On Conformational Preferences in Aromatic Methyl Ethers

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The recent claim that preferred conformations of aromatic methyl ethers have been detected by nuclear Overhauser enhancement (n.O.e.) difference spectroscopy cannot in most cases be supported by analysis of the results.

Kruse and Cha have recently published measurements of nuclear Overhauser enhancements (n.O.e.s) in aromatic methyl ethers.[1] They interpreted their results as demonstrating that unequal resonance contributions lead to specific conformational preferences of the methyl ether group. We believe that unfortunately their conclusions are based on a fundamentally wrong approach to the analysis of n.O.e.s, and we show here that *as presented* there is, with one dramatic exception, virtually no evidence for their desired conformational preferences.

Kruse and Cha measured enhancements from the methoxy-group to H_A and H_B in systems of the type (A) $\rightleftharpoons$ (B),† and simply took the ratios of the observed enhancements to be equal to the ratios of the populations. The error of this simplistic analysis is most simply illustrated by the spin systems shown in Figure 1(a) and (b), where, for the purpose of argument, M represents a simple proton. In Figure 1(a), irradiation of proton M will give over 49% n.O.e.s to X and to Y because the total maximum enhancement is 50% and M dominates the relaxation of both X and Y.[2] In Figure 1(b) an additional proton Z is added. Irradiation of M still gives a 49% enhancement to X but only 24.8% to Y *even though nothing has changed in the X–M–Y system.* Y is now getting equal amounts of relaxation from M and Z.[3]

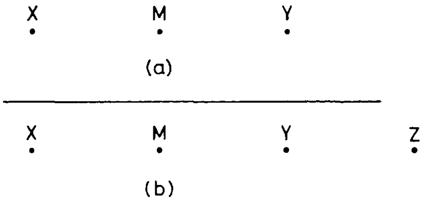

Figure 1. (a) A linear three-spin system with $r_{xm} = r_{my}$; (b) a linear four-spin system with $r_{xm} = r_{my} = r_{yz}$.

It is precisely this situation which obtains in most of Kruse and Cha's compounds; *e.g.* in (**3**) H_A is essentially an isolated proton but H_B has an *ortho*-neighbour. Therefore for equal populations of conformations (A) and (B) the n.O.e. to H_A should be much larger than to H_B. Crude calculations suggest that the methoxy-group should cause a significant (but slowly growing) n.O.e. at H_A even in conformation (A), and the small observed differences in H_A and H_B look rather like a conformational preference in the opposite direction to that claimed! Similar considerations apply to some extent to all the other compounds except (**1**).

The situation in (**1**) is quite different. The distance from H_A to its *peri*-proton neighbour H_P is significantly less than from H_B to its *ortho*-neighbour H_C. Therefore a 1 : 1 conformational mixture would give a substantially smaller n.O.e. to H_A than to H_B, and the observed ratio of 4.5 reflects a much larger conformational preference than Kruse and Cha realised.‡

Quantitative conclusions are elusive. For example there are some important discrepancies in the n.O.e. results which are reported: *e.g.* why should the addition of a 2-methyl group in

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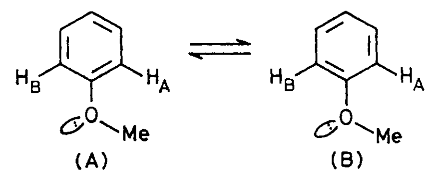
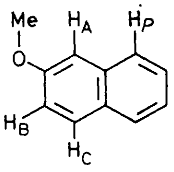
† We have retained the lettering and numbering scheme in the original references.

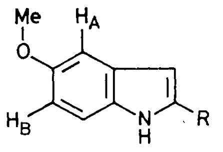
‡ Since submission of this manuscript we have confirmed, by observation of n.O.e.s at the methoxy-group, that the conformational preference is *at least* 15 : 1.



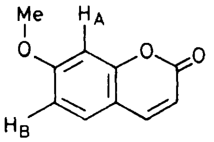
(A) (B)



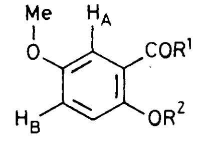
(1)



(2) a; R = H
b; R = Me



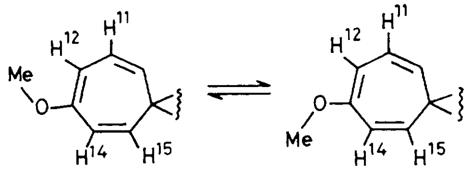
(3)



(7) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = CD_3$
c; $R^1 = Me, R^2 = H$
d; $R^1 = Me, R^2 = CD_3$

indole, (**2b**) *vs.* (**2a**), reduce by over half the n.O.e.s from the OMe group and why are n.O.e.s in (**7a** and **b**) over four times as large as in (**7c** and **d**)? In each case the substitution is too remote to have a direct effect, and the variations are not explicable in any other simple way.

Without some evidence of relaxation mechanisms, or measurements of n.O.e. growth rates, the results of these particular experiments are difficult if not impossible to interpret. In all these compounds a reliable measurement would require observations of the n.O.e.s at the methoxy-group following separate irradiation of H_A and H_B. In most cases this experiment is frustrated by chemical shift problems as may be seen from Kruse and Cha's Table 1 (and our unpublished results).[4] In our original work[5] on the methoxyheptatriene (**10**) we were able to use the methoxy-irradiation experiment to draw valid conformational conclusions concerning the equilibrium (**10a**) $\rightleftharpoons$ (**10b**) only because H^{12} in (**10a**) and H^{14} in (**10b**) are in essentially the same environment *vis-à-vis* other neighbours. Even so we drew attention to the large effects which even very small bond length variations can have on the apparent position of equilibrium; we also reported the inverse experiment, observing n.O.e.s at the methoxy-group.



(10a) (10b)

Undoubtedly there are interesting reaction specificities in these compounds, and n.O.e. measurements are potentially a powerful way of elucidating their origins.[4] Kruse and Cha may have uncovered part of the answer, but with the clear exception of compound (**1**) the present evidence is, at best, doubtful.

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References

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