The Prediction of Nuclear Magnetic Resonance Ring Proton Shifts in Heteroaromatic Molecules

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I. *Unsubstituted Rings.* The ring-proton chemical shifts of pyrazine, *s*-triazine, *as*-triazine, and 1,2,4,5-tetrazine may be estimated from a knowledge of the experimentally determined chemical shifts of pyridine, pyridazine, and pyrimidine. A recent attempt[1] to derive the shifts of the diazines from the chemical shifts of pyridine gave some results well in excess of the variation observed in this work and the authors concluded that additivity was not operative.

The present approach is an extension of the method used by Reed[2] to predict the chemical shifts of substituted benzenes. The results indicate that the ring n.m.r. shifts of heterocycles and their derivatives can be calculated in terms of additive perturbations due to hetero-atoms or ring substituents.

Empirical additivity constants are based on the influence, relative to benzene, of the following partial structures, $(\overset{\cdots}{-}N\overset{\cdots}{-})$, $(\overset{\cdots}{-}N\overset{\cdots}{-}N\overset{\cdots}{-})$, and $(\overset{\cdots}{-}N\overset{\cdots}{-}\mathrm{CH}\overset{\cdots}{-}N\overset{\cdots}{-})$, on the proton shifts in the heterocyclic ring. In the partial structures, the σ-bonds and non-bonding electrons are indicated by full lines and the π-bonds by dotted lines.

(a) The effects of a ring nitrogen $(\overset{\cdots}{-}N\overset{\cdots}{-})$ on shifts of protons at the α-, β- and γ- positions are calculated from data for pyridine.[3]

$$\Delta\alpha\mathrm{H} = \delta^{\alpha\mathrm{H}}\ \text{pyridine} - \delta\ \text{benzene} = (8{\cdot}60) - (7{\cdot}23) = +\,1{\cdot}37\ \text{p.p.m.}\dagger$$

$$\Delta\beta\mathrm{H} = \delta^{\beta\mathrm{H}}\ \text{pyridine} - \delta\ \text{benzene} = (7{\cdot}00) - (7{\cdot}23) = -\,0{\cdot}23\ \text{p.p.m.}$$

$$\Delta\gamma\mathrm{H} = \delta^{\gamma\mathrm{H}}\ \text{pyridine} - \delta\ \text{benzene} = (7{\cdot}60) - (7{\cdot}23) = +\,0{\cdot}37\ \text{p.p.m.}$$

The large constant for the α-hydrogen is due to the magnetic anisotropy of the adjacent nitrogen atom.

(b) The effect of a ring diazo-group $(\overset{\cdots}{-}N\overset{\cdots}{-}N\overset{\cdots}{-})$ on the chemical shift of a proton on an adjacent

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† Unless otherwise noted, all literature chemical shift data were converted to p.p.m. from tetramethylsilane, according to the conversion values given in "Interpretation of NMR Spectra", Roy H. Bible, Plenum Press, 1965, p. 15.

carbon atom is calculated from data for pyridazine.[3]

$$\Delta^{\alpha H}\,\mathrm{NNC} =$$

$$\delta^{\alpha H}\text{ pyridazine} - \delta\text{ benzene} - \Delta\,\alpha H - \Delta\beta H = (9{\cdot}21) - (7{\cdot}23) - (1{\cdot}37) - (-\,0{\cdot}23) = +\,0{\cdot}84\text{ p.p.m.}$$

(c) The effect of two flanking ring nitrogen atoms, $(\cdots N \cdots CH \cdots N \cdots)$, on the chemical shift of the central methine proton is calculated from data for pyrimidine.[4]

$$\Delta\text{ NCN} =$$

$$\delta^{2\text{-}H}\text{ pyrimidine} - \delta\text{ benzene} - 2 \times \Delta\alpha H = (9{\cdot}26) - (7{\cdot}23) - 2(1{\cdot}37) = -\,0{\cdot}71\text{ p.p.m.}$$

Since all of the above constants have been calculated from spectra run on solutions in $CDCl_3$, the predictions are for shifts determined for solutions in that solvent.

(i) With these shift-derived constants, one can evaluate the ring-proton shift for pyrazine:

$$\delta\text{ pyrazine} = \delta\text{ benzene} + \Delta\alpha H + \Delta\beta H = (7{\cdot}23) + (1{\cdot}37) + (-\,0{\cdot}23) = 8{\cdot}37\text{ p.p.m.}$$

Experimental value: δ pyrazine = 8·60 p.p.m. (solvent $CDCl_3$).

(ii) For symmetrical 1,3,5-triazine:

$$\delta\ s\text{-triazine} = \delta\text{ benzene} + 2 \times \Delta\alpha H + \Delta\gamma H + \Delta\text{NCN} = (7{\cdot}23) + 2(1{\cdot}37) + (0{\cdot}37) + (-0{\cdot}71) = 9{\cdot}63\text{ p.p.m.}$$

Experimental value[5] for *s*-triazine = 9·25 p.p.m.

The only determination for *s*-triazine available was carried out on a solution in carbon tetrachloride rather than deuteriochloroform and thus the solvent effect may account for a lower accuracy.

(iii) For asymmetrical 1,2,4-triazine, the three different ring protons give:

$$\delta^{3\text{-}H}\ as\text{-triazine} =$$

$$\delta\text{ benzene} + \Delta\alpha H + \Delta\beta H + \Delta\text{NCN} + \Delta\text{NNC} = (7{\cdot}23) + 2(1{\cdot}37) + (-\,0{\cdot}23) + (-\,0{\cdot}71) + (0{\cdot}61) = 9{\cdot}74\text{ p.p.m.}$$

Experimental value[6] 9·88 p.p.m. (solvent $CDCl_3$)

$$\delta^{5\text{-}H}\ as\text{-triazine} =$$

$$\delta\text{ benzene} + \Delta\alpha H + \Delta\beta H + \Delta\gamma H = (7{\cdot}23) + (1{\cdot}37) + (-\,0{\cdot}23) + (0{\cdot}37) = 8{\cdot}74\text{ p.p.m.}$$

Experimental value: 8·84 p.p.m.

$$\delta^{6\text{-}H}\ as\text{-triazine} =$$

$$\delta\text{ benzene} + 2\Delta\beta H + \Delta\text{NNC} + \Delta\alpha H = +\,(7{\cdot}23) + 2(-\,0{\cdot}23) + (0{\cdot}84) + (1{\cdot}37) = 8{\cdot}98\text{ p.p.m.}$$

Experimental value: 9·48 p.p.m.

(iv) For symmetrical 1,2,4,5-tetrazine, whose n.m.r. spectrum has not yet been published, one should expect the proton shift:

$$\delta\ s\text{-tetrazine} = \delta\text{ benzene} + 2\Delta\alpha H + 2\Delta\beta H + \Delta\text{NCN} + 2\Delta\text{NNC} = (7{\cdot}23) + 2(1{\cdot}37) + 2(-\,0{\cdot}23) + (-\,0{\cdot}71) + 2(0{\cdot}84) = 10{\cdot}48\text{ p.p.m.}$$

II. *Substituted Rings*. The approach of deriving chemical shift additivity constants from known simple molecular structures, which are useful in the study of more complex structures, is also applicable to substituted heterocycles providing the same solvent is used. The method is illustrated below with examples. Greater accuracy is obtained for cases of this type (substituted rings) than for cases where complex parent heterocycles are examined in terms of simpler parent heterocycles (unsubstituted rings).

(i) The ring proton shift for 2,5-dimethylfuran can be calculated from a knowledge of the corresponding shifts[7] of furan (I) and 2-methylfuran (II). The solvent used in all cases was tetramethylsilane.

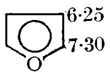
Effect of an α-methyl on the proton shift of the near β-hydrogen = (6·25) − (5·82) = + 0·43.

Effect of an α-methyl on the proton shift of the far β-hydrogen = (6·25 − (6·11) = + 0·14.

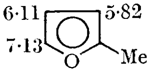
Therefore, the predicted ring proton shift for 2,5-dimethylfuran = (6·25) − (0·43) − (0·14) = 5·68 p.p.m.

Experimental value:[7] 5·69 p.p.m.

(ii) The ring proton shift for 2,4-dimethylthiazole is predictable from the determined proton shifts of thiazole (III), 2-methylthiazole (IV), and 4-methylthiazole (V). Pure liquids were used with reference to water.



(I)



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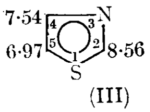

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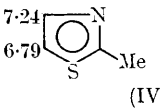

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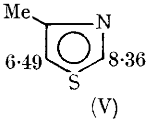

(V)

Effect of 2-methyl on 4-H shift = (7·54) − (7·24) = 0·30.

Effect of 2-methyl on 5-H shift = (6·97) − (6·79) = + 0·18.

Effect of 4-methyl on 2-H shift = (8·56) − (8·36) = + 0·20.

Effect of 4-methyl on 5-H shift = (6·97) − (6·49) = + 0·48.

Therefore, the 5-H shift for 2,4-dimethylthiazole = (6·97) − (0·18) − (0·48) = 6·31 p.p.m.

Experimental value:[8] 6·27 p.p.m.

Finally, I suggest that this approach is capable of wider applicability to parent and substituted heterocyclic molecules in organic synthetic work and natural product structure determinations.

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