HETEROAROMATICITY. 9 . THE ROLE OF ZWITTERIONS IN THE TAUTOMERISM OF HYDROXY- AND MERCAPTOHETEROCYCLES[*†]

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Abstract - The application of the Aromaticity Index, I_A, shows that the zwitterions derived from a variety of hydroxy or mercaptoheterocycles have comparable aromaticities to their precursors, thus emphasising the potential role of zwitterionic species in tautomeric equilibria.

It is well established[1] that in aqueous solution 3-hydroxypyridine is in equilibrium with an approximately equal amount of the zwitterion, Scheme 1. This behaviour is of particular importance to the chemistry of pyridoxine and its congeners[2]. The factors governing the extent of formation of analogous zwitterions by other hydroxy or mercapto heterocycles are not well understood. Amongst the potential contributory factors is the difference in ring resonance energy between the hydroxy or mercapto heterocycle and the derived zwitterion.

Scheme 1. Tautomeric Equilibrium of 3-Hydroxypyridine

A means of estimating this energy difference is provided by our recently introduced[3] aromaticity index, I_A. This index is based upon the extent of variation of ring bond orders and is directly proportional to the resonance energy[3,4] with a unitary increment on the I_A scale corresponding to 0.02β, that is 0.36 Kcal mol $^{-1}$ if the commonly ascribed value of 18 Kcal mol $^{-1}$ for β is adopted. In general substituents have little effect on ring aromaticity so that hydroxy/mercapto heterocycles usually have virtually the same I_A as the parent heterocycle. X-ray crystallographic data, and hence I_A's are also available for a variety of mesoionic compounds that can be confidently accepted as models for the anticipated zwitterions.

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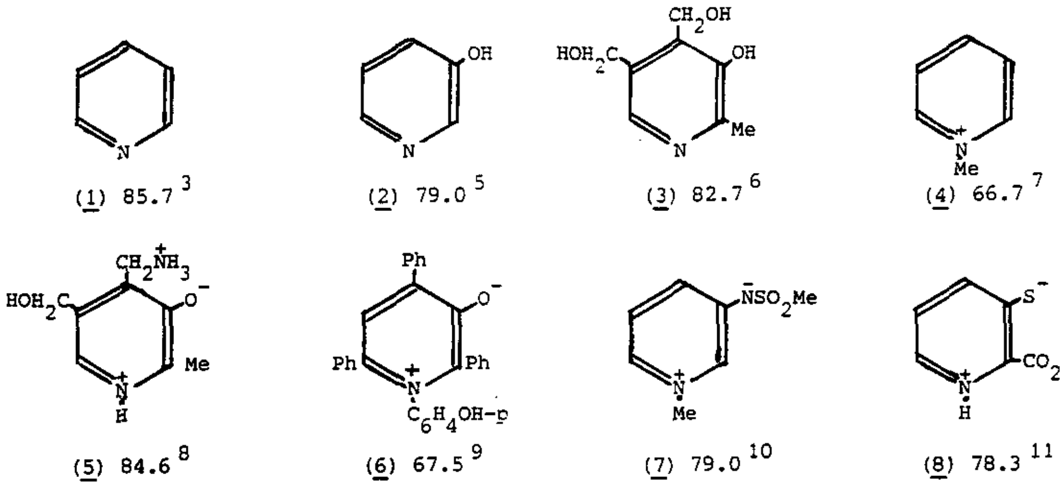
[*] Dedicated to Professor Alan Katritzky on the occasion of his sixtyfifth birthday.

[†] For part 8 of this series cf. C.W. Bird, Tetrahedron, 1993, 49, 8441.



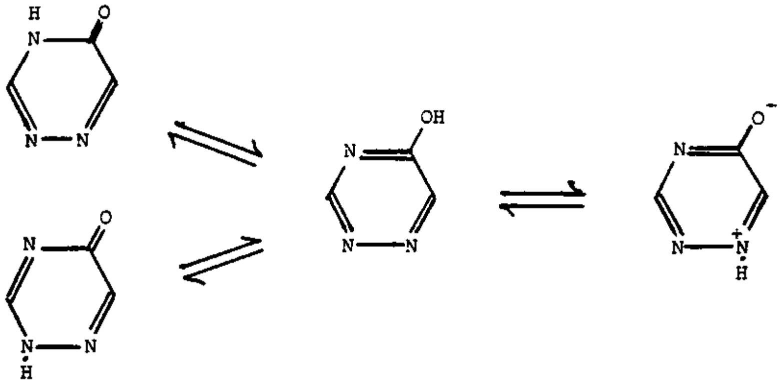
(1) 85.7[3] (2) 79.0[5] (3) 82.7[6] (4) 66.7[7]

(5) 84.6[8] (6) 67.5[9] (7) 79.0[10] (8) 78.3[11]

Scheme 2. I_A's of 3-Hydroxypyridines and Related Compounds. (References are to the sources of crystallographic data).

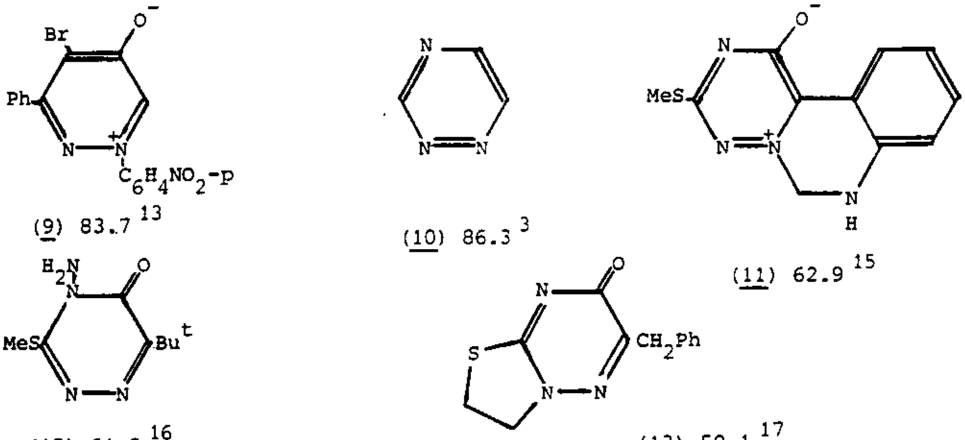
In Scheme 2 are presented the calculated I_A's for a range of 3-hydroxypyridines and related compounds. It will be noted that some 3-hydroxypyridines such as 2 and 3 exist as such in the crystal lattice while others such as 5 form the zwitterion. The zwitterion is of comparable aromaticity to the hydroxypyridines, and appreciably more aromatic than the pyridinium cation (4). We have reported elsewhere[12] that hydrogen bonding in the crystal lattice can provide conditions comparable to those experienced in aqueous solution. The somewhat lower value of I_A for 6 may result from much reduced possibilities for similar hydrogen bonding. It is interesting to recall[12] that the keto tautomers of 2- and 4-hydroxypyridine have very much lower I_A's, 59 and 61 respectively, than the present zwitterions. The slightly lowered I_A's for the 3-hydroxypyridines relative to pyridine may be attributed to intermolecular hydrogen boding. The methanesulfonamido group is often used as a surrogate for a phenolic hydroxyl by medicinal chemists. The I_A of 79 for 7 is in keeping with the observation[1] that 10% of 3-methanesulfonamidopyridine exists in the zwitterionic form in aqueous solution. Somewhat surprisingly 3-mercaptopyridine-2-carboxylic acid preferentially relocates the thiol proton, rather than the carboxyl one, to form the zwitterion (8) in the solid state. 3-Mercaptopyridine exists virtually exclusively as the zwitterion in aqueous solution.

Appropriate structural information on other pertinent six-membered heterocycles is limited. The I_A calculated for the pyridazine betaine (9), Scheme 4, is comparable with that anticipated, 79, for a 4-hydroxypyridazine and far higher than expected for the pyridazin-4(1*H*)-one tautomer which normally predominates in solution.[1] In the case of 5-hydroxy-1,2,4-triazine model compounds 10 to 13 are available for all four possible tautomers, cf. Scheme 3. It is clear that the zwitterion model (11) has comparable aromaticity to that of



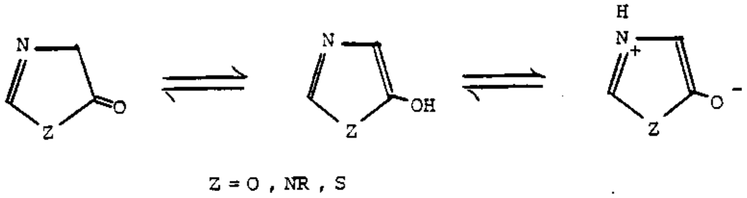
Scheme 3. Tautomeric Equilibria of 5-Hydroxy-1,2,4-triazine

the keto tautomer models (12 , 13), but all are lower than the I_A of 86 expected for the 5-hydroxy tautomer. Information presently available[18] indicates that the 5(2*H*)-one tautomer predominates in solution and the 5-hydroxy tautomer in the solid state.

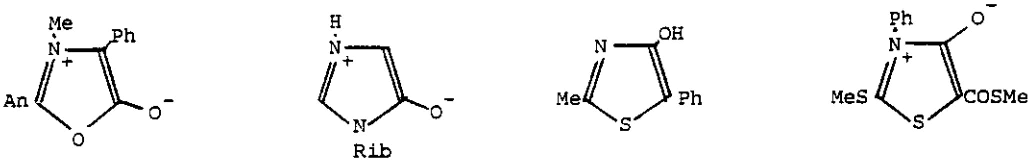

(9) 83.7 [13]
(10) 86.3 [3]
(11) 62.9 [15]
(12) 61.2 [16]
(13) 50.1 [17]

Scheme 4. I_A's of 5-Hydroxy-1,2,4-triazines and Related Compounds. (References are to the sources of crystallographic data).

The nominal 5-hydroxyoxazoles are well established[19] as existing either as the 2-oxazolin-5-one or as the 1,3-oxazolium 5-oxide (munchnone), Scheme 5 Z = O. The elusive 5-hydroxyoxazole would be expected to have the same I_A of 47 as oxazole while the munchnone (14) has an I_A of 36.3, cf. Scheme 6. An analogous situation arises with 5-hydroxy-1-substituted imidazoles (Scheme 5 Z = NR), which exist as the zwitterionic species as evidenced by 15 with an I_A of 68, rather than as the hydroxy tautomer with an anticipated I_A of 79. Although 5-hydroxythiazoles (Scheme 5 Z = S) appear to display similar tautomeric behaviour there are no appropriate crystal structures available. However, 4-hydroxythiazoles such



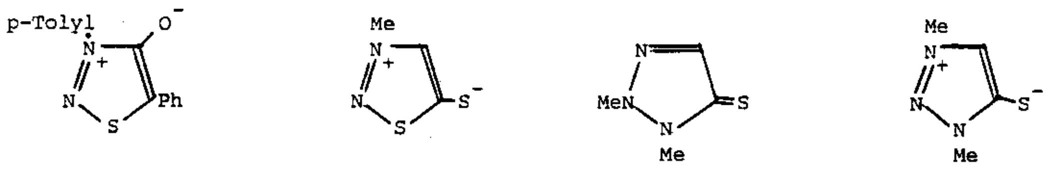
Scheme 5. Tautomeric Equilibria of Hydroxy-1,3-azoles



(14) 36.3 [20] (15) 68 [21] (16) 79.9 [22] (17) 70.7 [23]

Scheme 6. I_A's of 1,3-Azoles and Related Compounds. (References are to the sources of crystallographic data).

as (16), $I_A = 79.9$, exist as such even though zwitterionic species, represented by (17) with an I_A of 70.7, need not differ greatly in aromaticity.

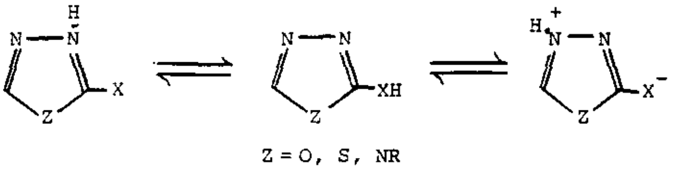


(18) 91.5 [25] (19) 79 [26] (20) 99.8 [27] (21) 99 [28]

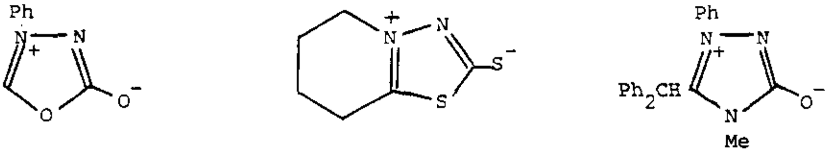
Scheme 7. I_A's of 1,2,3-Thiadiazoles and 1,2,3-Triazoles. (References are to the sources of crystallographic data).

Little is known about the tautomeric preferences of hydroxy or mercapto 1,2,3-thiadiazoles. However, the I_A's of 91.1 for 18 and 79 for 19, Scheme 7, are far larger than the expected I_A of 67 for hydroxy/mercapto-1,2,3-thiadiazole. The experimental situation regarding the tautomerism of 5-mercapto-1-substituted 1,2,3-triazoles is also unclear.[1] The compounds (20) and (21), as models for the potential keto and zwitterionic tautomers, have higher I_A's of 99.8 and 99 respectively than the value of 90 predicted for the mercapto tautomer.

The 2-hydroxy/mercapto derivatives of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 4-substituted 1,2,4-triazoles, Scheme 8, all show a marked preference for the 2-oxo/thione tautomer.[1] The I_A's for the zwitterion model compounds (22), (23) and (24), Scheme 9, of 53, 73.8 and 81 may be compared with the anticipated values of 62, 80 and 81.5 respectiv-



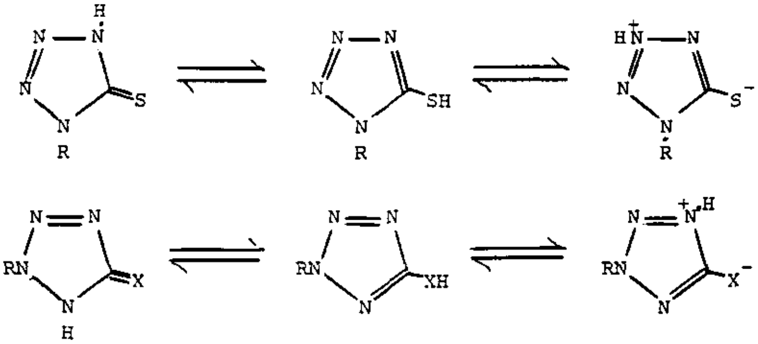
Scheme 8. Tautomeric Equilibria of 2-Hydroxy-1,3,4-oxadiazole and Related Heterocycles



(22) 53 [29] (23) 73.8 [30] (24) 81 [31]

Scheme 9. I_A's of 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles and 1,2,4-Triazoles. (References are to the sources of crystallographic data).

ely for the corresponding hydroxy/mercapto tautomers. The latter compound may also be viewed as a model for the zwitterion from 3-hydroxy-1-substituted 1,2,4-triazoles, which would have an I_A of about 100 when unionised.



Scheme 10. Tautomeric Equilibria of Hydroxy- or Mercaptotetrazoles

(25) 95 [29]

(26) X = O 98 [29]

(27) X = S 109[32]

Scheme 11. I_A's of Tetrazole Zwitterions

Although 1-aryl-5-mercaptotetrazoles, Scheme 10, apparently prefer the thione structure it is notable that 25 , as a model for the zwitterion, has a comparable I_A of 95 to that of 92 expected for the mercaptotetrazole. Nothing appears to be known about the tautomeric preferences of 5-hydroxy/mercaptotetrazoles, but the corresponding zwitterions as represented by 26 , $I_A = 98$, and 27 , $I_A = 109$, Scheme 11, display comparable aromaticity to the hydroxy/mercaptotetrazole with an anticipated I_A of about 107.

Many workers in this area have ignored the potential role of zwitterionic species in tautomeric equilibria, possibly because they were assumed to be energetically unlikely. The foregoing survey shows that in most cases the zwitterions derived from hydroxy or mercapto heterocycles have comparable aromaticities to their precursors, and thus should always receive due consideration in studies of the tautomeric equilibria of heterocycles.

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