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DETERMINATION OF OPTICAL PURITY AT ISOTOPICALLY CHIRAL SITES BY ^{2}H NMR

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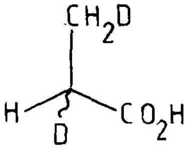
Abstract Techniques have been developed which permit the direct analysis of optical purity in α-deuterated amines and carboxylic acids.

A study of the asymmetric hydrogenation of monosubstituted olefins[1] by rhodium phosphine complexes required efficient methods for the analysis of optical purity in α-deuterated amides and carboxylic acid derivatives. Traditionally, the estimation of enantiomeric excess in compounds chiral by virtue of deuterium substitution has been carried out by chiroptical methods[2]. Because of the low rotations involved and generally weak CD spectra such methods are fraught with difficulty and may give misleading or erroneous results. α-Deuterated benzyl alcohols may be directly assayed by NMR using chiral shift reagents[3] but this method is not applicable in other cases. A number of chiral deuterated compounds form cholesteric mesophases in admixture with nematic solutions[4]; where applicable this may prove to be a valuable method. We report the direct observation of optical purity by ^{2}H NMR employing methods of wide applicability, based on simply prepared derivatives.



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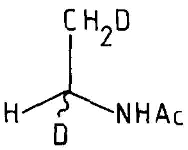

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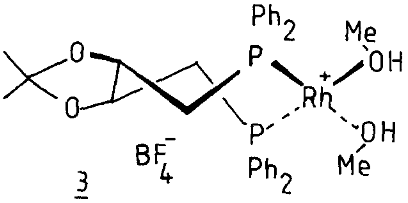

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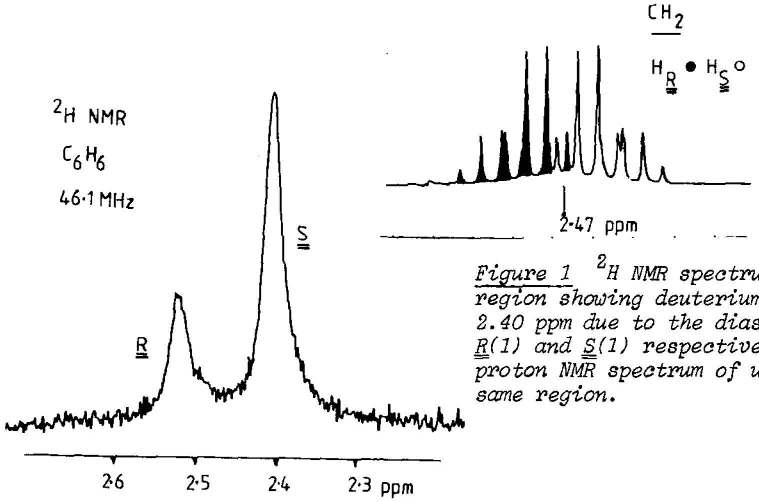
Compounds (1) and (2) were prepared by the addition of deuterium to propenoic acid and N-vinylacetamide. With DIOP-Rh$^+$ (3) as catalyst in methanol solution reductions were carried out on a sufficient scale to measure the optical rotations of product and hence absolute configurations by literature comparison[5,6]. Deuterated propenoic acid was converted into its methyl mandelate ester (4) by reaction with S methyl mandelate in CH_2Cl_2 promoted by DCC, and catalysed by 4-dimethyl-aminopyridine[7] at 0°. This procedure was demonstrated to induce $< 3\%$ of deuterium loss at C2, and by inference a similarly small extent of racemisation. The product was purified by preparative t.l.c. and examined directly by ^{2}H NMR in C_6D_6 with broad-band proton decoupling. The deuterium resonance at C2 in the RS-diastereomer of (4) is 0.12 p.p.m. downfield from the corresponding signal in the SS-diastereomer, and baseline resolution of the two peaks is readily obtained. Since ^{2}H spin-lattice relaxation times are relatively short[8], the optical purity may be obtained directly by integration of the spectrum. In this manner the optical yield for reduction of propenoic acid and its tetramethylammonium salt by a range of chiral rhodium catalysts was obtained, a typical spectrum being shown in Figure 1.



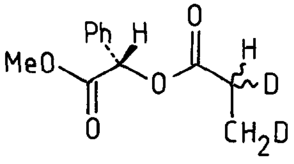


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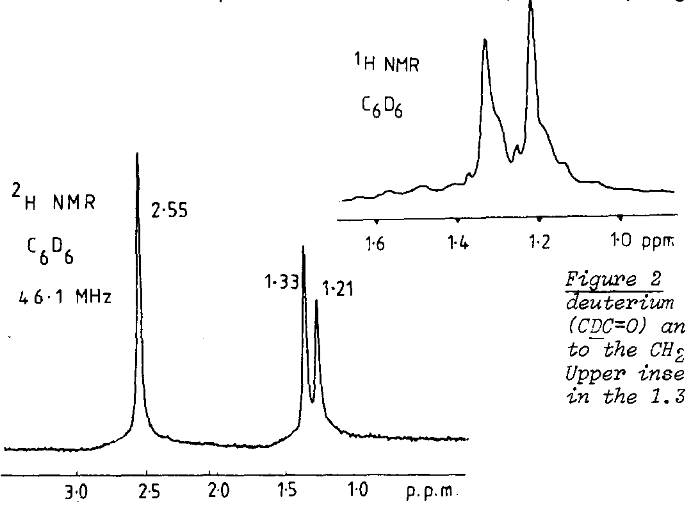
Figure 1 *^{2}H NMR spectrum of (4) in the 2.5 ppm region showing deuterium resonances at 2.52 and 2.40 ppm due to the diastereomers derived from R(1) and S(1) respectively. Upper inset is the proton NMR spectrum of undeuterated (4) in the same region.*

Deuterium NMR may also be used to determine the optical purity of 2,3,[^{2}H]$_2$ iso-butyric acid; Figure 2 shows the spectrum of (5) derived by asymmetric reduction of tetramethylammonium methacrylate with deuterium, and reaction of the product with S-methyl mandelate as before. Deuterium substitution in the two diastereotopic methyl groups is clearly distinguished by their 0.12 p.p.m. chemical shift separation. In contrast the 'H NMR spectrum of (5) at 300 MHz is considerably broadened in the 1.3 p.p.m. region because of deuterium isotope shifts and deuterium-proton coupling.



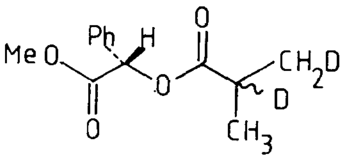


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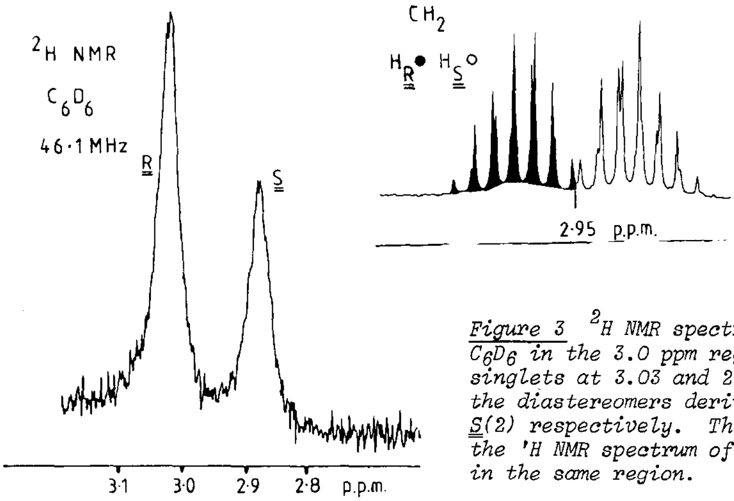
Figure 2 *^{2}H NMR spectrum of (5) showing deuterium resonances at 2.55 p.p.m. (CDC=O) and at 1.33 and 1.21 p.p.m. due to the CH$_2$D-groups of the two diastereomers. Upper inset is the proton NMR spectrum of (5) in the 1.3 ppm region.*

The optical purity of α-deuterated amines (and by implication α-deuterated amides) may also be determined by ^{2}H NMR, as exemplified by (2)[9]. Conversion of (2) into deuterated ethylamine hydrobromide was effected by refluxing 40% HBr (18 h.) and the product reacted with (-) camphanoyl chloride[10] (NEt_3, CH_2Cl_2, -10°), giving (6), m.p. 92-4° after sublimation. The proton NMR spectrum of (6) in the CHD region (C_6D_6) exhibits overlapping multiplets for the CH-protons in separate diastereomers, whereas the deuterium NMR spectrum of (6) has two distinct singlets separated by 0.15 p.p.m. and again the optical purity may be directly determined by integration (Figure 3).

In the original paper[10], (-) camphanoyl chloride was employed to determine the optical purity of α-deuterated alcohols, by proton NMR, but H_R and H_S multiplets were only separated on addition of 35 mol % Eu $(dpm)_3$. Application to α-deuterated amines was intimated[10], but never published. The reagent was subsequently employed[11] in estimation of ^2H-glycine, and here deuterium decoupling was necessary to effect sufficient separation of H_S and H_R for proton NMR determination.

The present method is rapid, direct, and likely to be of general utility[12] in chemical and biochemical estimation of optical purity at HCDXY chiral sites. Determination of optical purity by ^2H NMR has not been carried out previously although chemical shift inequivalence of diastereotopic CD_2 groups has been observed[13].



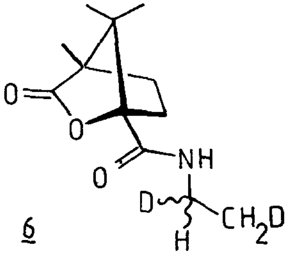


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Figure 3 ^2H *NMR spectrum of (6) in* C_6D_6 *in the 3.0 ppm region showing singlets at 3.03 and 2.88 p.p.m. due to the diastereomers derived from R(2) and S(2) respectively. The upper inset is the* ^1H *NMR spectrum of undeuterated (6) in the same region.*

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