377. *A Kinetic Study of the Effect of Substituents on the Rate of Formation of Alkylpyridinium Halides in Nitromethane Solution.*

By K. Clarke and K. Rothwell.

The rates of reaction of a series of mono- and di-substituted pyridine bases with various organic halides in nitromethane have been measured. Substituents in the pyridine ring influence both the Arrhenius parameters. Variations from the Hammett relation have been found, the reactivity conferred by a group in the 3-position being greater, relative to its effect when in the 4-position, than is predicted by the Hammett substituent constants. The importance of the contribution of steric hindrance to the *ortho*-effect has been demonstrated, the contribution of non-steric effects having been estimated from pK_a values for the bases. Changes in the free energy of ionisation brought about by two or more groups are equal to the algebraic sum of the changes caused by the groups acting individually. For most of the disubstituted pyridines the free energies of activation are in agreement with those calculated, but additivity is not observed when both the groups are in positions adjacent to the nitrogen atom.

It is well known that substituents in the benzene ring may influence aromatic reactions and many reactions have been investigated, especially those affecting a side chain. Substituents change the distribution of electron densities and therefore influence the reactivity of a molecule by affecting bond strengths and repulsion forces. The influence of substituents on benzene side-chain reactions is essentially the same even in widely differing systems, any slight differences resulting from variations in the susceptibility of the systems to change.[1] Further, apart from some anomalous cases, the effect of two or more substituents is approximately the algebraic sum of the effects of the individual groups.[2]

[1] Hammett and Pfluger, *J. Amer. Chem. Soc.*, 1933, **55**, 4079; Hammett, *Chem. Rev.*, 1935, **17**, 125; Bradfield and Brynmor Jones, *Trans. Faraday Soc.*, 1941, **37**, 726.

[2] Brynmor Jones *et al.*, *J.*, 1928, 1006; 1931, 2903; 1941, 267; 1942, 418, 676; 1954, 1775; 1955, 2921, 3845; Shorter and Stubbs, *J.*, 1949, 1180; Hinshelwood, Newton, and Stubbs, *J.*, 1953, 3384.

These conclusions were mainly based on evidence from hydrocarbons, so we have investigated some heterocyclic systems, in particular the effect of substituents in the pyridine nucleus on the rate of formation of alkylpyridinium halides.

The anomalous effect of substituents in a position *ortho* to the reaction centre has received a wide variety of explanations.[3] The pyridine system affords a rigid structure free from many of the usual complications.

The Non-exponential Term of the Arrhenius Equation.—The recorded information on the effect of substituents on the Arrhenius parameters for the Menschutkin reaction involving substituted pyridine compounds is scant and conflicting. Baker and Nathan [4] found that benzyl bromide reacted more slowly with 2-methylpyridine than with pyridine itself, and this was reflected entirely in a lowering of the probability factor, the energy of activation remaining constant. On the other hand, Laidler [5] found that log PZ remained constant for the reactions of pyridine, 2-methylpyridine, and ethyl nicotinate with methyl iodide in nitrobenzene solution, the influence of substituents on the rate being due to changes in the energy of activation only. Brown and Cahn [6] studied the reactions of several monoalkyl-pyridines with methyl iodide and ethyl iodide in nitrobenzene and, although not concerned primarily with this particular question, their results suggested that variation of the substituents brought about a change in both the Arrhenius parameters. The results for the Menschutkin reaction with substituted *NN*-dimethylanilines are equally conflicting.[7,8]

The present results show that substituents influence both the parameters of the Arrhenius equation, the energy term increasing with decreasing values of log PZ. The changes in log PZ are small and in some cases within the possible limits of experimental error. However, had the latter been the cause of these changes a more haphazard scattering of the points in Fig. 1, rather than the good linear relation obtained, might have been expected. Brown and Cahn,[6] working with a similar solvent but different experimental method, obtained similar results.

An expression of Fairclough and Hinshelwood [9] accounted for cases where log PZ and E changed in the same direction but cannot explain the present results. It has been suggested [9,10] that, in the Menschutkin reaction, stabilisation of the transition state by solvent molecules may occur and give rise to variations in log PZ. Verification of this by an investigation of the gas-phase reaction has, however, not been forthcoming.[11,12]

Nitromethane is highly polar (dielectric constant *ca.* 38) and weakly acidic. These properties suggest that a high degree of association will exist between the solvent and the polar and basic solute molecules. The factor PZ of the collision theory can be identified with $(kT/h) \exp (\Delta S^{*}_{*}/R + 1)$ of the transition-state theory and the effect of solvation, ΔS^{*} (the entropy of activation), can be more easily expressed than can its effect on P.

A decrease in the entropy of a system occurs with the formation of the transition complex and, if the complex becomes solvated, ΔS^{*}_{*} has an even greater negative value. Thus the observed entropy of activation would be given by:

$$\Delta S^{*}_{*} = \Delta S^{*} + \Delta S'$$

[3] Meyer, *Ber.*, 1894, **27**, 510; Evans, Gordon, and Watson, *J.*, 1937, 1430; Evans, Watson, and Williams, *J.*, 1939, 1348; Dippy, Evans, Gordon, Lewis, and Watson, *J.*, 1937, 1421; Jenkins, *J.*, 1939, 640, 1138, 1780; Brown and Fried, *J. Amer. Chem. Soc.*, 1943, **65**, 1841; Brown, Widiger, and Letang, *ibid.*, 1939, **61**, 2597; Laidler and Hinshelwood, *J.*, 1938, 858; Hughes and Ingold, *J.*, 1935, 245; 1946, 173; 1948, 1283.

[4] Baker and Nathan, *J.*, 1935, 519.

[5] Laidler, *J.*, 1938, 1786.

[6] Brown and Cahn, *J. Amer. Chem. Soc.*, 1955, **77**, 1715.

[7] Davies and Cox, *J.*, 1937, 614.

[8] Evans, Watson, and Williams, *J.*, 1939, 1348.

[9] Fairclough and Hinshelwood, *J.*, 1937, 538.

[10] Hinshelwood *et al.*, *J.*, 1936, 1353; 1937, 1573; 1938, 236.

[11] Moelwyn-Hughes and Hinshelwood, *J.*, 1932, 230.

[12] Goldt-schmidt and Petrachkov, *Zhur. fiz. Khim.*, 1954, **28**, 1213.

TABLE 1. *Summary of rate constants and derived data for the reactions of pyridine bases with allyl bromide in nitromethane solution.*

		10^4k						
No.	Subst.	20°	30°	40°	50°	60°	*E* (cal.)	log *PZ*
1	H	3·36	—	13·2	25·6	46·3	12,730	6·00
2	2-Me	0·47	1·02	2·13	—	7·53	13,620	5·83
3	3-Me	5·37	10·84	20·8	—	71·4	12,520	6·06
4	4-Me	6·30	12·50	24·4	—	81·7	12,440	6·07
5	2,3-Me_2	0·42	0·92	—	—	7·34	13,860	5·96
6	2,4-Me_2	—	—	4·08	—	14·6	13,200	5·82
7	2,5-Me_2	0·80	—	3·49	—	12·4	13,310	5·83
8	2,6-Me_2					~0·18		
9	3,4-Me_2	—	—	40·5	—	131·5	12,200	6·13
10	3,5-Me_2	—	—	33·0	—	109·1	12,370	6·14
11	2-Et	—	—	0·95	—	3·65	13,940	5·71
12	4-Et	—	—	25·5	—	85·0	12,460	6·11
13	2,4,6-Me_3	—	—	—	—	~0·31		
14	2-OMe				No reaction			
15	3-OMe	—	—	12·1	—	41·3	12,730	5·96
16	4-OMe	7·16	—	28·0	—	91·9	12,380	6·08
17	3-OEt	—	—	—	—	45·7		
18	4-OEt	—	—	31·2	—	104·0	12,440	6·18
19	3-Br, 5-OMe	—	—	1·48	—	5·56	13,720	5·75
20	3-Br, 5-OEt	—	—	1·70	—	6·38	13,690	5·78
21	2-F				No reaction			
22	2-Cl				No reaction			
23	3-F	—	—	—	3·00	5·69	13,760	5·77
24	3-Cl	—	—	1·45		5·45	13,720	5·74
25	3-Br	—	—	1·57	—	5·87	13,670	5·73
26	3,5-Br_2				No reaction			
27	3,5-Br_2, 4-OMe				No reaction			
28	3,5-Br_2, 4-Cl				No reaction			
29	2-CO_2Et				No reaction			
30	3-CO_2Et			2·46	—	8·98	13,580	5·87
31	4-CO_2Et			2·75	—	10·0	13,510	5·87
32	4-OMe, 5-NO_2				No reaction			
33	4-OEt, 5-NO_2				No reaction			

TABLE 2. *Summary of rate constants and derived data for the reactions of pyridine bases with methyl iodide in nitromethane solution.*

		10^4k						10^4k			
No.	Subst.	40°	60°	*E* (cal.)	log *PZ*	No.	Subst.	40°	60°	*E* (cal.)	log *PZ*
34	H	17·2	62·5	13,390	6·57	39	2,6-Me_2		3·36		
35	2-Me	8·27	31·3	13,800	6·55	40	2,4,6-Me_3		6·84		
36	4-Me		111·0			41	2-F		No reaction		
37	2-Et	4·40	17·1	14,030	6·44	42	2-OMe		No reaction		
38	4-Et	34·5	122·7	13,150	6·72						

TABLE 3. *Summary of rate constants and derived data for the reactions of pyridine bases with benzyl bromide in nitromethane solution.*

		10^4k			
No.	Subst.	40°	60°	*E* (cal.)	log *PZ*
43	H	39·5	125	11,960	5·95
44	2-Me	6·18	21·1	12,720	5·66
45	4-Me	76·8	236	11,620	6·01

TABLE 4. *Summary of rate constants and derived data for the reactions of pyridine bases with n-propyl bromide in nitromethane solution.*

		10^4k			
No.	Subst.	40°	60°	*E* (cal.)	log *PZ*
46	H	1·325	5·96	15,580	6·00
47	4-Me		11·62		

TABLE 5. pK_a *Values for pyridine bases at* 20°.

Subst.	pK_a	Subst.	pK_a	Subst.	pK_a	Subst.	pK_a
H	5·17	2,5-Me_2	6·47	4-Et	6·02	4-OEt	6·67
2-Me	5·97	2,6-Me_2	6·77	2,4,6-Me_3	7·48	3-F	3·0
3-Me	5·68	3,4-Me_2	6·52	2-Me, 5-Et	6·51	3-Cl	2·84 [6]
4-Me	6·02	3,5-Me_2	6·14	2-OMe	3·40	3-Br	2·84 [6]
2,3-Me_2	6·60	2-Et	5·99	3-OMe	4·91	3-CO_2Et	3·35
2,4-Me_2	6·72	3-Et	5·70	4-OMe	6·55	4-CO_2Et	3·45

Solvation of one of the reactant molecules would cause the total entropy change to be reduced by a term $\Delta S''$, the entropy of solvation of the reactant:

$$\Delta S^{*}_{*} = \Delta S^{*} + \Delta S' - \Delta S''$$

Solvation of the pyridine bases undoubtedly occurs, and since variation of substituents brings about a change in both the basicity and the polarity of the pyridine ring, it is

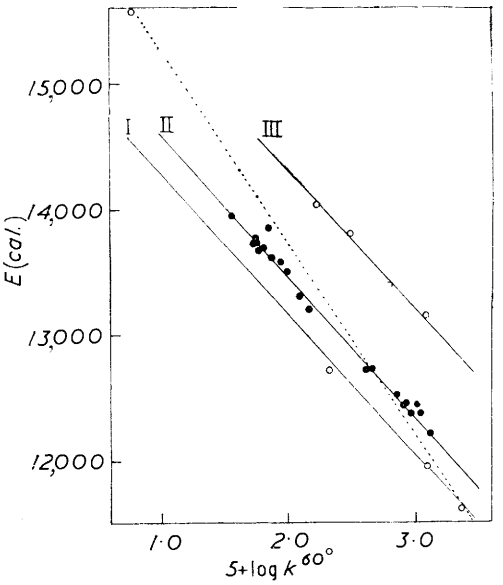

FIG. 1. *Relation between E and log* $k^{60°}$. (I) *Benzyl bromide.* (II) *Allyl bromide.* (III) *Methyl iodide. The dotted line represents* $-2{\cdot}303\boldsymbol{R}T$.

reasonable to assume that the degree of solvation will also vary. Since the basicity and to some extent the polarity of the bases are inversely proportional to the energy of activation, an increase in E will be concomitant with a reduction in $\Delta S''$, an increase in ΔS^{*}_{*}, and hence a decrease in the log PZ term of the Arrhenius equation.

In this argument lies an assumption that the degree of solvation of the transition state is independent of substituents. However, there is evidence [13] that the structure of the transition state in the Menschutkin reaction is very similar to that of the final products. Since the latter consist of two ions, the charge of which will not vary with different substituents, it can be assumed that the degree of solvation of the complex will be independent of the substituent.

Substituent Effects in Different Processes.—(1) *Relation between dissociation and rate constants.* Since substituents influence the electron density at the nitrogen atom of the pyridine ring, a relation should exist between the rate of the Menschutkin reaction and the

[13] Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 418.

dissociation constants of the bases. A relation between the rate of reaction of substituted benzoic acids and their dissociation constants has been shown to have the form

$$\log k = A \log K + B$$

in which A and B are numerical constants.

It will be observed from Fig. 2 that the equation used for the 3- and 4-substituted compounds cannot be applied when the substituent is in the 2-position. The difference, however, is confined to the magnitude of the final constant and is attributed to the *ortho*-effect.

The position of the points for the 4-alkoxypyridines is somewhat surprising. As the rate constants were measured at 60° in nitromethane solution, whereas the pK_a determinations were carried out at 20° in water solution, the deviations may be due to the use of either different solvents or different temperatures. A plot of the $pK_a^{20°}$ values against $\log k^{20°}$ still exhibited the same deviations, so change in solvent must be the critical factor.

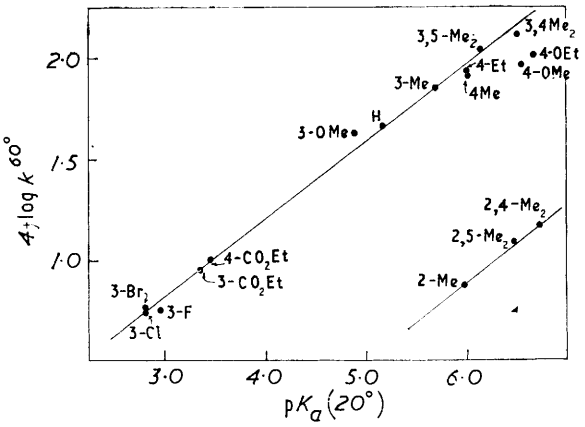

FIG. 2. *Relation between log $k^{60°}$ and pK_a.*

In the absence of mesomerism, unshared electrons of the oxygen atom confer basic characteristics on the alkoxyl group. This has been shown by the isolation of dimethyl ether hydrobromide, b. p. 3°, m. p. −13°, and by the fact that the mesomerism between the methoxyl group and the benzene ring in anisole is lower in 70% perchloric acid solution than in an inert medium. Nitromethane, being acidic, would be expected to protonate an alkoxyl group more than the less acidic solvent water. Hence, the electron density at the nitrogen atom being lower in nitromethane than in water, log k would be lower than expected from the value of pK_a.

(2) *Comparison of the effect of substituents in the pyridine ring with their effect in the benzene ring.* Comparison of the values of log k obtained in the present work with those for the same reaction of a series of *NN*-dimethylanilines [14] does not suggest any relationship. The more reasonable approach, to plot log k for the reactions of the pyridine series against the Hammett substituent constants,[15] gives a rather scattered series of points. However, two lines of different gradient result, the points for the 3-substituted compounds lying on one, and for the 4-substituted compounds on the other. It appears possible to account for this in the term $1/d^2$ of the Hammett equation but further confirmation of the result is required.

The ortho-*Effect.*—The nature of the *ortho*-effect and the way in which the effect of *ortho*-substituents on the velocity constant is reflected in changes in the parameters of the Arrhenius equation, have received considerable attention during the past thirty years.[3] Most of the work was concerned with rates of esterification of benzoic acids, of ester

[14] Crocker and Brynmor Jones, *J.*, 1959, 1808.
[15] Brown and Murphey, *J. Amer. Chem. Soc.*, 1951, **73**, 3308.

hydrolysis, and of quaternary salt formation of amines. The results show that the *ortho*-effect may arise from inductive effects, effects of hydrogen bonding and co-ordination, effects due to the steric inhibition of resonance, and primary steric effects. In the simple and rigid pyridine system, steric inhibition of resonance need not be considered and the inductive and primary steric effects, being negligibly obscured by secondary phenomena, can be assessed and their individual contributions to the *ortho*-effect found.

The pK_a *Values of the Bases.*—The increase in pK_a on the introduction of a methyl group into the 3-position of the pyridine ring is presumably caused by an inductive effect. However, the reactivity of the methyl group in some circumstances [15] suggests that there may be a slight contribution from hyperconjugation. A slight reduction of the inductive effect and a larger contribution due to hyperconjugation result in a further increase in pK_a when the group is in the 4-position.

The 2-methyl group has unexpectedly a slightly smaller effect than a 4-methyl group. This cannot be explained in terms of hydrogen bonding, for in solution intermolecular bonding with the solvent is more probable than intramolecular bonding, and the possibility of steric hindrance is ruled out by the absence of deviation from additivity of group effects shown by the pK_a values of the di-*ortho*-substituted bases studied. An explanation, which also accounts for the greater prototropic activity,[15] is that hyperconjugation of a methyl group *ortho* to the ring nitrogen atom involves less stable resonance structures than for the 4-position and is therefore of less significance.

The Methoxyl Group.—The 4-methoxy-group increases pK_a from 5·17 to 6·55, but the 3-methoxy-group decreases it to 4·91, indicating a difference in the balance of the inductive and mesomeric effects, which in the case of the methoxyl group are opposite.

The 2-methoxy-group brings about a sharp drop in pK_a from 5·17 to 3·40. Because of the proximity of the group to the nitrogen atom, the negative inductive effect will be very pronounced and, further, for the same reason that hyperconjugation of a 2-methyl group is lowered, it is expected that mesomerism of the methoxyl group will be diminished.

Halogen Substituents.—The pK_a values of the 2-halogenopyridines could not be determined by potentiometric titration but they have been obtained by spectroscopic methods.[16] The values range from −0·44 for 2-fluoropyridine to 1·82 for 2-bromopyridine. The very large drop in pK_a brought about by a halogen group in this position was attributed [16] to a strong inductive effect opposed by an insignificant mesomeric effect.

Thus the pK_a values show that a negligible *ortho*-effect operates in the 2-alkylpyridines, a rather more pronounced one in 2-methoxypyridine, and a large one in the 2-halogenopyridines. Because of the small space required by a proton, it can be assumed that a primary steric effect makes no contribution to the *ortho*-effect exhibited by pK_a values, and the latter can, therefore, be taken as an indication of the contribution made by non-steric effects. On this assumption it follows that deviations of reaction rates from the relation $\log k = A \log K + B$, shown earlier, must be due to, and to some extent a measure of, a primary steric effect. The validity of this conclusion is shown in the following study where reaction rates of 2-substituted pyridines with halides of varying size have been measured (Tables 1, 2, and 3).

That a relation involving the rate constants of reactions carried out in an organic solvent and pK_a values measured in aqueous solution is valid has been shown by the potentiometric determinations of the base strengths of amines in non-proteolytic solvents.[17]

The Effect of ortho-*Substituents on the Parameters of the Arrhenius Equation.*—From a study of esterification reactions, Hinshelwood and Legard [18] concluded that the *ortho*-effect affected only the energy of activation and was thus energetic rather than geometrical. In the alkaline hydrolysis of benzoic esters,[3] both parameters were affected, and a similar result was obtained for the reactions of a series of *NN*-dimethylanilines with methyl

[16] Brown and McDaniel, *ibid.*, 1955, **77**, 3752.
[17] Hall, *J. Phys. Chem.*, 1956, **60**, 63.
[18] Hinshelwood and Legard, *J.*, 1935, 587.

iodide.[8] Laidler [5] found that the steric effect altered the energy of activation only, for the reaction of 2-methylpyridine with methyl iodide. On the other hand, Baker and Nathan,[4] using benzyl bromide, concluded that the steric effect was reflected in the value of log PZ.

In the present results the low reaction rates of 2-substituted compounds are due to both increases in E and decreases in PZ. However, from the summary of data (Table 1) and from Fig. 1, it can be seen that variations of log PZ are neither an individual characteristic of the reactions of 2-substituted compounds, nor are they enhanced at all by these members of the series. Consequently, it is concluded that the *ortho*-effect in the series of reactions with allyl bromide operates entirely by variation of the energy of activation. In Fig. 1 the lines for the reactions of the other two halides have been drawn parallel to that for the allyl bromide reactions, the latter having been chosen for reference because of the greater weight of evidence supporting its gradient. Since the points for each series lie on the lines drawn, the arguments advanced in favour of interpreting the *ortho*-effect in terms of E are also applicable to the reactions of the other two halides.

To draw this conclusion from the data of the reactions of benzyl bromide with only three bases may be considered unwise. However, if the gradient of the log $k - E$ plot was other than as suggested, any deviations from a parallel relationship between the reactions of benzyl bromide and those of allyl bromide would have been caused by the only variable factor, the halide. Comparison of the reactions of pyridine with three related halides having the basic structure $R{\cdot}CH_2Br$ shows the validity of the assumption made.

$R{\cdot}CH_2Br$	$10^4k^{60°}$	E	log PZ
n-Propyl bromide	5·96	15,580	6·00
Allyl bromide	46·3	12,730	6·00
Benzyl bromide	125	11,960	5·95

It is therefore possible to estimate the contribution of steric hindrance to the *ortho*-effect in terms of the energy of activation in the case of all the reactions studied.

Effect of Variation of the Halide and/or the ortho-*Substituent.*—The 2-halogenopyridines and 2-methoxypyridine failed to react with both allyl bromide and methyl iodide. It has not been possible to compare the reactivity of the 4-halogenopyridines because they are too unstable and cannot be obtained in a reliably pure state. However, the 3-isomers are fairly reactive and hence there is no reason why the 4-isomers should not be also. For 2-fluoropyridine there is little reason to suspect a contribution by steric hindrance to the low reactivity found and, as was concluded from the low values of the base strengths, the reason must lie in the strong negative inductive effect exerted by the substituent.

The results obtained for 2-methoxypyridine contrast sharply with the reactivity found for the 4-isomer. The low base strength suggested that an appreciable *ortho*-effect, due to the inductive and mesomeric effects, was to be expected. However, the pK_a value (3·40) indicates a sufficiently high electron density at the nitrogen atom to allow the Menschutkin reaction to occur. A reaction rate comparable with those of ethyl nicotinate (pK_a 3·35) and ethyl isonicotinate (pK_a 3·45) would be expected. Even the 3-halogenopyridines (pK_a 2·80—3·00) react with allyl bromide at a measurable rate. It is concluded, therefore, that in the case of 2-methoxypyridine, although inductive effects make a considerable contribution to the *ortho*-effect, yet a larger one is made by a primary steric effect.

The pK_a values for the 2-alkylpyridines are only slightly different from those of the 4-substituted compounds and hence, in the absence of steric hindrance contribution to the *ortho*-effect, comparable reaction rates are to be expected. In fact, wide differences are observed. A 4-methyl group doubles the reaction rate, decreasing the energy of activation by 300 cal.; on the other hand, when the group is in the 2-position, the rate is only one-seventh of that of the unsubstituted base and the energy of activation is increased by 900 cal. The Table 6 shows the difference between the energy terms found for the reactions

of 2-substituted bases and those expected. The latter can be taken as the values for the 4-isomers except in the case of 2,6-disubstituted compounds where the value is obtained from the plot of pK_a against log k.

TABLE 6. *Difference between calculated and observed values of E for 2-substituted compounds.*

Halide	Subst.		Halide	Subst.	
Methyl iodide	2-Me	650	Allyl bromide	2-Me	1180
	2-Et	880		2-Et	1480
	2,6-Me_2	1930		2,6-Me_2	3290
			Benzyl bromide	2-Me	1100

It can be seen that, as the size of the group in the 2-position increases, the values of ΔE increase. When both the 2-positions are occupied the difference is more pronounced. Further, an increase in ΔE results from an increase in the size of the halide molecule.

The reason why benzyl bromide and allyl bromide exert the same amount of steric hindrance on the reaction lies in the transition states: the regions of these halides which would hinder formation of the transition complex, or render the complex unstable, have the same size and structure.

The results of this work show that steric hindrance, or a primary steric effect, must not be underestimated in considering the nature of the *ortho*-effect.

Cumulative Effect of Substituents.—In previous investigations, the cumulative effect of substituents has been assessed in terms of activation energy, velocity coefficients, free energy of activation, and free energy of ionisation.[2] In the present work, since the effect

TABLE 7.

	$RT \cdot pK_a$	$d\Delta F$	$-RT \cdot \ln k$	ΔE		$-RT \cdot \ln k$	ΔE
Pyridine	6935		3558		3-Bromopyridine ...	4926	1368
2-Methylpyridine ...	8008	1073	4760	1202	3-Methoxypyridine	3633	75
3-Methylpyridine ...	7619	684	3271	−287	3-Ethoxypyridine ...	3567	−9
4-Methylpyridine ...	8075	1140	3182	−376			
3-Ethylpyridine	7645	710					

TABLE 8. *Comparison of observed and calculated increments in free energy of ionisation and of activation.*

Subst.	Increment $d\Delta F$ obs.	calc.	$\frac{\text{Obs.}}{\text{Calc.}} \times 100$	Increment $d\Delta E'$ obs.	calc.	$\frac{\text{Obs.}}{\text{Calc.}} \times 100$
2,3-Me_2	1918	1757	109	1219	915	133
2,4-Me_2	2079	2213	94	765	826	93
2,5-Me_2	1743	1757	99	870	915	95
2,6-Me_2	2146	2146	100	3688	2404	153
3,4-Me_2	1810	1824	99	690	663	104
3,5-Me_2	1301	1368	95	568	574	99
3-Et, 6-Me	1797	1783	101			
3-Br, 5-OMe				1404	1443	97
3-Br, 5-OEt				1312	1377	95
2,4,6-Me_3	3098	3286	94	3305	2028	163
„ *				3305	3312	100

* Calc. from 2,6-dimethyl- and 4-methyl-pyridine. The following compounds did not react measurably with allyl bromide: 3,5-Br_2; 3,5-Br_2, 4-Cl; 3,5-Br_2, 4-OMe; 3-NO_2, 4-OMe; 3-NO_2, 4-OEt.

of substituents on the rate of the Menschutkin reaction is reflected in both the parameters of the Arrhenius equation, the assessment has been made in terms of the free energy of activation. The additivity of increments in the free energy of ionisation of the bases has also been considered. The changes brought about by single substituents in the free energy of ionisation and in the free energy of activation for the reactions of the bases with allyl bromide are shown in Table 7.

The observed and calculated increments (Table 8) show that the principle of additivity predicts the cumulative effect of substituents in most of the cases studied. Previous investigations have established that additivity is always found in the case of 3,5-di-substituted benzene compounds, but seldom when one of the groups is in the *ortho*-position, and often not at all when the groups are adjacent to one another.

In the present work, the *ortho*-effect can be attributed to primary steric hindrance and, since this is not likely to be affected by another substituent in the 4- or the 5-position, additivity can be expected. The deviations in the case of 2,6-dimethyl- and 2,4,6-trimethyl-pyridine are almost the same, the 4-methyl group having the predicted effect. For the reactions of 2-methylpyridine with allyl bromide and methyl iodide, the steric strain is estimated at 1180 and 650 cal., respectively, and for the same reactions of 2,6-dimethylpyridine, 3290 and 1930 cal. For the monosubstituted compounds, the transition state can bend slightly to minimise the energy but, when both the positions are occupied, this method of lowering the energy is no longer available. As a result the effect of a second *ortho*-group is not equivalent to that of the first and therefore additivity cannot be expected. In the case of the free energy of ionisation for the mono- and di-*ortho*-substituted bases, additivity is found because the steric effect does not affect the values of pK_a.

The absence of reactivity in the 4-alkoxy-3-nitro-compounds is unexpected, particularly in view of the results obtained for the reactions of similarly substituted dimethylanilines with allyl bromide,[14] where the observed rate was twice as great as that predicted. It is concluded that, as a group in the 3-position of a pyridine compound is nearer to the reaction centre than the corresponding group in a benzene side-chain reaction, its inductive effect is more pronounced and less easily outweighed by that of the 4-alkoxy-group.

The principle of additivity is violated in the case of the reaction of 2,3-dimethylpyridine with allyl bromide, where the rate of reaction is much lower than predicted. That the basicity of this compound is slightly higher than predicted suggests that the low rate is caused by the *ortho*-effect. It has been mentioned above that the attainment of the transition state with *ortho*-substituted compounds requires some degree of bending, and it can readily be visualised that another group in the 3-position will restrict this.

Experimental

Solvent.—Nitromethane was purified by the method of Evans, Jones, and Osbourne,[19] a typical sample having b. p. 101·6—102·0°/765·5 mm.

Kinetic Measurements.—0·1M-Solutions of the reactants were made up at 20°, and 20 ml. of each solution were put into either limb of an H-shaped reaction vessel which was immersed in a thermostat of requisite temperature. After 15 min., the solutions having reached this temperature, the vessel was shaken, and the reaction started. Since all solutions were measured at 20°, corrections for the variations in the concentrations of the reactants at other temperatures were made. At intervals, samples of the reaction mixture were added to 30 ml. of di-isopropyl ether, and the bromide ion was extracted with distilled water (3 × 10 ml.). The combined aqueous extracts were added to 5 ml. of 0·04N-silver nitrate acidified with 5 ml. of 6N-nitric acid (free from nitrous acid). A drop of freshly prepared starch solution was added to prevent coagulation of the precipitate, and the excess of silver nitrate was estimated by titration with 0·01N-ammonium thiocyanate by Volhard's method.

The precision of the experimental method was satisfactory and the results were readily reproducible. The only significant source of error lay in the titration of the excess of silver nitrate. All titrations were carried out under standard light conditions, and the end-point, which had been checked by conductometric titration, was easily obtained to within one drop (±0·03—0·04 ml.). An uncertainty of 0·04 ml. leads to an error in k of ±1·5—0·8% over the range of volumes titrated.

Velocity coefficients were calculated from the usual expression, $k = x/at(a - x)$, and the activation energies and log PZ terms were calculated from the integrated form of the Arrhenius

[19] Evans, Jones, and Osbourne, *Trans. Faraday Soc.*, 1954, **50**, 16.

equation. Where the velocity constants were determined at more than two temperatures, the activation energy has been taken as the mean of the values calculated over the several temperature ranges.

pK_a *Values.*—These have been obtained by potentiometric titration using a glass electrode, and corrections for the activity coefficient of the anion have been made.

Purification of Halides.—Methyl iodide was purified by the method of Evans, Watson, and Williams.[8] Allyl bromide, n-propyl bromide, and benzyl bromide were washed successively with sodium hydrogen carbonate solution and distilled water, dried ($CaCl_2$), and fractionally distilled. Finally, the halides were fractionated in complete darkness through a 45 cm. Vigreux column. The samples used had the following physical constants: methyl iodide, b. p. 42·60°/765 mm., n_D^{20} 1·5300; allyl bromide, b. p. 70·80°/773 mm., n_D^{20} 1·46924; propyl bromide, b. p. 70·50°/753 mm.; benzyl bromide, b. p. 85°/12 mm., m. p. −4°.

Purification of Pyridine and Some of its Alkyl Derivatives.—All commercial samples were steam-distilled from a solution containing 1·2 equiv. of 20% sulphuric acid until about 10% of the base had been carried over along with the non-basic impurities. The remaining acid solution was made alkaline, and the base separated, dried (NaOH), and fractionally distilled. Pyridine (b. p. 115·28°/760 mm., n_D^{20} 1·51002), 2,3-dimethylpyridine (b. p. 160·6°/760 mm.), and 2,5-dimethylpyridine (b. p. 156·7°/759 mm., m. p. −15·3°) were obtained by further fractional distillation. 2- (b. p. 129·54°/763 mm., m. p. −67°, n_D^{20} 1·50102) and 4-Methylpyridine (m. p. 3·6°, n_D^{20} 1·50566) were obtained by further distillation followed by fractional freezing.

The following alkyl pyridines were converted into their picrates. These were purified and the free bases regenerated: 2-ethylpyridine, b. p. 150·0°/771 mm.; 4-ethylpyridine, b. p. 167·9°/762 mm.; 2,4-dimethylpyridine, b. p. 156·9—157·4°/749 mm.; 2,6-dimethylpyridine, b. p. 143·0—143·4°/752 mm., m. p. −6·4°; 3,4-dimethylpyridine,[20] b. p. 70°/15 mm., −16°; 3-ethyl-6-methylpyridine, b. p. 178·5°/765 mm.

3-*Methylpyridine.*—Attempts to purify normal commercial samples failed to yield 3-methylpyridine with a purity greater than 95%. However, a special sample was supplied by British Industrial Solvents, Hull, and on purification gave a product with a purity of 99·2—99·6%. After steam-distillation from acid solution, the base was mixed with an equal weight of glacial acetic acid and azeotropically fractionated at 212 mm. The column, 24″ × 0·6″, packed with single-turn glass helices, was surrounded by an electrically heated, evacuated jacket and surmounted by a total condensation, variable take-off still-head. The base, liberated from the fraction of b. p. 114—115°, was extracted with pure ether, dried, and fractionally distilled; it then had b. p. 143·5°/748 mm., m. p. −18·5°.

3,5-*Dimethylpyridine.*—A solution of t-butyl-lithium (from 1·7 g. of lithium) in ether [21] was cooled to −35° to −40° and 3,5-dibromopyridine (5 g.) in ether (75 ml.) was added. The bright red mixture was stirred for 30 sec. and an excess of methyl iodide in ether was quickly added. After removal of the ether, the residual dark brown paste was acidified and steam-distilled to remove traces of unchanged 3,5-dibromopyridine. After the residue had been made alkaline, the 3,5-dimethylpyridine was obtained by further steam-distillation and precipitated from the distillate as its picrate; 1·7 g. (24%) of the picrate, m. p. 249—250° (decomp.), were obtained as yellow needles from acetic acid (Found: C, 46·7; H, 3·4. Calc. for $C_{13}H_{12}N_4O_7$: C, 46·5; H, 3·6%). Decomposition of the picrate gave 3,5-dimethylpyridine, b. p. 170·0—170·5°/760 mm., m. p. −10°.

2,4,6-*Trimethylpyridine.*—This was purified as the hydrobromide. The base, liberated by sodium hydroxide, dried, and fractionally distilled, had b. p. 60·7°/13 mm.

Halogenopyridines.—All the monohalogenopyridines were obtained by methods to be found in the literature. 3,5-Dibromopyridine, along with 3-bromopyridine, was prepared by Englert and McElvain's method [22] from the perbromides of pyridine hydrobromide, C_5H_5N,HBr,Br and C_5H_5N,HBr,Br_2. The latter perbromide gave, in addition to the products required, 25—30 g. of a mixture of tribromopyridines from which 2,3,5-tribromopyridine (11 g.), b. p. 160°, m. p. 45·0—45·5°, was obtained (Found: C, 19·3; H, 1·1; N, 4·4; Br, 75·4. Calc. for $C_5H_2Br_3N$: C, 19·1; H, 0·6; N, 4·4; Br, 75·9%).

Alkoxypyridines.—4-Hydroxypyridine was obtained by decarboxylation of chelidamic acid and converted into 4-chloropyridine with phosphorus pentachloride. 2- and 4-Methoxy- and

[20] Wibaut and Kooymans, *Rec. Trav. chim.*, 1944, **63**, 231.
[21] Gilman, Bell, Brannen, Bullock, Dunn, and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 1499.
[22] Englert and McElvain, *J. Amer. Chem. Soc.*, 1929, **51**, 863.

2- and 4-ethoxy-pyridine were obtained by boiling the relevant chloropyridines with the appropriate alcoholic solution of sodium alkoxide. 3-Methoxy- and 3-ethoxy-pyridine were obtained by heating 3-bromopyridine with the appropriate potassium alkoxide at 130°. It was necessary to purify these compounds as their hydrobromides.

3-Bromo-5-methoxypyridine.—3,5-Dibromopyridine (15 g.) was boiled under reflux for 8 hr. in a solution of potassium methoxide (from 10 g. of potassium) in methanol (100 ml.). The solution was filtered and acidified, the methanol removed, and the residue steam-distilled to eliminate unchanged 3,5-dibromopyridine. The residue was made alkaline, and the steam-distillation continued, the product being extracted from the distillate with ether. After removal of the ether, the residue was dissolved in absolute alcohol; addition of hydrobromic acid gave colourless crystals, m. p. 178·5—179·5°. Sodium hydroxide liberated the base, m. p. 33·5—34·0° (7·05 g.). Analysis of the free *base* and of its *hydrobromide* indicated that 3-bromo-5-methoxypyridine had been prepared in 74% yield [Found: C, 38·3; H, 3·3. $C_5H_3NBr{\cdot}OMe$ requires C, 38·1; H, 3·6. Found: C, 26·9; H, 2·5; N, 4·85. $C_5H_3BrN{\cdot}OMe,HBr$ requires C, 26·8; H, 2·6; N, 5·2%].

3-Bromo-5-ethoxypyridine.—This compound, prepared by the method outlined for the 5-methoxy-analogue, had b. p. 111°/5 mm., m. p. 8·2—8·8°.

3,5-Dimethoxypyridine.—3,5-Dibromopyridine was heated with potassium methoxide at 140° for 5 min., then steam-distilled, and the product precipitated as its picrate from the distillate (yield 32%). The base was characterised as it *chloroplatinate*, which recrystallised from alcoholic hydrochloric acid as orange rods, m. p. 212—213° (decomp.) [Found: C, 24·4; H, 3·1; N, 3·8. $C_5H_3N(OMe)_2,H_2PtCl_6$ requires C, 24·4; H, 2·9; N, 4·1%].

3,5-Dibromo-4-methoxypyridine.—An aqueous suspension of chelidamic acid (20 g.) mixed with bromine (25 g.) was stirred for 24 hr. and the product filtered off, washed, and dried. The residue (33·5 g., 90%) was decarboxylated at 200—240° for 1 hr., a solution of phosphorus pentachloride (15 g.) in phosphorus oxychloride (15 g.) was added, and the mixture heated at 125° for ½ hr. After cooling, the residue was dissolved in water and poured into iced potassium hydroxide solution. Steam-distillation gave 3,5-dibromo-4-chloropyridine (15·1 g.), which crystallised from alcohol as needles, m. p. 98·0—98·5°. This compound (10 g.) was added to potassium methoxide (from 10 g. of potassium) in cold methanol (100 ml.). A vigorous reaction set in immediately. Dilution with water gave a white *ether* which, extracted with ether and crystallised from alcohol, had m. p. 85—86° (yield 4 g., 40%) (Found: C, 27·1; H, 2·0; N, 4·9. $C_6H_5Br_2NO$ requires C, 27·0; H, 1·9; N, 5·25%).

Picolinic Acid.—This was prepared by the method of Clemo and Ramage.[23]

Ethyl Picolinate, Nicotinate, and Isonicotinate.—A solution of the acid (20 g.) in absolute ethanol (50 g.) and concentrated sulphuric acid (50 g.) was boiled under reflux for 4 hr., then poured on ice, made strongly alkaline with ammonia gas, and extracted with ether. The yields were: ethyl picolinate, 5 g. (20%), b. p. 153—154°/47 mm.; ethyl nicotinate, 20 g. (80%), b. p. 116°/21 mm., m. p. 9·6—10·0°; ethyl isonicotinate, 10 g. (40%), b. p. 111·5—112·0°/21 mm., m. p. 7·0—7·5°.

Nitration of 4-Hydroxypyridine.—The method used was described by Koenigs and Freter.[24] No mononitro-derivative could be isolated, and only a 15% yield of 4-hydroxy-3,5-dinitropyridine, m. p. 315°, was obtained.

Nitration of 4-Methoxypyridine.—4-Methoxypyridine nitrate (2·5 g.) was added to a cold mixture of fuming nitric acid (10 g.) and sulphuric acid (10 g.; 20% of SO_3), and the whole heated on a boiling-water bath for 24 hr. The product was poured on ice, neutralised, and extracted with ether. After removal of the ether, the *4-methoxy-3-nitropyridine* crystallised from water as faintly yellow prisms, m. p. 76·0—76·5° (0·7 g., 34%) (Found: C, 46·4; H, 3·5; N, 18·2. $C_6H_6N_2O_3$ requires C, 46·7; H, 3·9; N, 18·2%).

4-Ethoxy-5-nitropyridine.—This was prepared as for the methoxy-derivative and obtained in 41% yield, with m. p. 48·0—48·4° (corr.).

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[23] Clemo and Ramage, *J.*, 1931, 440.
[24] Koenigs and Freter, *Ber.*, 1924, **57**, 1188.