High-Resolution ^{13}C and ^{1}H Solution NMR Study of Poly(lactide)

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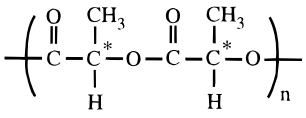
ABSTRACT: High-resolution 500 MHz solution-state ^{1}H and ^{13}C NMR spectra of various poly(lactides) indicate at least hexad stereosequence sensitivity. The poly(lactides) were prepared in vials by melt polymerization of various combinations of L-lactide, D-lactide, and *meso*-lactide at 180 °C for 3 h using tin(II) bis(2-ethylhexanoate) (tin(II) octoate) as the catalyst in a 1:10 000 ratio. The intensity distribution of the various stereosequence resonances in the NMR spectra indicates a preference for syndiotactic addition during the polymerization process. Minimal evidence of transesterification was observed for these polymerization conditions.

Introduction

Lactic acid based aliphatic polyesters are well-known bioresorbable polymers which can replace nondegradable bioresistant polymers in a number of applications.[1] Wastes generated from the use of nondegradable polymer products are increasingly becoming a source of ecological problems.[1] In addition, these nondegradable polymer products are generally produced from nonrenewable resources like crude oil and natural gas. Poly(lactide) (PLA) made using L-lactic acid derived from natural renewable sources (e.g. corn) decomposes rapidly and completely in a typical compost environment. The degradation products of PLA have also been shown to promote plant growth.[2] This makes PLA an ideal replacement for nondegradable polymers in numerous applications like yard-waste bags, food containers, agricultural mulch films, etc. Furthermore, the bulk production cost of PLA has been sufficiently reduced by recent technological developments such that it is now potentially competitive with petroleum derived plastics.[3,4]



Poly(lactide)

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. Poly(lactide) polymer is formed by ring-opening polymerization[5,6] of lactic acid cyclic dimers (lactides) which exist as either the *RR*, *SS*, or *RS* configuration. The acronym "PLA" has often been used to represent poly(lactic acid), but in this paper PLA refers to poly(lactide). The *RR* configuration of the cyclic dimer is sometimes referred to as D-lactide while *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 the *meso* monomer. High purity *RR*- and *SS*-lactides are known to polymerize to stereoregular (*isotactic*) poly(D-lactide) and poly(L-lactide) respectively.[7−10]

A number of physical properties of poly(lactide) are linked to its stereosequence distribution. For example, pure isotactic poly(L-lactide) crystallizes at a faster rate and to a larger extent than when L-lactide is polymerized with small amounts of either D-lactide or *meso*-lactide. Hence the isotactic *S*-length distribution, which is determined primarily by the fraction of L-lactide in the PLA, may be linked to the crystallization properties of the polymer.[11] Once polymerized, it is difficult to identify whether the individual stereogenic centers (*R* and *S*) in the PLA backbone came from L-lactide, D-lactide, or *meso*-lactide. However, the stereosequence distribution in the polymer will reflect its history, including the lactide composition, polymerization kinetics, and extent of transesterification and racemization. As an example, consider a poly(lactide) with equal amounts of *R* and *S* stereogenic centers which has not undergone any transesterification or racemization reactions. The composition of this polymer can be various combinations of D,L-lactide and *meso*-lactide. In case of poly(D,L-lactide), all the observed stereosequences will contain pairs of *R* and *S* stereoconfigurations *e.g.* *−RRSSSS−*, *−RRSSRR−*, *−RRRSSS−*, etc. An unpaired stereosequence like *−SSSSRS−*, *−SSRSSR−*, etc. should not be observed. In the case of poly(*meso*-lactide), on the other hand, the stereosequence containing three adjacent identical configurations *e.g.* *−RRRSRR−*, *−RSSSRS−*, etc. will not be observed. In contrast, if the polymer is prepared using a mixture of *meso*-lactide and D,L-lactide, then most of the possible stereosequences may be observed. If the polymerization process is truly random, the stereosequence distribution will be predicted by pairwise Bernoullian statistics.

The fraction of *R* configuration in PLA can be determined by saponification of the polymer to lactic acid and subsequent separation of the *R*-lactic acid by HPLC or measurement of optical activity. However, identification of the stereosequences in the polymer provides the ability to identify the source of *R*-configuration, whether it is D-lactide (*RR*) or *meso*-lactide (*RS*), and hence estimate the isotactic chain length distribution. Furthermore, if the lactide feed composition is known, this stereosequence information can be used to determine the extent of transesterification and possibly determine the kinetic rate constants for polymerization. As a result it may be possible to predict the stereosequence in a polymer prepared from any lactide composition.

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A number of studies have used NMR spectroscopy to identify the stereosequence distribution in PLA.[6,12−16] Kricheldorf *et al.* have used the methine resonance in ^{1}H and ^{13}C NMR spectra to identify the stereosequence distribution of a number of poly(lactides) prepared under various reaction conditions and using numerous initiators/catalysts.[6,15] The resolution in their spectra limited them to assigning the observed peaks to tetrad stereosequence distribution. At polymerization temperatures of less than 120 °C and with a tin(II) octoate initiator/catalyst to lactide ratio of 1:100, they observed syndiotactic stereospecificity. At higher temperatures transesterification was significant, and they were unable to distinguish between transesterification and syndiotactic stereospecificity. Using ^{13}C NMR, Kasperczyk could quantify the syndiotactic preference for solution polymerization of D,L-lactide with lithium *tert*-butoxide initiator/catalyst (1:400) as the coefficient of probability for isotactic addition = 0.24 and the coefficient of probability for syndiotactic addition = 0.76.[16] Specific polymerization conditions such as temperature, duration of reaction, and the amount and type of catalyst used are likely to affect the extent of syndiotactic preference that can be observed in the polymer.[15,16] Recently it was reported that highly stereoselective monomer specific polymerization could be carried out using a new stereogenic Schiff's base aluminum alkoxide initiator/catalyst.[17]

In this paper, we report the use of high-resolution ^{1}H and ^{13}C NMR spectroscopy to identify the stereosequence distribution and determine a stereospecific preference for lactide addition during tin(II) octoate catalyzed polymerization.

Methods

Polymerization. Various mixtures of lactides were sealed in a silanized glass vial and placed in an oil bath at 180 °C for 3 h. The ring-opening polymerization of the lactides was catalyzed by tin(II) octoate (tin(II) bis(2-ethylhexanoate)) in a 1:10 000 catalyst:monomer ratio. The polymer in the quenched vials was first dissolved in chloroform and then precipitated from methanol to separate any residual lactide. Subsequently, it was dried for 1−2 days under vacuum to remove any residual solvent. The extent of polymerization was not determined, but from previous studies it is expected to be between 92−98%.[18]

Poly(lactide) samples with various composition of L-lactide, D-lactide, and *meso*-lactide prepared for this study are listed in Table 1. The *meso*-lactide used in the preparation of these polymers contained between 6−8% *racemic* lactide.

In the experiments to verify unequal polymerization kinetic rate constants for isotactic and syndiotactic additions, the lactide mixture containing 1:10 000 tin(II) octoate catalyst was sealed in a number of silanized glass vials which were simultaneously immersed in an oil bath at 180 °C. At various time intervals, glass vials were pulled out from the oil bath and placed in crushed ice to quench the polymerization. Samples from various sections of the vials were taken, and the ^{1}H NMR spectra acquired without separating the unpolymerized residual lactide.

NMR Spectroscopy. The ^{13}C and ^{1}H solution NMR spectra were acquired on a Varian 500 MHz NMR spectrometer at 125.7 and 499.9 MHz respectively. The ^{13}C NMR spectra were acquired as 10% solution in $CDCl_3$ with proton decoupling. A total of 64 000 data points were acquired at a spectral width of 30 kHz corresponding to an acquisition time of 2.1 s. The recycle time was set at 1 s, and 4000 scans were averaged. The ^{1}H NMR spectra were acquired as a 1% solution in $CDCl_3$ with the methyl protons decoupled from the methine protons (homonuclear decoupling) 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 an acquisition time of 4 s, and a pulse delay of 1 s was used.

Table 1. Lactide Composition of Polymers by Formulation

sample	% L-lactide	% D-lactide	% *meso*-lactide
1	3	3	94
2	51.5	1.5	47
3	70.9	0.9	28.2
4	50	50	0
5	60	40	0
6	70	30	0

In the experiments to verify unequal polymerization kinetic rate constants, the presence of unreacted lactide monomers whose ^{1}H NMR chemical shift is upfield from that of the poly(lactide) at *ca.* 5.05 ppm facilitated the measurement of extent of conversion.

Monte Carlo Calculation of Lactide Polymerization. In order to predict the stereosequence distribution for lactide polymerization in a batch process such as in a vial, Monte Carlo (MC) calculations were utilized. In the MC calculations, poly(lactide)s were grown randomly in a step-by-step procedure. Each of the steps consists of a collision with a randomly selected lactide and of an attempted addition reaction with stereospecific reaction efficiencies. The normalized collision probabilities were obtained from the relative concentrations of the lactide monomers (L-lactide, D-lactide, and *meso*-lactide) in the reaction vessel. The collision probability values were updated after each successful addition to reflect the changes in the relative concentrations. The configuration of the current active site at the growing end of the polymer was also updated after each addition. 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 0−1). However, since we were only interested in the ratio of the reaction efficiencies, the probability of the more efficient reaction was set to 1 for computational convenience. Thus each cycle of our growth process involved the computation of two random numbers (uniformly distributed between 0 and 1): the first determined the type of collision, the second determined 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. The addition cycle was then repeated until full completion of the reaction, i.e. until all monomer units were successfully added to the growing polymer.

The stereosequence distribution corresponding to Bernoullian statistics can be obtained when the reaction efficiencies for isotactic and syndiotactic additions are equal (set to 1). The observed intensity distributions in the NMR spectra, which did not match the Bernoullian statistics predictions, were fit by adjusting the relative reaction efficiencies for isotactic and syndiotactic additions.

Results and Discussion

In the NMR spectra of PLA, the observed resonances can be assigned to stereosequence combinations in the polymer. 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 would have identical chemical shifts, as would $-RS-$ and $-SR-$. For stereosequence sensitivity of length *n*, there are $2^{(n-1)}$ possible combinations of pairwise relationships that can observed in the NMR spectra. For example, there are $2^2 = 4$ possible combinations for triads, $2^3 = 8$ possible combinations for tetrads, $2^5 = 32$ possible combinations for hexads, and so on. Often, due to either insufficient resolution, overlap of chemical shifts, or

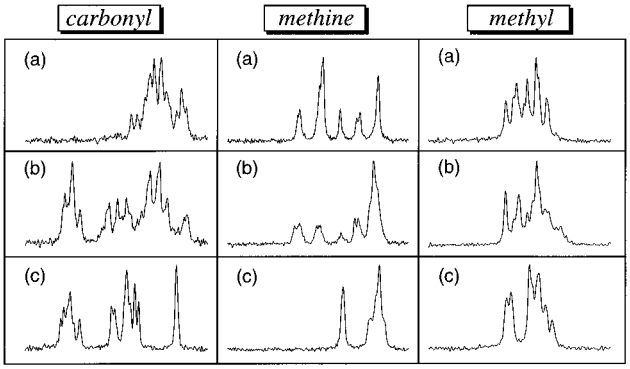

Figure 1. Carbonyl, methine, and methyl resonance in the ^{13}C NMR spectra of samples (a) **1**, (b) **2**, and (c) **4** in Table 1 as a 10% solution in $CDCl_3$.

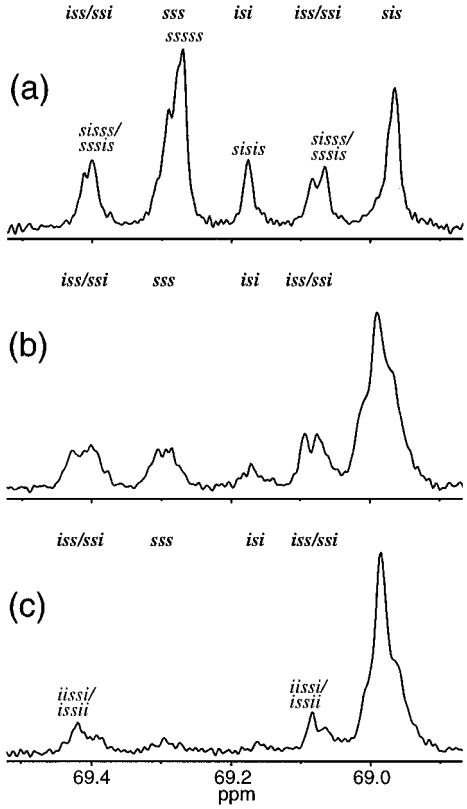

Figure 2. Methine resonances in the ^{13}C NMR spectra of poly(lactide) samples (a) **1**, (b) **2**, and (c) **3** in Table 1. The peak at *ca.* 68.95 ppm comprises resonances from *iii*, *iis*, *sii*, and *sis* core stereosequences.

probability of stereosequence formation, not all the possible stereosequence combinations are observed in the NMR spectra.

The ^{13}C spectra of three representative PLA samples **1**, **2**, and **4** (listed in Table 1) are shown in Figure 1. Previously, tetrad stereosequence distribution in the methine (−CH) resonance of ^{13}C and ^{1}H NMR spectra of PLA has been reported.[6,14−16] However, the resolution in their spectra was insufficient to observe the fine structure in the peaks as seen in Figure 1. Since there are more than eight peaks clearly resolved in the methine resonance of sample **2**, the stereosequence sensitivity is greater than the tetrad assignments reported in previous studies.[6,15,19]

In case of the carbonyl resonance, Kasperczyk has reported hexad stereosequence assignments for poly(D,L-lactide).[16] Here again as shown in Figure 1c, the carbonyl resonance in its ^{13}C spectrum indicates significantly higher resolution with more than 13 distinct peaks. For poly(D,L-lactide), only five out of eight possible peaks (stereosequences) are expected for tetrad sensitivity, seven out of 16 for pentad sensitivity, 11 out of 32 for hexad sensitivity, 15 out of 64 for heptad sensitivity, and 23 of 128 possible peaks are expected for octad sensitivity. Hence, the more than 13 distinct peaks in the carbonyl resonance of poly(D,L-lactide) (Figure 1c) imply that the stereosensitivity is greater than hexad and is most likely to be octad. However, due to the large number of peaks observed, many of them with significant overlap, conclusive assignments of the peaks to octad stereosequences were difficult. Similarly in case of the methyl resonance, the high degree of overlap of the peaks made conclusive assignments difficult, but hexad stereosensitivity is probable.

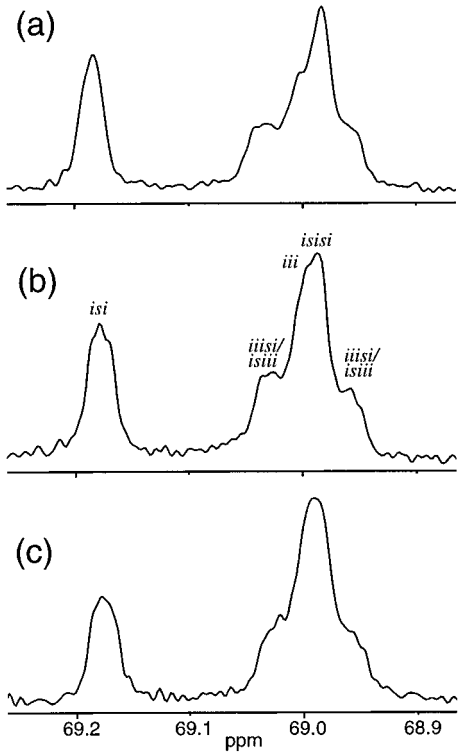

Figure 3. Methine resonances in the ^{13}C NMR spectra of poly(lactide) samples (a) **4**, (b) **5**, and (c) **6** in Table 1. The assignments shown in part b apply to all three spectra.

The ^{13}C methine resonances with major peak assignments based on hexad stereosequences for a number of poly(lactide)s are shown in Figure 2 and 3. It should be noted that Figures 2 and 3 have different ppm scales. Here, the core tetrad stereosequences *sss*, *isi*, *ssi*, and *iss* are well-resolved and their assignments are consistent with previous studies.[6,13,15,16] The *iss* and *ssi* stereosequences have identical probability and cannot be distinguished.[6,15] The hexad stereosequence assignments for the major peaks were made by comparing the distributions expected in a number of samples with varying lactide feed compositions.

A ^{1}H NMR spectrum of PLA has a significantly better signal-to-noise ratio as compared to the ^{13}C NMR spectrum and can provide better values for quantification of stereosequence probabilities. However, it is complicated by the coupling between the methyl protons and the methine (−CH) protons at each of the stereogenic centers in PLA. Fortunately, homonuclear decoupling of the methyl protons can significantly improve the resolution of the methine resonance. The methine resonance in the ^{1}H spectra of sample **2** (in Table 1) with

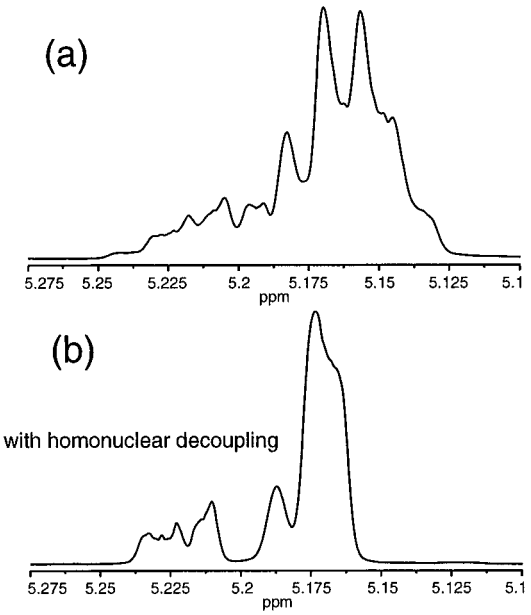

Figure 4. Effect of homonuclear decoupling (of the methyl resonance) on the methine resonance in the ^{1}H NMR spectrum of sample **2** in Table 1 as a 1% solution in $CDCl_3$.

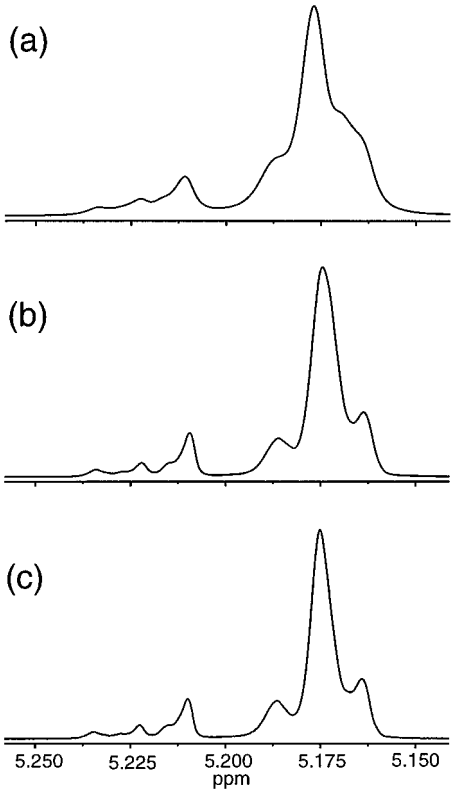

Figure 5. Effect of poly(lactide) concentration in $CDCl_3$ on the homonuclear decoupled ^{1}H NMR spectrum of sample **3** in Table 1 as (a) 10% solution, (b) 1% solution, and (3) 0.1% solution.

and without homonuclear decoupling is shown in Figure 4. Furthermore, as shown in Figure 5 for sample **3**, the resolution in the decoupled spectra was sensitive to the concentration of the poly(lactide). The spectra with lower PLA concentration were better resolved, but the integrated intensity distribution of the various peaks remained unchanged. Since the difference between a 1% solution and 0.1% solution was minimal, we have used a 1% polymer solution in $CDCl_3$ for all ^{1}H NMR measurements.

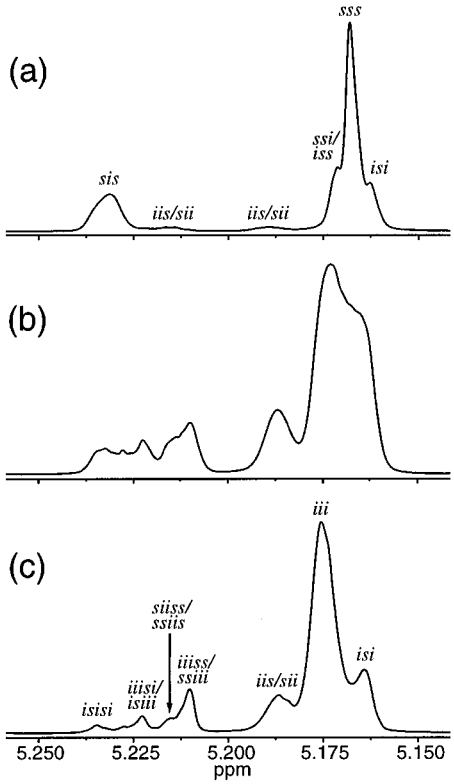

Figure 6. Methine resonances in the homonuclear decoupled ^{1}H NMR spectra of poly(lactide) samples (a) **1**, (b) **2**, and (c) **3** in Table 1.

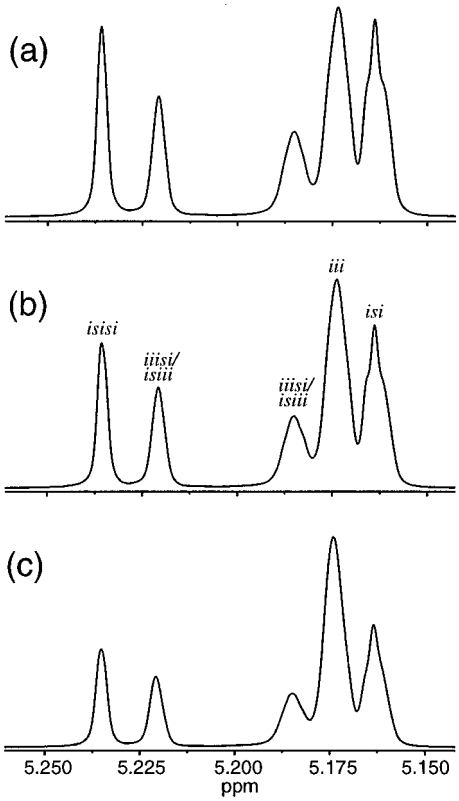

Figure 7. Methine resonances in the homonuclear decoupled ^{1}H NMR spectra of poly(lactide) samples (a) **4**, (b) **5**, and (c) **6** in Table 1.

The homonuclear-decoupled ^{1}H spectra of a number of PLA solutions are shown in Figures 6 and 7. Here again, peaks corresponding to hexad stereosequences are observed. The assignments were made by comparing trends observed in the spectra of a number of PLA

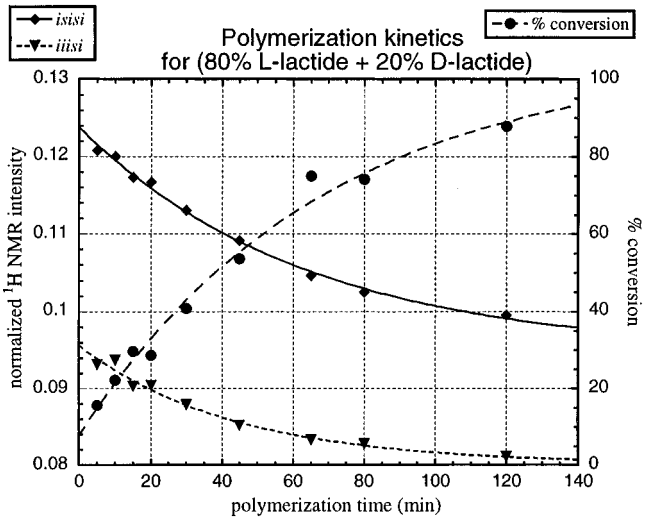

Figure 8. Normalized intensity of *isisi* and *iiisi* stereosequence resonances in the homonuclear decoupled ^{1}H NMR spectra of poly(lactide) formed at various time intervals during the polymerization of 80% L-lactide + 20% D-lactide at 180 °C using Sn(II) octoate as the catalyst in a 1:10 000 catalyst: monomer ratio. Each of the data point is an average of three NMR measurement sampling different sections of the quenched vial. The smooth lines through the data points are least-squares fit to the data using an exponential function. The extent of conversion was also measured by ^{1}H NMR.

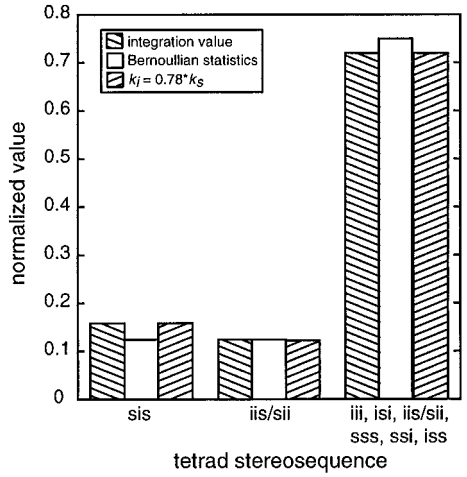

Figure 9. Comparison of the integrated intensity of the tetrad core sequences of *sis*, *iis/sii*, and *iii*+*isi*+ *sii/iis* in the ^{1}H NMR spectra of poly(D,L-lactide) (sample **4** in Table 1) with the probability distribution predicted by Bernoullian statistics ($k_i = k_s$) and by Monte Carlo calculations using $k_i = 0.78k_s$. The normalized intensity for *iis/sii* region includes contribution from *iiisi/isiii* and *iiiss/ssiii*, while *sis* includes only the *isisi* resonance.

to the probability distribution expected on the basis of their lactide feed composition. The tetrad core stereosequences of *sis* and *iis/sii* which were not resolved in the ^{13}C NMR spectra are well-resolved in the ^{1}H NMR spectra. It is not possible to identify whether the better resolved core sequences (between 5.2 ppm and 5.225 ppm) are *iis* or *sii* since they are expected to have identical probability. Nonetheless, the better resolved sequences will be referred to as *iis* even though they could instead be *sii*. The spectrum of sample **1** shown in Figure 6a shows peaks corresponding to *iis* and *sii* due to the presence of approximately 6% D,L-lactide in the polymer. Samples **2** and **3** have comparable amounts of *meso*-lactide and L-lactide, and hence all possible stereosequence combinations are observed in their spectra (See Figure 6b,c).

The spectrum of poly(D,L-lactide) (sample **4**) is shown in Figure 7a. The two well-resolved peaks representing hexad stereosequences of *isisi* and *iiisi* at *ca.* 5.23 ppm and *ca.* 5.22 ppm respectively have unequal normalized intensity. The unequal intensity for *isisi* and *iiisi* is also observed for other polymers with only L-lactide and D-lactide compositions as shown in parts b and c in Figures 7 for samples **5** and **6,** respectively. This implies that the polymerization process is not truly random since pairwise Bernoullian statistics predict equal probability for *isisi* and *iiisi* stereosequences in these three PLA (samples **4**−**6**).

The only two well-resolved stereosequences expected for poly(D,L-lactide) in the region between 5.2 and 5.25 ppm of the ^{1}H NMR spectra are *isisi* and *iiisi*. However, a tiny peak (<0.2%) observed at *ca.* 5.21 ppm in Figure 7a is probably due to the *iiiss/ssiii* stereosequence which arises from stereogenic sequences such as −*SSSSRS*−, −*RRRRSR*−, etc. Since this stereosequence is not formed during polymerization of L-lactide (*SS*) and D-lactide (*RR*), it is a result of either transesterification or racemization. For racemization, a bond at the stereogenic center needs to be broken and reformed. Under such conditions transesterification, which is thought to occur by cleavage of the acyl bond (OC−O),[6] will also be significant. Since only a small fraction (<0.2%) of the *iiiss/ssiii* peak is observed in the spectrum of poly(D,L-lactide), minimal transesterification and negligible racemization may be inferred for the polymerization conditions used.

For poly(D,L-lactide), Bernoullian statistics predict an equal probability of 12.5% for the *isisi* and *iiisi* stereosequences. In order to understand the discrepancy of 15.9 (±0.5)% and 11.9 (±0.5)% normalized intensity observed in the ^{1}H NMR spectra for *isisi* and *iiisi*, respectively, a simple kinetic scheme (Scheme 1) for polymerization with just two rate constants was assumed. The ±0.5% error for the normalized intensity of the two resonances was not determined statistically, but is a conservative estimate of the maximum possible errors due to varying instrument conditions (such as shimming, poor line shape, etc.) and due to subjective judgments in the integration cutoff values in the NMR spectra. In Scheme 1, *R** and *S** represent the active site of the growing polymer chain end with *R* and *S* stereoconfiguration, respectively.

Scheme 1

$S^* + SS \rightarrow S^*$ rate $= k_i$ [*S**][L-lactide]

$S^* + RR \rightarrow R^*$ rate $= k_s$[*S**][D-lactide]

$S^* + SR \rightarrow R^*$ rate $= k_i$[*S**]0.5[*meso*-lactide]

$S^* + RS \rightarrow S^*$ rate $= k_s$[*S**]0.5[*meso*-lactide]

$R^* + SS \rightarrow S^*$ rate $= k_s$[*R**][L-lactide]

$R^* + RR \rightarrow R^*$ rate $= k_i$[*R**][D-lactide]

$R^* + SR \rightarrow R^*$ rate $= k_s$[*R**]0.5[*meso*-lactide]

$R^* + RS \rightarrow S^*$ rate $= k_i$[*R**]0.5[*meso*-lactide]

The *isisi* represents −*SSRRSS*− and −*RRSSRR*− sequences while *iiisi* represents −*SSSSRR*− and −*RRRRSS*− sequences. A higher *isisi* probability implies syndiotactic stereospecificity since two syndiotactic additions are necessary to form this stereosequence as

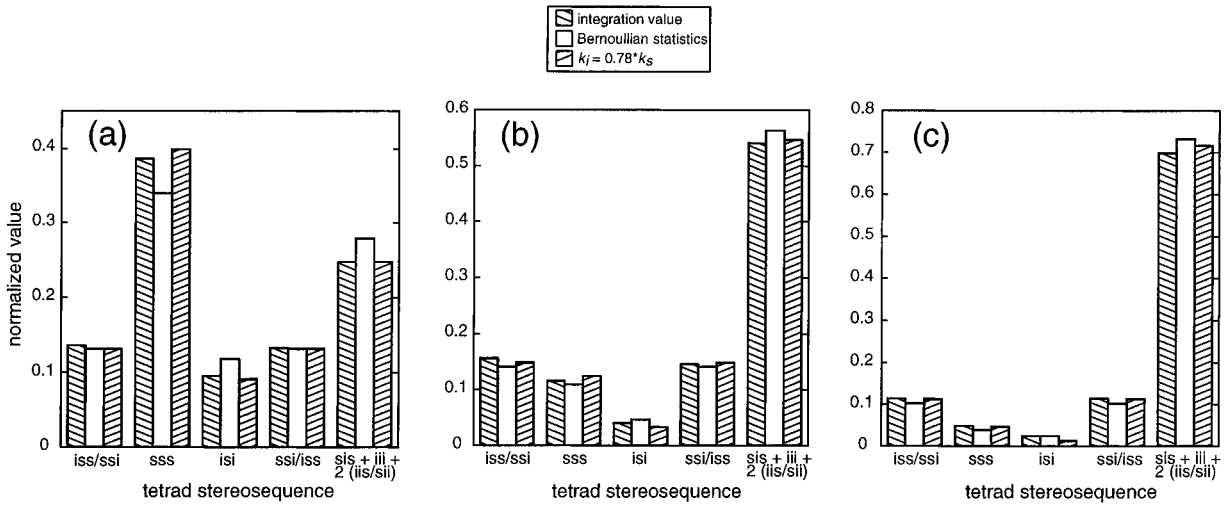

Figure 10. Comparison of the integrated intensity of the tetrad core sequences of *iss/ssi*, *sss*, *isi*, *ssi/iss*, and *sis*+*iii*+2**iis/sii* in the ^{13}C NMR spectra of poly(lactide) samples (a) **1**, (b) **2**, and (c) **3** (listed in Table 1) with their probability distribution predicted by Bernoullian statistics and by Monte Carlo calculations using $k_i = 0.78k_s$.

compared to one isotactic and one syndiotactic addition for formation of *iiisi* stereosequence formation. It is known that lactide polymerization is a reversible process and achieves equilibrium between 92 and 98% conversion.[18] However, as a first approximation to determining the final stereosequence in the polymer, the reversible process of lactide removal from the growing polymer chain end can be neglected. According to the simple kinetic Scheme 1, an *isisi* probability of 15.9% for poly(D,L-lactide) corresponds to $k_i = 0.774k_s$, while 15.4 and 16.4% *isisi* probability correspond to $k_i = 0.803k_s$ and $k_i = 0.746k_s$, respectively as calculated by Monte Carlo calculations. Details of the Monte Carlo calculations are described in the Methods section.

Additional experiments were performed to confirm the syndiotactic preference during lactide polymerization. If k_i and k_s were equal, Bernoullian statistics would apply and the polymerization rate would be independent of the lactide feed composition. In such an event, the polymer composition would also be independent of the extent of polymerization. But since the rate constants for isotactic addition (k_i) and syndiotactic addition (k_s) are different, the "pseudo rate constants" for depletion of L-lactide, D-lactide, and *meso*-lactide will be a function of the relative concentration of the three lactides. As a specific example, during the polymerization of 80% L-lactide + 20% D-lactide the polymerization rate of D-lactide and L-lactide monomers will be different. For syndiotactic stereospecificity, *i.e.* $k_s > k_i$, the minor component (D-lactide) will polymerize at a higher rate than the major component (L-lactide) even though k_i and k_s are independent of lactide composition. Consequently, the polymer will start out richer in D-lactide content and asymptotically reach the initial lactide composition of 20% D-lactide. Figure 8 shows the change in normalized intensity in the experimental data for the two well-resolved resonances corresponding to *isisi* and *iiisi* stereosequences in the polymer for (80% L-lactide + 20% D-lactide) polymerization as a function of polymerization time. Since *isisi* and *iiisi* are correlated with the D-lactide content in the polymer, the decrease in their normalized intensities with polymerization time (or extent of conversion) is further evidence for syndiotactic stereospecificity.

Similarly, the stereosequence distribution in any poly(lactide) prepared in a batch process will be dependent on the extent of polymerization as well as on the lactide feed stock. Only during the polymerization of either D,L-lactide (*viz.* 50% L-lactide + 50% D-lactide) or *meso*-lactide (*viz.* 50% *SR*-lactide + 50% *RS*-lactide) should the stereosequence distribution be independent of polymerization time. According to Scheme 1, during D,L-lactide polymerization there should be no distinction between the equimolar L-lactide and D-lactide since k_i and k_s are independent of the lactide. Indeed, the normalized intensity of the *iiisi* resonance in poly(D,L-lactide) was found to remain constant (~12%) within experimental error when measured at a number of polymerization time intervals (results not shown).

The probability distributions predicted by Monte Carlo calculations using the relative values of $k_i = 0.78k_s$ provide a reasonable fit to the observed stereosequence distribution of poly(D,L-lactide). In Figure 9, the normalized intensity of the three well-resolved regions of the ^1H NMR spectrum corresponding to tetrad core resonances of *sis*, *iis* and (*sii* + *iii* + *isi* + *sss* + *ssi* + *iss*) stereosequences in poly(D,L-lactide) are compared to the predicted stereosequence probability values. In poly(D,L-lactide), the *sss*, *ssi*, and *iss* stereosequences are not expected to be present. The stereosequence distribution in ^{13}C spectra of PLA samples **1**−**3** which contain *meso*-lactide also indicate a reasonable correlation to probability values calculated using $k_i = 0.78k_s$. The integrated peak values for well-resolved tetrad core stereosequences in their methine ^{13}C resonance are compared with the calculated values assuming 100% polymerization in Figure 10. A poor match for some of the spectral values in Figure 10 are probably due to (1) errors in the integration of the ^{13}C NMR spectra caused by relatively poor signal to noise and (2) incomplete conversion of the lactide feed during the polymerization. Even though the simple kinetic model reasonably predicts the final stereosequence distribution, it does not accurately represent the actual reversible polymerization kinetics which achieve equilibrium between 92 and 98% conversion.[18] Nonetheless, it is clear that syndiotactic stereospecificity exists under the polymerization conditions used.

This behavior is distinct from the "stereoselectivity" reported recently for lactide polymerization using a stereogenic catalyst which preferentially polymerizes D-lactide.[17] The tin(II) octoate catalyst used in this study is thought to be achiral and shows no detectable "stereoselectivity". The syndiotactic stereospecificity

observed for tin(II) octoate may be due to some steric hindrance at the active site of the growing polymer chain end. Further work incorporating the effects of reversible lactide polymerization to accurately characterize the kinetics of polymerization of various lactide compositions is in progress and will be reported in a future paper.

Conclusion

High-resolution 500 MHz ^{1}H and ^{13}C NMR spectra of various poly(lactides) indicate at least hexad stereosequence sensitivity. A preference for syndiotactic addition during the polymerization process was inferred from the stereosequence distribution in the NMR spectra. The syndiotactic preference is also evidenced by the change in ^{1}H NMR spectra over the course of a polymerization indicating a faster depletion of the minor lactide component. Monte Carlo calculations of the batch polymerization using a simple kinetic scheme indicated the rate constant for isotactic addition to be about 78% the value of the rate constant for syndiotactic addition. Under the polymerization conditions used in this study, minimal transesterification was observed.

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