV}-$ . The integrals of the two central doublets are almost equal to each other at any polymer composition because the numbers of triad sequences  $-\text{MV}-\text{L}-\text{L}-$  and  $-\text{L}-\text{L}-\text{MV}-$  remain normally the same. The integral of the doublet at the highest magnetic field increases with an increase in the MV content, thus confirming that the doublet is  $-\text{MV}-\text{L}-\text{MV}-$ . The remaining doublet has the same chemical shift as that of poly(LA). The methyl part of MV has two doublets, one of which has the same chemical



**Figure 2** Melting points ( $T_m$ ), glass transition temperatures ( $T_g$ ) and heats of fusion ( $\Delta H$ ) determined by d.s.c. (heating rate  $10^\circ\text{C min}^{-1}$ ) for poly(MV-co-LA) versus MV content: (●)  $T_m$ , (▲)  $T_g$ , (■)  $\Delta H$

shift as that of poly(MV). The integral of the other increases when the MV content increases. Therefore it is only fair to suggest that the higher-field one is from diad homo sequence and the other is from diad hetero sequence.  $^{13}\text{C}$  n.m.r. assignments were carried out by  $^{13}\text{C}\{^1\text{H}\}$  selective decoupling and correlation of signal integrals and polymer composition. Average block lengths were calculated from the integral ratios of homo and hetero sequence signals, corresponding to methyl protons of L and MV units for  $^1\text{H}$  n.m.r., and methylene carbons for  $^{13}\text{C}$  n.m.r. The  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. results show that the copolymers have short average block length, which means that these polymers are statistical (Table 4).

Since L-lactide is composed of two L-lactic acid units, the n.m.r. spectra of the copolymers were expected to have continuous  $-\text{L}-\text{L}-$  sequence. However, another signal based on  $-\text{MV}-\text{L}-\text{MV}-$  sequence was clearly observed in addition to the sequence  $-\text{L}-\text{L}-\text{L}-$ ,  $-\text{MV}-\text{L}-\text{L}-$  and  $-\text{L}-\text{L}-\text{MV}-$ . This suggests that the transformation of the ester bond, from  $-\text{L}-\text{L}-$  to  $-\text{L}-\text{MV}-$ , has occurred. Similar transesterification reactions have been previously reported by Kricheldorf *et al.*<sup>28</sup>.

#### Thermal properties

Figure 2 shows  $T_m$ ,  $T_g$  and heat of fusion ( $\Delta H$ ) values of the copolymers having various polymer compositions. Poly(LA) has a  $T_m$  of  $177^\circ\text{C}$  and a  $T_g$  of  $56^\circ\text{C}$ .

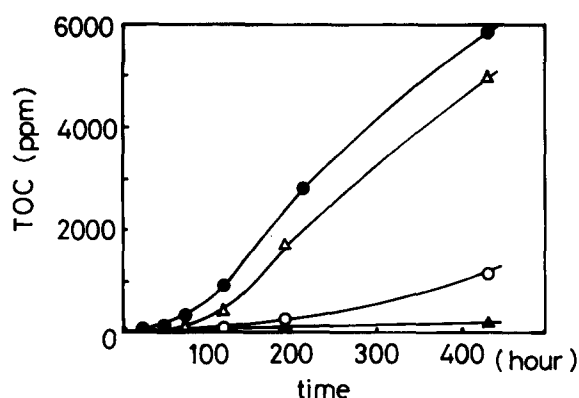
The copolymers have only one single peak at lower temperatures than the  $T_m$  of poly(LA), which proves that the synthesized copolymers are statistical. An increase in the content of MV in the copolymer resulted in lower  $T_m$  and  $T_g$  values. It is noteworthy that when the composition ratio of MV unit was higher than 20 mol%, the copolymer became amorphous (no  $T_m$ ). The  $T_g$  values of the copolymers lower gradually from a poly(LA)  $T_g$  of  $56^\circ\text{C}$  to a poly(MV)  $T_g$  of  $-65^\circ\text{C}$ , thus reflecting the high flexibility of the MV-rich polymers. Heat of fusion increases with the increase in the L unit content, thus showing that the crystallinity becomes higher when the polymer becomes rich in L.  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra showed that the copolymers containing many L units have long continuous  $-\text{L}-\text{L}-$  sequence. Therefore, it seems that long  $-\text{L}-\text{L}-$  chain causes the occurrence of crystallinity, which could be remarkably reduced by cleavage of  $-\text{L}-\text{L}-$  chain due to the insertion of MV unit among the  $-\text{L}-\text{L}-$ .

#### Mechanical properties

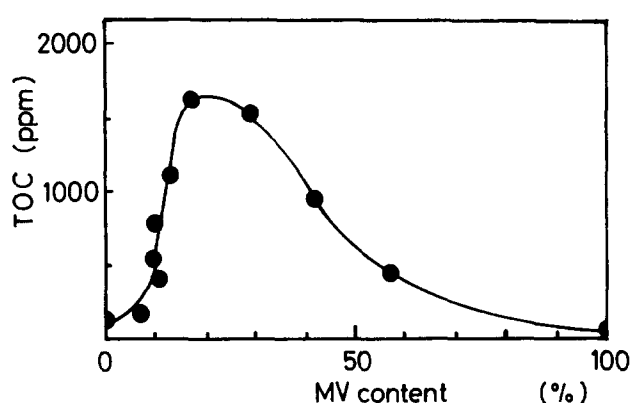
Test specimens were prepared by casting films ( $3 \times 10 \text{ mm}^2$ ) from 10% solution in chloroform. The films were transparent. The results of the tensile tests are shown in Table 5. The mechanical properties were found to depend strongly on the composition of the copolymers and to be greatly affected even by the introduction of a small amount of MV units. The yield stress increases with increasing L unit content. The tensile strength did not change considerably within the range 8–15 mol% of L unit content, while the elongation at break decreases gradually. The copolymer of 10 mol% MV showed plastic properties of higher yield stress (initial modulus). However, the sample was extended up to 530% with gradual crystallization when extension speed was as slow as  $10 \text{ mm min}^{-1}$ . The sample of 15 mol% MV was a tough plastic with fair flexibility, though this showed a little permanent set after 500–800% extension. On the other hand, the copolymer of about 20 mol% MV exhibited typical rubber properties and managed to recover completely from 900% extension even though some crystallization occurred at the end of extension (after 500%). As a conclusion, it could be said that the copolymers having 8–20 mol% MV content were found to be superior to polyethylene with regard to mechanical properties and in conjunction with their anticipated biodegradability (see section below on 'Hydrolysis') are expected to find applications as disposable packaging materials.

**Table 5** Mechanical properties of poly( $\beta$ -methyl- $\delta$ -valerolactone-co-L-lactide)s

Copolymer, MV/L (mol%)	Tensile strength (MPa)	Yield point (MPa)	Elongation at break (%)
8/92	37.8	23.5	680
10/90	36.7	40.8	530
15/85	42.9	10.4	800
19/81	23.5	0.0	880
21/79	10.8	0.0	900



**Figure 3** Accelerated hydrolysis measured by *TOC* (ppm) of the poly(MV-co-LA)s in distilled water (70°C) versus exposure time. Conditions: sample 25 mg, distilled water 2 ml; (○) MV/L=0/100, (△) MV/L=11/89, (●) MV/L=42/58, (▲) MV/L=100/0



**Figure 4** Accelerated hydrolysis measured by *TOC* (ppm) of the poly(MV-co-LA)s versus polymer composition. Conditions: sample 25 mg, distilled water 2 ml, hydrolysis time 120 h, temperature 70°C

### Hydrolysis

The hydrolysability of these polymers was evaluated by measurement of *TOC* values, which show the amount of the hydrolysed water-soluble products.

Accelerated hydrolysis was carried out with copolymers of various compositions from poly(MV) to poly(LA). *TOC* measurements were taken periodically over a period of time of 18 days to evaluate the degree of hydrolysis (Figure 3). Although poly(MV) was hardly hydrolysed, the hydrolysis of all its copolymers was proportional to their exposure time. The hydrolysis rates of these copolymers were much faster than that of poly(LA), which is well known to be a hydrolysable polymer. The samples showing high *TOC* values were reduced to powder residue after hydrolysis. Bearing in mind that *TOC* values around 7000 ppm indicate a 100% dissolution of the copolymer in water, the copolymer of MV/L=42/58 was hydrolysed approximately by 85% in 18 days.

Figure 4 shows the dependence of hydrolysability on the polymer composition. The higher *TOC* values were recorded for the amorphous copolymers whose content in MV was within the range 18–25 mol%. The hydrolysis results for poly( $\epsilon$ -caprolactone-co-LA)s<sup>32</sup>, which have similar polymer structure except for a methyl group on MV unit, gave a similar curve concerning the correlation of the lactone/lactide composition with the hydrolysis rate as those of poly(MV-co-LA)s (Figures 3 and 4). That

**Table 6** Enzymatic hydrolysis of poly(MV-co-LA)<sup>a</sup> (MV/L = 29/71)

Enzyme (lipase)	<i>TOC</i> value (ppm)
Without enzyme	9 ± 2
<i>Rhizopus arrhizus</i>	1400 ± 140
<i>Rhizopus delemar</i>	2050 ± 50
<i>Pseudomonas</i> sp.	37 ± 2
<i>Candida cylindracea</i>	28 ± 4

<sup>a</sup> Conditions: 37°C, 24 h, lipase 200 units, buffer 2 ml, sample 25 mg coated to tube with fixed area

is, the hydrolysis peak occurred at around 20 mol% of  $\epsilon$ -caprolactone (CL) unit, and the 144 h *TOC* value of hydrolysis was found to equal 800 ppm. Therefore, the results could possibly be summarized as follows:

- Poly(MV) is hardly hydrolysed.
- Poly(LA) exhibits a low rate of hydrolysis because of its high crystallinity.
- Poly(MV-co-LA)s are amorphous and have better hydrolysability than the homopolymers.
- The tendency of the hydrolysis of poly(MV-co-LA)s is similar to that of poly(CL-co-LA)s; this means that the methyl group on MV unit has little effect on hydrolysis.
- The optimum copolymer composition ratio for achieving maximum *TOC* values is influenced jointly by hydrolysability and crystallinity.

Ester bonds are prone to hydrolysis by lipase and are cleaved into water-soluble oligomers, thus finally resulting in  $\omega$ -hydroxycarboxylic acid. The enzymatic hydrolysis was carried out with the copolymers of MV/L=29/71, which were easily hydrolysed at 70°C (Table 6). In a previous paper<sup>33</sup>, it was reported that in the enzymatic hydrolysis using *Rhizopus arrhizus* lipase both the homopolymers had low hydrolysability whereas the copolymers had high hydrolysability, reaching a maximum at 30 mol% of MV. On the contrary, poly(CL-co-LA)s display the highest hydrolysability around 80 mol% of CL although in non-enzymatic hydrolysis the tendency for both poly(MV-co-LA) and poly(CL-co-LA) is similar. These results suggest that the methyl group on MV unit suppresses the lipase hydrolysis, thus shifting the *TOC* peak, where maximum hydrolysis occurred, from LA side to MV/CL side. The blank test without any enzymes corresponds to simple hydrolysis at 37°C. It should be mentioned that, although non-enzymatic hydrolysis of polymers hardly occurred within the first 24 h, all lipases used and, in particular, the lipases from *Rhizopus arrhizus* and *R. delemar*, proved to be very effective in promoting hydrolysis. Since these lipases are from different origins, such as fungi, yeast and bacilli, these novel copolymers are expected to show high susceptibility to environmental degradation.

### REFERENCES

- Huang, S. J. 'Biodegradable polymers', in 'Encyclopedia of Polymer Science and Engineering', 1985, Vol. 2, p. 220
- Vert, M., Li, M. S., Spenlehauer, G. and Guerin, P. J. *Mater. Sci.: Mater. Med.* 1992, **3**, 432
- Doi, Y., Kunioka, M., Nakamura, Y. and Soga, K. *Macromolecules* 1988, **21**, 2722
- Tokiwa, Y. and Suzuki, T. *Nature* 1977, **266**, 270
- Kawabata, N. *Kobunshi Ronbunshu* 1993, **50**, 809
- Nakayama, A., Iyoda, J., Yamamoto, N. and Shimohara, I. *Kobunshi Ronbunshu* 1993, **50**, 747

- 7 Satyanarayana, D. and Chatterji, P. R. *J. Macromol. Sci.-Rev. Macromol. Chem. Phys. (C)* 1993, **33**, 349
- 8 Gilding, D. K. and Reed, A. M. *Polymer* 1979, **20**, 1459
- 9 Pitt, C. G., Jeffcoat, A. R., Zweidinger, R. A. and Schindler, A. E. *J. Biomed. Mater. Res.* 1979, **13**, 497
- 10 Asano, M., Yoshida, M. and Kaetsu, I. *Makromol. Chem., Rapid Commun.* 1985, **6**, 509
- 11 Helder, J., Feijen, J., Lee, S. J. and Kim, S. W. *Makromol. Chem., Rapid Commun.* 1986, **7**, 193
- 12 Gogolewski, S. and Pennings, A. J. *Makromol. Chem., Rapid Commun.* 1983, **4**, 213
- 13 Ouchi, T. and Fujino, A. *Makromol. Chem.* 1989, **190**, 1523
- 14 Otani, N., Kimura, Y. and Kitao, T. *Kobunshi Ronbunshu* 1987, **44**, 701
- 15 Jamshidi, K., Hyon, S.-H. and Ikada, Y. *Polymer* 1988, **29**, 2229
- 16 Reeve, M. S., McCarthy, S. P., Downey, M. J. and Gross, R. A. *Macromolecules* 1994, **27**, 825
- 17 Feng, X. D., Song, C. X. and Chen, W. Y. *J. Polym. Sci., Polym. Lett. Edn.* 1983, **21**, 593
- 18 Fukuzaki, H. and Aiba, Y. *Makromol. Chem.* 1989, **190**, 1553
- 19 Albertsson, A.-C., Löfgren, A. and Sjöling, M. *Makromol. Chem., Macromol. Symp.* 1993, **73**, 127
- 20 Kimura, Y., Matsuzaki, Y., Yamane, H. and Kitao, T. *Polymer* 1989, **30**, 1342
- 21 Zhu, K. J., Xiangzhou, L. and Shilin, Y. *J. Polym. Sci. (C) Polym. Lett.* 1986, **24**, 331
- 22 Cohen, D. and Younes, H. *J. Biomed. Mater. Res.* 1988, **22**, 993
- 23 Sawhney, A. S. and Hubbell, J. A. *J. Biomed. Mater. Res.* 1990, **24**, 1397
- 24 Hu, D. S. and Liu, H.-J. *J. Appl. Polym. Sci.* 1994, **51**, 473
- 25 Helder, J., Kohn, F. E., Sato, S., Van den Berg, J. W. and Feijen, J. *Makromol. Chem., Rapid Commun.* 1985, **6**, 9
- 26 Bero, M., Kasperczyk, J. and Adamus, G. *Makromol. Chem.* 1993, **194**, 907
- 27 Kricheldorf, H. R., Berl, M. and Scharnagl, N. *Macromolecules* 1988, **21**, 286
- 28 Kricheldorf, H. R. and Kreiser, I. *J. Macromol. Sci.-Chem. (A)* 1987, **24**, 1345
- 29 Zhang, X., Wyss, U. P., Pichora, D. and Goosen, M. F. A. *J. Macromol. Sci.-Pure Appl. Chem. (A)* 1993, **30**, 933
- 30 Hamitou, A., Jerome, R. and Teyssie, Ph. *J. Polym. Sci., Polym. Chem. Edn.* 1977, **15**, 1035
- 31 Tokiwa, Y., Suzuki, T. and Ando, T. *J. Appl. Polym. Sci.* 1979, **24**, 1701
- 32 Nakayama, A., Kawasaki, N., Yamamoto, N. and Arvanitoyannis, I. *Sen-i Gakkaishi* submitted
- 33 Nakayama, A., Kawasaki, N., Arvanitoyannis, I. and Yamamoto, N. 'Biodegradable Plastics and Polymers', Elsevier, Amsterdam, 1994, p. 557