Stereochemical Aspects of Lactide Stereo-Copolymerization Investigated by ^{1}H NMR: A Case of Changing Stereospecificity

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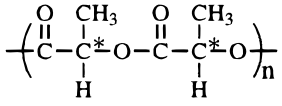
ABSTRACT: Poly(lactide) is synthesized by ring-opening copolymerization of various combinations of L-lactide, D-lactide, and *meso*-lactide. The influence of the stereochemical differences of the three lactides on the kinetics of melt copolymerization was determined by monitoring the change in the polymer stereosequence distribution as a function of conversion. The living stereo-copolymerization catalyzed by Sn(II) bis2-ethylhexanoate (Sn(II) octoate) in 1:10 000 molar ratio at 180 °C was investigated by comparing to the values predicted by a reversible polymerization scheme that achieves equilibrium at ∼95% conversion. The stereosequence distribution was measured by high-resolution 500 MHz ^{1}H NMR. A preference for *syndiotactic* addition was observed and is thought to be due to steric hindrance at the growing site of the polymer. Furthermore, the *syndiotactic* preference decreased as the polymerization proceeded in a batch process. Similar behavior was observed during lactide polymerization catalyzed by butyl Sn(IV) tris2-ethylhexanoate. The increasingly random addition during the polymerization process is due to the interplay of kinetic and equilibrium effects. Kinetic effects control the stereochemistry during the early stages of the polymerization whereas equilibrium effects dominate at later stages. Viscosity changes in the melt additionally influence the stereospecificity by increasing the residence time of the lactide at the active site. Monte Carlo calculations were used for stereosequence predictions because analytical equations are not available for these complicated kinetics.

Introduction

Lactic acid-based aliphatic polyesters are increasingly being explored for use in several applications, including biodegradable packaging materials, food containers, bioresorbable medical implants and sutures, drug delivery systems, etc.[1−6] Cargill, Incorporated has been developing poly(lactide) (PLA) products such as yard-waste bags, food containers, and agricultural mulch films to replace nondegradable polymer products. The nondegradable polymer products produced from nonrenewable resources (e.g., crude oil and natural gas) are increasingly becoming a source of ecological problems. On the other hand, high molecular weight PLA (see structure) is prepared by ring-opening polymerization



Poly(lactide)

of lactide acid dimers that in turn are produced using lactic acid derived from natural renewable sources (e.g., corn) or waste recycled products (e.g., agricultural starch waste[2]). Furthermore, PLA decomposes rapidly and completely in a well-managed compost environment, and its degradation products have been shown to promote plant growth.[7]

Lactic acid possesses one asymmetric carbon and exists in two configurations, *R* and *S*. The lactic acid with *S* configuration is referred to as L-lactic acid in comparison with L-glyceraldehyde. Lactic acid cyclic dimers (lactides) are diastereoisomers that exist in either the *RR*, *SS*, or *RS* configuration. The *RR* configuration of the cyclic dimer is referred to as D-lactide, whereas the *SS* configuration is referred to as L-lactide. An equimolar ratio of *RR*- and *SS*-lactide is referred to as *racemic* or D,L-lactide, and the *RS*-lactide is referred to as *meso*-lactide. High purity *RR*- and *SS*-lactides are each known to polymerize into stereoregular (*isotactic*) poly(D-lactide) and poly(L-lactide), respectively, whereas poly(*racemic*-lactide) and poly(*meso*-lactide) are *atactic* polymers.[8−11].

A number of physical properties of PLA are linked to its stereosequence distribution.[3,12−14] The stereosequence distribution is influenced by a number of factors, including the lactide feed composition, polymerization kinetics, and extent of conversion.[15] The polymerization kinetics in turn are influenced by the catalyst, temperature, impurities, batch versus continuous process, etc. A number of studies have been reported in the past decade on lactide polymerization using various catalysts and polymerization conditions.[16−25] It has been demonstrated that lactide polymerization is a reversible process that reaches equilibrium at 92−99% conversion depending on the polymerization conditions.[17,19,20,26] Spassky et al.[25] synthesized a chiral aluminum alkoxide catalyst that was shown to be highly stereoselective. Recently, they reported an achiral form of that aluminum alkoxide catalyst that has a preference for *isotactic* addition during lactide polymerization in solution.[27] A few other studies have attempted to elucidate the influence of stereoisomers on the polymerization kinetics by analyzing the stereosequence distribution in PLA.[15,28−33] In these studies, the stereosequence distribution in the PLA was identified by NMR spectros-

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copy. Depending on the magnetic field strength used, the NMR chemical shifts of ^{13}C and ^{1}H nuclei in PLA are influenced by the stereoconfiguration of 1−3 adjacent stereogenic centers on either side. If the polymerization process is truly random, the stereosequence distribution should match the distribution predicted by pairwise Bernoullian statistics. Using ^{13}C NMR, Kasperczyk[33] has shown that during the polymerization of D,L-lactide catalyzed by lithium *tert*-butoxide there is preference for *syndiotactic* addition (*syndiotactic* stereospecificity). Kricheldorf et al.,[32] using ^{1}H and ^{13}C NMR, also observed some evidence for *syndiotactic* addition during Sn(II) octoate lactide polymerization at 90 and 120 °C, but were unable to conclusively identify the stereospecificity due to competing transesterification reactions.[32] Recently, it was shown by us that the lactide polymerization process using Sn(II) octoate as a catalyst at 180 °C in the melt proceeded with *syndiotactic* stereospecificity.[15] Coudane et al.[34] also confirmed the presence of *syndiotactic* preference during Sn(II) octoate-catalyzed D,L-lactide polymerization. In this report, we examine more thoroughly the Sn(II) octoate-catalyzed melt polymerization kinetics at 180 °C by analyzing the stereosequence distribution of lactide stereoisomers copolymerized to various extents of conversion and comparing with the predicted distribution for a reversible polymerization model.

Experimental Section

Polymerization. Each of the lactide mixtures was sealed in a number of glass vials and simultaneously placed in an oil bath at 180 °C. Sn(II) bis2-ethylhexanoate (Sn(II) octoate) or butyl Sn(IV) tris2-ethylhexanoate was used in a 1:10 000 catalyst:monomer molar ratio to catalyze the ring-opening polymerization of the lactides. The hydroxyl impurities in the catalyst and the lactide act as initiators. No additional initiators were added. At various time intervals, glass vials were pulled out from the oil bath and placed in water at room temperature to quench the polymerization. Samples from various sections of the vials were taken and the ^{1}H NMR spectra were acquired without separating the unpolymerized residual lactide.

NMR Spectroscopy. The ^{1}H solution NMR spectra were acquired on a Varian 500 MHz NMR spectrometer. Unless specifically stated, the spectra were acquired as ∼1% solution in $CDCl_3$, with the methyl protons decoupled from the methine protons (homonuclear decoupled) during the acquisition time. A total of 64 scans were acquired, each with 40 000 data points at a spectral width of 10 kHz corresponding to acquisition time of 4 s. A delay of 1 s was used between transients.

Monte Carlo Calculation of Lactide Polymerization. To predict the stereosequence distribution for lactide stereo-copolymerization in a batch process, such as in a vial, Monte Carlo (MC) calculations were utilized. Analytical equations to represent the observed kinetics (vide infra) and predict stereosequence distributions were not available. As mentioned earlier, the ring-opening lactide polymerization is a reversible reaction that reaches equilibrium between 92 and 99% conversion depending on the polymerization conditions. Because formation of *meso*-lactide was not observed during the copolymerization of L-lactide and D-lactide, it is inferred that the polymer depolymerizes in steps of two chiral centers (as lactide only). In the MC calculations, PLA was grown randomly by a step-by-step procedure in a reversible process. Each of the steps consists of either (a) a collision with a randomly selected lactide and an attempted addition reaction with stereospecific reaction efficiencies or (b) attempted removal of a lactide from the growing active end of the polymer chain using stereospecific reaction efficiencies. The normalized collision probabilities for the addition reaction were obtained from the relative concentrations of the lactide monomers (L-lactide, D-lactide, and *meso*-lactide) in the reaction vessel. The probability values were updated after each successful addition or removal to reflect the changes in the relative concentrations. In the case of a collision of the growing polymer with a *meso*-lactide, the *R* and *S* ends of the *meso*-lactide were selected with equal probability for the attempted addition. The stereospecific reaction probabilities (efficiencies) for *isotactic* and *syndiotactic* additions were freely adjustable parameters (in the range of 0 to 1). However, because we are only interested in the ratio of the reaction efficiencies, the probability of the more efficient reaction was set to 1.0 for computational convenience. Each cycle of our growth process involved the computation of a maximum of four random numbers (uniformly distributed between 0 and 1): the first to determine whether to add or remove a lactide, the second to determine whether a lactide collided with the active site, the third to determine the type of lactide in the collision, and the fourth to determine whether to accept or reject the attempted addition. The initial state of all our calculations consisted of 5 million lactide monomers of given relative concentrations and one seed particle. For the present study, the reaction efficiencies (r) for *isotactic* addition (k_i/k_s) and removal (k_{xi}/k_{xs}) were set at 0.60. The r was either kept constant (case I) or set to increase in proportion to residual lactide concentration to reach 0.76 in the limit of no residual lactide (case II). The probability of lactide removal was set at 0.035 (i.e. 3.5%). The values of case II provided a reasonable fit to the stereosequence distribution measured experimentally for various partially polymerized PLA (vide infra). Possible effects of transesterification and racemization were not incorporated in the calculations.

Results and Discussion

In a previous report examining the non-Bernoullian stereosequence distribution observed in various PLA, it was determined that during the lactide copolymerization using Sn(II) octoate in a 1:10 000 catalyst: monomer molar ratio at 180 °C there is a preference for *syndiotactic* addition.[15] The value of the rate constant for *isotactic* addition (k_i), defined in Scheme 1, was shown to be lower than the value of the rate constant for *syndiotactic* addition (k_s). Monte Carlo calculations employing a simple *irreversible* kinetic scheme were used in that report to assign the stereosequence resonances observed in the NMR spectra and to gain some insight into the polymerization process. In this paper, we examine the stereosequence distribution in partially polymerized PLA quenched at various time intervals during batch polymerization in vials and determine the kinetic rate constants that can more accurately predict the observed stereosequence distribution changes in the polymer.

A preference for *syndiotactic* addition during the copolymerization of D-lactide and L-lactide will cause the minor component to be depleted with a higher pseudo rate constant than the major component. For example,

Scheme 1. Proposed Kinetic Scheme

$$—S^* + SS \underset{k_{xi}}{\overset{k_i}{\rightleftharpoons}} —SSS^*$$

$$—S^* + RR \underset{k_{xs}}{\overset{k_s}{\rightleftharpoons}} —SRR^*$$

$$—R^* + SS \underset{k_{xs}}{\overset{k_s}{\rightleftharpoons}} —RSS^*$$

$$—R^* + RR \underset{k_{xi}}{\overset{k_i}{\rightleftharpoons}} —RRR^*$$

during copolymerization of 80% L-lactide and 20% D-lactide, the D-lactide will be depleted with a higher apparent rate constant. The active growing site will often be $-SS^*$ because of the excess of L-lactide, so the D-lactide (*RR*) will be preferentially polymerized. At low conversions, the polymer will be enriched with D-lactide and asymptotically reach the feedstock composition in the limit of 100% conversion. Two exceptions to this behavior should be D,L-lactide (viz., 50% L-lactide + 50% D-lactide), because the catalyst is achiral and does not preferentially polymerize either *S* or *R* stereoconfigurations of the lactide, and *meso*-lactide. Hence, the stereosequence distribution in poly(D,L-lactide) and poly(*meso*-lactide) was anticipated to be independent of its conversion (or extent of polymerization).

The ^{1}H NMR spectra of PLA with major fractions of either L-lactide or D-lactide have been shown to contain sufficient information to enable the determination of lactide stereoisomer composition.[35] In the NMR spectra of PLA, the observed resonances can be assigned to various stereosequence combinations in the polymer.[15] The assignments are designated as various combinations of "*i*" *isotactic* pairwise relationships ($-RR-$ and $-SS-$) and "*s*" *syndiotactic* pairwise relationships ($-RS-$ and $-SR-$). In the NMR spectra, the diads $-RR-$ and $-SS-$ are indistinguishable and have identical chemical shifts, as do $-RS-$ and $-SR-$. Furthermore, because the chemical shift of the lactide is different from that of the polymer, it is not necessary to separate the residual lactide to determine the stereosequence distribution in the polymer. The chemical shift of the end groups in PLA are also well resolved from that of the polymer.[21,36]

For various copolymers of L-lactide and D-lactide, the stereosequences of *isisi* and *iiisi*/*isiii* are well resolved in the homonuclear decoupled methine resonances in the ^{1}H NMR spectra.[15] The spectrum of poly(D,L-lactide) is shown in Figure 1. Bernoullian statistics for random pairwise addition predict equal probability for the *isisi* and *iiisi* stereosequences in the polymer.[15] The unequal normalized intensity observed for these two well-resolved stereosequences reveals a preference for stereospecific addition.

The normalized intensity of *isisi* and *iiisi* resonances observed for poly(D,L-lactide) quenched at various polymerization time intervals is shown in Figure 2. The intensity of both the resonances was expected to be independent of the extent of conversion because the composition of the residual lactide will be invariant (viz.,

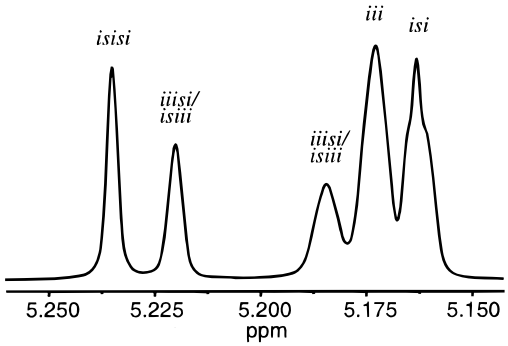


Figure 1. The methine resonance in the homonuclear decoupled ^{1}H NMR spectra of poly(D,L-lactide) with the well-resolved stereosequence resonances of *isisi* and *iiisi* identified.

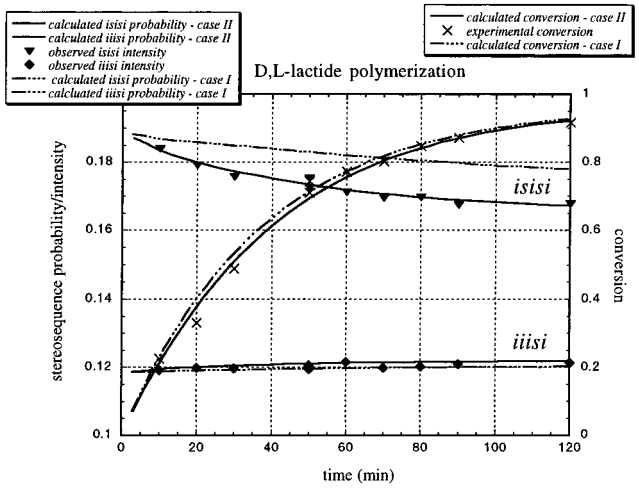


Figure 2. The normalized intensity of *isisi* and *iiisi* stereosequence resonances in Sn(II) octoate-catalyzed partially polymerized poly(D,L-lactide) and the corresponding extents of conversion are plotted against the time intervals at which the polymerization was quenched. The dash−dotted line is the stereosequence probability predicted by MC calculations for a reaction efficiency ratio of 0.6 (case I). The solid line is the probability predicted for a changing reaction efficiency ratio from 0.6 to 0.76 (case II). See the text for details.

50% L-lactide and 50% D-lactide). Instead, the *isisi* intensity reduces with extent of conversion, whereas the *iiisi* intensity gradually increases by a tiny fraction. The almost constant value for the *iiisi* resonance that represents sequences such as $-SSSSRR-$ and $-RRRRSS-$ implies that the relative fractions of L-lactide and D-lactide in the polymer are independent of the extent of polymerization. This result is also evidence for the catalyst being nonstereoselective (i.e. it does not preferentially polymerize either L-lactide or D-lactide). A higher value for the *isisi* resonance which represents the sequences $-SSRRSS-$ and $-RRSSRR-$, implies that during the polymerization, alternation of the two lactides is preferred. In other words, there is a preference for *syndiotactic* addition. The reduction in this *isisi* value with extent of polymerization represents (cumulative) lowering of the preference for *syndiotactic* addition. This changing value for the *syndiotactic* preference was not anticipated. The differences in the stereosequence distributions of various partially poly(D,L-lactide) can also be observed in their methyl ^{1}H NMR resonance. This additional evidence for changing stereospecificity is shown in Figure 3.

In Figure 2, the dash−dotted lines are the normalized probability values predicted by MC calculations using

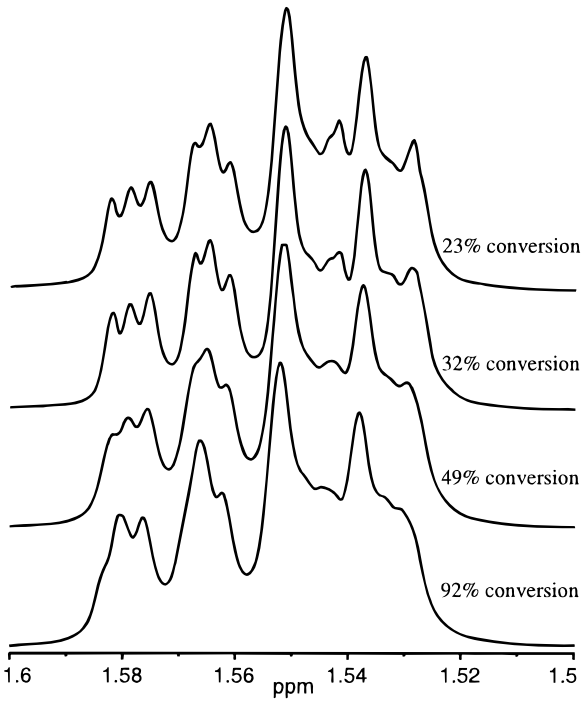


Figure 3. The methyl resonance in the ^{1}H NMR spectrum of four partially polymerized poly(D,L-lactide) catalyzed by Sn(II) bis2-ethylhexanoate. The spectra were acquired as ~0.5% w/w solution in $CDCl_3$. The differences in the spectra are due to changing stereospecificity during the reversible lactide stereocopolymerization.

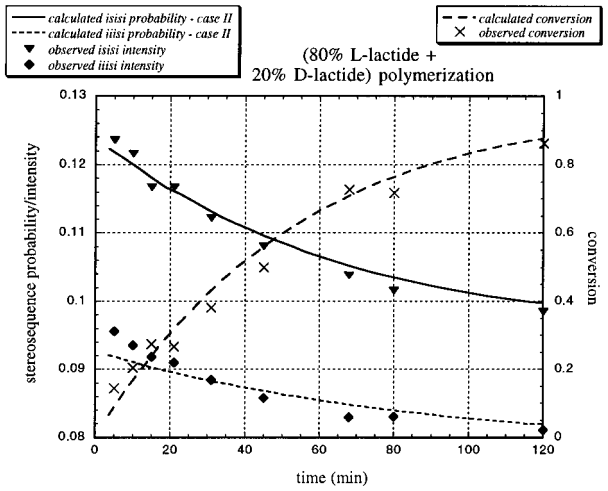


Figure 4. The normalized intensity of *isisi* and *iiisi* stereosequence resonances in Sn(II) octoate-catalyzed partially copolymerized 80% L-lactide and 20% D-lactide along with the corresponding extents of conversion are plotted against the time intervals at which the polymerization was quenched. The smooth lines are the stereosequence probability predicted by MC calculations that assume changing reaction efficiency ratio of 0.60 to 0.76 (case II). See the text for details.

reaction efficiency ratios for *isotactic* addition ($= k_i/k_s$) and removal ($= k_{xi}/k_{xs}$) of 0.60 (case I). The predicted change in *isisi* resonance intensity, representing reduced *syndiotactic* stereospecificity, is a result of the reversible nature of the polymerization (vide infra). However, the experimental data suggested an even larger reduction in the *isisi* intensity with increased polymerization. To approximately match the predictions of the MC calculations to the experimental data, the initial reaction efficiency ratios in the limit of zero polymerization ($r = k_i/k_s = k_{xi}/k_{xs}$) of 0.60 were set to increase with polymerization to a value of 0.76 in the limit of zero residual lactide concentration (solid line − case II). These parameters artificially reproduce the more rapid change in stereospecificity. The *x*-axis values in the simulation were adjusted to match the time (120 min) at approximately the conversion of the last experimental data point. Possible transesterification and racemization events were ignored. The details of the MC calculations are provided in the *Experimental Section*. A reasonable fit of the predicted change in normalized intensity and the experimental data is observed.

As mentioned earlier, during the copolymerization of 80% L-lactide and 20% D-lactide (80L20D), the minor component of D-lactide should be polymerized with a relatively higher rate constant than the major component of L-lactide. Experimental data representing normalized values for the *isisi* and *iiisi* stereosequences in various partially polymerized poly(80L20D) are plotted in Figure 4. The lines are normalized probability values predicted by MC calculations using parameter values identical to those used for case II in Figure 2. Here again, changing the reaction efficiency ratio *r* of 0.60 to 0.76 was assumed. The *isisi* and *iiisi* values are related to the concentration of the minor component (viz., D-lactide). As expected, at low conversions, the polymer is enriched in the minor component and asymptotically reduces to a final value with increasing conversion. The change in intensity predicted by the calculations is reasonably close to the change observed in the experimental data.

During the copolymerization of *meso*-lactide we can assume that the probability of attempts at polymerization by *meso*-lactide as either *SR*-lactide or *RS*-lactide is identical. Hence, irrespective of the stereoconfiguration of the active site, the overall rate constant for the polymerization of *meso*-lactide should be invariant except for changes due to the reversible nature of the polymerization. When *meso*-lactide is a minor component in the copolymerization, we can monitor its fraction in the polymer by observing the normalized intensity of the *iiiss* stereosequence.[35] If D-lactide is also present in the polymerization feedstock as a minor component, it should be enriched in the polymer at lower conversions and gradually reduce with increasing polymerization time. The kinetics of the *tert*-polymerization of 80% L-lactide, 10% D-lactide, and 10% *meso*-lactide (80L10D10M) was also investigated by quenching at various polymerization time intervals and acquiring homonuclear decoupled ^{1}H NMR spectra. The normalized intensities for the three partially resolved regions representing *isisi*, *iiisi*, and *iiiss* stereosequences for various partially polymerized poly(80L10D10M) are plotted in Figure 5. Here, the *ssisi*, *isiss*, *ssiss*, *siisi*, and *siiss* peaks in the spectra, which have nonzero intensity and are unresolved, are incorporated in the absolute integrated values of *isisi*, *iiisi*, and *iiiss* reported. The solid lines are the probability values predicted by MC calculations using parameters identical to those used earlier in Figures 2 and 4 for case II. The predicted values of *isisi*, *iiisi*, and *iiiss* shown in Figure 5 include the minor nonzero probability values of (*ssisi* + *isiss*), (*ssiss* + *siisi*), and *siiss*, respectively. As expected, the *meso*-lactide fraction in the polymer is almost independent of the conversion, whereas the D-lactide is enriched at lower conversions as was observed for 80L20D polymerization. The change in the normalized intensity

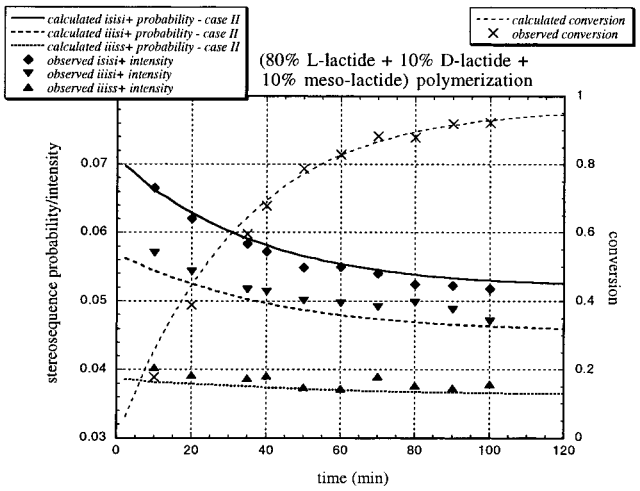
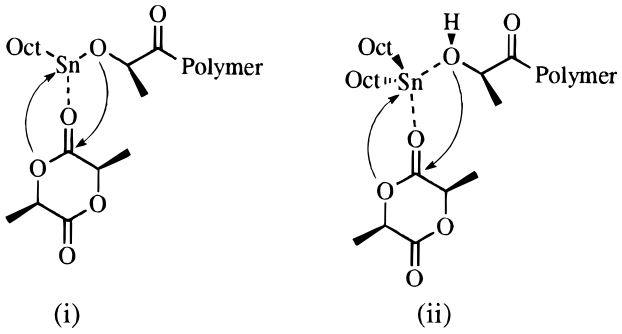


Figure 5. The normalized intensity of regions in the ^{1}H NMR spectra representing *isisi*, *iiisi*, and *iiiss* stereosequence resonances in partially *tert*-polymerized 80% L-lactide, 10% D-lactide, and 10% *meso*-lactide along with the corresponding extents of conversion are plotted against the time intervals at which the polymerization was quenched. The integrated regions include contributions from the *ssisi*, *isiss*, *ssiss*, *siisi*, and *siiss* resonances that have nonzero intensity and are unresolved. The smooth lines are the stereosequence probability predicted by MC calculations that assume changing reaction efficiency ratio of 0.60 to 0.76 (case II). See the text for details.

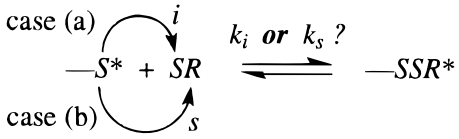
Scheme 2. Lactide Polymerization by Insertion



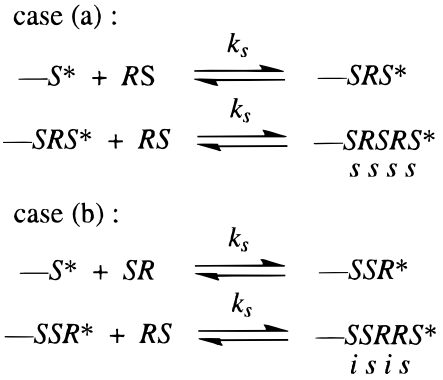
values observed in the data compares well with the probability changes expected from the MC calculations (case II). A closer match of the three normalized integrated areas of the spectrum and the probability values plotted is not obtained because some of the unresolved resonances are distributed between the integrated regions representing *isisi* and *iiisi* resonances.

The preference for *syndiotactic* addition can result from steric hindrance at the polymer growing active site. Kricheldorf et al.[21] proposed that the polymerization proceeds by lactide insertion at the growing active site with the catalyst either covalently bound to the polymer or coordinatively complexed to the hydroxyl end of the polymer. These two mechanisms are shown in Scheme 2 as parts i and ii, respectively. It is conceivable that due to the limited space available around the Sn(II) catalyst, there is less steric hindrance for *syndiotactic* addition as compared with *isotactic* addition. The *syndiotactic* preference could be due to the steric hindrance between the active site and either (a) the lactic acid subunit of the lactide bonding to it or (b) the subunit forming the new active site. This situation is shown in Scheme 3 for the polymerization of $-S^*$ active site with a (*meso*) *SR*-lactide. During the copolymerization of L-lactide and D-lactide this issue does not arise because both the subunits are identical (*SS* and *RR*, respectively). The validity of case (a) versus case (b) can be evaluated by measuring the stereosequence distribution in poly(*meso*-lactide). Because $k_s > k_i$, for poly(*meso*-lactide), case (a) predicts an excess of sequences such as $-RSRSRS-$ (*ssssss*), whereas case (b) predicts excess of sequences such as $-RSSRRS-$ (*sisis* and *isisi*), as shown in Scheme 4. Comparing the predicted stereosequence distributions with that observed experimentally for poly(~6% D,L-lactide + ~94% *meso*-lactide) polymerized under similar conditions, it is found that case (b) is not possible. In comparison with the 19.6 (±0.2)% normalized intensity observed experimentally for the *sis* region in the ^{1}H NMR spectra, cases (a) and (b) predict probability values of 19.7 and 25.9%, respectively. Hence, the steric hindrance is between the nearest neighbors; that is, between the active site and the subunit attempting to bond to it.

Scheme 3. Two Possibilities for Steric Hindrance



Scheme 4. Stereosequences Formed by Syndiotactic Additions During *meso*-Lactide Polymerization for the Two Possibilities Shown in Scheme 3



The reducing *syndiotactic* stereospecificity during the lactide stereo-copolymerization process, which represents increasingly random addition, is due to the reversible nature of the lactide polymerization. Initially, the polymerization process is controlled primarily by differences in the activation energies (i.e., kinetic effects) and can be considered "irreversible" because before the lactide has any significant opportunity to depolymerize, another lactide attempts addition to the polymer chain. But, as the residual lactide concentration reduces, there are increased opportunities for the lactide at the polymer chain end to depolymerize. As a result, equilibrium effects play a more dominant role and the polymerization increasingly comes under thermodynamic control. In a thermodynamically controlled reaction, the differences in the activation energy values do not control the stereochemistry of lactide addition.

A possible schematic relationship among various states involved during *isotactic* and *syndiotactic* lactide addition is shown in Figure 6. The enthalpy change for *isotactic* addition and *syndiotactic* addition (ΔH_i and ΔH_s, respectively) are assumed to be similar (~23 kJ/mol[37–39]) because L-lactide and D-lactide are energetically identical and only a marginal energy difference may be expected between an *isotactic* bond ($S-S$ or

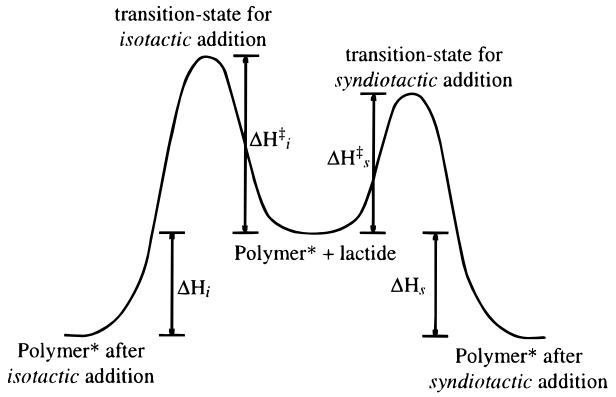


Figure 6. A schematic diagram of the relative energy values for the various states defined for *isotactic* and *syndiotactic* lactide polymerization: $\Delta H^{\ddagger}_i$ and $\Delta H^{\ddagger}_s$ represent activation energies for *isotactic* and *syndiotactic* lactide addition of ~71 and ~69 kJ/mol, respectively; ΔH_i and ΔH_s, respectively, represent the change in enthalpy for the two reactions and are expected to be equal ~23 kJ/mol.

R−*R*) and a *syndiotactic* bond (*S*−*R*). The activation energy for the two processes ($\Delta H^{\ddagger}_i$ and $\Delta H^{\ddagger}_s$, respectively) are expected to be different. The activation energy for L-lactide polymerization (*isotactic* addition), which is $\Delta H^{\ddagger}_i$, has been reported to be ~71 kJ/mol.[37] Using the value of 0.6 for k_i/k_s at 180 °C, the activation energy for *syndiotactic* addition is calculated to be ~69 kJ/mol.

Monte Carlo calculations representing the relative energy states shown in Figure 6 predict reduction in observed stereospecificity (*isisi* probability) even when the relative reaction efficiencies were kept constant (case I). This prediction may be explained by examining the following equations:

From Scheme 1, the rates of *syndiotactic* addition (d*s*/d*t*) and *isotactic* addition (d*i*/d*t*) are:

$$ {}^{ds}/_{dt} = k_s[S^*][RR] - k_{xs}[SRR^*] + k_s[R^*][SS] - k_{xs}[RSS^*] \quad (1)$$

$$ {}^{di}/_{dt} = k_i[S^*][SS] - k_{xi}[SSS^*] + k_i[R^*][RR] - k_{xi}[RRR^*] \quad (2)$$

For the special case of D,L-lactide polymerization, at any given instant of time:

$$[SS] = [RR] = {}^{[residual\ lactide]_t}/_2 = {}^{[lac]_t}/_2$$

$$[S^*] = [R^*] = {}^{[end]}/_2$$

$$[SRR^*] = [RSS^*] = {}^{[end_s]_t}/_2$$

$$[SSS^*] = [RRR^*] = {}^{[end_i]_t}/_2$$

$$[end_s]_t + [end_i]_t = [end]$$

The relative values of $[end_s]_t$ and $[end_i]_t$ are dependent on the relative rates for *syndiotactic* and *isotactic* addition at any given instant. Defining a time-dependent fractional preference for *syndiotactic* addition (f_s) and *isotactic* addition (f_i) as follows:

$$(f_s)_t = \frac{({}^{ds}/_{dt})_t}{({}^{di}/_{dt})_t + ({}^{ds}/_{dt})_t} \quad (3)$$

$$(f_i)_t = \frac{({}^{di}/_{dt})_t}{({}^{di}/_{dt})_t + ({}^{ds}/_{dt})_t} \quad (4)$$

we have:

$$[end_s]_t = (f_s)_t[end]$$

and

$$[end_i]_t = (f_i)_t[end] = (1 - (f_s)_t)[end]$$

From eqs 1 and 2,

$$({}^{ds}/_{dt})_t = k_s[end]\{0.5[lac]_t - [lac]_{eq}(f_s)_t\} \quad (5)$$

$$({}^{di}/_{dt})_t = k_i[end]\{0.5[lac]_t - [lac]_{eq}(1 - (f_s)_t)\} \quad (6)$$

where $[lac]_{eq}$ is the lactide concentration at equilibrium $= 1/K_{eq} = k_{xi}/k_i = k_{xs}/k_s$, because we expect $\Delta H_i = \Delta H_s \approx -23$ kJ/mol. The parameter K_{eq} is the equilibrium constant for both, *isotactic* and *syndiotactic* additions. Substituting eqs 5 and 6 in eq 3 and solving for $(f_s)_t$ we obtain the following quadratic equation:

$$(f)^2_{st}(k_i - k_s)[lac]_{eq} + (f_s)_t(0.5[lac]_t(k_s + k_i) + [lac]_{eq}(k_s - k_i)) - 0.5[lac]_t k_s = 0 \quad (7)$$

For an irreversible reaction controlled only by kinetic effects, $[lac]_{eq} = 0$; hence:

$$f_s = \frac{k_s}{k_s + k_i} = \text{constant}$$

In a reversible reaction, in the limit of zero polymerization, $[lac]_t \gg [lac]_{eq}$, and

$$\lim_{t \to 0} (f_s)_t \cong \frac{k_s}{k_s + k_i}$$

In the other extreme limit, at equilibrium, the total lactide concentration $[lac]_t = [lac]_{eq}$ is constant and the solution to the quadratic eq 7 is:

$$\lim_{t \to \infty} (f_s)_t = \frac{1}{2}$$

which represents totally random polymerization (*i.e.*, the rates for *syndiotactic* and *isotactic* additions are equal). These equations clearly demonstrate that a reversible polymerization mechanism will lead to a change in apparent stereospecificity over the course of a reaction, as was observed. The stereochemistry is controlled by kinetic effects during the initial stages of polymerization, which then at later stages is increasingly dominated by thermodynamic effects, leading to totally random polymerization at equilibrium. The *isisi* normalized intensity in Figure 2 represents the cumulative change in stereospecificity and hence does not reduce to the 12.5% probability expected for a totally random polymerization (Bernoullian statistics).

The observed cumulative change in stereospecificity is larger than this predicted change (see Figure 2) as

expected from MC calculations (case I). The more rapid reduction of stereospecificity is a result of additional complications/perturbations to the polymerization kinetics employed in the calculations. For example, in Figure 6, the relative energy level of the complex comprised of the catalyst, polymer, and the lactide (shown in Scheme 2) is not known. This complex was ignored in the calculations. Inclusion of finite lifetimes for this complex in the MC calculations indicated reduced stereospecificity but still could not reproduce the observed rapid change of stereospecificity (*isisi* intensity). Studying the kinetics of D,L-lactide polymerization at 140 °C instead of 180 °C, revealed that the *isisi* intensity reduced even more rapidly for 140 °C polymerization relative to the extent of conversion (data not shown). At lower temperature, the increase in viscosity of the polymer is larger than is the increase in viscosity of the lactide. On this basis, we postulate that changes in viscosity of the melt during the polymerization, which are larger at 140 °C than at 180 °C, are the cause of the more rapid change in stereospecificity than that predicted by the reversible polymerization model (case I). The increasing viscosity of the melt with extent of polymerization reduces the mobility and diffusion of the residual lactide and increases the residence time of the lactide complexed to the active site. In effect, the increased residence time translates into increased opportunities (probability) for addition of the less preferred stereoisomer. Even though the two effects of reduced diffusion rate and increased residence time counteract each other in their influence over the overall polymerization rate, they both reduce the stereospecificity in this reversible polymerization process. Furthermore, the change in stereospecificity should be almost independent of the composition of lactide copolymerized because the increase in residence time of lactide at the active site is primarily dependent on the extent of conversion. It should be noted that the low-temperature polymerization was not complicated by crystallization effects because poly(D,L-lactide) does not crystallize.

The stereosequence distribution in partially polymerized poly(D,L-lactide) catalyzed by another tin catalyst (viz., butyl tin tris2-ethylhexanoate) was also measured. Here again, *syndiotactic* stereospecificity was observed and the stereospecificity reduced with increasing polymerization. The similar change in the stereosequence distribution observed for poly(D,L-lactide) polymerized to various extents by two different catalysts enforces the concept that stereospecificity (or reactivity ratio) in any *reversible* polymerization process may vary with extent of polymerization. The extent of variation would depend on the relative energy levels of the various states involved in the polymerization.

Transesterification events are not expected to be frequent enough to cause an observable change in the stereosequence distribution. This conclusion is based on two factors. First, the *iiiss* stereosequence resonance representing isolated $-R-$ or $-S-$ sites is undetectable during the D,L-lactide polymerization. Second, the reduction in the preference for *syndiotactic* addition, which follows the reduction in residual lactide concentration, is larger during the initial part of the polymerization and almost invariant near equilibrium. The effect of transesterification on the stereosequence distribution should be related to increasing time and hence increasingly randomize with increasing polymerization time until the stereosequence distribution in the polymer becomes random. This situation is clearly not observed. The limiting invariant stereosequence intensity in PLA near equilibrium shows that transesterification and racemization are not frequent enough to influence the stereosequence distribution at the polymerization conditions used in this study.

It is possible that additional complications exist in the mechanisms suggested to be responsible for the changing stereospecificity during the reversible lactide polymerization process. For example, determination of the transition state for the polymerization by molecular modeling should provide additional insights into the validity of the cause for the preference for *syndiotactic* addition. In this regard, interaction of the catalyst and the lactide may be through the acyl oxygen instead of the carbonyl oxygen as suggested by Kricheldorf et al.[21] In the schematic shown in Figure 6, there may be additional states with finite lifetimes (e.g., complex with lactide) that would provide perturbations to the kinetic scheme used. It should also be noted that the optimal values for the parameters used in the MC calculations were determined subjectively from correlations with stereosequence data for melt polymerization. These values are likely to be dependent on the polymerization conditions, including the temperature. At lower temperatures, the proposed mechanism predicts higher stereospecificity during the early stages of the polymerization, which was observed during the D,L-lactide polymerization at 140 °C. Furthermore, solution polymerization may also cause severe perturbations to the kinetics observed for these melt polymerization by altering the transition state and reducing the effects due to viscosity changes.

Conclusion

Partial stereosequence distribution values from a few well-resolved resonances in the ^{1}H NMR spectra of PLA have been successfully used to investigate the stereochemical aspects of lactide copolymerization. A preference for *syndiotactic* addition has been observed for reversible lactide polymerization catalyzed by Sn(II) bis2-ethyl hexanoate and butyl Sn(IV) tris2-ethylhexanoate. This preference decreased with increasing extent of polymerization. Steric hindrance at the polymer growing site is probably responsible for the *syndiotactic* stereospecificity, and the increasingly random lactide addition is due to an interplay of kinetically and thermodynamically controlled reactions. Changes in viscosity during the melt polymerization additionally influence the stereochemistry. Similarly, in other polymerization systems that are reversible, it is possible that the reactivity ratios change with conversion when polymerized in a batch process.

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