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SIMPLE LINEAR RELATIONSHIPS BETWEEN PROTON CHEMICAL SHIFTS AND CALCULATED π-ELECTRON DENSITIES IN NITROGEN HETEROCYCLES

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For homocyclic aromatic species, there is strong support for a simple linear correlation between the proton chemical shift and the local electron density on the carbon atom to which the proton is bonded, and the derived electron densities agree well with those calculated by molecular-orbital methods (1,2). The presence of heteroatoms apparently obscures any simple relationship of this type: thus Gawer and Dailey (3) conclude from a study of the proton chemical shifts for the neutral molecules of eleven nitrogen-heteroaromatic compounds that "the proton chemical shifts appear to be a somewhat unreliable measure of π-electron densities, especially in positions adjacent to a nitrogen atom". Since Gil and Murrell (4) suggest that the paramagnetic effect arising from the low-lying $n-\pi^*$ transition is most important for the α-protons in pyridine, such effects could be the major factor obscuring chemical shift – electron density relationships in heterocyclic species.

Protonation of pyridine giving pyridinium ion (thus eliminating the influence of the $n\text{-}\pi^*$ transition) might then reveal such relationships, but Kotowycz, Schaefer, and Bock (5) have found poor agreement between the proton chemical shifts for pyridinium ion and V.E.S.C.F. calculations of π-electron densities for this ion (6), and they were led to postulate marked counterion effects. However, their failure to observe a simple correlation may arise from their choice of calculated densities. The V.E.S.C.F. calculation assigns the 2-position of the pyridinium ion a <u>greater</u> π-electron density than the 4-position, while for the pyridine molecule the 4-position is predicted to have the greater π-electron density: it seems unlikely that the increase in electronegativity resulting from protonation of the nitrogen atom would lower the π-electron density to a greater extent at the remote 4-position. Zahradnik and Parkanyi (7) have shown recently that if the simple Huckel method is used, the calculated π-electron densities in the conjugate acids of nitrogen heteroaromatic compounds are linearly correlated with those of the neutral molecules. The value chosen for the Coulomb parameter h affects the <u>magnitudes</u>, <u>but not the relative order</u> of the calculated densities at the various carbon atoms.

Thus, we find that a plot of the proton chemical shifts observed by Kotowycz, Schaefer, and Bock for a 3% solution of pyridine hydrochloride in acetonitrile (2-, δ 8.70; 3-, 7.93; 4-, 8.46) against π-electron densities calculated by the simple Huckel method (using $h = +\frac{1}{2}$ (7,8)) is linear: the equation $\delta = 7.97 + 9.52\ (1 - q)$ reproduces the observed chemical shifts to within 0.01 p.p.m. Although the parameter choice of h = +½ has been suggested as appropriate for the neutral molecule of pyridine (7,8), the slope of the relationship we observe (9.52 p.p.m./electron) is comparable with the values of ca. 10 p.p.m./electron found for homocyclic systems, and an increase in h would decrease the slope. The predicted chemical shift for a proton attached to a carbon atom with unit π-electron density is 7.97, rather than 7.27 as observed with benzene; this difference may reflect σ-electron polarization, but we reserve further comment at this time.

In view of the success of this simplified approach with pyridinium ion, we have measured the proton chemical shifts of pyrazole and imidazole, their 1-methyl derivatives, and pyrimidine, in dilute ($<5\%$ w/v) solution in trifluoroacetic acid (where we presume that protonation will be complete), and have compared the shifts with calculated π-electron densities. Pyrimidine was also examined in dilute solution in carbon tetrachloride.

Once again, linear chemical shift - electron density relationships are apparent. For the diazoles, the calculated π-electron densities were from Huckel calculations (9) which assumed both nitrogens identical, and used h = +1 (as noted above, the order of π-electron densities is independent of h: a higher value than for pyridine is used to allow for the formal presence of both pyrrole- and pyridine-type nitrogen atoms in five-membered rings). The proton chemical shifts for the diazoles in trifluoroacetic acid are reproduced within 0.05 p.p.m. by the equation $\delta = 8.00 + 7.52\ (1 - q)$. The observed chemical shifts in p.p.m. from tetramethylsilane, together with the shifts calculated from the above equation (in parentheses), and the corresponding π-electron densities q are (imidazole = Im; pyrazole = Pz): 2-Im proton, 8.67 (8.70) 0.907; 3(5)-Pz, 8.25 (8.20), 0.973; 4(5)-Im, 7.53 (7.48), 1.067; 4-Pz, 6.95 (6.98), 1.136. The 1-methyldiazoles showed closely similar behavior, where the ring proton chemical shifts were reproduced within 0.04 p.p.m. by the equation $\delta = 7.98 + 7.90\ (1 - q)$, as follows (observed shift, shift calculated from equation): 2-Im, 8.70, 8.71; 3(5)-Pz, 8.15, 8.19; 4(5)-Im, 7.49, 7.45; 4-Pz, 6.87, 6.91. The slightly different slope noted for the 1-methyl derivatives as compared with the parent diazoles can readily be rationalized by assuming a slight decrease in the electronegativity of nitrogen accompanying the replacement of N-H by $N-CH_3$. The lower slope for the five-membered ring compounds as compared with pyridinium ion could be ascribed to the different ring size. However, as noted above, the slope depends critically upon the choice of h: a small variation in h would give the same slope as for the pyridinium ion.

Generally similar results were obtained with pyrimidine. The observed shifts in trifluoroacetic acid are related linearly to π-electron densities calculated either using the simple Huckel method (with $h = +\frac{1}{2}$)(8) or an S.C.F. method (10). The shifts are: 2-proton, δ 9.88; 4-, 9.55; 5-, 8.36, while the calculated π-electron densities are: (Huckel): 2-, 0.845; 4-, 0.874; 5-, 1.009; (S.C.F.): 2-, 0.900, 4-, 0.926; 5-, 1.026. The shifts are reproduced within 0.03 p.p.m. by the equation $\delta = 8.43 + 9.15(1 - q_{\text{Huckel}})$, and within 0.01 p.p.m. by $\delta = 8.66 + 12.10(1 - q_{\text{S.C.F.}})$. Surprisingly in view of previous comment (11) that "the absolute magnitudes of the shifts in pyrimidine are not easy to interpret", the shifts for the protons of the neutral pyrimidine molecule in carbon tetrachloride are also related to the above sets of calculated π-electron densities. The shifts are: 2-proton, 9.13; 4-, 8.67; 5-, 7.27, and are reproduced within 0.10 p.p.m. by $\delta = 7.33 + 11.40(1 - q_{\text{Huckel}})$, and within 0.05 p.p.m. by $\delta = 7.62 + 14.60(1 - q_{\text{S.C.F.}})$. These latter relationships may well be coincidental, since paramagnetic effects must be present in the neutral pyrimidine molecule.

Thus, in the examples we have studied, simple calculations of π-electron densities for heteroaromatic species reliably indicate the order of their proton chemical shifts in trifluoroacetic acid solution. We hope to test the generality of these relationships by examination of substituted pyridines, diazoles, and pyrimidines in acidic solvents.

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