Theoretical Prediction of Molecular Weight on Autocatalytic Random Hydrolysis of Aliphatic Polyesters

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ABSTRACT: A new prediction model for the autocatalytic random hydrolysis of aliphatic polyesters is proposed. The model predicts changes in the number- and weight-average degrees of polymerization. The model enables to avoid certain errors liable to occur in the estimation of hydrolysis with only the number-average molecular weight. The prediction model successfully interpreted the hydrolysis data of some aliphatic polyesters, such as poly(*p*-dioxanone), poly(β-propiolactone), poly(L-lactic acid), etc.

1. Introduction

Aliphatic polyesters have been used for medical applications such as surgical sutures and implants.[1,2] Recently, aliphatic polyesters have been recognized as environmental friendly materials and their development is being promoted as raw materials for many industrial applications such as film, fiber, nonwoven fabrics, molds, etc.[3,4] A typical common characteristic of aliphatic polyesters is hydrolytic property, which makes them usable in bioabsorbable surgical applications. However, to use the polyesters for many applications, more accurate control of the hydrolytic property is required, because a more reliable prediction in the durability of the products is needed.

Many works concerning the hydrolytic degradation of aliphatic polyesters have been reported. Generally, it has been recognized that polyesters undergo an autocatalytic random chain scission hydrolysis by their carboxylic acid end groups.[5−9] For example, Huffman et al.[5] have reported that the hydrolysis of poly(glycolic acid) (PGA) in deionized water at 37 °C shows a linear relationship between log[COOH] and reaction time. They suggested that the hydrolysis is catalyzed by carboxyl end groups. Pitt et al.[7] have observed a kinetic relationship of $M_{n_t}/M_{n_0} = \exp(-kt)$ on the hydrolysis of poly(ϵ-caprolactone) (PCL), poly(L-lactic acid) (PLLA), and the copolymer of glycolic acid and L-lactic acid in phosphate buffer (pH 7.4), in which M_{n_t} and M_{n_0} mean the number-average molecular weight values at time t and initial time. They concluded that the hydrolysis of these polyesters proceeded by the autocatalytic random chain scission by carboxylic acid end groups.

On the other hand, the hydrolysis in basic organic solvents and in the presence of a stronger acid than carboxylic acid end groups, such as HCl, proceeds nonautocatalytically.[8−10] However, since the hydrolysis of the industrial products generally proceeds under neutral aqueous conditions, e.g., in vivo and in the environment, we would often encounter the autocatalytic hydrolysis process during use and storage.

Theoretical treatment of the hydrolytic degradation processes is important for the prediction of the durability of industrial products. It has been reported that the tensile strength of aliphatic polyesters decreases steeply after a period during the hydrolysis processes.[6,11−13] Such period of a sudden decline in the property can be regarded as a measure of durability.

Generally, the decrease in molecular weight occurs prior to the changes in mechanical properties and morphology. Some works concerning the prediction of polyester hydrolysis have been carried out.[5−10,14−16] Most of analytical methods of the hydrolysis kinetics have been estimated using the number-average molecular weight (M_n) value or number-average degree of polymerization (P_n). However, there are some cases in which the estimation by M_n or P_n are not appropriate, for example, in a case where the loss of a small amount of low molecular weight fractions occurs with the degradation. The loss is apt to influence the M_n and P_n emphatically. This has already been pointed out by Kotliar et al. in treatment of the radiation-induced degradation.[17] Calculating the influence of a polymer with the most probable distribution (MPD), even the loss of 1 wt % in the lower molecular weight fractions results in about 15% increase in M_n, in contrast to the weight-average molecular weight (M_w) increase of 0.95%. On the other hand, if all fractions were taken into account in the estimation of the degradation process, it is obvious that the random chain scission and the chain-end session are impossible to distinguish merely by using the change in M_n or P_n.

Therefore, estimation using the values of M_w or weight-average degree of polymerization (P_w) is more reliable for the prediction of the degradation process, because distinction between random and nonrandom chain scission is possible and the influence of loss of lower molecular weight fractions is less than for M_n or P_n.

The theoretical treatment of the change in M_w with the random chain scission processes has been developed

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by many workers to interpret the radiation-induced degradation.[17−19] These works have been limited to nonhydrolytic and nonautocatalytic processes. Concerning hydrolytic degradation of polyesters, Yoon et al.[15,16] have attempted to theoretically calculate the change in P_w of poly(hydroxyalkanoates). They derived a linear relationship between $\tau^{1/3}/P_w$ and $\tau^{4/3}$ ($\tau = k_h[\text{water}]t$) for random chain scission. However, they derived the equation on the assumption that the hydrolysis proceeds as a nonautocatalytic reaction. When the theoretical calculation was compared with the experimental data of Lauzier et al.[10] and Doi et al.,[14] some discrepancies were found, principally in the data of Doi et al. because they carried out the hydrolysis in a neutral buffer solution (pH 7.4). Pitt et al.[6] indicated that logarithmic plots of $[\eta]$ vs time for the PCL hydrolysis show the same linear relationship as that of log M_n vs time. This result was based on the fact that the molecular weight distribution does not change appreciably during the hydrolysis. Lemoine et al.[20] found that logarithmic plots of M_{w_t}/M_{w_0} vs time of PCL, PLA, and P(LA/GA) hydrolysis in water showed a linear relationship. They reported that polymer degradation can be empirically assumed to follow a first-order kinetic. Recently, the hydrolysis in solutions[9] with aqueous organic solvent was carried out to eliminate any solid-state contributions.[21] However, no useful prediction concerning the change in M_w was obtained.

In this paper, we attempt to theoretically calculate the change in P_w of aliphatic polyesters during the autocatalytic random hydrolysis, especially in the range up to a critical point, at which a sudden weight loss and a steep change in M_n are observed.[6,22,23] The critical changes would be regarded as a measure of the durability of polyesters. Theoretical equations for the changes in P_n, P_w, and polydispersity (PD) during the hydrolysis are derived. The derived equations are compared with experimental hydrolysis data with some kinds of aliphatic polyesters.

2. Description of the Model

The model is an autocatalytic random hydrolysis model adding the influence of carboxylic acid end groups to Yoon's model.[15]

When all the bonds in a given polymer are assumed to degrade with equal probability, the mechanism of the hydrolysis can be written as

$$\mathrm{P}_n + \mathrm{W} \rightarrow \mathrm{P}_{n-r} + \mathrm{P}_r \quad (r = 1, 2, ..., n-1) \qquad (1)$$

where P_n is a fraction with degree of polymerization of n and W is a water molecule. If the reaction is accelerated by carboxylic acid end groups and the rate constant of the hydrolysis of each step is k_h, the mole balance equation is as follows:

$$\mathrm{d[P]}/\mathrm{d}t = k_h\left(\sum_{n=1}^{\infty} n[\mathrm{P}_n] - \sum_{n=1}^{\infty}[\mathrm{P}_n]\right)[\mathrm{W}][\mathrm{COOH}] \qquad (2)$$

$[\mathrm{P}] = \sum_{n=1}^{\infty}[\mathrm{P}_n]$ and [COOH] is the concentration of the carboxylic acid end groups. In this study, it is assumed that $[\mathrm{W}] \gg [\mathrm{COOH}]$ is maintained during the hydrolysis.

Using the moment, $\lambda_\kappa = \sum_{n=1}^{\infty} n^\kappa[\mathrm{P}_n]$, theoretical derivation of equations for the number- and weight-average degrees of polymerization and polydispersity resulted in the following (see Appendix):

$$\frac{1}{P_n} = \frac{1}{P_{n,0}}e^{\boldsymbol{k}t} \quad \text{or} \quad \ln P_n = \ln P_{n,0} - \boldsymbol{k}t \qquad (3)$$

$$\frac{1}{P_w} = \frac{1}{2P_{n,0}}\left\{e^{\boldsymbol{k}}t + \left(\frac{2}{\mathrm{PD}_0} - 1\right)e^{-(1/3)\boldsymbol{k}t}\right\} \qquad (4)$$

$$\frac{\mathrm{dPD}}{\mathrm{d}t} = \frac{2\boldsymbol{k}}{3}\mathrm{PD}(2 - \mathrm{PD}) \qquad (5)$$

in which $\boldsymbol{k} = \lambda_1 k_h$ (constant) because the first moment λ_1 is constant, and PD and PD_0 are values of the polydispersity at time t and initial time. Equation 3 is the same as that derived by Pitt et al.[7] Equation 4 is a new expression for the change in P_w. Equation 4 predicts that the change in P_w depends on the initial number-average molecular weight, P_{n_0}, the initial polydispersity, PD_0, and the rate constant, $\boldsymbol{k}$. The P_{n_0} and PD_0 are adequate values followed the Schultz−Zimm distribution.[24] Equation 5 indicates that PD converges to 2 with t, that is, the most probable distribution. Equation 4 also predicts

$$\lim_{t\to\infty}\left(\frac{2}{\mathrm{PD}_0} - 1\right)e^{-(1/3)\boldsymbol{k}t} = 0 \qquad (6)$$

Therefore, if PD = 2 (constant), eq 4 is rearranged into

$$\frac{1}{P_w} = \frac{1}{P_{w,0}}e^{\boldsymbol{k}t} \quad \text{or} \quad \ln P_w = \ln P_{w,0} - \boldsymbol{k}t \qquad (7)$$

Equation 4 converges to eq 7 with degradation. Equation 7 is also a special solution when $\mathrm{PD}_0 = 2$. Equations 3 and 7 predict that both sets of logarithmic plots of P_n and P_w vs t show linear relationships with the same slope, $\boldsymbol{k}$.

3. Experimental Section

3.1. NMR Spectroscopy. Proton (^{1}H) and ^{13}C nuclear magnetic resonance (NMR) spectra were taken on a 500-MHz JEOL JNM-LA500 FT-NMR system at 30 °C using chloroform-*d* as the solvent (50 mg of polymer/mL) and tetramethylsilane as the internal standard at 0.00 ppm. ^{1}H NMR chemical shifts in parts per million (ppm) are reported downfield from the internal standard. Peak areas for ^{1}H NMR spectra were determined by spectrometer integration and are reported as relative intensities representing a given number of hydrogens. Solution ^{13}C NMR spectra were recorded at 125.65 MHz on the FT-NMR system. The instrument parameters were as follows: pulse width, 5.0 μs; data points, 65.5 K; acquisition time, 1.821 s; relaxation delay, 1.18 s; and 10000−30000 transients.

3.2. Measurement of Molecular Weights. All molecular weights reported were determined by gel permeation chromatography (GPC) using a TOSOH HLC-8120 GPC system with a refractive index (RI) detector under the following conditions: double TSK-GEL Super HM-H linear type columns and chloroform (HPLC grade) eluent at a flow rate of 0.6 mL min^{-1} at 40 °C. The calibration curves for GPC analysis were obtained using polystyrene standards with a low polydispersity (2.8×10^3, 6.2×10^3, 1.03×10^4, 4.39×10^4, 1.02×10^5, 3.55×10^5, 1.26×10^6, TOSOH Corporation). By use of $[\eta]M$ as a universal calibration parameter,[25] the polystyrene calibration was converted into one for PPL by the relationship

$$\log M_1 = (1 + \mathbf{a}_1) - \log(\mathbf{K}_2/\mathbf{K}_1) + \{(1 + \mathbf{a}_2)/(1 + \mathbf{a}_1)\}\log M_2 \qquad (8)$$

where **K** (mL/g) and **a** are the Mark−Houwink−Sakurada parameters for PPL (subscript 1) and polystyrene (subscript 2), respectively. The Mark−Houwink-Sakurada equations used for the two polymers in chloroform were as follows:

$$\text{PPL}^{26} \qquad [\eta] = 2.59 \times 10^{-2} M_1^{\ 0.72} \tag{9}$$

$$\text{polystyrene}^{27} \qquad [\eta] = 4.9 \times 10^{-3} M_2^{\ 0.794} \tag{10}$$

3.3. Materials. The monomer, 2-oxetanone (β-propiolactone, β-PL, from Grand Lab.), was recrystallized four times from methanol and twice from diethyl ether, then dried over molecular sieves 4A. The β-PL was distilled under reduced pressure (45−46 °C/10 mmHg) before use. The other monomer, 1,4-dioxan-2-one (*p*-dioxanone, PDO), was synthesized from diethylene glycol over Cu(0) catalyst supported on silica particles at 275 °C. The raw PDO was dried over molecular sieves 4A, followed by fractional distillation (92−93 °C/10 mmHg) before use. The monomers were handled in an atmosphere of dry nitrogen. Tetramethylammonium acetate (TMAA, from Tokyo Chemical Industry Co., Ltd.) was dried under reduced pressure and dissolved in anhydrous acetonitrile in a concentration of 0.21 M. Stannous 2-ethylhexanoate (tin(II) octoate, from Wako Pure Chemicals Industries, Ltd.) was dissolved in anhydrous toluene in a concentration of 1.00 M. Methanol and chloroform (Wako Pure Chemicals Industries, Ltd.) were used as received.

The poly(L-lactide) (PLLA) sample (M_n = 182 000, M_w = 324 000) was kindly supplied by Shimadzu Co. The PLLA sample was purified by precipitation from chloroform solution with methanol and dried in vacuo.

3.4. Polymer Preparations. Poly(β-propiolactone) (PPL) was prepared by the ring-opening polymerization of β-PL in the presence of TMAA in bulk. Ten grams of β-PL (139 mmol) was charged into a 20 mL vial. The vial was sealed with a butyl rubber stopper. The catalyst, TMAA solution (10 μL, 2.1 μmol), was injected into the vial through the butyl rubber stopper with a syringe and then placed in a water bath thermostated at 20 °C for 48 h with magnetic stirring. The resulting PPL was purified by precipitation from chloroform solution with methanol and dried in vacuo. ^{1}H NMR (δ, $CDCl_3$): 2.66 ($-CH_2CH_2COO-$, t, 2H), 4.37 ppm ($-CH_2CH_2COO-$, t, 2H) (lit.[28] δ 2.66, t; 4.37 ppm, t). ^{13}C NMR (δ, $CDCl_3$): 170.2 (C = 0), 60.1 ($-CH_2OCO-$), 33.5 ppm ($-CH_2COO-$). GPC: M_n = 35 500, M_w = 80 700.

Poly(*p*-dioxanone) (PPDO) was also prepared by the ring-opening polymerization of PDO in the presence of tin(II) octoate in bulk. Five grams of PDO (49 mmol) was charged into a 20 mL vial. The vial was sealed with a butyl rubber stopper. The catalyst, tin(II) octoate solution (10 μL, 10 μmol), was injected into the vial through the butyl rubber stopper with a syringe and then placed in a silicone oil bath thermostated at 120 °C for 5 h with magnetic stirring. The resulting PPDO was purified by precipitation from chloroform solution with methanol and dried in vacuo. ^{1}H NMR (δ, $CDCl_3$): 4.17 ($-OCH_2COO-$, s, 2H), 3.80 ($-OCH_2CH_2OCO-$, t, 2H), 4.35 ppm ($-OCH_2CH_2OCO-$, t, 2H). ^{13}C NMR (δ, $CDCl_3$): 170.1 (C = 0), 69.3, 68.3, 63.8 ppm (lit.[29] δ 170.0, 69.1, 68.2, and 63.6 ppm). GPC: M_n = 107 000, M_w = 221 000.

Films (approximately 80 μm thickness) were prepared by conventional solvent-casting techniques from chloroform solutions of the polyesters, PPDO, PPL, and PLLA, using glass Petri dishes as casting surfaces in an atmosphere of dry nitrogen. The films were dried in vacuo at ambient temperature for 1 night.

3.5. Polymer Hydrolysis. Hydrolysis of the films (10 × 30 mm) was carried out in an atmosphere of saturated water vapor at 50 °C with a Yamato Humidic Chamber IG-42. Samples were recovered periodically and dried at ambient temperature for 1 night in vacuo. Each sample was dissolved in 5 mL of chloroform and filtered through a PTFE membrane filter (ADVANTEC; pore size, 0.45 μm) before molecular weight measurement. Molecular weight of the sample was determined by GPC.

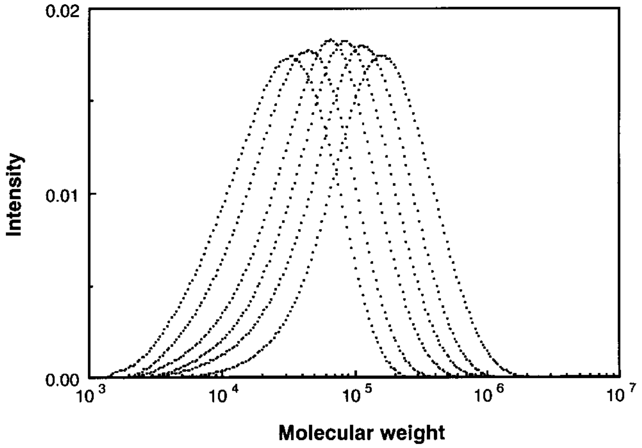

Figure 1. Change in GPC profile of PPDO film during hydrolytic degradation in an atmosphere of saturated water vapor at 50 °C. Hydrolysis time: 0, 1, 2, 3, 4, and 5 days.

4. Results and Discussion

In this study, the hydrolysis was carried out in an atmosphere of saturated water vapor at 50 °C and not under immersion in water or buffer solution, to avoid the influence of loss of a small amount of lower molecular weight fractions on P_n and P_w as mentioned above. Therefore, all fractions of reacted polymers were taken into account in the calculation of molecular weights and molecular weight distributions. In the prediction, we assumed that the water concentration is [W] ≫ [COOH]. In fact, [W] is the actual concentration of water at the reaction site. However, it was determined that the aliphatic polyesters rapidly absorbed water and easily reached the saturation under the same conditions. For example, the water absorption of PPL pellets reached the saturation (uptake: about 0.3 wt %) up to 18 h. Obviously, this uptake is very fast compared with the hydrolysis rate of the polyesters and the absorbed water molecules are sufficiently in excess of the ester bonds hydrolyzed in the range of treatment on the prediction.

We applied the analysis results of the autocatalytic random hydrolysis model to hydrolytic degradation in three kinds of the aliphatic polyesters, PPDO, PPL and PLLA. Each of these polyesters has different initial polydispersity (PD_0), i.e., $PD_0 \cong 2$ (PPDO), >2 (PPL), and <2 (PLLA).

4.1. Hydrolysis of PPDO ($PD_0 \cong 2$). PPDO has been used to make monofilament sutures. The PPDO sample prepared by tin(II) octoate has a typical most probable distribution (PD_0 = 2.07), similar to the distribution of PCL prepared with same catalyst as reported by Schindler et al.[30] Figure 1 shows changes in GPC profile of PPDO sample with the reaction time of the hydrolysis. The initial profile parallel-shifted to the lower molecular weight, while maintaining nearly the same distribution. This is determined from the small change in PD in Figure 2.

In Figure 2, $1/P_n$ and $1/P_w$ as a function of hydrolysis time are plotted. The theoretical predictions of $1/P_n$ and $1/P_w$ based on eqs 3 and 4 are also shown. Using P_{n_0} = 1049 and PD_0 = 2.07 as parameters and $\boldsymbol{k}$ = 0.355 (day^{-1}) as the rate constant of the predictions, good agreement between the theoretical calculations and the experimental data was obtained. In this case, since PD_0 is nearly equal to 2, a special solution of eq 7 is available. Figure 3 shows the changes in ln P_n and ln P_w. Good agreement between the experimental data and

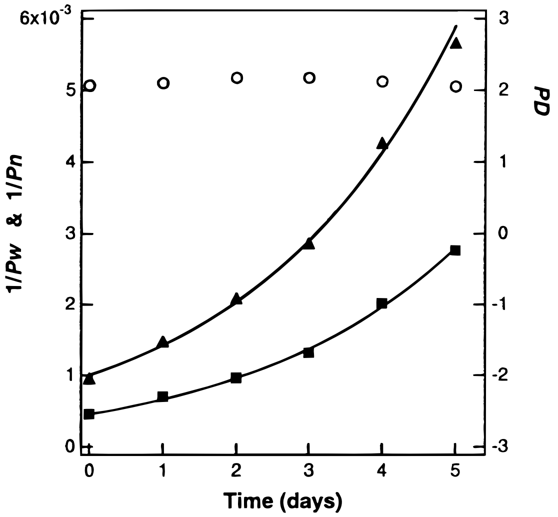

Figure 2. Plots of PD, $1/P_\mathrm{n}$, and $1/P_\mathrm{w}$ vs time t for PPDO film: PD (○); $1/P_\mathrm{n}$ (▲); $1/P_\mathrm{w}$ (■). Solid lines indicate the predictions by eqs 3 and 4.

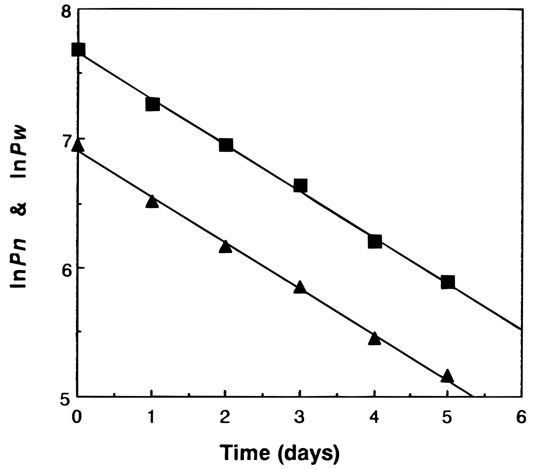

Figure 3. Plots of ln P_n and ln P_w vs time t for PPDO film: ln P_n (▲); ln P_w (■). Solid lines indicate the predictions by eqs 3 and 7.

the predictions based on eqs 3 and 7 was obtained with the same $\boldsymbol{k}$ value, 0.355 (day^{-1}). Regression coefficients were close to 1 ($r^2 = 0.997$ and 0.998 for ln P_n and ln P_w, respectively).

These results indicate that the derived theoretical predictions successfully interpret the hydrolysis data of PPDO under the reaction conditions based on the autocatalytic random hydrolysis model.

4.2. Hydrolysis of PPL ($\mathbf{PD_0 > 2}$). PPL is a biodegradable polyester and regarded as a polymer that can fill the gap in the enzymatic degradability between a microbial polyester, poly(3-hydroxybutyrate) (PHB), and PCL.[31] A PPL sample, which has a broad $\mathrm{PD_0} = 2.27$, was prepared by bulk polymerization. In Figures 4 and 5, changes in GPC profile and PD with the hydrolysis are shown. In the beginning, the broad $\mathrm{PD_0}$ gradually narrowed to 2 as shown in Figure 5, but then increased. In the first half of the reaction, the profile shifted to lower molecular weight, while maintaining the distribution nearly equal to 2. However, the profile suddenly broadened at a particular point of time (Figure 4). Since the GPC profiles are normalized in such a way that $\sum$ intensity $= 1$, the change of the distribution is reflected in change in the peak height. This change agreed with an increase in PD after 60 days (Figure 5).

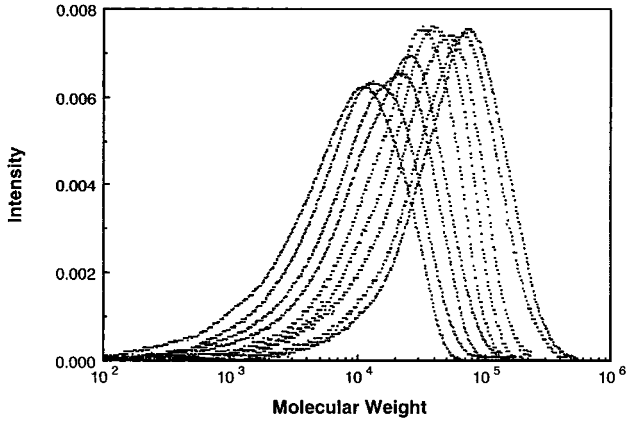

Figure 4. Change in GPC profile of PPL film during hydrolytic degradation in an atmosphere of saturated water vapor at 50 °C. Hydrolysis time: 0, 9, 20, 30, 40, 51, 60, 69, and 79 days.

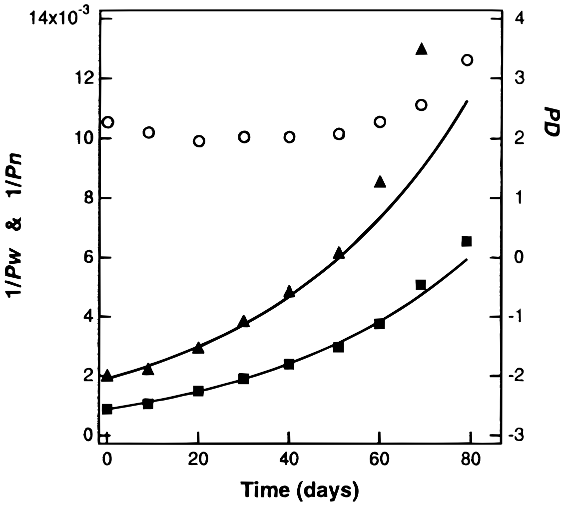

Figure 5. Plots of PD, $1/P_\mathrm{n}$ and $1/P_\mathrm{w}$ vs time t for PPL film: PD (○); $1/P_\mathrm{n}$ (▲); $1/P_\mathrm{w}$ (■). Solid lines indicate the predictions by eqs 3 and 4.

In Figure 5, $1/P_\mathrm{n}$ and $1/P_\mathrm{w}$ are plotted as a function of the hydrolysis time and the theoretical predictions of $1/P_\mathrm{n}$ and $1/P_\mathrm{w}$ based on eqs 3 and 4 are also shown. Using $P_{\mathrm{n}_0} = 493$, $\mathrm{PD_0} = 2.27$ and $\boldsymbol{k} = 0.0225$ (day^{-1}) for the predictions, good agreement between the theoretical calculations and the experimental data in the period of 0−51 days was obtained. However, after 60 days, discrepancies between the calculations and the data became clear. This can be attributed to certain factors, such as the disintegration of amorphous regions. This structural change would result in failure of the most probable distribution and the broadening of distribution. The values of $P_\mathrm{n} = 162$ ($M_\mathrm{n} = 11\,700$) and $P_\mathrm{w} = 338$ ($M_\mathrm{w} = 24\,300$) at the point (51 days) are the so-called critical values demonstrated by Pitt et al.[32]

Consequently, the derived predictions interpret well the autocatalytic random hydrolysis of PPL up to the critical point.

4.3. Hydrolysis of PLLA ($\mathbf{PD_0 < 2}$). Commercially produced PLLA sample with narrow $\mathrm{PD_0} = 1.78$ was used. In Figures 6 and 7, changes in GPC profile and PD with the hydrolysis are shown. In the beginning, the narrow $\mathrm{PD_0}$ rapidly broadened to about 2. The GPC profile maintained the distribution for a while, then inclined monotonically to broaden the distribution with shifting to lower molecular weight. The PD value in

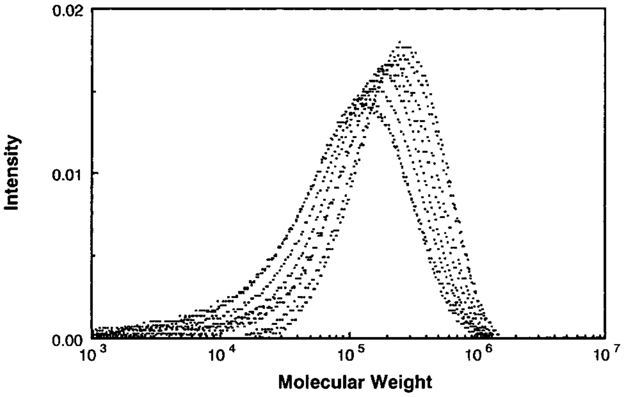

Figure 6. Change in GPC profile of PLLA film during hydrolytic degradation in an atmosphere of saturated water vapor at 50 °C. Hydrolysis time: 0, 4, 7, 11, 18, 26, 32, and 38 days.

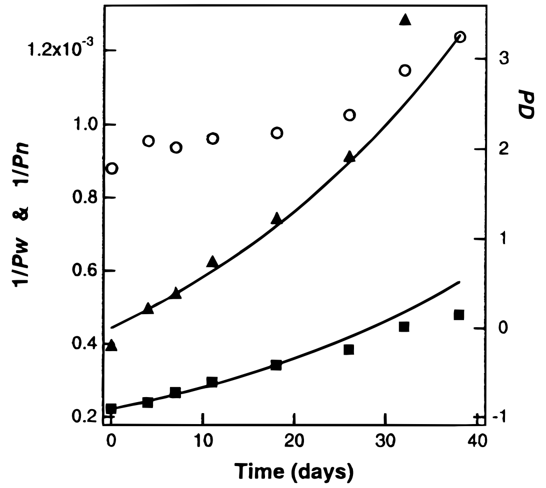

Figure 7. Plots of PD, $1/P_n$ and $1/P_w$ vs time t for PLLA film: PD (○); $1/P_n$ (▲); $1/P_w$ (■). Solid lines indicate the predictions by eqs 3 and 4.

Figure 7 reflected the GPC results. The PD maintained at 2 for 4−18 days, then increased.

In Figure 7, $1/P_n$ and $1/P_w$ are plotted as a function of the hydrolysis time and the theoretical predictions of $1/P_n$ and $1/P_w$ based on eqs 3 and 4 are also shown. Concerning the prediction of $1/P_w$, good agreement was obtained between the experimental data for 0−18 days and the theoretical calculation using $P_{n_0} = 2524$, $PD_0 = 1.78$ and $\boldsymbol{k} = 0.027$ (day^{-1}) for eq 4. On the other hand, regarding the prediction of $1/P_n$, using the corrected $P_{n_0} = 2250$ and the same $\boldsymbol{k} = 0.027$ (day^{-1}) for eq 3, good agreement was found in the same period. The correction of P_{n_0} is because eq 3 does not include a compensation term with PD_0 for the shift to a most probable distribution in the expression.

After 26 days, discrepancies between the calculations and the data became apparent. This is a thought to have been caused by the disintegration at the amorphous regions, similar to the case of PPL. The critical values are regarded as $P_n = 1090$ ($M_n = 78\,500$) and $P_w = 2600$ ($M_w = 187\,200$) in 26 days. Such high critical values would be due to many factors on the solid-state degradation as reported by Vert et al.[33] They may be caused by a change in limitation of the random chain scission in the amorphous regions with progress in the hydrolysis, for example, a T_g decrease from T_{g_0} of PLLA, which is slightly higher (55−60 °C) than the reaction temperature of 50 °C.

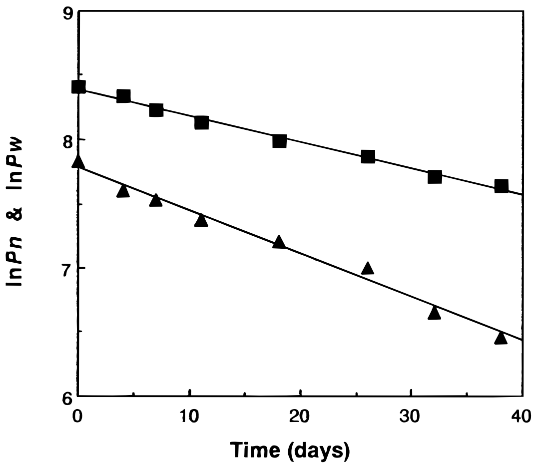

Figure 8. Plots of ln P_n and ln P_w vs time t for PLLA film: ln P_n (▲); ln P_w (■). Solid lines indicate calculations by the least-squares method.

Figure 8 shows the changes in ln P_n and ln P_w, and the straight lines fitted by the least-squares method for each set of data are also shown. Apparently, the approximation lines well agree with both sets of data, indicating regression coefficients close to 1 ($r^2 = 0.988$ and 0.990 for ln P_n and ln P_w, respectively). However, the rate constants obtained from the slopes were in discrepancy with each other, 0.0341 and 0.0206 (day^{-1}) for ln P_n and ln P_w, respectively. These rate constants do not agree with the $\boldsymbol{k}$ 0.027 (day^{-1}) calculated from eqs 3 and 4. From these results, it is considered that the plots of ln P_n and ln P_w as a function of hydrolysis time merely show apparent linear relationships, including some transient states of degradation manner. In contrast to the approximation, effectiveness of the predictions by eqs 3 and 4 is well-defined.

4.4. Applicability to Other Polyester Hydrolysis. We also applied the prediction model to some experimental results of the hydrolytic degradation of aliphatic polyesters reported by other workers. Pitt et al.[6] have reported that in the hydrolysis of PCL ($PD_0 = 1.66$) in vivo a liner relationship between log M_n vs implant period in rabbit was found, and an almost identical rate of chain cleavage was also observed in water at 40 °C. What is important is that the molecular weight distribution converged to about 2 with the degradation. The theoretical predictions of $1/P_n$ and 1/Pw based on eqs 3 and 4 using $P_{n_0} = 446.5$, $PD_0 = 1.66$ and $\boldsymbol{k} = 0.003$ (day^{-1}) showed good agreement for 96 weeks up to the critical point. This rate constant value was identical with the reported value 0.00307 (day^{-1}).

Doi et al.[14] have reported the hydrolytic degradation of microbial polyesters, poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (P(3HB-*co*-3HV)) and poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate) (P(3HB-*co*-4HB)), in 0.01 M phosphate buffer at 55 °C. The theoretical predictions agreed fairly well with a series of P(3HB-*co*-3HV) (3HV 45 mol %, $PD_0 = 2.6$; and 71 mol %, 2.0), in which PD values converged to about 2 or not changed. Estimated $\boldsymbol{k}$ values were 0.016 and 0.010 (day^{-1}), respectively. On the other hand, the predictions for P(3HB-*co*-4HB) (4HB 10, 17, and 27 mol %), in which PD values did not converge to 2 but enlarged to more than 3, could not succeed in finding the same $\boldsymbol{k}$ value in eqs 3 and 4, though the prediction of each set of $1/P_n$ and $1/P_w$ data was possible independently. The discrepancy in both $\boldsymbol{k}$ values enlarged with increasing 4HB content. A homogeneous random chain scission in the matrix of the copolymers may not be achieved.

Results of acid-catalyzed hydrolysis of PHB by 3 N HCl, which were reported by Lauzier et al.,[10] were impossible to predict with eqs 3 and 4, just as expected.

5. Conclusions

To predict the change in the molecular weight of aliphatic polyesters by an autocatalytic random hydrolysis, theoretical equations for the average degrees of polymerization and polydispersity were derived. Especially, a new prediction equation for the weight-average molecular weight was proposed. The new prediction model successfully interpreted the changes in the average molecular weights during the hydrolysis of aliphatic polyesters, such as poly(*p*-dioxanone), poly(β-propiolactone), poly(L-lactic acid), poly(ϵ-caprolactone), and poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate).

The prediction will be useful to avoid certain errors liable to occur in the estimation of the degradation process with only the number-average degree of polymerization. However, this predictions cannot be applied to nonautocatalytic processes such as acid-catalyzed hydrolysis, nonrandom processes and changes in the average molecular weights after the critical point.

6. Appendix

6.1. Derivation of the P_n Expression. If τ can be defined as $\tau = k_h[W]t$ for isothermal reactions, eq 2 becomes

$$d[P]/d\tau = (\sum_{n=1}^{\infty} n[P_n] - \sum_{n=1}^{\infty} [P_n])[COOH] \qquad (A1)$$

Since the moment is $\lambda_\kappa = \sum_{n=1}^{\infty} n^\kappa [P_n]$, eq A1 becomes

$$d\lambda_0/d\tau = \lambda_0(\lambda_1 - \lambda_0) \qquad (A2)$$

in which $\lambda_0 = \sum_{n=1}^{\infty}[P_n] = [P] = [COOH]$. Since λ_1 is the same as the concentration of the monomer unit, it is a constant. Therefore, $d\lambda_1/d\tau = 0$ and

$$\frac{d\lambda_2}{d\tau} = \frac{\lambda_0(\lambda_1 - \lambda_3)}{3} \qquad (A3)$$

If the molecular weight distribution is assumed to follow the Schultz–Zimm equation,[24] λ_3 in eq A3 can be expressed as follows:

$$\lambda_3 = \frac{\lambda_2(2\lambda_2\lambda_0 - \lambda_1^{\ 2})}{\lambda_1\lambda_0} \qquad (A4)$$

The P_n is defined as $P_n = \lambda_1/\lambda_0$. When P_n is differentiated with respect to τ

$$\frac{dP_n}{d\tau} = \frac{\lambda_1}{\lambda_0}(\lambda_1 - \lambda_0) = -kP_n\left(1 - \frac{1}{P_n}\right) \cong -kP_n \qquad (A5)$$

where $k = \lambda_1$ (const.). Integration of eq A5 yields

$$\frac{1}{P_n} = \frac{1}{P_{n,0}}e^{k\tau} \text{ or } \ln P_n = \ln P_{n,0} - k\tau \qquad (A6)$$

Therefore, a linear relationship between $\ln P_n$ and τ is predicted for the autocatalytic random chain scission of polyesters. Since term $\tau = k_h[W]t$, if $[W] \gg [COOH]$, eq A6 becomes eq 3.

6.2. Derivation of the P_w and PD Expressions. Meanwhile, P_w is defined as $P_w = \lambda_2/\lambda_1$. When P_w is differentiated with respect to τ

$$\frac{dP_w}{d\tau} = \frac{d(\lambda_2/\lambda_1)}{d\tau} = \frac{\lambda_1\lambda_2}{3_{\lambda_1}}\left(\frac{\lambda_0}{\lambda_2} - 2\frac{\lambda_0\lambda_2}{\lambda_1^{\ 2}} + 1\right) \cong \frac{k}{3}P_W(2PD - 1) \qquad (A7)$$

If PD = **PD** (const), integration of eq A7 yields

$$\ln P_w = \ln P_{w,0} - k'\tau \qquad (A8)$$

where $k' = k(2\mathbf{PD} - 1)/3$. Moreover, if $\mathbf{PD} \cong 2$, eq A8 becomes eq 7.

However, in practice, PD_0 is often not 2 and tends to change with degradation. PD is expressed as

$$\frac{dPD}{d\tau} = \frac{d(P_w/P_n)}{d\tau} = \frac{1dP_w}{P_n\,d\tau} - \frac{P_w dP_n}{P_n^{\ 2}\,d\tau} \qquad (A9)$$

Considering eqs A5 and A7

$$\frac{dPD}{d\tau} = \frac{1}{3}\lambda_1\frac{\lambda_0\lambda_2}{\lambda_1^{\ 2}}\left(\frac{\lambda_0\lambda_1}{\lambda_1\lambda_2} - \frac{\lambda_0\lambda_3}{\lambda_1\lambda_2} + 3 - \frac{3\lambda_0}{\lambda_1}\right) = kPD\left(1 - \frac{1}{P_n} + \frac{1}{3P_nP_w} - \frac{P_z}{3P_n}\right) \cong kPD\left(1 - \frac{P_z}{3P_n}\right) \qquad (A10)$$

Since $P_z \cong 2P_w - P_n$ for the polyesters with the Schultz–Zimm distribution, eq A10 becomes eq 5. Equation 5 predicts that PD converges to 2 with τ. Considering eq 5, eq A7 becomes

$$\frac{1}{P_w}dP_w = -\frac{k}{3}(2PD - 1)d\tau = -\frac{k}{3}(2PD - 1)\frac{d\tau}{dPD}dPD$$
$$= \left\{\frac{1}{4PD} - \frac{3}{4(2 - PD)}\right]dPD \qquad (A11)$$

or

$$= \left\{\frac{1}{4PD} + \frac{3}{4(PD - 2)}\right\}dPD \qquad (A11')$$

When PD < 2, integration of eq A11 yields

$$\ln P_w^{\ 3/4} - \ln(2 - P_w/P_n)^{3/4} = a - \ln P_n^{\ 1/4} \qquad (A12)$$

where $a = \ln P_{w,0} - \ln PD_0^{\ 1/4} - \ln(2 - PD_0)^{3/4}$ (const). Considering $P_n = P_{n,0}e^{-k\tau}$ from eq A6, eq 12 becomes

$$\frac{3}{4}\ln\left(\frac{2P_{n,0}e^{-k\tau}}{P_w} - 1\right) = -k\tau + \frac{3}{4}\ln\left(\frac{2 - PD_0}{PD_0}\right) \qquad (A13)$$

Now, eq A13 can be rearranged into eq 4. When PD > 2, integration of eq A11′ also yields the same solution as eq 4.

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