Study on Hydrolytic Kinetics of Langmuir Monolayers of Biodegradable Polylactide Derivatives

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Abstract: The rate of hydrolysis of Langmuir monolayer films of biodegradable polylactide (PLA) derivates was investigated at the air/water interface. The present study investigated such parameters as surface pressure, pH, and time. The hydrolysis of polyester monolayers depended strongly on the subphase pH, the concentration of active ions. Under the conditions studied here, polymer monolayers showed faster rates of hydrolysis when they were exposed to a basic subphase rather than they did when exposed to acidic or neutral subphases. By increasing the concentration of the degradation medium, the hydrolytic rate of *dl*-PLA monolayers was accelerated (accelerating effect). In addition, the basic hydrolysis of modified PLA with small amounts of hydrophilic (benzyloxycarbonyl) methyl morpholine-2,5-dione or glycolide was much faster than that of the PLA homopolymer.

Keywords: Langmuir, polylactide, hydrolysis, accelerating effect.

Introduction

Polylactides (PLA), produced by some chemical synthetic methods, is a biodegradable and biocompatible thermoplastics. These polymers also have applications in many therapeutic processes such as drug release carriers in films and spheres.[1-5] A controlled degradation of plastics affords a workable solution to programmed release of drug from carriers. Many variables affecting degradability have been revealed, including morphology, molecular weight, hydrophobic/hydrophilic properties and the type of hydrolyzable linkage.[1] Many workers have attempted to control the range of mechanical properties and hydrolytic degradability of many types of polyesters by blending and copolymerization for biomedical applications.[1-9]

A weight loss method has widely been applied to determine the degradation rate of polyesters. One of other suitable techniques for studying the hydrolytic behavior is to use a Langmuir film balance, since the hydrolysis of a polyester usually occurs through the cleavage of ester groups and eventually produces water-soluble oligomers and monomers. The hydrolysis of polyester monolayers would result in a change in the occupied area when the monolayer is maintained at a constant surface pressure. The study of polyester monolayers at the air/water interface will, therefore, give a fundamental understanding of the hydrolytic mechanism of polyesters, such as polymers and copolymers derived from lactic acid (LA), glycolic acid (GA), and ε-caprolactone (CL).

Despite several reports on the structural study on polyester monolayers at the air/water interface,[10,11] few studies have been made on the hydrolysis of monolayers at the air/water interface.[12-15] In this study, the hydrolytic degradation of modified polylactides has been systematically investigated at the air/water interface as a function of subphase pH, concentration of degradation medium (alkaline or enzyme), and degradation time.

Experimental

Materials. *l*- and *dl*-lactide were obtained from Aldrich and recrystallized from anhydrous ethyl acetate. CL (Aldrich Chem. Co., Milwaukee, WI, U.S.A.) and stannous octoate

(Sigma Chem. Co., St. Luis, MO, U.S.A.) were used as received. (Benzyloxycarbonyl) methyl mophorline-2,5-dione (BMD) was prepared by the method described by Wang and Feng[16](see Scheme I). Bulk polymerizations of l-LA, CL, and copolymerization of l-LA and BMD were carried out in vacuum-sealed glass ampoules under N_2 gas at a given temperature using stannous octoate as a catalyst. The products in the ampoules were dissolved in chloroform and then precipitated with excess of methanol. The obtained copolymer was characterized using ^{1}H-NMR (GEMINI 300, Palo Alto, CA, U.S.A., CDCl$_3$: $\delta = 1.6$ (CHCH$_3$), $\delta = 4.7$ (NHCH), $\delta = 7.3$ (CH$_2$COOBz)). Poly(dl-lactide-co-glycolide) (dl-LA-co-GA, 7/3 by wt) was purchased from Polysciences Inc. (Warrington, PA, U.S.A.). The molecular characteristics of homopolymers and the copolymers used in this study are listed in Table I. All other chemicals were of reagent grade and were used without further purification. Reagent grade HCl and NaOH were used to adjust the pH of the water. A pH meter equipped with an electrode (Orion Research, Beverly, MA, U.S.A.) was used to measure the pH of solutions.

Langmuir Trough. Monolayer properties were studied by using a computer-controlled KSV 2200 film balance (KSV Instruments Ltd., Helsink, Finland) held at 293 K. A compression rate of 30 cm^2/min was used throughout. The surface pressure could be measured with an accuracy of 0.1 mN/m. The water subphase was purified with a Mega-Pure system (MP-6A, Prairie, WI, U.S.A.). The purified water of ca. 1,600 mL was used as a subphase liquid. The spreading solvent used in this study was chloroform (Fisher, Hampton, NH, U.S.A., 99%+). The concentrations of all solutions were ca. 2 $m$mol/mL. After spreading, the solvent was allowed to evaporate over 1 min (the residual solvent is evaporated during compression), in order to minimize the hydrolysis during the solvent evaporation and the compression. The time for solvent evaporation was determined on the basis of

the reproducibility of PCL monolayer on pure water taking advantage of very slow hydrolysis, under measured conditions.

Results and Discussion

The Langmuir technique has been used to measure the hydrolytic degradation of polyester monolayers on a molecular scale, since most polyesters are capable of forming monolayers owing to their hydrophilic/ hydrophobic balance.[10-15] The low molecular weight oligomers and monomers generated by hydrolysis dissolve into water. This would result in a change in the occupied area if the monolayer is maintained at a constant surface pressure.

Since the hydrolysis of the ester bond in polyesters produces carboxylic acid- and alcohol-end groups, octadecanoic acid and octadecanol were used as model systems to study the solubility of the hydrolytic product in the subphase. As shown in Figure 1(a), the area per molecule for octadecanoic acid significantly decreased with increasing pH, and eventually no monolayer was formed at pH 9.4 (not shown here). Since the shape of the isotherms at both pH 7.3 and 8.5 are similar to each other, this area change would be related to the solvation of some octadecanoic acids into subphase during the evaporation of solvent and the barrier compression. No change, however, was observed in the areas of octadecanol monolayers on both subphases of pH 7.3 and 8.5, as shown in Figure 1(b). This behavior implies that the carboxyl acid group, not the alcohol group generated by the chain cleavage of ester bond is mainly related to the molecular loss likely due to the formation of carboxyl acid salts with sodium ion and then the increase of the solubility into subphase.[13-15] Therefore, the diffusion of acid fragments away from the reacting monolayer may well be the rate determining step.

Figure 2 shows the surface pressure-area isotherms for dl-PLA monolayers on subphase of pH 10.5 measured with different pause times of 1 and 2 hr. As a pause time increased, the overall area occupied by the monolayers dramatically decreased. This result can be explained by the fact that the measured surface pressure-area isotherm reflects the dissolution of some oligomers generated by hydrolysis during the compression and interfacial counter ions at the air/water interface are submerged into subphase by compression of

BMD   A=H: GA, A=CH$_3$: LA
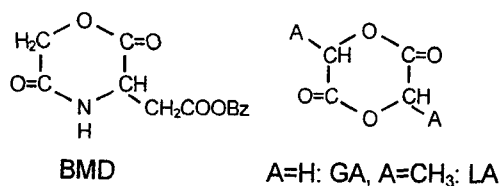
Scheme I. Structures of monomers.

Table I. Characterization of the Materials Used in This Study

	M_n	M_w/M_n	T_g (K)	T_m (K)	Sources
l-PLA	19 k	2.9	324	440	Synthesized for this study
dl-PLA	11 k	1.4	318	$n.d.$	Synthesized for this study
dl-LA-co-GA	21 k	1.6			Polysciences(7/3 by wt)
l-LA-co-BMD	20 k	1.7	328	418	Synthesized for this study(4 mol% BMD)
PCL	16 k	1.6		321	Synthesized for this study

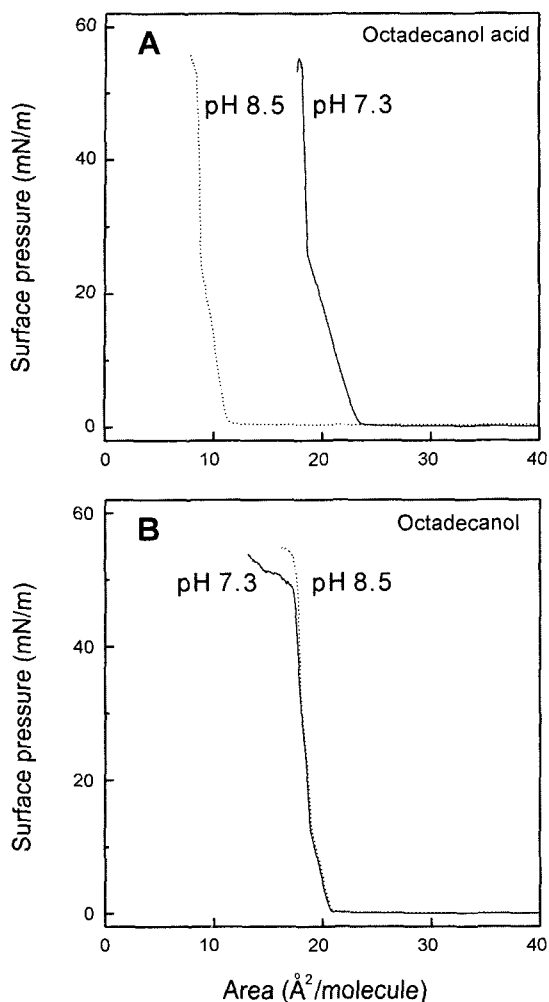**Figure 1.** Pressure-area isotherms of octadecanoic acid (A) and octadecanol (B) monolayer films on subphases of two different pH's.
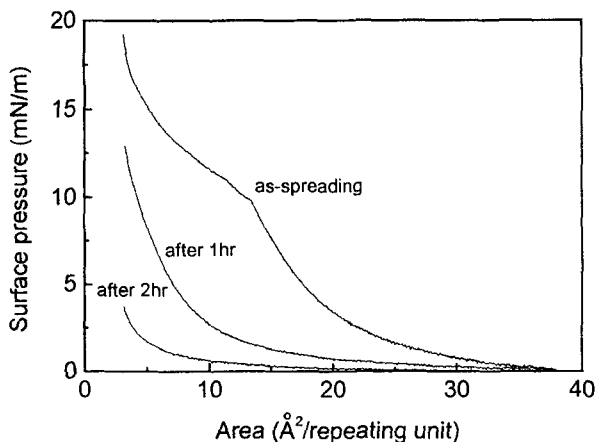
monolayers. The dramatic decrease in the area is complicated by the fact that the dissolution of hydrolytic product into the subphase is increased during the pause time. A similar behavior was observed in the surface pressure-area isotherm of *dl*-LA-*co*-GA, which shows faster hydrolysis than *dl*-PLA.

For bulk polymer degradation, it is well known that the morphology of the polymers strongly affects hydrolysis rates.[1] Amorphous regions of many biodegradable semi-crystalline polymers are preferentially hydrolyzed, since the tightly packed crystalline regions are less accessible to water. High surface pressure before transition and collapse results from a reduction in the space occupied by each individual molecule. This point of view may be useful in interpreting hydrolytic behaviors of polyester monolayers because a high surface pressure increases regularity of monolayers and density in unit area. Therefore, it is expected that the hydrolysis rate of polyester monolayers would be increased as a constant surface pressure decreases. Figure 3 shows the change of area ratio (A/A_0) occupied by *dl*-PLA monolayers with time at various constant surface pressures on subphases of pH 3.5 and 10.5, where A_0 and A represent the areas occupied by the film at time 0 and t, respectively. The initial time, $t = 0$ was considered when the surface pressure reaches a desired surface pressure, meaning that the effect of dissolving low molecular oligomers due to hydrolysis was neglected during the compression. This effect is considered to be marginal, if any, since there is little difference in A/A_0 ratios with hydrolysis time. The measured kinetic curves follow a typical sigmoid shape, that is, the faster the reduction of A/A_0 ratio, the smaller the real initial area. The extent of area ratio reduction appears to increase upon lowering the constant surface pressure. Under the condition of this measurement, however, no significant difference in the area with time up to 100 min was observed when *dl*-PLA was exposed to acidic subphase, pH 3.5, which has been adjusted by addition of HCl. This latter result is in accordance with other reported work,[13,17] which also showed a significant hydroly-
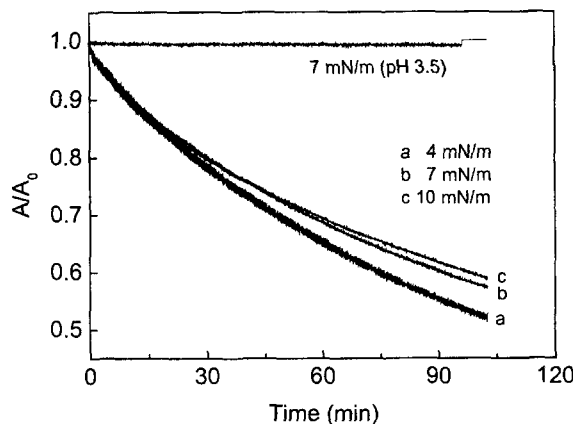

Figure 2. Pressure-area isotherms of *l*-PLA monolayer films onto subphase of pH 10.5 with two different pause times.

Figure 3. Area ratio *vs.* time for *dl*-PLA monolayer films on subphases of pH's 3.5 and 10.5 at various surface pressures.

sis on basic pH's. Ivanova *et al.*[12] reported that hydrolysis of the *dl*-PLA monolayer at pH=1.9 occurred, but used a very different experimental procedure than used. Under alkaline subphase of pH 10.5, the extent of area reduction appears to increase upon lowering the surface pressure. This trend would result from increasing number of the base attack sites per ester bond unit and irregularity.

To investigate the effect of activity of ions in the subphase on the hydrolysis, kinetic curves of *l*-PLA monolayers on different concentrations of NaOH in subphase were measured. Figure 4 shows a plot of the kinetic curves with for *l*-PLA monolayers maintained at 7 mN/m on different pH's between 7.3 and 10.5, which have been adjusted by addition of NaOH. As expected, the occupied area of *l*-PLA monolayers on pure water (pH=7.3) was almost unchanged with time. On increasing pH, however, the areas occupied by monolayers are significantly decreased. At subphase pH's between 9.9 and 10.2, kinetic curves of *l*-PLA monolayer films show the region of rapid decrease in occupied areas. This region moved to shorter hydrolysis time as subphase pH increases and finally disappeared at pH=10.5. Makino *et al.* observed that *l*-PLA degraded rapidly in alkaline solution or in solutions of high ionic strength.[18] Also, the degradation was affected by salt concentration in buffer solutions, suggesting that the cleavage of polymer ester bonds was accelerated by conversion of the acidic degradation products into neutral salts. These are supported by the result in Figure 1. Therefore, these regions might be related to the salt formation between acid groups produced by hydrolysis of ester groups and Na^{+} ions in subphase because the carboxyl acid can easily react to the sodium ion in water and the solubility of the oligimer-Na^{+} salts into water is much higher than that of carboxyl acid-end oligomers. High concentration of Na^{+} ions in subphase accelerates hydrolysis and salt formation and then shows rapid decrease of occupied areas. Figure 5 shows a plot of A/A_0 *vs.* time of *dl*-PLA monolayer at a constant surface pressure of 7 mN/m on subphases of different pHs. As expected, the extent of area reduction appears to increase upon higher subphase pH. The data in Figure 5 indicate that the reduction fraction of the original area was approximately 0.04, 0.19, and 0.36 (experimental error of ± 2%) after a hydrolysis time of 60 min exposed to pH's, 10.3, 10.4, and 10.5, respectively, even though the concentration of Na^{+} ions in the subphase of pH's 10.4 and 10.5 controlled by adding NaOH is nearly two and three times of that of pH 10.3, respectively. By increasing the concentration of degradation medium, the hydrolytic rate of *dl*-PLA monolayers was much accelerated (*accelerating effect*).

Figure 6 shows change of A/A_0 with time of various polyester monolayer films on the subphase of pH 10.5 at a constant surface pressure of 7 mN/m was calculated from A/A_0 data. The extent of hydrolysis, under the condition studied here, follows the order: *dl*-LA-*co*-GA > *dl*-PLA ≈ *l*-LA-*co*-BMD > *l*-PLA > PCL. The rate of alkaline hydrolysis of
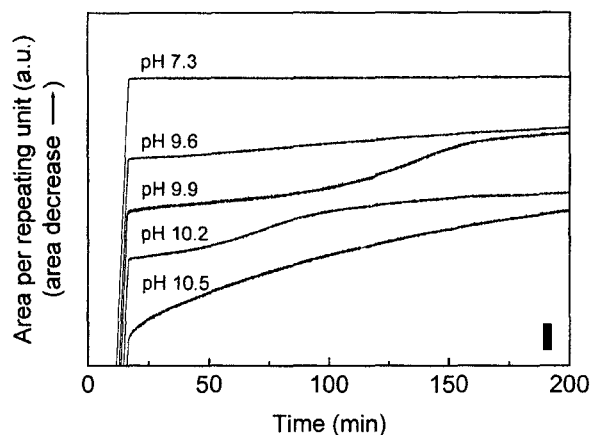

Figure 4. Area with time for *l*-PLA monolayer films at a constant surface pressure of 7 mN/m on subphases of different pHs(Bar: - 1 Å/repeating unit).
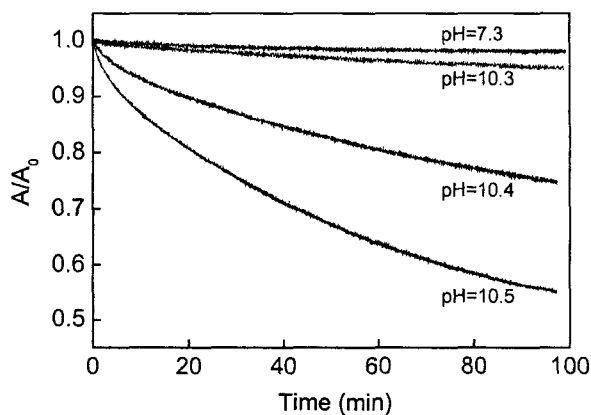

Figure 5. Area ratio *vs.* time for *dl*-PLA monolayer films at a constant surface pressure of 7 mN/m on subphases of pH's 7.3 and 10.5.
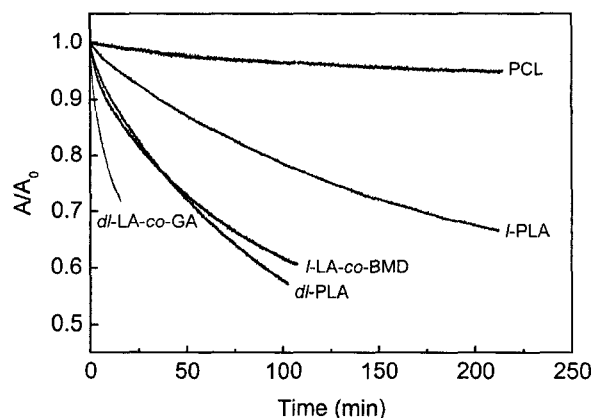

Figure 6. Area ratio *vs.* time for *l*-PLA, *dl*-PLA, PCL, *dl*-LA-*co*-GA, and *l*-LA-*co*-BMD monolayer films maintained at a constant surface pressure of 7 mN/m on subphase of pH 10.5.

PLA was much accelerated by copolymerization with BMD or GA.

Conclusions

The hydrolysis of polyester monolayers maintained at a constant surface pressure leads to the reduction in the area occupied by films when they are exposed to a basic subphase. The extent of hydrolysis was increased with increasing pH of the subphase, the concentration of degradation medium, and copolymerization with hydrophilic monomer. This behavior was attributed to the increase of solubility of oligomers into subphase due to the salt formation of carboxyl-end groups generated by hydrolysis with sodium ions in subphase.

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