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Visualization of enantiomers in cholesteric solvents through deuterium NMR

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Visualization of enantiomers in cholesteric solvents through deuterium NMR

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Proton decoupled deuterium NMR of mixtures of enantiomers in homogeneously oriented cholesteric solvents produces simple spectra with linewidths of 10 to 50 Hz in cases where the proton spectra would give second order patterns so complicated as to defy analysis. The chiral solvent orders each of a pair of enantiomers differently which results in a difference in the residual quadrupolar coupling constant yielding well resolved spectra for each enantiomer. That the technique constitutes a new tool for measurement of enantiomeric ratios is illustrated using several chiral benzylic alcohols.

This laboratory has recently reported a new cholesteric mixture whose helix axis orients homogeneously, parallel to the magnetic fields commonly used in NMR experiments [1]. It is made of a 1·35/1 by weight ratio of cholesteryl propionate and a eutectic mixture of bicyclohexyl derivatives, purchased from Merck under the trade name ZLI 2806. Among the unique features of this anisotropic solvent are: (1) it orients almost as fast as a nematic solvent; (2) it orients homogeneously with its helix axis parallel to the magnetic field on a macroscopic scale in such a way that the proton linewidth is typically 2 to 3 Hz as for nematic solvents; (3) it gives different dipolar spectra for each of a pair of dissolved enantiomers. These effects have been demonstrated using a three proton chiral molecule, 1,1,1-trichloro-2,3-epoxypropane, whose spectrum is reproduced in figure 1 together with the simulated spectra of both enantiomers using the parameters listed in table 1.

Even though this new tool is much more effective than that previously reported [2] for obtaining separate spectra of enantiomers, it will be severely limited for proton NMR because the spectra of even fairly simple chiral molecules will be too complicated to be analysed. This now classical limitation of NMR in liquid-crystalline solvents may be seen in figure 2 which shows the six spin proton spectrum of racemic epoxypropane dissolved in the cholesteric solvent. How could we say with certainty whether this spectrum is that of a pair of enantiomers or not? It is the purpose of this preliminary communication to show that deuterium NMR overcomes this limitation.

Examination of table 1 shows that the only parameters which change from one enantiomer to the other are the dipolar couplings. The chemical shifts and the scalar

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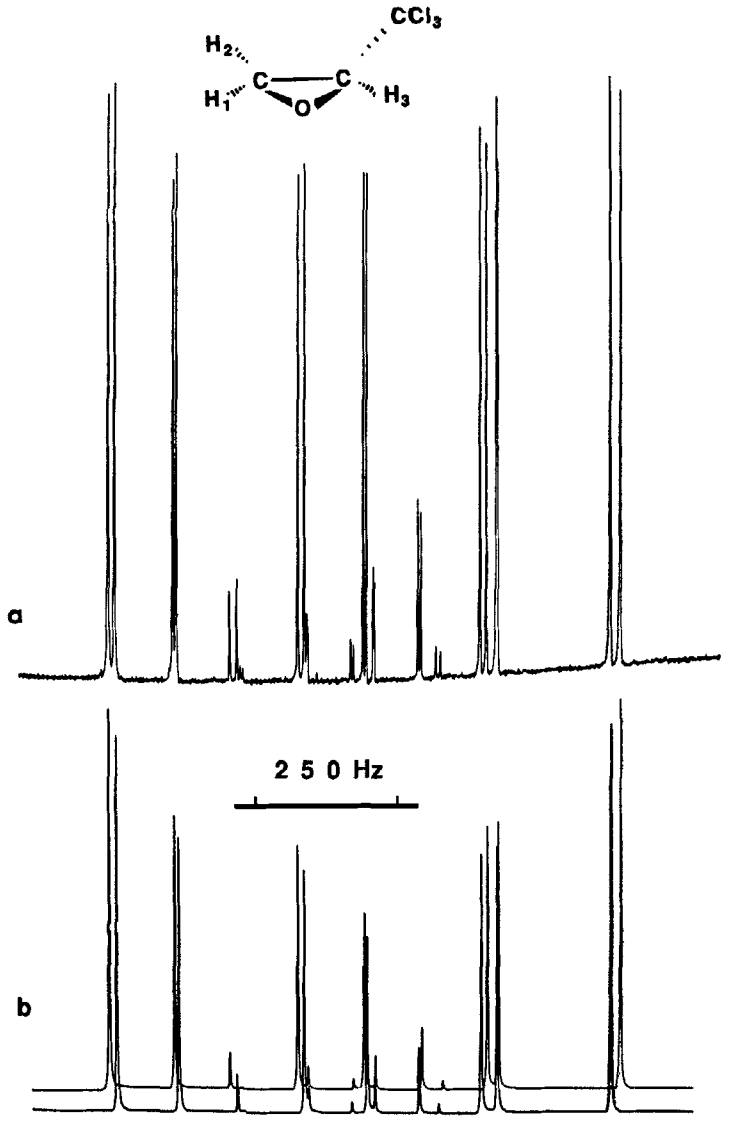

Figure 1. (*a*) 250 MHz proton spectrum of racemic 1,1,1-trichloro-2,3-epoxypropane in the homogeneously aligned cholesteric solvent described in the text. (*b*) Simulated spectra of both enantiomers using the parameters in table 1.

Table 1. Parameters of the spin hamiltonian for racemic 1,1,1-trichloro-2,3-epoxypropane approximately 2 per cent by weight in the cholesteric solvent described in the text. The values given result from a fit of calculated transition frequencies for each enantiomer to the observed spectrum. The scalar couplings have been locked to their isotropic values of 4·66, 2·15 and 3·65 Hz for J_{12}, J_{13} and J_{23} respectively, and the chemical shift of proton 1 has been taken as an arbitrary zero reference. The r.m.s. error was 0·4 Hz in each case. The experimental and calculated spectra are shown in figure 1.

	Chemical shifts/Hz			Dipolar couplings/Hz		
	ν_1	ν_2	ν_3	D_{12}	D_{13}	D_{23}
One enantiomer	0·0	−5·5	144·2	−135·1	221·0	−20·4
The other enantiomer	0·0	−5·1	144·1	−123·9	216·4	−23·1

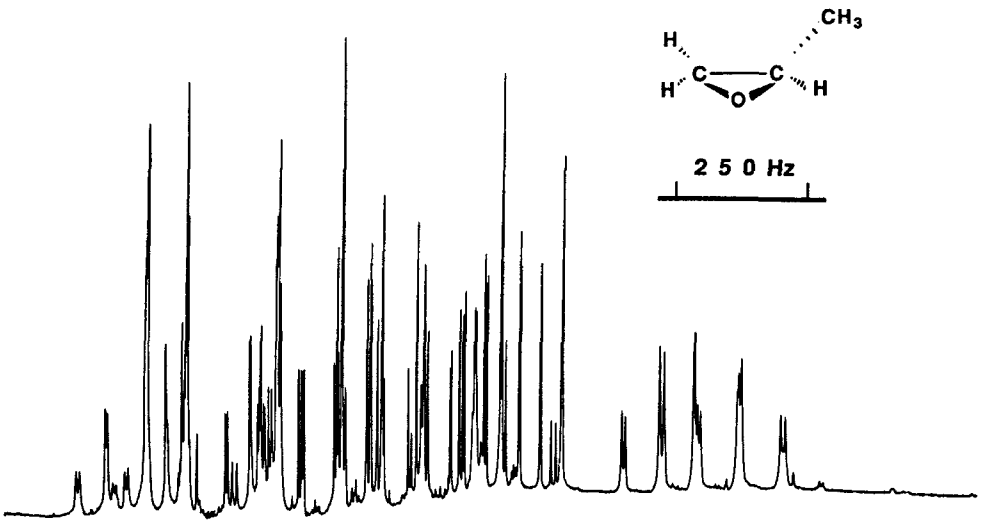

Figure 2. 250 MHz proton spectrum of racemic epoxypropane in the homogeneously aligned cholesteric solvent described in the text.

couplings are the same to within the experimental error. Furthermore, it is well known that the dipolar coupling is directly proportional to the ordering matrix and inversely proportional to the cube of the distance between the coupled nuclei. Neglecting any difference in conformation between enantiomers [3, 4] the internuclear distances can be assumed to be the same in each molecule. So the spectral differences have to be ascribed to the ordering matrices which are different for each optical isomer in this cholesteric solvent. In this context it becomes evident that the residual quadrupolar splitting of the resonance from a single quadrupolar nucleus should also be different for each of two enantiomers, since it depends on the ordering matrix according to [5]

$$\Delta = \frac{1}{2I(I+1)} Q_c [3S_{aa} + \eta(S_{bb} - S_{cc})],$$

where Δ is the quadrupolar splitting, Q_c is the quadrupolar coupling constant, η is the asymmetry parameter of the quadrupolar coupling tensor, and the S_{ii} are the elements of the ordering matrix in the principal axis system of the electric field gradient tensor. The notation is the same as that used in [5]. Thus, the ordering matrices associated with the electric field gradient would be expected to be different for each of two optical isomers, and, consequently, Δ would be different.

Deuterium NMR should be well suited for such an experiment as the transitions are known to be quite narrow if broadband proton decoupling is used to eliminate the numerous proton–deuterium dipolar couplings which would broaden the lines. Furthermore it is known that the residual quadrupolar couplings are usually one to two orders of magnitude greater than the dipolar couplings. So deuterium NMR should provide a more sensitive method than NMR of a spin 1/2 nucleus. Additionally, only one deuterium in a molecule is required to produce the effect instead of at least two as is the case when studying dipolar coupling constants.

This technique is now illustrated using, as examples, some chiral benzyl alcohols. Figure 3 (*a*) shows the 76·728 MHz deuterium NMR spectrum of a racemic mixture of *o*-CH_3–C_6H_4–CDOH–CH_3 dissolved in the cholesteric solvent at 80°C using 3 W

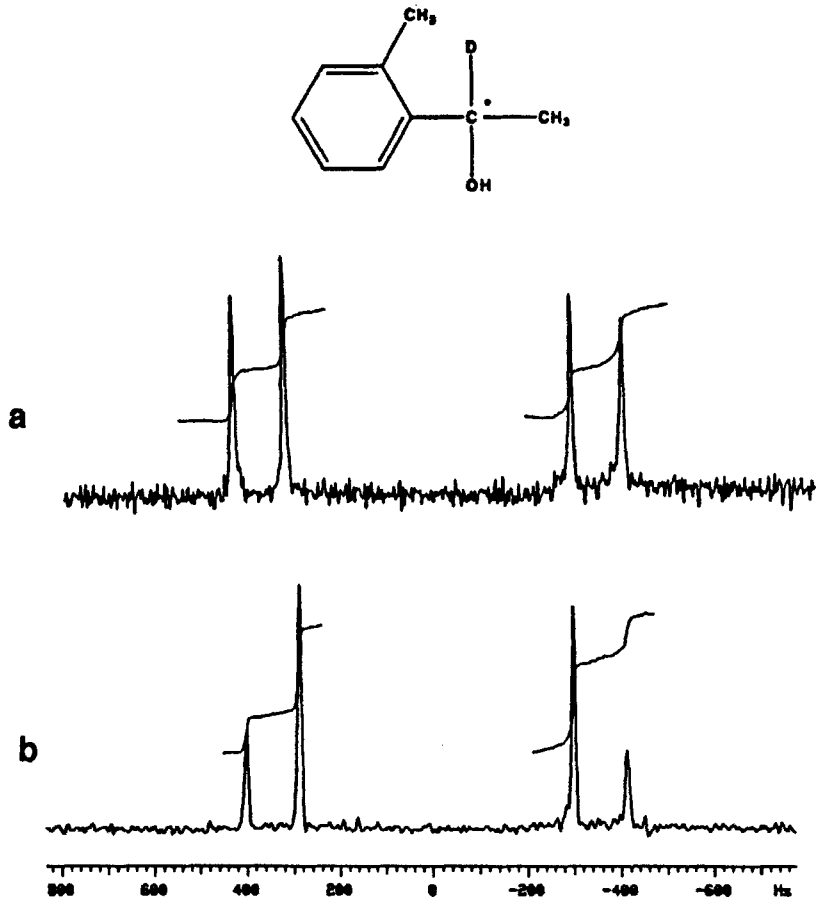

Figure 3. (*a*) Proton decoupled deuterium NMR spectrum (76·728 MHz) of racemic *o*-CH_3–C_6H_4–CDOH–CH_3 in the homogeneously aligned cholesteric solvent described in the text. (*b*) Same as spectrum (*a*) but with 70 per cent of the R enantiomer and 30 per cent of the S configuration. The residual quadrupolar slitting are 334 and 444 Hz for the R and the S isomers respectively.

of proton decoupling power with WALTZ-16 modulation to produce broadband decoupling. Clearly there are two quadrupolar doublets, one from each enantiomer. In order to establish the effect more certainly and to be able to know which signal belongs to the R and which to the S isomers a similar sample was prepared with 70 per cent of the R enantiomer and 30 per cent of the S following a standard procedure [6]. The spectrum obtained under the same conditions as for the racemic mixture is shown in figure 3 (*b*). Obviously the S isomer is more oriented than the R; the quadrupolar splittings differ by 28 per cent. Integration of the spectrum yields a ratio of 69 per cent R and 31 per cent S, which is in good agreement with the expected ratio. Clearly this method can be used to measure relative concentrations of enantiomers with a high accuracy.

In order to illustrate the generality of this effect the deuterium spectra of C_6H_5–CDOH–CH_3 60 per cent enriched in the R enantiomer and of racemic mixtures of *m*-CH_3O–C_6H_4–CDOH–CH_3 and C_6H_5–CDOH–CF_3, taken using the same

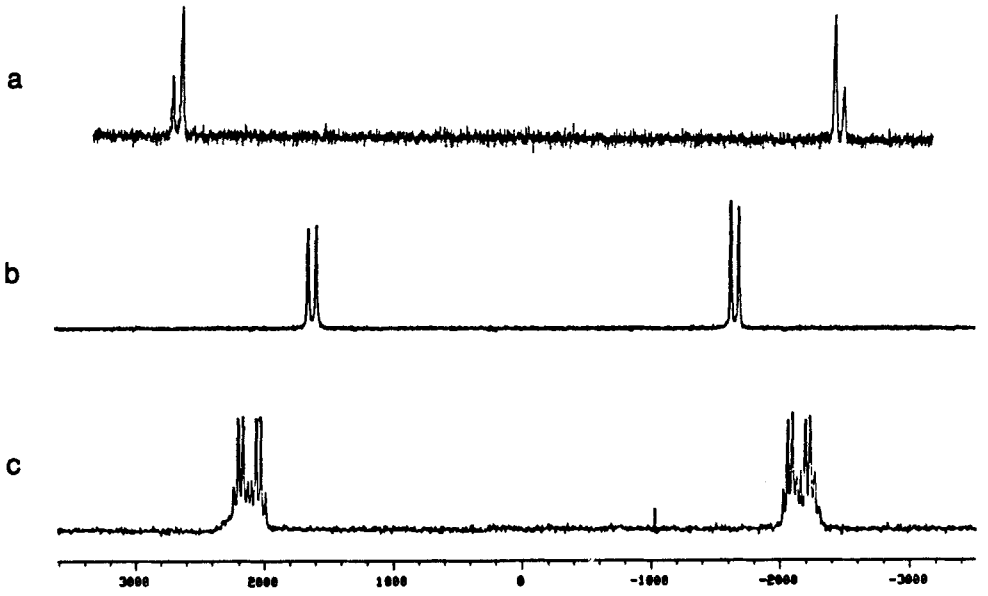

Figure 4. Broadband proton decoupled deuterium spectra of C_6H_4–CDOH–CH_3 60 per cent enriched in the R enantiomer (*a*), and of racemic mixtures of *m*-CH_3O–C_6H_4–CDOH–CH_3 (*b*), and C_6H_5–CDOH–CF_3 (*c*) dissolved in the homogeneously aligned cholesteric solvent described in the text.

Table 2. Deuterium quadrupolar splitting of each enantiomer of various compounds together with the relative percentage difference.

Compounds	Quadrupolar splitting/Hz		Difference/per cent
C_6H_5–CDOH–CH_3	4816(R)	4934(S)	2·42
o-CH_3–C_6H_4–CDOH–CH_3	334·5(R)	444·5(S)	28·21
m-CH_3O–C_6H_4–CDOH–CH_3	3216	3390	5·24
C_6H_5–CDOH–CF_3	4128	4401	6·10

conditions are shown in figure 4. The difference in the quadrupolar splitting between enantiomers varies greatly from one compound to the other as can be seen in table 2. Figure 4 (*c*) shows that the residual dipolar couplings between the three equivalent fluorines and the deuterium nucleus is 35·8 Hz for both enantiomers indicating that the effect of differential ordering on these interactions is too small to be observable. In figure 4 the deuterium lines are 30 to 40 Hz wide, substantially greater than would be expected based on the proton linewidths. This may be due to temperature gradients across the sample, insufficient decoupling power or quadrupolar relaxation effects.

It has been shown that proton decoupled deuterium NMR provides a convenient and efficient way to overcome the limitations encountered in proton NMR of chiral molecules in homogeneously aligned cholesteric solvents. This should provide a new and very effective tool to measure relative concentrations of enantiomers. The data indicate that the difference in orientation from one enantiomer to the other varies greatly even among fairly similar compounds. A systematic study on a large number of chiral compounds is presently underway in this laboratory in order to look for a possible relationship between the relative orientation and the absolute configuration of a chiral molecule.

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