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Microstructure of Poly(lactide). Phase-Sensitive HETCOR Spectra of Poly(*meso*-lactide), Poly(*rac*-lactide), and Atactic Poly(lactide)

Malcolm H. Chisholm,* Suri S. Iyer, David G. McCollum, Martin Pagel, and Ulrike Werner-Zwanziger

Department of Chemistry and Magnetic Resonance Laboratory, Indiana University, Bloomington, Indiana 47405

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ABSTRACT: We report the synthesis and ^{1}H, ^{13}C{^{1}H}, and phase-sensitive HETCOR NMR spectra of atactic poly(lactide), poly(*meso*-lactide) and poly(*rac*-lactide). The new and existing spectroscopic data are discussed in terms of four alternative explanations: (i) Kricheldorf's tetrad assignments with the presumption that the adjacent chiral units exert an asymmetric influence on chemical shifts which is propagated in opposite directions along the polymer chain for ^{1}H and ^{13}C nuclei, respectively, (ii) alternative tetrad assignments we have recently proposed, (iii) assignments based on pentad stereosequences, and (iv) assignments based on the observation of triad and pentad stereosequences rather than tetrads. We show that the available data are insufficient to unequivocally distinguish between explanations i or iv.

Introduction

High molecular weight aliphatic polyesters constitute a class of biodegradable and biocompatible polymers which is rapidly emerging as a potential environmentally friendly replacement for bioresistant polymers such as poly(α-olefins).[1] For example, poly(lactide) (PLA)[2] and its co- and terpolymers have already found applications including bulk commodity materials[3] and specialty medicinal products such as resorbable sutures,[4,5] drug delivery agents,[5] and artificial tissue matrices.[6] Cargill, Inc., and The Dow Chemical Co. have recently announced a joint polymers venture for the production of PLA in quantities of 125 000 metric tons per year by 2001,[7] in response to the rapidly expanding market for these materials. Whereas the cost of the production of these materials has previously been regarded as prohibitive, recent advancements in production and processing,[8] in combination with the ecological hazards and limited resources of polymers derived from petroleum products, have catapulted this class of polymers into a competitive market position.

PLA is typically produced by the ring-opening polymerization of the lactide cyclic dimers shown in Figure 1. A variety of catalyst precursors are used in these processes including tin octoate,[9] Al(acac)$_3$,[10] and alkoxides of aluminum,[11] lithium,[12] and the rare earth metals.[13] In many of these cases, the actual catalytic species is unknown. In the case of tin octoate, for example, kinetic evidence implicates an initial hydrolysis as a necessary step.[14] None of these examples enable controlled kinetic selectivity in the ring-opening process. It is well established that the physical properties of these polymers, including crystallization kinetics[15] and degradation properties,[16] are directly related to their stereochemical microstructure. Hence, control over the latter is of considerable importance. We have recently initiated an investigation of a class of discrete magnesium alkoxide catalysts bearing tris(pyrazolyl)borate ligands with this objective in mind.[17] In these systems, we hope to achieve stereoselective polymerization by control of the single-site catalytic stereocenter. However, an interpretation of these results requires a knowledge of the appropriate microstructural assignments of the polymer.

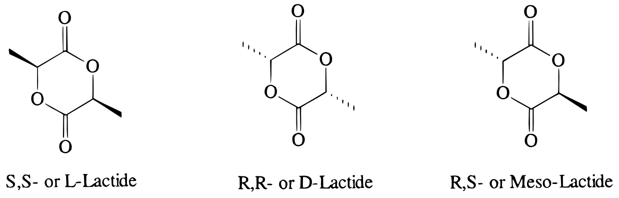

Figure 1. The three distinct forms of lactide.

Previous Assignments. The four possible triad sequences in PLA are illustrated in Figure 2. In contrast

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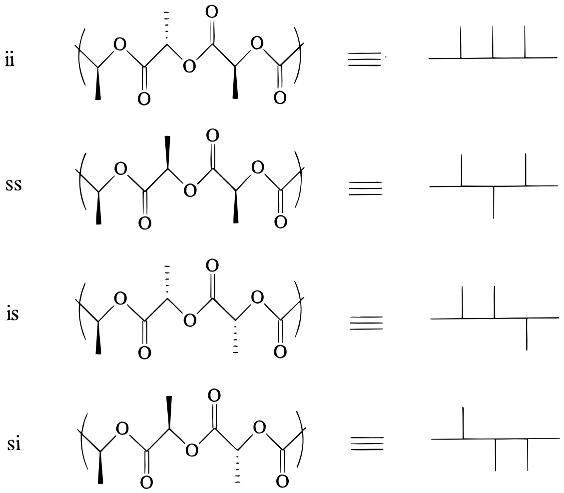

Figure 2. The four possible triads for poly(lactide) shown as a chain section and a line drawing. Note a triad consists of one and one-half equivalents of the lactide unit.

to poly(propylene) or other poly(α-olefins), poly(lactide) is an asymmetric polymer, due to the presence of an oxygen atom at every third position along the polymer chain. Hence, the microstructural analysis of PLA has an added degree of complexity arising from the fact that heterotactic triad sequences (**is** and **si**) are inequivalent.[18] Furthermore, we note that the tacticity assignments refer only to the relative configurations of the stereocenters along the polymer chains and are not related to the physical (up or down) orientations of the methyl groups with respect to the main polymer chain. Thus, again in contrast to poly(propylene), in which all the methyl groups in the isotactic polymer are directed to one side of the polymer chain, isotactic PLA consists of an alternating “up−down” orientation of the methyl groups along the fully extended chain (see Figure 2).

Several groups have attempted to elucidate the stereochemical properties of these polymers using ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. Whereas the carbonyl,[9,10,19] methyl,[9,20] and methine[9−12,20] regions of these spectra have all been analyzed at one time or another, most studies have concentrated on the methine ^{1}H and ^{13}C{^{1}H} resonances, as the methine region appears to exhibit minimal overlapping of resonances in $CDCl_3$ solutions.[9] Work has proceeded to infer stereochemical preferences in some polymerization processes based on deviations of the observed distribution of methine ^{1}H and ^{13}C resonances from that predicted by Bernoullian statistics.[9,12,21,22] However, these conclusions hinge on the assumption that the NMR chemical shift assignments are correct, an assumption that we have recently found reason to question.[23]

Of the three distinct diastereomers of monomeric lactide (Figure 1), two (L,L and D,D) are enantiomeric and are referred to collectively as *rac*-lactide. The third (L,D) is the *meso*-isomer. Neither *rac*- nor *meso*-lactide can be polymerized (independently) to give a completely atactic structure in the absence of side reactions such as transesterification. This is a consequence of the inherent bias of each monomer to generate isotactic (**i**) and syndiotactic (**s**) dyads in the respective polymers, due to the coexistence of two chiral centers in each unit of monomer. Assuming that polymerizations initiated by common reagents such as $Al(acac)_3$ and tin octoate occur in a random fashion (e.g., with no end group control), the resultant polymers should show a statistical bias in stereosequences that may, in principle, be used to assign ^{1}H and ^{13}C{^{1}H} NMR resonances in a given spectral region. In this manner, Kricheldorf and co-workers[9a] have assigned the methine regions of the NMR spectra of poly(*rac*-lactide) and poly(*meso*-lactide) according to tetrad sensitivity. Consistent with this hypothesis are the following facts: (i) Only five out of a possible eight tetrads for a completely random polymer arise in either polymer (from *rac*- or *meso*-lactide), given the **i** or **s** bias described above (see Figure 3), and never are more than five resonances detected in this region. (ii) In the instances where five lines are observed, the approximate integrations of these peaks correlate well with the probabilities for the possible tetrad sequences as predicted by Bernoullian statistics.[24]

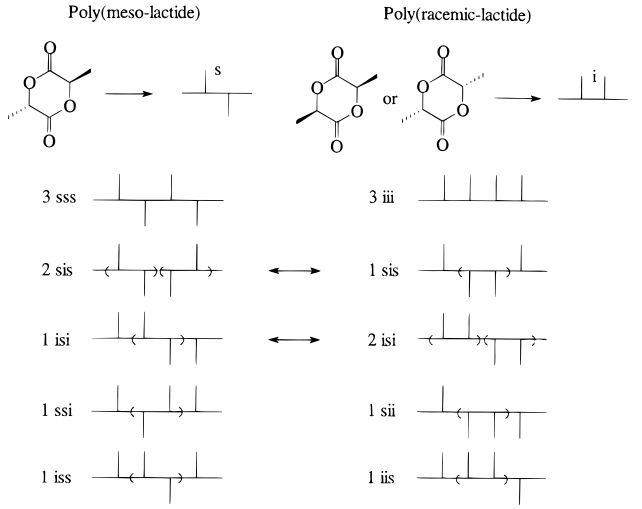

Figure 3. Tetrads arising from poly(*meso*-lactide) (left) and poly(*rac*-lactide) (right) with their ratios as predicted by Bernoullian statistics.[9a] Only two tetrads are common to both polymers, and these are predicted to occur in a different integral ratio.

We find the assignment of tetrad sensitivity to a chiral center on a polymer chain to be very unusual because this requires the chemical shift of the nucleus under observation to be influenced by the stereochemistry of one chiral center to the left and two to the right (or vice versa) along the polymer chain. The proposal is not implausible, given the asymmetric nature of the repeat unit, but we find it puzzling that this unusual behavior has warranted no comment to date. The only precedent for this type of sensitivity of which we are aware was reported by Bovey and co-workers[25] in their analysis of atactic poly(propylene oxide) (PPO) using 2D *J*-resolved spectroscopy. Even in this instance the observation was deemed atypical, and no attempt was made to explain the origin of the phenomenon. Others have observed asymmetric microstructural sensitivity in, for example, the methylene ^{13}C{^{1}H} NMR signals of PPO.[26] However, in this case clear differences in the distances of the two next-nearest neighbors from the nucleus under observation can be identified, as well as differences in the number of heteroatoms encountered along the polymer chain in each direction. These qualifications do not pertain to the methine ^{1}H or ^{13}C nuclei of either PPO or PLA.

Results and Discussion

We have employed heteronuclear correlated {^{1}H, ^{13}C} (HETCOR) two-dimensional spectroscopy in the analysis of the methine chemical shift regions of poly(*rac*-

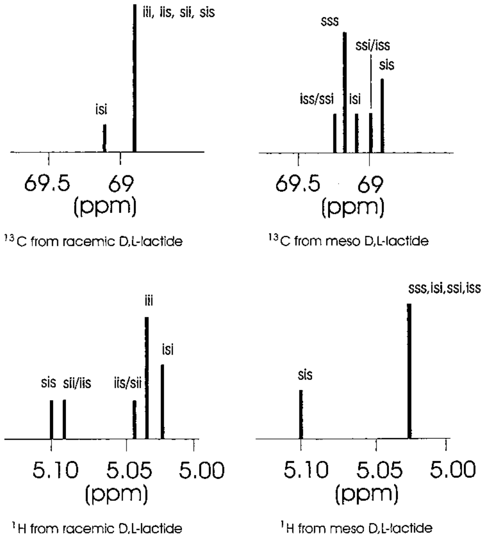

Figure 4. Tetrad assignments for poly(*rac*-lactide) and poly(*meso*-lactide) based on the work of Kricheldorf.[9a]

lactide) and poly(*meso*-lactide). The resultant 2-D plot of $F_1(^1H)$ vs $F_2(^{13}C)$ consists of peaks that correspond to the chemical shift coordinates of protons and carbons connected through bonds in the two dimensions. Splittings due to *J*-couplings are removed by the application of a π-pulse to the ^{13}C nucleus at time $t_1/2$ and decoupling during t_2.[27]

Our argument against the proposed tetrad assignments is based on the inconsistency of the observed HETCOR spectra of both the *rac*- and *meso*-lactide polymers.[23] In the methine region of the proton spectrum of poly(*rac*-lactide), five lines are observed. These were assigned[9a] to tetrad sequences according to the approximate correlation between their line integrations and a Bernoullian distribution of tetrad stereosequences. In the methine region of the $^{13}C\{^1H\}$ spectrum of poly(*meso*-lactide), five lines are also observed and were similarly assigned. In the proton spectrum of poly(*meso*-lactide), however, only two lines are resolved. These resonances occur at identical chemical shifts as two of the lines in the poly(*rac*-lactide) material. Since two tetrads, **sis** and **isi**, ought to be common to the two polymers (see Figure 3), this result is not surprising. Again on the basis of the approximate integrations of the two lines, it was concluded that four of the five tetrads of poly(*meso*-lactide) were spectroscopically degenerate; all collapsed into the higher field resonance, so that the lower field line represented only the **sis** tetrad. A similar conclusion was inferred for the two lines observed in the $^{13}C\{^1H\}$ spectrum of poly(*rac*-lactide).[9a] An illustration of these assignments is shown in Figure 4.

The HETCOR spectra of each of these polymers are shown in Figures 5 and 6 and reveal that a resonance in either the ^{1}H or $^{13}C\{^1H\}$ spectrum which was previously assigned to a single tetrad stereosequence clearly correlates with *two* resonances in the spectrum of the other nucleus. We therefore proposed new assignments (see Figure 7) which were easily reconcilable with the HETCOR data but inconsistent with a Bernoullian analysis of poly(*meso*-lactide). We rationalized this discrepancy by supposing the possibility that end group control may perturb the statistical makeup of this polymer. However, on further analysis, we find that this may not be sufficient to justify our assignments. The principal difference between our assignments and those proposed by Kricheldorf is that we have reversed the **isi** and **sis** assignments in the ^{13}C NMR spectrum of poly(*meso*-lactide). According to Bernoullian probability, the **sis** tetrad should occur twice as often as the **isi** and the **sss** tetrad three times as often as **isi**. To explain the increase in **isi** tetrads relative to **sss** ones (inherent in our assignments), we must infer some type of preference for isotactic insertion (given that minimal transesterification occurs, as Kricheldorf has shown).[9a] Such a situation ought to comply with a Markovian statistical analysis (first or second order) of this polymer.[28] We find, however, that, in the event that the polymerization of *meso*-lactide is biased toward either isotactic or syndiotactic insertion, the formation of **sis** tetrad sequences is always statistically more probable than the formation of **isi** sequences. Thus, it appears that our assignments are statistically unreasonable. A description of our statistical analysis is provided in the Appendix.

An alternative argument has recently been proposed,[29] namely that the tetrad sequences assigned by Kricheldorf are in fact correct, but the chemical shift tensors are propagated in opposite directions along the polymer chain for ^{1}H and ^{13}C nuclei. In other words, the methine ^{1}H is influenced by two chiral centers to the left and one to the right, and the corresponding ^{13}C nucleus is influenced by one center to the left and two to the right (or vice versa for each). In this case, resonances from certain tetrad sequences in the proton spectrum would be expected to correlate with multiple resonances in the carbon spectrum, and vice versa.

For example, the pentad sequence **isii**, which is allowed in poly(*rac*-lactide) but not in poly(*meso*-lactide), is illustrated in Figure 8. If we suppose that the methine $^{13}C\{^1H\}$ resonance of the designated carbon (*) is sensitive to the effects of one stereocenter to the left and two to the right, then the appropriate chemical shift represents the **sii** tetrad stereosequence. We also suppose that the methine ^{1}H resonance at the designated position (*) is sensitive to the environment defined by two stereocenters to the left and one to the right, in which case the corresponding line in the proton spectrum represents an **isi** tetrad sequence. Thus, in the HETCOR spectrum of poly(*rac*-lactide), the **sii** resonance in the $^{13}C\{^1H\}$ spectrum will correlate only with the **isi** resonance of the ^{1}H spectrum. It must be noted, however, that the **isi** tetrad is also a component of the **isis** pentad sequence, which is also allowed for poly(*rac*-lactide) and is depicted in Figure 9. Clearly, the steric environment defined by two centers to the left and one to the right of the designated methine center (**) is identical to that shown in Figure 8, which yields the **isi** tetrad resonance in the ^{1}H spectrum. However, the environment defined by one center to the left and two to the right has changed, corresponding to the **sis** tetrad in the $^{13}C\{^1H\}$ spectrum. Thus, it would be expected that the **isi** resonance in the ^{1}H spectrum should correlate with *both* the **sii** and **sis** resonances in the $^{13}C\{^1H\}$ spectrum, in the HETCOR of poly(*rac*-lactide).

This argument does explain the HETCOR data, but to our knowledge it is an unprecedented phenomenon. Whereas we are not so naive as to suppose that every physical property which exists has been observed, we are now faced with an explanation that assumes *two* very unusual characteristics, and the only proof of the theory is the circular logic that it explains the available

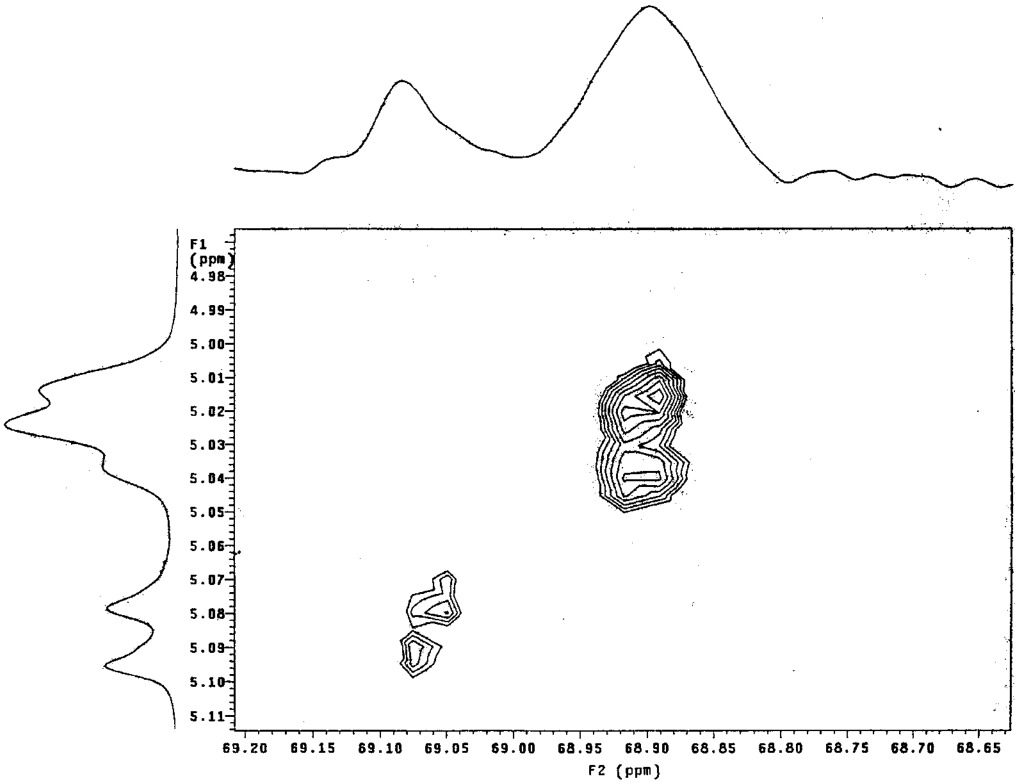

Figure 5. HETCOR spectrum of poly(*rac*-lactide) obtained in $CDCl_3$ solution at 25 °C on a Brüker AM500 spectrometer.

data. The tables of expected $^1H-^{13}C$ correlations are presented in Tables 1 and 2.

Yet another argument, which we have periodically entertained, is the possibility that the observed microstructural sensitivity is not at the tetrad but rather at the pentad level. It happens that only seven of 16 possible pentads can occur in either poly(*rac*-lactide) or poly(*meso*-lactide) and also that four are impossible in either polymer (see Figure 10). It does not seem completely unreasonable that accidental degeneracy may lead to the observation of a maximum of five lines in each of these polymers. Furthermore, Bernoullian statistics can be readily justified under this mode of assignment for either polymer.

A further possibility is that fundamentally the methine ^1H and ^{13}C nuclei exhibit triad sensitivity and that certain stereosequences are susceptible to next-nearest-neighbor effects in each direction along the polymer chain. For example, it is possible that the stereosequences **ii** and **ss** show unique triad resonances, whereas the heterotactic sequences **is** and **si** are split by neighboring effects to yield resonances that correlate with pentad sensitivity. As is illustrated in Figures 11 and 12, such behavior would give rise to a maximum of five lines in the methine regions of the NMR spectra of either poly(*rac*-lactide) or poly(*meso*-lactide). Clearly, if this were to be the case, a Bernoullian distribution of the resonances in poly(*rac*-lactide) would be **ii**:**iisi**:**sisi**:**isis**:**isii** = 4:1:1:1:1, and this is not the case. However, a Markovian statistical distribution (first or second order) would account for the observed perturbations in the integrated peak values from those expected for a random polymerization process.[30]

Whereas all available ^1H NMR data for poly(*meso*-lactide) and poly(*rac*-lactide) can be explained in terms of the triad−pentad argument, the $^{13}C\{^1H\}$ data reported for poly(*meso*-lactide)[9a,b] (see Figure 6) do not appear to correlate well with a *X*:*Y*:*Y*:*Z*:*Z* distribution. It is possible, in this case, that the remaining triad sequence, **ss**, is split into pentads, e.g., **ssss**, **sssi,** and **isss**. The phenomenon would then give rise to seven resonances; the coincidental overlap of two pairs in so small a region of the spectrum would not be unreasonable. Better resolved spectra[9b,29] indicate that these resonances do show fine structure which would be consistent with this result.

We note that the only difference between the **ii** triad and the **is** triad is the inversion of the stereochemistry of the chiral center on the right end of the sequence as drawn. In poly(*rac*-lactide), this arises from a juncture between units of LL- and DD-lactide. As a consequence of the stereochemical constraints of the monomer, the configuration of the next stereocenter to the right is fixed, so that the resultant pentads that arise from an **is** triad are distinguished only by the orientation of the furthest stereocenter to the left. It may seem peculiar that inversion of a stereocenter on one end of a triad sequence effectively induces greater sensitivity of the central stereocenter to the chirality of the environment on the other end. However, ample precedent exists relating conformational preferences of polymer chains to their tacticities, and the effects are manifested in the NMR spectral data.[31] It seems reasonable to infer that a difference in the conformational preferences of the **ii** and **is** triad sequences can significantly affect the observable microstructural sensitivity of the central stereocenter.

In an attempt to determine whether the methine regions should be described in terms of tetrad or pentad sensitivity, we analyzed atactic PLA using ^1H, $^{13}C\{^1H\}$, and HETCOR NMR spectroscopy. We reasoned that in true atactic polymer the four pentad sequences that do not occur in either poly(*rac*-lactide) or poly(*meso*-lactide) would now be allowed and that at least one might be

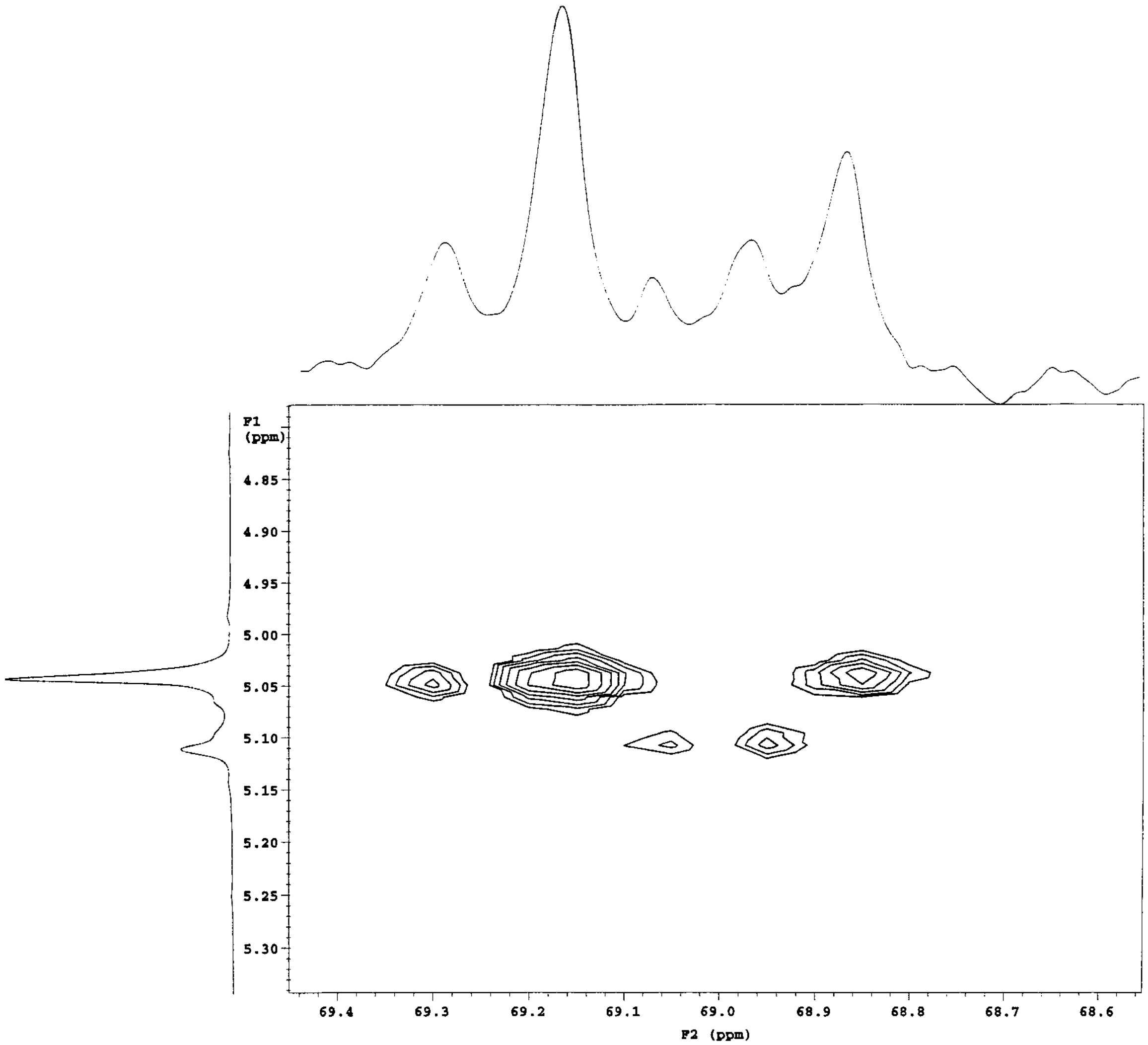

Figure 6. HETCOR spectrum of poly(*meso*-lactide) obtained in $CDCl_3$ solution at 25 °C on a Varian I400 spectrometer.

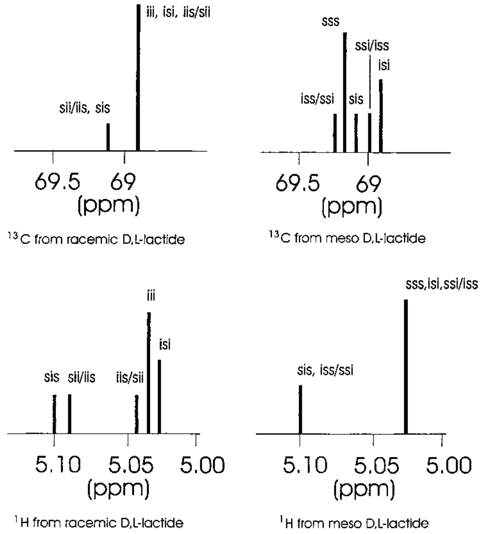

Figure 7. Tetrad assignments for poly(*rac*-lactide) and poly(*meso*-lactide) based on the HETCOR spectra as proposed by Chisholm.[23]

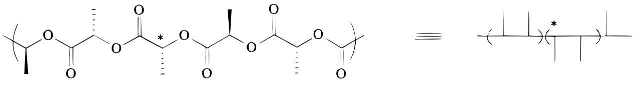

Figure 8. Pentad sequence **isii**, which can arise for poly(*rac*-lactide), is seen to give rise to an **ssi** tetrad assignment in the ^{13}C and an **isi** in the ^{1}H if the chemical shift tensors are influenced for ^{13}C one to the left and two to the right and for the ^{1}H one to the right and two to the left.

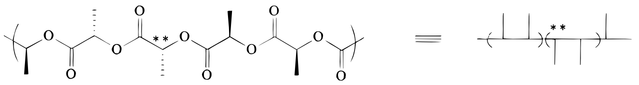

Figure 9. The **isi** tetrad is shown here to be a component of the **isis** pentad sequence, which can arise from both poly(*rac*-lactide) and poly(*meso*-lactide).

expected to produce a discrete NMR signal if pentad sensitivity is correct. We found that atactic PLA could be synthesized by polymerizing a 1:1 mixture of *rac*:*meso*-lactides using tin octoate as the initiator *in toluene solution* at 100 °C.[32] To confirm the random copolymerization of these isomers under the defined conditions, we followed the polymerization of a 2:1 *meso*:*rac*-lactide mixture by NMR spectroscopy.[34] In Figure 13 we show the evolution of the ^{1}H NMR methine regions of polymer (5.15 ppm) and *meso*- (4.44 ppm) and (4.27 ppm) *rac*-lactides in toluene-d_8 at 100 °C with 2% tin octoate. The ratio of the integrated values of the *meso*- and *rac*-monomers is relatively constant until >80% conversion. Thus, it is reasonable to infer that from a 1:1 isomer mixture we obtain predominantly atactic polymer.

The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of atactic PLA are shown in Figures 14 and 15. In each spectrum, five principal lines are observed. It is noted that the reso-

Table 1. [a] **NMR Correlations of Tetrad Stereosequences in Poly(*rac*-lactide)**

^{13}C	^{1}H	^{13}C	^{1}H
iii	**iii** + **sii**	**iis**	**iii**
isi	**sis** + **iis**	**sii**	**isi**
sis	**isi**		

[a] The correlation depicted in this table is based on the arbitrary assumption that the ^{13}C nucleus is influenced by one center to the left and two to the right, and the ^{1}H nucleus is influenced by two centers to the left and one to the right.

Table 2. [b] **NMR Correlations of Tetrad Stereosequences in Poly(*meso*-lactide)**

^{13}C	^{1}H	^{13}C	^{1}H
sss	**sss** + **iss**	**iss**	**sis**
isi	**sis**	**ssi**	**sss**
sis	**isi** + **ssi**		

[b] See footnote to Table 1.

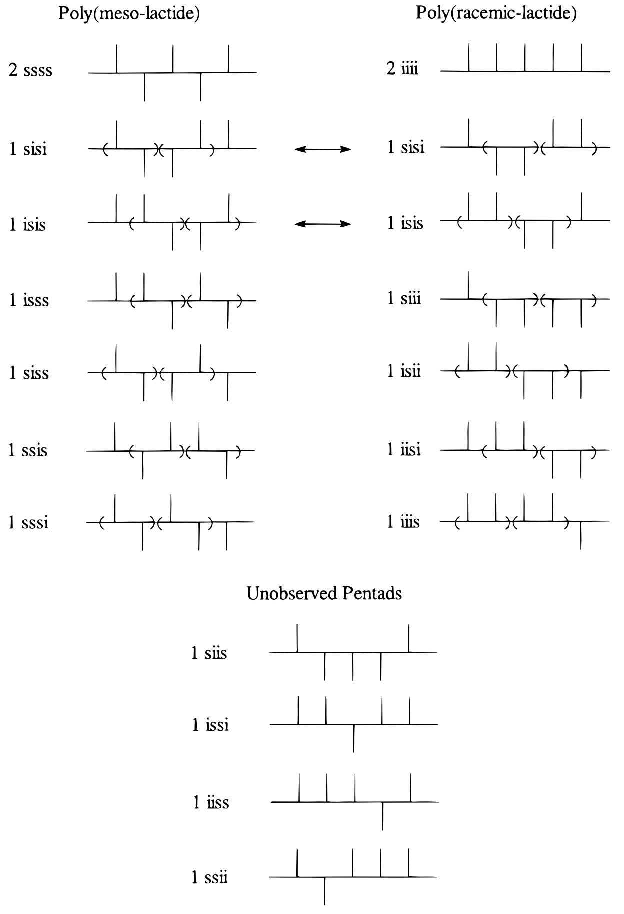

Figure 10. Pentad sequences for poly(*meso*-lactide) (left) and poly(*rac*-lactide) (right) along with the ratios predicted by Bernoullian statistics. The four pentad sequences shown at the bottom cannot occur in either of these polymers.

nance at ~5.16−5.17 ppm in the ^{1}H spectrum is broad, unlike the sharp line observed for the putative **sii**/**iis** tetrad in poly(*rac*-lactide). These spectra qualitatively resemble the spectra reported by Kricheldorf and Boettcher[35] for poly(*rac*-lactide) in which transesterification reactions are presumed to have randomized the stereochemical microstructure. It is important to note that neither of these spectra are consistent with a random, i.e., Bernoullian, distribution of tetrad stereosequences as assigned by Kricheldorf.[9a]

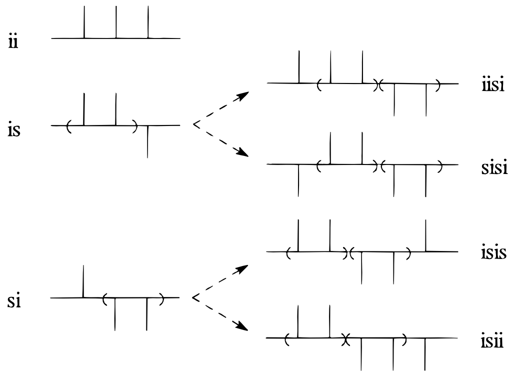

Figure 11. Possible triad to pentad splittings in poly(*rac*-lactide).

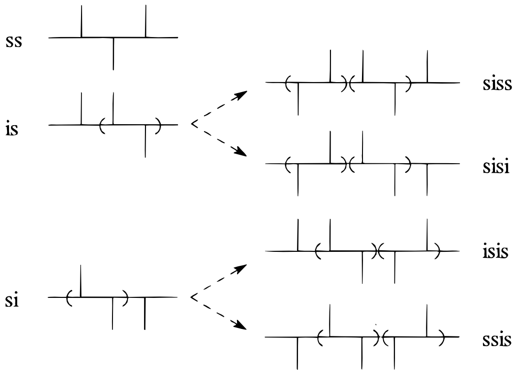

Figure 12. Possible triad to pentad splitting in poly(*meso*-lactide).

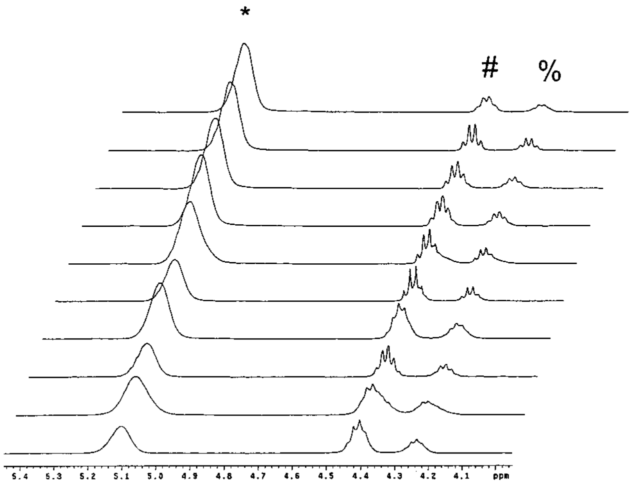

Figure 13. Polymerization of a *rac*- to *meso*-lactide (1:2) mixture by a 2% solution of $Sn(oct)_2$ in toluene-d_8 at 100 °C shown as a function of time revealing that, within the limits of ^{1}H integration, *rac*- and *meso*-lactide are polymerized at the same rate up to 80% conversion. * represents the growing poly(atactic)lactide; # and % represent the *meso*- and *rac*-dilactide, respectively.

The phase-sensitive HETCOR spectrum[36] of this sample of atactic PLA is shown in Figure 16. The spectrum strongly resembles that which would be expected from a composite of the HETCOR spectra of poly(*rac*-lactide) and poly(*meso*-lactide). The spots arising from stereosequences found in poly(*rac*-lactide) are the three which correlate to 69.12−69.16 ppm and the two which correlate to 69.36 ppm in the $^{13}C\{^{1}H\}$ dimension. Those derived from stereosequences in poly(*meso*-lactide) are the three which correlate to 5.14−

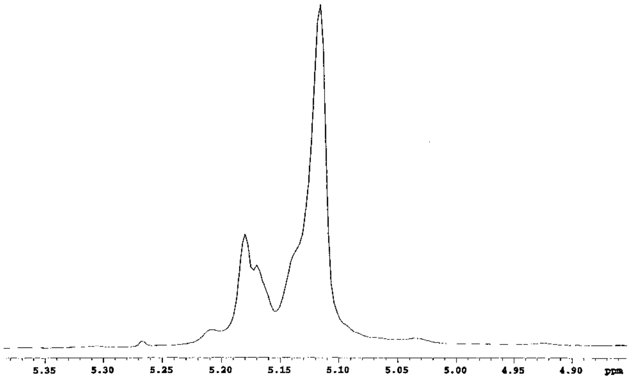

Figure 14. ^{1}H NMR spectrum (CDCl$_3$, 400 MHz) of the homodecoupled C*H* resonance of a completely random polymer of poly(*meso*- + *rac*-lactide) from a 1:1 mixture of *meso*- and *rac*-lactide.

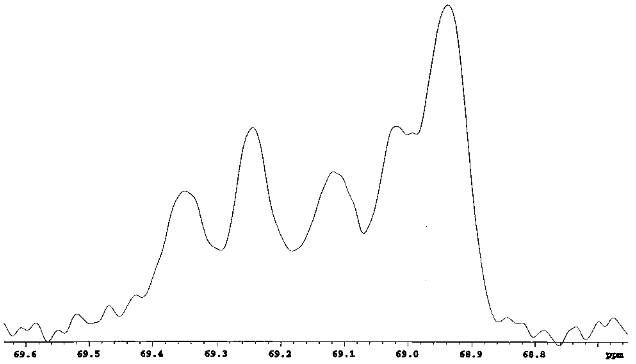

Figure 15. ^{13}C{^{1}H} NMR spectrum (CDCl$_3$, 100 MHz) of the methine carbon signals of a completely random polymer of poly(*meso*- + *rac*-lactide) formed from a 1:1 mixture of *meso*- and *rac*-lactide.

5.15 ppm and the two which correlate to 5.21 ppm in the ^{1}H dimension. [Recall that two spots are common to the spectra of both polymers.] However, a new spot is observed at 69.26 and 5.19 ppm (^{13}C{^{1}H}, ^{1}H). In the proton dimension, this spot correlates with the resonance that is broadened (the putative **sii**/**iis** tetrad) and derives from poly(*rac*-lactide). In the ^{13}C dimension, this spot correlates with the resonance that has been assigned to the **ssi**/**iss** tetrad, which derives from poly(*meso*-lactide). We will attempt to disentangle the evident confusion which this result presents by interpreting it according to each of the three remaining hypotheses under consideration.

We first consider the modified tetrad assignments of Kricheldorf, in which the methine ^{1}H and ^{13}C nuclei are influenced by different portions of the polymer chain. In Figure 17 is shown an illustration depicting the expected HETCOR spectrum that would result if the correlations described in Tables 1 and 2 are correct. Clearly the general appearance of the spectrum is quite similar to the expected spectrum. The expected ^{1}H$-$^{13}C correlations for this polymer are presented in Table 3.

We note that some of the ambiguity in the assignment of **iss**/**ssi** and **iis**/**sii** tetrads in the ^{13}C{^{1}H} and ^{1}H spectra, respectively, is removed if these assignments are corect. Specifically, only one permutation is possible if the methine ^{13}C is influenced by two centers to the left and one to the right, and only one distinct permutation is possible if the methine ^{13}C is influenced by one center to the left and two to the right.

The appearance of a new spot could also be interpreted as evidence of pentad sensitivity. We are skeptical of this interpretation principally because only one new spot is observed, meaning that the remaining 15 pentad resonances must be collapsed into the eight original spots. We therefore consider strictly a pentad assignment of the ^{1}H and ^{13}C{^{1}H} NMR signals of PLA to be unlikely.

If we consider the possibility that the sensitivity is fundamentally at the triad level, with only the heterotactic stereosequences exhibiting pentad sensitivity, it is again possible to explain the observed HETCOR. In this scenario, only two new pentad sequences would be expected to emerge in atactic polymer (**ssii** and **iiss**, shown in Figure 18). Thus, a maximum of only 10 spots (two from the triads **ii** and **ss**, the six distinct heteroatactic pentads shown in Figures 11 and 12, and the two heteroatactic pentads shown in Figure 18) would be expected in the HETCOR spectrum of this polymer, which is much more easily reconciled with the observed spectrum (bearing nine spots). The possibility that the putative **ss** triad splits into pentads in the ^{13}C{^{1}H} domain may or may not be consistent with this interpretation depending upon specific assignments.

Concluding Remarks

Whereas the tetrad assignments of the methine ^{1}H and ^{13}C resonances which we proposed in our previous paper are consistent with the two-dimensional HETCOR spectra of poly(*meso*-lactide), poly(*rac*-lactide), and atactic poly(lactide), they are clearly inconsistent with any sort of statistical analysis of the polymers and do not warrant further consideration. We also consider an assignment at the pentad level of sensitivity to be unlikely, because it seems to require an assumption of an unreasonable degree of spectral degeneracy among stereosequences. We are therefore led to the following conclusion.

The available spectroscopic and statistical evidence appear to be consistent with at least two stereochemical assignments. The proposal[29] that the original tetrad assignments[9a] are correct, but that the ^{1}H and ^{13}C chemical shift tensors are propagated in opposite directions along the polymer chain, certainly seems to fit the accumulated spectral data. However, in the absence of independent confirmation of this unusual phenomenon, we are disinclined to accept this proposal as fact. For example, one can understand that for a section of a helical polymer the methine carbon may be influenced more strongly by two stereocenters in one direction than the other because of proximity effects. However, why this should be so for the carbon nucleus but not so for the proton, which is influenced in the opposite direction, is not at all obvious.

An alternative explanation exists, specifically that the observed spectral evidence can be explained in terms of triad and pentad sensitivity. This proposal appears to be equally consistent with the accumulated data and is also consistent with well-established tenets of polymer microstructure. Consequently, independent evidence, perhaps obtained from spectroscopic studies on model compounds or from isotopically labeled polymers, must be obtained before any hypothesis can be accepted unequivocally.

Experimental Section

Materials. Tin octoate (2-ethylhexanoic acid, tin(II) salt, Aldrich) and was used as received. *rac*-Lactide (Aldrich) was

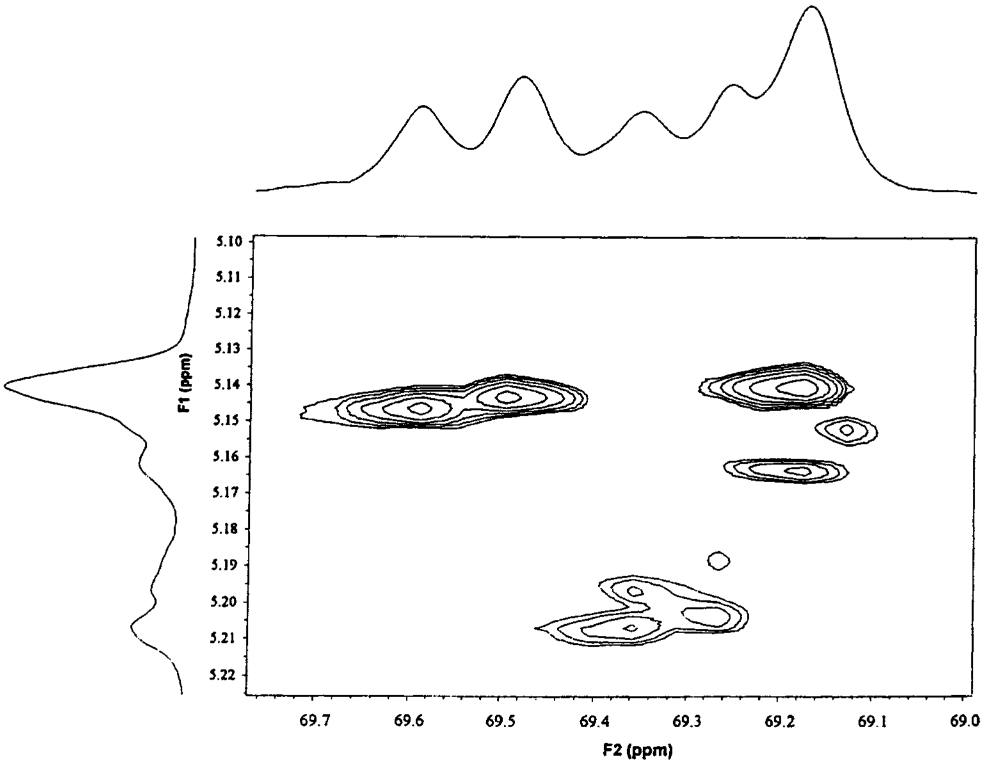

Figure 16. Phase-sensitive HETCOR spectrum showing the correlation of the homo decoupled methine protons with the methine carbon signals, $^{13}C\{^1H\}$, of poly(*meso-* + *rac*-lactide) in $CDCl_3$ at 400 MHz. This atactic sample was formed from copolymerization of a 1:1 mixture of *rac-* and *meso*-lactide as described in the text.

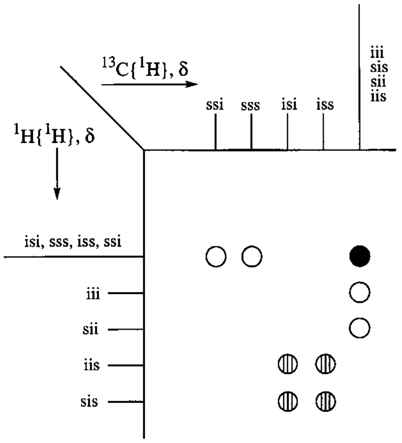

Figure 17. Cartoon drawing showing what a HETCOR of atactic PLA should look like if Kricheldorf's assignments[9a] are correct, but the ^1H and ^{13}C tensors are influenced in opposite directions. The assignments of the **iss** and **ssi** tetrad sequences along the $^{13}C\{^1H\}$ axis and of the **iis** and **sii** tetrad sequences along the $^1H\{^1H\}$ axis are absolute, with the assumption that the methine ^{13}C nucleus is sensitive to one neighboring center to the left and two to the right.

Table 3. NMR Correlations of Tetrad Stereosequences in Atactic PLA

^{13}C	^1H	^{13}C	^1H
iii	**iii, sii**	**iss**	**iis, sis**
sss	**sss, iss**	**ssi**	**sss, iss**
isi	**iis, sis**	**sii**	**ssi, isi**
sis	**ssi, isi**	**iis**	**iii, sii**

double recrystallized from ethyl acetate and dried under a high vacuum before use. *meso*-Lactide (96%) was obtained as a generous gift from Mark Hartman at Cargill and was dried under high vacuum prior to use. Toluene was distilled over sodium–benzophenone, and toluene-d_8 was distilled over CaH_2 prior to use.

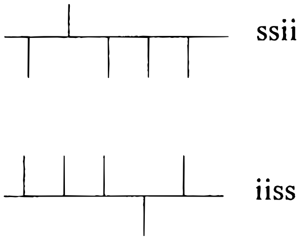

Figure 18. Pentad sequences which are unique to atactic PLA.

meso-Lactide:rac-Lactide Mixture. DL-Lactic acid (85%) was condensed to form low molecular weight PLA according to the method described by Deane and Hammond.[37] The polymer was cracked with ZnO, and a mixture of lactide isomers was distilled from the reaction mixture.[37] Recrystallization from ethyl acetate yielded a 2.3:1 mixture of *meso*-lactide:*rac*-lactide which was free of contamination by lactic acid and any lower molecular weight linear oligomers within the detection limits of ^1H NMR spectroscopy. ^1H NMR (400 MHz, toluene-d_8): *meso*-isomer, δ 4.44 (q, 1H), 1.23 (d, 3H); *rac*-isomer δ 4.27 (q, 1H), 1.31 (d, 3H).

Polymerization of a 2.3:1 Mixture of meso-Lactide:rac-Lactide. To a mixture of *meso-* and *rac*-lactide (135 mg, 0.94 mmol) in toluene-d_8 (0.75 mL) was added tin octoate (0.5 M solution in toluene-d_8, 40 μL, 20 μmol) under a stream of Ar in an NMR tube. The tube was then sealed under vacuum. A ^1H NMR spectrum recorded after 1 h at 20 °C revealed that no reaction had occurred. A spectrum recorded after 30 min at 50 °C revealed that the polymerization had proceeded to 10% conversion. After a further 90 min the temperature was stabilized at 100 °C, and reaction had proceeded to 40% conversion with no change in the composition of unreacted monomer. At this time, the array experiment presented in Figure 13 was commenced, and the reaction was followed to 94% conversion. Relatively little change in the composition of the remaining monomer was evidenced by the relative integration values of the methine ^1H resonances of *meso-* and *rac-*

lactide (at 4.44 and 4.27 ppm, respectively) until >80% conversion to polymer.

Atactic PLA. A 1:1 mixture of *meso*-lactide:*rac*-lactide was prepared by diluting the 2.3:1 mixture (1.66 g, 11.5 mmol) with pure *rac*-lactide (0.57 g, 4.0 mmol). The resultant mixture of lactide isomers (2.23 g, 15.5 mmol in total) was dissolved in toluene (15 mL) at 65 °C. The 1:1 ratio of isomers in this solution was confirmed by ^{1}H NMR analysis of an aliquot of this solution (CDCl$_3$). To this mixture was added tin octoate (50 μL, 0.15 mmol). The solution became slightly cloudy on mixing. The reaction mixture was heated to 100 °C for 2 h. ^{1}H NMR analysis of an aliquot revealed that no reaction had occurred in this time. A further portion of tin octoate (75 μL, 0.225 mmol) was added to the reaction mixture, and heating was continued for 4.5 h. ^{1}H NMR analysis of an aliquot revealed that polymerization had occurred to ~95% conversion at this time. The reaction mixture was cooled to room temperature and was diluted with MeOH (15 mL). The polymer separated from the resultant solvent mixture as an oil. The solvents were partially decanted, and the polymer was then concentrated to dryness under reduced pressure.

Poly(rac-lactide) and poly(meso-lactide) were prepared at 150 °C for 2 h (bulk polymerizations) as described in ref 9a.

NMR Spectroscopy. All spectra of atactic PLA were observed on a 5 wt % solution in CDCl$_3$ at 25 °C on a Varian I 400 MHz (proton frequency) NMR spectrometer and were referenced against either the residual C*H*Cl$_3$ peak at $\delta = 7.26$ ppm or the natural abundance ^{13}C{^{1}H} resonance at $\delta = 77.23$ ppm arising from *C*DCl$_3$.

The parameters of the phase-sensitive HETCOR experiment are as follows: The sweep widths were 18962 Hz in the F_2 dimension (^{13}C) and 202 Hz in the F_1 dimension (^{1}H). The recycle time was 1.216 s between FIDs. Sixteen FIDs were accumulated for each t_1 increment. The data matrix consisted of 150 spectra of 8192 points each and was zero-filled before the second Fourier transform. The advantage of this experiment over an absolute value HETCOR experiment is that it produces a spectrum with narrower lines as a consequence of the fact that the imaginary component of the Fourier transform is retained in the processing of the data.

The HETCOR spectra of poly(*rac*-lactide) and poly(*meso*-lactide) were recorded in chloroform-d_1. The sweep width was 2565.4 Hz in the F_2 dimension (^{13}C) and 2400.7 Hz in the F_1 dimension (^{1}H). The recycle time was 1.4 s between FIDs. Twenty-eight FIDs were accumulated for each t_1 increment. The data matrix consisted of 1024 spectra of 2048 points each and was zero filled before the second Fourier transform.

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Appendix

The statistical analysis of the stereochemistry of polymers obtained by ring-opening of heterocyclic monomers has been developed by Sepulchre.[28] It has been further shown[38] that polymers derived from monomers bearing two chiral centers may be analyzed using the same statistical equations as are used for polymers involving monomeric units containing only one stereocenter. In this case, *dyad*, *triad*, and higher sequences are defined (for statistical purposes) in terms of the orientation of every other stereocenter along the polymer chain (in accordance with an arbitrary breakdown of the polymer into monomeric units). Thus, the probability equations refer to isotactic sequences represented by *D*,L-*D*,L (or *L*,D-*L*,D) placements for *dyads*, *D*,L-*D*,L-*D*,L (*L*,D-*L*,D-*L*,D) for *triads*, syndiotactic sequences by *D*,L-*L*,D (*L*,D-*D*,L) for *dyads*, and so forth. We emphasize that the terminology *dyad* and *triad* (designated in this text by italics) bears no relation to the stereosequences dyad and triad which are observed by physical methods. The term *dyad* refers to the orientation of one inserted monomer with respect to the next; the term dyad refers to the orientation of any two consecutive stereocenters in the chain. To illustrate this distinction, we note that the isotactic *dyad* represented by *D*,L-*D*,L corresponds to the physically observed tetrad sequence **sss**.

Table 4. Sequence Correlations for Poly(*rac*-lactide)

tetrad stereosequence	insertion sequence
iii	*L*,L-*L*,L/*D*,D-*D*,D *L*,L-*L*,L-*L*,L/*D*,D-*D*,D-*D*,D
isi	*L*,L-*D*,D/*D*,D-*L*,L
sis	*L*,L-*D*,D-*L*,L/*D*,D-*L*,L-*D*,D
iis	*L*,L-*L*,L-*D*,D/*D*,D-*D*,D-*L*,L
sii	*L*,L-*D*,D-*D*,D/*D*,D-*L*,L-*L*,L

Table 5. Sequence Correlations for Poly(*meso*-lactide)

tetrad stereosequence	insertion sequence
sss	*L*,D-*L*,D/*D*,L-*D*,L *L*,D-*L*,D-*L*,D/*D*,L-*D*,L-*D*,L
sis	*L*,D-*D*,L/*D*,L-*L*,D
isi	*L*,D-*D*,L-*L*,D/*D*,L-*L*,D-*D*,L
ssi	*L*,D-*L*,D-*D*,L/*D*,L-*D*,L-*L*,D
iss	*L*,D-*D*,L-*D*,L/*D*,L-*L*,D-*L*,D

In Tables 4 and 5 are summarized the correlations of all possible tetrad sequences with the *dyads* and *triads* on which the statistical arguments are based, for poly(*rac*-lactide) and poly(*meso*-lactide), respectively. We note that for each polymer one tetrad sequence (**iii** or **sss**) can result from either a *dyad* or *triad* insertion sequence, one tetrad (**isi** or **sis**) can be formed only from a *dyad* insertion sequence, and three tetrads (**sis**, **iis**, **sii** or **isi**, **ssi**, **iss**) can only result from *triad* insertion sequences. Since a given *dyad* insertion sequence is twice as probable as any *triad* insertion sequence,[39] it is obvious that a Bernoullian statistical distribution of insertion sequences will result in a 3:2:1:1:1 distribution of probabilities for the observation of (for example) **iii**:**isi**:**sis**:**iis**:**sii** tetrads in poly(*rac*-lactide). Such a distribution is not observed. The discrepancy is attributed to end-group effects of the terminus of the growing polymer chain which impose an energetic preference for the insertion of one lactide enantiomer over the other.[9,28] If these effects are derived from the ultimate stereocenter of the polymer only, the resultant probability distribution of the observed stereosequences should be described by first-order Markovian statistics. If both the ultimate and penultimate stereocenters are involved, then second-order Markovian statistics should apply.

To evaluate the applicability of first- or second-order Markovian statistics, the observed ratios of line integrations can be used as solutions to the equations for *dyad* and *triad* insertion sequences as derived by Sepulchre[28,40] (for a given set of assignments) in order to calculate the probabilities of syndiotactic versus isotactic monomer insertion. We attempted to determine these probabilities using the tetrad stereosequence assignments we proposed,[23] but we could not obtain a unique solution to satisfy all the equations, indicating that our assignments could not be justified by Markovian statistics.

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(30) For example, if the stereochemistry of monomer insertion is dominated by interaction with the terminus of the growing polymer chain (that is, subject to end-group control), the resultant stereosequence distribution will not be Bernoullian. A situation could be envisaged wherein an *S*-terminated chain selects monomer of *R*-configuration (and vice versa), which would produce a bias toward **s** dyads in the resultant polymer. In this case, if the triad/pentad model is correct, one would expect the pentads **sisi** and **isis** to be statistically favored over **iisi** and **isii** in poly(*rac*-lactide) and an overall statistical relationship where **ii**:**iisi**:**sisi**:**isis**:**isii** = *X*:*Y*:*Z*:*Z*:*Y*. This roughly fits the spectral data in ref 9b. Similar arguments have been proposed in support of tetrad assignments. See ref 9a,b.

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