Determination of the Enantiomeric Purity of Compound Chiral by Virtue of C-13 Labelling

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Summary Suitable chiral additives can render non-equivalent the n.m.r. spectra of the enantiomers of compounds chiral by virtue of ^{13}C labelling, thereby allowing direct determination of the enantiomeric purities of these isotopic chiral compounds.

RECENTLY, the optical rotation of a sample of chiral [$^{12}CH_2$]benzyl [$^{13}CH_2$]benzyl sulphoxide (**1**) of high but unknown enantiomeric purity has been reported.[1]† We describe a means for the direct determination of the enantiomeric purity of this sulphoxide and illustrate the method by the determination of the enantiomeric purity of dimethyl sulphoxide (DMSO), chiral by virtue of ^{13}C labelling. The method, although not necessarily the experimental details, is general in principle for compounds chiral by virtue of ^{13}C substitution.

Treatment of an unequal (21% diastereoisomeric purity) mixture of the diastereoisomeric [(*R*) configuration at sulphur in excess)] (−)-menthyl methanesulphinates with 45% enriched [^{13}C]methylmagnesium iodide affords (*R*) enriched $^{13}CH_3SOCH_3$. The ^1H n.m.r. spectrum of this material in $CFCl_3$ shows a sharp singlet at δ 2·60 arising from the $^{12}C^{12}C$ component. The $^{13}C^{12}C$ sulphoxide shows four quartets centred at δ 2·60 arising from short- and long-range ^{13}C–H couplings (138 and 4·6 Hz) and H–H coupling (0·45 Hz). Upon addition of a *ca.* sixfold excess of (*R*)-

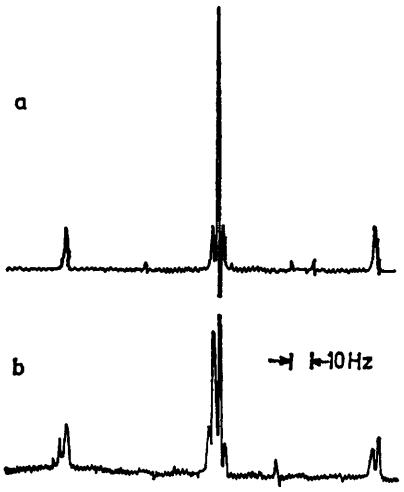

FIGURE. Partial 100 MHz ^1H n.m.r. spectrum of (*R*)-enriched $^{13}CH_3SOCH_3$ in: (a) $CFCl_3$; (b) $CFCl_3$ with added (*R*)-(−)-2,2,2-trifluorophenylethanol (**2**).

† An effort was made to estimate the diastereotopic purity of the sulphinate precursors of (**1**) since, in the event of total conversion of the sulphinates into (**1**), the diastereoisomeric and optical purities correspond. Since the cost of ^{13}C enriched Grignard reagents may preclude their use in large excess, kinetic differences may cause the two ratios to differ (*e.g.* see ref. 2).

(—)-2,2,2-trifluorophenylethanol (**2**),[2] the methyl groups in the [^{12}C,^{12}C] DMSO become diastereotopic[3] (δ 2·49 and 2·51) and each of the four quartets of the [$^{13}C^{12}C$] DMSO is doubled since the enantiomers now have non-identical chemical shifts ($\Delta\delta$ 0·02 p.p.m.). While the inner quartets of the [$^{13}C^{12}C$] enantiomers partially overlap the two central $^{12}C^{12}C$ multiplets, the outer quartets of the enantiomers clearly show intensity differences which indicate the sample had an enantiomeric purity of 18%. As expected in the presence of (*R*)-(**2**), the outer resonances of the (*R*)-sulphoxide enantiomer occur at higher field than those of the (*S*)-enantiomer.[4] The converse is true for the inner resonances. The Figure shows this spectrum under resolution conditions such that the weak proton–proton couplings are not completely resolved.

The 9-(10-methylanthryl) analogue of (**2**) affords larger nonequivalence magnitudes than does (**2**) (*e.g.* 0·08 p.p.m. for DMSO) and causes marked doubling ($\Delta\delta$ 0·16 p.p.m.) of the AB multiplet normally observed for the methylene protons of dibenzyl sulphoxide in $CDCl_3$. The presence of ^{13}C in either of the now diastereotopic methylene groups would cause strong ^{13}C–**H** splitting and, as in the case of DMSO, determination of the enantiomeric purity of isotopically chiral (**1**) reduces to determination of the relative intensities of the two AB patterns in either the high- or low-field set of ^{13}C satellites.

The method just described is not restricted to sulphoxides but will, in general, be applicable to any compound in which resonances of ^{13}C-coupled nuclei enantiotopic‡ by internal comparison show chemical shift nonequivalence as they become diastereotopic in the presence of a chiral additive[3,5] or derivatizing agent.

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‡ Enantiotopic, that is, in the absence of ^{13}C labelling.

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