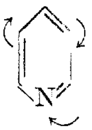
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VILLANOVA COLLEGE]

STUDIES ON PYRIDINES: I. THE BASICITY OF PYRIDINE BASES

ALEXANDER GERO AND JAMES J. MARKHAM[1]

Received June 25, 1951

We were interested in studying the base strength of pyridine and its homologs, particularly those methylpyridines which contain the methyl group attached to the 2- and 4-positions. These positions are made electron-deficient by the resonance of the pyridine ring



and it was thought worthwhile to investigate what effect an electron-donor methyl group would exercise in those positions.

Brown and Barbaras (1) attacked this problem by a study of the addition compounds of pyridine bases with trimethylborine. They point out that, while the hyperconjugative effect alone should make both 2- and 4-picoline stronger bases than pyridine, the +I effect should be greater in the 2-position, due to its proximity to the nitrogen. The base strengths of these three bases would therefore be expected to increase in the order pyridine, 4-picoline, 2-picoline. Actually, while pyridine and 4-picoline behave as expected, the addition compound of trimethylborine with 2-picoline dissociates much more readily than the corresponding adducts with the other bases, and Brown and Barbaras attribute this to steric hindrance due to the bulk of the methyl group which counteracts its electron-donor effect when in the 2-position.

We attempted to determine the aqueous ionization constants of pyridine and some of its homologs from their *p*H titration curves. Results of direct determinations of these ionization constants can be found in the literature (2) but agreement between various authors is not good. This is only to be expected since pure pyridine bases were not easily available and since the carbon dioxide error is liable to interfere greatly with measurements on such weak bases. In order to overcome these difficulties, we purified our bases carefully and devised an experimental technique aimed at the complete exclusion of atmospheric carbon dioxide. As a further measure of safety we disregarded the *p*H of the aqueous solutions of the bases themselves (where error due to CO_2 may be great) as well as the *p*H at the inflection point of the titration curve (where considerable error is likewise possible due to the steep drop of the *p*H) and took our results from the point of half-neutralization where $[B] = [BH^+]$ and therefore the *p*H of the solution is equal to the pK_A of the conjugate acid of the base titrated. These pK_A values and the corresponding K_B's are shown in Table I.

---

[1] Present address: Department of Oceanography, Agricultural & Mechanical College of Texas, College Station, Texas.

An interesting regularity becomes apparent if we plot the above pK_A values against the number of methyl groups in the molecule. As seen in Fig. 1 the points obtained lie very close to a straight line which means, since this is a logarithmic diagram, that each methyl group multiplies the fundamental basicity of pyridine by the same factor (about 6). Closer inspection reveals another fact; the points corresponding to bases with 2-methyl groups deviate from the straight line

TABLE I

IONIZATION CONSTANTS OF PYRIDINE AND HOMOLOGS

BASE	pK_A[a]	K_B[a]
Pyridine	5.23	1.7×10^{-9}
2-Picoline	5.96	9.1×10^{-9}
4-Picoline	6.05	1.1×10^{-8}
2,6-Lutidine	6.62	4.2×10^{-8}
2,4-Lutidine	6.79	6.1×10^{-8}
2,4,6-Collidine	7.45	2.8×10^{-7}

[a] No absolute validity is claimed for the figures in this table since the activities of the pyridinium ions are not known and no correction could be applied for this factor. However, since we were interested only in a comparison of the basicities of the several bases rather than in their absolute pK_A values, we felt we could neglect the activities. These are being determined and will be reported separately.

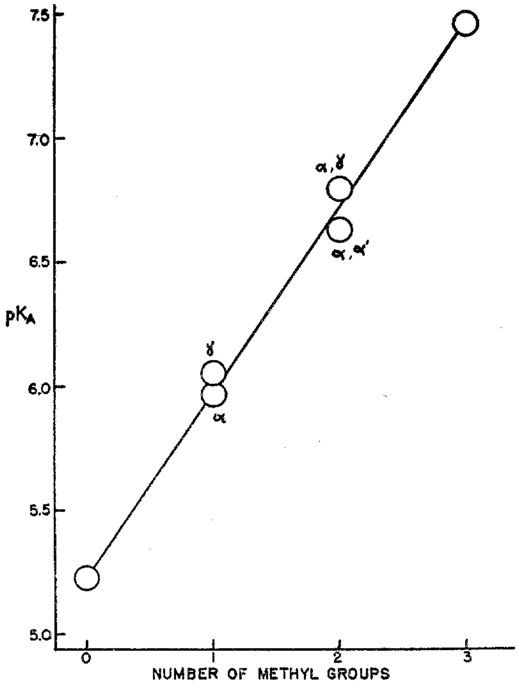


FIGURE 1. PLOT OF pK_A vs NUMBER OF METHYL GROUPS OF PYRIDINE BASES

by lying slightly below it while those corresponding to bases with a 4-methyl group lie slightly above the straight line.

This means that the multiplication factor for 2-methyl groups is somewhat different from that for 4-methyl groups. A mathematical relationship was sought which would express these observations, and it was found that the figures of Table I are solutions of the following equation:

$$pK_A = pK_{py} + 0.82\gamma + 0.73\alpha - 0.03\alpha(\alpha - 1)$$

in which pK_{py} represents the pK_A of pyridine, γ the number of methyl groups in the γ-position and α the number of methyl groups in the α-position.

The theoretical interpretation of the equation is clear: a methyl group manifests its electron-donor character by increasing the electron density at the N atom (expressed in the pK_A) by a constant of 0.73 if the methyl group is in the α-position and 0.82 if it is in the γ-position. The fact that the γ-constant is greater than the α-constant is reasonably interpreted to demonstrate qualitatively the same steric effect as found by Brown and Barbaras while quantitatively the effect we found is much smaller because the hydronium ion is smaller than the trimethylborine molecule.

The presence of two methyl groups, one in the α- and one in the γ-position, increases the pK_A of pyridine (5.23) by both the α- and the γ-constants. But if both methyl groups are in the α-position, they increase the fundamental basicity of the ring by less than twice the α-constant, showing that their steric hindrance is more than twice that of only one methyl group and necessitating the correction of 0.03 for the α-constant. This is quite plausible; steric hindrance by one α-methyl group seals off only one side of the nitrogen while two methyl groups in the two α-positions restrict hydronium ions to a narrow avenue of access.

It might be objected that the restriction suffered by the hydronium ion may be due to electrostatic repulsion by the positive methyl group as much as to genuine steric hindrance. But no steric hindrance is completely free of electrostatic effects since the outside of any atom or group is an electron cloud. It is therefore reasonable to compare the hydronium ion with the trimethylborine molecule in this context although the former is charged and the latter is not.

EXPERIMENTAL

1. Materials. In the purification of pyridine and the picolines we followed closely the method of Brown and Barbaras (1).

The *lutidines* were generously supplied by the Koppers Company in 95% purity. For further purification we took advantage of the low solubility of the complexes formed by the lutidines with mercuric chloride (3). The crude lutidines were dissolved in dilute hydrochloric acid and the solutions slowly stirred into a hot 10% solution of $HgCl_2$ in the proportion 3 $HgCl_2$ to 1 lutidine. The precipitates were filtered and recrystallized repeatedly from very dilute aqueous HCl until the melting points were constant (127° for the adduct of 2,4-lutidine, 162° for that of 2,6-lutidine, both uncorrected). Then the bases were liberated with 40% sodium hydroxide, dried with CaO, and distilled. The boiling points were in agreement with earlier data (3).

2,4,6-Collidine was synthesized by the method of Hantzsch (4).

After distillation, all bases were stored in small wash bottles over potassium hydroxide under a nitrogen atmosphere. Both openings of the wash bottles were hermetically sealed, the long tube with a rubber sleeve slipped over it, the short tube with a small rubber balloon. Under these conditions all bases were perfectly colorless and showed no tendency towards discoloration even after several months.

2. Method. The titrations were carried out in a weighing bottle of about 32 ml. capacity, with a carefully ground stopper. The inside diameter of the weighing bottle was such that the electrodes of a Beckman Model G *p*H meter fitted into it easily.

This weighing bottle was flushed out with dry nitrogen and weighed. Then the stopper was lifted slightly, the rubber sleeve was removed from the outlet tube of a wash bottle containing one of the bases and by slight pressure on the bulb a drop of base was transferred into the weighing bottle. During this operation dry nitrogen was blown into the weighing bottle so that not only was the base under nitrogen all the time but also, when the pressure on the balloon was released, nitrogen and not air was sucked back into the wash bottle. Then the rubber sleeve was replaced on the wash bottle outlet and the stopper was replaced on the weighing bottle. The latter was then weighed again.

Operations were conducted in $M/200$ solution so as not to run into complications due to high ionic strength. Ideally, exactly 0.1 milliequivalent of base should have been placed in the weighing bottle and diluted to 20 ml. Actually, the drops were always slightly too large. The second weighing showed the accurate amount of base in the weighing bottle, and enough conductivity water, usually 22–27 ml. was then added to obtain a $M/200$ solution.

The titration was carried out as follows: $N/2$ hydrochloric acid was added from a microburette graded in 1/100 ml. which allowed 1/1000 ml. to be estimated with fair accuracy. For each addition the stopper was removed while nitrogen was blown gently over the surface of the solution. After addition the weighing bottle was stoppered, inverted repeatedly for thorough mixing, then opened again under nitrogen and the electrodes inserted for measurement. Clear-cut titration curves were obtained in all cases. The results are shown in Table I.

The *p*H measurements were easily reproducible within about ± 0.05 *p*H unit. Since only the midpoint of the titration curve was considered (as explained above) where $pK_A = pH$, the pK_A values in the table are also accurate to ± 0.05. All measurements were performed at 25°.

SUMMARY

1. The pK_A of pyridine, 2- and 4-picoline, 2,4- and 2,6-lutidine, and 2,4,6-collidine was determined using special precautions to operate with pure bases and to eliminate the carbon dioxide error.

2. A diagram plotting the pK_A of these pyridine bases against the number of methyl groups results in a straight line.

3. Deviations of individual points from the straight line indicate that each methyl group in an α-position increases the pK_A of pyridine by 0.73, and each methyl group in a γ-position by 0.82, but two methyl groups in α-positions only by $2 \times 0.73 - 0.06$. These findings are attributed to steric hindrance.

VILLANOVA, PENNSYLVANIA

REFERENCES

(1) BROWN AND BARBARAS, *J. Am. Chem. Soc.*, **69,** 1137 (1947).

(2) CONSTAM AND WHITE, *Amer. Chem. J.*, **29,** 1 (1903); LUNDÉN, *J. Chim. Phys.*, **5,** 574 (1907); VELEY, *J. Chem. Soc.*, **93,** 2137 (1908); ARNALL, *J. Chem. Soc.*, **117,** 835 (1920); KOLTHOFF, *Biochem. Zeitschr.*, **162,** 289 (1925); BARRON, *J. Biol. Chem.*, **121,** 313 (1937).

(3) GARRETT AND SMYTHE, *J. Chem. Soc.*, **81,** 449 (1902).

(4) HANTZSCH, *Ann.*, **215,** 1 (1882).