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COMPARATIVE BASICITIES OF SUBSTITUTED PYRIDINES AND ELECTRONEGATIVITY SERIES FOR SUBSTITUENTS IN THE PYRIDINE SERIES

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Relationships between basicity of the pyridine ring and the nature and position of substituents are found. Comparative electronegativity series are constructed for substituents (α, β, and γ) in the pyridine series. In isolated cases transmission of an effect from the β position by a M effect is found.

In research on pyrazoles, we were able to discover a number of regularities regarding the effect of substituents on the basicity of the aromatic ring [1]. However, in a number of cases the pyrazole system, with two nitrogen atoms and a capacity for tautomerism, was too complex for generalization, so we considered it necessary to check our observations on the "simpler" pyridine systems.

When determining pH values of solutions of sulfates of substituted pyridines, we previously [2] found that the pH values obtained could be converted to actual pK_a values by applying the formula $pK_a = 1.475\ pH + 0.42$. Thus, in respect of relative basicities, it was possible to compare our experimental material with the dissociation constants (pK_a) of various pyridines, determined directly by the usual methods (see [3]). In most cases, the results obtained by our method agree with the existing ones, (see table), but, in a number of cases, real differences are found which give additional information about molecular structure and the detailed properties of the substances investigated.

Introduction of a methyl group into the pyridine ring at position 2, 3, or 4 increases the latter's basicity by, respectively, 0.80, 0.51, and 0.85 pK_a units. Only in the case of 3-picoline can this increase in basicity be ascribed mainly to the +I effect of the Me group. Not only is the basicity of 4-picoline not less than, but it is higher than that of 3-picoline, and this can only be due to hyperconjugation.

Maximum basicity might have been expected for 2-picoline, since the +I effect is maximal at position 2, but it appeared that the basicity of 2-picoline is very close to that of 4-picoline. The steric demands of the proton being small, this can hardly be due to steric hindrance. It is possible that the hyperconjugation effect in 2-methylpyridine is less important, than in 4-methylpyridine, due to lower stability of the ortho-quinonoid structure in comparison with the para-quinonoid one [4].

Increase in number of alkyl substituents further increases basicity of the pyridine ring (Nos. 5-8). 2, 6-, 2, 5-, and 2, 4-lutidines give the same sequence for change in basicity as 2-, 3-, and 4-picolines. Replacement of methyl by ethyl is practically without effect on the basicity (Nos. 5, 7).

As would be expected, introduction of halogen substituents markedly lowers the basicity of the pyridine ring, and this is to be ascribed to the large -I effect of a halogen atom. The effect increases with decreasing atomic number of the halogen (basicity of chloro compounds lower than those of the corresponding bromides). Obviously, the + M effect for halogen substituents in pyridine is negligible, since no appreciable increase in basicity of 2- and 4-halogenopyridines as compared with the 3-isomer was found (Nos. 9-13).

Substituents such as formyl, acetyl, carboxyl, and nitro groups greatly lower the basicity of the pyridine ring (due to cooperative -I and -M effects), the predominant effect being, as with halogenopyridines, the -I effect, as the distance between the ring nitrogen atom and substituent increases, the basicity of the pyridine ring increases (Nos. 14-25). The following sequence is obtained by arranging the above-mentioned substituents according to degree of lowering of pyridine ring basicity: $NO_2 > COOR > COCH_3 > CHO$.

An aldehyde group is a much less powerful electron acceptor than an acetyl or carboxyl one. The difference is so great that it cannot be explained by a difference in electronic effect between H of formyl and Me of acetyl. Possibly it is connected with the ease of hydration of the aldehyde group in water, and with formation of even more basic acetals in methanol solution when determining the hydrolysis pH. This may also explain the difference between pK_a values obtained by calculation, and by direct titration (Nos. 15, 16).

In connection with the existence of tautomeric forms, 2- and 4-hydroxypyridine were not considered, though this tautomerism unconditionally affects the basicity. 3-Hydroxypyridine cannot exist in the pyridine form, and here the linear relationship between pH of sulfate hydrolysis and actual pK_a value (viz. $pK_a = 1.475\ pH + 0.42$) is not retained. The pK_a value of 3-hydroxypyridine, as found by potentiometric titration, is 4.85 (pK_a for pyridine 5.17), i.e., the β hydroxyl group behaves like an electron acceptor. Application of the same method to determine the hydrolysis pH of sulfates gives the following basicity values: 3.20 for pyridine itself, 3.62 for 3-hydroxypyridine. Just the same sort of

Compound No.	Substituent in pyridene nucleus	pH of sulfate soln. ± 0.01	pK_a, calculated from pH value ± 0.02	pK_a value according to the literature
1	2	3	4	5
1	Pyridine	3.20	5.14	5.17[4]
2	2-Methyl	3.87	6.12	5.97
3	3-Methyl	3.70	5.87	5.68
4	4-Methyl	3.89	6.15	6.02
5	2, 6-Dimethyl	4.28	6.73	6.75
6	2, 5-Dimethyl	4.09	6.45	6.55[6]
7	2, 4-Dimethyl	4.29	6.74	6.80
8	2-Methyl-5-ethyl	4.06	6.40	—
9	2, 4, 6-Trimethyl	4.89	7.45	7.45[9]
10	2-Chloro	0.61	1.31	—
11	3-Chloro	1.18	2.16	—
12	4-Chloro	1.62	2.80	—
13	2-Bromo	0.80	1.60	—
14	3-Bromo	1.21	2.20	—
15	2-Formyl	2.85	4.63	3.80[10]
16	3-Formyl	2.70	4.40	3.80
17	4-Formyl	3.10	4.99	4.77
18	2-Acetyl	1.17	2.14	—
19	3-Acetyl	1.79	3.06	—
20	2-Methoxycarbonyl	—	—	2.21[11]
21	3-Methoxycarbonyl	—	—	3.13
22	4-Methoxycarbonyl	—	—	3.26
23	3-Ethoxycarbonyl	1.53	2.67	—
24	4-Ethoxycarbonyl	1.80	3.07	—
25	3-Nitro	—	—	0.81[4]
26	3-Hydroxy	3.62	5.75	4.86[12]
27	2-Methyl-3-hydroxy	4.27	6.71	—
28	2-Methyl-5-hydroxy	4.02	6.34	—
29	2, 6-Dimethyl-3-hydroxy	4.92	7.67	—
30	2, 4, 6-Trimethyl-3-hydroxy	5.26	8.17	—
31	2-Propyl-3-hydroxy	4.55	7.13	—
32	2-Ethyl-6-methyl-3-hydroxy	4.74	7.41	—
33	2-Isobutyl-6-methyl-3-hydroxy	4.70	7.35	—
34	2-Isobutyl-3-hydroxy	4.50	7.05	—
35	N-oxide	1.01	1.90	0.79[13]
36	2-Methyl-N-oxide	1.50	2.63	—
37	3-Methyl-N-oxide	1.34	2.39	1.08
38	4-Methyl-N-oxide	1.66	2.86	1.29
39	3-Chloro-N-oxide	0.63	1.34	—
40	4-Nitro-N-oxide	0.47	1.11	(−1.7)
41	2-Vinyl	3.15	5.06	4.92[14]
42	4-Vinyl	3.46	5.51	—
43	2-Methyl-5-vinyl	3.71	5.83	—
44	2-Phenyl	—	—	4.48[15]
45	3-Phenyl	—	—	4.80
46	4-Phenyl	—	—	5.55
47	2-Methoxy	—	—	3.28[12]
48	3-Methoxy	—	—	4.88
49	4-Methoxy	4.51	7.06	6.62
50	2-α-Methylvinyl	3.52	5.62	—
51	2-α-Phenylvinyl	2.88	4.66	—
52	2-(1'-Cyclohexyl)	3.50	5.58	—
53	2-Phenoxy	1.14	2.10	—
54	2-p-Nitrophenyl	—	—	3.63[15]
55	2-o, p-Dinitrobenzyl	2.71	4.41	—
56	2-α-Hydroxybenzyl	2.80	4.55	—
57	2-Benzyl	3.26	5.22	—
58	2-Hydroxymethyl	3.58	5.70	—
59	2-Isobutyl	—	—	5.76[4]

(Table Continued)

pH and pK_a Values of Substituted Pyridines

Compound No.	Substituent in pyridene nucleus	pH of sulfate soln. ± 0.01	pK_a, calculated from pH value ± 0.02	pK_a value according to the literature
1	2	3	4	5
60	2-β-Hydroxyethyl	3.67	5.83	—
61	2-Isopropyl	—	—	5.83[4]
62	2-Methyl-3-ethyl	2.50	4.10	—
63	3-Isopropyl	—	—	5.72[4]
64	3-Isobutyl	—	—	5.82
65	4-Phenylethyl	—	—	4.62[15]
66	4-p-Nitrophenyl	—	—	4.90
67	4-m-Nitrophenyl	—	—	4.87
68	4-p-Nitrostyryl	—	—	5.15[16]
69	4-Benzyl	3.48	5.55	—
70	4-p-Chlorostyryl	—	—	5.66[16]
71	4-Styryl	3.72	5.90	5.92
72	4-p-Methylstyryl	3.74	5.93	5.94
73	4-Isobutyl	—	—	5.99
74	4-p-Isopropylstyryl	3.79	6.01	—
75	4-p-Methoxystyryl	3.80	6.02	6.03[16]

increase in basicity was found when the hydroxyl group was introduced at position 3 in a number of alkyl pyridines (Nos. 26–34), i.e., according to the results of our measurements, the β-hydroxyl group is electron-donating. It would appear to us that this contradiction arises through a difference between the conditions under which the basicity of 3-hydroxypyridine was determined. Metzler and Snell [5] investigated the UV spectra of 3-hydroxy derivatives of pyridine and showed that in aqueous solution 3-hydroxypyridine contains equal amounts of neutral and bipolar forms of the base

Hence, under the conditions of potentiometric titration, an aqueous solution of 3-hydroxypyridine consists partly of the bipolar form, which naturally, in neutral and slightly acid solution, has a depressed basicity value. Under our actual conditions, i.e., when measuring pH in acid ethanolic solution (pH ~ 3), 3-hydroxypyridine exis 2) in a form which is protonated at the nitrogen atom, but not ionized at the hydroxyl group, and which has a higher basicity than pyridine itself. These results indicate a rather powerful +M effect for the β-hydroxyl group, agreeing with the results of Bryson, who demonstrated the possibility of transmission of + M effects of substituents at the β position in the pyridine ring [6].

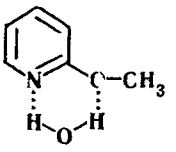
Using the conversion formula, we similarly obtained enhanced pK_a values for N-oxides too. Possibly this is connected with decreased solvation of the strongly polar oxide in methanol solution as compared with water, or with protonization at N or O atoms, depending on the pH of the solution. In any case, when various substituents were introduced into the pyridine N-oxide molecule, the same relationship was observed as with substituents introduced into pyridine (Nos. 35–40).

The vinyl, phenyl, and methoxy groups increase the basicity of the ring when introduced at position 4, and decrease the basicity of pyridine when introduced at position 2 or 3 (Nos. 41–49). All the substituents considered are electron-accepting in inductive effect and electron-donating in mesomeric effect (vinyl and phenyl can also be electron-acceptors.) At position 3 the –I effect of the substituents is manifest, which also leads to lowering of the basicity of the pyridine ring. The enhanced basicities of 4-vinyl-4-phenyl-, and 4-methoxypyridines are evidently due to the + M effect.

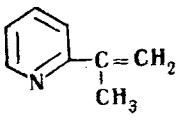
Thus with 4-substituted pyridines, phenyl, vinyl, and methoxy are powerful electron donors with respect to the pyridine ring. It is more difficult to explain the electron accepting capacity of the substituent considered at position 2 in the pyridine ring. There should be no real steric effect with 2-vinylpyridine (since replacement of methyl by ethyl or n-propyl leaves the basicity of the ring practically unaltered [4]). It can be postulated that the +M effect is not so con-

siderable in 2-vinylpyridine as in 4-vinylpyridine, due to the lower stability of the ortho-quinonoid form in comparison with the para one in the resonance structure. Furthermore, the –I effect of the vinyl group should be more powerful at postion 2, than at positions 3 and 4. The same reasoning applies to 2-phenylpyridine.

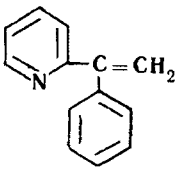
The basicity of 2-methoxypyridine drops very sharply. There, apart from factors mentioned for 2-vinyl- and 2-phenylpyridine, it may be that the closeness of the lone pair of electrons of the oxygen atom to the reaction center, inhibiting protonization of the nitrogen atom due to formation of stable solvated compounds, is significant:



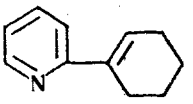
A number of 2-vinylpyridine derivatives, e.g.,



$pK_a = 5.62$



$pK_a = 4.66$



$pK_a = 5.58$

exhibit the usual regularities of effect of substituents: alkyl groups in the vinyl group somewhat enhance ring basicity, while the phenyl group, due to additional conjugation, somewhat decreases it.

It should be generally mentioned that, in interpreting the basicity data of 2-substituted pyridine, it is very difficult to sort out inductive, mesomeric, steric, and solvation effects. Obviously, to do that it would be necessary to use a combination of a number of methods of investigating a compound.

For substituents at the α, β, and γ positions in the pyridine ring, the order of electronegativity is given below:

α substituents:

$$Cl > Br \geqslant I > C_6H_5O > CH_3CO > CH_3O > C_6H_4NO_2\text{-}m > C_6H_4NO_2\text{-}p > CHO >$$
$$> CH_2C_6H_3(NO_2)_2\text{-}2,4 > C_6H_5 > CH(OH)C_6H_5 > -C(C_6H_5)=CH_2 > CH=CH_2 >$$
$$> H > -CH_2C_6H_5 > -\langle\!\rangle \geqslant C(CH_3)=CH_2 > CH_2OH > (CH_3)_2CHCH_2 \geqslant$$
$$\geqslant CH_2CH_2OH > (CH_3)_2CH \geqslant CH_3$$

β substituents:

$$NO_2 > Cl > Br > COOC_2H_5 > COCH_3 > CHO > C\equiv CH > C_6H_5 > CH_3O > CH=CH_2 >$$
$$> H > OH > CH_3 \geqslant C_2H_5 \geqslant (CH_3)_2CH \geqslant (CH_2)_2CHCH_2$$

γ substituents:

$$NO_2 > Cl > COOC_2H_5 > COCH_3 > -C\equiv C-C_6H_5 > CHO > C_6H_4NO_2\text{-}p > C_6H_4NO_2\text{-}m >$$
$$> CH=CH-C_6H_4NO_2\text{-}p > H > CH=CH_2 > CH_2C_6H_5 > C_6H_5 > CH=CHC_6H_4Cl\text{-}p > C_6H_5CH=$$
$$=CH > CH=CH-C_6H_4CH_3\text{-}p > CH_3(CH_3)_2CHCH_3 > CH=CH-C_6H_4CH(CH_3)_2\text{-}p \geqslant CH_3 \geqslant$$
$$\geqslant C_2H_5 \geqslant (CH_3)_2CH \geqslant CH=CH-C_6H_4OCH_3\text{-}p > OCH_3$$

The following are general regularities in the transmission of the effects of substituents to the pyridine ring:

1) +M effect of external π-electron systems is very strongly manifest at position 4, and rather weakly at position 2;

2) A +M effect is also found from position 3 (in the case of the OH group);

3) There is an unusually strong —I effect from position 2, though on the whole (as in the benzene series) many anomalies have to be taken into account when evaluating the effect of substituents from position 2.

Experimental

Low-boiling compounds with stable functional groups were distilled through a column. The other compounds were purified by column chromatography on aluminum oxide. Purities of preparations were checked by thin-layer chromatography using aluminum oxide [7]. Substances were considered to be pure if they gave only one spot with not less than two solvent systems.

The physical constants of the compounds investigated were in accordance with those given in the literature. Details of the method of measuring pH were previously given [1]. We wish to express our sincere thanks to E. F. Razadovskii, who kindly gave us a considerable number of the substances, and to K. M. Lyumaevyi, who gave us all the 3-hydroxypyridine derivatives.

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