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Steric Effects in Displacement Reactions. II. The Rates of Reaction of Alkyl Iodide s with the Monoalkylpyridines. Steric Strain in the Activated Complex

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A new convenient method has been developed for determining the rates of reaction of weak pyridine bases with alkyl halides. The method has been applied to the study of the rates of reaction of pyridine and the 2-, 3- and 4-monoalkylpyridines (alkyl = methyl, ethyl, isopropyl and *t*-butyl) with methyl, ethyl and isopropyl iodides in nitrobenzene solution. Energies and entropies of activation have been calculated from the rate data at several temperatures. The reaction rates decrease sharply from methyl to ethyl iodide, and further from ethyl to isopropyl iodide. The energies of activation show a corresponding increase, while the entropies of activation remain sensibly constant. Introduction of a methyl group into the 3- or 4-position of the pyridine base results in a small increase in rate, with no significant additional change as the alkyl group is varied from methyl to ethyl, or further to isopropyl and to *t*-butyl. The introduction of these alkyl groups in the 2-position results in a decrease in rate which becomes very pronounced in the case of 2-*t*-butylpyridine. Maintaining constant the steric requirements of the base, the rate of reaction decreases and the energy of activation increases with increasing steric requirements of the alkyl halide. Similarly, maintaining constant the steric requirements of the alkyl halide results in a rate which decreases and an energy of activation which increases with the increasing steric requirements of the pyridine base. Simultaneous increases in the steric requirements of both the alkyl halide and the pyridine base cause cumulative changes in the reaction rates and activation energies. The effects of increasing steric requirements of the alkyl halide and the pyridine base on the stability of the activated complex are very similar to the effects of increasing steric requirements of the acid and base on the stability of molecular addition compounds. It is proposed that steric hindrance effects in these displacement reactions are primarily the result of steric strains in the activated complex and should be related to steric strains in molecular addition compounds of similar steric requirements.

The study of the dissociation of molecular addition compounds has provided a quantitative approach to the evaluation of steric strains.[3] It appeared possible that the approach which had been utilized for the estimation of steric strains in addition compounds might be applied to the study of steric strains in the activated complexes of typical displacement reactions. In this way a better understanding might be attained regarding the magnitude of the steric requirements of groups within the activated complex.

An earlier investigation uncovered some evidence that a relatively simple relationship may actually exist between the steric requirements of the two components in an addition compound and the steric requirements of the two components in the activated complex of a displacement reaction. It was then concluded from the relative stabilities of the addition compounds of trimethylboron that quinuclidine must be a base of far lower steric requirements than triethylamine.[4] Likewise, in the reactions of these two bases with isopropyl iodide it was observed that the base of lower steric requirements, quinuclidine, requires an activation energy considerably lower than that of the base of higher steric requirements, triethylamine.[5]

As a test of the validity of this proposed relationship it appeared desirable to undertake a study of the reactions of a series of closely related pyridine bases both with a group of alkyl halides of varying steric requirements and with a group of reference acids of closely related steric requirements. The present paper reports on the first of these items—a study of the rates of reaction of pyridine and the monoalkylpyridines[6] (alkyl = methyl, ethyl, isopropyl and *t*-butyl) with methyl, ethyl and isopropyl iodides. Subsequent papers in this series will

(1) Based upon a thesis submitted by Arno Cahn in August, 1950, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Research Fellow at Purdue University, 1948–1950, under a contract with the Office of Naval Research for the study of "Steric Strains in Chemical Reactions."

(3) H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, THIS JOURNAL, **66**, 435 (1944); H. C. Brown and G. K. Barbaras, *ibid.*, **69**, 1137 (1947); H. C. Brown and M. D. Taylor, *ibid.*, **69**, 1332 (1947); H. C. Brown and M. Gerstein, *ibid.*, **72**, 2926 (1950); H. C. Brown and G. K. Barbaras, *ibid.*, **75**, 6 (1953).

(4) H. C. Brown and S. Sujishi, *ibid.*, **70**, 2878 (1948).

(5) H. C. Brown and N. R. Eldred, *ibid.*, **71**, 445 (1949).

(6) The preparation and properties of the monoalkylpyridines used in this study are described in the first paper of this series: H. C. Brown and W. A. Murphey, *ibid.*, **73**, 3308 (1951).

present data on the strengths of these pyridine bases and on the heats of formation of addition compounds of these pyridine bases with various reference acids. These data provide strong supporting evidence both for the validity of the proposed relationship and for the importance of steric strains in the activated complexes of displacement reactions.

Results

The reaction of tertiary amines with alkyl halides (Menschutkin reaction) has been studied extensively.[7] Simple bimolecular kinetics invariably have been observed. In the majority of cases the reaction was followed by analysis for halide ion. In view of the marked tendency for alkyl iodides to react directly with the standard silver nitrate solution, analysis of the reaction mixture by titration of the free, unreacted pyridine base was considered to have advantages. After considerable experimentation both with indicators and with potentiometric procedures, a new method, involving titration with perchloric acid in glacial acetic acid, proved highly satisfactory and yielded precise results.

The rates of reaction were determined from measurements covering not more than the first 30% of the reaction. By limiting the measurements to this range, deviations arising from salt effects and from reversibility of certain of the reactions[7e] are minimized. By far the largest error in the procedure arises from uncertainties in the initial concentration of the alkyl halides, particularly in the case of the volatile methyl iodide. Since the effect of such errors become more important as the reaction proceeds, the above procedure also served to minimize the effects of such errors.

In developing the method we set outselves the goal of determining both the rate constants and the energies of activation with a precision of 1%. In a number of cases the repeated determination of the rate constants at widely separated intervals of time and with fresh solutions yielded results which agreed within the limits indicated.

Data for a representative rate determination are given in Table I.

The precision in the energies of activation and the frequency factors are indicated by a number of separate determinations at widely separated intervals of time. From the results it appears that the uncertainty in the activation energy may be estimated to be 0.1 kcal., slightly better than the desired 1% precision.

TABLE I

REPRESENTATIVE RATE DATA FOR THE REACTION OF 2-PICOLINE AND ETHYL IODIDE AT 90.0°

Time, min.	Perchloric acid, ml.	$\frac{1}{a-x}$	Deviation[b]	k_2,[a] l. mole^{-1} sec.$^{-1}$
		Run I		
0.0	18.36	10.83	0.00	6.19×10^{-4}
14.5	17.50	11.36	+ .01	
30.0	16.64	11.95	− .01	
45.0	15.87	12.53	− .03	
60.0	15.24	13.05	+ .01	
70.0	14.62	13.60	+ .01	
90.0	14.02	14.18	− .01	
		Run II		
0.0	18.30	10.88	+0.01	6.24×10^{-4}
15.0	17.36	11.47	− .01	
32.0	16.44	12.11	− .02	
51.0	15.56	12.80	.00	
75.0	14.53	13.70	.00	

[a] The equation for a second-order reaction with the concentrations of the two reactants equal was applied: $k_2 = 1/t(1/(a-x) - 1/a)$. The value of k_2 was obtained graphically (by the method of least squares) from a plot of $1/a - x$ *versus* time. [b] The deviation is the discrepancy between the observed values of $1/(a-x)$ and the values calculated from the least squares line.

TABLE II

RATE CONSTANTS FOR THE REACTIONS OF METHYL IODIDE WITH ALKYLPYRIDINE IN NITROBENZENE SOLUTION

Pyridine base RC_5H_4N, R−	Specific rate constants, $k_2 \times 10^5$ (l. mole^{-1} sec.$^{-1}$) 10°	20°	30°	40°	50°	60°	70°	80°	100°	Derived data E_{act}, kcal./mole	log A
Hydrogen	10.0		50.5		213					13.89[b]	6.72[b]
3-Methyl	21.2		104.5		422					13.59	6.82
3-Ethyl			110.6								
3-Isopropyl			118								
3-*t*-Butyl			138								
4-Methyl	22.4		111		448					13.62	6.86
4-Ethyl			113.5								
4-Isopropyl			112								
4-*t*-Butyl	22.6		111.5		457					13.68	6.91
2-Methyl		10.8	23.9[a]	49.9		193				13.98[c]	6.46[c]
2-Ethyl		5.06	11.4[a]	24.2		95.7				14.22	6.31
2-Isopropyl			3.69		17.1		64.8			14.84	6.27
2-*t*-Butyl			0.0130[a]			0.182		0.824	3.08	17.52	5.75

[a] Calculated. [b] K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 858 (1938), report E_{act} = 13.6 and log A = 6.50. [c] K. J. Laidler, *ibid.*, 1786 (1938), reports E_{act} = 13.9, log A = 6.42.

Reactions with Methyl Iodide.—The rate data for the reaction of methyl iodide with the pyridine bases are summarized in Table II.

The reaction of 2-*t*-butylpyridine with methyl iodide revealed interesting differences with the corresponding reactions of this halide with the other pyridine bases. These other reactions exhibited simple second-order kinetics with no evidence of any contributions from a reverse reaction (see Fig.

(7) (a) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 519 (1935); (b) W. G. Brown and S. Fried, THIS JOURNAL, **65**, 1841 (1943); (c) D. P. Evans, H. B. Watson and R. Williams, *J. Chem. Soc.*, 1348 (1939); (d) K. J. Laidler, *ibid.*, 1786 (1938); (e) K. J. Laidler and C. N. Hinshelwood, *ibid.*, 858 (1938); (f) F. S. Long, *ibid.*, **99**, 2164 (1911); (g) N. Menschutkin, *J. Russ. Phys. Chem. Ges.*, **34**, 411 (*Chem. Centr.*, **73**, II, 86 (1902)).

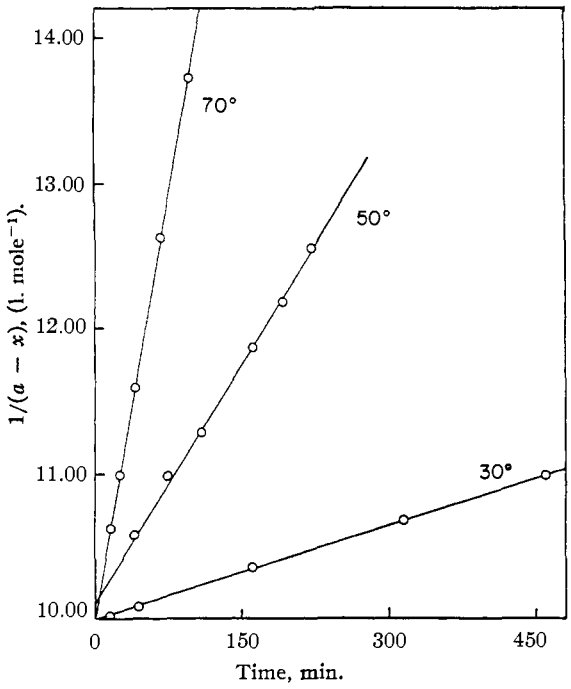


Fig. 1.—Rate data for the reaction of 2-isopropylpyridine with methyl iodide.

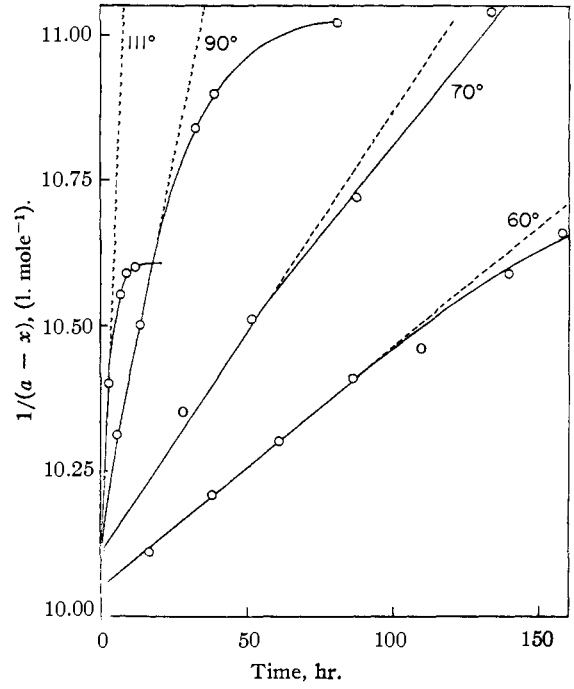


Fig. 2.—Rate data for the reaction of 2-*t*-butylpyridine with methyl iodide.

1 for typical results in the case of 2-isopropylpyridine). In the case of 2-*t*-butylpyridine, considerable deviation from simple second-order kinetics was observed. In a plot, the experimental values of $1/(a - x)$ at 70° were observed to level off after some time, indicating an approach to an equilibrium concentration of the product. At 90° the effect was more pronounced, and at 111° the reaction proceeded to the extent of only 5%. The behavior of this reaction at the different temperatures is illustrated in Fig. 2.

By applying the expression for a reversible reaction, second order in both directions

$$k = \frac{x_e}{2ta(a - x_e)} \ln \frac{x(a - 2x_e) + ax_e}{a(x_e - x)}$$

(where x_e is the concentration of the products at equilibrium) only moderately reproducible rate constants could be obtained.

The use of very concentrated solutions of methyl iodide (1.0 *M*) overcame the difficulty. This concentration of the halide suppressed the reverse reaction sufficiently so that only at the highest reaction temperature (100°) was there observed any significant deviation from linearity in the plot of log $a(b - x)/b(a - x)$, *versus* time. The precision attained in these experiments is indicated by the data in Table III.

TABLE III

RATE CONSTANTS FOR THE REACTION OF 2-*t*-BUTYLPYRIDINE WITH METHYL IODIDE IN NITROBENZENE SOLUTION

Temp., °C.	Specific rate constants × 10^6 (l. mole^{-1} sec.$^{-1}$) Observed		Average	Calcd.
60	1.85	1.79	1.82	1.82
80	8.29	8.20	8.24	8.15
100	31.1	30.5	30.8	30.8

Reaction with Ethyl Iodide.—The rate constants for the reactions of ethyl iodide with the pyridine bases are summarized in Table IV.

The reactions with ethyl iodide proceed considerably slower than the corresponding reactions with methyl iodide. The phenomenon observed in the reaction of 2-*t*-butylpyridine with methyl iodide was much more pronounced in the reaction of this base with ethyl iodide. In this case the reverse reaction could not be suppressed even by the use of a highly concentrated ethyl iodide solution. Consequently, no rate data were obtained for this system.

Reaction with Isopropyl Iodide.—The reactions with isopropyl iodide proceeded at a considerably slower rate and therefore required somewhat higher temperatures for convenient measurement. In these experiments the appearance of free iodine in the solution was observed. This was particularly noticeable in the slower reactions involving the more hindered bases.

It was considered that the iodine might be arising as a result of an elimination reaction involving the amine and the secondary halide, followed by oxidation of the hydrogen iodide formed in the elimination step. It was observed that a 0.003 *N* solution of hydrogen iodide in nitrobenzene developed free iodine shortly after the solution had been heated to 80°.

The extent of the side reaction was estimated in two ways. First, the amount of hydrogen iodide formed was determined by potentiometric titration of the reaction mixture with standard sodium hydroxide. The amount of acid was less than 0.5% of the original concentration of the alkyl halide. Second, the amount of free iodine in the reaction mixture was estimated by colorimetric comparison with a series of standard solutions of iodine in nitro-

TABLE IV

RATE CONSTANTS FOR THE REACTION OF ETHYL IODIDE WITH ALKYLPYRIDINES IN NITROBENZENE SOLUTION

Pyridine base RC_5H_4N, R-	Specific rate constants, $k_2 \times 10^5$ (l. mole^{-1} sec.$^{-1}$) 40°	50°	60°	70°	80°	90°	100°	120°	Derived data E_{act}, kcal./mole	log A
Hydrogen		15.1	30.9[a]	63.2		235			15.98	6.98
3-Methyl	14.1		62.7		239				15.53	6.98
3-Ethyl			64.1							
3-Isopropyl			63.3							
3-*t*-Butyl			67.3							
4-Methyl	14.7		67.7		257				15.70	7.12
4-Ethyl			67.9							
4-Isopropyl			68.1							
4-*t*-Butyl			67.6							
2-Methyl		3.69	7.85[a]	16.75		62.1			16.46	6.70
2-Ethyl			3.77		16.1		55.4		16.64	6.49
2-Isopropyl			1.15[a]		5.08		18.7	60.2	17.07	6.26

[a] Calculated.

benzene. The concentration of iodine rose to an amount corresponding to 2.8% of the initial concentration of the isopropyl halide in a typical rate study of this halide with 4-picoline at 80°. At 100°, in the same reaction mixture, the concentration of iodine was slightly lower, 1.5%.

The relative importance of these side reactions appeared to increase with time. By limiting the rate studies to the first 30% of reaction the effect of these side reactions was apparently reduced to a factor of minor importance. For example, a detailed study of the reaction of 3- and 4-picoline with isopropyl iodide showed a difference no greater than 3% in the values of the rate constants determined from rate data over the first 10% of reaction as compared to the usual 30% range.

An exact kinetic analysis of these side reactions was not attempted. These side reactions introduce an estimated uncertainty in the values of the isopropyl rate constants of approximately 3–4%.

It was possible to measure the rate for the reaction of 2-picoline with isopropyl halide, but the difficulties described became prohibitive for reactions with bases containing more bulky alkyl groups in the 2-position. Thus a plot of the data obtained in the reaction of 2-ethyl- and 2-isopropylpyridine yielded a line the slope of which appeared to increase with time. It is probable that in these cases the reaction is complicated not only by the elimination reaction described above, but also by the tendency for reversibility previously noted in the reactions of 2-*t*-butylpyridine with methyl and ethyl iodides. For this reason no rate data are reported for 2-ethyl-, 2-isopropyl- and 2-*t*-butylpyridine. The available data are summarized in Table V.

TABLE V

RATE CONSTANTS FOR THE REACTION OF ISOPROPYL IODIDE WITH ALKYLPYRIDINES IN NITROBENZENE SOLUTION

Pyridine base RC_5H_4N, R-	Specific rate constants, $k_2 \times 10^5$ (l. mole^{-1} sec.$^{-1}$) 60°	80°	100°	Derived Data E_{act}, kcal./mole	log A
Hydrogen	2.21	10.0	38.4	17.67[c]	6.93[c]
3-Methyl	4.02	17.6,[a] 16.9[b]	66.7	17.39	7.01
3-Ethyl		17.5			
3-Isopropyl		16.5			
3-*t*-Butyl		15.5			
4-Methyl	4.41	19.4,[a] 18.8[b]	72.0	17.29	6.98
4-Ethyl		19.0			
4-Isopropyl		18.7			
4-*t*-Butyl		18.9			
2-Methyl	0.157	0.813	3.51	19.22	6.80

[a] Measured over the first 30% of reaction. [b] Measured over the first 10% reaction. [c] K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 858 (1938), report E_{act} = 16.7, log A = 6.43.

Discussion

The data (Table II) reveal that the energies of activation and the frequency terms are practically identical for the reaction of methyl iodide with 3-picoline (E_{act} 13.6, log A 6.82), with 4-picoline (E_{act} 13.6, log A 6.86), and with 4-*t*-butylpyridine (E_{act} 13.7, log A 6.91). The identity of these quantities is retained in the reactions of ethyl iodide (Table IV) with 3-picoline (E_{act} 15.5, log A 6.98) and with 4-picoline (E_{act} 15.7, log A 7.12). The reactions of isopropyl iodide (Table V) with 3-picoline (E_{act} 17.4, log A 7.01) and with 4-picoline (E_{act} 17.3, log A 6.98) show a similar constancy in these quantities. Consequently it appears safe to assume that within experimental error the values of the energies of activation and the frequency terms will be essentially identical for all of the 3- and 4-monoalkylpyridines.

With the aid of this assumption rate constants at a common temperature (25°) have been calculated for all of the reactions investigated. For convenience in following the discussion these calculated rate constants together with derived data are summarized in Table VI.

The Effect of the Structure of the Alkyl Halide.— The entropies of activation show a remarkable constancy throughout the series of reactions. Particularly for pyridine bases without large bulky substituents in the 2-position, the entropy of activation appears to be essentially constant at -29.4 ± 0.8. This is a fortunate circumstance in that it permits discussion of the differences in reactivities of the alkyl halides with those bases not containing bulky 2-substituents in terms of the relative activation energies.

There is a general decrease in the rate of reaction and an accompanying increase in the energies of activation as the alkyl halide is varied from methyl to ethyl to isopropyl. The increase in the activation energy is quite regular and apparently independent

TABLE VI

SUMMARY OF RATE DATA FOR THE REACTION OF PYRIDINE BASES WITH ALKYL HALIDES IN NITROBENZENE SOLUTION[a]

Pyridine base RC_5H_4N, R–	Methyl iodide					Ethyl iodide					Isopropyl iodide				
	k_2^{25} × 10^6	E_{act}	log A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	k_2^{25} × 10^6	E_{act}	log A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	k_2^{25} × 10^6	E_{act}	log A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Hydrogen	343[b]	13.9	6.72	13.3	−29.8	18.3[b]	16.0	6.98	15.4	−28.8	0.941[b]	17.7	6.93	16.9	−29.5
2-Methyl	162[b]	14.0	6.46	13.4	−31.0	4.27[b]	16.5	6.70	15.8	−30.2	0.0509[b]	19.2	6.80	18.5	−29.8
2-Ethyl	76.4[b]	14.2	6.31	13.7	−31.5	1.95[b]	16.6	6.49	15.9	−31.3					
2-Isopropyl	24.5[b]	14.8	6.27	14.2	−32.1	0.555[b]	17.1	6.26	16.3	−32.4					
2-*t*-Butyl	0.080[b]	17.5	5.75	16.8	−34.6										
3-Methyl	712[b]	13.6	6.82	13.0	−29.4	40.0[b]	15.5	6.98	14.9	−28.8	1.73[b]	17.4	7.01	16.6	−29.0
3-Ethyl	761[c]					41.0[c]					1.81[c]				
3-Isopropyl	810[c]					40.4[c]					1.68[c]				
3-*t*-Butyl	950[c]					43.3[c]					1.56[c]				
4-Methyl	760[b]	13.6	6.86	13.0	−29.2	41.9[b]	15.8	7.12	15.1	−28.3	1.99[b]	17.3	6.98	16.5	−29.0
4-Ethyl	777[c]					42.1[c]					2.01[c]				
4-Isopropyl	767[c]					42.2[c]					1.98[c]				
4-*t*-Butyl	757[b]	13.7	6.91	13.0	−29.0	41.9[c]					2.00[c]				

[a] The heats and entropies of activation were calculatedly directly from the experimental kinetic data by the method of least squares with the aid of the expression given by F. W. Cagle, Jr., and H. Eyring, THIS JOURNAL, **73**, 5628 (1951). [b] Calculated from the Arrhenius equation $k = Ae^{-E/RT}$. [c] Calculated from rate constant at higher temperature with the Arrhenius expression using assumption that log A is same as that for the corresponding 3- or 4-methylpyridine.

of the structure of the base. Thus the increase in the energy of activation from methyl to ethyl iodide is 2.00 ± 0.08 kcal./mole, and the increase from ethyl to isopropyl iodide is 1.71 ± 0.10 kcal./mole (Table VII).

TABLE VII

INCREMENTS IN THE ENERGIES OF ACTIVATION ACCOMPANYING A CHANGE IN THE ALKYL IODIDE

Base	Solvent	Ethyl–methyl ΔE_{act}, kcal./mole	Isopropyl–ethyl ΔE_{act}, kcal./mole
Pyridine	Nitrobenzene	2.1	1.7
3-Picoline	Nitrobenzene	1.9	1.9
4-Picoline	Nitrobenzene	2.1	1.6
Quinuclidine[a]	Nitrobenzene	1.4	2.7
Triethylamine[a]	Nitrobenzene	2.8	3.5
Triethylamine[b]	Benzene	1.7	5.7
Pyridine[b]	Benzene	1.5	2.2

[a] Ref. 5. [b] C. A. Winkler and C. N. Hinshelwood, *J. Chem. Soc.*, 117 (1935), and ref. 7e.

The observation that the increase in the energy of activation is greater for the methyl–ethyl than for the ethyl–isopropyl pair is surprising. In the reaction of quinuclidine with this series of three halides there is observed (Table VII) a larger increase (2.7 kcal./mole) for ethyl–isopropyl than for methyl–ethyl (1.4 kcal./mole). The reactions of triethylamine show a similar trend (Table VII). This behavior of quinuclidine and triethylamine is precisely that which would be predicted on the basis that the decrease in reaction rate with increasing substitution results primarily from steric hindrance effects. Consequently, it is necessary to enquire whether factors other than steric may be influencing the relative reactivities of the alkyl halides under discussion.

The decrease in reactivity toward displacement reactions observed in the methyl, ethyl, isopropyl series has attracted considerable attention. Originally the decrease was attributed by Hughes and Ingold to the inductive effect of the alkyl substituents.[8,9] More recently, these workers have proposed that about half of the effect should be ascribed to the polar factor with the remainder attributed to steric interactions.[10]

On the other hand, A. G. Evans ascribes the entire effect to steric interactions.[11] Our earlier study of the effect of steric requirements of the base on the reaction rate in this series led us to prefer this view.[5,12]

As has been pointed out previously, the smaller increase observed with ethyl–isopropyl than with methyl–ethyl cannot be accounted for in terms of steric interactions alone. Some other factor must be playing an important role in the sequence. It does not appear feasible to account for the effect even in terms of the more recent Hughes–Ingold proposal of a 50–50 polar–steric contribution.

A possible explanation is suggested by the data for the reactions of triethylamine and pyridine with this sequence of alkyl iodides in benzene solution (Table VII). In this solvent the energies of activation behave as expected, with the increase being greater for the ethyl–isopropyl pair than for the methyl–ethyl pair. Apparently the higher ionizing properties of the nitrobenzene solvent must be playing an important role in reducing the expected increase in the activation energies of the ethyl–isopropyl pair.

Evidence has been advanced recently that displacement reactions exhibit a smooth transition from those which are essentially pure ionization type (SN1) to those which are essentially pure bimolecular displacements (SN2).[13] According to these views most displacement reactions will be of intermediate types with both SN1 and SN2 components.[14] Since the ionizing properties of the solvent will affect the SN1 component quite strongly, it

(8) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 245 (1935).

(9) For a relatively detailed exposition of this point of view, see ref. 7e.

(10) I. Dostrovsky, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 173 (1946); 1283 (1948).

(11) A. G. Evans, *Trans. Faraday Soc.*, **42**, 719 (1946); *Nature*, **159**, 166 (1947).

(12) Additional support for this position is provided by a recent Communication: W. Reeve, E. L. McCaffery and J. E. Kaiser, THIS JOURNAL, **76**, 2280 (1954).

(13) S. Winstein, E. Grunwald and H. W. Jones, *ibid.*, **73**, 2700 (1951); C. G. Swain and W. P. Langsdorf, *ibid.*, **73**, 2813 (1951).

(14) In this discussion the term "SN1 and SN2 components" is used in the sense of SN1 and SN2 contributions to a single transition state. For a recent discussion of the SN1 contribution to the Menschutkin reaction in liquid sulfur dioxide, see E. D. Hughes, C. K. Ingold, *et al.*, *J. Chem. Soc.*, 634, 647 (1954).

follows that the relative amounts of the two components which are present in a given bimolecular displacement reaction will be a function of the solvent used. A highly ionizing solvent should favor an increase in the SN1 component, while a solvent of low ionizing properties should tend to increase the SN2 at the expense of the SN1 component.

It is therefore proposed that the reactions of tertiary amines with alkyl halides in benzene a solvent of low ionizing properties, occur with a negligible SN1 component. In this solvent, we therefore observe, with increasing branching of the alkyl halide, the accelerating increase in activation energy, such as is anticipated on steric grounds. In a solvent of higher ionizing capacity, such as nitrobenzene, displacement reactions will exhibit an increased SN1 component.

The relative importance of this component in a particular solvent will increase with the increasing tendency of the alkyl halide for ionization mechanisms, and should be particularly significant for isopropyl and *t*-butyl halides. Accompanying the increased SN1 component, there will be a decreased SN2 component. Consequently, in the case of a base with small steric requirements, such as pyridine, the increase in the energy of activation will not be as great as is expected from steric considerations alone. With bases of larger steric requirements, such as triethylamine and 2-picoline, the steric factor is so large that it completely hides this effect of the solvent in modifying the relative amounts of the SN1 and SN2 components.[15]

In summary, then, the observed decreases in reactivity in displacement reactions of methyl, ethyl and isopropyl halides can be accounted for in terms of an increase in steric hindrance with increased branching of the alkyl halide, modified by an increasing SN1 component for the more highly branched alkyl halide in ionizing solvents. At the present time there does not appear to be any evidence which *requires* the interpretation that the inductive effect of the methyl groups play any significant role in the observed decrease in rate with increased branching of the alkyl halide.

The Effect of Methyl Substitution in the Pyridine Base.—The introduction of a methyl group in the 3- or 4-position of the pyridine nucleus causes an approximately twofold increase in rate with a decrease in the energy of activation of 0.3–0.4 kcal. (Table VI). These changes in reactivity are essentially constant for the three halides examined.

(15) The effect would be expected to be even more important in the case of the *t*-butyl halides. Unfortunately, practically no data are available for bimolecular displacements of *t*-butyl halides other than those involving halogen–halogen exchange. The published data on this reaction appear to show *t*-butyl halide as even more reactive than isopropyl [J. B. Conant and R. E. Hussey, THIS JOURNAL, **47**, 476 (1925); L. J. LeRoux, C. S. Lu, S. Sugden and K. Thomson, *J. Chem. Soc.*, 586 (1945); H. A. C. McKay, THIS JOURNAL, **65**, 702 (1943)]. However, unpublished data [quoted in C. K. Ingold, "Structure and Mechanism," Cornell University Press, Ithaca, N. Y., 1953, p. 408], apparently establishes the order as *t*-butyl < isopropyl. Even in these data it is observed that the decrease in rate from isopropyl to *t*-butyl is considerably smaller than the decrease observed in the preceding members of the series. The effect under discussion is therefore present in the *t*-butyl halides. However, any attempt to make a quantitative assessment of the importance of the effect in the halides is best deferred until more data become available.

The increase in the rate of reaction or the decrease in the energy of activation is presumably a result of the increase in the strength of the base resulting from the introduction of the methyl groups.[16]

The introduction of a methyl group in the 2-position likewise results in an increase in base strength. Indeed, 2-picoline (pK_a 5.97) is stronger than 3-picoline (pK_a 5.68) and is almost as strong as 4-picoline (pK_a 6.02).[16] Consequently, a similar increase in rate would be anticipated. However, the reaction rate with methyl iodide is smaller rather than larger than pyridine. The activation energy is 14.0 kcal./mole *versus* 13.6 for 3- and 4-picoline. The difference, 0.4 kcal., we attribute to steric strain in the activated complex arising from steric interactions involving the methyl group of the methyl iodide and the methyl group of the 2-picoline.

It is of interest in this connection that Baker and Nathan[7a] observed that the activation energy of 2-picoline was the same as that of pyridine in reactions with a series of *para* substituted benzyl halides. These authors concluded that introduction of a 2-methyl group had no effect on the activation energy, but was reflected solely in a decrease in log *A*.

While this statement is formally correct, it tends to hide the important role of steric strain in the reactions of 2-picoline. We believe that 3- and 4-picoline provide better standards than pyridine for estimating the effect of the 2-methyl substituent on the activation energy. The argument is illustrated in Fig. 3, where S represents the difference between the predicted and observed activation energies which we attribute to steric strains of that magnitude in the activated complex.

On the basis of our proposed interpretation, an increase in the steric requirements of the alkyl halide should result in an increase in the steric strain in the activated complex. This is observed (Table VI). Instead of the predicted energy of activation of 15.6 kcal./mole for the reaction of 2-picoline with ethyl iodide, the observed value is 16.5. The strain is therefore estimated to be 0.9 kcal. In the reaction of 2-picoline with isopropyl iodide, the strain is estimated similarly to be approximately 1.9 kcal. The data and treatment are represented graphically in Fig. 3, where the quantities S indicate the increasing strains estimated for the activated complexes in the reactions of 2-picoline with methyl, ethyl and isopropyl iodides.

The Effect of Alkyl Substituents in the 3- and 4-Position.—The methyl groups in 3- and 4-picoline were systematically replaced by ethyl, isopropyl and *t*-butyl in order to provide a basis for estimating the strains for the corresponding 2-derivatives. Surprisingly, the change in the structure of the alkyl group resulted in only minor changes in the reaction rates.

For example, the rates of reaction of the 4-alkylpyridines with ethyl iodide at 60° gave the result 67.8 ± 0.2. Similar results were obtained in the corresponding reactions of the 4-alkylpyridines with methyl and isopropyl iodides. In the case of

(16) H. C. Brown and X. R. Mihm, THIS JOURNAL, **77**, 1723 (1955).

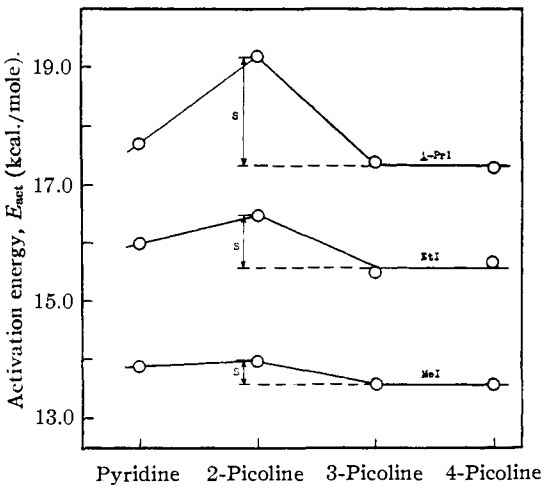


Fig. 3.—Effect of steric strain (S) on the activation energies in the picoline series.

the 3-alkylpyridines there is evidence for a slight increase in rate as the methyl group is successively varied to ethyl, isopropyl and t-butyl.[17]

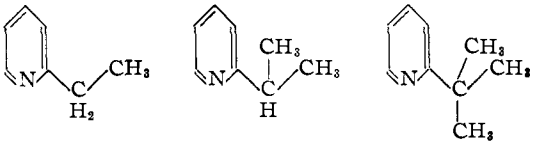
The introduction of a methyl group in the 3- or 4-position results in a considerable change in the reaction rate. Further modification of this group to ethyl, isopropyl and t-butyl has very little additional effect. An alkyl group in the 4-position could modify the electron density at the nitrogen atom in the ring by operation of both the hyperconjugation and inductive effects. Since the importance of these effects changes in the opposite direction in the methyl–t-butyl sequence, the constancy of the effect of the 4-alkyl derivatives could be explained as resulting from a net cancellation of the essentially equal but opposite hyperconjugative and inductive effects. However, hyperconjugation should not be a significant factor for the 3-alkyl groups. Consequently this explanation cannot be extended to cover the relative slight trend in the rate constants of the 3-alkyl derivatives. We conclude that the difference in the inductive effect of the different alkyl groups in the 3-position must be quite small.

The smallness of the effect is indeed unexpected. Nevertheless, the relative constancy of the effect of the different alkyl groups in the 3- and 4-position is a great advantage in simplifying the present problem. The constancy of the effect makes possible a simple estimation of the rates of reaction and the energies of activation of the 2-alkylpyridines, assuming the absence of steric interactions.

The Effect of Bulky Substituents in the 2-Position.—The introduction of bulky alkyl substituents in the 2-position of the pyridine base results in both an increase in the energy of activation and a decrease in the frequency term (Table VI). Thus in the reaction with methyl iodide log A decreases from 6.72 for pyridine to 6.46 for 2-methyl, to 5.75 for 2-t-butyl. Of the two factors, E_{act} and log A (or $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) the first appears to play a more important role in accounting for the observed decrease in rate. Accordingly the discussion will deal mainly with the effect of the 2-substituent on the energy of activation of the reaction.

The 0.4 kcal. strain estimated for the steric interaction of 2-methyl with methyl iodide in the activated complex rises to 0.6 kcal. for 2-ethyl- and to 1.2 kcal. for 2-isopropyl-. A much larger increase in strain, 3.9 kcal./mole, is observed for 2-t-butylpyridine.

The slow rise in strain from methyl to ethyl to isopropyl is attributed to the geometry of these groups. The ethyl and isopropyl groups can rotate away from the alkyl halide, so that their steric requirements in the transition state are but little greater than those of the 2-methyl substituent. In the case of the t-butyl group, rotation cannot cause any reduction in strain and a sharp increase in such strain consequently results.



Similar effects are observed in the reactions of these bases with ethyl iodide. The results are shown graphically in Fig. 4. As was pointed out earlier, experimental difficulties prevented the extension of the study to the reactions of ethyl iodide with 2-t-butylpyridine and isopropyl iodide with 2-ethyl-, 2-isopropyl- and 2-t-butylpyridine.

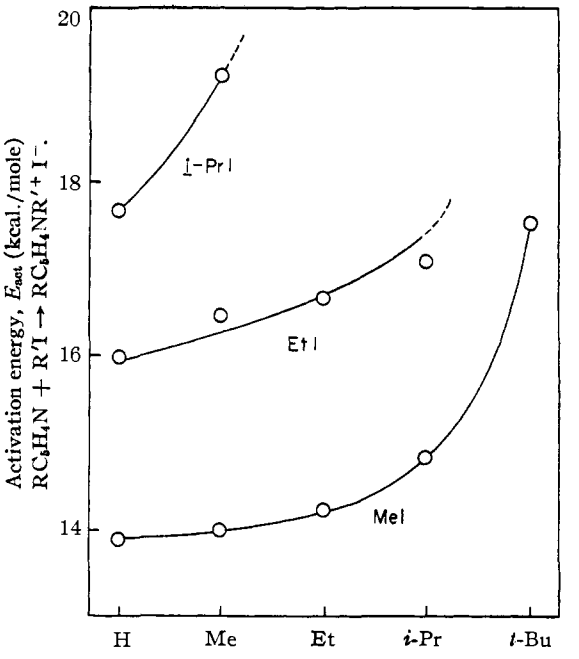


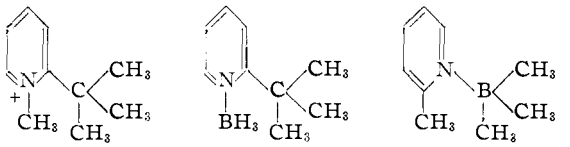
Fig. 4.—Effect of increasing steric strain on the activation energies in the reactions of the 2-alkylpyridines.

The high degree of strain, 3.9 kcal./mole, in the 2-t-butylpyridine–methyl iodide activated complex must mean that an even larger strain is present in the product, methyl-2-t-butylpyridinium ion. This

(17) It should be pointed out that the trend is clearest in the reactions with methyl iodide which were run at 30° (Table II). With ethyl iodide at 60° (Table IV) the trend is still evident, although somewhat smaller. In the case of isopropyl iodide at 80° (Table V) the trend is no longer evident. It should be recalled that the isopropyl iodide rate data are considered to have a larger experimental uncertainty (3–4%).

ion is homomorphic with *o*-*t*-butyltoluene, and evidence for large strains in homomorphs of this structure were discussed previously.[18] The great tendency toward reversibility observed in this reaction is understandable in terms of the large strains which must be present in the product.

Recently, the strains present in 2-*t*-butylpyridine–borine and 2-picoline–trimethylboron have been estimated as 6.0 ± 0.2 kcal./mole from calorimetric data on the heats of formation of the addition compounds.[19] It follows from the thesis proposed[18] that the product, methyl-2-*t*-butylpyridinium ion, also should be strained to the extent of approximately 6.0 kcal./mole. Consequently, the strain in the activated complex amounts to approximately 65% of the strain in the final product.



It is tempting to hope that there will be a relatively simple relationship of this kind between the strains present in the transition state and the strains present in related addition compounds. Some evidence that this is the case is offered by the other papers in this group.

Experimental Part

Materials.—The solvent used was nitrobenzene (du Pont, technical grade), d^{25}_4 1.1974, n^{25}_D 1.5518. The solvent was used directly after comparison experiments had shown that further purification by careful fractional distillation or crystallization had relatively little influence on the value of the specific rate constants. The same batch of solvent was used to make all stock solutions of reactants and to avoid possible errors arising from any changes in different batches of material.

The alkyl halides, methyl, ethyl and isopropyl iodides, were Eastman Kodak Co. products. They were purified by rectification through an 18-inch fractionating column packed with $^1/_{16}$-inch glass helices. The center cuts, boiling over a range of 0.1°, were used to prepare the stock solutions. The purity of the alkyl halides was further checked by analysis for iodide by the method described later for analysis of the stock solutions.

Commercial samples of pyridine, 2-, 3- and 4-picoline (Reilly Coal Tar Chemicals Co.) were distilled through a 70-theoretical plate column; center cuts with a boiling range of less than 0.1° were used. The purities of the bases were checked by means of cooling curves. In all cases purities of not less than 99 mole per cent. were indicated. The remaining alkylpyridines were samples synthesized by W. A. Murphey[6] with similar purities. Since the only impurities likely to be present were other isomeric pyridine bases of similar reactivities, it was considered that the less than 1% impurity would cause a negligible error in the rate constants.

Stock Solutions.—Stock solutions of the reactants in nitrobenzene, 0.200 *N*, were prepared in the following manner. The correct amount of reactant was weighed into a small glass-stoppered Erlenmeyer flask. The flask was then opened under a quantity of nitrobenzene and the resulting solution made up to volume at 25°. The normality of the alkylpyridine solutions thus prepared was checked by titration with perchloric acid.

The alkyl iodide solutions usually were made up slightly more concentrated than 0.200 *N*. An aliquot of the solution was then placed into an excess of standard alcoholic silver nitrate, allowed to stand overnight, and the excess silver nitrate back-titrated with potassium thiocyanate solution. The solutions were then diluted with nitrobenzene to 0.200 *N*. After dilution, and immediately before use in a rate measurement, the alkyl iodide solutions again were titrated by this procedure. These precautions were found to be necessary to avoid errors arising from loss of the volatile iodides from the stock solutions.

Preparation of Standard Perchloric Acid.—A total of 158 g. of acetic anhydride was placed in a 500-ml., round-bottom, 3-neck flask, fitted with a thermometer and a stirrer. The flask was cooled in ice. From a separatory funnel, 69 g. of 60% perchloric acid (Baker, C.P.) was added dropwise so that the temperature in the flask never rose above 25°. (The addition was carried out with the apparatus behind a protective screen.) The solution had a light yellow color. Some glacial acetic acid was now added and the solution transferred to a 2-gallon flask. Additional glacial acetic acid was added until the solution was at the desired concentration.

Standardization of Perchloric Acid.—The perchloric acid was standardized both against sodium bicarbonate and pyridine. About 0.05 g. of the dried carbonate, accurately weighed on a microbalance, was dissolved in 20 ml. of glacial acetic acid, and titrated in the presence of crystal violet as indicator. In the course of the work it proved more convenient and equally accurate (±0.2%) to use standard solutions of pyridine in nitrobenzene as primary standards. A blank, measuring the effect of the indicator, was subtracted from all buret readings.

Due to the high coefficient of thermal expansion of glacial acetic acid, the normality of perchloric acid changes significantly with temperature. Assuming linear expansion, Herd[20] suggested the formula

$$N_1 = \frac{N_0}{1 + 0.001(T_1 - T_0)}$$

where N_1 is the normality at T_1 and N_0 the normality at the temperature T_0 at which the acid was standardized. In the present study the acid was restandardized against the standard pyridine solution whenever $T_1 - T_0$ exceeded 2°.

Titration of Pyridine Solutions.—The normality of the nitrobenzene stock solutions of the pyridine bases could be checked conveniently by titration with the standard solution of perchloric acid in glacial acetic acid.[21] Nitrobenzene is sufficiently low in basicity that it does not interfere with the titration. The same procedure was used to titrate aliquots of the reaction rate solutions.

Five ml. of the 0.200 *N* stock solution (or a 5.0-ml. aliquots of the reaction rate solution) was pipetted into 20 ml. of glacial acetic acid containing 3 drops of crystal violet solution (0.2 g. of the indicator in 100 ml. of glacial acetic acid). The standard perchloric acid was added from a buret until the crystal violet indicator changed from blue to green, corresponding to the addition of the first proton.[22]

In order to attain higher precision in titrating the aliquots of the reaction mixture, a special buret was used. This buret was constructed by sealing the reservoir of a 10-ml. pipet onto the top of a 10-ml. buret graduated in 0.02 ml. In this way it was possible, after calibration, to deliver volumes from 10 to 20 ml. with the accuracy of the original microburet.

Rate Measurements.—Flasks containing the two stock solutions (0.200 *N*) were allowed to come to bath temperature. Insulated pipets maintained at bath temperature were used to remove and transfer 50-ml. aliquots to the reaction flask. The transfer pipets were filled by means of air pressure rather than by suction, in order to minimize changes in concentration of the stock solutions. The reaction flask was painted black to prevent exposure to light and it was fitted with a narrow neck which just admitted the pipets. At intervals of time a 10-ml. sample of the reaction mixture was withdrawn, discharged into 20 ml. of cold glacial acetic acid, and immediately titrated with the standard perchloric acid.

With the much slower reactions requiring higher temperatures it was necessary to modify the procedure by utilizing small thin walled ampules. The reaction mixture was prepared at 25° as previously described, and 9 aliquots of 10

(18) H. C. Brown, G. K. Barbaras, H. L. Berneis, W. H. Bonner, R. B. Johannesen, M. Grayson and K. L. Nelson, THIS JOURNAL, **75**, 1 (1953).

(19) Unpublished work with D. Gintis and L. Domash.

(20) R. L. Herd, *J. Am. Pharm. Assoc.*, **31**, 9 (1942).

(21) The authors are indebted to Dr. Saul Chodroff of the Nopko Chemical Company for drawing their attention to this analytical procedure.

(22) J. B. Conant and T. H. Weiner, THIS JOURNAL, **52**, 4436 (1930).

TABLE VIII

EXPANSION OF NITROBENZENE WITH TEMPERATURE

Temp., °C.	Volume at 25° / Volume at t°	Source
40	0.9875	[a]
50	.9791	[a]
60	.9718	Measured
70	.9635	Interpolated
80	.9556	Measured
90	.9476	Interpolated
100	.9394	Measured
110	.9319	Interpolated
120	.9235	Measured

[a] "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1928, Vol. III, p. 29.

ml. were placed into the ampules. The ampules were cooled, sealed, and placed in the constant temperature bath. At intervals of time the ampules were crushed in 20 ml. of glacial acetic acid and the free pyridine base titrated as before.

The density of nitrobenzene at elevated temperatures was determined in order to permit correction for the change in concentration in the reagents arising from the expansion of the solvent. The data are given in Table VIII.

Calculation of the Specific Rate Constant.—With the exception of those cases involving highly hindered substituents, discussed in the Results section, simple second-order kinetics were obtained and the equation

$$k = \frac{1}{t}\left(\frac{1}{a-x} - \frac{1}{a}\right)$$

applied. Here a is the initial concentration of both alkylpyridine and alkyl halide, and $a - x$ the concentration of unreacted alkylpyridine at time t. The values of the specific rate constants were calculated from the slope (determined by the method of least squares) of the straight line obtained from a plot of $1/(a - x)$ *versus* t. Typical rate data are reported in Table I and Fig. 1.

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Steric Effects in Displacement Reactions. III. The Base Strengths of Pyridine, 2,6-Lutidine and the Monoalkylpyridines

BY HERBERT C. BROWN AND XAVIER R. MIHM[1]

RECEIVED JULY 8, 1954

Ultraviolet absorption spectra have been applied as a convenient method for determining the dissociation constants of a number of alkyl substituted pyridine bases. The following pK_a values in water at 25° have been observed: pyridine, 5.17; 2-methyl-, 5.97; 2-ethyl-, 5.97; 2-*n*-propyl-, 5.97; 2-isopropyl-, 5.83; 2-*t*-butyl-, 5.76; 3-methyl-, 5.68; 3-ethyl-, 5.70; 3-isopropyl-, 5.72; 3-*t*-butyl-, 5.82; 4-methyl-, 6.02; 4-ethyl-, 6.02; 4-isopropyl-, 6.02; 4-*t*-butyl-, 5.99; 2,6-dimethyl-, 6.75. The introduction of an alkyl group in the 2-, 3- or 4-position results in an increase in the pK_a value of 0.5–0.8 unit. The nature of the alkyl group (methyl, ethyl, isopropyl, *t*-butyl) in the 3- or 4-position has little effect on the base strength. In the 2-position the more highly branched alkyl groups bring about a decrease in the strength of the base. The increase in base strength from pyridine to 2-picoline (0.80 pK_a unit) is the same as the increase from 2-picoline to 2,6-lutidine (0.78 pK_a unit). This points to the absence of any important steric effects in the addition of the proton to the latter base or in the solvation of the ion.

The ionization of acids and bases represents one of the few reversible reactions available to the chemist for the study of the effect of structure on chemical behavior. The available data in this area far exceed data on other chemical reactions. Consequently it appeared desirable to measure the ionization constants of the alkyl substituted pyridines. Such data would then permit an examination of the effect of the alkyl substituents on the ability of these bases to unite with the proton, as compared with their ability to react with the alkyl halides[2] and with Lewis acids.[3,4]

Data now published on the ionization constants of the pyridine bases are largely restricted to the commercially available methyl derivatives.[5,6] In order to have a consistent body of data for all of the alkylpyridines utilized in these studies, it was decided to measure the pK_a values for pyridine, 2,6-lutidine and 2-, 3- and 4-monoalkylpyridines (alkyl being methyl, ethyl, isopropyl and *t*-butyl). In the course of this study it proved desirable to include 2-*n*-propylpyridine among the bases examined.

(1) Based upon a thesis submitted by Xavier R. Mihm in August, 1951, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) H. C. Brown and A. Cahn, THIS JOURNAL, **77**, 1715 (1955).

(3) H. C. Brown and R. H. Horowitz, *ibid.*, **77**, 1733 (1955).

(4) Unpublished work with L. Domash and D. Gintis.

(5) A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951).

(6) E. F. G. Herington, *Discussions Faraday Soc.*, **9**, 26 (1950).

Results

A review of the available methods led to the conclusion that the use of ultraviolet absorption spectra would provide the most convenient accurate procedure for the measurement of the pK_a values.[7,8] The spectra of the 15 pyridine bases were determined from 220 to 280 mμ in 0.1 *N* sodium hydroxide and 0.1 *N* hydrochloric acid. For each series of pyridine bases four wave lengths at the peaks of absorbancies were selected. Conformity to Beer's law in acidic and basic solutions was established for concentrations of pyridine bases of 5.00×10^{-5}, 1.00×10^{-4} and 2.00×10^{-4} *M*.

The absorbancies of solutions of the same known concentration of the pyridine base in 0.1 *N* hydrochloric acid, 0.1 *N* sodium hydroxide and in two acetic acid–sodium acetate buffers were measured at four different wave lengths. The temperature of the solutions was 25 ± 1°. The *p*H of the buffered solution was measured immediately after the absorbancy measurements. The pK_a' values were calculated for each wave length with the aid of the equation

$$pK_a' = pH + \log \frac{A_B - A_{NaOH}}{A_{HCl} - A_B}$$

where A_B, A_{NaOH} and A_{HCl} is the absorbancy in

(7) W. Stenstrom and N. Goldsmith, *J. Phys. Chem.*, **30**, 1683 (1926).

(8) E. B. Hughes, H. H. Jellinek and B. A. Ambrose, *J. Phys. Colloid Chem.*, **53**, 410 (1949).