An alternative interpretation of the HETCOR NMR spectra of poly(lactide)

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An alternative to the assignments proposed recently by Chisholm *et al.* for the ^{1}H and ^{13}C NMR resonances of poly(lactide) based on their HETCOR spectra is presented; we find that the HETCOR spectra are consistent with older assignments of the tetrad and hexad stereosequence resonances in the ^{1}H and ^{13}C NMR spectra and we believe that the influence of adjacent chiral units on the NMR chemical shift extends asymmetrically and is opposite in the case of ^{1}H and ^{13}C nuclei; this is in contrast to the assumption that the observed chiral repeat unit for any particular stereosequence resonance is the same for ^{1}H and ^{13}C NMR spectra as used by Chisholm *et al.* in their analysis.

NMR spectroscopy has been shown to be an effective method for characterizing the stereosequence distribution in poly(lactide) (PLA) samples.[1,2] Homonuclear decoupled ^{1}H NMR and proton-decoupled ^{13}C NMR spectra have been used to explore the kinetics and predict the stereoisomer composition in PLA.[2–5] Recently, Chisholm *et al* have proposed an alternative set of stereosequence assignments for the ^{1}H and ^{13}C NMR resonances based on heteronuclear correlation (HETCOR) spectra for poly(*rac*-lactide) and poly(*meso*-lactide).[6] The nomenclature for stereosequence assignments of NMR resonances of PLA has been detailed in a number of previous reports.[1,2,6] Fig. 1 reproduces the spectra and assignments obtained for poly(*rac*-lactide) and poly(*meso*-lactide) from one of those reports.[2]

Chisholm *et al.* found cross-peaks between **sis** resonances in the ^{1}H NMR spectra and **isi** and **iss**/**ssi** resonance in the ^{13}C spectra in the HETCOR of poly(*meso*-lactide).[6] In the HETCOR of poly(*rac*-lactide), they found cross-peaks between the **sis** and **iis**/**sii** resonances in the ^{1}H spectra and the **isi** resonance in the ^{13}C spectra. Since these results appeared to contradict the previous assignments, they proposed a new set of stereosequence assignments. However, we believe these are inconsistent with the intensity distribution predicted from simple probability rules. For example, in the ^{13}C NMR spectrum of poly(*meso*-lactide), their assignment of the **isi** and **sis** resonances are reversed such that the **isi** resonance has a higher intensity than the **sis** resonance. The **sis** stereosequence is formed by isotactic addition of two *meso*-lactides, and should have a significantly larger intensity than the **isi** stereosequence, which requires two isotactic additions of three *meso*-lactide monomers. Under polymerization conditions such that no transesterification or epimerization occurs, the **sis** intensity should always be greater than the **isi** intensity.

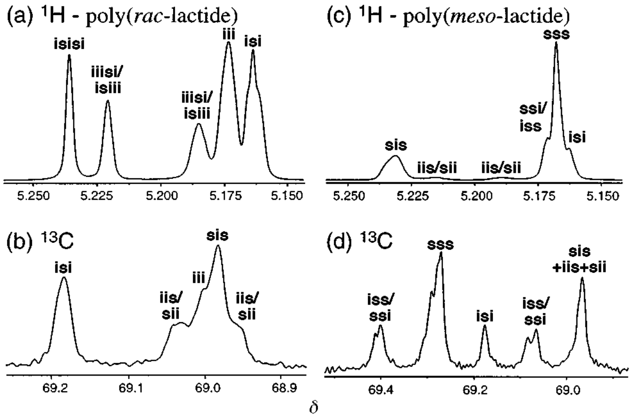

Fig. 1 Methine resonances in ^{1}H and ^{13}C NMR spectra of poly(*rac*-lactide) (a,b), and poly(*meso*-lactide) (c,d). The poly(*meso*-lactide) contained 6% *rac*-lactide as an impurity.

The observed nucleus in a resonance representing a tetrad (or hexad) stereosequence is from one of the two chiral repeat units at the center of the sequence. The tetrad sensitivity arises due to an asymmetrical extent of influence of adjacent chiral repeat units on NMR chemical shifts. If the influence were symmetrical, only triad or pentad stereosequence resonances would be observed in the NMR spectra. The cause of the asymmetrical influence in a tetrad stereosequence resonance in PLA is not known. It may be related to the presence of asymmetric repeat units having a carbonyl on one side and an ester oxygen on the other. It is also possible that the asymmetrical influence on the chemical shift in the ^{1}H NMR spectra is opposite as compared to the ^{13}C NMR spectra. The consequence is that the observed repeat unit for a given stereosequence resonance is not identical in the ^{1}H and ^{13}C NMR spectra, but are adjacent chiral repeat units at the center of the sequence. For example, in the stereosequence –*R**RS**S*–, represented by **isi**, the observed repeat unit could be either –***R***– or –***S***–. The HETCOR spectra reported by Chisholm *et al.* would result if in case of the ^{1}H NMR spectra the observed nucleus comes from –**R**, and in the case of the ^{13}C NMR spectra, the observed nucleus is from –*S*– (or *vice versa*). Our justification for the analysis of the specific cross peaks present in the HETCOR spectra of poly(*rac*-lactide) and poly(*meso*-lactide), based on the assumption of opposite asymmetrical influence for ^{1}H and ^{13}C NMR, follows.

In poly(*rac*-lactide), –*RRSSR*– and –*RRSSS*– sequences may be represented as **isi** adjacent to **sis** and **sii**, respectively. If in the ^{13}C spectra the observed repeat unit representing **isi** is –*S*–, this would appear in the ^{1}H NMR spectra as either **sis** or **sii** depending on which repeat unit (*R* or *S*) is adjacent to the **isi** stereosequence. Unfortunately, due to equal probability of occurrence, it is not possible to experimentally distinguish and identify the **iis** resonance from the **sii** resonance.[1,2,6] Hence as observed in the HETCOR, the **isi** resonance in ^{13}C NMR spectrum should have cross peaks with **sis** and one of the **sii**/**iis** resonances in the ^{1}H NMR.

In poly(*meso*-lactide), –*RRSSR*– and –*SRSSR*– are represented as **isi** and **ssi**, respectively, adjacent to a **sis**. Assuming a similar relationship as above, the –***S***– would appear as a **sis** in the ^{1}H NMR spectrum and either **isi** or **ssi** (not **iss**) in the ^{13}C NMR spectrum. And as observed in the HETCOR, the **sis** resonance in the ^{1}H NMR should have cross peaks with **isi** and one of the **ssi**/**iss** resonances in the ^{13}C NMR spectrum.

Table 1 shows the cross peaks expected to occur if the observed repeat unit in ^{13}C NMR is on the right side and in the ^{1}H NMR it is on the left side of the central two units for poly(*rac*-lactide), and Table 2 shows similar information for poly(*meso*-lactide). It is also possible that the reverse is true, *i.e.* the observed repeat unit in ^{13}C NMR is on the left side and in ^{1}H NMR is on the right side of the central two units. Owing to

Table 1 poly(*rac*-lactide); **ss** not possible

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

Table 2 poly(*meso*-lactide) **ii** not possible

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

limitations in the experimental data and equal probability of asymmetric stereosequences,[1,2,6] it is not possible to determine the direction of the asymmetric influence on ^{13}C and ^{1}H NMR chemical shifts. However, we have clearly shown that the asymmetric influence must be opposite in ^{13}C and ^{1}H NMR, and the observed repeat unit for a given stereosequence resonance is not identical in ^{13}C and ^{1}H NMR.

Further work is in progress to uniquely identify the direction of the asymmetric influence with respect to the molecular coordinates. These and other experiments using ^{13}C labeled PLA to conclusively identify the stereosequence resonances are in progress and will be reported in the near future.

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Notes and References

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