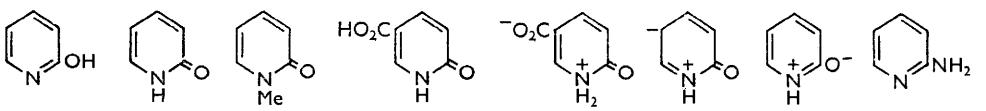
210. *Ionization Constants of Heterocyclic Substances. Part IV.*[1] *The Effect of a Tautomerizable α-Substituent on the Ionization of a Second Substituent.*

By Adrien Albert.

It is found that the –NH·CO– group in 2-pyridone (I ⟷ II) exerts an acid-strengthening effect on a further substituent, and that it is at least as electron-attracting as the –N=C– group of pyridine. This behaviour of the molecule in its ground state is contrasted with the electrophilic substitution of 2-pyridone and its *N*-methyl-derivative (III), which proceeds so very much more readily than in pyridine. It is concluded that electrophilic substitution of (II) and (III) involves an electromeric change in the polarity of the –NH·CO– group, to give a transition state such as (VI). By contrast, 2-aminopyridine is found to be electron-releasing in both ground and transition states.

The electrophilic substitution of a hydrogen atom in pyridine is difficult because of the lack of available electrons on all the carbon atoms. Thus a temperature of 300° is required for nitration of pyridine, and the yield is only 5%.[2] However, in all monoamino- and hydroxy-pyridines, electrophilic substitution proceeds readily, even at room temperature, a facility which is usually attributed to the electron-releasing properties of these substituents. Nevertheless, there are in 2- and 4-hydroxypyridine respectively 340 and 2200 molecules of the amide form, *e.g.*, (II), to each molecule of the enol form, *e.g.*, (I),[3] and analogues in which the amide form is fixed, as in (III), are no less easily substituted electrophilically.



(I) (II) (III) (IV) (V) (VI) (VII) (VIII)

For example, 1,2-dihydro-1-methyl-2-oxopyridine (*N*-methyl-2-pyridone) (III) is nitrated so readily to give the 5-nitro-derivative, at 40°, that the nitric acid must be diluted to prevent formation of the 3,5-dinitro-derivative (the latter is exclusively formed at 100°).[4] Again, the compound (III) is converted by bromine in acetic acid, without

[1] Part III, Albert and Barlin, *J.*, 1959, 2384.
[2] den Hertog and Overhoff, *Rec. Trav. chim.*, 1930, **49**, 552.
[3] Albert and Phillips, *J.*, 1956, 1294.
[4] Fischer and Chur, *J. prakt. Chem.*, 1916, **93**, 363; Tschischibabin and Konovalova, *Ber.*, 1925, **58**, 1712.

warming, into the 3,5-dibromo-derivative. 1,4-Dihydro-1-methyl-4-oxopyridine similarly gives a 3,5-dibromo-derivative.[5]

Thus the $-NH\cdot CO-$ group of (II) and (III) acts as an electron-releasing group in response to the approach of a cationic reagent. This is reminiscent of the acetamido-group in acetanilide which accelerates the bromination of the benzene ring by a factor of a million. But under static conditions aromatic amide-groups are electron-attracting. Thus *m*-acetamidobenzoic acid has been reported as 0·1 or 0·35 unit of pK stronger than benzoic acid (refs. 6*a* and *b*, respectively). Also, in the present work, *m*-acetamidophenol (see Table) is found to be 0·5 unit of pK stronger than phenol. Hence it was thought that the $-NH\cdot CO-$ group of (II) and (III) might also be electron-attracting under static conditions. As no relevant data for the effect of this group on the ionization of a second group could be found in the literature, model substances were prepared. The 5-position was chosen for the substituent, the ionization of which was to be examined. The 5-position is sufficiently remote from other groups to eliminate steric effects, and it is one of the positions where a hydroxyl group cannot take part in the type of tautomerism peculiar to α- and γ-hydroxypyridines.[7]

Ionization constants of pyridines in water at 20°.

No.	Pyridine	pK_a		Spread ±	Concn.[e] (M)
1	(Unsubst.)	5·23[a]	B[d]		
2	2-OH (II)	11·62[b]	A		
		0·75[b]	B		
3	3-OH	8·72[b]	A		
		4·86[b]	B		
4	1,2-Dihydro-1-methyl-2-oxo (III) (*N*-Me derivative of No. 2)	0·32[b]	B		
5	2,5-$(OH)_2$	8·51	A	0·01	0·005
6	3-CO_2H (nicotinic acid)	4·81[c]	A		
		3·75[c]	A		
7	6-OH-3-CO_2H	3·82	A	0·02	0·005
8	6-OH-3-CO_2Me (Methyl ester of No. 7)	9·92	A	0·04	0·01
9	3-Carboxy-1,6-dihydro-1-methyl-6-oxo (*N*-Me derivative of No. 7)	3·84	A	0·02	0·005
		−1·7	B	0·1	0·0001
10	2-NH_2	6·86[a]	B		
11	3-NH_2	6·07	B	0·05	
		−1·5	B′		0·0001
12	2,5-$(NH_2)_2$	6·55	B	0·03	0·05
		2·13	B′	0·07	0·05[g]
13	*m*-Acetamidophenol	9·49	A	0·04	0·005
14	Phenol	9·98[h]	A		

[a] From ref. 8. [b] From ref. 3. [c] From ref. 9; the higher figure is for the zwitterion. [d] B means "basic pK" (*i.e.*, proton gained by titration with acid); A means "acidic pK" (*i.e.*, proton lost by titration with alkali). [e] An entry in this column shows that the constant was determined during present studies. [f] Spectrometric determination (all others, potentiometric). [g] Appropriate activity correction used. [h] From Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058.

It is seen from the Table that 2,5-dihydroxypyridine (No. 5) has an acidic pK of 8·51. Comparison with the pK's of 2- and 3-hydroxypyridine (Nos. 2 and 3) shows that this pK is too low to represent the ionization of the 2-hydroxy-group (which would be weakened to more than 12 by the mesomeric effect of the 5-hydroxy-group). Thus the value 8·5 refers to the ionization of the 5-hydroxy-group. A closer comparison of this value with that of 3-hydroxypyridine enables us to estimate the polarity of the $-NH\cdot CO-$ group of (II) in the ground state of the molecule. It is evident that No. 5 is no less acidic than

[5] Decker and Kaufmann, *J prakt. Chem.*, 1911, **84**, 440; Haitinger and Lieben, *Monatsh.*, 1885, **6**, 307.

[6] (*a*) Ostwald, *Z. phys. Chem.*, 1889, **3**, 369; (*b*) Bordwell and Boutain, *J. Amer. Chem. Soc.*, 1956, **78**, 854.

[7] Albert, "Heterocyclic Chemistry," London, Athlone Press, 1959, pp. 52—62.

[8] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

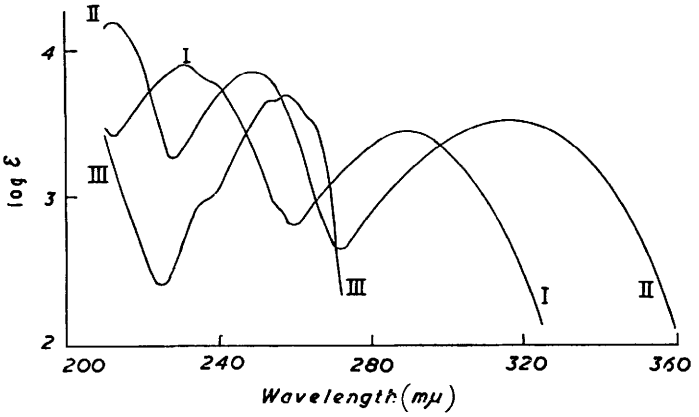
[9] Green and Tong, *J. Amer. Chem. Soc.*, 1956, **78**, 4896; Evans, Herington, and Kynaston, *Trans. Faraday Soc.*, 1953, **49**, 1284; Jaffé, *J. Amer. Chem. Soc.*, 1955, **77**, 4445.

No. 3 (in fact, 0·21 logarithmic unit stronger). Thus it appears that the –NH·CO– group in (II) is strongly electron-attracting, like the –N=C– group in pyridine.

Next, 6-hydroxypyridine-3-carboxylic acid (No. 7) has an acidic pK of 3·82 which is hardly changed on N-methylation (No. 9). The methyl ester (No. 8) has an acidic pK of 9·92, which must represent the ionization of 2-hydroxypyridine (No. 2) strengthened, by 1·7 units, through the inductive effect of the ester group. Thus the value of 3·82 for No. 7 must refer to the carboxyl group.

It is necessary to decide between formulæ (IV) and (V) for the acid [it is known that 2-pyridone (II) forms salts by protonation on the nitrogen atom [10]]. Nicotinic acid is known to be an equilibrium mixture of zwitterion and neutral molecule [9] in the ratio of 11 : 1. But it is evident that 2-pyridone, with its tautomeric ratio of 340 : 1 (see above), has the hydrogen atom more firmly attached to the ring-nitrogen atom than nicotinic acid has. Thus in 6-hydroxypyridine-3-carboxylic acid, the assumption of a form corresponding to (II) rather than to (I), must make the ring-nitrogen atom too weak for zwitterion

Ultraviolet spectra of 3-*aminopyridine.* I, *molecule at* pH 8; II, *monocation at* pH 3·5; III, *dication at* pH −4·2 (H_0).



formation by the carboxylic acid group (see No. 9 for an indication of this weakness). Thus the acid has structure (IV), and the pK (3·82) is to be compared with the carboxylic acid value for the molecule (3·75) of nicotinic acid (No. 6) and not with that for the zwitterion (4·81). Hence once again the –NH·CO– and –N=C– groups are found to be qualitatively and quantitatively similar.

Thus the electron-releasing effect of the –CO·NH– group during the electrophilic substitution of pyridines is opposed to the electron-attracting effect of this group in the ground state of the molecule. Electrophilic substitution may involve an electromeric transition state similar to (VI) which can be derived from both (II) and (VII) [canonical forms of a resonance hybrid to which (II) is the major contributor].

In contrast to 2-pyridone, 2-aminopyridine is known to have a 200,000-fold preponderance of the tautomer without hydrogen on the ring-nitrogen atom, *i.e.*, (VIII), at equilibrium in aqueous solution.[11] The ionization of 2-aminopyridine is known simultaneously to involve both nitrogen atoms in a resonance hybrid of the cation,[8] but both nitrogen atoms of 3-aminopyridine ionize independently. The determination of both ionization constants of the latter enables the spectrum of each of its cations to be isolated and measured for the first time. It is evident from the Figure that the first ionization,

[10] Spinner, *J.*, in the press.
[11] Angyal and Angyal, *J.*, 1952, 1461.

which involves a bathochromic shift, must correspond to protonation of the ring-nitrogen atom,[12] but addition of the second proton must correspond to the protonation of the primary amino-group because it is hypsochromic and gives the spectrum of pyridine hydrochloride, which has $\lambda_{max.}$ 260 mμ.

This information enables the ionization of 2,5-diaminopyridine to be discussed. If the more basic pK (6·55) (compared with those of Nos. 10 and 11) corresponds to the combined ionization of the ring-nitrogen atom and the 2-amino-group, the less basic pK (2·13) refers to the ionization of the 3-amino-group which is seen to be 3·6 logarithmic units stronger than in 3-aminopyridine. Thus the amino-group in 2-aminopyridine is highly electron-releasing in the ground state, just as it is during electrophilic substitution. Even if the pK 6·55 of No. 12 is assigned to the ionization of the 3-amino-group, the same qualitative conclusion is reached.

Experimental

Microanalyses were carried out by the analytical section of this Department, under Dr. J. E. Fildes.

2,5-Dihydroxypyridine was made by persulphate oxidation of 2-pyridone [13] and recrystallized from 100 parts of ethanol (Found, for material dried at 20°/15 mm.: C, 54·6; H, 4·7; N, 12·45. Calc. for $C_5H_5O_2N$: C, 54·05; H, 4·5; N, 12·6%). The $\lambda_{max.}$ in water were 230 and 320 mμ, in agreement with the literature.

6-Hydroxypyridine-3-carboxylic acid was made by the action of ammonia on 2-pyrone-5-carboxylic acid.[14] It was recrystallized from water (100 parts) and dried at 110° (Found: C, 51·5; H, 3·7; N, 9·85. Calc. for $C_6H_5O_3N$: C, 51·8; H, 3·6; N, 10·1%). The methyl ester, m. p. 166°, was made by the successive reaction of the above with thionyl chloride and methanol [15] and recrystallized from acetone. 1,6-Dihydro-1-methyl-6-oxopyridine-3-carboxylic acid was made by the action of methylamine on 2-pyrone-5-carboxylic acid.[13,16] Recrystallized from 9 parts of water, then 18 parts of alcohol, it gave colourless crystals, m. p. 241° (lit., 239°) (Found: C, 55·1; H, 4·8; N, 9·15. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6; N, 9·15%).

3-Aminopyridine, m. p. 64°, was purified by recrystallization from light petroleum (b. p. 60—70°). 2,5-Diaminopyridine was obtained by hydrogenating 2-amino-5-nitropyridine, m. p. 189°, in alcohol over Raney nickel. The product, sublimed at 80°/0·005 mm., had m. p. 106° (lit., 104°).[17]

The ionization constants were determined as in ref. 3.

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[12] As Ref. 7, p. 303. Some spectra of 3-aminopyridine were measured by Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397, but without reference to ionization constants.
[13] Behrman and Pitt, *J. Amer. Chem. Soc.*, 1958, **80**, 3717.
[14] Pechmann and Welsh, *Ber.*, 1884, **17**, 2384.
[15] Meyer, *Monatsh.*, 1901, **22**, 440.
[16] Meyer, *Monatsh.*, 1905, **26**, 1318.
[17] den Hertog and Jouwersma, *Rec. Trav. chim.*, 1953, **72**, 125.