Relative Gas-Phase Basicities of Some Amines, Anilines, and Pyridines. An Application of Some Brønsted Acids as Reactants in Chemical Ionization Mass Spectrometry

Ismet Dzidic

Contribution from the Institute for Lipid Research, Baylor College of Medicine, Houston, Texas 77025. *Received March 6, 1972*

Abstract: Using the Brønsted acids $BH^+ = NH_4^+$, $CH_3NH_3^+$, and $(CH_3)_2NH_2^+$ as reactant ions in the chemical ionization source of the mass spectrometer, the general proton transfer reaction $BH^+ + M \rightarrow MH^+ + B$ was studied. The following order of relative proton affinities, *i.e.*, gas-phase basicities, was observed: quinuclidine, decylamine, pyridine, 4-*N*,*N*-dimethylaminopyridine, *N*,*N*-dimethylaniline > dimethylamine > *N*-methylaniline, *m*-phenylenediamine, *N*,*N*,*N*-triphenylamine > methylamine, *o*-phenylenediamine, *p*-phenylenediamine, *N*,*N*-diphenylamine, aniline > ammonia. The relative order of basicities observed suggests that certain intrinsic electronic effects which have been invoked in order to explain the solution basicities of anilines and pyridines do not play a significant role. The gaseous acids BH^+ can be used as analytical chemical ionization reactants. Selective protonation by those acids can lead to detection of specific basic groups in the compounds studied.

The relative strength of organic and inorganic bases in the gas phase is of considerable interest since it reveals intrinsic electronic effects on basicities without the interference of the solvent. While considerable work on gas-phase basicities has been done by Brauman[1] and others,[2] still a number of very important compounds like anilines, pyridines, conjugated ketones,[3a] amides,[3b] etc., have not been considered. In addition, since analytical chemical ionization (CI) mass spectrometry[4] is based mainly on reactions between gas-phase acids (*i.e.*, CH_5^+, $t\text{-}C_4H_9^+$, H_3O^+, NH_4^+,[5] etc.) and organic bases, it is important to know the relative basicities of different functional groups in order to select the most useful set of gas-phase acids which might selectively protonate specific basic sites in the molecule. For example, gas-phase acids, BH^+, where B = NH_3, CH_3NH_2, and $(CH_3)_2NH$, will not protonate the basic groups such as alcohols, esters, or ethers in the gas phase since the basicity of these groups is lower than that of B.[6] However, the acid NH_4^+ will protonate amino and amido groups, for example, while $(CH_3)_2NH_2^+$ will protonate only certain amines in the presence of other basic nitrogen or oxygen groups whose basicity is lower than that of dimethylamine. Selective acid–base reactions in the gas phase will be illustrated by several examples.

Experimental Section

(a) Apparatus and Conditions. Mass spectra were obtained with CEC 21-110B mass spectrometer modified for CI as previously described.[7] The accelerating voltage was 8.4 kV, the ionizing voltage 200 eV, and the low repeller field 0–1 V/cm. Reagent gas pressure in the ion source was maintained at 0.5 Torr and sample pressure as ~ 1mTorr. Liquid samples (2 μl) were introduced into the source through the heated glass reservoir, and solid samples (~5 μg) were introduced by direct probe. Temperatures of the ion source were maintained at 150–200°. Reagent gases were obtained from Matheson Co. Gas and compound purities were determined mass spectrometrically and were found free of interfering contamination.

(b) Determination of Relative Basicity. The basicities of amines $NH_3 < CH_3NH_2 < (CH_3)_2NH$ are known to increase regularly in the order shown above.[1] This fact was used in the present study for ordering the basicities of the compounds M shown in Table I,

Table I. Intensities[a] of Molecular Ionic Species of Some Organic Bases (M) Using Different Reagent Gases (B)

	Reagents		
Compound	Ammonia MH^+	Methylamine MH^+	Dimethylamine MH^+
Quinuclidine	100	95	97
Decylamine	100	92	70
Aniline	100	4	2
N-Methylaniline	100	88	3
N,*N*-Dimethylaniline	100	92	40
N,*N*-Diphenylamine	100	15	1
N,*N*,*N*-Triphenylamine	100	80	2
o-Phenylenediamine	100	8	1
p-Phenylenediamine	100	12	1
m-Phenylenediamine	100	85	2
Pyridine	100	91	65
4-*N*,*N*-Dimethylaminopyridine	100	87	95

[a] The intensity of MH^+ is arbitrarily defined as 100 when NH_3 is used as reagent gas. The intensities of MH^+ using CH_3NH_2 and $(CH_3)_2NH$ gases were measured relative to that of MH^+ with NH_3.

relative to the basicities of the above amines. In other words these amines were used as the reactant acids BH^+, where B = NH_3, CH_3NH_2, and $(CH_3)_2NH$. Shown in Table I are the intensities of MH^+ ions observed with mixtures of M (present at pressures of ~1 mTorr) and B present at pressures of 0.5 Torr.

When pure B compounds were used, the major ions observed were BH^+ and B_2H^+. Thus essentially all primary ions resulting from electron impact ionization of B are converted by ion–molecule reactions to BH^+. The B_2H^+ results from the association (clustering) reaction 1 in which B serves also as the third body required for the stabilization of B_2H^+.[8]

(1) J. I. Brauman, J. M. Riveros, and L. K. Blair, *J. Amer. Chem. Soc.*, **93**, 3914 (1971), and references therein.
(2) For review article see J. L. Beauchamp, *Annu. Rev. Phys. Chem.*, **22**, 1 (1971).
(3) (a) I. Dzidic and J. A. McCloskey, *Org. Mass Spectrom.*, **6**, 939 (1972); (b) I. Dzidic, unpublished results.
(4) For leading references see (a) F. H. Field, *Accounts Chem. Res.*, **1**, 42 (1968); (b) B. Munson, *Anal. Chem. Rev.*, **43**, 28 (1971).
(5) M. S. Wilson, I. Dzidic, and J. A. McCloskey, *Biochim. Biophys. Acta*, **240**, 623 (1971).
(6) M. A. Haney and J. L. Franklin, *J. Phys. Chem.*, **73**, 4328 (1969).
(7) I. Dzidic, D. M. Desiderio, M. S. Wilson, P. F. Crain, and J. A. McCloskey, *Anal. Chem.*, **43**, 1877 (1971).
(8) (a) A. M. Hogg and P. Kebarle, *J. Chem. Phys.*, **43**, 449 (1965); (b) S. K. Searles and P. Kebarle, *J. Phys. Chem.*, **72**, 742 (1968); (c) M. S. B. Munson, *ibid.*, **70**, 2039 (1966).

$$BH^+ + B + B \rightleftharpoons B_2H^+ + B \quad (1)$$

In the presence of M the following reactions may occur.

$$BH^+ + M \xrightarrow{k_2} MH^+ + B \quad (2)$$

$$BH^+ + M + B \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} MBH^+ + B \quad (3)$$

$$MH^+ + B + B \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} MBH^+ + B \quad (4)$$

Reaction 2 will occur if the proton affinity (PA) of M $\geq$ proton affinity of B.[9] However, since the pressure of M is several hundred times lower than that of B, one will observe the high abundance of MH^+ ions only if reaction 2 is exothermic, PA(M) > PA(B). Thus this reaction is used as the diagnostic reaction by which the unknown PA's of the compounds M are ordered relative to the three known PA's of ammonia, methylamine, and dimethylamine. The forward clustering reactions 3 and 4 are not dependent on PA(M) being larger than PA(B). The decomposition of the cluster MBH^+ will proceed *via* (−4) if PA(M) > PA(B) and *via* (−3) if the reverse is true. Thus in all cases the presence of an intense MH^+ ion indicates that PA(M) > PA(B). However, the presence of an additional intense MBH^+ ion may not be diagnostically useful. In order to eliminate the presence of MBH^+ all experiments were done at elevated temperatures where the MBH^+ concentration was relatively low due to dissociation *via* (−3) or (−4).

The amount of sample M, added to all three reagent gases, B, was maintained constant under the assumption that the partial pressure of the sample relative to the pressure of the reagent gas remains approximately the same at constant ion source temperature for all three reagent gases.

The observed intensities of MH^+ ions are shown in Table I. The intensities of MH^+ using NH_3 were arbitrarily defined as having an intensity of 100. The intensities of MH^+ using CH_3NH_2 and $(CH_3)_2NH$ were measured relative to that of MH^+ with NH_3. It must be noted that the total ion current remained the same in the experiments with different reagent gases. It should be also noted that none of the fragmentation reactions of MH^+ were observed. The high intensity of MH^+ observed from reaction of NH_4^+ with aniline, for example, shows that proton transfer occurs from NH_4^+ to aniline. In the experiments with methylamines the intensity of MH^+ is very low. Thus one may conclude that basicity of aniline is lower than that of methylamines. The basicity order becomes NH_3 < aniline < CH_3NH_2 < $(CH_3)_2NH$. The basicities of the other compounds M relative to the basicities of ammonia and methylamines were established in the same manner as illustrated above. The order of basicities obtained is given in Table II and will be considered in the next section.

Table II. Relative Gas-Phase Basicities

Compounds more basic than dimethylamine
Quinuclidine
Decylamine
Pyridine
4-*N*,*N*-Dimethylpyridine
N,*N*-Dimethylaniline
Compounds more basic than methylamine
m-Phenylenediamine
N,*N*,*N*-Triphenylamine
Compounds more basic than ammonia
o-Phenylenediamine
p-Phenylenediamine
N,*N*-Diphenylamine
Aniline

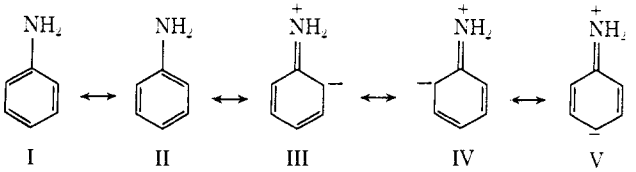
Results and Discussion

(a) Relative Basicities and Comparison of Gas-Phase and Solution Basicities. As shown in Table II the present results indicate that the basicity of quinuclidine is greater than that of dimethylamine. This results is not surprising since quinuclidine is a tertiary amine.

(9) V. L. Tal'rose, *Pure Appl. Chem.*, 5, 455 (1962).

It is also found that decylamine (see Table II) has a higher basicity than dimethylamine. Since decylamine is a primary amine this result is rather unexpected; however, Brauman and coworkers have found that the basicity of aliphatic amines increases with increasing chain length and that a large alkyl substituent can compensate for increasing degree of substitution.[1]

The results in Table II show that the basicity of aniline is higher than that of ammonia. Similarly *N*-methylaniline is more basic than methylamine, and *N*,*N*-dimethylaniline is more basic than dimethylamine. Thus the gas-phase basicities of aniline and N-substituted methylanilines are higher than that of ammonia and the corresponding methyl-substituted amines, which is opposite to solution basicities. The basicities of the anilines in aqueous solution are very much lower than those of ammonia and the methylamines ($pK_b(C_6H_5NH_2)$ = 9.42 while $pK_b(NH_3)$ = 4.77), which has been explained in terms of the resonance structures[10] I–V. It has been argued that the resonance stabiliza-



I II III IV V

tion due to structures III–V is removed when aniline is protonated, and consequently the anilinium ion has lower stability. There have been objections to this argument, since the difference between the resonance energies of benzene and aniline has been estimated on the basis of heats of combustion as being not greater than 2–4 kcal/mol.[11] Furthermore, structures III–V involve charge separation and may be expected to make only a minimal contribution. In addition to the resonance effect, the electronegativity of the phenyl group has also been invoked as responsible for reducing the basicity of aniline.[10] If the resonance and electronegativity indeed have an important influence on the basicity of the anilines, then this effect should be especially pronounced in the gas phase where one actually deals with properties of isolated molecules. As mentioned above the gas-phase results give a higher basicity to aniline than ammonia. Probably the higher basicity of aniline is influenced by the high polarizability of the phenyl group which stabilizes the positive charge of the proton. Thus one should say that the phenyl group is "electron donating" relative to hydrogen in the gas phase, while it is "electron withdrawing" relative to a comparable saturated system. The present data (Table II) give the basicity order *N*,*N*,*N*-triphenylamine > aniline, *i.e.*, an increase in basicity of aromatic amines with increasing phenyl substitution. This trend is supported also by ionization potential considerations. The ionization potential of *N*,*N*,*N*-triphenylamine is lower than that of aniline.[12] Assuming that ionization potentials involve the nonbonding electron on the nitrogen atom, one might expect that the PA's will increase as the electron becomes more easily available, *i.e.*, with de-

(10) G. W. Wheland, "Resonance in Organic Chemistry," Wiley, New York, N. Y., 1965, pp 355–357.

(11) F. Klages, *Chem. Ber.*, 82, 358 (1949).

(12) J. L. Franklin, *et al.*, "Ionization Potentials, Appearance Potentials and Heats of Formation of Gaseous Positive Ions," NSRDS-NBS26, National Bureau of Standards, Washington, D. C., 1969.

crease of the ionization potential. Thus it appears that phenyl substitution might increase the intrinsic basicity by enriching the electron density of the molecule itself instead of decreasing the basicity of nitrogen by aromatic resonance stabilization. The gas-phase basicity trend *N,N,N*-triphenylamine > aniline is consistent with the consideration taken up in the discussion of aniline (see above). The phenyl groups stabilize the positive charge by polarizability-type interactions and thus stability increases with increasing phenyl substitution.

The effect of electron delocalization on basicity among a group of isomeric aromatic amines can be illustrated by *o*-, *p*-, and *m*-phenylenediamine. The present results give the order *m*- > *o*- ≈ *p*-phenylenediamine. It appears that in the gas phase the influence of one electronegative nitrogen in reducing the basicity of the other is more significant in the ortho and para isomers than in meta isomer.

In order to test further the significance of electronic effects in relation to basicity, a group of pyridines was studied.[13] The results in Table II also show that the basicities of pyridine and 4-*N,N*-dimethylpyridine in the gas phase are higher than or comparable to that of dimethylamine. Thus the much lower basicity of pyridine with respect to ammonia and methylamines in solution is not only due to hybridization effects in the pyridine molecule as has generally been assumed but instead largely to solvation effects as in the case of anilines.

The above results can be given a simple interpretation. The observed low basicities of the aromatic amines in solution are not only due to electron delocalization on the nitrogen atom caused by phenyl substitution, as has generally been assumed, but rather the much lower basicities of aromatic amines *vs.* ammonia and aliphatic amines in solution are mainly due to solvation effects.

Solution *vs.* gas-phase basicities for a series of amines have been recently analyzed by Arnett, who proposed a simple thermodynamic cycle based on gas-phase basicities which promises to lead to a meaningful separation of solvent and intrinsic molecular effects.[14]

(b) Analytical Applications. It has been shown that the main advantage of CI compared with EI (electron ionization) is the ability of the former to enhance the production of ions in the molecular ion region, mainly MH^+ ions. Molecular ions for a number of substances are not observed with EI, and it is often difficult to determine the molecular structure of an unknown from the fragment ions produced.[15] Although the usefulness of CI mass spectrometry in structural studies has been recognized,[4,15,16] selective CI is still undeveloped. In order to consider selective protonation (*i.e.*, gas-phase acid–base reactions) as an analytical tool, one may visualize the following scheme. Consider that the gas-phase basicities of a large group of compounds and the substituent effects on the basicities are known. Furthermore, a number of convenient BH^+ acids are available. Observation of protonation or nonprotonation by BH^+ of the compounds studied could then lead to identification of the most basic group in the known or unknown molecule. Another application of the technique could be important in cases where the observation of only one peak, related to the molecular mass, is desired.[17] In such a case, a reagent B could be selected whose basicity approximates that of the compound M to be studied. Either only proton transfer occurs [PA(M) > PA(B)] or, if the proton transfer cannot occur, one may select experimental conditions such as lower ion source temperature so that only the cluster MBH^+ forms [PA(B) > PA(M)]. An example of proton transfer is illustrated by L-Pro-L-Ala which gives an intense MH^+ ion (78% of total ion current) when the reactant acid $(CH_3)_2NH_2^+$ is used. The observation of MH^+ ion thus indicates the presence of a functional group in M which is as basic or more basic than $(CH_3)_2NH$; that is, either a secondary or tertiary amino group must be present. In this case it is the presence of the secondary amino nitrogen in the proline ring of L-Pro-L-Ala. However, no information on the presence of the other additional functional groups like NH_2, $CONH_2$, COOH, etc., which are less basic than $(CH_3)_2NH$, can be obtained. If compound M contains these functional groups in the absence of the groups which are more basic than $(CH_3)_2NH$, one should then observe only the cluster formation of MBH^+ when $(CH_3)_2NH_2^+$ is treated with M. An example of this is illustrated by Phe-Phe-NH_2. When Phe-Phe-NH_2 is allowed to react with $(CH_3)_2NH_2^+$, MBH^+ (76% of total ion current) is by far the most abundant ion observed, indicating that there is no functional group in the molecule which is more basic than $(CH_3)_2NH$, and thereby able to readily accept a proton from $(CH_3)_2NH_2^+$. The examples above thus illustrate how one can detect the presence or absence of a functional group in compound M which is of similar basicity to $(CH_3)_2NH$. The promising potential of BH^+ acids in analytical studies involving complex molecules of biological origin is currently being investigated in this laboratory.

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(13) After submission of this paper, a communication appeared by M. Taagepera, W. G. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, *J. Amer. Chem. Soc.*, **94**, 1369 (1972), which described gas-phase basicities of pyridine and substituent effects.

(14) E. M. Arnett, paper presented at the Third Conference on Structure Energy Relationships, Tallahassee, Fla., Feb 17–19, 1972.

(15) D. M. Desiderio, R. Burgus, T. F. Dunn, W. Vale, R. Guillemin, and D. N. Ward, *Org. Mass Spectrom.*, **5**, 221 (1971).

(16) (a) H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Amer. Chem. Soc.*, **92**, 1590 (1970); (b) G. W. A. Milne, T. Axenrod, and H. M. Fales, *ibid.*, **92**, 5170 (1970); (c) W. R. Gray, L. H. Wojcik, and J. H. Futrell, *Biochem. Biophys. Res. Commun.*, **41**, 1111 (1970).

(17) I. Dzidic, E. C. Horning, and M. G. Horning, paper in preparation.