Concerning the stereochemistry of poly(lactide), PLA. Previous assignments are shown to be incorrect and a new assignment is proposed

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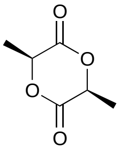
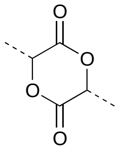
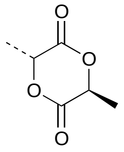
HETCOR NMR spectra reveal that previous assignments of the stereochemistry of poly(lactide) derived from *rac* and *meso*-lactide are incorrect; an alternative assignment is made at the tetrad level of resolution.

Poly(lactide), PLA,[1] and its co-[2] and ter-polymers[3] provide an important class of biodegradable and biocompatible polymers with wide ranging applications from bulk commodity materials (Ecochem®)[4] to specialty medicinal products such as sutures, staples, fibers and rods (Dexon® and Vicryl®),[4] drug delivery agents (Leupron Depot® and Zoladex®)[5] and artificial tissue matrices.[6] The specific properties of these polymers relate directly to their microstructure and the latter is thus of considerable importance.[7] PLA is typically produced by ring-opening polymerization of the lactide cyclic dimers shown below by catalyst precursors such as tin octoate,[8] Bu$_3$SnOMe[9] and Al(acac)$_3$[10] which allow for little kinetic selectivity in the ring-opening process. Attempts to establish the stereochemical microstructure of PLA have been based on NMR studies and Bernoullian statistics.[1a,2,10,11] Work has proceeded to infer stereochemical preferences in polymerization processes and by going to higher magnetic field strengths assignments of ^{1}H and ^{13}C{^{1}H} chemical shifts have been extended from the tetrad to the hexad level.[12] It is the purpose of this work to correct an error in the assignment of the microstructure and therefore to halt the propagation of errors relating to continuing studies of this polymer and assumptions and claims concerning stereo-preferential polymerizations.[11c,12,13]

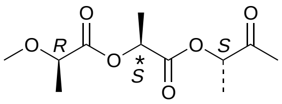

SS or L-lactide


RR or D-lactide

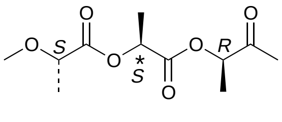

RS or *meso*-lactide

In considering this polymer it is important to recognize that the ring opening of either an L- or D-lactide unit will generate an isotactic junction whereas opening a *meso*-lactide unit forms a syndiotactic unit. Thus at the triad level poly(L-lactide) and poly(D-lactide) will be denoted **ii** but polymerization of either racemic (50 : 50 D and L lactide) or *meso*-lactide will, in addition, contain both **si** and **is** units and unlike a poly(α-alkene) or poly(vinyl acetate) these two are not equivalent as shown below.†

si

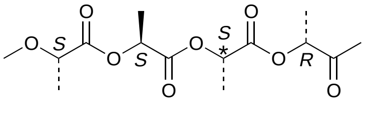


is

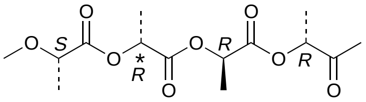


At the tetrad level of assignment of PLA we are faced with the situation that the chemical shift of a given carbon or proton must be influenced by the stereochemistry of the polymer as read two to the left and one to the right, or two to the right and one to the left. There will always be ambiguity over the assignment **iis**/**sii**, shown below, because Bernoullian statistics renders them equivalent.

iis



sii



All previous assignments of PLA have followed from the work of Kriechldorf *et al.*[11a] based on (1) the homodecoupled methine proton and carbon resonances of polymers derived from the polymerization of *rac*- and *meso*-lactide and various mixtures thereof and (2) the assumption of Bernoullian statistics in polymer formation.[11b,c] These assignments of poly(*rac*-lactide) and poly(*meso*-lactide) are shown schematically in Fig. 1. In the absence of epimerization, which is effected by strong bases such as KOBu^t, poly(*rac*) will contain only **iii**, **iis**, **sii**, **sis** and **isi** tetrads whereas poly(*meso*) will be comprised of **sss**, **ssi**, **iss**, **sis** and **isi**. Thus common to both polymers are tetrad units **sis** and **isi**.

The assignments of **iii**, which can be identified independently from polymerization of either pure L-or pure D-lactide, and **sss**, which is favored statistically by polymerization of *meso*-lactide are correct but as shown by the HETCOR NMR spectra in Figs. 2 and 3 others are incorrect. The HETCOR spectra

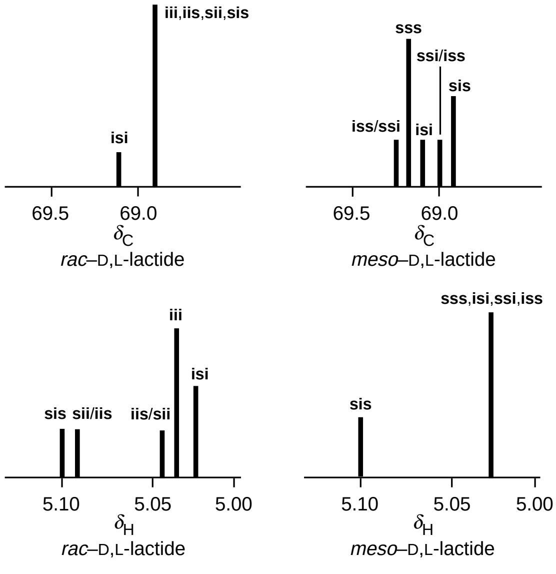


Fig. 1 Schematic representation of the currently accepted assignments (CH) for PLA at the tetrad level following from ref. 11(*a*)

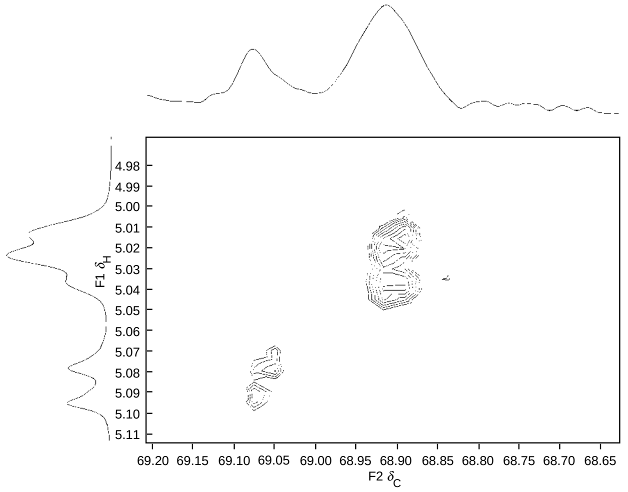


Fig. 2 HETCOR spectrum showing the correlation of the homodecoupled methine protons with the methine carbon signals, $^{13}C\{^{1}H\}$, of poly(*rac*-lactide) in $CDCl_3$, 27 °C, recorded on a Brüker AM 500

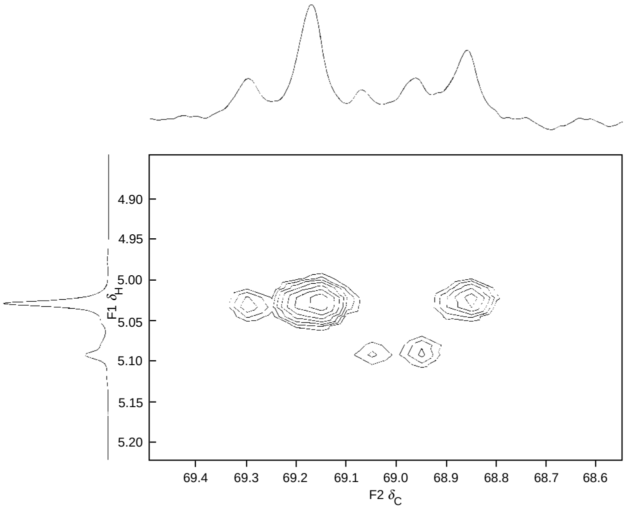


Fig. 3 HETCOR spectrum showing the correlation of the homodecoupled methine protons with the methine carbon, $^{13}C\{^{1}H\}$, signals of poly(*meso*-lactide) in $CDCl_3$, 27 °C, recorded on a Varian I 400

correlate the homodecoupled methine protons with the methine carbons. We propose the alternate assignments shown in Fig. 4.

We have worked at field strengths of 400, 500, 600 and 750 MHz (^{1}H) and also employed long range HETCOR experiments. As other workers[12] have pointed out with higher magnetic field strengths resolution at the hexad level becomes possible but only when the correct assignment at the tetrad level is made will this be meaningful and useful in terms of microstructural analysis and in stereochemical preference in polymer formation, *i.e.* kinetic resolution of propagating steps. Work is in progress to elucidate further the microstructure of this polymer and to introduce stereospecificity into the polymer by use of chiral catalysts.

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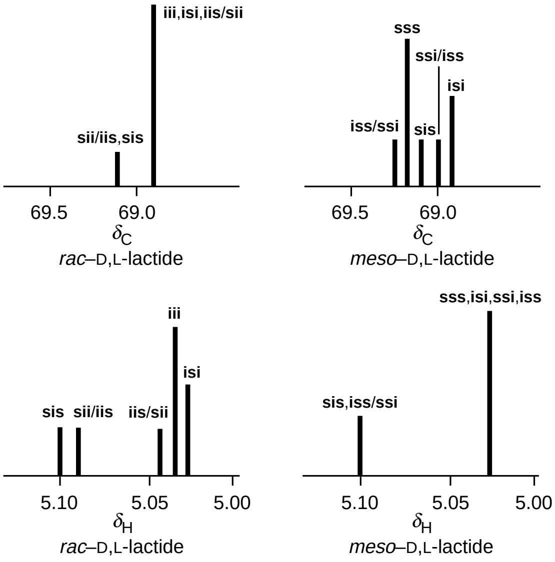

Fig. 4 Proposed assignments for PLA at the tetrad level based on the HETCOR NMR spectra shown in Figs. 2 and 3

Footnotes and References

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† While the normal representation of m and r can be used in the polylactide system, the authors would like to spare the reader of the possible confusion arising from this nomenclature as the monomers used are also m(eso) and r(acemic). For this reason we choose to use **i** (isotactic) and **s** (syndiotactic).

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4 Ecochem® is a polylactide based packaging material developed by DuPont ConAgra.

5 Dexon®, Vicryl®, Leupron Depot® and Zoladex® are products of Davis & Geek Corporation, Wayne, New Jersey; Ethicon, Inc., Somerville, NJ; Takeda Chemical Industries, Ltd., Japan, and Zeneca Pharmaceuticals, respectively. The first two are biodegradable sutures and Leupron Depot® is a drug delivery system.

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