

695. *Structure and Reactivity in the Pyridine Series. Part I. Acid Dissociation Constants of Pyridinium Ions.*

By A. FISCHER, W. J. GALLOWAY, and J. VAUGHAN.

The thermodynamic pK values of pyridine and thirty-three 3- and 4-substituted pyridines have been determined in water at 25°. The results show that there is resonance interaction between 4-(+ M)-substituents and the reaction centre. In contrast, 4-(− M)-substituents appear to exert an inductive effect only.

STRUCTURE-REACTIVITY correlations have been tested extensively in the benzene series, but there have been relatively few systematic studies of such correlations in other aromatic systems. Nuclear substitutions of benzene involve a different balance between the inductive and resonance effects of *para*-substituents than do side-chain reactions. Substituent effects in this first class of reactions might be expected to find a parallel in pyridine reactions in which the nuclear nitrogen atom acts as the functional centre. Furthermore, because the reaction centre is within the nucleus, pyridine reactivities should be particularly sensitive to the effect of substituents. Again, polarisation of the aromatic ring by the nuclear nitrogen atom might be expected to modify substituent effects.

The acid dissociation constants of a wide range of substituted pyridines have been measured previously but the measurements have been carried out by different investigators, at different temperatures, in solvents other than water and frequently under non-thermodynamic conditions. We now report measurements of the thermodynamic dissociation

constants of the pyridinium ion and thirty-three 3- and 4-substituted pyridinium ions in water at 25°. For ten of these compounds (4-*n*-propyl-, 3-benzoyl-, 4-benzoyl-, 4-benzyl-, 4-acetyl-, 3,5-dichloro-, 3,5-dibromo-, 3-bromo-5-methoxy-pyridine, methyl nicotinate, and methyl isonicotinate), dissociation constants have not been reported previously.

EXPERIMENTAL

Pyridines.—3-Nitropyridine was prepared by oxidising 3-aminopyridine with Caro's acid. To a cooled (10°) mixture of 3-aminopyridine (3.8 g.) in concentrated sulphuric acid (40 ml.), a mixture of fuming sulphuric acid (88 ml., containing 25% excess of sulphur trioxide) and hydrogen peroxide (44 ml.; 30%) was added carefully over a period of 1 hr. The resultant mixture was warmed gently on a water-bath and the vigorous reaction controlled by cooling in ice. When reaction ceased, the mixture was heated on the water-bath for 1 hr., allowed to stand for 24 hr., and heated for a further 1 hr. The cooled solution was poured on ice (500 g.), and neutralised, and the product was extracted with chloroform. Removal of the chloroform and recrystallisation of the residue from ether gave 3-nitropyridine (0.5 g., 10%), m. p. 39.5°.

Other pyridines. Solids were recrystallised to constant m. p., and liquids were purified, when possible, through their picrates. All compounds were shown to be pure by gas chromatography. Physical constants, and source of compounds that were not obtained commercially, were: pyridine, b. p. 115–116°, picrate m. p. 168–169°; 3-methyl-, b. p. 143–144°, picrate m. p. 150°; 4-methyl-, b. p. 143–144°, picrate m. p. 164.5°; 3,4-dimethyl-, b. p. 175–176°, picrate m. p. 162–162.5°; 3,5-dimethyl-, b. p. 168°, picrate m. p. 239.5°; 4-isopropyl-, b. p. 179–180°, picrate 139–139.5°; 4-*n*-propyl-, b. p. 186–187°, picrate m. p. 133–133.5°; 4-ethyl-, b. p. 163°, picrate m. p. 172.5–173°; 3-cyano-, m. p. 49.5–50°, picrate m. p. 154.5–155°; 4-cyano-, m. p. 79–79.5°, picrate m. p. 200°; 3,5-dichloro-, m. p. 64.5°, picrate m. p. 99–99.5°; 3-benzoyl- (from nicotinic acid), m. p. 39°, picrate m. p. 164–164.5°; 4-benzoyl-, m. p. 72.5–73°, picrate m. p. 159–160°; 4-nitro- (nitration of pyridine *N*-oxide), m. p. 48.5–49.5°, picrate m. p. 109° (decomp.); 3-amino-, m. p. 61.5°, picrate m. p. 202.5–203°; 4-amino- (from 4-nitropyridine *N*-oxide), m. p. 158–159°, picrate m. p. 215.5–216°; 3-chloro-, b. p. 147–148°, picrate m. p. 145–146°; 4-chloro- (from 4-nitropyridine *N*-oxide and acetyl chloride), hydrochloride m. p. 222–224° (decomp.); 3-bromo- (bromination of pyridine), b. p. 75°/12 mm., picrate m. p. 152.5–153.5°; 3,5-dibromo- (bromination of pyridine), m. p. 110°, picrate m. p. 133.5–134.5°; 3-methoxy- (from 3-bromopyridine), b. p. 78°/12 mm., picrate m. p. 137–138°; 3-bromo-5-methoxy- (from 3,5-dibromopyridine), m. p. 32.5–33°, picrate m. p. 159–160°; 4-methoxy- (from 4-nitropyridine), b. p. 88°/10 mm., picrate m. p. 173.5°; 4-phenyl- (from pyridine and aniline), m. p. 74°, picrate 196–198°; 4-acetyl-, b. p. 56–57°/1 mm., picrate m. p. 132.5°; 4-benzyl- (from pyridine and benzyl chloride), b. p. 102°/1 mm., picrate m. p. 138–138.5°; 4-bromo-pyridine, hydrochloride m. p. 240–241°, picrate m. p. 155–156°; isoquinoline, b. p. 80°/1 mm., picrate m. p. 228–229°; nicotinic acid, m. p. 235°, picrate m. p. 220°; isonicotinic acid, m. p. 316°, picrate m. p. 216°; methyl nicotinate (esterification of nicotinic acid), m. p. 41–41.5°, picrate m. p. 145°; methyl isonicotinate (esterification of isonicotinic acid), b. p. 54–55°/1 mm., picrate m. p. 171–172°; pyridine-4-aldehyde, b. p. 79°/14 mm., semicarbazone m. p. 215.5°.

Acid Dissociation Constants.—These were measured by spectrophotometry. The pyridinium ion/pyridine ratio was, in general, obtained from difference spectra (between solutions of the amine in acid and buffer, and buffer and alkali, at the same total amine concentration). In those cases where hydrolysis (*e.g.*, methyl esters) or polymerisation (*e.g.*, 4-chloropyridine) was possible, or where there were other complicating equilibria (*e.g.*, nicotinic acid), the ratio was determined from the optical density of acid, buffer, and alkali solutions of the amine. Because pyridine-4-aldehyde, 4-cyanopyridine and methyl nicotinate appeared to react with 0.1M-alkali, the optical density of solutions of these free bases was determined in phosphate buffer (pH = 7). For all solutions, repeated scans showed that no change occurred in the spectra during 1 hr. Optical densities were measured on a Beckman DK-2A ratio recording spectrophotometer, by use of jacketed 1 cm. quartz cells kept at 25 ± 0.1°. Tests showed that Beer's law was obeyed for all absorbing species in the wavelength region used. Absorption by the buffer was always small ($D < 0.05$) but allowance was made for such absorption when it was significant. Values of pK were, in general, evaluated at three wavelengths and the average was taken with the maximum deviation being, unless otherwise stated, less than 0.02 unit.

The buffers used were: (i) borax, accurate pH values have been reported;¹ (ii) potassium hydrogen phosphate-sodium dihydrogen phosphate,² $pK_{HX} = 7.198$; (iii) sodium hydrogen succinate-sodium succinate, accurate pH values are known;³ (iv) acetic acid-sodium acetate, $pK_{HX} = 4.756$;⁴ (v) formic acid-sodium formate, $pK_{HX} = 3.752$;⁵ (vi) chloroacetic acid-sodium chloroacetate, $pK_{HX} = 2.869$;⁶ (vii) hydrochloric acid solutions.

pK' values ($= pK - bI$) were evaluated using the appropriate equations.⁷ For most pyridines pK' values were obtained at not less than four different values of the ionic strength covering the range 0.005–0.025. Variation of the ionic strength was achieved by varying the buffer concentration. When phosphate and succinate buffers were used the ionic strength range was 0.02–0.10 and 0.04–0.20, respectively. The thermodynamic pK was obtained as the intercept ($I = 0$) of a plot of pK' against I . In measurements on the very weakly basic pyridines for which hydrochloric acid was used to set the acidity the ionic strength range was more limited. The ionic strength was never greater than 0.22. Only random variation of pK' with ionic strength (0.05–0.15) was found for 4-nitropyridine and for the other weakly basic pyridines and pK values were taken as the mean of the pK' values.

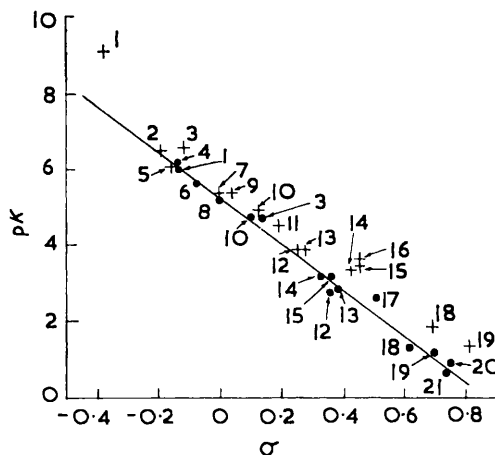
RESULTS

The values of the acid dissociation constants obtained are in the Table. pK values are estimated to be accurate to ± 0.02 units unless otherwise specified. A Hammett * plot of pK against σ° or σ (Table) is shown in the Figure. The value of ρ obtained from the slope of the

Hammett plot for dissociation of pyridinium ions in water at 25°.

● 3-Substituents. + 4-Substituents.

- 1, NH₂. 2, 3,4-Me₂. 3, MeO. 4, 3,5-Me₂.
5, R(Me, Et, Prⁿ, and Prⁱ). 6, Me. 7, Ph.
8, H. 9, 3,4-Benzo (Isoquinoline).
10, CO₂⁻. 11, CHO. 12, Cl. 13, Br. 14, Bz.
15, CO₂Me. 16, Ac. 17, 3-Br-5-MeO.
18, CN. 19, NO₂. 20, 3,5-Br₂. 21, 3,5-Cl₂.



regression line fitted to the pK against σ° data for the substituents H, 3-CH₃, 3-Cl, 3-Br, 3-CO₂CH₃, 3-CN, and 3-NO₂ is 6.01, pK_0 is 5.19, the correlation coefficient (r) is 0.998 and the standard deviation (s) is 0.041. Using the equation $\bar{\sigma} = (pK_0 - pK)/\rho$, we found effective substituent constants ($\bar{\sigma}$) for all substituents; these are in the Table, together with σ° (or σ) - $\bar{\sigma}$.

* In the ensuing discussion, σ° is Taft's⁸ inductive substituent constant for a m - or a p -substituted phenyl group derived from reactivities in which resonance interaction between the functional group and aromatic ring is prevented by an interposed methylene group; σ is Hammett's original substituent constant, $\equiv \log(K/K_0)$ for ionisation of benzoic acids; $\bar{\sigma}$ is an effective sigma value derived from a particular reaction series, $\bar{\sigma} = (1/\rho) \log(k/k_0)$; σ^+ is an exalted $\bar{\sigma}$ value, the exaltation arising from resonance interaction between a $+M$ substituent and a $-M$ side-chain, as in the transition state of the solvolysis of aryl dimethylcarbinyl chlorides; σ^- is an exalted $\bar{\sigma}$ value, the exaltation arising from resonance interaction between a $-M$ substituent and a $+M$ side-chain as in p -nitroaniline.

¹ Manov, DeLollis, Lindvall, and Acree, *J. Res. Nat. Bur. Stand.*, 1946, **36**, 543.

² Bates and Acree, *J. Res. Nat. Bur. Stand.*, 1943, **30**, 129.

³ Pinching and Bates, *J. Res. Nat. Bur. Stand.*, 1950, **45**, 322.

⁴ Harned and Ehlers, *J. Amer. Chem. Soc.*, 1932, **54**, 1350.

⁵ Harned and Enbree, *J. Amer. Chem. Soc.*, 1934, **56**, 1042.

⁶ Ives and Pryor, *J.*, 1955, 2105.

⁷ Fickling, Fischer, Mann, Packer, and Vaughan, *J. Amer. Chem. Soc.*, 1959, **81**, 4226.

⁸ Taft (jun.), *J. Phys. Chem.*, 1960, **64**, 1805.

p*K* values and substituent constants * for dissociation of pyridinium ions at 25°.

| Substituent | σ° | σ | σ_r^s | p <i>K</i> | $\bar{\sigma}$ | $\sigma^{\circ} - \bar{\sigma}$ |
|--|--------------------|--------------------|--------------------|------------|----------------|---------------------------------|
| H | 0.00 | | 0.00 | 5.21 | 0.00 | 0.00 |
| 3-CH ₃ | -0.07 | | -0.03 | 5.67 | -0.08 | 0.01 |
| 4-CH ₃ | -0.15 | | -0.03 | 6.03 | -0.14 | -0.01 |
| 4-Et | | -0.15 ⁹ | | 6.03 | -0.14 | -0.01 |
| 4-Pr ⁿ | | -0.15 ⁹ | | 6.05 † | -0.14 | -0.01 |
| 4-Pr ^l | | -0.15 ⁹ | | 6.04 | -0.14 | -0.01 |
| 3-MeO | 0.13 | | 0.29 | 4.78 | 0.07 | 0.06 |
| 4-MeO | -0.12 | | 0.29 | 6.58 | -0.23 | 0.11 |
| 3-NH ₂ | -0.14 | | 0.10 | 6.04 | -0.14 | 0.00 |
| 4-NH ₂ | -0.38 | | 0.10 | 9.12 | -0.65 | 0.27 |
| 3-Cl | 0.37 | | 0.47 | 2.81 ‡ | 0.40 | -0.03 |
| 4-Cl | 0.27 | | 0.47 | 3.83 | 0.23 | 0.04 |
| 3-Br | 0.38 | | 0.45 | 2.85 | 0.39 | -0.01 |
| 4-Br | 0.26 | | 0.45 | 3.75 | 0.24 | 0.02 |
| 3-Bz | | 0.34 ¹⁰ | | 3.18 † | 0.33 | 0.01 |
| 4-Bz | | 0.43 ¹⁰ | | 3.35 | 0.31 | 0.12 |
| 3-CN | 0.62 | | 0.58 | 1.35 | 0.64 | -0.02 |
| 4-CN | 0.69 | | 0.58 | 1.86 † | 0.55 | 0.14 |
| 3-NO ₂ | 0.70 | | 0.63 | 1.18 † | 0.67 | 0.03 |
| 4-NO ₂ | 0.82 | | 0.63 | 1.39 | 0.63 | 0.19 |
| 4-C ₆ H ₅ -CH ₂ | | | 0.04 ¹¹ | 5.59 | -0.07 | |
| 4-Ph | 0.00 ¹² | | | 5.35 | -0.03 | 0.03 |
| 4-Ac | 0.46 | | 0.28 | 3.51 | 0.28 | 0.18 |
| 3-CO ₂ Me | 0.36 | | 0.32 ¹¹ | 3.09 † | 0.35 | 0.01 |
| 4-CO ₂ Me | 0.46 | | 0.32 ¹¹ | 3.49 † | 0.28 | 0.18 |
| 3,4-Me ₂ | (-0.22) | | | 6.48 | -0.21 | (0.01) |
| 3,5-Me ₂ | (-0.14) | | | 6.14 ‡ | -0.16 | (0.02) |
| 3,5-Cl ₂ | (0.74) | | | 0.67 | 0.75 | (-0.01) |
| 3,5-Br ₂ | (0.76) | | | 0.82 | 0.73 | (0.03) |
| 3-Br-5-MeO | (0.51) | | | 2.60 | 0.43 | (0.08) |
| 3,4-(CH) ₄ § | | 0.04 ¹³ | | 5.40 | -0.03 | 0.07 |
| 4-CHO | | 0.22 ¹⁴ | | 4.52 | 0.11 | 0.11 |
| 3-CO ₂ ⁻ | | 0.10 ¹⁴ | | 4.76 ¶ | 0.07 | 0.03 |
| 4-CO ₂ ⁻ | | 0.13 ¹⁴ | | 4.90 ‡ | 0.05 | 0.08 |

* Values in parentheses were obtained on the assumption that substituent constants are additive: † error = ±0.03. ‡ Error = ±0.04. § Isoquinoline. ¶ Error = ±0.05.

A positive value of $\sigma^{\circ} - \bar{\sigma}$ implies that the substituent exerts a greater electron-donating effect in the dissociation of pyridinium ions than it does in the side-chain reactions of benzene derivatives.

DISCUSSION

The p*K*'s obtained in the present work show good agreement (±0.05 unit) with the literature values except those for 3-methoxy- (lit., 4.83,¹⁵ 4.86,¹⁶ 4.91,¹⁷), 3-cyano- (lit., 1.44,¹⁸), 3-amino- (lit., 5.88,¹⁹), 3-nitro- (lit., 0.81,²⁰), and 4-nitropyridine (lit., 1.60,²¹). Literature values cited in parentheses have been corrected, where necessary, to 25° using the appropriate temperature coefficient found by Essery and Schofield.²² The reasons for the deviations are not clear.

The value of $\rho(6.01)$ is large, as expected (the reaction centre is in the ring). The

⁹ McDaniell and Brown, *J. Amer. Chem. Soc.*, 1959, **81**, 1635.

¹⁰ White, Schlitt, and Gwynn, *J. Org. Chem.*, 1961, **26**, 3613.

¹¹ Taft (jun.) and Lewis, *J. Amer. Chem. Soc.*, 1958, **80**, 2436.

¹² Taft (jun.), Ehrenson, Lewis, and Glick, *J. Amer. Chem. Soc.*, 1959, **81**, 5352.

¹³ Fischer, Packer, Vaughan, Wilson, and Wong, *J. Org. Chem.*, 1959, **24**, 155.

¹⁴ Jaffé, *Chem. Rev.*, 1953, **53**, 191.

¹⁵ Albert and Phillips, *J.*, 1956, 1294.

¹⁶ Murmann and Basolo, *J. Amer. Chem. Soc.*, 1955, **77**, 3484.

¹⁷ Clarke and Rothwell, *J.*, 1960, 1885.

¹⁸ Jaffé and Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.

¹⁹ Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

²⁰ Bryson, *J. Amer. Chem. Soc.*, 1960, **82**, 4871.

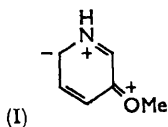
²¹ Essery and Schofield, *J.*, 1963, 2225.

²² Essery and Schofield, *J.*, 1961, 3939.

corresponding ρ value for dissociation of dimethylanilinium ions⁷ is 3.43. There are larger changes in electron density at the reaction centre resulting from the introduction of a substituent in pyridine than in dimethylaniline, because in the latter case electronic effects have to be transmitted beyond the ring to the side-chain. Taft⁸ has shown that ρ values for acid dissociation reactions in water are encompassed by the relation $\rho = (2.8 \pm 0.5)^{1-i}$, where i is the number of "saturated" links between the ring and the atom at which there is unit decrease in formal charge on ionisation of the proton. The value of ρ for the dissociation of the pyridinium ions is consistent with this relationship ($i = -1$). The fact that ρ is positive indicates that the ionisation is aided by electron-withdrawing groups, which tend to destabilise the protonated pyridine relative to the free pyridine.

The pK of pyridine-4-aldehyde is that for the loss of the first proton from the 4-dihydroxymethylpyridinium ion. Katritzky and Lagowski²³ have concluded that the equilibria proposed by Nakamoto and Martell²⁴ for pyridine-4-aldehyde in aqueous solution, in which the proton is lost from the hydrated aldehyde group of the 4-dihydroxymethylpyridinium ion, is incorrect. The first proton is lost from the ring nitrogen although this may be accompanied by a change in the extent of hydration of the aldehyde group.

With the exception of that for methoxy, the $\bar{\sigma}$ values for the 3-substituents do not deviate from σ° values by more than ± 0.02 unit. The exaltation of the substituent constant for the 3-methoxy-group may be attributed to the increased contribution from resonance structures like (I) in the 3-methoxypyridinium ion. Consequently, there is a resonance effect even though the group is in the 3-position. Similar results have been found for certain reactions in the benzene series in which a formal positive charge is placed on a nuclear carbon atom, e.g., reactions of benzenediazonium chloride.¹² A resonance effect would also be expected for 3-amino, the other strong $+M$ group. However, the $\bar{\sigma}$ value for 3-amino is not exalted.



The pK 's of the 4-alkyl-substituted pyridinium ions are the same within experimental error, indicating that the hyperconjugative and inductive effects are evenly balanced. As would be expected, the 4-($+M$) groups, amino and methoxy, show a large exaltation of their σ values. Of the $\bar{\sigma}$ values for the 4-phenyl, 4-chloro-, and 4-bromo-groups (all $-I + M$ substituents with relatively weak $+M$ effects), only that for 4-chloro differs significantly from σ° (in the direction of σ^+). The deviations of the other two groups are smaller than the accepted deviation in σ° values, but are also in the direction consistent with resonance stabilisation of the pyridinium ion.

The remaining 4-substituents are all $-I - M$ groups, and all show large deviations from the Hammett line with the $\bar{\sigma}$ values differing by 0.07 to 0.19 unit from the corresponding σ° (or σ) values. The direction of this deviation is the same as that for $+M$ substituents, and implies that there is either resonance of the $+M$ type (donation of electrons from the substituent to the functional centre), or that the σ_R contribution to the σ value is reduced. The latter alternative appears the more reasonable. Indeed, comparison (Table) of $\bar{\sigma}$ and σ_I values for these substituents shows close agreement with the deviation being greater than 0.03 unit in only one case (3-CO₂Me). The ring nitrogen, being much more electronegative than carbon, polarises the ring by attracting electrons to itself by both inductive and resonance mechanisms; such an effect is greatly accentuated in the pyridinium ion where the hetero-atom bears a formal positive charge. A contribution (σ_R°) from the resonance of the $-M$ group with the benzene ring is contained in the σ° values, but this resonance will be reduced in pyridine and the pyridinium ion since the π -electrons are attracted towards the nuclear nitrogen atom and away from the site of substitution (the 4-position). Indeed it appears that there is no significant resonance interaction between the $-M$ substituent and the ring. A similar conclusion was reached

²³ Katritzky and Lagowski in "Advances in Heterocyclic Chemistry," Vol. 1, ed. Katritzky, Academic Press, London, 1963, p. 435.

²⁴ Nakamoto and Martell, *J. Amer. Chem. Soc.*, 1959, **81**, 5863.

by Essery and Schofield,²¹ who studied the acid dissociation constants of 3-R-4-nitropyridinium ions, where R = alkyl; they found that there was no variation in $\bar{\sigma}$ for the 4-nitro-substituent over a range of alkyl groups of varying steric requirements.

The values of $\bar{\sigma}$ obtained from disubstituted compounds are equal to the sum of the $\bar{\sigma}$ values obtained from the corresponding monosubstituted compounds. Thus the $\bar{\sigma}$ values are additive.

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UNIVERSITY OF CANTERBURY,
CHRISTCHURCH 1, NEW ZEALAND.

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