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

$$pK_a' = p\mathrm{H} + \log \frac{A_B - A_{NaOH}}{A_{HCl} - A_B}$$

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).

the buffered solution, in 0.1 N sodium hydroxide and 0.1 N hydrochloric acid, respectively.

At least four series of measurements were made for each pyridine base. The pK_a' values were converted to the thermodynamic pK_a value by correcting for the activity of the pyridinium ion[8] at 25°. The correction proved to be relatively small and constant: -0.085 pK_a unit for pyridine and -0.09 for the other pyridine bases.

The average deviation in the pK_a' values is ± 0.02. The inherent error in the pH meters used was also ± 0.02 unit.

The pK_a values are summarized in Table I.

TABLE I

pK_a VALUES FOR THE PYRIDINE BASES AT 25° IN AQUEOUS SOLUTION

Pyridine base RC_5H_4N, R–	Position of substituent 2-	3-	4-
Hydrogen	5.17	5.17	5.17
Methyl	5.97	5.68	6.02
Ethyl	5.97	5.70	6.02
Isopropyl	5.83	5.72	6.02
t-Butyl	5.76	5.82	5.99
2-n-Propyl	5.97		
2,6-Dimethyl	6.75		

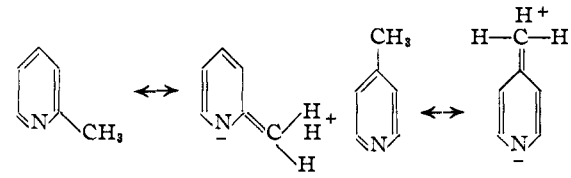
Discussion

The introduction of a methyl group in the 3-position of the pyridine ring results in an increase of the pK_a value from 5.17 to 5.68. The increase is presumably the result of the inductive effect of the methyl group (hyperconjugative effects should not be significant in the 3-position). Replacement of the methyl group by ethyl, isopropyl and t-butyl results in a small increase with increasing bulk of the alkyl group. The increase is quite small compared to that which occurs with the original introduction of the methyl group. It must be concluded that the increase in the inductive effect with increasing bulk of the four alkyl groups is relatively small, at least small in the present case where the groups are relatively far removed from the reaction center.

In the 4-position a methyl group causes an increase in the pK_a value from 5.17 to 6.02. The fact that the increase is considerably larger than that observed for the same group in the 3-position is taken to mean that hyperconjugation must be quite significant as a mechanism for electron release from a 4-alkyl substituent to the nitrogen atom. Change of the methyl group to ethyl, isopropyl and t-butyl does not cause any significant further change in the base strength (pK_a for 4-t-butylpyridine is 5.99 as compared to 6.02 for 4-picoline). This must mean that the decrease in hyperconjugation in the series from methyl to t-butyl is relatively small and essentially compensated for by the slightly increased inductive effect of the more bulky alkyl substituents.

In the 2-position a methyl group is only slightly less effective than in the 4-position (pK_a for 2-picoline is 5.97). However, hyperconjugation should operate in the 2- as well as in the 4-position. With the inductive effect presumably more powerful in the nearer 2-position than in the further 4-position, a decrease in the electron release by the substituent would not have been anticipated.

Two explanations appear possible. Steric hindrance to solvation of the 2-picolinium ion could reduce the apparent stability of the ion and therefore reduce the apparent polar effect of the methyl groups.[9,10] Alternatively, hyperconjugation of a group in the 2-position, involving as it does o-quinoid structures, could be less important than in the 4-position, where p-quinoid structures are involved.



In the prototropic reactions of the picolines 4-picoline appears to be considerably more reactive than the 2-isomer.[11] This observation suggests that the effect is primarily due to the enhanced ability of the 4-methyl to participate in hyperconjugation. Moreover, the solvation interpretation is rendered improbable by the observation that the second methyl group in 2,6-lutidine produces no enhancement of the effect.

There is no change in base strength accompanying the change of a methyl substituent to ethyl. With isopropyl a decrease from 5.97 to 5.83 is observed, while t-butyl results in a further decrease to 5.76. Although we have argued that steric hindrance to solvation cannot be of importance in 2-picoline, we cannot eliminate the possibility that this factor may be significant with the more bulky 2-substituents. Discussion of this question will be deferred pending publication of more recent studies on pyridine bases with bulky substituents in the 2, 6-positions.[12]

It was surprising that the pK_a value of 2-ethylpyridine was identical with that of 2-picoline. Accordingly it appeared desirable to examine the next higher homolog. However, 2-n-propylpyridine exhibited the same behavior, a pK_a value of 5.97.[13] Thus 2-methyl, 2-ethyl and 2-n-propyl all have identical effects on the base strength of pyridine.

It is important that the pK_a value for 2,6-lutidine is 6.75. Thus we observe that the first methyl group in the 2-position brings about an increase of 0.80 pK_a unit, and the second methyl group results in an increase of 0.78 pK_a unit. These values are considered identical, within experimental error. This result suggests that the pK_a values in the pyridine series will be additive.[14] Even more impor-

(9) A similar explanation has been proposed to account for the weakness of 2,4,6-tri-t-butylphenol as an acid and 2,4,6-tri-t-butylaniline as a base: P. D. Bartlett, M. Roha and R. M. Stiles, THIS JOURNAL, **76**, 2349 (1954).

(10) Steric strains of the type proposed to account for the behavior of o-alkylanilines are not considered to be significant in 2-picolinium ion: H. C. Brown and A. Cahn, *ibid.*, **72**, 2939 (1950).

(11) H. C. Brown and W. A. Murphey, *ibid.*, **73**, 3308 (1951).

(12) Part of the data are contained in a recent communication: H. C. Brown and B. Kanner, *ibid.*, **75**, 3865 (1953).

(13) A value of 5.95 was observed at 28° for both 2-methyl- and 2-n-propylpyridine, as compared to 5.97 at 25° for 2-methyl-. In converting the value to 25° it has been assumed that the temperature coefficients for these two bases will not differ significantly over the small temperature range of 3°.

(14) Additivity has now been established for a number of pyridine bases, including 2,4-lutidine, 2,6-methyl-t-butylpyridine, 2,6-diisopropylpyridine and other derivatives. Additivity in the pK_a values of benzoic acid derivatives is discussed by J. Shorter and F. J. Stubbs, *J. Chem. Soc.*, 1180 (1949).

tant the results argue against any significant steric effects involving either addition of the proton to 2,6-lutidine or the solvation of the ion.

Hammett has demonstrated the existence of linear free energy relationships between rate data involving *m*- and *p*-benzoic acid derivatives and the ionization constants of the corresponding acids.[15] It is of interest to examine the possible existence of a similar relationship between the rate data for the reaction of methyl iodide with these pyridine bases[2] and their ionization constants.

Plots of this kind are shown in Figs. 1 and 2. It is evident that a linear relationship is indicated for pyridine and the 3- and 4-alkylpyridines. However, the 2-alkylpyridines deviate and the magnitude of the deviation evidently is related to the steric requirements of the alkyl substituents. It therefore is concluded that the deviations must arise from steric strains in the activated complex, strains resulting from the large steric requirements of the 2-alkyl substituents in the reaction with methyl iodide. These strains are presumably absent in the reactions of these bases with the proton in aqueous solutions.

Experimental Part

Apparatus.—The Beckman spectrophotometer, model DU, was checked according to the procedure recommended by Ewing and Parsons.[16] The absorbancy values obtained were 0.424 at 264 mμ, and 0.643 at 281 mμ. The width of the silica cells was 1.00 cm. A band width of 1 mμ was used for all measurements.

Both a Cambridge research model and a Beckman Model G *p*H meter were used for the *p*H measurements to provide cross checks on the measurements. They were calibrated with Leeds and Northrup buffers, *p*H at 25°, 4.01, 6.86 and 9.16; Eimer and Amend buffer, 6.99; and Cambridge buffer, 4.00.

TABLE II

POSITIONS OF MAXIMA AND MINIMA ON ABSORBANCY INDEX CURVES FOR THE PYRIDINE BASES FROM 220 TO 280 mμ

	0.1 *N* NaOH				0.1 *N* HCl	
	Maxima		Minima		Maxima	
	a_M (× 10^{-3})	(mμ)	a_M (× 10^{-3})	(mμ)	a_M (× 10^{-3})	(mμ)
Pyridine	2.45	251	2.13	253.5	5.29	255.7
	2.75	257	1.60	261		
	1.80	263				
2,6-Lutidine	4.51	266.5			8.54	269.5
2-Methylpyridine	3.56	262	2.45	266.5	6.63	262.5
	2.60	268.3				
2-Ethylpyridine	3.69	262	2.56	266.4	7.14	263
	2.66	267.8				
2-Isopropylpyridine	3.78	261.5	2.57	266.3	7.53	263.3
	2.68	267.8				
2-*t*-Butylpyridine	3.40	261	2.25	265.7	7.43	263.3
	2.36	267.3				
3-Methylpyridine	3.11	263	2.15	267.4	5.47	262.5
	2.29	269.3				
3-Ethylpyridine	3.21	262.3	2.15	265	5.73	262.3
	2.29	268.7				
3-Isopropylpyridine	3.25	262	2.15	266.5	5.79	262.3
	2.31	268.3				
3-*t*-Butylpyridine	3.23	261.3	2.15	266	5.85	261.2
	2.29	267.5				
4-Methylpyridine	2.09	255	1.46	260	4.51	252.5
	1.65	261.9				
4-Ethylpyridine	2.15	255	1.54	260	4.61	252
	1.62	261.7				
4-Isopropylpyridine	2.10	255	1.56	260	4.61	251.7
	1.59	261				
4-*t*-Butylpyridine	2.12	255	1.57	260	4.55	252.5
	1.59	261				

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

(16) G. W. Ewing and T. Parsons, Jr., *Anal. Chem.*, **20**, 423 (1948).

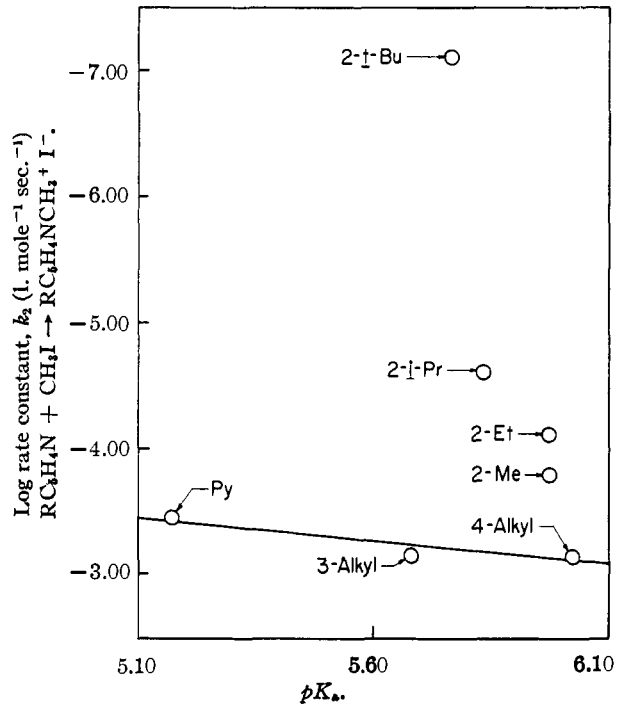


Fig. 1.—Relationship between the logarithm of the rate constants for the reaction of methyl iodide with the pyridine bases (25°) and their pK_a values.

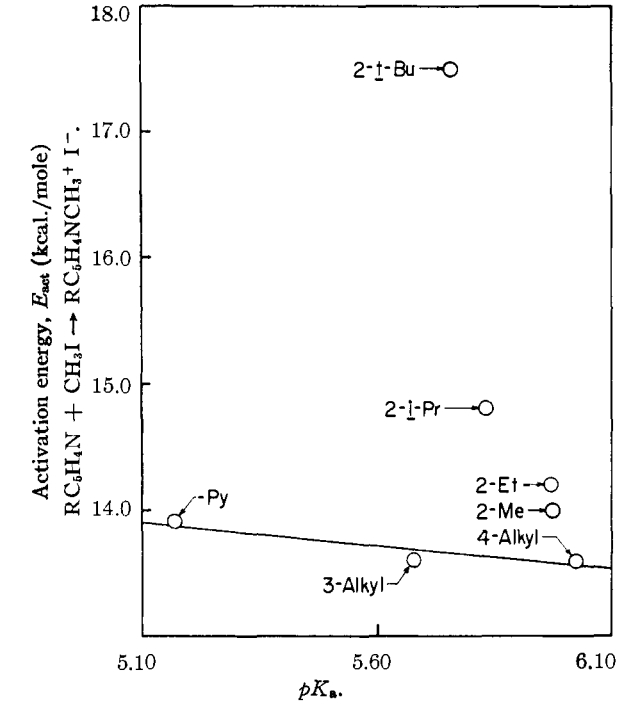


Fig. 2.—Relationship between the energies of activation for the reaction of methyl iodide with the pyridine bases and their pK_a values.

Materials.—The purest available grades of pyridine, 2-, 3- and 4-picoline were distilled over calcium hydride in a column rated at 70 theoretical plates. Constant boiling center fractions were collected and used: pyridine, b.p. 114° (743 mm.), $n^{20}D$ 1.5092; 2-picoline, b.p. 127° (740

TABLE III

DATA FOR THE SPECTROPHOTOMETRIC EVALUATION OF pK'_a FOR PYRIDINE

Stock solution number	Wave length, mμ	Absorbancies (A) of solutions of the amine in buffers (B): in HCl (0.1 N)	in NaOH (0.1 N)	pH 5.18 B′	pH 5.45 B″	$\log \frac{A_B - A_{NaOH}}{A_{HCl} - A_B}$: B′	B″	pK'_a: B′	B″
1a	250	0.479	0.240	0.374	0.333	0.11	−0.20	5.29	5.25
	251	.485	.244	.376	.337	.08	− .20	5.26	5.25
	255	.540	.239	.404	.359	.08	− .18	5.26	5.27
	256	.540	.271	.421	.381	.10	− .16	5.28	5.29
1b	250	.462	.238	.357	.330	.06	− .16	5.24	5.29
	251	.466	.240	.360	.332	.05	− .16	5.23	5.29
	255	.521	.238	.385	.351	.03	− .18	5.21	5.27
	256	.525	.268	.402	.369	.06	− .17	5.24	5.27
2	250	.462	.240	.357	.325	.05	− .21	5.23	5.24
	251	.466	.245	.360	.330	.04	− .20	5.22	5.25
	255	.522	.240	.390	.344	.06	− .23	5.24	5.22
	256	.526	.269	.406	.364	.07	− .228	5.25	5.23
3	250	.468	.248	.363	.333	.04	− .20	5.22	5.25
	251	.475	.252	.366	.337	.02	− .21	5.20	5.24
	255	.530	.245	.394	.354	.04	− .21	5.22	5.24
	256	.533	.276	.411	.374	.06	− .20	5.24	5.25
							Average value	5.24	5.26
		pK'_a 5.25 ± 0.02		pK_a 5.17 ± 0.02			Average deviation	±0.02	±0.02

mm.), $n^{20}D$ 1.5010; 3-picoline, b.p. 142 (747 mm.), $n^{20}D$ 1.5058; 4-picoline, b.p. 143 (740 mm.), $n^{20}D$ 1.5051.

The remaining pyridine bases with the exception of 2,6-lutidine and 3-*t*-butylpyridine were samples which had been prepared by Murphey.[11] The purity of these samples had been established by cooling curve studies. 2,6-Lutidine was a sample purified by fractional crystallization with a purity of 99.6 mole % established by a cooling curve determination.[17] The 3-*t*-butylpyridine was a sample synthesized by B. Kanner. Cooling curve data on the purity of his sample are not available.

Absorption Spectra.—The absorption spectra (220–280 mμ) of the pyridine bases are affected by the addition of a proton to the nitrogen atom as well as by the number, position and type of alkyl groups attached to the ring. There is a marked increase in absorbancy in acid solution. Moreover, the addition of the proton results in a much smoother absorption curve.[18]

The addition of alkyl groups results in the disappearance of some of the absorption peak in both acidic and basic solutions. The position of the alkyl group affects the shape of the curve much more than the structure of the alkyl group. The position and absorbancy index values of the maxima and minima of the absorbancy *versus* wave length curves are given in Table II.

Experimental Procedure.—For pyridine and the three picolines, small dry ampules were filled with approximately 0.3 g. of the base, cooled to −80° (with protection from water and carbon dioxide) and sealed. The ampules were weighed to 0.0001 g. empty and after sealing. The amount of water required to produce a 0.0500 M solution of the base was measured by means of a transfer pipet, the ampule broken under the water, and the solution prepared. This solution was diluted successively to produce 2.00×10^{-4}, 1.000×10^{-4} and 5.00×10^{-5} M solutions.

The insolubility of the higher pyridine bases made a slight change in the procedure necessary. In these cases 0.005 mole of the base was weighed out and dissolved in sufficient water to make 1 l. of solution. This 0.005 M solution then was diluted successively as before.

To prepare a sample for absorption measurements, 5.00 ml. of 1.00 N hydrochloric acid (or 1.00 N sodium hydroxide or 0.5 M sodium acetate buffer) was placed in each of two 50-ml. volumetric flasks. To one of these, 5.00 ml. of the 1.00×10^{-3} M pyridine base solution was added and both flasks were made up to volume with distilled water. The same supply of distilled water was used to make up the pyridine base solution and all other volumetric solutions of the same series.

The absorbancy of each sample was measured against a reference having the same composition except for the nitrogen base. The measurements were corrected for cell variations.

Table III summarizes data for a typical determination of the pK_a value for pyridine.

LAFAYETTE, INDIANA

(17) A more convenient purification procedure has been developed: H. C. Brown, S. Johnson and H. Podall, THIS JOURNAL, **76**, 5556 (1954).

(18) For the spectra of these bases, consult the Ph.D. Thesis of X. R. Mihm, Purdue University Libraries.