Quantitative Measure of the Aromatic Stabilization Energy of 2-Pyridone and Related Compounds

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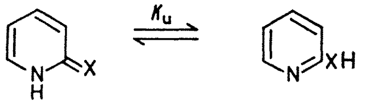
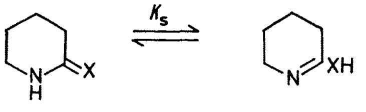
Summary Consideration of tautomeric equilibria allows the estimation of the aromatic stabilization energy of 2-pyridone as 25 kcal mol^{-1}: the method is applied to related compounds.

THE concept of aromatic character remains a cornerstone in the teaching and practice of organic chemistry, despite difficulties in its precise definition and quantitative measurement. The significant interest is in additional stabilization energy that aromatic compounds possess over and above that for hypothetical similar but non-conjugated systems. 2-Pyridone (**1** X = O) exemplifies a large and important class of heterocycles for which no generally accepted estimate of aromatic stabilization is available. Elvidge and Jackman[1] from proton chemical shifts estimated 2-pyridones to possess *ca.* 35% of the aromaticity of benzene, *i.e.* 12—15 kcal mol^{-1} stabilization. The use of ring current considerations of this type has been criticized,[2,3] defended,[4] and used further[5] but it remains highly controversial as a quantitative criterion.[6]



(1) (2)



(3) (4)

We believe that the aromaticity of pyridonoid compounds of type (**2**), where X = O, S, NR, or CR$_2$, can be estimated by a comparison of the corresponding tautomeric equilibria [(**1**) ⇌ (**2**)] and [(**3**) ⇌ (**4**)]. This is a more convenient and more generally applicable method than the calorimetric study of the equilibria between 1-methyl-2-pyridone and 2-methoxypyridine, and *N*-methyl valerolactam and *O*-methyl valerolactim reported by Beak *et al.*[7] (see also ref. 8).

We assume [9] (a) that the electronic stabilization energy resulting from interaction between the nitrogen atom and the XH group is approximately equal in (**2**) and (**4**), and (b) that the electronic interaction between the NH group and the X atom in (**3**) is approximately equal to the non-aromatic stabilization in (**1**). Equation (1) then follows, where A_{py} and A_x are the resonance energies of the parent system (pyridine) and the appropriate pyridonoid system (**1**), respectively and ΔH_s^0 and ΔH_u^0 are defined by equations of type (2).

$$A_{py} - A_x = \Delta H_s^0 - \Delta H_u^0 \tag{1}$$

$$\Delta H_s^0 = \Delta G_s^0 + T\Delta S_s^0 = -RT\ln K_s + T\Delta S^0 \tag{2}$$

$$\Delta G_s^0 - \Delta G_u^0 = 1{\cdot}37\,[\mathrm{p}K_3(\text{X–Me}) - \mathrm{p}K_2(\text{N–Me}) - \mathrm{p}K_4(\text{X–Me}) + \mathrm{p}K_5(\text{N–Me})] \tag{3}$$

TABLE[a]. *Equilibrium constants and energy differences*

X	pK_2 (N-Me)	pK_3 (*X*-Me)	log K_u	ΔG_u kcal mol^{-1}	pK_4 (N-Me)	pK_5 (X-Me)	log K_s	ΔG_s kcal mol^{-1}	($A_{py} - A_x$) kcal mol^{-1}
O	0·32[b]	3·28[b]	2·96	−4·1	−0·19[g]	7·5[j]	7·7	−10·6	+6·5
S	−1·22[c]	3·62[c]	4·84	−6·7	−1·76[h]	6·9[k]	8·7	−12·0	+5·3
NH	13·02[d]	6·86[d]	−6·16	+8·5			0[m]	0	+8·5
CH$_2$	19·8[d]	5·97[e]	−13·8[f]	+19·0	11·4[i]	9·43[l]	2·0	+2·7	+16·3

[a] All values refer to aqueous solutions.

[b] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.

[c] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384.

[d] This work.

[e] H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723.

[f] K. Schofield, 'Heteroaromatic Nitrogen Compounds,' Butterworths, London, 1967, page 325, quotes log K_u as −12 from S. F. Mason and C. F. Reynolds, unpublished work.

[g] Value for *NN*-dimethylacetamide, A. R. Goldfarb, A. Mele, and N. Gutstein, *J. Amer. Chem. Soc.*, 1955, **77**, 6194.

[h] Value for thioacetamide, D. Rosenthal, and T. I. Taylor, *J. Amer. Chem. Soc.*, 1957, **79**, 2684.

[i] 1,2-Dimethyl-1,4,5,6-tetrahydropyridine, R. Adams and J. E. Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588.

[j] Value for ethyl iminoacetate [MeC(:NH).OEt], T. C. Pletcher, S. Koehler, and E. H. Cordes, *J. Amer. Chem. Soc.*, 1968, **90**, 7072.

[k] Value for ethyl iminothioacetate [MeC(:NH).SEt], G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3863; R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Amer. Chem. Soc.*, 1967, **89**, 6984.

[l] *N*-Methylcyclohexane imine, M. Brezina and P. Zuman, *Chem. Listy*, 1953, **47**, 975.

[m] By inspection.

The measureable pK_a values relate to ΔG^0 quantities by equation (3), whereas ΔH^0 quantities are required for use in equation (1). There are several methods available to convert ΔG^0 into ΔH^0 using linear free energy relationships,[10] or the variation of either pK_a or K_T values with temperature;[11] we chose here to take ΔG^0 as providing an approximation for ΔH_{int}, which excludes solvent interactions[12] (it can be shown that all the methods give consistent results[11]).

Most of the pK_a values were taken from the literature, but that for 1-methyl-2-pyridine imine was redetermined[11] by the spectrophotometric method, and that for 1-methyl-2-pyridine methide measured[11] by the procedures of Bowden and Cockerill.[13] Results are shown in the Table; if pyridine is taken[14] to have an aromatic stabilization energy of 32 kcal mol^{-1} then 2-pyridone has a stabilization energy of *ca.* 25 kcal mol^{-1}.[7] The corresponding energy for 2-pyridine thione is a little more and that for 2-pyridine imine significantly less, but all these compounds are clearly 'aromatic'. By contrast, a considerable fall in stabilization occurs for the methide, which has only about half the resonance stabilization of pyridine itself.

We believe that tautomeric equilibria offer useful quantitative energy estimates of general interest to chemists.

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[1] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 1961, 859.

[2] R. J. Abraham, R. C. Sheppard, W. A. Thomas, and S. Turner, *Chem. Comm.*, 1965, 43.

[3] R. J. Abraham and W. A. Thomas, *J. Chem. Soc.* (*B*), 1966, 127.

[4] J. A. Elvidge, *Chem. Comm.*, 1965, 160.

[5] L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Austral. J. Chem.*, 1965, **18**, 1221.

[6] A. J. Jones, *Rev. Pure and Appl. Chem.*, 1968, **18**, 253.

[7] P. Beak, J. Bonham, and J. Lee, jun., *J. Amer. Chem. Soc.*, 1968, **90**, 1569, concluded that the 2-pyridone system had aromatic stabilization of *ca.* 6 kcal mol^{-1} less than pyridine, but with considerable uncertainty in this figure. Their comments that the corresponding tautomeric equilibria are unsuitable for discussion of aromatic stabilization because the equilibria could be dominated by intermolecular association effects we believe to be unjustified. Whereas these effects can dominate the equilibria in the solid or melt and even in concentrated solutions in non-polar solvents, this does not apply to dilute solutions in water. Support for this conclusion derives from the good qualitative agreement between K_T from pK_a measurements on methyl derivatives (for which association is not possible, at least by hydrogen bonding) and by u.v. and other spectroscopic techniques when both can be applied. (See A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 311, 339).

[8] P. Beak and J. T. Lee, jun., *J. Org. Chem.*, 1969, **34**, 2125.

[9] Support for these assumptions is provided by similar dipole moments between the compound pairs for the oxygen systems; H. Lumbroso and D. M. Bertin, *Bull. Soc. chim. France*, 1970, 1728.

[10] See *e.g.* E. M. Arnett, R. P. Quirk, and J. J. Burke, *J. Amer. Chem. Soc.*, 1970, **92**, 1260; E. M. Arnett, J. V. Carter, and R. P. Quirk, *ibid.*, **92**, 1770; E. M. Arnett, R. P. Quirk, and J. W. Larsen, *ibid.*, 92, 3977; also unpublished work from our laboratory.

[11] Details will be given in the full paper.

[12] J. W. Larsen and L. G. Hepler in 'Solute-Solvent Interactions' Ed. J. F. Coetzee and C. D. Ritchie, Dekker, New York, 1969, p. 1. However, a refinement introduces a solvent dependent parameter γ, and $\Delta G = \Delta H_{\text{int}} (1 + \gamma)$.

[13] K. Bowden and A. F. Cockerill, *J. Chem. Soc.* (*B*), 1970, 173.

[14] A. F. Bedford, A. E. Beezer, and C. T. Mortimer, *J. Chem. Soc.*, 1963, 2039.