

**Albert A & Phillips J N.** Ionization constants of heterocyclic substances. Part II. Hydroxy-derivatives of nitrogenous six-membered ring-compounds. *J. Chem. Soc.* 1956:1294-304.  
[Dept. Medical Chemistry, Australian National Univ., London, England (now at Canberra, Australia)]

This paper reported the acidic and basic ionization constants of the 'hydroxy' derivatives of six-membered heteroaromatic rings, and their O- and N-methyl derivatives (in all, 87 examples). The results showed that the cyclic-amide tautomer (-CO.NH) was greatly favored over the enolic tautomer (HO.C=N) in all  $\alpha$ - and  $\gamma$ -hydroxy derivatives, e.g., pyridin-2-one predominated over 2-hydroxypyridine. These results, from which tautomeric ratios were calculated, were supported by measurements of dipole moments. [The SCI<sup>®</sup> indicates that this paper has been cited in over 285 publications since 1961.]

Adrien Albert  
Department of Chemistry  
Australian National University  
Canberra, ACT 2600  
Australia

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"In 1948, Reg Goldacre, John Phillips, and I, working together at the University of Sydney, determined the ionization constants of 120 bases belonging to 30 different heteroaromatic (nitrogenous) ring systems.<sup>1</sup> At the present time, it is hard to believe that reliable values for even the simplest heterocyclic bases were unknown in those days. Moreover, the enormous increase in basic strength brought about by amino substituents was quite unexpected (our 'vinylogous amidine effect,' as seen in 4-aminopyridine). Eight years later, Phillips and I, finding ourselves together in London, decided to collaborate on a project that would throw more light on the corresponding 'hydroxy' derivatives which some workers were suggesting had properties more appropriate to a tautomeric oxo-form.<sup>2</sup>

"What we did was to prepare both the O- and the N-methyl derivatives of many such substances and determine their  $pK_a$  values. It involved a tremendous amount of synthetic and instrumental work, but we were

buoyed up by the thought that our results might help many workers in heterocyclic chemistry and in biological research.

"It turned out that the O-methyl derivatives (e.g., 2-methoxy quinoline) were much stronger bases than their N-methyl isomers (e.g., 1-methylquinolin-2-one). The unmethylated compounds possessed the weaker basic strength of the N-methyl derivatives and hence were principally in the cyclic amide tautomeric form. We went on to calculate the approximate ratio (R) of these tautomers at equilibrium in water, using Ebert's equation, and found that R was always a large number, e.g., 3,000 for '2-hydroxyquinoline' and ten million for '9-hydroxyacridine.' Henceforth, names of the type 'pyrid-2-one' replaced the former '2-hydroxypyridine.' Substances like quinolin-4-one were seen as vinylogous amides. Altogether, 17 heterocyclic nuclei were explored in this way, including examples with two or even three nitrogen atoms, and the same predominance of amide tautomers was nearly always found.

"Later, this work was confirmed by Stephen Mason in the same laboratory, using spectrometric (uv) measurements, a modification which gave similar but more exact tautomeric ratios.<sup>3</sup> In 1959 and 1962, Gordon Barlin and I extended these studies to the 'mercapto' analogs of these substances, using both potentiometric and spectrometric methods, and found that the equilibria greatly favored the thioamide tautomers. The most recent work on these amide and thioamide equilibria shows that self-association in nonaqueous solvents displaces the equilibria in favor of the hydroxy forms, and that the vapor phase greatly favors the hydroxy forms.<sup>4</sup>

"I think that the frequent citation of our 1956 paper owes much to its demonstration that favoring the amide tautomer is a widespread phenomenon for  $\alpha$ - and  $\gamma$ -substituted examples, and that a hydroxy-group in other positions produces a normal phenol, as we showed for the 5-, 6-, 7-, and 8-hydroxyquinolines. The use of these results has been widespread; for instance, the amide-enol equilibrium of uracil is thought to underlie instances of genetic mutation."

1. Albert A, Goldacre R J & Phillips J N. The strength of heterocyclic bases. *J. Chem. Soc.* 1948:2240-9.
2. Tucker G F, Jr. & Irvin J L. Apparent ionization exponents of 4-hydroxyquinoline, 4-methoxyquinoline, and N-methyl-4-quinolone: evaluation of lactam-lactim tautomerism. *J. Amer. Chem. Soc.* 73:1923-9, 1951.
3. Mason S F. The tautomerism of N-heteroaromatic hydroxy-compounds. Part II. Ultraviolet spectra. *J. Chem. Soc.* 1957:5010-17.
4. Beak P. Energies and alkylations of tautomeric hydroxy compounds: old problems and new answers. *Account. Chem. Res.* 10:186-92, 1977.