06-1; **3e,** 37528-68-0; **4,** 1713-37-7; **6,** 16618-72-7; **7,** 37488-35-0; **8a,** 37488-36-1; **8b,** 37488-37-2; **8c,** 37488-38-3; **10,** 37500-24-6; **11,** 37488-39-4; isopropylamine hydrobromide, 29552-58-7; benzylamine hydrobromide, 37488-40-7.

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Ionization in Liquid Ammonia of Methyl and Amino Groups Bonded to Pyridine and Pyrazine. A Method of Determining Their pK_a Values[1]

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Proton magnetic resonance spectra of ionized 2-methyl and 2-amino derivatives of pyridine and pyrazine along with spectra of 2-pyridone and 2-pyrazinone in liquid ammonia are reported. Changes in chemical shifts produced by ionization of the pyridines are linearly related to those for the pyrazines. Competition experiments show that 2-methyl- is less acidic than 4-methylpyridine; estimates of the pK_a values for these two acids are given. It is suggested that the results provide a basis for determining the equilibrium acidities of weak heterocyclic acids.

The acidities of heterocyclic molecules containing carbon or nitrogen side chains having pK_a values >20 are largely undetermined.[3,4] Liquid ammonia is an attractive solvent for the determination of pK_a values of these weak acids. Ammonia has long been used to study the kinetic acidities of weak acids, both carbocyclic and heterocyclic.[3,7] Its very low self-ionization constant (pK = 32.5 at −33°)[8] allows high concentrations of the conjugate bases of the weak acids to be formed. The recent determination of pK_a values for a few carbocyclic nitrogen and carbon acids in ammonia by means of potentiometry, nmr, and ultraviolet spectroscopy[9] encouraged us to study weak heterocyclic acids.

We have found nmr to be a useful way to study the ionization of pyridines and pyrazines in ammonia and report results dealing with the ionization of methyl and amino groups bonded to these heterocyclic rings. That simple ionization takes place in the presence of amide ion was established by consideration of nmr spectra and by a correlation involving changes in chemical shifts resulting from the deprotonation of these weak acids and the more readily ionizable compounds 2-pyridone and 2-pyrazinone.[10] Our results pave the way for the determination of pK_a values for these and many more weakly acidic heterocyclic molecules in ammonia. They also provide the first reliable estimates of the pK_a values for 2- and 4-methylpyridines.

Results and Discussion

Pyridines.—Addition of 2-methylpyridine to an excess of KNH_2 in ammonia gives a highly colored solution. Its nmr spectrum shows at −40° no evidence of unreacted starting material or any other component in addition to ionized substrate. Chemical shifts and coupling constants are given in Table I. The ring protons of the anion are shielded by 1.6, 1.7, 2.3, and 1.3 ppm for the 3, 4, 5, and 6 positions, respectively, relative to the starting carbon acid in ammonia. The methylene group shows a clear AB pair of doublets at −40°, τ 7.4 and 7.55 (J = 3.2 Hz). These shifts are very similar to that of the methyl group, τ 7.5. No change in the spectrum could be detected after the sample stood for 1 week at room temperature, indicating a surprising stability. The large shielding values and the nonequivalent methylene protons indicate that a largely ionic compound is formed;[13] charge delocalization into the ring leads to double-bond character and restricted rotation about the methylene–ring bond. When the carbon acid is incompletely neutralized, signals for both the acid and its conjugate base are present. There is no evidence of signal averaging. This is to be expected.[16]

The nmr spectrum of this 2-pyridylmethylpotassium in ammonia is very similar to that of 2-pyridylmethyllithium in tetrahydrofuran.[17] The shielding of ring and methylene protons of the sample in ammonia is no greater than 12 Hz; coupling constants for ring protons

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(1) Presented in part at the Gordon Conference on Heterocyclic Chemistry, New Hampton, N. H., June 26-30, 1972.

(2) To whom correspondence should be addressed.

(3) N. N. Zatsepina, A. V. Kirova, and I. F. Tupitsyn, *Org. Reactiv.* (*USSR*), **5**, 70 (1968).

(4) In marked contrast, considerable effort has been applied to the determination of pK_a values for weakly acidic aromatic hydrocarbons.[5,6]

(5) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965; A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 41 (1965).

(6) H. Fischer and D. Rewicki, *Progr. Org. Chem.*, **7**, 116 (1967).

(7) A. I. Shatenshtein and I. O. Shapiro, *Russ. Chem. Rev.*, **37**, 845 (1968); A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 156 (1963); *Tetrahedron*, **18**, 95 (1962); N. N. Zatsepina, I. F. Tupitsyn, A. V. Kirova, and A. I. Belyashova, *Org. Reactiv.* (*USSR*), **8**, 787 (1971).

(8) L. V. Coulter, J. R. Sinclair, A. G. Cole, and G. C. Roper, *J. Amer. Chem. Soc.*, **81**, 2986 (1959).

(9) J. J. Lagowski, *Pure Appl. Chem.*, **25**, 429 (1971).

(10) Anions of the type considered here can be trapped by electrophiles in ammonia; the reactions are of preparative value.[11,12]

(11) H. C. Brown and W. A. Murphy, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

(12) W. Schwaiger and J. P. Ward, *Recl. Trav. Chim. Pays-Bas*, **90**, 513 (1971); S. V. Kannan and H. Pines, *J. Org. Chem.*, **36**, 2304 (1971); G. W. H. Cheeseman and E. S. G. Werstiuk, *Advan. Heterocycl. Chem.*, **14**, 99 (1972).

(13) It is expected that ion pairing will be important in ammonia for this and the other compounds considered here.[9,14,15] Hence, pK_a values are ion-pair values.[6]

(14) M. Fisher and M. Szwarc, *Macromolecules*, **3**, 23 (1970); M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, **3**, 287 (1964); "Ions and Ion Pairs in Organic Reactions," Vol. 1, M. Szwarc, Ed., Wiley-Interscience, New York, N. Y., 1972.

(15) J. H. Takemoto and J. J. Lagowski, *J. Amer. Chem. Soc.*, **91**, 3785 (1969).

(16) T. Birchall and W. L. Jolly, *ibid.*, **87**, 3007 (1965).

(17) K. Konishi, K. Takahashi, and R. Asami, *Bull. Chem. Soc. Jap.*, **44**, 2281 (1971).

TABLE I

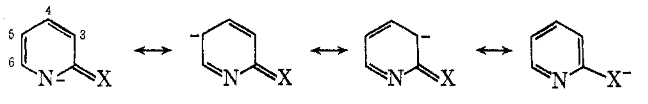
CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR IONIZED 2-SUBSTITUTED PYRIDINES IN AMMONIA

	τ				J, Hz					
X	3	4	5	6	3,4	3,5	3,6	4,5	4,6	5,6
I, CH_2	4.51	3.93	5.23	3.00	9.0	1.3	1.0	6.0	2.0	4.8
NH	4.24	3.34	4.54	2.55	8.5	1.5	1.0	6.5	2.0	5.0
O	3.98	2.89	4.03	2.26	8.5	1.2	1.0	6.5	2.5	5.0

differ by less than 0.7 Hz. (The methylene group was said to be broad.[17]) Because the material in ammonia is largely ionic and because the spectra of the two salts in the two solvents are so similar, it seems likely that the lithium compound also is largely ionic.

The nmr spectra of ionized 2-aminopyridine and 2-pyridone in ammonia also were obtained. Since 2-methylpyridine is completely ionized by an excess of amide ions, the more acidic amino and oxy compounds also must undergo total ionization in the presence of excess amide ions. Again, deprotonation brings about shielding of the ring protons but shielding factors are smaller than those for methyl group ionization, being in the range 0.3–1.1 ppm. Unlike the carbon acid just considered, separate signals for these acids and their conjugate bases are not expected, owing to rapid proton exchange.[16]

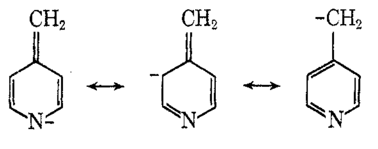
Comparison of the three isoelectronic conjugate bases, Table I, reveals that coupling constants are virtually identical. Chemical shifts vary in an understandable way. As more negative charge resides on the side chain in the order expected from atom electronegativity considerations, *i.e.*, X = CH_2, NH, and O, respectively, in I, smaller shielding factors result for the ring protons. Indeed, the spectral similarities firmly support the idea that the three pyridines only undergo simple ionization in the presence of amide ions to give charge-delocalized ion I.



I, X = CH_2, NH, O

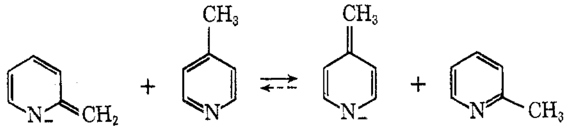
The nmr spectrum of the anion of 2-pyridone in D_2O has been reported.[18] Comparison of the spectra obtained from ammoniacal and aqueous solutions indicates that there are only minor differences in coupling constants (<0.5 Hz) but there are large differences in chemical shifts, those protons for the sample in ammonia all being shielded. Differences are 24 (H-3), 20 (H-4), 28 (H-5), and 6 Hz (H-6). Differences are likely to be due to solvation of the anion. It would appear from these large differences in chemical shifts that this anion could be useful in solvation studies.

4-Methylpyridine reacts completely with excess KNH_2 at −40° to give its conjugate base II. The AA′XX′ spectrum consists of a broadened doublet at τ 3.3 for the H-2,6 protons; the H-3,5 signals at τ 4.55 consist of a pair of doublets with small wing peaks. The separation of the main (outer) doublet peaks is 5.5 Hz. The methylene singlet is at τ 7.3 while the methyl group of starting material is at τ 7.7 Again, when the acid is incompletely converted to its conjugate base in the presence of a deficiency of amide ion, no signal averaging of the acid and its conjugated base are apparent.



II

A comparison of the relative acidities of 2- and 4-methylpyridines revealed that the 2-methyl- is a weaker acid than the 4-methylpyridine. Two types of experiments were performed. A mixture of 2-methylpyridine and its conjugate base was prepared using a deficiency of amide ion. This then was added to excess 4-methylpyridine. Analysis of the resultant mixture (−40°) indicated that no conjugated base of 2-methylpyridine was present; instead the conjugated base of 4-methylpyridine was formed.[19] This result clearly indicates that 2-methyl- is a weaker carbon acid than 4-methylpyridine (eq 1).



(1)

In other experiments a mixture of 2- and 4-methylpyridines was allowed to compete for a deficiency of amide ion in ammonia. No ionized 2-methylpyridine could be detected in the presence of both ionized and un-ionized 4-methylpyridine and of un-ionized 2-methylpyridine. This is consistent with the result given in eq 1. From the concentrations obtained by integration and the assumption that no more than 1% of the conjugate base of 2-methylpyridine was present in the mixture, it may be calculated that the ionization constant, K_a, for the 4-methyl compound must be at least 75 times greater than that for 2-methylpyridine. The acidifying effect of the para annular nitrogen atom is considerably greater than that of the ortho annular nitrogen atom.

A comparison between the acidity of the methylpyridines and ammonia may be made by using the shape of the ammonia solvent peak to provide an estimate of the amide ion concentration.[20,21] When both 4-methylpyridine and its conjugate base are present in ammonia at −40° in a 1:1 ratio, the solvent peak is a partially collapsed triplet rather than a singlet. This means that the amide ion catalyzed hydrogen exchange of ammonia is slow because the amide ion concentration in the carbon acid buffer mixture is low. The

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(18) R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, **73**, 2465 (1969).

(19) Experiment kindly performed by T. M. Oestreich.

(20) R. A. Ogg, Jr., *Discuss. Faraday Soc.*, **17**, 215 (1954); J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, Chapter 4.

(21) T. J. Swift, S. B. Marks, and W. G. Sayre, *J. Chem. Phys.*, **44**, 2797 (1966); D. R. Clutter and T. J. Swift, *J. Amer. Chem. Soc.*, **90**, 601 (1968).

amide ion concentration may be estimated from the coupling constant for ammonia (44 Hz) and the rate constant for hydrogen exchange ($1.7 \times 10^6\ M^{-1}\ \text{sec}^{-1}$ at $-40°$[21]). Hence $[NH_2^-] \sim 44\pi/(\sqrt{2} \times 1.7 \times 10^6)$ or $[NH_2^-] \sim 6 \times 10^{-5}\ M$. Use of this estimate, the carbon acid buffer ratio, and the known ionization constant for ammonia (pK_{NH_3}[8] = 33.2 at −40°) allows an estimate of the ionization constant of the carbon acid to be made (eq 2).

$$\frac{[PyCH_3][NH_2^-]}{[PyCH_2^-]} = \frac{10^{-33.2}}{K_a} \qquad (2)$$

The pK_a value of 4-methylpyridine at −40° is ∼29. It is fortuitous that the amide ion concentration is such that the solvent signal is a partially collapsed triplet. This is an ideal situation for the accurate determination of the amide ion concentration by means of a computer-assisted line-shape analysis. It appears that a more refined pK_a value could be obtained from studies involving various ratios of acid to conjugate base and an accurate line-shape determination of the amide ion concentration. Such a study is highly desirable not only because a more refined pK_a value would be obtained but also because this value could then serve as a reference value. Comparisons with other acids in competition experiments of the type employed with the two methylpyridines then lead to pK_a values for other compounds.

When both 2-methylpyridine and its conjugate base are present in ammonia at −40° in a 3:1 ratio, the solvent peak is a broadened singlet. Before this information can be used to estimate a lower limit of the amide ion concentration and of the pK_a of the carbon acid, it must be established that the triplet to singlet conversion of the solvent signal by proton exchange is catalyzed only by amide ion; *i.e.*, the possibility of catalysis by the 2-pyridylmethyl anion (general base catalysis) must be eliminated. This possibility can be dismissed because it has been reported that a mixture of this carbon acid and its conjugate base in ND_3 slowly undergoes H–D exchange in the side chain. Although the carbon base must dedeuterate the solvent in the course of H–D exchange, the pseudo-first-order constant[22] for this process is only $<10^{-6}\ \text{sec}^{-1}$ at −45°. This is much too slow to bring about collapse of the triplet solvent signal which requires a pseudo-first-order rate constant of $\sim 44\ \pi/\sqrt{2}$ or $\sim 10^2\ \text{sec}^{-1}$ at −45°. Clearly, then, collapse of the solvent triplet is essentially catalyzed by amide ion and the shape of the solvent peak provides a valid estimate of the amide ion concentration. Hence $[NH_2^-] > 6 \times 10^{-5}\ M$. From eq 2, the pK_a of 2-methylpyridine at −40° is likely to be >29. That this acid is completely ionized by amide ion means $pK_a < 33.2$. In other words the pK_a is >29 but <33. Moreover, consideration of the results of the competition experiment, eq 1, and of the estimated pK_a of 4-methylpyridine allows an estimate of ∼31 to be made for the pK_a of 2-methylpyridine. The pK_a values for 2- and 4-methylpyridines are similar, for example, to the pK_a[15] (28.6) of di(4-methoxyphenyl)methane in ammonia at −34.5°.

The pK_a values for the methylpyridines are the first reliable estimates of the acidities of these two carbon acids. Other values based upon the rates of hydrogen–deuterium exchange in ethanol-*O-d* and an assumed Brønsted relationship[3] are known to be incorrect.[23]

Toluene, the deaza analog of the methylpyridines, does not undergo detectable ionization in the presence of amide ion.[11,24] Clearly, the acidifying effect of the annular nitrogen atom in the heterocyclic compounds is enormous.

Pyrazines.—The identity of the product resulting from the reaction of 2-methylpyrazine with amide ion is of special interest. Pyrazine itself (but not pyridine) reacts with amide ion to give an anionic σ complex, III.[25] It therefore becomes of interest to learn whether addition or ionization is the preferred reaction of 2-methylpyrazine.

In the presence of excess KNH_2 at −40° no unreacted 2-methylpyrazine could be detected. Instead the spectrum (Table II) of a single substance was evident. The large shielding and the presence of an AB pair of doublets at τ 7.22 and 7.35 (*J* = 2.8 Hz) provide evidence that 2-methylpyrazine undergoes deprotonation to give charge-delocalized anion IV, X = CH_2, rather than addition of amide ion to give an anionic σ complex. The latter complex would be expected to show a singlet for the methyl group.

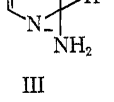
Table II

Chemical Shifts and Coupling Constants for Ionized 2-Substituted Pyrazines in Ammonia

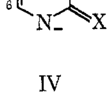
	τ			J, Hz	
X	3	5	6	3,6	5,6
IV, CH_2	3.13	4.14	3.25	1.5	3.0
HN	2.80	3.40	2.80	*a*	2.7
O	2.48	2.77	2.31	1.2	2.7

[a] Signal overlap prevents accurate analysis.

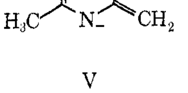
Signal assignments were aided by a consideration of the spectrum of ionized 2,6-dimethylpyrazine in ammonia. Monoanion V is formed and has the following characteristics: τ 3.27 (H-3), 4.23 (H-5), 7.21, 7.39 (CH_2), and 8.41 (CH_3). The methylene protons are nonequivalent at −40°, *J* = 2.5 Hz. Since the ring protons in V appear as singlets, meta spin coupling ($J_{3,5}$) is insignificant. Hence, the significant couplings in the monomethyl anion can only be $J_{5,6}$ and $J_{3,6}$. The assumption that ortho ($J_{5,6}$) is larger than para coupling ($J_{3,6}$) allows all the signal assignments in IV to be made. The H-3 and H-5 protons of IV and V have consistent assignments.



III



IV



V

Although pyrazine reacts with amide ion to give III, methylpyrazines undergo deprotonation to give delocalized carbanions IV, X = CH_2, and V. This suggests that such aromatic anions are lower in energy

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[22] N. N. Zatsepina, I. F. Tupitsyn, A. V. Kirova, and A. I. Belyashova, *Org. Reactiv. (USSR)*, **6**, 257 (1969). The fractional amount of substrate in the anion form is ∼0.2.

[23] A. Streitwieser, Jr., W. B. Hollyhead, G. Sonnichsen, A. H. Pudjaatmaka, C. J. Chang, and T. L. Kruger, *J. Amer. Chem. Soc.*, **93**, 5096 (1971).

[24] T. Birchall and W. L. Jolly, *ibid.*, **88**, 5439 (1966).

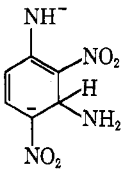
[25] J. A. Zoltewicz and L. S. Helmick, *ibid.*, **94**, 682 (1972).

than carbon-methylated derivatives of nonaromatic ion III. This conclusion is of special interest in that heteroaromatic molecules containing a methyl group bonded to an annular carbon atom often show a greatly diminished reactivity in the Chichibabin amination reaction. This was interpreted to mean that the methyl group underwent ionization under the conditions of the amination and thereby hindered the addition of amide ion to an annular carbon atom, a necessary first step in the Chichibabin reaction.[26] Our results provide the first direct evidence to support this suggestion. Since a number of methylated heterocyclic compounds show diminished reactivity[26] in the amination reaction, ionization often must be preferred over addition.

Again the nmr spectra of amino and oxy acid analogs were obtained. The spectral properties of the conjugate bases of 2-aminopyrazine and 2-pyrazinone are given in Table II. Coupling constants for the three isoelectronic pyrazine bases are very similar. Ionization of the pyrazine acids result in smaller shielding factors for the anions having the more electronegative nitrogen and oxygen side chains, just as in the pyridine series.

The nmr spectrum of the anion of 2-pyrazinone in methanol has been reported.[18] Comparison of this with that obtained using ammonia solvent shows minor differences in coupling constants but greater shielding (5–12 Hz) in ammonia. As in the 2-pyridone case, solvation differences probably are responsible.

We find no evidence of dianion formation of the type reported for 2,4-dinitroaniline in ammonia containing amide ion. This aniline undergoes both ionization (amino group) and addition reactions with amide ion to give VI.[24]



VI

Correlation of Chemical-Shift Changes Resulting from Ionization.—The effect of ionization on the chemical shifts of the ring protons (shielding factors) is given by the difference in shift between an ion and its conjugate acid. For the pyridine and pyrazine series the position (H-5) para to the side chain has the largest shielding factor; usually, but not always, the shielding factor for the ortho position (H-3) is larger than that for a meta position (H-6). The factors generally are larger in the pyrazine series. When the factors for the 3, 5, and 6 positions of the pyrazine family of acids are plotted against those for the corresponding pyridine acids, a linear relationship (Figure 1) is obtained. The least-squares line (correlation coefficient 0.988) is given by eq 3 where SF is shielding factor.

$$\text{pyrazine SF} = 1.01 \text{ pyridine SF} + 0.135 \text{ ppm} \qquad (3)$$

It should be noted that the chemical shifts of 2-pyridone and 2-pyrazinone could not be employed in making this correlation because these compounds are not analogous structurally to the methyl and amino acids. The hydroxy tautomer is the appropriate structural analog. Unfortunately, nmr spectra of the hydroxy compounds are unavailable because the molecules exist largely in tautomeric forms having the proton bonded to nitrogen rather than to oxygen,[27] VII.

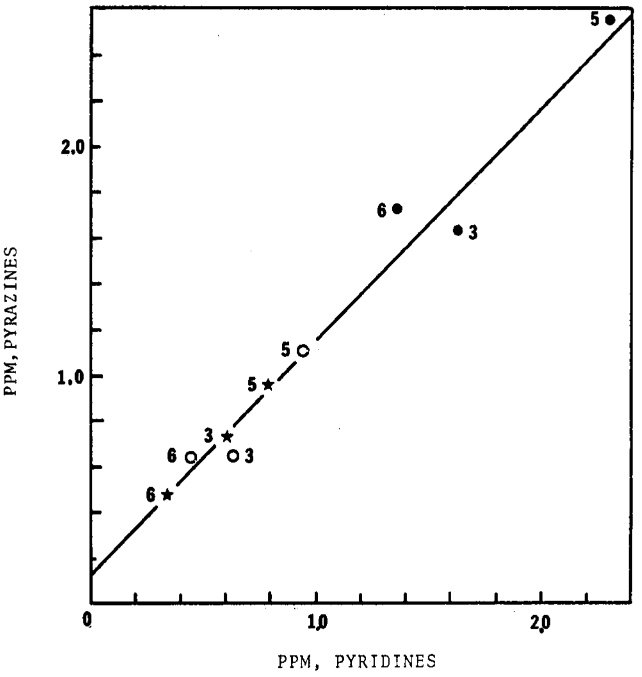
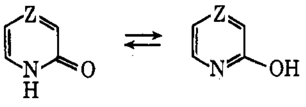


Figure 1.—Plot of the change in chemical shift resulting from the ionization of pyrazines *vs.* that for the ionization of pyridines in ammonia. The change is given by the difference between the shift of an ion and its conjugate acid. Filled circles refer to methyl, open circles to amino, and stars to oxy compounds. The proton positions are indicated.



VII, Z = CH,N

To overcome this limitation the nmr spectra of methoxy compounds were employed as models of the hydroxy compounds. Since the nmr spectra of the un-ionized compounds are not significantly dependent on solvent, chemical shifts obtained using DMSO solvent were employed.[28]

The shielding factors may be correlated in other ways. For example, the shielding factors for H-5 of the three acids are linearly related to those for H-3, pyridines and pyrazines showing the same correlation.

These correlations can be understood in familiar, general terms. As a position carries a greater fraction of the negative charge, larger shielding factors are observed. The presence of a second annular nitrogen atom in the pyrazine series provides additional (inductive) stabilization of the negative charge, leading to a larger fraction of the charge on the ring positions.

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[26] F. W. Bergstrom, *J. Amer. Chem. Soc.*, **53**, 3027, 4065 (1931); *J. Org. Chem.*, **3**, 233 (1938).

[27] A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).

[28] G. S. Marx and P. E. Spoerri, *J. Org. Chem.*, **37**, 111 (1972). R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, **72**, 1646 (1968).

These correlations provide additional support for the nmr assignments as well as further support for our claim that only ionization of acids is being observed.

In conclusion, we have established that some pyridine and pyrazine carbon and nitrogen acids in ammonia containing amide ion only undergo simple deprotonation reactions. Competitive ionization experiments which are expected to provide relative pK_a values were shown to be possible. Solvent line-shape analysis could provide an accurate pK_a value for 4-methylpyridine, a compound which can then serve as a reference standard.

At this early stage in the development of acidity scales using liquid ammonia as a solvent, it is imperative that independent approaches be developed to verify the validity of the pK_a values.[5,6] Our method makes possible the establishment of an acidity scale for ammonia solutions which is independent of other scales. It extends from very weak acids such as 2-methylpyridine to moderately strong acids such as 2-pyrazinone.[29] This scale could easily be related to the newly reported one[9,30] and thereby establish whether both scales provide the same pK_a values for the same compounds in ammonia. It should be noted that many more compounds will have to be added to our list in order to carry out competition experiments to cover a wide pK_a range.

It is expected that our method will make possible the determination of pK_a values for many weak heterocyclic acids. The information obtained from these acidity studies would greatly add to our understanding of the effects of structure on the acidity of weak acids, now largely based on studies of hydrocarbons.[5]

Experimental Section

Materials.—All compounds are commercially available; they were used as received. The sodium salt of 2-pyrazinone was used directly.

General Procedure for Obtaining Nmr Spectra of Ammonia–Amide Ion Reaction Mixtures.—The apparatus consisted of a 25-ml, three-neck round-bottom flask, to which was added a 2-mm ground glass stopcock near the bottom, and 7- and 10-ml calibration lines. The flask was fitted with a stopper, a septum through which liquids were added by syringe, and a Dry Ice–acetone condenser with attached drying tube ($CaCl_2$). A glass-enclosed stirring bar was used for magnetic stirring. The stopcock was connected to a glass capillary tube by a 1-cm piece of Tygon tubing. The capillary was tapered so that it would fit into a standard nmr tube.

The apparatus was flame dried under a slow stream of dried nitrogen. Ammonia then was condensed into the flask. Potassium amide was generated by the addition of a pin-head size piece of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst and potassium metal; 1 to 3 hr are required for amide ion formation, as evidenced by a change from a blue to a gray color.

A weighed amount of heterocyclic substrate was added to the flask or to an nmr tube. Ammonia solution then was drained through the capillary tube into an nmr tube immersed in a Dry Ice–acetone bath. The tube was then capped. The substrate concentration was $\sim$0.5 *M*.

Trimethylamine (τ 7.87) or benzene (2.60) internal standard were added to the nmr tube. In the case of trimethylamine, 2 ml of vapor were removed by syringe from a flask cooled to 0° and fitted with a septum. The vapor was injected into the tube at a level below that of the cooling bath.

The tube was sealed with a torch. The contents of the tube were mixed by inverting the tube; the tube was cooled in the bath every few seconds to maintain a low temperature. However, the heterocycle dissolves more readily at higher temperatures.

For low temperature nmr work, the level of liquid NH_3 should be below the spinner; otherwise poor cooling may result. This, in turn, may give pressures high enough to explode the tube and damage the probe. Standard thin wall (0.4-mm thickness) nmr tubes may be used safely to 0° or even 25°. For higher temperatures medium wall (0.75 mm) tubes should be employed. When possible, it is desirable to test the seals of the tubes by immersion into baths at temperatures at or above probe temperatures.

Spectra were obtained with a Varian A-60A spectrometer equipped with a V-6040 variable-temperature controller.

Competion Experiments Involving 2- and 4-Methylpyridines.—Two different experiments were employed. (a) A mixture of ionized and un-ionized 2-methylpyridine was prepared by adding excess 2-methylpyridine to KNH_2–NH_3. A portion of this solution was taken to confirm that the carbon acid and its conjugate base were present. The mixture then was added to an nmr tube cooled in acetone–Dry Ice containing excess 4-methylpyridine. The temperature of the mixture was raised to 0° for $<$1 min before a spectrum was obtained at $-40°$. No ionized 2-methylpyridine could be detected, only ionized 4-methylpyridine. (b) The KNH_2 was added to a cooled nmr tube containing both 2- and 4-methylpyridine.

Registry No.—Pyridine, 110-86-1; pyrazine, 290-37-9.

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