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A QUANTITATIVE RELATION BETWEEN HETEROAROMATIC TAUTOMERIC EQUILIBRIUM CONSTANTS AND SOLVENT POLARITY (1)

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Although it is well recognised that heteroaromatic tautomeric equilibria are sensitive to changes in solvent (3) and that solvents of low dielectric constant generally shift the equilibrium in favour of the less polar tautomer, no quantitative relation has yet been demonstrated. For solely electrostatic interactions between solvent and solute, the Kirkwood equation (i) is applicable (4). For rate processes, this can be written in the form (ii) where U is a constant independent of the solvent. However, equation (ii) is not very successful in correlating reaction rates, doubtless due to the existence of differential interactions between ground and transition state other than purely electrostatic ones. Grunwald and Winstein (5) introduced the solvent parameter Y which when used in the empirical equation (iii) correlates many reaction rates (6). The Kirkwood equation has been applied to keto-enol equilibria, with limited success (7). We now find that heteroaromatic tautomeric equilibria can be precisely correlated by equation (iv) analogous to (iii) where K_{T1} and P_1 are the equilibrium constant in, and the polarity of, one particular solvent. Of the various solvent parameters available, we chose (8) to work with the Kosower Z-parameters (9) because these are derived

$$\Delta G = -\frac{\mu^2}{r^3}\left(\frac{D-1}{2D+1}\right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots \text{(i)}$$

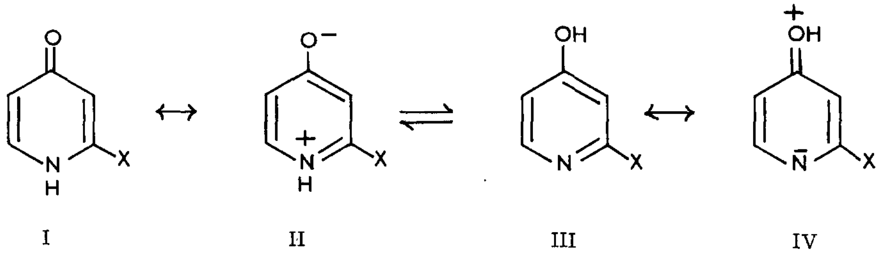
$$\ln k = \ln k_o + U\left(\frac{D-1}{2D+1}\right) \qquad \ldots\ldots\ldots\ldots\ldots\ldots \text{(ii)}$$

$$\ln k = \ln k_o + mY \qquad \ldots\ldots\ldots\ldots\ldots\ldots \text{(iii)}$$

$$\ln (K_{T1}/K_{T2}) = a(P_1 - P_2) \qquad \ldots\ldots\ldots\ldots\ldots\ldots \text{(iv)}$$

from 1-alkylpyridinium iodides, cations of similar size and shape to the heteroaromatic compounds under investigation.

The ultraviolet spectra of five compounds were determined in a series of ethanol-water and methanol-water mixtures (appropriately buffered), ethylene glycol, acetonitrile, chloroform and iso-octane, appropriate allowance being made (8) for changes in the extinction of the individual tautomers with polarity. Z-Values for dilute aqueous methanol and ethanol were calculated as suggested (9) from available Y-values. The plots shown in the Figure show good linearity, with similar slopes (0.116 - 0.151). However there is a curious abnormality for 2,6-dimethoxycarbonyl-4-pyridone, which exists to an appreciable extent as the oxo-form in chloroform and carbon tetrachloride (but not iso-octane) (10).

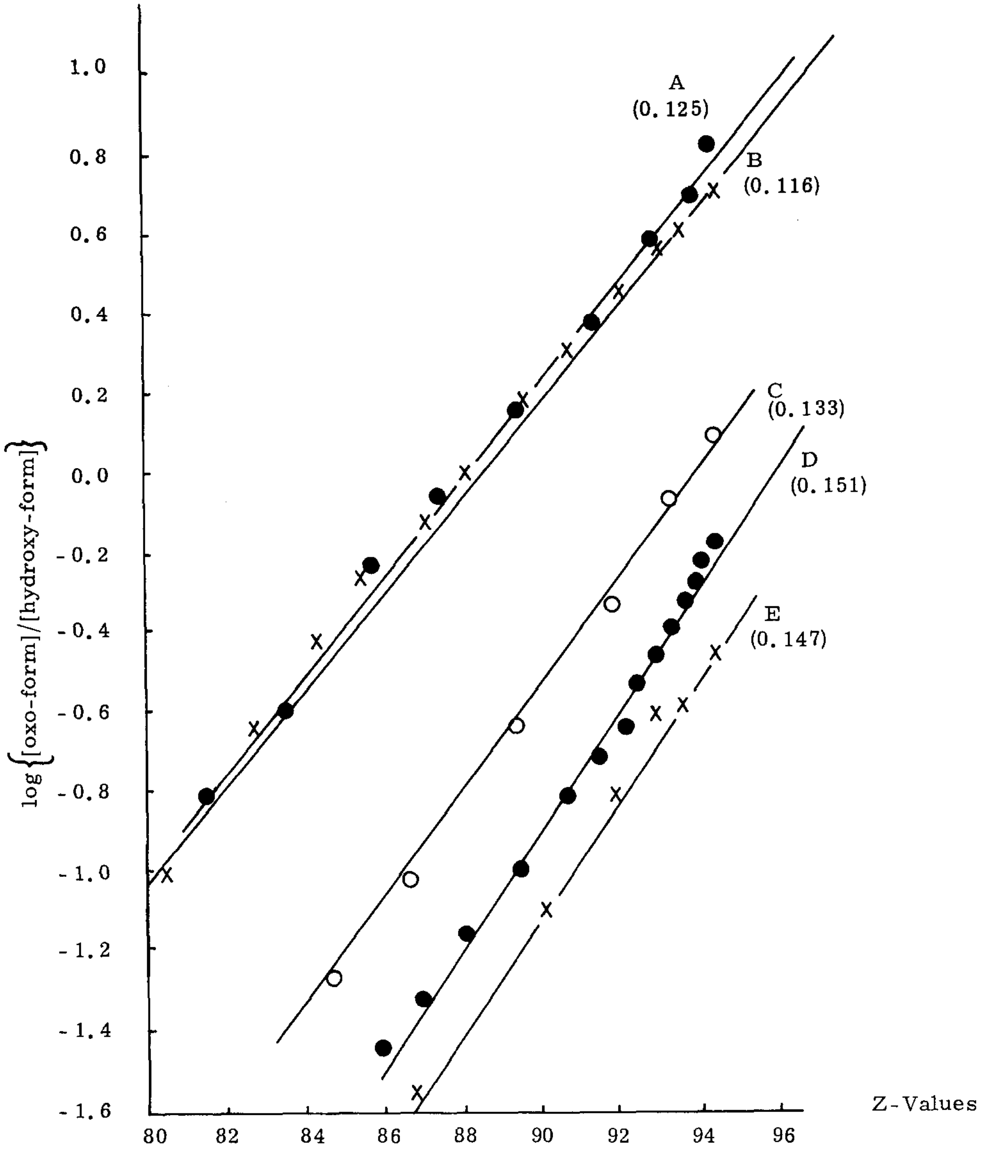


There is a definite trend to smaller slopes for compounds which tend to exist more in the oxo-form (Figure). That this trend is significant is shown by consideration of 2- and 4-pyridone themselves: in aqueous solution these compounds show log K_T values of ca. 3 in favour of the oxo-form. We have reconfirmed that they also exist predominantly in this form in iso-octane, where log $K_T \gtrsim 1$. Hence the slope for these compounds is $\lesssim 0.06$. Qualitatively, the reasons for this are apparent from a consideration of the effect of a 2-chlorine atom on the tautomerism of 4-pyridone (I - IV; X = H or Cl). 4-Pyridone is stabilised in the oxo-form by charge separation (II) and the "aromatic" stability so conferred. An α-chlorine atom selectively destabilises structures of type (II) (11), hence the participation of such structures in the resonance hybrid becomes particularly sensitive to the solvent polarity.

The weakness of the above treatment, and indeed of any use of solvent polarity parameters, is the implicit assumption that solute-solvent interactions are proportional to those between the solvent and the compound used to set up the solvent polarity scale (12). It should be possible to use an equation of type (v), to correlate rates and equilibria, where P, Q and R represent various types of solvent interaction of which electrostatic interactions

$$\ln (K/K_0) = aP + bQ + cR \qquad \text{(v)}$$

are one. This approach is now being actively pursued.



FIGURE

Plots of log [oxo-form]/[hydroxy-form] measured in ethanol-water mixtures against Z-values for (A) 6-chloro-2-(solid points); (B) 2,3,5-trichloro-4-(crosses); (C) -2-chloro-4-pyridone; (D) 3-hydroxypyridine; and (E) 2,6-dimethoxycarbonyl-4-pyridone. The lines shown for each compound were fitted by the least squares method; the slopes are given.

References

1. Tautomeric Pyridines, Part XI.
2. Holder of S. R. C. Research Studentship 1965-1967.
3. (a) For a discussion and references see A. R. Katritzky and J. M. Lagowski, Advances in Heterocyclic Chemistry, 1, 339 (1963), 2, 1, 27 (1963);

   (b) for an early treatment see S. F. Mason, J. Chem. Soc., 5010 (1957).
4. J. G. Kirkwood, J. Chem. Phys., 2, 351 (1934).
5. E. Grunwald and S. Winstein, J. Amer. Chem. Soc., 70, 846 (1948).
6. See e.g. A. H. Fainberg and S. Winstein, J. Amer. Chem. Soc., 78, 2770 (1956).
7. J. Powling and H. J. Bernstein, J. Amer. Chem. Soc., 73, 4353 (1951).
8. For full details see A. Gordon, Ph.D. Thesis, University of East Anglia, (1967).
9. E. M. Kosower, J. Amer. Chem. Soc., 80, 3253 (1958).
10. See also A. Gordon and A. R. Katritzky, J. Chem. Soc. (B), in press.
11. A. R. Katritzky, J. D. Rowe and S. K. Roy, J. Chem. Soc. (B), 758 (1967).
12. C. Reichardt, Angew. Chem. Internat. Edn., 4, 29 (1965).