280. *The Basic Strength of Amines.*

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It is suggested that greater solvation of amine ions than free amines makes the amine ions appear more stable when their dissociation constants are measured in water than when measured in an inert solvent. The stabilisation is greater for the ions of secondary amines than for those of tertiary, and still greater for those of primary. The catalytic coefficients of 13 tertiary, secondary, and primary anilines for the decomposition of nitroamide in anisole are cited as evidence for this view. Its consequences are examined in the cases of the relative solvating power of solvents, the neutralisation of nitroethane by methylamines, the entropy of ionisation of methylamine ions, the substituent constants for aromatic bases, the dissociation constants of amino-acids, and the stabilities of silver amminium ions.

The attempts which have been made to explain the basic strengths of amines, as measured by their dissociation constants in water, in terms of their structures have not been nearly as successful as have similar attempts with the ions of organic acids. Different authors have favoured various explanations; thus Moore and Winmill (*J.*, 1912, 1635) suggested that the amines were hydrated, Hammett ("Physical Organic Chemistry," New York 1940, p. 225) proposed a proximity effect, Brown (*Science*, 1946, **103**, 385) a steric effect, and Palit (*J. Phys. Coll. Chem.*, 1947, **51**, 1028) a "polarstriction effect." Here the suggestion is made that much confusion has been caused by the fact that the argument has centred around the aqueous ionisation constants of the amines, and that an allowance must be made for the solvation, and consequent stabilisation, of the amine ions.

The catalytic coefficients of aniline bases for the decomposition of nitroamide in anisole were found by Bell and Trotman-Dickenson (preceding paper) not to be related to their dissociation constants by one simple Brönsted equation. However, each class of amines obeys a separate equation, as follows:

Tertiary amine .... $K_c = 3{\cdot}8 \times 10^{-5} (1/K_H)^{0{\cdot}64}$
Secondary amine .... $K_c = 1{\cdot}1 \times 10^{-5} (1/K_H)^{0{\cdot}64}$
Primary amine .... $K_c = 4{\cdot}1 \times 10^{-6} (1/K_H)^{0{\cdot}64}$

where K_c is the catalytic coefficient expressed in decadic logarithms and reciprocal minutes, and K_H is the dissociation constant of the aniline ion in water at 25°.

Since the tertiary amines are the best catalysts, it is very unlikely that steric factors are responsible for this separation, as they would be expected to act in the opposite way.

Potential-energy curves have been used (Horiuti and Polanyi, *Acta Phys. Chem. U.R.S.S.*, 1935, **2**, 505; Bell, *Proc. Roy. Soc.*, 1936, **154**, *A*, 414) to provide a physical picture of the Brönsted relation. The separation of the anilines into different classes might be ascribed to the alteration in the shapes of the potential-energy curves; but this would involve a change in the value of the Brönsted exponent, whereas within the limits of experimental error it is 0·64 in each case. The value of the other constant in each equation would probably be altered at the same time.

In Fig. 2 of Bell and Trotman-Dickenson's paper (*loc. cit.*) the logarithms of the catalytic coefficients of dimethylaniline, methylaniline, and four nuclear-substituted anilines in anisole are plotted against the logarithms of their dissociation constants in *m*-cresol. These are the only six bases for which the data are available. The dissociation constants in *m*-cresol were determined by Brönsted, Delbanco, and Tovborg-Jensen (*Z. physikal. Chem.*, 1934, **169**, 207) and are defined by the relation

$$K_m = [B][C_7H_7OH]/[BH^+][C_7H_7O^-].$$

One straight line is obtained of slope 0·64 despite the amines being drawn from each of the three classes. It may be noted that Brönsted, Nicholson, and Delbanco (*ibid.*, 1934, **169**, 379) found that the values of the catalytic coefficients of methylaniline and dimethylaniline for the decomposition of nitroamide in *m*-cresol did not obey the same relation as the primary anilines, if they used aqueous dissociation constants, but did if they used those determined in *m*-cresol. Brönsted and Pedersen (*ibid.*, 1924, **108**, 185) also found that the three tertiary and heterocyclic bases which they studied as catalysts for the decomposition of nitroamide in aqueous solution did not obey the same relation as the primary anilines, using aqueous dissociation constants; the magnitude of the separation appears to be smaller than in anisole, perhaps indicating some specific interaction of the solvent with the transition state.

These considerations indicate that the cause of the classification is to be found in the use of aqueous dissociation constants. The dissociation process of an amine ion can be represented:

$$NR_3H^+ + H_2O \rightleftharpoons H_3O^+ + NR_3$$

where R is either hydrogen or a substituent. The constant for this dissociation process will be used for the dissociation constant of the amine in this paper unless otherwise stated. It has the advantages of representing a symmetrical process and of being the usual constant determined experimentally; the basic dissociation constant being calculated by using a value for the ionic product of water.

The rate-determining step in basic catalysis by an amine may be represented as:

$$SH + NR_3 \longrightarrow S\text{–}H\text{–}NR_3$$

where SH is the substrate and $S^-H^-NR_3$ represents the transition state, for which no satisfactory conventional electronic formula can be written. The transition state subsequently yields NHR_3^+ and S which undergoes further reaction. The stability of the free amine ion is not involved, but only that of the amine. The stability of solute species can be increased by solvation, which with water and many other solvents may be regarded as taking place by a hydrogen-bonding mechanism. The water molecule and the hydroxonium ion in aqueous solution are normally regarded as the standards for dissociation-constant measurements in water, so for the purposes of this argument their relative solvation can be neglected. Both the amine and the amine ion will be solvated to some extent, but the hydrogen bonding between the amine ion and the water will probably be much stronger, as suggested by Huggins (*J. Org. Chem.*, 1936, **1**, 407) and Pauling (" Nature of the Chemical Bond," Ithaca, 1940, p. 287). The types of bonding are essentially different; the bonding between an amine and a hydroxylic solvent takes place through the hydrogen atom supplied by the solvent, as shown by the use of deuterated solvents (Gordy, *J. Chem. Physics*, 1939, **7**, 93). Indeed this is the only type possible for a tertiary amine. In the case of the ion, the hydrogen in the bond will be one of those originally on the nitrogen atom.

Now a secondary and a tertiary amine whose proton-accepting capacity in an inert solvent are the same may be considered. In water or other hydroxylic solvent the amines will be slightly stabilised owing to solvation, but the ions will be stabilised much more, thus lowering their dissociation constants. Because the ion of the secondary amine carries one more hydrogen atom than that of the tertiary amine, the ion of the secondary amine has greater capacity for forming hydrogen bonds, and consequently will be the more stabilised. For this reason, the ratio of the dissociation constants measured in hydrogen-bonding solvents will not be a suitable measure of the proton-accepting powers of the amines when considered as catalysts among different classes of amines, though it will be quite suitable when, say, only tertiary amines are studied. The catalytic powers of the amines can better be compared with the dissociation constants of their ions in solvents such as *m*-cresol where hydrogen bonding with the ion cannot take place. Dissociation constants in water will represent the secondary bases as being too strong in comparison with the tertiary amines. Similar arguments can be applied to the primary amines.

Gordy (*loc. cit.*) has found that the hydrogen-bonding power of the amines is proportional to the logarithm of their basic dissociation constants. If the bonding between water and the free amines were appreciable, this would lead to the Brönsted relations for the different classes of amine having different exponents, which within the limits of experimental error is not so.

In a hydrogen-bonding solvent the ions of primary amines will be more solvated than those of secondary amines, which in turn will be more solvated than those of tertiary amines. Those solvents which will solvate most strongly are those with oxygen atoms carrying some negative charge; on structural grounds a list of solvents in order of decreasing solvating power is : ethyl alcohol, methyl alcohol, water, *m*-cresol, and anisole. Comparison of the absolute values of dissociation constants of electrolytes in different solvents does not directly reveal their relative solvating powers, because other factors, such as dielectric constant, affect the degree of dissociation. Since the kinetic data show that amine ions are very little solvated in *m*-cresol (Brönsted, Nicholson, and Delbanco, *loc. cit.*), and we have seen that the kinetic data in anisole fit a Brönsted relation based on dissociation constants in *m*-cresol, *m*-cresol will be taken as a convenient example of an " ideal " solvent in which very little hydrogen bonding with the amine ions takes place. It is convenient also to regard tertiary amines as a norm, and to express the stabilisation of other ions in terms of them. The stabilisation can be estimated from the dissociation constants in *m*-cresol, which the kinetic data in anisole show to be applicable in anisole also. The dissociation constants for the amine ions in *m*-cresol for which direct measurements have not been made can readily be found from the kinetic data. The stabilisation is best expressed as that correction which must be applied to the negative logarithms of the aqueous dissociation constants of the secondary and primary anilinium ions in order that a plot of the negative logarithms of the constants in water and *m*-cresol will give a line of unit slope. The corrections are $-0{\cdot}83$ $\mathrm{p}K_{\mathrm{H}}$ units for secondary amines and $-1{\cdot}50$ for primary amines. From the measurements of the dissociation constants of amine ions in ethyl and methyl alcohols (Larrson, *Z. physikal. Chem.*, 1934, **169**, 207; Goldschmidt and Matthiesen, *ibid.*, 1926, **119**, 439), similar corrections for use with dissociation constants measured in these solvents can be found. They are $-1{\cdot}63$ for secondary and $-2{\cdot}29$ for primary bases in ethyl alcohol, and $-1{\cdot}48$ for secondary and $-2{\cdot}07$ for primary bases in methyl alcohol. The magnitude of these corrections is in agreement with the hydrogen-bonding capacity of the solvents predicted on structural grounds.

There is very little experimental kinetic data on amines which can be used to check these corrections, as the data for the mutarotation of glucose and decomposition of nitramide in water are not sufficiently extensive. One case is the neutralisation of nitroethane by ammonia and methylamines (Pearson, *J. Amer. Chem. Soc.*, 1948, **70**, 204) in water. The data, which are given in the following table, relate to the velocity of the reaction at 0° and 5·2°, but an extrapolation using the activation energy may be made to 25°.

Base.	log K_B.	Correction.	log K_B corr.	log k_{25} (obs.).	log k_{25} (calc.).
Trimethylamine	$\bar{5}$·80	0	$\bar{5}$·80	1·56	1·55
Dimethylamine	$\bar{4}$·78	−0·83	$\bar{5}$·95	1·64	1·65
Methylamine	$\bar{4}$·62	−1·50	$\bar{5}$·12	1·08	1·08
Ammonia	$\bar{5}$·22	—	—	$\bar{1}$·84	—

log K_B is the logarithm of the dissociation constant of the base in water at 25°, the correction is the one found above for water, log K_B corr. is the corrected value for the dissociation constant, k_{25} (obs.) is the velocity constant for the reaction :

$$CH_3{\cdot}CH_2{\cdot}NO_2 + B \longrightarrow C_2H_4NO_2^- + BH^+$$

expressed in l./mol.-minute at 25°, and log k(calc.) is the logarithm of the velocity constant calculated from the equation

$$k_{25} = 1{\cdot}93 \times 10^4 \,(K_B \text{ corr.})^{0{\cdot}67}.$$

This equation represents the best line that can be drawn through the three points obtained by plotting log k_{25} against log K_B corr. By an extrapolation the logarithm of the corrected dissociation constant of ammonia is found to be $\bar{7}$·27; this represents a correction of −1·95 units which is of the order that would be expected from an extrapolation of the corrections for the primary and seconday amines.

Since the entropy of a system may be regarded as a measure of the degree of order existing in that system, the entropy of ionisation of substances will be affected by the degree of solvation of the ions. The hydroxonium ion in water is believed to be strongly solvated, and the amine ion will undergo hydrogen bonding with water molecules though perhaps not to the same extent as the hydroxonium ion; comparatively, the difference between the solvation of the free water molecule and the amine will be small. The dissociation of the amine ion will therefore involve a negative entropy change corresponding to a transition to a state of greater order. The less the amine ion is hydrogen bonded the greater will be the negative entropy change of ionisation. As the hydrogen bonding is greater where there is the larger number of hydrogen atoms in the amine ion, the following gradation of entropy changes can be drawn up :

$$\Delta S_{NH_4^+} > \Delta S_{NMeH_3^+} > \Delta S_{NMe_2H_2^+} > \Delta S_{NMe_3H^+}$$

Everett and Wynne-Jones (*Trans. Faraday Soc.*, 1939, **35**, 1380) found

Acid.	ΔS (cals./mol./degree).
Ammonium ion	− 0·54
Methylammonium ion	− 4·7
Dimethylammonium ion	− 9·5
Trimethylammonium ion	−15·3

However, the values of ΔC_p, if interpreted in terms of hydrogen bonding, lead to results in direct contradiction to those deduced from entropy changes. Other, as yet unknown, factors must be involved.

It has been observed by Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469) that para-substitution of a methyl group in aniline to form *p*-toluidine is accompanied by an increase in basic strength in water of 0·48 pK_H unit, where pK_H is the negative logarithm of the acid dissociation constant; but *N*-substitution to give *N*-methylaniline increases the basic strength by only 0·23 pK_H unit. It is strange that substitution on the active part of the molecule should produce the smaller change. This may be due to the fact that *N*-substitution involves two conflicting effects : (*a*) an increase in basic strength due to the inductive effect of the substituent, (*b*) a decrease in basic strength due to the replacement of a hydrogen atom on the nitrogen by a non-bonding group. The magnitude of the second effect is the correction involved for a change from a primary to a secondary amine or from a secondary to tertiary, that is 0·67 or 0·83 pK_H unit respectively. These corrections when applied to the aniline methylaniline change give 0·90 pK_H unit as the substituent constant for a methyl group on the nitrogen atom. If these corrections are applied to all the available data on aromatic amines, it is found that, when the first and second substituents are the same group, the second produced a far greater change in the pK_H of the amine, the ratio being 1 : 1·8.

The difference in the solvation of amines with different numbers of hydrogen atoms on the nitrogen provides an explanation of the reversal in order of strength of amine bases, judged by their dissociation constants, which has been observed, in passing from measurements in water to measurements in ethyl alcohol. From the corrections for the comparison of secondary amines with tertiary amines in the different solvents, it can be seen that such a reversal of apparent strength will occur for any tertiary amine within $-1{\cdot}63 + 0{\cdot}83 = -0{\cdot}80$ pK_H units in water of a secondary base. Such a reversal is observed with methyl-*n*-propylaniline and ethylaniline (Hall and Sprinkle, *loc. cit.*).

Branch and Calvin (" Theory of Organic Chemistry," New York, 1941, p. 229) have pointed out that the aqueous acid dissociation constants of the *N*-substituted glycines provide evidence of the hydrogen bonding of the hydrogen atoms on the positively charged nitrogen atom with the water molecules. It would be expected that *N*-methyl substitution would increase the basic strength because of the stabilisation of the positive change, but this effect is more than counteracted by the reduction in stabilisation by hydrogen bonding. The dissociation constants are from Cohn and Edsall (" Proteins, Amino Acids, and Peptides," New York, 1943, p. 85).

Acid.	pK_a.	Acid.	pK_a.
$H_3\overset{+}{N}{\cdot}CH_2{\cdot}CO_2H$	2·34	$(CH_3)_2\overset{+}{N}H{\cdot}CH_2{\cdot}CO_2H$	1·94
$CH_3{\cdot}\overset{+}{N}H_2{\cdot}CH_2{\cdot}CO_2H$	2·23	$(CH_3)_3\overset{+}{N}{\cdot}CH_2{\cdot}CO_2H$	1·84

Several workers (Larrson, *loc. cit.*; Britton and Williams, *J.*, 1935, 796; Bruehlman and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401) have measured the dissociation constants of the ions $(AgAm)^+$ and $(AgAm_2)^+$ in water, where Am represents an amine molecule. If the logarithms of the dissociation constants of the silver amminium ions are plotted against the logarithms of the dissociation constants of the amine ions, the points for the different classes of amines lie on three separate straight lines. This would be expected, because the silver amminium ion of the tertiary amine cannot be stabilised by hydrogen bonding, as it has no hydrogen atoms attached to the nitrogen. Hence the ions formed with the tertiary amines are the least stable. The silver amminium ions of the primary amines are the most stable; those of the secondary amines are intermediate, as would be expected.

Much more work is required both on the catalytic effect of amines and upon their dissociation constants in non-bonding solvents. Results of dissociation-constant measurements on two secondary and three tertiary amines in benzene by Davis and Schuhmann (*J. Res. Nat. Bur. Stand.*, 1947, **39**, 221) show separation into types similar to that found in *m*-cresol, but the results are not sufficiently extensive to gauge the magnitude of the effect.

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