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Autocatalytic hydrolysis of amorphous-made polylactides: effects of L-lactide content, tacticity, and enantiomeric polymer blending

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Abstract

Poly(DL-lactide), i.e., poly(DL-lactic acid) (PDLLA), poly(L-lactide), i.e. poly(L-lactic acid) (PLLA), and poly(D-lactide), i.e., poly(D-lactic acid) (PDLA) were synthesized to have similar molecular weights. The non-blended PDLLA, PLLA, and PDLA films and PLLA/PDLA(1/1) blend film were prepared to be amorphous state, and the effects of L-lactide unit content, tacticity, and enantiomeric polymer blending on their autocatalytic hydrolysis were investigated in phosphate-buffered solution (pH7.4) at 37 °C for up to 24 months. The results of gravimetry, gel permeation chromatography (GPC), and tensile testing showed that the autocatalytic hydrolyzabilities of polylactides, i.e. poly(lactic acid)s (PLAs) in the amorphous state decreased in the following order: nonblended PDLLA > nonblended PLLA, nonblended PDLA > PLLA/PDLA(1/1) blend. The high hydrolyzability of the nonblended PDLLA film compared with those of the nonblended PLLA and PDLA films was ascribed to the lower tacticity of PDLLA chains, which decreases their intramolecular interaction and therefore the PDLLA chains are susceptible to the attack from water molecules. In contrast, the retarded hydrolysis of PLLA/PDLA(1/1) blend film compared with those of the nonblended PLLA and PDLA films was attributable to the peculiar strong interaction between PLLA and PDLA chains in the blend film, resulting in the disturbed interaction of PLLA or PDLA chains and water molecules. The X-ray diffractometry and differential scanning calorimetry (DSC) elucidated that all the initially amorphous PLA films remained amorphous even after the autocatalytic hydrolysis for 16 (PDLLA film) and 24 [nonblended PLLA and PDLA films, PLLA/PDLA(1/1) blend film] months and that the melting peaks observed at around 170 and 220 °C for the PLLA/PDLA(1/1) blend film after the hydrolysis for 24 months were ascribed to those of homo- and stereocomplex crystallites, respectively, formed during heating at around 100 and 200 °C but not during the autocatalytic hydrolysis.

Keywords: Poly(lactide); Stereocomplex; Autocatalytic hydrolysis

1. Introduction

Polylactide, i.e. poly(lactic acid) (PLA) has been attracting much attention because it is producible from renewable resources, non-toxic, and degradable in the human body as well as in the environment [1–7]. Its applications include the bioabsorbable scaffolds for tissue regeneration, the matrices for drug delivery systems, and the alternatives for the commercial polymers such as polyethylene, polypropylene, and polystyrene [1–7]. Optically active poly(L-lactide), i.e. poly(L-lactic acid) (PLLA) and poly(D-lactide), i.e. poly(D-lactic acid) (PDLA) comprise isotactic sequences and therefore are crystallizable, while optically inactive poly(DL-lactide), i.e. poly(DL-lactic acid) (PDLLA) is composed of both isotactic and atactic sequences, and therefore is amorphous.

The hydrolysis of PLAs in aqueous media at around pH7 is believed to proceed via the self- or autocatalytic effect of their terminal carboxyl groups [1–7]. The effects of numerous parameters of molecular characteristics and highly-ordered structures on the autocatalytic hydrolysis of PLAs have been intensively studied in phosphate-buffered solution [1–23]. The crystallinity and crystalline thickness are the important parameters for determining the autocatalytic hydrolysis rates [1–23]. Despite these findings, in most of the studies concerning the effects of L-lactide unit content [$X_{\mathrm{LLA}} =$ (weight of L-lactide)/(weight of L-and D-lactides)] and tacticity of PLAs on their autocatalytic hydrolysis, the highly-ordered structures such as crystallinity and crystalline thickness were not controlled. In such studies, the hydrolysis of PLAs was affected by the complexed effects of X_{LLA}, tacticity and highly-ordered structures. In spite of the importance, few studies have been reported so far for the pure effects of X_{LLA} and tacticity of PLAs on their autocatalytic hydrolysis under controlled highly-ordered structures.

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On the other hand, in a previous paper, the autocatalytic hydrolysis of well-stereocomplexed enantiomeric blend and nonblended films from PLLA and PDLA has been studied [21]. It became evident that the autocatalytic hydrolysis of the well-stereocomplexed blend was retarded compared with that of the nonblended PLLA and PDLA films. This result was ascribed to the enhanced elution of the catalytic oligomers caused by the three-dimensional (3D) network structure of the blend film, and/or to the peculiar strong interaction between PLLA and PDLA in the amorphous region, which may have hindered the diffusion of water molecules into the blend specimens. However, it has not been elucidated which factor is crucial to lower autocatalytic hydrolysis rate of the blend film. The effects of the latter factor, i.e. the strong peculiar interaction between PLLA and PDLA, can be studied using amorphous-made blend specimens.

Similar to the investigation of the autocatalytic hydrolysis of PLAs, the effects of molecular characteristics, highly-ordered structures, and enantiomeric and diastereoisomeric polymer blending on proteinase K-catalyzed hydrolysis of PLAs have been intensively studied [7,24–31]. In a previous study, we studied the effects of molecular weight, X_{LLA}, and enantiomeric and diastereoisomeric polymer blending on proteinase K-catalyzed hydrolysis of PLA films [31]. In this study, all the specimens were made amorphous by melt-quenching to remove the effects of highly-ordered structures on their enzymatic hydrolysis. It was found that nonblended PLA films are enzymatically hydrolyzable when their X_{LLA} and average L-lactyl (a half of L-lactide) unit sequence length ($\mathrm{l_L}$) are higher than 0.3 and 3, respectively, and their average D-lactyl unit sequence length (l_{D}) is lower than 10, and that the presence of long D-lactyl unit sequences ($l_{\mathrm{D}} > 4$) as in PDLA hinders the enzymatic hydrolysis of long L-lactyl unit sequences even when long D- and L-lactyl unit sequences are present in the different molecules.

The purposes of this study are: (1) to investigate the pure effects of X_{LLA}, tacticity, and enantiomeric polymer blending on the autocatalytic hydrolysis of PLAs in the amorphous state; (2) to determine which parameter (3D network structure or peculiar strong interaction between PLLA and PDLA) is crucial to lower the autocatalytic hydrolysis rate of PLLA/PDLA blend; and (3) to compare the obtained results with those reported for proteinase K-catalyzed hydrolysis of PLAs. For these purposes, PDLLA, PLLA, and PDLA were synthesized to have similar molecular weights, and the autocatalytic hydrolysis of nonblended PDLLA, PLLA, PDLA films and PLLA/PDLA(1/1) blend film was carried out in the amorphous state in phosphate-buffered solution at 37 °C for up to 24 months. The hydrolyzed films were studied using gravimetry, gel permeation chromatography (GPC), tensile testing, differential scanning calorimetry (DSC), and X-ray diffractometry.

2. Experimental

2.1. Materials

The synthesis and purification of PDLLA, PLLA, and PDLA used in this work were performed according to the procedures reported previously [32–35]. The specific optical rotations measured in chloroform at 25 °C and at a wavelength of 589 nm ($[\alpha]_{\mathrm{D}}^{25}$) were 0, −155, and +156 deg dm^{-1} g^{-1} cm^{3}, respectively, for the purified PDLLA, PLLA, and PDLA, in good agreement with reported values [33,34]. The films used for hydrolysis experiments were prepared from the purified polymers by the method described in previous papers [32,34,35]. Each solution of the polymers in methylene chloride was separately prepared to have a polymer concentration of 1.0 g dL^{-1}. The PLLA and PDLA solutions were admixed with each other equimolarly under vigorous stirring for preparation of an enantiomeric blend film. The solutions were cast onto Petri-dishes, followed by solvent evaporation at room temperature for approximately 1 day. The resulting films were dried in vacuum for 1 week prior to thermal treatment or hydrolysis. The films excluding an amorphous PDLLA film were made amorphous as follows. Each of the films was placed between two Teflon sheets and then sealed in a glass tube under a reduced pressure. The sealed films were melted at 250 °C for 3 min and then quenched at 0 °C. The characteristics of the nonblended PLA films after melt-quenching are given in Table 1. The appearance of all the films was transparent. The nonblended PDLLA, PLLA, and PDLA films and PLLA/PDLA(1/1) blend film are abbreviated as DL, L, D, and L/D films, respectively.

2.2. Hydrolysis

The hydrolysis of each of the films (3 mm× 30 mm × 50–150 μm and 18 mm × 30 mm × 25 μm) was performed in 10 mL of phosphate-buffered solution (pH7.4 ± 0.1) containing 0.02 wt% sodium azide at 37 °C for predetermined periods of time exchanging the buffered solution once a month [19–21]. To exclude the acceleration effect of oligomers trapped at the core of PLA specimens as reported by Li et al. [10] and Grizzi et al. [36] for PLA specimens with thickness above 2 mm, the thickness of all the PLA films was kept below 150 μm. After hydrolysis, the films were washed thoroughly with distilled water at room temperature, followed by drying under a reduced pressure for at least 2 weeks. The distilled water used for preparation of the phosphate-buffered solution and washing of the hydrolyzed films was of HPLC grade (Nacalai Tesque Inc., Kyoto, Japan).

2.3. Measurements and observation

The weight- and number-average molecular weights (M_{w} and M_{n}, respectively) of the films (50–150 μm thick) were evaluated in chloroform at 40 °C with a Tosoh GPC

Table 1
Characteristics of amorphous-made PLA films before and after hydrolysis in phosphate-buffered solution (pH7.4) at 37 °C for 16 (DL film) or 24 (L, D, and L/D film) months

Sample code	$M_n/10^5$ (g mol^{-1})		M_w/M_n		T_g (°C)		T_c (°C)		$T_{m,H}$ (°C)		$T_{m,S}$ (°C)		Tensile strength (kg mm^{-2})		Young's modulus (kg mm^{-2})		Elongation at break (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
DL	3.7	0.02	2.0	6.3	54	–[a]	–	–	–	–	–	–	4.0	0.0	184	0	21.0	0.0
L	5.4	0.23	2.2	2.9	68	65	109	87	177	173	–	–	4.8	1.4	183	99	6.5	0.8
D	4.4	0.15	1.9	3.5	68	62	112	85	178	171	–	–	5.2	0.3	209	34	5.3	0.2
L/D	4.4	0.38	2.1	2.1	69	68	101	91	177	175	222	229	4.2	1.5	155	132	14.5	1.2

[a] Glass transition peak was too diffuse to evaluate T_g.

system (refractive index monitor: RI-8020) with TSK Gel columns (GMH$_{XL}$ × 2) using polystyrene as a standard. The glass transition, crystallization, and melting temperatures (T_g, T_c, and T_m, respectively) of the films were determined by a Shimadzu DT-50 differential scanning calorimeter. The films were heated at a rate of 10 °C min^{-1} under a nitrogen gas flow of 50 ml min^{-1} for DSC measurements. T_g, T_c, and T_m were calibrated using tin, indium, and benzophenone as standards.

The tensile properties of the films (50–150 μm thick) were measured at 25 °C and 50% relative humidity using a tensile tester at a crosshead speed of 100% min^{-1} (20 mm min^{-1}). The initial length of specimens between the two gages was always kept at 20 mm. X-ray diffractometry was performed at 25, 150, and 200 °C using a Rigaku RINT-2500 equipped with a CuKα source. X-ray diffractometry revealed that all the PLA films were amorphous before and after the hydrolysis for 16 (DL film) or 24 (L, D, and L/D film) months.

The morphology of the films (25 μm thick) was studied with a SEM (Hitachi S-2300) and a Zeiss polarization microscope. The films for SEM observation were coated with carbon to a thickness of about 20 nm.

3. Results

3.1. Remaining weight

Fig. 1 shows the remaining weight of the DL, L, D, and L/D films (50–150 μm thick) as a function of hydrolysis time. The weight loss is an index for the content of water-soluble oligomers formed by hydrolysis and then released from the mother films into the surrounding media. The weight of the DL film started to decrease after the induction period of

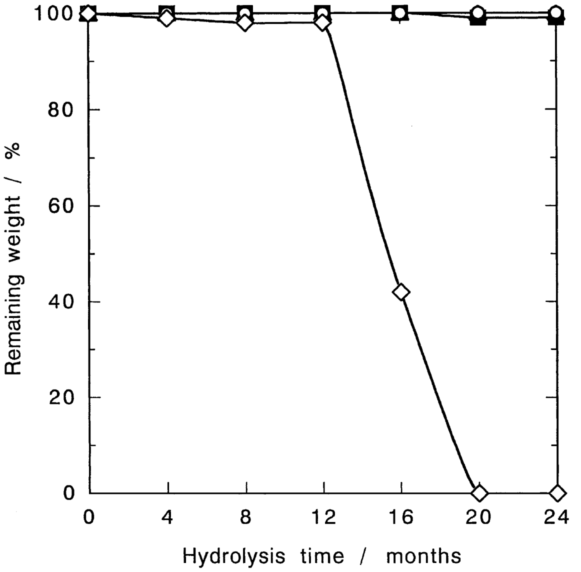

Fig. 1. Remaining weight of DL (◇), L (▲), D (■), and L/D (○) films as a function of hydrolysis time.

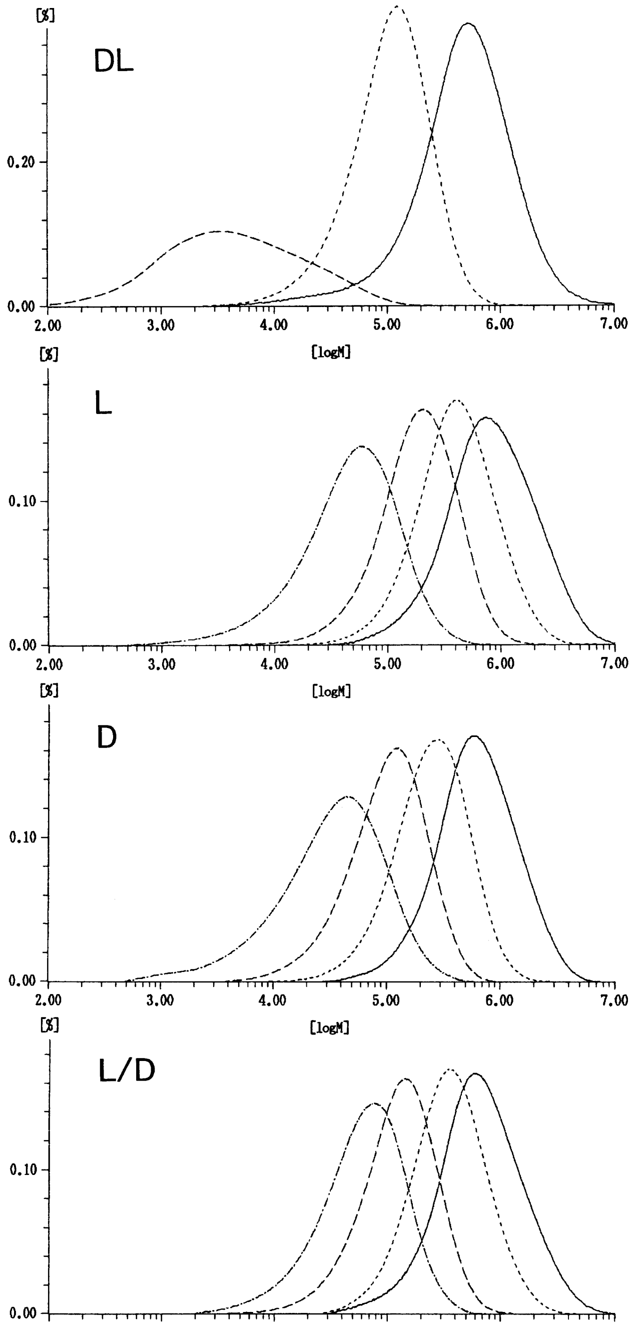

Fig. 2. GPC curves of DL, L, D, and L/D films hydrolyzed for different times: —: 0 month; - - - -: 8 months; – – –: 16 months; – · – · –: 24 months.

12 months and then decreased rapidly to zero at 20 months, while those of the L, D, L/D films remained unchanged for 24 months, meaning that no significant amount of water-soluble oligomers was formed in these films or the formed water-soluble oligomers were trapped in the films. The high weight loss of the DL film for the hydrolysis period longer than 12 months compared with those of the L and D films are comparable with the results reported for low molecular weight PLAs with different X_{LLA} values, where the crystallization of PLAs with high and low X_{LLA} occurred during specimen preparation and/or storage before hydrolysis [37].

3.2. Molecular weight

Fig. 2 demonstrates the GPC curves of the L, D, DL, and L/D films hydrolyzed for different times. The molecular weight distributions of all the films shifted to a lower molecular weight on the whole without formation of any specific peaks originating from crystalline residues for the hydrolysis periods studied here. The shift rates of the molecular distribution curves or hydrolyzabilities of PLA films became lower in the following order: DL film > L and D films > L/D film. The rather high shift rate of the DL film compared with those of L and D films coincides well with the results for massive PDLLA and PLLA plates, where the initial crystallinity of the PLLA plate was not evaluated [38].

Fig. 3 gives the M_n of the DL, L, D, and L/D films as a function of hydrolysis time. The decrease rate of M_n of the DL film for the hydrolysis period of 0–12 months was the highest among those of the films and became higher at the hydrolysis period longer than 12 months. The M_n decrease rates were similar for the L, D, and L/D films for the hydrolysis period of 0–16 months, while those of the L and D films became higher than that of the L/D film at the hydrolysis period longer than 16 months. The increased M_n slope of the DL, L, and D films for the hydrolysis period longer than 12, 16, and 16 months, respectively, may be due to the accumulation of the catalytic oligomers formed by hydrolysis.

The hydrolytic rate constant (k) for the hydrolysis period of 0–12 months was evaluated using the following

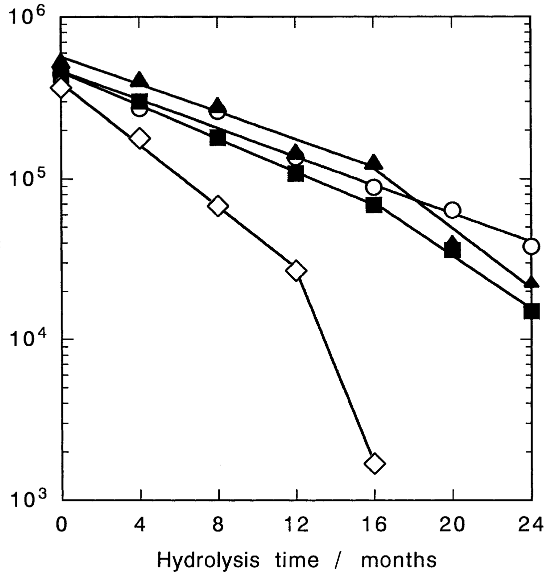

Fig. 3. M_n of DL (◇), L (▲), D (■), and L/D (○) films as a function of hydrolysis time.

equation [4–7]:

$$\ln M_n(t_2) = \ln M_n(t_1) - kt \quad (1)$$

where $M_n(t_2)$ and $M_n(t_1)$ are M_n values at the hydrolysis times of t_2 and t_1, respectively. The estimated k values for the L and D films (3.49 and 3.88×10^{-3} day^{-1}, respectively) are significantly smaller than 7.22×10^{-3} day^{-1} estimated for the DL film but slightly higher than 2.96×10^{-3} day^{-1} estimated for the L/D film. The k values of the L, D, and L/D films are comparable with 2.59×10^{-3} day^{-1} (0–12 months) reported for an amorphous-made PLLA film ($M_w = 1.2 \times 10^6$, $M_w/M_n = 2.6$) [19], while that of the L/D film is one order higher than 0.73×10^{-3} day^{-1} of an as-cast well-stereo-complexed PLLA/PDLA blend film with a low molecular weight [21].

3.3. Mechanical properties

Fig. 4(a)–(c) illustrates the tensile strength, Young's modulus, and elongation at break, respectively, of the DL, L, D, and L/D films as a function of hydrolysis time. The DL, L, and D films retained their initial tensile strengths for 12, 16, and 8 months, respectively, and then the tensile strengths decreased monotonically to zero at 16 months and to 1.4 and 0.2 kg mm^{-2} at 24 months, respectively. On the other hand, the tensile strength of the L/D film increased in the initial 8 months, followed by the gradual decease to 1.5 kg mm^{-2} at 24 months. The Young's modulus of each of the films showed the time dependence similar to that for the tensile strength. However, at 24 months for each of the films excluding the DL film, the final percentage value of Young's modulus was higher than that of tensile strength.

The initial elongation at break of the DL film was the highest among those of the films. The elongation at break of the DL film decreased monotonically to zero at 16 months, while those of the L, D, and L/D films decreased gradually to non-zero values at 24 months. The final mechanical properties at 24 months or hydrolysis-resistance decreased in the following order: L/D film > L and D films > DL film.

3.4. Highly-ordered structures

Fig. 5 gives the DSC thermograms of the L, D, and L/D films before and after the hydrolysis for 24 months. The DSC thermograms of the DL films before and after the hydrolysis for 16 months showed only the glass transition peak at around 60 °C (data not shown here). In addition to the glass transition peak, the crystallization and melting peaks of homo-crystallites at around 100 and 170 °C,

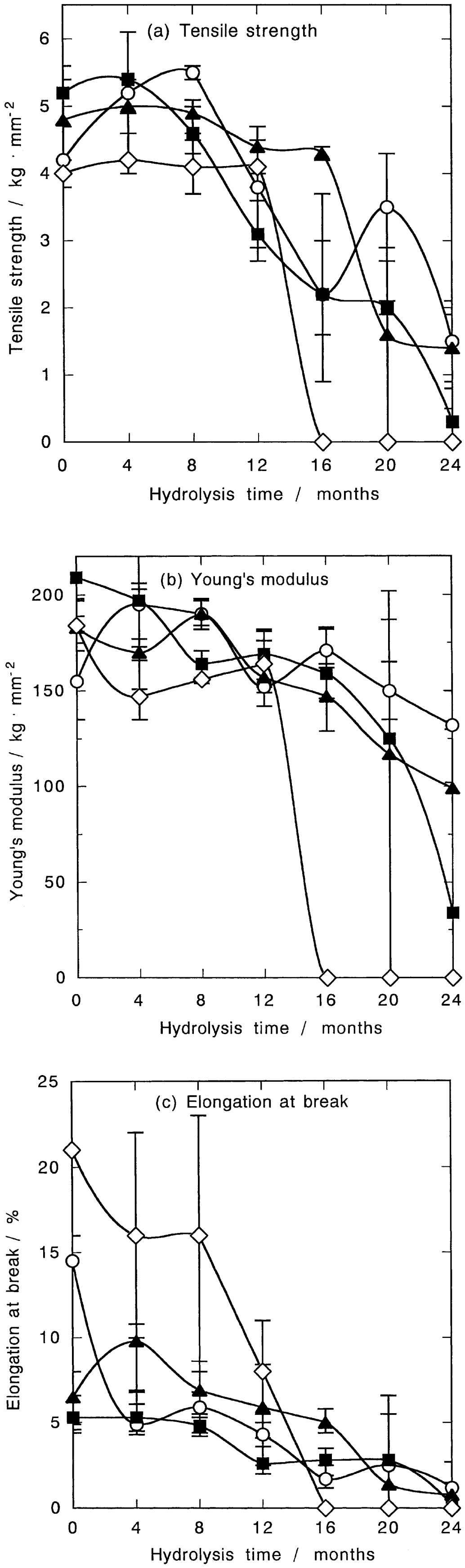

Fig. 4. Tensile strength (a), Young's modulus (b), and elongation at break (c) of DL (◇), L (▲), D (■), and L/D (○) films as a function of hydrolysis time.

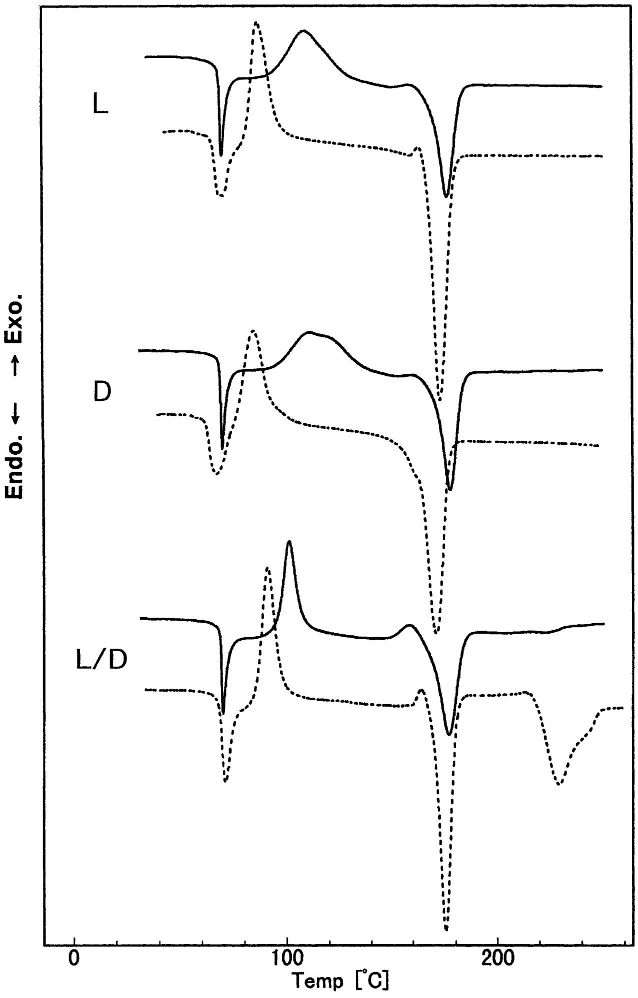

Fig. 5. DSC thermograms of L, D, L/D films before (—) and after (- - - -) hydrolysis for 24 months.

respectively, were observed for the L and D films before and after the hydrolysis for 24 months, while besides the peaks mentioned above, the melting peak of stereocomplex crystallites was observed at around 220 °C for the L/D film before and after the hydrolysis for 24 months. Here, the homo- and stereocomplex crystallites are defined to be composed of either PLLA or PDLA chains and of equimolar PLLA and PDLA chains, respectively.

The X-ray diffractometry at 25 °C revealed that all the films were amorphous before and after the hydrolysis for 16 (DL film) and 24 (L, D, and L/D films) months. Therefore, all the melting peaks observed for the L, D, and L/D films are attributable to those of the crystallites formed during DSC heating. The values of T_g, T_c, and T_m of homo-crystallites ($T_{m,H}$) and stereocomplex crystallites ($T_{m,S}$) for PLA films before and after the hydrolysis for 16 (DL film) or 24 (L, D, and L/D films) months were estimated from the DSC thermograms and were listed in Table 1. The decrease in T_g, T_c, and $T_{m,H}$ by the hydrolysis for 24 months was smaller for the L/D film than for the L and D films. The high T_g, T_c, and $T_{m,H}$ values of the L/D film at 24 months compared with those of the L and D films strongly suggest that the final molecular weight of the L/D film was higher than those of the L and D films, in good agreement with the GPC results.

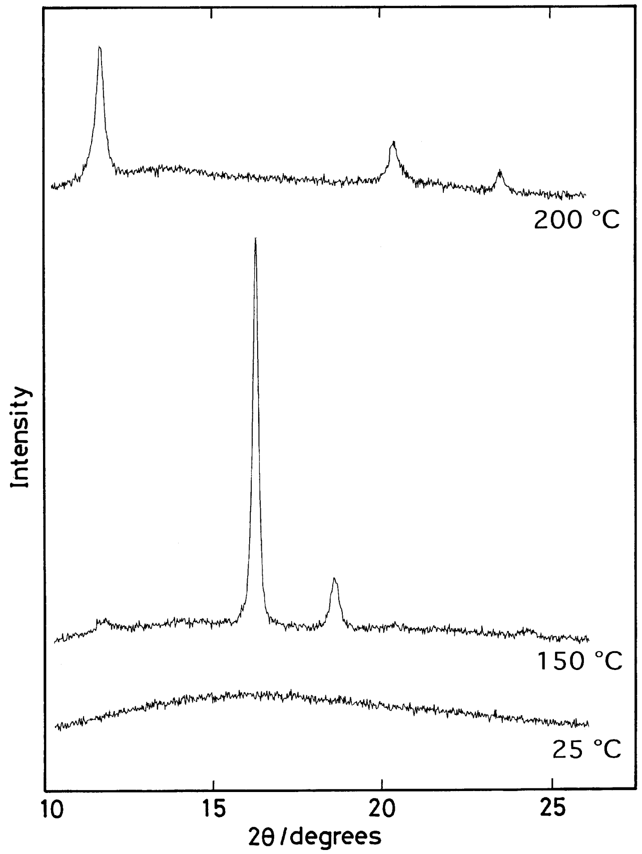

Fig. 6. X-ray diffraction profiles at different temperatures for L/D film hydrolyzed for 24 months.

It is not clear at what temperatures crystalline species, homo- and stereocomplex crystallites, were formed during DSC scanning. To elucidate it, the X-ray diffractometry was carried out at different temperatures for the L/D film hydrolyzed for 24 months at different temperatures (Fig. 6). At 25 °C no crystalline peak was observed for the L/D film, showing that it remained amorphous even after the hydrolysis for 24 months, while the crystalline peaks that appeared at 2θ are equal to 17 and 19° [39–42] when the temperature was increased to 150 °C. These peaks are comparable with the α form of PLLA crystallized in a pseudo-orthorhombic unit cell of dimensions: $a = 1.07$ nm, $b = 0.595$ nm, and $c = 2.78$ nm, which contains two 10_3 helices [40]. The diffraction peaks of the α form at 150 °C reflects that the formation of homo-crystallites occurred in the L/D film during the heating up to 150 °C. On the other hand, the peaks for the α form disappeared and the most intense peaks of the L/D film were observed at 2θ values of 12, 21, and 24° when the temperature was elevated to 200 °C. These 2θ values are in excellent agreement with the reported values [39–42] for PLA stereocomplex crystallized in a triclinic unit cell of dimensions: $a = 0.916$ nm,

$b = 0.916$ nm, $c = 0.870$ nm, $\alpha = 109.2°$, $\beta = 109.2°$, and $\gamma = 109.8°$, in which L-lactide and D-lactide segments are packed parallel taking 3_1 helical conformation [40]. This finding reveals that the stereocomplex crystallites were formed after the melting of homo-crystallites during the heating up to 200 °C. The melting peak area of the stereocomplex crystallites in the DSC thermograms was rather larger for the L/D film after the hydrolysis for 24 months than for that before the hydrolysis (Fig. 5). This can be attributed to high stereocomplexationability of the melted L/D film having a low molecular weight, as reported previously [43].

4. Discussion

The results of gravimetry, GPC, and tensile testing revealed that the autocatalytic hydrolyzability of the DL film was the highest among those of the PLA films. The 75.5 MHz ^{13}C NMR measurements revealed that the DL film is composed of the sequences of iii, isi, iis/sii, sii/iis, and sis, but those of ssi/iss and of sss formed by transesterification after random addition of L- and D-lactide or random pair addition of L- and D-lactyl units, were not contained [31]. Therefore, the DL film is composed of predominant isotactic sequences and small amount of atactic sequences, while the L, D, and L/D films comprise PLLA and PDLA chains having only isotactic sequences. The total X_{LLA} values in the DL and L/D films are 0.5, while those of the L and D films are 1.0 and 0.0, respectively. Therefore, the highest autocatalytic hydrolyzability of the DL film indicates that the reduced tacticity or the introduction of atactic sequences into isotactic sequences enhances the autocatalytic hydrolysis of PLA films and that tacticity is an important parameter to determine the autocatalytic hydrolysis rate compared with total X_{LLA}. The low tacticity or disordered helical conformation of the PDLLA chains increases the interaction between PDLLA chains and water molecules, resulting in their enhanced attack from water molecule. In contrast, it is probable that the 10_3 or 3_1 helical conformation of PLLA or PDLA chains as in the crystalline region is retained to some extent even in the amorphous L, D, and L/D films and such regular structure increases the intramolecular interaction, resulting in the prevented attack of water molecules on the PLLA and PDLA chains compared with that on the PDLLA chains. The result for the autocatalytic hydrolysis is in marked contrast with those reported for the proteinase K-catalyzed hydrolysis of nonblended PLA films and enantiomeric and diastereoisomeric PLA blend films with different X_{LLA} values, where predominant hydrolysis occurs at the L-lactyl (a half of L-lactide) unit sequences, and therefore X_{LLA}, l_{L}, and l_{D} values are crucial to determine their enzymatic hydrolyzabilities [24,25,28,31].

The results of gravimetry, GPC, and tensile testing also reflect that the L/D film was autocatalytically hydrolysis-resistant compared with the L and D films. This is probably due to the peculiar strong interaction between L- and D-lactyl unit sequences in the amorphous state, resulting in the further decreased interaction of PLLA or PDLA chains and water molecules. The previous article ascribed the retarded autocatalytic hydrolysis of the well-stereocomplexed PLLA/PDLA blend film to its 3D network structure and/or to the peculiar strong interaction between PLLA and PDLA chains in the amorphous region [21]. This study showed that the peculiar strong interaction surely retards the autocatalytic hydrolysis of the L/D film compared with the L and D films, though its contribution to the retarded hydrolysis is very small. However, the peculiar strong interaction between PLLA and PDLA chains may have caused the retarded proteinase K-catalyzed hydrolysis of the PLLA/PDLA blend film compared with that the expected from the hydrolysis rates of nonblended PLLA and PDLA films [31]. Finally, this study also revealed that the autocatalytic hydrolyzability of PLAs in the amorphous state can be controlled by the stereocopolymerization of L-lactide and D-lactide and the enantiomeric polymer blending.

5. Conclusions

The following conclusions were derived from this study for the autocatalytic hydrolysis of the DL, L, D, and L/D films.

1. The autocatalytic hydrolyzabilities of PLAs in the amorphous state decreased in the following order: DL film > L and D films > L/D film.
2. The higher hydrolyzability of the DL film compared with those of the L and D films was ascribed to the lower tacticity of PDLLA chains, which decreases the intramolecular interaction and therefore enhances the attack from water molecules.
3. The retarded hydrolysis of the L/D film compared with those of the L and D films was attributable to the peculiar strong interaction between PLLA and PDLA chains, resulting in the disturbed interaction of PLLA and PDLA chains and water molecules.
4. All the initially amorphous PLA films remained amorphous even after the autocatalytic hydrolysis for 16 (DL film) or 24 (L, D, and L/D films) months.
5. The melting peaks observed at around 170 and 220 °C for the L/D film after the hydrolysis for 24 months were ascribed to those of homo- and stereocomplex crystallites, respectively, formed during heating at around 100 and 200 °C not during the autocatalytic hydrolysis.

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