Study of Biodegradability of Poly(δ-valerolactone-*co*-L-lactide)s

A. NAKAYAMA,[1] N. KAWASAKI,[1] Y. MAEDA,[1] I. ARVANITOYANNIS,[2] S. AIBA,[1] N. YAMAMOTO[1]

[1] Osaka National Research Institute, AIST, Department of Organic Materials, 1-8-31 Midorigaoka, Ikeda, Osaka 563, Japan

[2] Aristotle University of Thessaloniki, Department of Food Science, School of Agriculture, P.O. Box 265, 54006 Thessaloniki, Greece

Received 27 November 1996; accepted 21 April 1997

ABSTRACT: The biodegradability of poly(δ-valerolactone-*co*-L-lactide)s was studied both with enzymatic (lipase from *Rhizopus arrhizus*) and nonenzymatic hydrolyses. The hydrolyzability was evaluated by recording the amount of the hydrolyzed water-soluble products. The enzymatic hydrolysis was considerably affected by copolymer composition. The copolyester, the most susceptible to enzymatic hydrolysis, was the one containing a 90 mol % δ-valerolactone unit. The copolymers were also nonenzymatically hydrolyzed at 70°C. The results were similar to those of enzymatic hydrolysis, confirming the influence of copolymer composition on the hydrolyzability. However, the L-lactide rich copolymers were more susceptible to hydrolysis. These results suggest that poly(δ-valerolactone) is easily degraded by lipase, whereas poly(L-lactide) is degraded through simple hydrolysis. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **66:** 741–748, 1997

Key words: δ-valerolactone; L-lactide; biodegradable polymer; polyester; hydrolysis

INTRODUCTION

The current environmental pollution, which is mainly attributable to the extensive use of bioresistant synthetic polymers, has become a crucial problem. Biodegradable polymers are expected to act as alternative materials for solving this problem.[1–10] Their synthetic routes are mainly biosynthesis, chemical synthesis, and blending of common plastics with biodegradable materials such as polysaccharides. Among these routes, chemical synthesis has the indisputable advantage of controlling biodegradability and mechanical properties by molecular design. Aliphatic polyesters have attracted many workers' research interest, and several research studies have been reported.[11–16]

It is well-known that poly(L-lactide) (PLLA) is biodegradable and hydrolyzable. Furthermore, since its monomer unit is L-lactic acid, which is present in living organisms, it is expected to be particularly useful as biomaterial.[17–21] However, it is essential that both the high crystallinity and T_m of PLLA be lowered to improve its flexibility. For example, random, block, or alternating copolymers of LLA with another comonomer, or star-shaped polymer, among others, have been previously reported.[22–30] Various possible applications of PLLA to biomaterials have been suggested occasionally, among which are as suture or implants for orthopedic use.

Recent studies were also focused on polyesters synthesized from lactones.[31–36] Poly(ε-caprolactone) (PCL) is a representative biodegradable polymer that has already been commercialized.

Correspondence to: A. Nakayama.

Journal of Applied Polymer Science, Vol. 66, 741–748 (1997)
 CCC 0021-8995/97/040741-08

However, its rather low T_m (70°C) constitutes a serious drawback.

Copolymerization of LLA with lactones results in copolymers of enhanced flexibility and intermediate T_m, thereby widening the range of their possible applications. For example, poly(CL-*co*-LLA)s have been studied in an attempt to lower the T_m of PLLA, to investigate the appropriate polymerization conditions in terms of temperature and catalyst, and to get an insight into the relationships between composition and thermal properties or biodegradability.[37–43] Copolymerization of LLA with CL and β-methyl-δ-valerolactone, their enzymatic–nonenzymatic hydrolyzabilities, bioabsorbability, and effect of polymer structure and composition on biodegradability have been reported.[44–47] δ-Valerolactone (VL) is a 6-membered lactone which, although lacking one methylene group compared with CL, is able to copolymerize rather satisfactorily. In this article, some further findings on the biodegradability of poly(VL-*co*-LLA) are reported.

EXPERIMENTAL

Reagents

VL (Aldrich) was purified by distillation in vacuum. LLA (Boehringer Ingelheim) was purified by recrystallization from ethyl acetate. Tetraphenyl tin (Wako) was used as an initiator without purification. The enzyme for the biodegradation test was lipase from *Rhizopus arrhizus* (Boehringer, Mannheim, 50,000 units/ml).

Measurements

IR spectra were recorded on a Nicolet 710 FT IR spectrometer using film samples cast on a sodium chloride plate from chloroform solutions. ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were recorded on a Jeol JNM A-500 spectrometer (solvent; chloroform-d). Thermal analyses were performed on a Rigaku Model-10A differential scanning calorimeter (DSC). Samples of 2–8 mg (weighed into aluminum pans) were measured from −60 to 200°C at a heating rate of 10°C/min. Molecular weight distributions were determined with a Tosoh gel permeation chromatography system (HLC-8020) using polystyrene standards and chloroform as elution solvent. The columns were a TSKgel G4000H_{XL} and a TSKgel G3000H_{XL} with a limited exclusion molecular weight of 4×10^5.

Copolymerizations

The copolymerizations of LLA with VL were carried out in bulk. Comonomers and tetraphenyl tin (0.3 mol % versus total monomers) were charged on a dried ampoule. After degassing, the ampoule was sealed under vacuum and heated at 120°C for 3 days. The contents of the ampoule were allowed to cool down to room temperature, and the contents were dissolved in chloroform after the addition of a few drops of methanol to suppress the polymerization. Crude polymer was obtained as a precipitate in excess methanol and was purified by repeated precipitations. A series of copolymers with different compositions were synthesized by varying the feed molar ratio of VL/LLA from 100/0 to 20/80. The molar compositions of the copolymers and the sequence distributions of the comonomer units were determined from ^{1}H-NMR and ^{13}C-NMR spectra.

Biodegradation Tests

Biodegradability was evaluated both by enzymatic and nonenzymatic hydrolysis tests.[48] In the case of enzymatic hydrolysis, 25 mg of polymer samples were coated over a fixed area to each of the three tubes, and 2 ml of phosphate buffer (KH_2PO_4/Na_2HPO_4, pH 7.0) was added to the tubes. Then, 200 units of the lipase from *Rhizopus arrhizus* was added to the tubes with the exception of one for a control test. The hydrolysis was carried out at 37°C for 24 h. After filtration (0.2 mm membrane filter), a small amount of 1*N* HCl was added to the filtrate to acidify the solution and to remove CO_2 from it. The total organic carbon concentration (TOC) was measured in duplicate. The TOC data were averaged and corrected appropriately by taking into account the blank levels.

In the case of nonenzymatic hydrolysis, 25 mg of polymer samples were added to each of three tubes. The first two tubes were used for accelerated hydrolysis tests and the other for a blank test at room temperature. TOC values were measured and averaged from the recorded data of the first two tubes after the blank levels were subtracted.

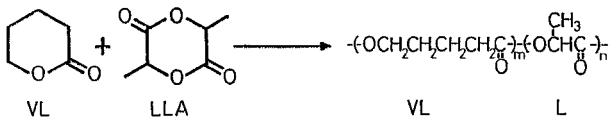
Table I Copolymerization of δ-Valerolactone (VL) with L-Lactide (LLA) Using Tetraphenyltin

Feed, VL/LLA (mol %) (eq %)	Polymer Composition VL/L (mol %)	Yield %	Molecular Weight		T_g (°C)	T_m (°C)	Block Length	
			Mn × 10^4	Mw/Mn			VL	L
0/100 (0/100)	0/100 (polyLA)		14.1	1.4	53	178	0	—
20/80 (11/89)	10/90	97	21.2	1.5	36	122	1.3	8.2
40/60 (25/75)	24/76	99	10.2	1.5	11	—	1.8	3.8
50/50 (33/67)	33/67	99	9.9	1.3	−15	—	2.1	2.8
67/33 (50/50)	50/50	88	10.3	1.5	−23	—	2.1	1.9
80/20 (67/33)	66/34	81	8.4	1.4	−39	—	3.1	1.5
86/14 (75/25)	75/25	85	10.7	1.4	−47	31	4.2	1.4
95/5 (90/10)	90/10	82	7.5	1.6	−55	45	9.8	1.2
100/0 (100/0)	100/0 (polyVL)		8.6	1.5	−66	62	—	0

RESULTS AND DISCUSSION

Characterization of poly(δ-valerolactone-*co*-L-lactide)

Several copolymerizations were carried out by varying the feed molar ratio of VL/LLA from 100/0 to 0/100 (Table I). In this table, LLA is replaced by the L-lactic acid unit (L), which is a half unit of L-lactide (Scheme **1**). The copolymers were obtained with satisfactory yields, and their copolymer compositions corresponded to the monomer feed ratio. The molecular weights and their polydispersity indexes were 7 to 20 × 10^4 and 1.3 to 1.6, respectively. The DSC curves show that L-rich copolymers have a relatively high T_m (higher than 100°C), whereas VL-rich copolymers have lower T_m (around 70°C). In the case of copolymer composition of approximately 50/50, no T_m was observed, and the copolymers were random and amorphous. The glass transition temperatures of VL/LLA copolymers followed a linear relationship versus VL content. The glass transition temperatures varied between two extreme values: 53°C for PLLA down to −66°C for PVL. The ^{1}H-NMR spectra of poly(VL-*co*-LLA) and their assignment are shown in Figure 4(a). Protons from (C=O)—O—C<u>H</u>$_2$ from the VL unit were observed at 4.06 ppm and at 4.15 ppm. The former was assigned to a diad homo (VL-<u>VL</u>) and the latter to diad hetero (L-<u>VL</u>). Protons from O—(C=O)—C<u>H</u>$_2$ were at 2.34 ppm (diad homo, <u>VL</u>-VL) and 2.43 ppm (diad hetero, <u>VL</u>-L). Furthermore, the methyne protons from the L unit were observed at 5.07 ppm as a triad homo sequence, and plural signals, which seemed to be from triad heteros, were observed [Fig. 4(a)]. These assignments were determined by the chemical shifts of both homopolymers, correlation of signal integrals and copolymer composition, and ^{1}H-^{1}H and ^{13}C-^{1}H cosy spectra. Since the signals of both homo and hetero sequences in VL and L units were clearly separated, the average block lengths of VL and L units in the main chain were calculated by using the intensity of the signals (Table I). The results confirm that the obtained copolymers were random.



Scheme 1

Hydrolysis of Copolymer

The biodegradability of the obtained copolymers was evaluated by nonenzymatic hydrolysis at 70°C and by enzymatic hydrolysis by using lipase from *Rhizopus arrhizus* at 37°C. To obtain excellent reproducibility, samples of a fixed weight (25 mg) were coated upon the inner surface of tubes with standard area (2 cm^2) by evaporation of chloroform solution. The measurement of hydrolyzability was based on the amount of the water-soluble part produced by hydrolysis and determined by measurement of TOC values.[48]

An accelerated hydrolysis test without enzyme was carried out with homopolymers (PVL and PLLA) and copolymers of various compositions. TOC measurements were taken periodically over

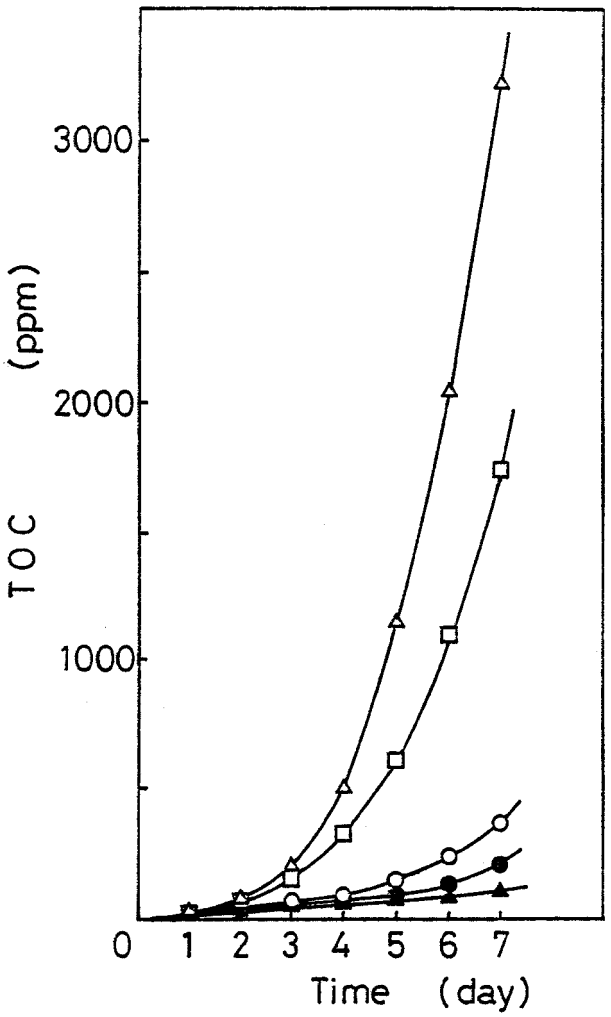


Figure 1 Nonenzymatic hydrolysis curves of poly(δ-valerolactone-*co*-L-lactide)s in distilled water at 70°C: (○) Poly(LLA); (△) VL/L = 24/76; (□) VL/L = 50/50; (●) VL/L = 90/10; (▲) poly(VL).

a period of 7 days to evaluate the degree of hydrolysis (Fig. 1). Although PVL was hardly hydrolyzed in a week, the hydrolysis of all its copolymers proceeded in proportion to their exposure time. The hydrolysis rates of these copolymers were considerably larger than PLLA, which is well known to be a hydrolyzable polymer. The copolymers with 24% VL and 50% VL were hydrolyzed with 85 and 100 wt % of copolymer in three weeks.

Figure 2 shows the dependence of hydrolyzability on the copolymer composition. The hydrolyzability was calculated by dividing the experimental TOC values by the theoretical TOC as follows:

$$\text{Hydrolyzability (\%)} = \text{TOC exp.}/\text{TOC theor.} \times 100$$

$$\text{TOC theor. (ppm)} = (225 + 150\upsilon)/(36 + 14\upsilon) \times 1000$$

υ = VL content in copolymer ($0 \leqq \upsilon \leqq 1$)*

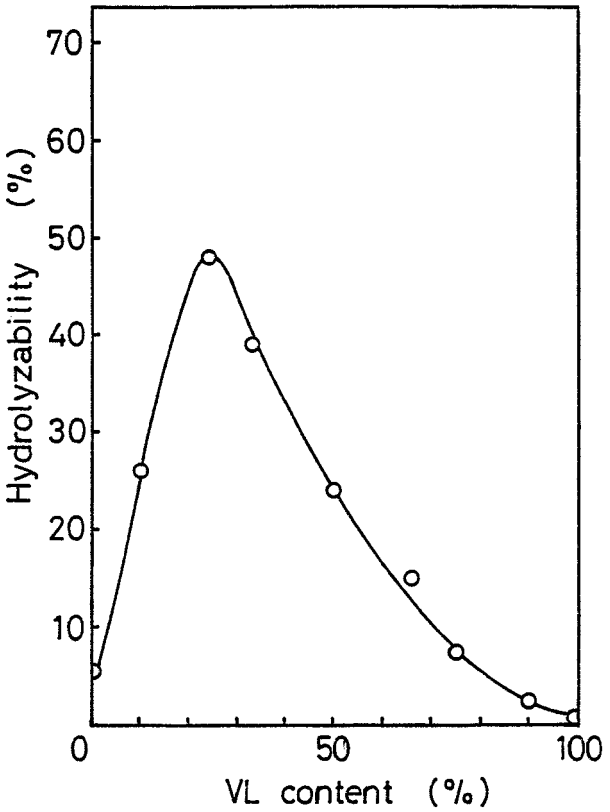


Figure 2 Correlation between nonenzymatic hydrolysis of poly(δ-valerolactone-*co*-L-lactide)s, in distilled water at 70°C for 7 days and polymer composition.

* The average (A) of copolymer that contains $\upsilon \times 100$ (%) of VL is represented as follows:

$$A = \upsilon(C_5H_8O_2) + (1 - \upsilon)(C_3H_4O_2)$$
$$= C_{3+2\upsilon}H_{4+4\upsilon}O_2.$$

Therefore, the weight percentage (W) of carbon in the copolymer is

$$W = 12(3 + 2\upsilon)/\{12 \times (3 + 2\upsilon) + 1 \times (4 + 4\upsilon) + 16 \times 2\} \times 100$$
$$= (9 + 6\upsilon)/(18 + 7\upsilon) \times 100.$$

The sample used was 25 mg and the solution volume was 2 ml, so the theoretical TOC value is calculated as follows:

$$TOC_{theor} = 25(W/100) \times (1000/2)$$
$$= (225 + 150\upsilon)/(36 + 14\upsilon) \times 1000.$$

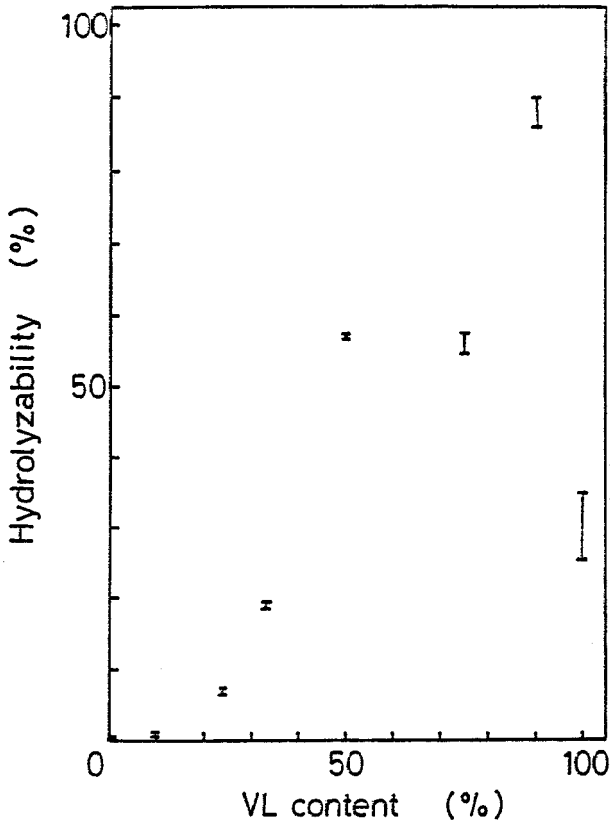


Figure 3 Enzymatic hydrolysis of poly(δ-valerolactone-*co*-L-lactide)s after its exposure to lipase from *Rhizopus arrhizus* (200 units) at 37°C for 24 h.

Nonenzymatic hydrolysis of poly(CL-*co*-LA)s has been reported by several groups.[18,23,49] Poly(CL-block-DLLA) was hydrolyzed at 50°C for 70 days, and the hydrolysis of the copolymer was faster than PCL, with an increase in L content producing accelerated hydrolysis.[18,23] The weight loss of poly(CL-random-LLA), (CL/L = 8/92), was faster at 37°C in a phosphate buffer compared with PLLA despite the fact that no change of tensile strength was observed before and after hydrolysis. Furthermore, biodegradation in living organisms proceeds quite rapidly in terms of molecular weight decrease.[49] The reports mentioned above are the results of poly(CL-*co*-LA) hydrolysis; however, those of poly(VL-*co*-LLA) hydrolysis show a similar trend, that is, the copolymers were hydrolyzed faster than both the homopolymers. In particular, 24% VL copolymer showed the maximum hydrolyzability in the series. PLLA was hydrolyzed rather slowly compared with the copolymers, and PVL was hardly hydrolyzed. These results show that PLLA is essentially biodegradable even when exposed to water. However, its quite high crystallinity limits its quick degradation. Therefore, copolymerization is expected to reduce the crystallinity, thereby increasing the hydrolyzability, especially within the region of L-rich composition.

Enzymatic hydrolysis of various composition copolymers was carried out with the lipase from *Rhizopus arrhizus,* a common fungi of the natural environment (Fig. 3). Therefore, the biodegradability assessment of a polymer exposed to such a lipase is equivalent to determination of polymer biodegradability in a natural environment. The relationships between copolymer composition and enzymatic hydrolyzability showed a different trend from the results of nonenzymatic hydrolysis. The enzymatic hydrolyzability was quite pronounced at the VL-rich region as compared with the L-rich region. It was previously reported that lipases can effectively degrade aliphatic polyesters. However, polyesters having side chains, for example, methyl group, are less degraded. In this case, it is clear that PVL is much more prone to hydrolysis than PLLA (Fig. 3). Therefore, in the presence of the enzyme, the maximum hydrolysis of polymer composition is at a VL-rich region, reflecting the affinity of PVL for enzymatic hydrolysis. On the contrary, without enzyme, the maximum hydrolyzability exists at the L-rich region because PVL is nonenzymatically inert to hydrolysis and PLLA is nonenzymatically hydrolyzed. The copolymers were hydrolyzed more easily than both the homopolymers, probably because of their decreased crystallinity and tacticity.

Hydrolyzed Products

The enzymatic and nonenzymatic hydrolysis products were studied by ^{1}H-NMR spectroscopy.*

* The composition (VL/L) of water-soluble hydrolyzed products was calculated from the intensities of O-methylene and (C=O)-methylene protons (VL unit) and methyne protons (L unit).

$$\mathrm{VL/L} = \Sigma\, \mathrm{I_{VL}}/(4 \times \Sigma\, \mathrm{I_L}) = \upsilon/(1-\upsilon)$$

Therefore, the unit structure of copolymers is shown as $(\mathrm{VL}_\upsilon \mathrm{L}_{1-\upsilon})_n$, and the repeating number, n, is represented as follows:

$$n = \frac{(\Sigma\, \mathrm{I_{VL,ester}} + 2 \times \Sigma\, \mathrm{I_{L,ester}})}{(\Sigma\, \mathrm{I_{VL,end}} + 2 \times \Sigma\, \mathrm{I_{L,end}})} + 1.$$

Figure 4(b, c) show the ^{1}H-NMR spectra of water-soluble products, where (b) and (c) stand for the copolymers VL/L = 90/10 and VL/L = 50/50, respectively. The samples were filtrated and dried after accelerated hydrolysis at 70°C for 3 weeks. The hydrolyzability of these samples was approximately 90%. In the following discussion, VL and L sequences are defined as follows:

$$\text{VL: } —OCH_2CH_2CH_2CH_2C(=O)—$$

$$\text{L: } —OCH(CH_3)C(=O)—$$

HO-VL and L-COOH stand for the end groups of alcohol or carboxylic acid types.

In Figure 4(b), methylene protons of —C<u>H</u>$_2$C(=O)— were observed at 2.4 ppm and were assigned as overlapped triplets of ester type (<u>VL</u>-VL) and carboxylic acid type (<u>VL</u>-COOH) diad sequences. Methylene protons of —O—C<u>H</u>$_2$— appeared at 4.1 and 3.6 ppm and assigned as an ester type (VL-<u>VL</u>) and an alcohol type (HO-<u>VL</u>), respectively. Furthermore, the intensity ratio was (VL-<u>VL</u>)/(HO-<u>VL</u>) = 3.5/1. These results are in favor of the existence of tetramer or pentamer VL, the end groups of which are hydroxyl and carboxyl groups. The average chemical structures of degraded products were calculated from the peak intensity and were (b): $VL_{3.2}L_{0.4}$, (c): $VL_{2.3}L_{1.2}$. By taking into account the value of (b), the average chain length of VL is approximately 3. The L-VL sequence was observed at 4.2 ppm, and the product was found to be the mixture of VL oligomers and trimers or tetramers, or both, consisting of VL and L units. The proton signals of methyne from the L unit were mainly observed at 4.2–4.4 ppm as multiple quartets assigned to HO-<u>L</u>-. Furthermore, quite weak signals of methynes at 4.9–5.2 ppm were assigned to ester types (VL-<u>L</u>- or L-<u>L</u>-). Therefore, it is concluded that most of the VL-L and L-L bonds were hydrolyzed and that only few remained intact. In the case of hydrolysis of VL/L = 50/50, the intensity of the signal at 3.6 ppm due to the alcohol type O-C<u>H</u>$_2$ (HO-<u>VL</u>) was rather weak, whereas that of the ester type O-C<u>H</u>$_2$s (that is VL-<u>VL</u> and L-<u>VL</u>) was particularly strong [Figure 4(c)]. Furthermore, the methyne signals of the alcohol type, HO-<u>L</u>, were typical for this group. From these results, most end groups of the alcohol side in the hydrolyzed products should be HO-<u>L</u>-. This suggests that L-L and VL-L bonds can be easily hydrolyzed compared with VL-VL or L-VL bonds when the polymer main chain is nonenzymatically hydrolyzed as shown below:

$$\text{L-L, VL-L} \gg \text{VL-VL, L-VL}$$

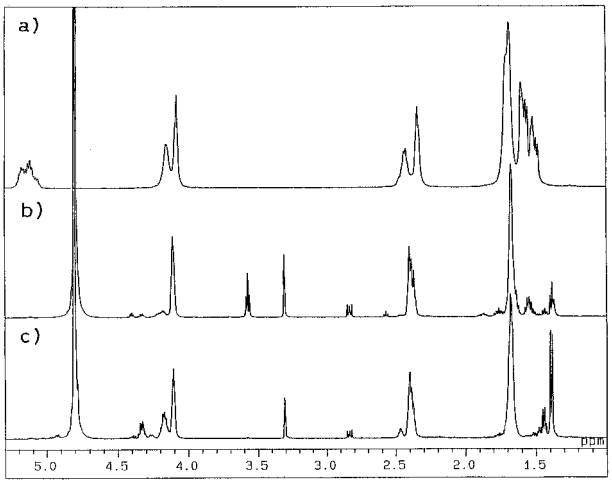


Figure 4 ^{1}H-NMR (500 MHz) spectra of water-soluble hydrolyzed products of poly(δ-valerolactone-*co*-L-lactide)s after nonenzymatic hydrolysis in distilled water at 70°C for 3 weeks: (a) copolymer (VL/L = 50/50) prior to hydrolysis ($CDCl_3$, *rt*); (b) hydrolyzed products from the VL/L = 90/10 copolymer (D_2O/CD_3OD(1/1), *rt*); (c) hydrolyzed products from the VL/L = 50/50 copolymer (D_2O/CD_3OD (1/1), *rt*).

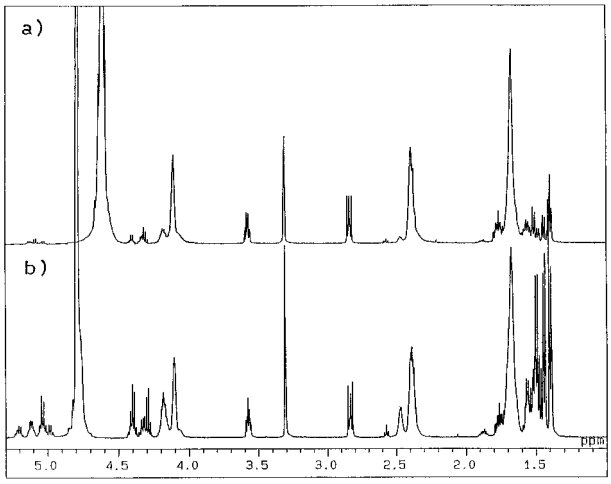


Figure 5 ^{1}H-NMR (500 MHz) spectra of water-soluble hydrolyzed products of poly(δ-valerolactone-*co*-L-lactide)s after exposure to lipase from *Rhizopus arrhizus* (200 units) at 37°C for 24 h: (a) hydrolyzed products from the VL/L = 90/10 copolymer (D_2O/CD_3OD(1/1), 45°C; (b) hydrolyzed products from the VL/L = 50/50 copolymer (D_2O/CD_3OD(1/1), *rt*).

The structure confirmation of the enzymatically hydrolyzed product was carried out by following the above-mentioned procedure after treatment with 1000 units of the lipase from *Rhizopus arrhizus* (Fig. 5). The chemical structures of the degraded products measured with ^{1}H-NMR were (a) $VL_{3.1}L_{0.8}$ (VL/L = 90/10) and (b) $VL_{1.2}L_{1.7}$ (VL/L = 50/50). The NMR spectrum and the anticipated chemical structure of the hydrolyzed product of VL/L = 90/10 were quite similar to those of the nonenzymatically hydrolyzed product of the same polymer (VL/L = 90/10). In the case of VL/L = 50/50, the ^{1}H NMR spectrum on the contrary, showed the alcoholic end group (HO-$\underline{VL}$) as multiple triplets, which were observed to be quite weak in the case of nonenzymatic hydrolysis. Furthermore, the average chemical structure showed that the block length of VL unit was considerably smaller than that of the nonenzymatic one, whereas the length of the L unit was greater. These results support our assumption that, in the case of the enzymatic hydrolysis, VL-VL and L-VL bonds are predominantly cleavaged.

REFERENCES

1. J. M. Curley, B. Hazer, R. W. Lenz, and R. C. Fuller, *Macromolecules,* **29,** 1762 (1996).
2. H. R. Kricheldolf and B. W. Schulz, *J. Polym. Sci.: Part A: Polym. Chem.,* **33,** 2193 (1995).
3. A.-C. Albertsson and M. Eklund, *J. Polym. Sci.: Part A: Polym. Chem.,* **32,** 265 (1994).
4. I. Arvanitoyannis, A. Nakayama, N. Kawasaki, and N. Yamamoto, *Polymer,* **36,** 857 (1995).
5. K. E. Uhrich, A. Gupta, T. Thomas, C. T. Laurencin, and R. Langer, *Macromolecules,* **28,** 2184 (1995).
6. M. Okada, Y. Okada, and K. Aoi, *J. Polym. Sci.: Part A: Polym. Chem.,* **33,** 2813 (1995).
7. M. Harkonen, K. Hiltunen, M. Malin, and J. V. Seppala, *J. Macromol. Sci.,* **A32,** 857 (1995).
8. Z. Jedlinski, P. Kurcok, and R. W. Lenz, *J. Macromol. Sci.,* **A32,** 797 (1995).
9. P. J. A. In't veld, Z.-R. Shen, G. A. J. Takens, P. J. Dijkstra, and J. Feijen, *J. Polym. Sci.: Part A: Polym. Chem.,* **32,** 1063 (1994).
10. I. Rashkov, N. Manolova, S. M. Li, J. L. Espartero, and M. Vert, *Macromolecules,* **29,** 50 (1996).
11. G. Scott and D. Gilead, in *Degradable Polymers,* Chapman & Hall, London, 1995, p. 1.
12. H. Abe, I. Matsubara, and Y. Doi, *Macromolecules,* **28,** 844 (1995).
13. T. Ikejima, N. Yoshie, and Y. Inoue, *Macromol. Chem., Phys.,* **197,** 869 (1996).
14. P. Schmidt, H. Keul, and H. Hocker, *Macromolecules,* **29,** 3674 (1996).
15. S. Mehta, R. S. Raghuvanshi, A. Misra, S. Ganga, and G. P. Talwar, *J. Appl. Polym. Sci.,* **58,** 1495 (1995).
16. Y. Maeda, A. Nakayama, N. Kawasaki, K. Hayashi, S. Aiba, and N. Yamamoto, *J. Environ. Polym. Deg.,* **4,** 225 (1996).
17. H. Tsuji and Y. Ikada, *J. Appl. Polym. Sci.,* **60,** 2367 (1996).
18. D. W. Grijpma and A. J. Pennings, *Macromol. Chem. Phys.,* **195,** 1633 (1994).
19. M. Asano, M. Yoshida, and I. Kaetsu, *Makromol. Chem., Rapid Commun.,* **6,** 509 (1985).
20. J. Helder, J. Feijen, S. J. Lee, and S. W. Kim, *Makromol. Chem., Rapid Commun.,* **7,** 193 (1986).
21. T. Ouchi and A. Fujino, *Makromol. Chem.,* **190,** 1523 (1989).
22. Y. Kimura, Y. Matsuzaki, H. Yamane, and T. Kitao, *Polymer,* **30,** 1342 (1989).
23. X. D. Feng, C. X. Song, and W. Y. Chen, *J. Polym. Sci., Polym. Lett. Ed.,* **21,** 593 (1983).
24. M. S. Reeve, S. P. McCarthy, M. J. Downey, and R. A. Gross, *Macromolecules,* **27,** 825 (1994).
25. A. M. Reed and D. K. Gilding, *Polymer,* **22,** 494 (1981).
26. H. Fukuzaki, Y. Aiba, M. Yoshida, M. Asano, and M. Kumakura, *Makromol. Chem.,* **190,** 1553 (1989).
27. H. R. Kricheldolf, T. Mang, and J. M. Jonte, *Macromolecules,* **17,** 2173 (1984).
28. A.-C. Albertsson, A. Lofgren, and M. Sjoling, *Makromol. Chem., Macromol. Symp.,* **73,** 127 (1993).
29. S. H. Kim, Y.-K. Han, Y. H. Kim, and S. I. Hong, *Makromol. Chem.,* **193,** 1623 (1992).
30. I. Arvanitoyannis, A. Nakayama, E. Psomiadou, N. Kawasaki, and N. Yamamoto, *Polymer,* **37,** 651 (1996).
31. J. Xu, R. A. Gross, D. L. Kaplan, and G. Swift, *Macromolecules,* **29,** 3857 (1996).
32. A.-C. Albertsson and A. Lofgren, *J. Macromol. Sci.,* **A32,** 41 (1995).
33. I. Arvanitoyannis, A. Nakayama, E. Psomiadou, N. Kawasaki, and N. Yamamoto, *Polymer,* **37,** 651 (1996).
34. Y. Hori, A. Yamaguchi, and T. Hagiwara, *Polymer,* **36,** 4703 (1995).
35. M. Yamashita, Y. Takemoto, E. Ihara, and H. Yasuda, *Macromolecules,* **29,** 1798 (1996).
36. Y. Yamashita, T. Tsuda, M. Okada, and S. Iwatsuki, *J. Polym. Sci.: Part A-1,* **4,** 2121 (1966).
37. D. W. Grijpma and A. J. Pennings, *Polym. Bull.,* **25,** 335 (1991).
38. M. Bero, J. Kasperczyk, and G. Adamus, *Makromol. Chem.,* **194,** 907 (1993).

39. X. Zhang, U. P. Wyss, D. Pichora, and M. F. A. Goosen, *J.M.S.-Pure Appl. Chem.,* **A30,** 933 (1993).
40. G. Perego and T. Vercellio, *Makromol. Chem.,* **194,** 2463 (1993).
41. J.-M. Vion, R. Jerome, and P. Teyssie, *Macromolecules,* **19,** 1828 (1986).
42. H. R. Kricheldorf, I. K. Saunders, C. Jurgens, and D. Wolter, *Macromol. Chem. Symp.,* **103,** 85 (1996).
43. M. Hiljanen, T. Karjalainen, and J. Seppala, *J. Appl. Polym. Sci.,* **59,** 1281 (1996).
44. A. Nakayama, I. Arvanitoyannis, N. Kawasaki, K. Hayashi, and N. Yamamoto, in *Advanced Biomaterials in Biomedical Engineering and Drug Delivery Systems,* Springer-Verlag, 1995, p. 241.
45. A. Nakayama, N. Kawasaki, I. Arvanitoyannis, J. Iyoda, and N. Yamamoto, *Polymer,* **36,** 1295 (1995).
46. A. Nakayama, N. Kawasaki, I. Arvanitoyannis, S. Aiba, and N. Yamamoto, *J. Environ. Polym. Deg.,* **4,** 205 (1996).
47. A. Nakayama, N. Kawasaki, N. Yamamoto, and I. Arvanitoyannis, *Sen-i Gakkaishi,* **51,** 131 (1995).
48. Y. Tokiwa, T. Suzuki, and T. Ando, *J. Appl. Polym. Sci.,* **24,** 1701 (1979).
49. T. Matsui, T. Nakamura, T. Tsuda, Y.-H. Le, Y. Shimizu, W.-I. Cha, S.-H. Hyon, Y. Ikada, and K. Nishiya, *J. Jpn. Soc. Biomater.,* **11,** 330 (1993).