

696. *Structure and Reactivity in the Pyridine Series. Part II.¹
Menschutkin Reaction with Ethyl Iodide in Nitrobenzene.*

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Rate constants have been measured for the reaction of ethyl iodide with pyridine and twenty 3- and 4-substituted pyridines in nitrobenzene at 60°. Whereas for 4-(+*M*)-groups the derived effective sigma ($\bar{\sigma}$) values are not significantly different from σ° constants, the $\bar{\sigma}$ values for 4-(−*M*)-groups approximate to σ_I rather than σ° ; 4-(−*M*)-groups therefore appear to exhibit inductive effects only.

WITH the exception of the recent work of Clarke and Rothwell² on the reaction of substituted pyridines with allyl bromide, kinetic studies of the Menschutkin reaction in the pyridine series have been limited to pyridine and the alkylpyridines as nucleophils. In Part I,¹ a Hammett equation analysis of the dissociation constants of substituted pyridines revealed that $\bar{\sigma}$ values for 4-(−*M*)-substituents did not differ significantly from σ_I values while $\bar{\sigma}$ values for 4-(+*M*)-substituents were exalted in the direction of σ^+ values. These results were explained in terms of the effect of the nuclear nitrogen atom in withdrawing π -electrons from the 4-position, thereby causing +*M* effects to be enhanced and −*M* effects to be inhibited. The present study was undertaken to see whether similar results were to be obtained from kinetics.

EXPERIMENTAL

Pyridines were prepared and purified as in Part I.¹ Nitrobenzene was used without further purification.³ Ethyl iodide was purified by shaking successively with 5% sodium carbonate solution, 5% sodium thiosulphate solution, and water before being dried (CaCl₂) for 24 hr. It was distilled twice (b. p. 72°) and stored over mercury in a dark bottle. All other reagents were of AnalaR grade without further purification.

Kinetics.—Solutions of the two reactants were prepared by diluting the appropriate weighed amount of each reactant to 100 ml. with nitrobenzene. Samples (25 ml. each) of the reactant solutions were kept in the constant temperature bath (60 ± 0.02°) for 0.5 hr. before mixing. The initial concentration of pyridine in the reaction mixture was 2—5 × 10^{−2}M and that of ethyl iodide was 2—5 × 10^{−1}M. At suitable intervals, 5 ml. aliquot portions were withdrawn and analysed, eight points being taken per run. All kinetic runs were repeated. In general, reactions were followed to 50—80% except for those compounds with rate constants less than 10^{−5} l. mole^{−1} sec.^{−1}, when the figure was 30—40%. Rate constants are estimated to be accurate to ±2%.

¹ Part I, preceding Paper.

² Clarke and Rothwell, *J.*, 1960, 1885.

³ Brown and Cahn, *J. Amer. Chem. Soc.*, 1955, **77**, 1715.

Two methods of analysis were employed. Following Brown and Cahn,³ the pyridine remaining in the reaction mixture was titrated with perchloric acid in glacial acetic acid. Crystal Violet was used as indicator and acetic anhydride (5%) was added to improve⁴ the end point. The blank (0.60 ml.) was subtracted from all titres. It was found that the method was only applicable to those pyridines with pK values above 3. The second method of analysis involved potentiometric titration of the iodide ion produced in the reaction. Aliquot portions (5 ml.) of the reaction mixture were quenched with ether (50 ml.), extracted with water (200 ml.), and the aqueous layer was titrated with acidified 0.01M-silver nitrate solution using a Cambridge portable pH meter with silver and calomel electrodes. Checks showed that the blank was immeasurably small, that ethyl iodide was not hydrolysed in the extraction (to give iodide ions), that one extraction with water was sufficient, and that under the reaction conditions, but in absence of pyridine, ethyl iodide did not give rise to iodide ion. Rate constants evaluated for 3-benzoylpyridine using both analytical methods agreed to within 0.5%. The potentiometric titration of iodide ions is a particularly sensitive method of following the Menschutkin reaction. The change in titre at the end point was less than 0.02 ml. of 0.01M-silver nitrate solution, equivalent to less than 0.1% of Menschutkin reaction; Clarke and Rothwell² found that the more highly deactivated pyridines (*e.g.*, 3,5-dibromopyridine) did not appear to react with allyl bromide. However the Hammett equation indicates that a slow reaction should occur. It is likely that their method of analysis (Volhard titration) was not sufficiently sensitive to detect the small extent of reaction taking place in the time allowed. Rate constants have been evaluated in the present work which are 50 times smaller than the lowest quoted by Clarke and Rothwell.

The rate constant k was evaluated, using the method of least squares, from the slope $[0.434k(a - b)]$ of a plot of $\log(a - x)/(b - x)$ against t , where a is the initial concentration of ethyl iodide, b is the initial concentration of the substituted pyridine being studied, and x is the concentration of the product at time t .

It was found impossible to measure the rate constants for the reaction with ethyl iodide of those compounds with labile groups (*e.g.*, Cl, NO₂) in the 4-position. Kinetic plots for these compounds were curved, presumably owing to polymerisations.⁵

The products were isolated from the reaction mixtures, recrystallised from ethanol-light petroleum, and analysed for iodide. All products had equivalent weights consistent ($\pm 3\%$) with those calculated for the expected *N*-ethyl-*X*-pyridinium iodide. The products from the reaction of 3- and 4-aminopyridine with ethyl iodide both exhibited medium-strong infrared absorption at 6.06 μ similar to that displayed by the parent aminopyridines. This medium-strong peak is characteristic of primary amines and its presence in the spectra of the products indicates that ethylation has indeed occurred at the tertiary nuclear nitrogen and not at the amino group.

RESULTS

The rate constants obtained and the method of analysis employed are given in the Table. A Hammett plot of $\log k$ against Taft's σ° (or σ , where σ° is not available) is given in Fig. 1. A regression line was fitted to the $\log k$ against σ° data for the substituents H, 3-CH₃, 3-CN, 3-NO₂, 3-Br, and 3-Cl. The slope (ρ) of this line was -2.94 , the correlation coefficient (r) was 0.999, the standard deviation (s) was 0.045, and the calculated $\log k_0$ was -3.45 (experimental $\log k_0 = -3.51$). Effective substituent constants ($\bar{\sigma}$) for all substituents were found from the equation $\bar{\sigma} = (-3.45 - \log k)/2.94$, and these are in the Table, together with the values of $\sigma^\circ - \bar{\sigma}$ (or $\sigma - \bar{\sigma}$). Values in parentheses were obtained on the assumption that substituent constants are additive.

DISCUSSION

There is very good agreement ($\pm 2\%$) between the results obtained in the present work and those of Brown and Cahn³ for the rate constants for the reaction of ethyl iodide with pyridine, 3-methylpyridine, and 4-methylpyridine. Our rate constant for 4-isopropylpyridine, however, differs by 13% from that of Brown and Cahn.

⁴ Fritz and Fulda, *Analyt. Chem.*, 1953, **25**, 1837.

⁵ Wibaut and Broekman, *Rec. Trav. chim.*, 1939, **58**, 885; Wibaut, Overhoff, and Geldof, *ibid.*, 1935, **54**, 807; den Hertog, Broekman, and Combe, *ibid.*, 1951, **70**, 105.

⁶ Taft jun., *J. Phys. Chem.*, 1960, **64**, 1805.

Rate constants and substituent constants for the reaction of substituted pyridines with ethyl iodide in nitrobenzene [$10^4 k$ (l. mole⁻¹ sec.⁻¹)].

Substituent	Non-aqueous titration	Potentiometric titration	$\bar{\sigma}$	$\sigma^\circ - \bar{\sigma}$
H	3.15		0.02	-0.02
3-Me	6.35		-0.09	0.02
4-Me	6.65		-0.09	-0.06
3-NH ₂	14.9		-0.21	0.07
4-NH ₂	50.7		-0.39	0.01
3-Cl		0.287	0.37	0.00
3-Br		0.307	0.36	0.02
4-MeO	8.20		-0.12	-0.04
3-CN		0.0531	0.62	0.00
4-CN		0.107	0.52	0.11
3-NO ₂		0.0314	0.70	0.00
3-Bz	0.419	0.420	0.30	0.04
4-Bz	0.755		0.23	0.20
4-C ₆ H ₅ -CH ₂		4.46	-0.03	
4-Pr ⁱ		6.02	-0.08	-0.07
4-Ph		3.45	-0.01	0.01
4-Ac	0.740		0.23	0.17
3,4-Me ₂	13.3		-0.19	(-0.03)
3,5-Me ₂	12.5		-0.18	(0.04)
3,5-Cl ₂		0.0284	0.71	(0.03)
3,4-(CH) ₄ *	4.32		-0.03	0.07

* Isoquinoline.

The magnitude of ρ (2.94) indicates that the reaction is less sensitive to changes in electron density on the nitrogen atom than is the dissociation of pyridinium ions, and the negative sign indicates that electron-withdrawing substituents hinder the reaction. ρ would

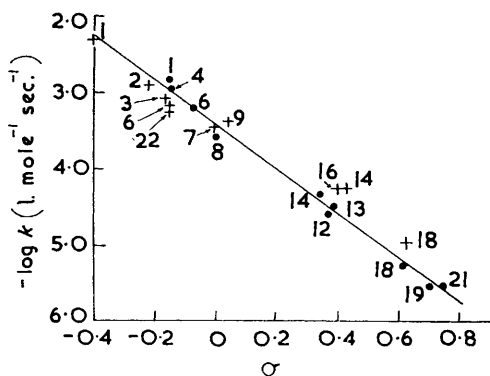


FIG. 1. Hammett plot for reaction of pyridines with ethyl iodide.

●, 3-Substituents. +, 4-Substituents.

1, NH₂. 2, 3,4-Me₂. 3, MeO. 4, 3,5-Me₂. 6, Me. 7, Ph. 8, H. 9, 3,4-Benzo-(Isoquinoline). 12, Cl. 13, Br. 14, Bz. 16, Ac. 18, CN. 19, NO₂. 21, 3,5-Cl₂. 22, Prⁱ.

be expected to be numerically smaller for the rate measurements because the charge developed in the transition state should be much less than the unit positive charge carried by the nuclear nitrogen atom of the pyridinium ion.

Rates for 3-substituted pyridines show good Hammett correlation with the exception of the values for amino- and, to a lesser extent, benzoyl-pyridine. Both these substituents appear to be better electron donors than would be predicted from σ° values. The deviation from the Hammett line of the rate constant for 3-benzoylpyridine may be attributed to a decrease in solvation (through hydrogen bonding) of the ketonic oxygen on going from water to nitrobenzene solution. This would tend to reduce the contribution of the dipolar structure to the carbonyl group hybrid, thus reducing the electron-withdrawing effect of the substituent. It is known that *para*-substituents containing carbonyl groups require different σ values for different solvents so it would not be unexpected for the corresponding *meta* (or 3-) substituents to show similar, but less pronounced, behaviour.

Of the 4-substituents, the $-I-M$ groups CO·CH₃, CO·C₆H₅, and CN show deviations from the normal Hammett equation using σ° values; correlation is good, however, when σ_1

values are used. As in the dissociation of pyridinium ions,¹ we attribute this result to polarisation of the ring π -electrons by the nuclear nitrogen. The π -electrons are thereby rendered essentially unavailable for conjugative withdrawal by a 4(- M) substituent.

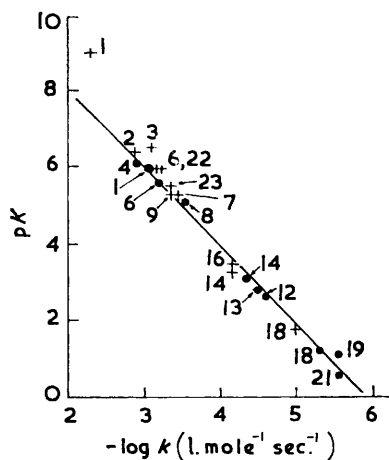
The 4-alkyl groups show minor deviations from the Hammett line, σ for 4-methyl being 0.06 unit more positive than σ° . Similar deviations were found by Clarke and Rothwell² for the Menshutkin reaction with allyl bromide in nitromethane solution. It has been suggested⁷ that the extent of hyperconjugation of a methyl group depends on the hydrogen-bonding power of the solvent. Such an explanation would account for the positive value of $\sigma - \sigma^\circ$ for the 4-methyl substituent since, in the absence of hydrogen bonding in nitrobenzene solvent, the methyl group would be a less effective electron donor than in hydroxylic solvents.

The two remaining groups are the 4(- $I + M$)-substituents NH_2 and MeO , the k values for which lie on or very close to the Hammett line. This indicates that there is little or no resonance between the substituent and the reaction centre for these two groups. As in

FIG. 2. Correlation of $\text{p}K$ (dissociation) with $\log k$ (Menschutkin reaction).

●, 3-Substituents. +, 4-Substituents.

- 1, NH_2 . 2, 3,4- Me_2 . 3, MeO . 4, 3,5- Me_2 . 6, Me .
7, Ph . 8, H . 9, 3,4-Benzo(Isoquinoline). 12, Cl .
13, Br . 14, Bz . 16, Ac . 18, CN . 19, NO_2 .
21, 3,5- Cl_2 . 22, Pr^i . 23, $\text{C}_6\text{H}_5\cdot\text{CH}_2$.



the case of the methyl group, operation of the $+M$ effect would cause a separation of the positive and negative charges in the transition state. In nitrobenzene such charges cannot be effectively dispersed by solvation, and consequently the dipolar canonical structure is disfavoured. Thus the $+M$ groups show only small (*i.e.*, σ_{R}°) $+M$ effects.

Comparison of Equilibrium (Dissociation) and Kinetic (Menschutkin) Results.—A plot of $\text{p}K$ (dissociation) against $\log k$ (Menschutkin reaction) is given in Fig. 2. A good linear relationship exists between $\text{p}K$ and $\log k$ for 3-substituents but some 4-substituents show marked deviations from this line.

The 4(+ M)-substituents are more effective electron donors [and the 4(- M)-substituents are more effective electron acceptors] in the dissociation reaction than in the Menshutkin reaction. Such effects may be attributed, at least in part, to the same cause, *viz.*, more effective charge dispersal in water than in nitrobenzene. The $-M$ groups have powerful $-I$ effects because of contributions from dipolar canonical structures to the resonance hybrids. In aqueous solution, the negative ends (in particular) of the dipoles can be dispersed by solvation, which thereby stabilises the ionic forms. Consequently the substituents show more powerful electron-withdrawing properties in aqueous solution. Similarly the $+M$ groups are better electron donors in the dissociation reaction because operation of the $+M$ effect also involves dipolar contributing structures which are again more effectively stabilised by solvation in aqueous solution.

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⁷ Kloosterziel and Backer, *J. Amer. Chem. Soc.*, 1952, **74**, 5806.