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HETEROAROMATICITY.7. SOME QUANTITATIVE ASPECTS OF THE TAUTOMERISM OF HYDROXY- AND MERCAPTOAZINES*

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Abstract - Aromaticity indices have been calculated from crystallographic data for a range of oxo tautomers of hydroxyazines. The differences between these indices and those for the hydroxyazines lead to values for changes in resonance energies accompanying tautomerisation. These values are closely parallel to those previously measured for the same process in aqueous solution.

Tautomeric equilibria play an important role in the chemistry of hydroxyheterocycles and also in their interaction with other biologically important compounds[1,2]. Consequently, the energetics of these processes are of considerable interest. The direct study of such equilibria is restricted to situations where the energy difference between the tautomers is small and the isomers are spectroscopically detectable. Otherwise recourse is usually made to the measurement of the relative basicities of the various O- and N-methyl derivatives. However, this approach is of questionable validity when applied to systems with multiple protonation sites. In this paper a new approach is presented whose only requirement is the availability of X-ray structures of appropriate model compounds. The approach is based upon the aromaticity index, I_A, introduced in an earlier paper[3]. Briefly, I_A is based upon a statistical evaluation of the extent of variation of ring bond order as given by the expression $I_A = 100F(1 - V/V_K)$ where $V = 100/\bar{N}\sqrt{(N - \bar{N})^2/n}$ and $\bar{N}$ is the arithmetic mean of the n various ring bond orders, N. These are readily obtained from the corresponding bond lengths. V_K is the value of V for the corresponding non-delocalised Kekulé form of the ring and F is a scaling factor with values of 1.235, 1, 2.085 and 1.84 for 5-, 6-, 5,6- and 6,6-membered ring systems respectively. On this scale benzene, with a resonance energy of 2β, has an I_A of 100 so that a unitary increment on the I_A scale corresponds to 0.02β, that is 0.36 Kcals/mole if we assume the commonly ascribed value of 18 Kcals/mole for β. It is pertinent to note that the majority of ring substituents have a marginal

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*Dedicated to Professor Charles Rees on the occasion of his sixtyfifth birthday and as a mark of a felicitous friendship going back to our Birkbeck days.

effect upon the dimensions of the ring to which they are attached, at least as regards the calculation of I_A's. The only exceptions arise in situations where strong mesomeric interactions are transmitted through the ring as for example in cytosine (vide infra).

A feature which is not always appreciated, although well documented, is that the aromaticity of a molecule may be affected by its interaction with adjacent molecules. Such an effect, for example, is involved in the shifting of tautomeric equilibria of the hydroxypyridine / pyridone type towards the pyridone by increasing the solvent polarity[4]. A similar effect is encountered in the solid state as illustrated by comparison of the I_A values of 46.4 and 59.2 calculated for N-(2',6'-dichlorobenzyl)-pyrid-2-one[5] and 5-chloropyrid-2-one[6] respectively. In the latter case substantive intermolecular hydrogen bonding in the crystal lattice, as indicated in Figure I, serves to bolster the diminished aromatic character of the pyridone ring. A similar enhancement of I_A for the pyridone ring to 58.5 is observed for the 1:1 complex of N-methylpyrid-2-one with 5,5-diethylbarbituric acid[7]. An important feature of the crystal lattice is the hydrogen bonds between the pyridone carbonyl oxygen and the N-H's of the diethylbarbituric acid.

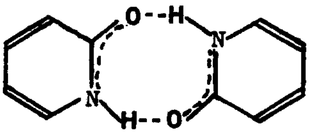
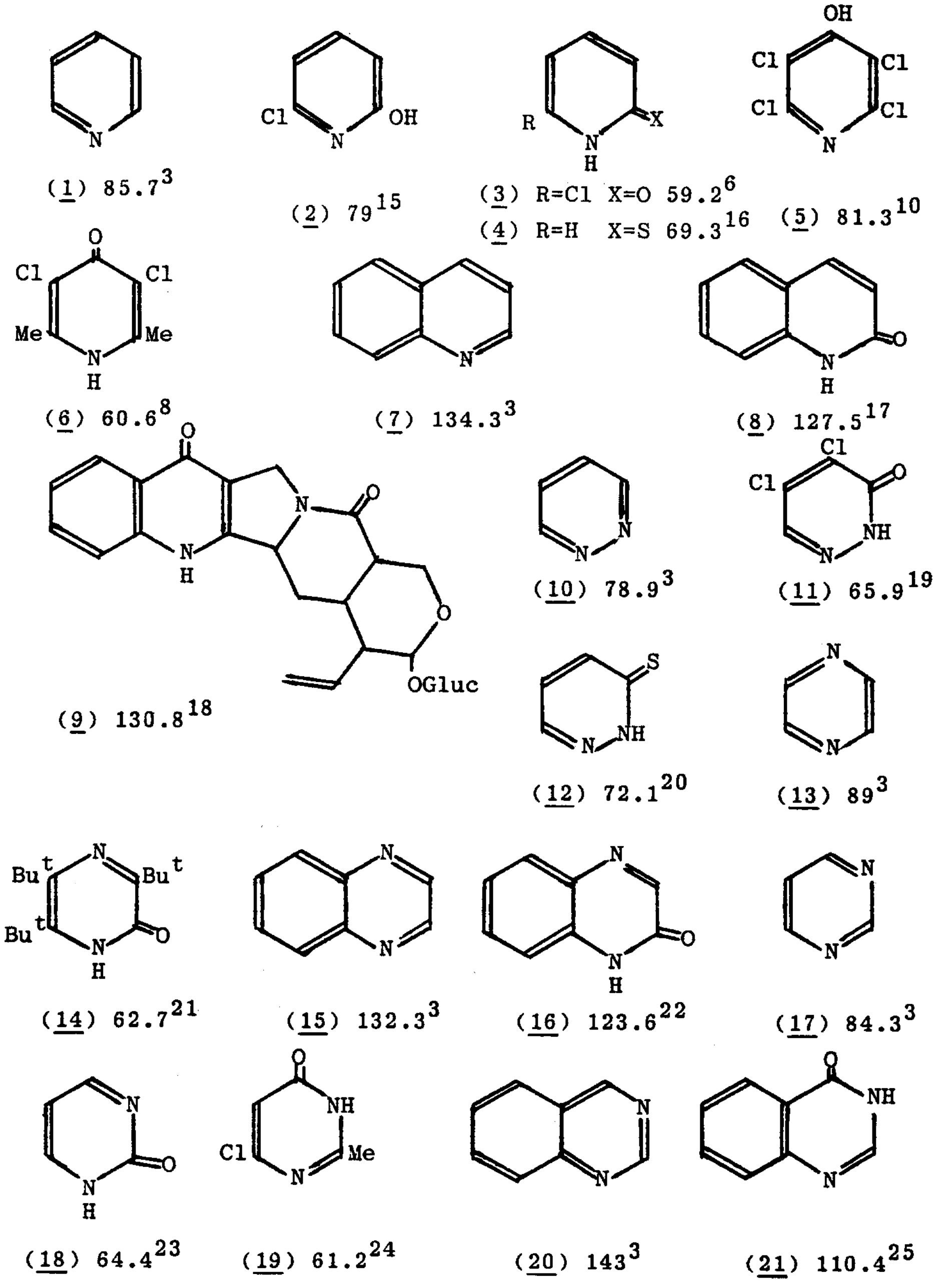


FIGURE 1

A similar situation arises in the 4-hydroxypyridine / pyrid-4-one system where, in the crystalline state, hydrogen bonding occurs between the N-H of one molecule and the carbonyl oxygen of the next[8,9]. Clearly this arrangement is only a short step away from complete proton transfer and formation of the hydroxypyridine tautomer. Indeed there are examples in the crystallographic literature of both 4-hydroxypyridines[10,11] and 1H-pyridones[8,9]. Again, the role of hydrogen bonding in increasing aromaticity is exemplified by the increase of I_A observed when N-methyl-2,6-dimethylpyrid-4-one, for which a value of ca. 57 can be assessed from other N-substituted pyrid-4-ones[12], is complexed with biphenylene-1,8-diol[13] to give an I_A of 66. In this case the carbonyl oxygen is hydrogen bonded to both hydroxyl groups and this probably accounts for the higher value obtained than that of about 61 observed in a normal lattice situation.



(1) 85.7[3]

(2) 79[15]

(3) R=Cl X=O 59.2[6]

(4) R=H X=S 69.3[16]

(5) 81.3[10]

(6) 60.6[8]

(7) 134.3[3]

(8) 127.5[17]

(9) 130.8[18]

(10) 78.9[3]

(11) 65.9[19]

(12) 72.1[20]

(13) 89[3]

(14) 62.7[21]

(15) 132.3[3]

(16) 123.6[22]

(17) 84.3[3]

(18) 64.4[23]

(19) 61.2[24]

(20) 143[3]

(21) 110.4[25]

FIGURE 2 Aromaticity indices for hydroxy and mercaptoazines. (The references are to the source of bond lengths used for their calculation.)

TABLE I Aromatic Resonance Energy Differences for Tautomers (Kcals/mole)

Tautomeric System	Ref. Compds.*	ΔI_A	$\Delta\Delta H$	Exptl.[14]
2-Hydroxypyridine/pyrid-2-one	(2),(3)	19.8	7.1	7.5±1
4-Hydroxypyridine/pyrid-4-one	(5),(6)	20.7	7.5	7.7±1.5
2-Mercaptopyridine/pyrid-2-thione	(1),(4)	16.4	5.9	6±1
2-Hydroxyquinoline/quinol-2-one	(7),(8)	6.8	2.45	2±0.5
4-Hydroxyquinoline/quinol-4-one	(7),(9)	3.6	1.3	-
3-Hydroxypyridazine/2H-pyridaz-3-one	(10),(11)	13.0	4.7	-
3-Mercaptopyridazine/2H-pyridaz-3-thione	(10),(12)	6.8	2.45	-
2-Hydroxypyrazine/pyrazin-2-one	(13),(14)	26.3	9.5	-
2-Hydroxyquinoxaline/quinoxalin-2-one	(15),(16)	8.7	3.1	-
2-Hydroxypyrimidine/pyrimid-2-one	(17),(18)	19.9	7.2	-
4-Hydroxypyrimidine/3H-pyrimid-4-one	(17),(19)	23.1	8.3	-
4-Hydroxyquinazoline/3H-quinazol-4-one	(20),(21)	32.6	11.7	-

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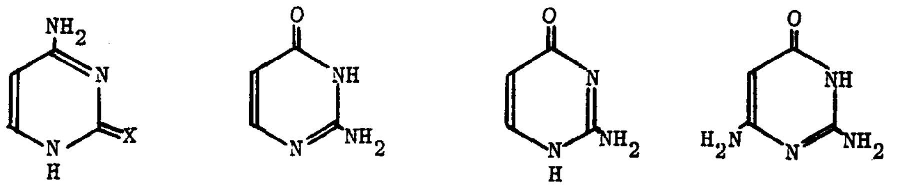
*See Figure 2

Using compounds (2) and (3) as models we can estimate the loss in resonance energy in the tautomerisation of 2-hydroxypyridine to pyrid-2-one as ΔI_A=19.8 which corresponds to 7.1 Kcals/mole. This figure is close to that, 7.5±1 Kcals/mole, measured for this conversion in aqueous medium[14]. Consequently, a similar analysis has been applied to other tautomeric systems for which appropriate crystallographic data are available. It will be noted that aromaticity indices are not available in all cases for the corresponding hydroxy tautomer and that the value for the parent heterocycle has been used instead. Although in the hydroxypyridines, intermolecular hydrogen bonding slightly lowers the ring I_A the effect is expected to be less pronounced with the other heterocycles under consideration. The results are summarised in Table 1 and show that, where available, there is a remarkable concurrence between the resonance energy differences deduced for the crystalline state and those obtained for the corresponding systems in aqueous solution. It should be noted that the energy differences for the first two entries are raised to 8.8 and 9.2 Kcals/mole respectively if pyridine (1) is used as the reference compound for the hydroxypyridine tautomers. Clearly the high dielectric constant anticipated for the crystal lattice accompanied by the extensive intermolecular hydrogen bonding provides an excellent surrogate for the aqueous phase. Consequently it seems likely that the conclusions regarding the other compounds in Table I will also be applicable to aqueous media.

The tautomeric equilibria of cytosine and related compounds are of especial biochemical interest[26]. In accord with what has been indicated earlier the introduction of the amino group into 1*H*-pyrimidin-2-one (18) results in a small reduction of I_A from 64 to 61.4 for cytosine (22). This in turn leads to an estimate of 7.7 Kcals/mole for the energy difference between cytosine and its 4-amino-2-hydroxypyrimidine tautomer*. A recent theoretical calculation has derived[2] a value of 8.1 Kcals/mole for aqueous solution. As might be expected the corresponding energy difference for thiocytosine (23) is much smaller, 5.7 Kcals/mole. Isocytosine is remarkable in that both possible oxotautomers coexist in a 1:1 ratio in the crystalline state[29]. The energy differences between (24) and (25) and their 2-amino-4-hydroxypyrimidine tautomer are 6.6 and 8.9 Kcals/mole respectively. The introduction of an additional amino group as in (26) boosts the I_A value further to 71.8 lowering the energy gap now to 4.5 Kcals/mole. The behaviour of the amino groups in this system can be readily rationalised as a "push-pull" effect resulting from mesomeric interaction of the amino and carbonyl groups.



(22) X=O 61.4[27] (24) 66[29] (25) 59.5[29] (26) 71.8[30]

(23) X=S 68.5[28]

FIGURE 3 Aromaticity indices for cytosine derivatives. (The references are to the source of bond lengths used for their calculation.)

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*Pyrimidine itself is used as a model compound for the aminohydroxypyrimidines for the purpose of the ensuing analysis.

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