Use of Differential Solvent Shifts in Nuclear Magnetic Resonance

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Summary In compounds containing a methyl group β to a hydroxy-group, an estimate of the dihedral angle between them can be obtained by measurement of the chemical shift of the methyl group in the solvent pairs dimethyl sulphoxide–pyridine or deuteriochloroform–pyridine; quinoline is also suggested as a solvent for use in such studies.

DURING experiments on some new secalonic acids,[1] we found that the position in the ^{1}H n.m.r. spectrum of a methyl group β to a hydroxy-group moved strongly upfield on changing the solvent from $CDCl_3$ to $(CD_3)_2SO$. However, in pyridine, the position of the methyl resonance moved strongly downfield. Although other proton resonances in the n.m.r. spectra of the secalonic acids showed general solvent shifts, these were not nearly so marked as when the methyl group was in close proximity to a hydroxy-group. A specific solvent shift between pyridine and $CDCl_3$ has been used to aid the determination of the *cis*- or *trans*-arrangement of methyl and hydroxy-groups in a small number of steroids[2] but no general relationship appears to have been formulated from the earlier very limited number of reported observations. We have studied a variety of hydroxy-compounds including, for example, sterols, terpenols, other aliphatic alcohols, and phenols and have found the solvent shift to be strongly dependent on the dihedral angle (θ) between the methyl and hydroxy-groups. Twenty-three compounds were studied and, because some of them contained more than one relevant methyl group, these gave twenty-eight data points covering a range of dihedral angles from 0 to 180°. The observed shifts ($\Delta\nu_1$ = shift from $CDCl_3$ to pyridine; $\Delta\nu_2$ = shift from $(CD_3)_2SO$ to pyridine in p.p.m. $\times$ 100) are given approximately by the relationships, $\Delta\nu_1 = 11 + 10\cos\theta$ (± 2) and $\Delta\nu_2 = 17 + 14{\cdot}6\cos\theta$ (± 3). The formulae also hold for a methyl group *ortho* to a phenolic group in aromatic compounds and therefore promise to be generally useful throughout the whole field of natural product chemistry. We ascribe the different effects of pyridine and $(CD_3)_2SO$ to hydrogen bonding from hydroxy to solvent. Examination of Dreiding models suggests that with pyridine, the methyl group will lie within the deshielding region of the π-system but with $(CD_3)_2SO$, in the shielding region. The effect seems not to be due to a dipole of the hydrogen-bonded hydroxy–solvent system because in triethylamine as solvent, the specific shifts noted for pyridine and $(CD_3)_2$-SO were not observed even though hydrogen-bonding should be quite strong. Also, in quinoline as solvent, the methyl resonance shift from its position in $CDCl_3$ solution was considerably greater than the shift in pyridine solution.

Hydrogen-bonding from the hydroxy-group to the quinoline nitrogen should bring the deshielding region of the aromatic rings (8-position) closer to the methyl than is the case with pyridine and so enhance the methyl shift.

In the compounds covered by this study, Dreiding models suggest that free rotation about the alcohol C–O bond would not be hindered by hydrogen-bonded complex formation between the alcohol and solvent. Where steric factors can interfere with this free rotation, it could be expected that the above correlations between $\Delta\nu$ and θ would no longer be accurate. These aspects will be discussed in a fuller publication.

The above formulae for $\Delta\nu_1$ and $\Delta\nu_2$ were found to be strongly disturbed when a carbonyl group was in close proximity to the methyl group, *i.e.* in 3β-hydroxy-4,4-dimethyl-6-oxocholestane. This effect is not unexpected in view of the marked shifts of methyl close to carbonyl observed on changing solvent from $CDCl_3$ to benzene.[3] In this context, the shifts ($\Delta\nu_1$) observed in 3-oxo-4,4-dimethylandrost-5-ene-17β-ol are illuminating. The shift of the 18-methyl group (now well separated from the ketone group) is not anomalous, one of the 4-methyl groups moves by 13 p.p.m. and the other by −2 p.p.m. If these 'corrections' for 4-methyl groups close to carbonyl groups are applied to 3β-hydroxy-4,4-dimethyl-6-oxocholestane then the shifts ($\Delta\nu_1$) are no longer anomalous. It may be therefore that where strongly disturbing functional groups other than hydroxy lie near a methyl, the solvent shifts may be sufficiently additive that the formulae given here can still be used.

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