Enzymatic Degradability of Poly(lactide): Effects of Chain Stereochemistry and Material Crystallinity

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Received April 8, 1996; Revised Manuscript Received July 19, 1996

ABSTRACT: Polylactide (PLA) stereocopolymers with (l) repeat unit contents of 75%, 80%, 82%, 85%, 90%, 91%, 92%, 94%, and 95% were prepared from mixtures of (l)/(d)-lactide and (l)/meso-lactide. Compression molding of these products gave amorphous films which, for (l) contents ≥ 90%, were also annealed above Tm to crystallize. Analyses by differential scanning calorimetry and wide angle X-ray scattering gave information on the crystalline order of PLA films. For identical (l) contents, stereocopolymers of (l)-(l)-lactide had higher crystallinities than those from (l)-meso-lactide. PLA films were incubated with proteinase K (from Tritirachium album), and the enzyme-catalyzed film weight loss rates were measured. Film crystallinity, chain stereochemical composition, and repeat unit sequence distribution were analyzed as independent variables affecting film enzymatic hydrolysis. Amorphous films from (l)/(d)-lactide copolymerizations with (l) compositions ranging from 80% to 95% exhibited film weight loss rates that were almost identical. Also, amorphous PLA films prepared from (l)-meso-lactide copolymers for (l) contents of 80–95% showed a similar invariability in weight loss rates. It was concluded that proteinase K has a high degree of tolerance for (d) repeat units. Amorphous PLA films from (l)-lactide/meso-lactide copolymerizations had weight loss rates which were about 43% slower than amorphous PLA films from (l)-(l)-lactide copolymerizations. These results were analyzed considering differences in chain stereosequence distributions. Proteinase K showed an extraordinarily high sensitivity to film crystalline order. For example, the decrease in the film weight loss rate due to crystalline order for a 95% (l) (l)/(l)-lactide stereocopolymer was 93%.

Introduction

Polylactides (PLAs) are known to be biocompatible

and are hydrodegradable.6–14 They have found use in materials for controlled release devices14,15 as well as other medical applications.4,16–20 In recent years there has been considerable effort to utilize PLAs for plastics which, upon disposal, will be biodegradable.21,22

The polymerization of lactide stereoisomers (see structures below) is believed to proceed primarily through a pair addition mechanism.23,24

![Polymerization of lactide stereoisomers](image)

Copolymerization of (l)/(d)-lactides leads to predominantly isotactic (iso) diad sequences, whereas polymerization of meso-lactide introduces syndiotactic (syn) lactic acid diad sequences. Thus, the main chain of PLAs can be designed to have numerous stereochemical variants, which provides a mechanism to regulate corresponding material properties. Polymerization of 100% (l)-lactide ([l]-(l) stereocenters) results in the formation of a semicrystalline (l)-PLA with a melting transition at ~180 °C and a Tm of ~67 °C.25,26 Copolymerizing equal quantities of (l)- and (d)-lactides using non-stereoregulating catalysts27 results in an amorphous material with a Tm of 58 °C.25,26 The configuration of lactide monomer chiral centers are retained on conversion to linear polymer chain repeat units when the initiators used are tin salts such as stannous octanoate, tin tetrachloride, or tetraphenyltin.27–30

While the hydrolytic degradability of PLA has been studied by a number of laboratories,3–13 reports on the enzymatic degradability of PLA have been few.3,5,6,31,32 In a previous study performed in our laboratory, Reeve et al.31 prepared various PLA stereocopolymers from mixtures of (o)- and (l)-lactide using stannous octanoate as the catalyst. Films of these polymers prepared by solution casting were annealed to crystallize and then exposed to proteinase K which is a fungal protease produced by the mold Tritirachium album.33 Proteinase K preferentially degraded (l)- as opposed to (o)-PLA. A decrease in the (l) repeat unit content from 100% to 92% led to a large decrease in crystalline order and corresponding increases in film weight loss rates. However, the experiments performed on semicrystalline PLA films only considered superimposed effects of polymer stereochemistry and material crystallinity on film degradability.31

Unlike PLA, the enzymatic degradability of poly-(hydroxyalkanoates) as a function of crystalline morphology and stereochemical composition has received considerable attention.34–46 Of particular relevance to this paper are the effects on biodegradability of polymer repeat unit sequence distribution at equivalent chain enantiopurity. The enzymatic degradability of P3HB stereoisomers having 50% (R)-(3)-HB content but differing in stereosequence distribution have been investigated. Studies by Kemnitzer et al.41 and Parandoosh et al.46 showed that predominantly syn-P3HB (syn-diad content ~0.67) was readily degraded by the Penicillium functionusom depolymerase whereas atactic P3HB was a poor substrate subsequent to an initial exposure period. Jesudason et al.35 used the depolymerase produced by Alcaligenes faecalis to study the enzymatic degradabil-

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† This paper is part of the Ph.D. thesis dissertation of Renée T. MacDonald, University of Massachusetts Lowell, 1995.
‡ Abstract published in Advance ACS Abstracts, October 1, 1996.
ity of 50% (R)-3HB stereoisomers which differed in iso-diacid content. Films formed from high (--88%) iso-diacid content showed little degradation while films from intermediate (63%) iso-diacid content degraded steadily at a rate less than that found for bacterial 3HB. In contrast, low iso-diacid (--48%) 50% (R)-3HB was a poor substrate after initial rapid degradation. 3HB has a T_g below room temperature and is semi-crystalline over a wide range of chain isotoxicities. Therefore, it is difficult to design studies directed at determining effects of stereochimical composition, stereosequence distribution, and crystallinity as independent parameters on polymer enzymatic degradability.

This paper builds on our previous investigation of PLA degradability by proteinase K. Since large changes in crystalline order and enzymatic degradability were expected for PLA with (l) contents from 90% to 95%, detailed investigations over this stereochimical range were performed. For this purpose, stereopolymermers were prepared by copolymerizations of (l-)/lactide and (l-)/meso-lactide. Amorphous films were prepared by compression molding and quenching from the melt. These films were also obtained with crystalline order by annealing above T_g. In addition, PLA stereopolymermers were prepared over the compositional range from 75% to 85% (l). The crystallinity of PLA films was determined by differential scanning calorimetry (DSC) and wide angle X-ray scattering (WAXS). The above series of polymers provided an opportunity to study how film crystalline order, chain stereochimical composition, and repeat unit sequence distribution, taken as independent variables, affected interactions between PLA films and proteinase K. Furthermore, the tolerance of proteinase K for (l)-lactide repeat units in PLA chains was investigated.

Experimental Section

(A) Instrumental Methods. Molecular Weight Measurements. All molecular weights were determined by gel permeation chromatography (GPC) utilizing a Waters Model 510 pump, Model 410 differential refractometer, and a Model 717 Plus autosampler with 500-, 103-, 104-, and 105-Å ultra-permeation chromatography (GPC) utilizing a Waters Model 440 data processor. Chemical shifts were referenced relative to CDCl_3 at a concentration of about 4.0% w/w. Chemical shifts in ppm were recorded relative to chloroform at 77.00 ppm. The following parameters were used for the data acquisi-

Remote sensing of (L)/(D)-lactide and (L)/(D)-lactide copolymers was transferred via syringe under an argon atmosphere into the vials, the vials were hand shaken to ensure mixing, the oil bath temperature was lowered to 120 °C, and the polymerization was carried out at this temperature for 6 h. Polymer products were isolated and purified as previously described. Typically, the yield of polymer from monomer was ~85%. 1HNMR spectra of selected synthesized samples were recorded, and the spectra obtained agreed with those previously published for PLA.

(C) Film Preparation. Fibrous PLA products were first dried in a vacuum desiccator for 24 h (0.05 mmHg). Films (about 0.1 mm thickness) were prepared by compression molding using a Dake hydraulic press equipped with heating plates. The polymers were placed between two polished metal plates lined with release sheets (NTI Technologies). The metal plates containing the polymer samples were inserted between the press heating plates; the metal plates were first maintained at 360 °F for 1 min with no applied pressure and then for 1 min with an applied pressure of ca. 255 psi. The processed films were then rapidly quenched by cooling with dry ice to give amorphous materials. To crystallize, films with (l)-contents ≥90% were annealed at 75 °C for 15 h. All films (annealed and not-annealed) were aged at 50 °C for 24 h to remove residual stress and then stored over Drierite at ambient temperature until use.

(D) Biodegradation Studies: Measurements of Film Weight Loss Rates. The method used follows that previously reported with the following modifications. PLA films (1.0 cm x 1.0 cm) with an approximate thickness of 0.1 mm were each placed in separate vials containing 5 mL of Tris-HCl buffer (pH 8.6), 1 mg of proteinase K (Sigma, lyophilized powder, 97% protein), and 1 mg of sodium azide (Fisher). Three replicate films in separate vials were used to determine film weight loss at a specified incubation time. The film–enzyme incubations were carried out in 150 mL Erlenmeyer flasks on a rotary shaker (250 rpm). At sampling times, the respective films were removed from the shaker incubator, rinsed thoroughly with distilled water, and then dried in vacuo (0.05 mmHg) at room temperature over P_2O_5 until a constant weight was
TABLE 1. Stereocchemical Composition, Molecular Weight, and Film Thickness Values for Synthesized PLA Stereosomers

<table>
<thead>
<tr>
<th>sample</th>
<th>mol % in feed (L,L)/(D,L)</th>
<th>mol % in feed (L,L)/(L,L)</th>
<th>$M_n$, (g/mol)</th>
<th>$M_{w/M_n}$</th>
<th>film thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA-95</td>
<td>95/5</td>
<td></td>
<td>71 000</td>
<td>(33 000)</td>
<td>0.12 (±0.01)</td>
</tr>
<tr>
<td>PLA-95M</td>
<td>90/10</td>
<td></td>
<td>nd</td>
<td></td>
<td>0.15 (±0.01)</td>
</tr>
<tr>
<td>PLA-94</td>
<td>94/6</td>
<td></td>
<td>61T000</td>
<td>(36 000)</td>
<td>0.13 (±0.01)</td>
</tr>
<tr>
<td>PLA-94M</td>
<td>88/12</td>
<td></td>
<td>70 000</td>
<td>(53 000)</td>
<td>0.11 (±0.01)</td>
</tr>
<tr>
<td>PLA-92</td>
<td>92/8</td>
<td></td>
<td>225 000</td>
<td>(110 000)</td>
<td>0.15 (±0.02)</td>
</tr>
<tr>
<td>PLA-92M</td>
<td>84/16</td>
<td></td>
<td>nd</td>
<td></td>
<td>0.13 (±0.02)</td>
</tr>
<tr>
<td>PLA-91</td>
<td>91/9</td>
<td></td>
<td>64 000</td>
<td>(30 000)</td>
<td>0.12 (±0.02)</td>
</tr>
<tr>
<td>PLA-90</td>
<td>90/10</td>
<td></td>
<td>187 000</td>
<td>(87 000)</td>
<td>0.17 (±0.02)</td>
</tr>
<tr>
<td>PLA-85</td>
<td>85/15</td>
<td></td>
<td>130 000</td>
<td>(30 000)</td>
<td>0.11 (±0.02)</td>
</tr>
<tr>
<td>PLA-85M</td>
<td>70/30</td>
<td></td>
<td>130 000</td>
<td>(70 000)</td>
<td>0.09 (±0.01)</td>
</tr>
<tr>
<td>PLA-82</td>
<td>82/18</td>
<td></td>
<td>120 000</td>
<td>(32 000)</td>
<td>0.10 (±0.01)</td>
</tr>
<tr>
<td>PLA-82M</td>
<td>64/36</td>
<td></td>
<td>70 000</td>
<td>(32 000)</td>
<td>0.10 (±0.02)</td>
</tr>
<tr>
<td>PLA-80</td>
<td>80/20</td>
<td></td>
<td>70 000</td>
<td>(44 000)</td>
<td>0.09 (±0.01)</td>
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<tr>
<td>PLA-80M</td>
<td>60/40</td>
<td></td>
<td>120 000</td>
<td>(70 000)</td>
<td>0.10 (±0.01)</td>
</tr>
<tr>
<td>PLA-75</td>
<td>75/25</td>
<td></td>
<td>70 000</td>
<td>(34 000)</td>
<td>0.10 (±0.02)</td>
</tr>
</tbody>
</table>

a Samples denoted with M indicate stereocopolymers prepared with meso-lactide. b Ratio of stereoisomerically pure (L)-lactide to (D)-lactide in monomer feed. c Ratio of stereoisomerically pure (L)-lactide to meso-lactide in monomer feed. d Determined by GPC (see Experimental Section). e Values given are for solution precipitated products while the numbers in parentheses are for compression molded amorphous films. f Not determined.

Results and Discussion

Polymer Film Characterization. Crystalline Morphology, Molecular Weight, and Repeat Unit Sequence Distribution. PLA products in a range of stereocchemical compositions and differing in repeat unit sequence distribution (see Table 1) were synthesized by the ring-opening copolymerization of lactide stereomers using stannous octanoate as the catalyst (see Experimental Section). Molecular weights of the solution precipitated products prior to thermal processing were measured by GPC, and the $M_n$ values ranged between 70 000 and 130 000 g/mol for the series of samples with (L) values between 75% and 85%. A few products with (L) values ≥90% prepared using meso-lactide had higher $M_n$ values (up to 225 000 g/mol, see Table 1). The formation of films by compression molding resulted in significant molecular weight loss (from 15% to 76%) as is shown in Table 1 (values in parentheses are subsequent to thermal processing). Since the variability in product molecular weights described above was a concern as to its effect on film biodegradability, a study was undertaken using PLA products prepared by copolymerization of (L)-(D)-lactide (90:10) which had $M_n$ values of 30 000, 100 000, and 200 000 g/mol. Interestingly, the normalized weight loss rates for these films of identical stereocchemical composition and crystallinity (based on DSC measurements) showed little deviation (4.3, 3.8, and 4.2 μg-mm mg⁻²-h⁻¹, respectively). Thus, it was concluded that, over a wide range of PLA molecular weights, the effects of PLA chain length on proteinase K catalyzed degradation rates are not significant. Furthermore, the lack of a molecular weight effect on polymer degradation suggests that proteinase K has endo enzyme activity.

Previous work has documented that PLA, when heated under conditions (temperature, time, catalyst) dissimilar to those used herein for film preparation, may undergo randomization due to transesterification. To determine whether the repeat unit sequence distribution of PLAs was altered due to compression molding, 62.9 MHz 13C NMR analyses (see Experimental Section) were performed on PLA-80 (80% (L) repeat units, copolymerization of (L)- and (D)-lactides) and PLA-80M (80% (L) repeat units, copolymerization of (L)- and meso-lactides) before and after compression molding. 13C NMR spectra of PLA stereocopolymers have been reported by others, and assignments of triad and pentad stereosequences were made by observation of the methine and carbonyl carbons. Comparisons of the relative intensities of triad stereosequences prior and subsequent to thermal processing showed no detectable randomization due to transesterification events (spectra not shown). Furthermore, previous work using stannous octanoate as the catalyst for lactide ring-opening polymerization showed that racemization of the monomer does not occur. Therefore, it was concluded that: (1) thermal processing did not alter product repeat unit sequence distribution, (2) the relative stereosequence fractions of products are predictable based on random propagation statistics, and (3) the (L) composition of the products was identical to that of the monomer feed.

All of the films prepared by compression molding followed by rapid quenching from the melt using dry ice were amorphous based on WAXS (no crystalline reflections) and DSC (absence of melting transitions). Furthermore, PLA samples prepared with (L) contents of 85% or less did not crystallize even after elevated temperature annealing (75 °C, 15 h). Thus, a series of amorphous films (no crystallinity effects) were obtained which differed in (L) content and stereosequence distri-
from observation of the DSC and WAXS results in Table 2. Increase in the (L) content of PLA products allows the preparation of films with relatively higher crystalline ordering (see Table 2). Interestingly, PLA products of identical (L) contents but synthesized using meso-lactide in place of (D)-lactide had relatively lower degrees of crystalline ordering. This is readily apparent from observation of the DSC and WAXS results in Table 2. Thus, the introduction of equivalent (o) units along a polymer chain as crystalline defects within an (L) crystalline lattice by using (o)-(L) or (L)-(o) dyad sequences results in a greater disruption to the material crystalline order than from paired (o)-(o) neighboring groups. This is understandable since, in the later case, the effective crystalline ordering disruption per (o) repeat unit is less because the (o) units are paired.

PLA-Enzyme Incubations. Film Weight Loss Studies. Incubation of PLA films with proteinase K in Tris-HCl buffer (pH 8.6) was carried out (see Experimental Section). By determining weight loss at specific time intervals, curves were generated of the normalized weight loss as a function of exposure time (not shown). The normalized weight loss is the measured weight loss divided by the initial surface area and is given in units of µg/mm². Plots of µg/mm² versus time (not shown) were linear up to film weight loss values of ~60%. The slopes of lines generated from these plots were used to determine the weight loss rates (µg-mm⁻²·h⁻¹), which are shown in Figures 1 and 2. Controls run where PLA films were incubated in the absence of enzyme for incubation periods as long as the maximum enzyme exposure times (48 h) showed no measurable weight loss.

Figure 1 shows the weight loss rates for amorphous PLA films prepared from (L)-/(D)-lactide copolymers having (L) contents from 75% to 95%.

The results of DSC and WAXS analyses on films subsequent to crystallization and aging are shown in Table 2. Increase in the (L) content of PLA products allows the preparation of films with relatively higher crystalline ordering (see Table 2). Interestingly, PLA products of identical (L) contents but synthesized using meso-lactide in place of (D)-lactide had relatively lower degrees of crystalline ordering. This is readily apparent from observation of the DSC and WAXS results in Table 2. Thus, the introduction of equivalent (o) units along a polymer chain as crystalline defects within an (L) crystalline lattice by using (o)-(L) or (L)-(o) dyad sequences results in a greater disruption to the material crystalline order than from paired (o)-(o) neighboring groups. This is understandable since, in the later case, the effective crystalline ordering disruption per (o) repeat unit is less because the (o) units are paired.

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Figure 1 shows the weight loss rates for amorphous PLA films prepared from (L)-/(D)-lactide copolymers having (L) contents from 75% to 95%.
Comparison of the film weight loss rates in Figure 1 shows that amorphous (L)-lactide/meso-lactide copolymer films with (L) contents between 80% and 95% degraded at a weight loss rate which was ∼43% slower than corresponding amorphous (L)-lactide/(D)-lactide copolymer films. These results demonstrate that PLA–enzyme interactions must be dependent on the composition of chain stereosequences. One possible explanation for these results is that (L)-(D)-(L) triad sequences present in (L)-meso-lactide but not (L)-(D)-(L)-lactide copolymers act as an inhibitor and that enzyme–inhibitor interactions are saturated at low inhibitor concentration (for the enzyme concentration used in this work). This explanation is consistent with the observation that an increase in the (D) content from 5% to at least 20% for amorphous (L)-meso-lactide copolymer films did not change film weight loss rates.

The weight loss rates for crystallized PLA films with (L) contents between 90% and 95% prepared by copolymerizations of (L)-(D)-lactide are shown in Figure 2. A decrease in the weight loss rates for PLA-95, PLA-94, PLA-92, PLA-91, and PLA-90 of 93% (6.9–0.48 µg mm⁻² h⁻¹), 93% (6.6–0.46 µg mm⁻² h⁻¹), 82% (6.5–1.2 µg mm⁻² h⁻¹), 75% (6.5–1.5 µg mm⁻² h⁻¹), and 38% (6.8–4.2 µg mm⁻² h⁻¹), respectively, was observed. As was discussed above, the weight loss rates for PLA-90 to PLA-95 were not affected by the polymer chain (L) content when stereochemistry was analyzed as the independent variable. Thus, assuming crystallinity is the independent parameter which controls the degradation rate, a plot of rateann/ram × 100 versus % crystallinity was constructed (see Figure 3). The decrease in weight loss rates was largest (∼14 times) when comparing the semicrystalline and amorphous forms of PLA-94 and PLA-95 due to the relatively high crystalline ordering of these PLA products. It is interesting that even though PLA-94 and PLA-95 have very different AH₁ and % crystallinity values (see Table 2), they have almost identical weight loss rates (0.46 and 0.48 µg mm⁻² h⁻¹, see also Figure 3). Possibly, constraints imposed on proteinase K enzyme degradation by crystalline ordering of PLA-94 and PLA-95 are similar. PLA-90 has an χ of only 10%, but this low crystallinity still results in a decrease in the weight loss rate by 38% (see Figure 3). Thus, even a low level of film crystallinity causes a substantial constraint on productive PLA–proteinase K interactions which lead to film weight loss.

The weight loss rates for annealed and amorphous films prepared from PLA-90M, PLA-91M, PLA-92M, PLA-93M, and PLA-95M (meso-lactide copolymers) are shown in Figures 2 and 1, respectively. Although not determined experimentally, it is reasonable to assume by interpolation that the weight loss rate for amorphous PLA-94M is ∼3.8 µg mm⁻² h⁻¹. The deceleration in the weight loss rates due to crystalline ordering for PLA-94M and PLA-92M (see Figure 3) was 60% (3.8–1.5 µg mm⁻² h⁻¹) and 26% (3.8–2.8 µg mm⁻² h⁻¹), respectively. The differences in weight loss rates were much less than was observed above for (L)-(D)-lactide copolymers of identical (L) repeat unit content (see above). These results are explained by the fact that annealed (L)-meso-lactide copolymers have poorer crystalline ordering and lower levels of crystallinity than corresponding (L)-(D)-lactide copolymers (see Table 2). The similarity in weight loss rates of annealed PLA-90 and PLA-90M films results from the fact that the former film is semicrystalline whereas the latter is amorphous but is decelerated by the introduction of meso-lactide repeat units. The % crystallinity of PLA-95M is intermediate to that for PLA-94 and PLA-95. Interestingly, the degradation rates of annealed PLA-95M, PLA-94, and PLA-95 relative to their corresponding amorphous films are identical (Figure 3), illustrating how crystallinity is the dominant factor controlling the weight loss rate. However, annealed PLA-95M film has a weight loss rate that is about 50% less than PLA-95 (see Figure 2). Thus, it appears that, at high film crystalline order, stereosequence effects caused by meso-lactide repeat units can also influence the weight loss rate. Since Figure 3 attempts to eliminate effects of sequence distribution between the two series of copolymers (L)-(D)-lactide and (L)-meso-lactide by normalizing the degradation rate relative to that of the amorphous polymer, it was anticipated that there would be close agreement between the two curves in Figure 3. Although there are not sufficient data points of similar crystallinity to separate the two copolymer sets, it appears that there was substantial deviation between the curves. This may be explained by other differences in film crystalline morphology which are not taken into account by % crystallinity measurements.

**Summary of Results**

By preparing both amorphous and semicrystalline films from polymers having variable (L) content, it was possible to consider crystalline order and chain stereochemical composition as independent parameters affecting PLA enzymatic degradability. In addition, comparison of polymers prepared from (L)-(D)-lactide and (L)-meso-lactide copolymerizations provided information on how chain stereosequence distribution affects PLA enzymatic degradability. Studies on amorphous films from (L)-(D)-lactide as well as (L)-meso-lactide copolymerizations showed a remarkable independence of film weight loss rates on (L) content for compositions ranging from 80% to 95%. These results show that proteinase K has a high degree of tolerance for (D) repeat units. However, amorphous PLA films from (L)-lactide/meso-lactide copolymerizations had weight loss rates which were about 43% slower than amorphous PLA films from (L)-lactide/(D)-lactide copolymerizations. These results demonstrate how polymer repeat unit sequence distribution, taken as an independent variable, can dramatically affect enzyme catalyzed polymer degrada-
tion. Furthermore, the deceleration of proteinase K catalyzed PLA degradation caused by crystallinity effects was determined. Proteinase K showed an extraordinarily high sensitivity to film crystallinity. For example, the decrease in the film weight loss rate due to crystallinity for PLA-95 was 93%. Furthermore, PLA-90 which has an χc of only 10% had a decrease in weight loss rate by 38% due to film crystallinity. The results of this study raise a number of questions that we plan to address in future work. For example, to better understand the PLA we plan to address in future work. For example, the decrease in the film weight loss rate due ordinarily high sensitivity to film crystalline order. For catalyzed PLA degradation caused by crystallinity effect. Furthermore, the deceleration of proteinase K had 13.8 units/mg of solid and 14.3 units/mg of proteinase K had 13.8 units/mg of solid and 14.3 units/mg of protein. The enzyme at PLA surfaces, (iii) reaction kinetics and (iv) PLA single crystal substrates as model systems.

Acknowledgment. The authors wish to thank the NSF Center for Biodegradable Polymer Research (BPRC) at the University of Massachusetts Lowell for financial support of this work.

References and Notes

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