Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.60; H, 6.23.

Diisopropyl L-*Tartrate, Di-α-naphthoate.* This compound was obtained in 59% yield after five recrystallizations from ethanol, m.p. 109.0–109.5°, $[\alpha]^{25}D$ −53.1° (c 19.2, chloroform).

Anal. Calcd. for $C_{32}H_{30}O_8$: C, 70.83; H, 5.57. Found: C, 70.60, 70.82; H, 5.45, 5.61.

d,l-Isopropyl mandelate, acetate was obtained in 68% yield as a liquid, b.p. 128–129° (1 mm.), $n^{24}D$ 1.4859.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.94; H, 6.69.

d,l-Isopropyl Mandelate, Methyl Ether. A mixture of 25 g. of isopropyl mandelate and 109.5 g. of methyl iodide was cooled in an ice bath, and 89.5 g. of freshly prepared silver oxide was added portionwise with stirring. The reaction mixture was slowly warmed to room temperature and refluxed for 3 hr. After cooling, an additional 55 g. of methyl iodide and 45 g. of silver oxide were added, and the reaction mixture was refluxed for 3 hr. The inorganic residue was removed by filtration and washed with ether, and the combined filtrate and washings were dried over magnesium sulfate. After removal of the solvent, the product was obtained in 89% yield, b.p. 108° (1 mm.), $n^{24}D$ 1.4882.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.10; H, 7.76.

The Influence of Hydration on Base Strength.
I. General Theory for Amines

F. E. Condon

Contribution from the Department of Chemistry, The City College of the City University of New York, New York, New York. Received March 27, 1965

The theory that preferential hydration of ammonium ions is an important factor influencing the base strengths of amines in aqueous solution is supplemented by considerations based on the general theory of substituent effects on reaction rates and equilibria. Possible effects on the base strength resulting from hydration of the amine as well as the ammonium ion are considered, and a general equation is proposed relating hydration effects to the number and nature of the substituents attached to nitrogen in the amine. On the theory that the hydration energy of an ammonium ion is larger than that of an amine solely because of the electrostatic potential between a positive charge on nitrogen and the dipole of a water molecule, the difference for the first water molecule is estimated as 4–8 pK units for values of the "internal" dielectric constant between 2 and 1. The effect is expected to diminish with increasing number of water molecules because of charge dispersal and repulsions between the dipoles of two or more water molecules.

The past 15 years have seen a growing realization of the importance of hydration effects on the base strengths of amines in aqueous solution, as measured by pK_a, the negative logarithm of the thermodynamic equilibrium constant for the dissociation

$$R_1R_2R_3NH^+ + H_2O \rightleftharpoons R_1R_2R_3N + H_3O^+ \quad (1)$$
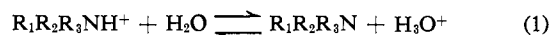
where one or more of the R_i's may be H. Trotman-Dickenson[1] expressed the ideas that hydration of the ammonium ion would be more important than that of the amine; that it would tend to stabilize the ion and thereby increase base strength; and that the amount of hydration would be directly related to the number of hydrogens attached to nitrogen in the ammonium ion. In this way he was able to account qualitatively for the well-known irregularities in the base strengths of the methylamines[2] and for a lack of correspondence between the pK_a values and catalytic constants for the decomposition of nitramide, when comparison was made between aromatic amines of different classes. Pearson came to the same conclusion from a study of amine-catalyzed ionization of nitroethane.[3]

Steric hindrance to hydration of ammonium ions has been invoked to explain the decreased base strength of certain aliphatic amines with bulky substituents[4] and of anilines with bulky *ortho* substituents.[1,5,6]

Hall[4] found that the base strengths of 77 aliphatic amines were well correlated by means of the substituent constants, σ^*, devised by Taft,[7] but that each class of amine fell on a different straight line plot of pK_a against a sum of substituent constants, one for each of the substituents attached to nitrogen. Folkers and Runquist found that a series of N-substituted anilines behaved similarly.[8] These findings were interpreted as favorable to the hydration theory and in opposition to alternative theories involving steric strain[2] or "polarstriction" effects.[9] None of these authors, however, took into consideration the statistical factor, which becomes significant (up to 0.60 pK_a unit) when one is comparing the

(1) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949).

(2) H. C. Brown, *J. Am. Chem. Soc.*, 67, 374, 378 (1945).

(3) R. G. Pearson, *ibid.*, 70, 204 (1948); R. G. Pearson and F. V. Williams, *ibid.*, 76, 258 (1954).

(4) H. K. Hall, Jr., *ibid.*, 79, 5441 (1957).

(5) P. D. Bartlett, M. Roha, and R. M. Stiles, *ibid.*, 76, 2349 (1954).

(6) (a) B. M. Wepster, *Rec. trav. chim.*, 76, 357 (1957); (b) J. Burgers, M. A. Hoefnagel, P. E. Verkade, H. Visser, and B. M. Wepster, *ibid.*, 77, 491 (1958).

(7) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 556 ff.

(8) E. Folkers and O. Runquist, *J. Org. Chem.*, 29, 830 (1964).

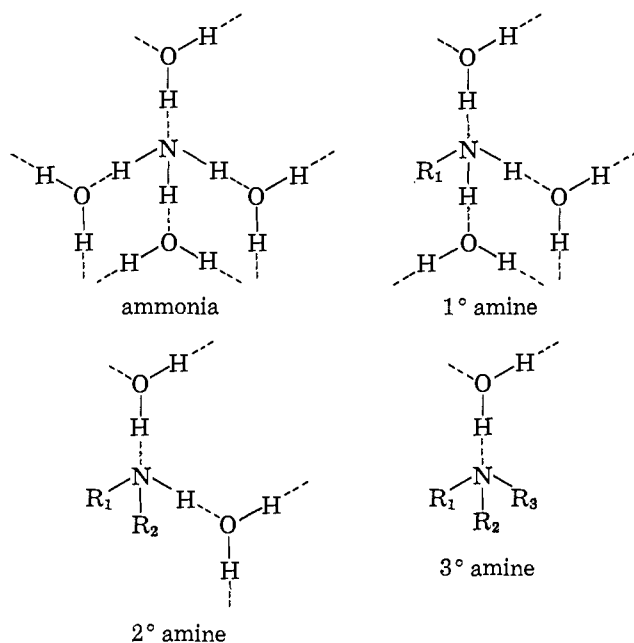(9) S. R. Palit, *J. Phys. Colloid Chem.*, 51, 1028 (1947).

Figure 1. Schematic representation of hydration of amines by hydrogen bonding.

acidities of ammonium ions having different degrees of substitution.[10]

In this paper, number one of a series, the hydration theory is supplemented by considerations based on the general theory of substituent effects on reaction rates and equilibria, developed by Hammett,[11] Taft,[7] and others.[12] Possible effects on the base strength resulting from hydration of the amine as well as the ammonium ion are considered; and a general equation is proposed relating hydration effects to the number and nature of the substituents attached to nitrogen. Subsequent papers of the series are devoted to specific applications of the theory to aliphatic amines, anilines, hydrazines, and hindered bases.

Hydration of Amines. The hydration by hydrogen bonding of ammonia and of primary, secondary, and tertiary amines is pictured in Figure 1. Let n be the number of hydrogens attached to nitrogen by primary bonds in the *ammonium ion* conjugate to the amine ($n = 4$ for ammonia and $n = 1$ for a tertiary amine, for example). Then n is also the number of water molecules hydrogen bonded to the amine; for one water molecule, the amine is hydrogen acceptor; for $n - 1$ water molecules, the amine is hydrogen donor.

The free energy of hydration by hydrogen bonding will depend on the nature of the substituents, R_i, attached to nitrogen, as well as upon their number. Inductive and field effects, resonance involving the electron pair on nitrogen, and steric factors will be involved. In addition, there may be effects due to the presence of hydrophilic groups within the substituents, as in hydrazines, hydroxylamines, and the ethanolamines, for example. The discussion that follows is limited, however, to a series of "regular" substituents

(10) S. W. Benson, *J. Am. Chem. Soc.*, **80**, 5151 (1958).
(11) (a) L. P. Hammett, *Chem. Rev.*, **17**, 125 (1935); (b) "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 184.
(12) See C. D. Ritchie and W. F. Sager, in "Progress in Physical Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1964, for a review.

for which resonance interaction with the electron pair on the nitrogen is absent (arylamines and amides, for example, are excluded), for which steric factors are absent, negligibly small, or constant in magnitude, and for which there are no hydrophilic groups within the substituents themselves. The only structural effects are those that may be described as inductive or direct field effects.

Let σ_i be a polar substituent constant for the substituent R_i, on a scale relative to *hydrated* hydrogen as zero; that is, $\sigma_{H\cdots OH_2} = 0$. Then the variation of the standard free energy of hydration, $\delta G'_h$, with the structure of the amine may be represented by eq. 2 to a first approximation (in pK units). This expression

$$\frac{\delta G'_h}{2.303RT} = pK'_h = pK'_\alpha + \rho'_\alpha \sum_{i=1}^{3} \sigma_i +$$

$$(n - 1)pK'_\beta + (n - 1)\rho'_\beta \sum_{i=1}^{3}\sigma_i \quad (2)$$

is based in the general theory of substituent effects, developed by Hammett,[11] Taft,[7] and others.[12]

In eq. 2, pK'_α is the free energy of hydration (in pK units) for the one water molecule acting as a hydrogen donor, and ρ'_α is a reaction constant relating this free energy to the structure of the amine through a sum of substituent constants, $\Sigma\sigma_i$; pK'_β is the free energy of hydration for one water molecule for which the amine acts as hydrogen donor, and ρ'_β is a reaction constant relating this free energy to the structure of the amine.

Equation 2 is based on the assumption that pK'_β is the same for each of one, two, or three water molecules for which the amine acts as hydrogen donor. This assumption may not be justified because of saturation effects and effects of interaction between the dipoles of two or more bound water molecules. These effects may be accommodated in a purely formal manner by expressing pK'_β as a power series in ($n - 1$), and we may write

$$pK'_h = pK'_\alpha + \rho'_\alpha\sum_{i=1}^{3}\sigma_i + \beta'(n - 1) +$$

$$\gamma'(n - 1)^2 + \delta'(n - 1)^3 + (n - 1)\rho'_\beta\sum_{i=1}^{3}\sigma_i \quad (3)$$

The cubic expression shown is sufficient, as it contains three constants, β', γ', and δ', and provides three independent terms, one each for ammonia and primary and secondary amines. It vanishes in the case of a tertiary amine ($n = 1$), in which the effects described would be absent. The reaction constant, ρ'_β, is assumed to be the same for all amines, as it relates to one and the same reaction (the formation of a hydrogen bond between an amine and a water molecule, with the amine acting as hydrogen donor).

The series of substituent constants, σ_i^*, developed by Taft[7] would serve for eq. 3, except that it is based on methyl as zero (that is, $\sigma^*_{Me} = 0$) and no σ^* value is given for "hydrated hydrogen." Let the latter be represented by ϵ, that is $\sigma^*_{H\cdots OH_2} = \epsilon$. Then we may write, $\sigma_i = \sigma_i^* - \epsilon$; and with this substitution, eq. 3 becomes

$$pK'_{h} = pK'_{\alpha} + \rho^{*\prime}_{\alpha}\sum_{i=1}^{3}\sigma_i^* - 3\rho^{*\prime}_{\alpha}\epsilon -$$

$$(n - 1)\rho^{*\prime}_{\alpha}(0.49 - \epsilon) + \beta'(n - 1) +$$

$$\gamma'(n - 1)^2 + \delta'(n - 1)^3 + (n - 1)\rho^{*\prime}_{\beta}\sum_{i=1}^{3}\sigma_i^* -$$

$$3(n - 1)\rho^{*\prime}_{\beta}\epsilon - (n - 1)^2\rho^{*\prime}_{\beta}(0.49 - \epsilon) \quad (4)$$

Each reaction constant has been changed to a ρ^* to point up its relationship to σ^*; terms in $(0.49 - \epsilon)$ have been added so that the value $\sigma^*_H = 0.49$ may be used when appropriate. These terms replace σ_H^* by $\sigma^*_{H\cdots OH_2}$ (ϵ) wherever it appears. Primed constants are retained for use with amines, double primes will be used with ammonium ions, and unprimed constants will be used in an expression for the difference, which will be designated as the "net hydration energy."

Upon expanding terms in eq. 4 and collecting like terms together, we may write eq. 5

$$pK'_{h} = a' + b'\sum_{i=1}^{3}\sigma_i^* + c'n + d'n^2 +$$

$$e'n^3 + f'n\sum_{i=1}^{3}\sigma_i^* \quad (5)$$

where

$$a' = pK'_{\alpha} - 4\rho^{*\prime}_{\alpha}\epsilon + 0.49\rho^{*\prime}_{\alpha} - \beta' + \gamma' - \\ \delta' + 4\rho^{*\prime}_{\beta}\epsilon - 0.49\rho^{*\prime}_{\beta}$$

$$b' = \rho^{*\prime}_{\alpha} - \rho^{*\prime}_{\beta}$$

$$c' = -0.49\rho^{*\prime}_{\alpha} + \rho^{*\prime}_{\alpha}\epsilon + \beta' - 2\gamma' + 3\delta' - \\ 5\rho^{*\prime}_{\beta}\epsilon - 0.98\rho^{*\prime}_{\beta}$$

$$d' = \gamma' - 3\delta' - 0.49\rho^{*\prime}_{\beta} + \rho^{*\prime}_{\beta}\epsilon$$

$$e' = \delta'$$

$$f' = \rho^{*\prime}_{\beta}$$

Further simplification is possible. When $n = 0$, hydration by hydrogen bonding is absent[13] ($pK'_{h} = 0$), and we may write therefore, eq. 6 and eq. 7.

$$0 = a' + b'\sum_{i=1}^{3}\sigma_i^* \quad (6)$$

$$pK'_{h} = c'n + d'n^2 + e'n^3 + f'n\sum_{i=1}^{3}\sigma_i^* \quad (7)$$

The result expressed in eq. 6 means also that $a' = b' = 0$ since $\Sigma\sigma^*$ is not a constant. Hence, from eq. 5 and the definition of b'

$$\rho^{*\prime}_{\alpha} = \rho^{*\prime}_{\beta} \quad (8)$$

This result (eq. 8) may appear surprising, since $\rho^{*\prime}_{\alpha}$ is a reaction constant for the nitrogen of ammonia acting as an electron donor, while $\rho^{*\prime}_{\beta}$ is a reaction constant for the nitrogen acting as an electron acceptor (through hydrogen); and so they might be expected to have opposite signs. The result may be accepted as correct, however, and a necessary consequence of the dynamic nature of the hydrogen bond and the resulting rapid exchange of hydrogen between an amine and water.[14] Because of this, the two types of hydrogen

(13) This is a hypothetical case, but the equation must provide for it.
(14) (a) J. S. Anderson, R. H. Purcell, T. G. Pearson, A. King, F. W. James, H. J. Eméleus, and H. V. A. Briscoe, *J. Chem. Soc.*, 1492 (1937); (b) Ya. K. Syrkin, *Dokl. Akad. Nauk SSSR*, **105**, 1018 (1955); *Chem. Abstr.*, **50**, 12594 (1956).

bond are indistinguishable and the reaction constants must be identical.

Hydration of Ammonium Ions. In the case of an ammonium ion, $R_1R_2R_3NH^+$, where one or more of the R_i's may be hydrogen, hydrated by hydrogen bonding to water, the nitrogen acts as hydrogen donor for each bound water molecule; and we write, in analogy to eq. 2 and 3

$$pK''_{h} = npK''_{\beta} + n\rho''_{\beta}\sum_{i=1}^{3}\sigma_i + \beta''(n - 1) + \\ \gamma''(n - 1)^2 + \delta''(n - 1)^3 \quad (9)$$

In eq. 9, pK''_{β} is the free energy of hydration for one water molecule, ρ''_{β} is a reaction constant relating this free energy to the structure of the amine, and the remaining terms of a power series in $(n - 1)$ are to accommodate (in this case) effects of charge dispersal and repulsive interactions between the dipoles of two or more bound water molecules. The power series vanishes, as it should, when $n = 1$, and provides three independent constant terms, one each for ammonia, primary amines, and secondary amines.

By replacement of σ_i by $(\sigma_i^* - \epsilon)$, as before, and by addition of a term in $(0.49 - \epsilon)$ to ensure replacement of σ^*_H by $\sigma^*_{H\cdots OH_2}$ (ϵ) wherever it appears, eq. 9 becomes eq. 10. Upon expansion of terms and collec-

$$pK''_{h} = npK''_{\beta} + n\rho^{*\prime\prime}_{\beta}\sum_{i=1}^{3}\sigma_i^* - 3n\rho^{*\prime\prime}_{\beta}\epsilon -$$

$$(n - 1)n\rho^{*\prime\prime}_{\beta}(0.49 - \epsilon) + \beta''(n - 1) +$$

$$\gamma''(n - 1)^2 + \delta''(n - 1)^3 \quad (10)$$

tion of like terms together, there is obtained eq. 11

$$pK''_{h} = a'' + c''n + d''n^2 +$$

$$e''n^3 + f''n\sum_{i=1}^{3}\sigma_i^* \quad (11)$$

where

$$a'' = -\beta'' + \gamma'' - \delta''$$

$$c'' = pK''_{\beta} - 4\rho^{*\prime\prime}_{\beta}\epsilon + 0.49\rho^{*\prime\prime}_{\beta} + \beta'' - \\ 2\gamma'' + 3\delta''$$

$$d'' = -0.49\rho^{*\prime\prime}_{\beta} + \rho^{*\prime\prime}_{\beta}\epsilon + \gamma'' - 3\delta''$$

$$e'' = \delta''$$

$$f'' = \rho^{*\prime\prime}_{\beta}$$

Finally, inasmuch as $pK''_{h} = 0$ when $n = 0$, we may write $a'' = 0$ and

$$pK''_{h} = c''n + d''n^2 + e''n^3 + f''n\sum_{i=1}^{3}\sigma_i^* \quad (12)$$

The Net Hydration Energy. The net effect of hydration on the dissociation equilibrium (eq. 1) will be the difference between the effects of hydration of the amine and of the ammonium ion. The "net hydration energy," δpK_h, may be defined as the difference between eq. 12 and 7, which may be written

$$\delta pK_h = cn + dn^2 + en^3 + fn\sum_{i=1}^{3}\sigma_i^* \quad (13)$$

where $c = c'' - c'$, $d = d'' - d'$, $e = e'' - e'$, and $f = f'' - f'$. The constants in eq. 13 remain to be evaluated; and this is done empirically in paper II
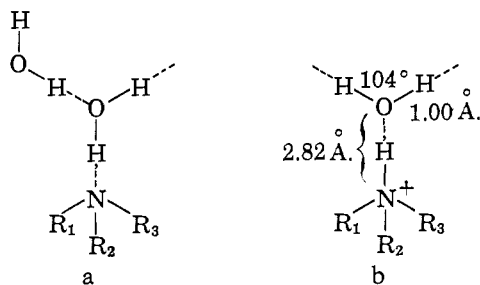
Figure 2. Models of hydrated tertiary amine (a) and ammonium ion (b).

of this series, by use of the pK_a data on 77 aliphatic amines, which were correlated by Hall.[4]

A theoretical estimate is made here, however, of the net hydration energy of a tertiary ammonium ion, for comparison with the empirical value obtained in paper II. This estimate is based on electrostatic considerations. For this purpose, the models of hydrated tertiary amine and ammonium ion shown in Figure 2 were assumed. Additional hydrogen bonds extending into the solvent water are indicated by dotted lines, as in Figure 1, but are not shown in their entirety. It was assumed that the difference in the free energies of hydrated amine and ammonium ion is wholly electrostatic potential energy arising out of interaction of the positive charge with the dipole of the water molecule as shown in Figure 2b; and δpK_h was calculated by means of the equation[15]

$$\delta pK_h = \frac{\mu e}{2.303 kTDr^2} \qquad (14)$$

where $\mu = 1.87 \times 10^{-18}$ e.s.u. cm., the dipole moment of water[16]; e is the electronic charge, 4.80×10^{-10}

(15) Cf. (a) J. G. Kirkwood and F. H. Westheimer, J. Chem. Phys., 6, 506 (1938); (b) F. H. Westheimer and J. G. Kirkwood, ibid., 6, 512 (1938); (c) F. H. Westheimer, J. Am. Chem. Soc., 61, 1977 (1939).

(16) "Handbook of Chemistry and Physics," 45th Ed., The Chemical Rubber Publishing Co., Cleveland, Ohio, 1964, p. E-40.

e.s.u.; k is the Boltzmann constant, 1.39×10^{-16} erg deg.$^{-1}$; $T = 298°K.$; D is an "internal" dielectric constant; and r is the distance from the charge to the center of the dipole.

It was assumed that the charge is centered on the nitrogen atom and that the center of the dipole is at the midpoint of the line joining the hydrogens of the water molecule. The NH$\cdots$O distance in Figure 2b is an average of the NH$\cdots$N distance in ammonium azide (2.98 Å.) and the NH$\cdots$F distance in ammonium fluoride (2.66 Å.).[17] From the geometry of the figure, $r = 3.44$ Å., and hence, $\delta pK_h = 8.04$ for $D = 1$ and 4.02 for $D = 2$, the value for hydrocarbons, adopted by Kirkwood and Westheimer[15]; that is

$$\delta pK_h = 6.03 \pm 2.01 \qquad (15)$$

for values of the "internal" dielectric constants between 1 and 2.

Because of the assumption that the charge is centered on nitrogen, this result (eq. 15) should be regarded as the δpK_h for the first water molecule on the symmetrical ion NH_4^+. Calculations of δpK_h for hydration by two, three, and four water molecules (involving repulsions between the dipoles of two or more water molecules) were made also. The results are not presented, however, because they are quite dependent on the interatomic distances and on the "internal" dielectric constant, $D;$ and evaluation of these requires a lot of guesswork. The effect per water molecule is expected to decrease with increasing number of water molecules, however, because of charge dispersal and repulsive interactions.

(17) L. Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell University Press, Ithaca, N. Y., 1960, pp. 463–464.