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CYCLODEXTRINS AS CHIRAL NUCLEAR MAGNETIC RESONANCE SHIFT REAGENTS

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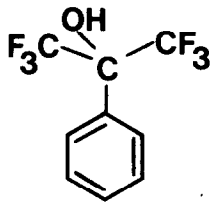
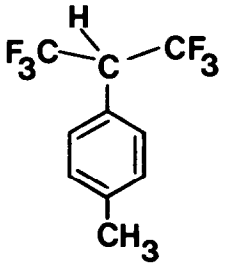
Although chemical shift non-equivalence between enantiotopic[1] groups in n.m.r. spectra has often been observed employing optically active solvents[2] or chiral lanthanide shift reagents,[3] or when a substrate is complexed to a chiral crown compound,[4] such methods are normally critically dependent upon suitable substrate functionality. We now report that guest binding within the chiral cavity of β-cyclodextrin in D_2O provides a method[5] for inducing ^{19}F n.m.r. chemical shifts between the prochiral CF_3 groups of compounds (1) and (2), it being particularly noteworthy that the latter molecule lacks the type of functional group usually required for such chiral effects.

Under conditions of proton noise-decoupling, the ^{19}F n.m.r. spectrum[6] of (1) in D_2O shows a single line. However, in the presence of β-cyclodextrin, β-CD (a torus-shaped molecule consisting of seven α-1,4-linked D-glucopyranose units with a central chiral void of approximate



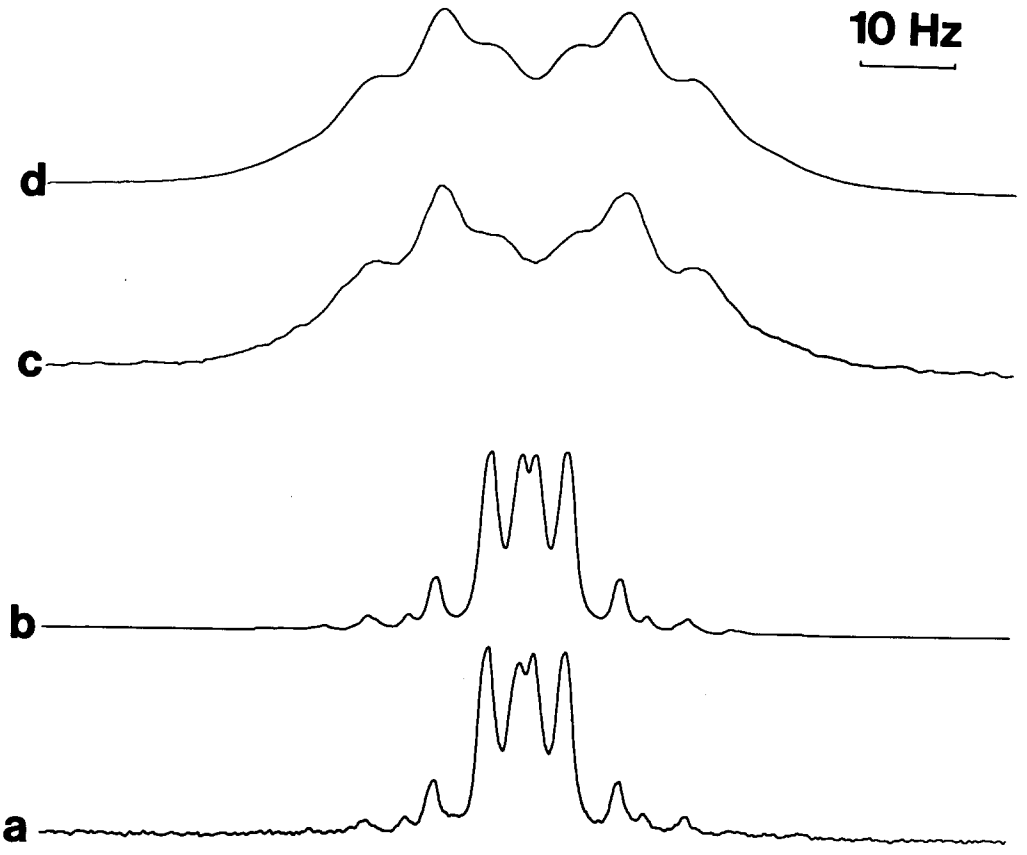
(1)



(2)

internal diameter 7.5 Å), a marked splitting of the fluorine resonance of (1) is observed, Figure (a). Computer simulation[7] as an A_3B_3 spin system, Figure (b), clearly establishes the induced non-equivalence of the CF_3 groups. Qualitatively we have found that either decreasing the temperature or increasing the proportion of β-CD to substrate causes an increase in shift. However, a more effective way of producing increased shifts is the addition of suitable salts to the solution. Thus, for 0.01M β-CD and 0.01M (1), the induced shift is 11.4 Hz at 75°, and this gradually increases with increasing sodium chloride concentration until it is 16 Hz at ca. 5M NaCl which is near the limit of saturation. However, lithium chloride offers advantages, being more soluble than sodium chloride, and improving the solubility of the β-CD complex, thereby enabling spectra to be obtained at ambient temperature. For the above concentrations of β-CD and (1), the induced shift is approximately doubled by the presence of 11M LiCl..

FIGURE



(a) Proton noise-decoupled ^{19}F n.m.r. spectrum of a D_2O solution containing 0.01M β-CD and 0.006M (1) at 50°.

(b) A_3B_3 spectrum calculated with ν(A-B)=13.8 Hz, J(AB)=8.9 Hz, and line-width=1.2 Hz.

(c) As (a), but solution contains 0.01M β-CD, 0.01M (1), and 11M LiCl at 25°.

(d) As (b), but with ν(A-B)=26.0 Hz, J(AB)=8.0 Hz, and line-width=6.5 Hz.

Observed and calculated spectra for the solution containing LiCl are shown in Figures (c) and (d) respectively; adequate simulation of the observed spectrum was found to be possible only by significantly increasing the line-width and decreasing the fluorine-fluorine coupling constant compared to Figure (b). Possible factors involved in this salt effect are "salting out" causing a higher proportion of the guest to be situated in the cavity, and a structural change in the complex reflecting modifications of the aqueous medium.

The hydroxyl function of (1) is not essential, as was shown by studying (2), a hexafluoro-analogue of p-cymene. For example, a solution containing 0.01M (2) and 0.02M β-CD in D_2O at 80° showed a chemical shift between the CF_3 groups of ca. 0.1 p.p.m.

Groups which are enantiotopic in external comparison[1] may also be distinguished. For a D_2O solution 0.045M in α-cyclodextrin (the analogue of β-CD with six D-glucopyranose units) and 0.015M racemic (±)-1-phenyl-2,2,2-trifluoroethanol, $CF_3CH(C_6H_5)OH$, the enantiotopic fluorine splitting was 4.3 Hz at 23°. Addition of the S(+)enantiomer of this alcohol, shows that its CF_3 resonance occurs at higher field.

The possibility of producing enantiotopic shifts in (1) and (2) using other methods was investigated, but no shifts were perceptible for (1) with 3M D-glucose in D_2O, or for (1) and (2) with 0.3 mole ratio of tris-[3-(trifluoroacetyl)-d-camphorato]-europium(III) in $CDCl_3$.[8] Despite previous reports of paramagnetic lanthanide ions causing shifts in methyl glycosides,[9] addition of Eu^{3+} or Pr^{3+} did not cause significant changes in the enantiotopic splittings of the guests (1) and (2) in β-CD. An attractive possibility under investigation is to employ structurally modified cyclodextrins where lanthanide ions may be tightly bound to the skeleton thereby amplifying the induced guest shifts.

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6. All ^{19}F n.m.r. spectra were measured at 94.15 MHz on a Varian XL-100 instrument in the pulsed Fourier transform mode with proton noise-decoupling.

7. Spectra were calculated using the n.m.r. simulation program SIMEQ II written for the Varian XL-100 FT system by Dr. C.W.F. Kort and Dr. M.J.A. de Bie.

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