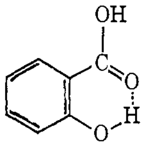
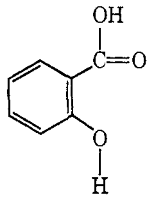

I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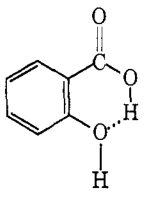
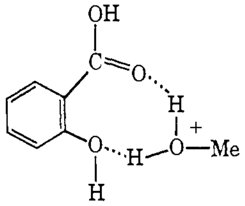

III


IV

Calculation of rates from nmr line widths followed established procedures.[7,14,15] The following chemical shifts (in parts per million) were used in the rate calculations: methanol OH, 0.00 (internal standard); salicyl OH, −5.62 (−103°), −5.66 (−80°); salicyl CO_2H, −7.91 (−103), −7.89 (−80°, assumed). At −103°, the areas under the salicyl OH and CO_2H resonances were equal, within the experimental error.

Kinetics of Proton Exchange When Reaction 1 Is Dominant. We shall assume that the rates of interconversion of I $\rightleftarrows$ II $\rightleftarrows$ III (see above) are fast relative to the rate of reaction 1. This is a reasonable assumption because the relaxation time for proton exchange was found to be greater than 5×10^{-4} sec in all experiments. This is considerably longer than known relaxation times for breaking hydrogen bonds in liquid solution[16] and also longer than relaxation times for the rotation of the OH group in most *ortho* hydrogen-bonded phenolic *solids*.[17] Furthermore, the salicyl OH proton resonance in the absence of exchange is a single, sharp line whose width is only slightly greater than that of the hydroxyl resonance of *p*-bromophenol ($1/T_2$ = 10 and 7 $\sec^{-1}$, respectively.)

If the equilibrium I $\rightleftarrows$ II $\rightleftarrows$ III is established rapidly relative to the rate of reaction 1, then we predict that, when reaction 1 is dominant, $R_{CO_2H} = R_{o\text{-}OH} = R_{MeOH} = k_+[III] + k_-[I] = 2k_+[III] = 2k_-[I]$. These equalities are derivable from simple stoichiometric considerations and microscopic reversibility in a system at equilibrium. Since, in fact, $R_{o\text{-}OH} << R_{CO_2H} \approx R_{MeOH}$, reaction 1 cannot be very important.

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[14] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 10.

[15] For theory of exchange broadening of the dominant line in a proton system consisting of several lines, see S. Meiboom *J, Chem. Phys.*, **34**, 375 (1961).

[16] See, for example, M. Eigen, *Chem. Eng. News.*, **41**, 38 (Dec 2, 1963).

[17] R. J. Meakings, *Trans. Faraday Soc.*, **51**, 371 (1966).

Rate Constants for the Dissociation of Amine–Water Hydrogen Bonds and the Effect of Nonpolar Groups in Aqueous Solution[1]

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Abstract: It is shown that the rate constant, k_H, for breaking the $R_3N\cdot HOH$ hydrogen bond measures the rate of diffusion of the water molecule into bulk solvent. In sulfuric acid–water mixtures, over a fivefold range of bulk viscosity η, k_H remains proportional to η^{-1}. Substituent effects of nonpolar R groups are large; k_H ranges from 2.2×10^{11} $\sec^{-1}$ for H_3N to 2.7×10^9 $\sec^{-1}$ for $(PhCH_2)_2NCH_3$. k_H is a monotonic function of the partial molar volume of the amine, but not of its basicity. A simple calculation shows that the substituent effect on k_H is of the same magnitude as the London dispersion interaction between the water molecule and the nonpolar groups. The results are thought to provide a sensitive test as to whether special water structure is induced by the nonpolar groups. No evidence for special ice-like water structure is found.

In experimental studies of solvation one would like to measure the properties of specific solvent molecules at specific sites near the solute molecule, but with few exceptions one is able to measure only those properties that reflect the total solvent–solute interaction. For amines in aqueous solution, one property that might illuminate the solvation mechanism for a specific water molecule at a specific site is the rate constant, k_H, for breaking the hydrogen bond that exists between the amino nitrogen and a water molecule. We shall tentatively formulate this process as in eq 1.

$$R_3N{\cdot}\mathit{HOH} + HOH(aq) \longrightarrow R_3N{\cdot}HOH + \mathit{HOH}(aq) \qquad (1)$$

Evidence has accumulated in the recent past[2–7] that k_H can be derived with fair accuracy from a kinetic analysis of proton exchange between the ammonium ion, R_3NH^+, and water in aqueous acid.

In this paper we wish to examine the process whose rate constant is k_H. We shall report new k_H values for amines of selected structure and recalculate certain older data for proton exchange in strong acid[3] with the

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[1] This work was supported by the National Science Foundation under Grant GP 3921, and by the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is made to the donors of that fund.

[2] C. G. Swain, J. T. McKnight, and V. P. Kreiter, *J. Am. Chem. Soc.*, **79**, 1088 (1957).

[3] M. T. Emerson, E. Grunwald, M. L. Kaplan, and R. A. Kromhout, *ibid.*, **82**, 6307 (1960).

[4] M. Sheinblatt, *J. Chem. Phys.*, **36**, 3103 (1962); **39**, 2005 (1963).

[5] E. Grunwald, *J. Phys. Chem.*, **67**, 2211 (1963).

[6] M. Sheinblatt and H. S. Gutowsky, *J. Am. Chem. Soc.*, **86**, 4814 (1964).

[7] E. K. Ralph and E. Grunwald, *ibid.*, **89**, 2963 (1967).

aid of improved acidity functions.[8,9] We shall then consider various processes that could lead to the rupture of the $R_3N \cdot HOH$ hydrogen bond and show that eq 1 represents the process that is actually measured. If this be granted, then k_H is the pseudo-first-order rate constant for the exchange of a water molecule between the site in the solvation shell adjacent to the amino nitrogen, from which a good hydrogen bond can be formed, and bulk solvent.

Having made this identification, we shall examine some medium and substituent effects on k_H. We shall find that k_H is remarkably sensitive to the nature of nonpolar substituents, ranging from 2.2×10^{11} sec^{-1} for NH_3 to 2.7×10^9 sec^{-1} for $(PhCH_2)_2NCH_3$. k_H cannot be correlated with basicity but decreases systematically with number and size of the nonpolar substituents. A simple calculation shows that the interaction between the water molecule and the nonpolar substituents could be primarily a London dispersion interaction.[10]

For methylamine and trimethylamine the available data cover a wide range in the bulk viscosity, η, of the aqueous acid solvent. We find that k_H varies precisely as $1/\eta$.

Finally, we shall consider the implications of these results concerning the structure of the hydration shells around nonpolar organic groups in aqueous solution. Our data can be accommodated nicely on the following basis. Water molecules adjacent to amino nitrogen and near nonpolar organic groups form a subspecies with a lower free energy than that of water molecules in the bulk solvent. The free energy is lower largely because the water molecules in the subspecies can interact more favorably, by London dispersion interaction, with the nearby nonpolar groups than they could if the space occupied by the nonpolar groups were filled with water molecules. The water molecules in the subspecies interact also with other water molecules. However, this interaction is not sufficiently different from that among water molecules in the bulk solvent to have a dominant effect on the free energy of the subspecies, nor is it sufficient to cause the effective viscosity for diffusion out of the solvation shell to deviate from that of the bulk solvent.

A popular theory concerning solvation phenomena in aqueous solution postulates that special ice-like water structures are built up near nonpolar organic groups.[11] The theory has been elaborated in varying detail, and the indirect evidence cited is often impressive.[12a,b] The key assumption of this theory is that, in the vicinity of hydrophobic alkyl groups, the interaction *among the water molecules* is strengthened, by special structure formation, relative to that in the bulk solvent.

We believe that our results provide a test of this theory. In the case of triethylamine and dibenzylmethylamine, at least one of the alkyl groups, for steric reasons, must be immediately adjacent to the water molecule that is hydrogen bonded to nitrogen.[7] For this reason, k_H should reflect the solvation of these nonpolar groups. As a matter of fact, there is no discontinuity in the relationship between k_H and alkyl size at triethylamine. While our results do not preclude *some* modification of the water–water interaction by the nonpolar groups, they do seem to rule out the kind of interaction suggested by the term "iceberg" in which water molecules cooperate to form ordered clusters that are several layers thick. If structure formation occurs at all, it appears to be limited to a single layer immediately adjacent to the nonpolar group.[12c]

Characterization of k_H

In this section we wish to summarize the evidence that leads to the evaluation of k_H and justify the identification of the process as reaction 1.

The rate, R, of NH–OH hydrogen exchange between ammonium salts and water or methanol in acid has been shown repeatedly to follow eq 2.[2-7]

$$R = k[R_3NH^+]/(1 + Q[H^+]) \qquad (2)$$

k and Q are parameters in the kinetic analysis; quantities in brackets denote molar concentrations.

To accommodate this rate law, the following reaction mechanism was proposed.[3]

$$R_3N\mathit{H}^+ \cdot OH_2 + H_2O \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} R_3N \cdot \mathit{H}OH + H_3O^+ \qquad (3)$$

$$R_3N \cdot \mathit{H}OH + H_2O(aq) \xrightarrow{k_H} R_3N \cdot HOH + \mathit{H}OH(aq) \qquad (4a)$$

$$R_3N \cdot HOH + H_3O^+ \xrightarrow{k_{-a}} R_3NH^+ \cdot OH_2 + H_2O \qquad (4b)$$

In this mechanism, acid dissociation leads reversibly to an amine hydrate, as shown in eq 3. Hydrogen exchange can occur only if the $R_3N \cdot \mathit{H}OH$ hydrogen bond breaks, in a process such as (4a), before the amine hydrate reacts with hydrogen ion. The rate of exchange becomes slow in strong acid because the reaction of $R_3N \cdot \mathit{H}OH$ with hydrogen ion becomes fast compared to the rate of breaking of the hydrogen bond.

According to this mechanism, the kinetic parameters k and Q in (2) are identified as follows: $k = k_a$ and $Q = k_{-a}/k_H$. Furthermore, because exchange is measured at dynamic equilibrium, the ratio k_a/k_{-a} is equal to K_A, the acid dissociation constant, which can be measured separately. Hence all three of the quantities k_a, k_{-a}, and k_H can be evaluated.

Kinetic data, interpreted on this basis, are summarized in Table I. The interpretation is confirmed by the fact that k_{-a} is consistently of the same magnitude as results obtained by various relaxation methods[13] and is consistently of the correct magnitude for a diffusion-controlled reaction.[13-15]

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(8) H. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).

(9) E. M. Arnett and G. W. Mach, *ibid.*, **86**, 2671 (1964).

(10) F. London, *J. Phys. Chem.*, **46**, 305 (1942).

(11) H. S. Frank, *J. Chem. Phys.*, **13**, 493 (1945); H. S. Frank and M. W. Evans, *ibid.*, 13, 507 (1945); H. S. Frank and W.-Y. Wen, *Discussions Faraday Soc.*, **24**, 133 (1957).

(12) (a) See, for example, B. E. Conway, *Ann. Rev. Phys. Chem.*, **17**, 482 (1966). (b) G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3401 (1962). (c) Professor H. A. Scheraga has pointed out to us that this conclusion is precisely consistent with the Némethy–Scheraga model, as shown particularly in Figure 2 of ref 12b. It should be noted, however, that the Némethy–Scheraga model includes certain details that are not tested by the present observations. In particular it visualizes that water molecules in the first layer around the solute are stablized only if they are four hydrogen bonded. We thank Professor Scheraga for his instructive comments.

(13) M. Eigen, W. Kruse, G. Maas, and L. DeMaeyer, *Progr. Reaction Kinetics*, 2, 285 (1964).

(14) M. Eigen, *Z. Physik. Chem.* (Frankfurt), **1**, 176 (1954).

(15) M. T. Emerson, E. Grunwald, and R. A. Kromhout, *J. Chem. Phys.*, **33**, 547 (1960).

Table I. Effect of Nonpolar Substituents on Proton Exchange in the System R_3NH^+–Aqueous Acid

Amine	Temp, °C	k_a, sec^{-1}	$10^{-10}k_{-a}$, $M^{-1}\,sec^{-1}$	$10^{-10}k_H$, sec^{-1}
NH_3	25	25	4.3	22
CH_3NH_2	25	...	...	6.2
$(CH_3)_3N$	25	4.7	3.0	1.0
$(C_2H_5)_3N$[a]	25	0.4	2.7	0.38
$(PhCH_2)_2NCH_3$	30	240 ± 30	1.3 ± 0.2	0.27
Im[b]	25	5200 ± 400	5.0	8.6
	−0.4	1040 ± 80	...	...

[a] Reference 7. [b] Im = imidazole, $C_3H_4N_2$.

We now wish to consider alternatives to the process shown in (4a). One alternative would be simply the rotation of the water molecule adjacent to the nitrogen atom, as in (5). A mechanism for hydrogen exchange

$$\mathrm{R_3N}\cdot \mathit{H}\mathrm{OH} \longrightarrow \mathrm{R_3N}\cdot\mathrm{HO}\mathit{H} \qquad (5)$$

consisting of reversible acid dissociation to an amine hydrate (eq 3) and rotation of the water molecule in the amine hydrate (eq 5) can accommodate rate law 2. However, the kinetic parameter k must now be identified with $^1/_2k_a$ rather than with k_a. This is because the species that reacts with hydrogen ion is either $\mathrm{R_3N}\cdot\mathrm{HO}\mathit{H}$ or $\mathrm{R_3N}\cdot\mathit{H}\mathrm{OH}$, and at sufficiently low concentrations of hydrogen ion the two reactions become equally probable. Fortunately, the question whether k is equal to k_a or $^1/_2k_a$ can be settled experimentally. At this time, data are available only for imidazolium ion, where k_a for acid dissociation has been measured directly by temperature jump.[16] The result, at 13° and 0.1 M ionic strength (mostly KNO_3), is $k_a = (1.5 \pm 0.5) \times 10^3$ sec^{-1}.[16] We have measured k for proton exchange in aqueous acid at −0.4° and at 25° and at *ca.* 0.05 M ionic strength (mostly imidazolium chloride). Interpolation to 13° gives the result, $k = (2.4 \pm 0.4) \times 10^3$ sec^{-1}. It appears that k is *not* equal to $^1/_2k_a$, but k could be equal to k_a.

There is also less direct evidence that $k = k_a$. For example, if k were equal to $^1/_2k_a$, then k_{-a} for the reaction of ammonia with hydrogen ion would have the implausibly high value of 9×10^{10} sec^{-1} M^{-1} at 25° (see Table I), which would require a "reaction diameter" (that is, center-to-center distance between NH_3 and H_3O^+ in a reactive encounter)[15] of nearly 10 A.

Another mechanism for breaking the $\mathrm{R_3N}\cdot\mathit{H}\mathrm{OH}$ hydrogen bond involves Walden inversion about nitrogen rather than removal of the water molecule by diffusion (eq 6). In this mechanism, $k = k_a$ and $k_H =$

$$\mathrm{HOH} + {\geqslant}\mathrm{N}\cdot\mathit{H}\mathrm{OH} \xrightarrow{k_{\mathrm{inversion}}} \mathrm{HOH}\cdot\mathrm{N}{\leqslant} + \mathit{H}\mathrm{OH} \qquad (6)$$

$k_{\mathrm{inversion}}$. The mechanism is acceptable because $k = k_a$, but can be ruled out because k_H is far greater than $k_{\mathrm{inversion}}$, at least in the case of dibenzylmethylamine, where the rate of Walden inversion has been measured independently.[17] While $k_{\mathrm{inversion}}$ in this case was found to be $(2 \pm 1) \times 10^5$ sec^{-1} at 25°, we find that k_H is 2.7×10^9 sec^{-1} at 30°, or about ten thousand times greater. It should be noted that the Walden inversion of dibenzylmethylamine is not exceptionally slow. Reported values of $k_{\mathrm{inversion}}$ for benzylmethylmethoxyamine[18] and for the 1-methylaziridines[19] are considerably smaller.

In the case of imidazole, a mechanism for breaking the $\mathrm{N}\cdot\mathit{H}\mathrm{OH}$ hydrogen bond by Walden inversion about nitrogen is prohibited by the planar structure of the five-membered ring. Preliminary results (Table I) show that k_H for imidazole is of the same order of magnitude as k_H for amines, for which Walden inversion is possible.

Another possibility is that k_H measures the rate of diffusion of the $\mathrm{R_3N}\cdot\mathrm{HOH}$ water molecule to another site in the solvation shell rather than into bulk solvent. This theory is ruled out by the simple dependence of k_H on the bulk viscosity of the solvent, which we shall consider next.

Effect of Viscosity

In this section we wish to interpret some previously measured[3] rate constants for isotopic exchange between R_3ND^+ and H_2SO_4–H_2O mixtures. We shall accept the mechanism shown in eq 3 and 4.

In strong acid, $k_{-a}[H^+]$ becomes large compared to k_H, so that reaction 3 is essentially a prior equilibrium step. Thus the rate of exchange follows eq 7, where $[\mathrm{R_3N}\cdot\mathrm{DOH}]$ is the conjugate base that exists in steady-state equilibrium with $\mathrm{R_3ND^+}\cdot\mathrm{OH_2}$. The symbol

$$R = k_H'[\mathrm{R_3N}\cdot\mathrm{DOH}] \qquad (7)$$

k_H' is used rather than k_H to denote that the departing molecule is DOH.

We believe that we can evaluate $[\mathrm{R_3N}\cdot\mathrm{DOH}]$ with fair accuracy, using appropriate acidity functions, and thus study k_H' as a function of solvent composition. We obtain the remarkable result that $k_H'\eta/\eta_0$ is nearly constant, even though η/η_0 varies widely. The result will be impressive even to those of our readers who are not quite prepared to grant the validity of acidity functions. At the very least, it will be clear that $k_H'\eta/\eta_0$ is a smooth function of solvent composition. We can guarantee that there are no critical solvent compositions at which the function undergoes sudden, stepwise, changes.

In the following, we shall relate the "equilibrium constant" K_A' for reaction 8 to K_A (eq 9) and then calculate k_H'. We shall suppose initially that R_3N is a tertiary amine. Subtracting (8) from (9) we obtain

$$\mathrm{R_3ND^+}\cdot\mathrm{OH_2} + \mathrm{H_2O} \overset{K_A'}{\rightleftharpoons} \mathrm{R_3N}\cdot\mathrm{DOH} + \mathrm{H_3O^+} \qquad (8)$$

$$\mathrm{R_3NH^+}\cdot\mathrm{OH_2} + \mathrm{H_2O} \overset{K_A}{\rightleftharpoons} \mathrm{R_3N}\cdot\mathrm{HOH} + \mathrm{H_3O^+} \qquad (9)$$

(10), for which the equilibrium constant is K_A/K_A'.

$$\mathrm{R_3NH^+}\cdot\mathrm{OH_2} + \mathrm{R_3N}\cdot\mathrm{DOH} \overset{K_A/K_A'}{\rightleftharpoons} \mathrm{R_3N}\cdot\mathrm{HOH} + \mathrm{R_3ND^+}\cdot\mathrm{OH_2} \qquad (10)$$

Note that eq 10 represents the distribution of deuterium atoms between NH and OH bonds, and denote the relevant fractionation factor by φ_1. It then follows that $\varphi_1 = K_A/K_A'$.

In the correlation of deuterium isotope effects on K_A it is sufficient (within 1% accuracy) to assume that fractionation factors are independent of the macroscopic

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[16] M. Eigen, G. G. Hammes, and K. Kustin, *J. Am. Ch.m. Soc.*, **82**, 3482 (1960).

[17] M. Saunders and F. Yamada, *ibid.*, **85**, 1882 (1963).

[18] D. L. Griffith and J. D. Roberts, *ibid.*, **87**, 4089 (1965).

[19] A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960).

solvent[20] and therefore, by implication, of the microscopic environment. If we omit neighboring molecules, eq 10 simplifies to (11).

$$R_3NH^+ + DOH \overset{\varphi_1}{\rightleftharpoons} R_3ND^+ + HOH \qquad (11)$$

For ammonium ion, φ_1 (per OH and NH bond) has been evaluated as 1.083 at 25°.[20] We shall adopt this value also for $CH_3NH_3^+$ and $(CH_3)_3NH^+$.

If there are g equivalent NH bonds in the alkylammonium ion, the preceding result needs to be modified. The rate constant for isotopic exchange, k_e, is defined per NH bond;[21] so is φ_1. To obtain K_A' in consistent units, we must write the equilibrium constant for (9) as K_A/g, where K_A is the conventional molar acid dissociation constant. Thus our final result for K_A' is (12), with $\varphi_1 = 1.083$.[20]

$$K_A' = K_A/g\varphi_1 \qquad (12)$$

To obtain an expression for k_H' in terms of k_e, we use eq 7, 8, 12, and a previously derived relationship[21] between k_e and R. Furthermore, for exchange in strong acid we introduce an appropriate acidity function,[22] H_0, and an auxiliary function, h_0 = antilog $(-H_0)$, such that $[R_3N \cdot DOH]/[R_3ND^+ \cdot OH_2] = K_A'/h_0$. The result is (13).

$$k_H' = k_e h_0 g \varphi_1 / K_a \qquad (13)$$

Table II summarizes the calculation of k_H' by this method for methylamine, trimethylamine, and ammonia. For methylamine, the most nearly appropriate acidity function is H_0', constructed from data for ring-substituted primary anilines.[8] For trimethylamine it is H_0''', constructed from data for tertiary (mostly N,N-dimethyl) anilines.[9] For ammonia (which, as an amine, is less-than-primary) an appropriate acidity function has not yet been constructed. We shall consider this matter later.

Table II. Kinetic Analysis of Isotopic Exchange between R_3ND^- and H_2SO_4–H_2O Mixtures, 25°[a]

Wt % H_2SO_4	Acidity h_0, M[b]	k_e, sec^{-1}	$k_H' \times 10^{-10}$, sec^{-1}	η/η_0	$(k_H'\eta/\eta_0) \times 10^{-10}$, sec^{-1}
1. $(CH_3)_3ND^+$, $K_A^0/\varphi_1 g = 1.45 \times 10^{-10}$					
0.00[c]	. . .	. . .	1.09	1.00	1.09
24.86	89[d]	8.7×10^{-3}	0.53	1.76	0.94
27.52	159	5.0×10^{-3}	0.55	1.89	1.04
31.43	377	1.74×10^{-3}	0.45	2.10	0.95
36.15	1,150	5.4×10^{-4}	0.43	2.40	1.03
54.27	102,000	2.7×10^{-6}	0.19	4.61	0.87
					Av 0.99 ± 0.07
2. $CH_3NH_2D^+$, $K_A^0/\varphi_1 g = 0.73 \times 10^{-11}$					
34.23	100[e]	1.86×10^{-3}	2.55	2.28	5.8
49.10	1910	6.9×10^{-5}	1.08	3.70	6.6
54.27	6,500	1.58×10^{-5}	1.41	4.61	6.5
58.86	20,900	3.8×10^{-6}	1.09	5.6	6.1
					Av 6.3 ± 0.3
3. H_3ND^+, $K_A^0/\varphi_1 g = 1.31 \times 10^{-10}$					
0.00 (extrapolated)				1.00	(22)
49.14	1,150[f]	6.6×10^{-3}	5.8	3.71	21.5
58.37	10,100	5.7×10^{-4}	4.4	5.4	23.5
69.38	231,000	1.28×10^{-5}	2.26	9.6	21.5

[a] Based on data in ref 3. [b] h_0 = antilog $(-H_0)$, where H_0 is the appropriate acidity function. [c] This is k_H for $(CH_3)_3N \cdot HOH$, measured directly in dilute aqueous HCl. See ref 5. [d] The appropriate acidity function was taken to be H_0''', as constructed from data for N-dimethylanilines. See ref 9. [e] The appropriate acidity function was taken to be H_0', as constructed from data for anilines. See ref 8. [f] Equation 14, $x = 0.191$.

It is clear from Table II that k_H' varies considerably and that $k_H'\eta/\eta_0$ is constant within the experimental error, which is about 10%. Furthermore, in the case of trimethylamine, $k_H'\eta/\eta_0$ differs at most by a few per cent from k_H as measured directly in dilute aqueous HCl.[23] The good agreement in this case rules out the possibility that the constancy of $k_H'\eta/\eta_0$ is accidental.[23a]

Implications. Diffusion coefficients were measured recently by proton magnetic resonance for an extensive series of electrolytes in aqueous solution up to high concentrations.[24] It was found that, when proton diffusion measures the diffusion of water molecules, η_0/η and the relative diffusion coefficients D/D_0 are nearly equal. We infer, therefore, from the constancy of $k_H'\eta/\eta_0$ that the mobility of a water molecule hydrogen bonded to R_3N parallels the mobility of water molecules in the bulk solvent.

At the same time, it is quite certain that the mobility measured by k_H is considerably smaller (except for $H_3N \cdot HOH$) than the mobility of water molecules in the bulk solvent. The analog of k_H for the separation of two adjacent water molecules can be estimated theoretically to be about 3×10^{11} sec^{-1};[25] k_H for trimethylamine is only 1×10^{10} sec^{-1}. Any theory we make concerning k_H should therefore have the following features. (1) The first layer of water molecules adjacent to R_3N has properties differing considerably from those of water molecules in the bulk solvent. In particular, the subspecies of water molecules adjacent to amino nitrogen has a lower free energy than that of water molecules in the bulk. (2) The second layer of water molecules is already very much like water in the bulk. Because of (1), diffusion from the site adjacent to amino nitrogen is slower than diffusion from an average site in the bulk solvent. Because of (2), the final sites and transition states in these processes are very much alike in their average properties and are affected very similarly by the addition of electrolyte.

A theory of solvation that limits the effective range of specific solute–solvent interaction to a monomolecular layer around the solute molecule is much like the Brunauer–Emmett–Teller theory of physical adsorption on solid surfaces.[26] It is *not* compatible with those models of solvation of nonpolar groups in aqueous

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[20] P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Phys. Chem.*, **68**, 410 (1964), and references cited therein.

[21] C. G. Swain and M. M. Labes, *J. Am. Chem. Soc.*, **79**, 1084 (1957).

[22] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 269.

[23] Other things being equal, we would expect k_H' for the diffusion of DOH to be smaller by a few per cent than k_H for the diffusion of HOH. Actual values of $k_H'\eta/\eta_0$ are slightly smaller, as expected, but the difference from k_H is not statistically significant.

[23a] NOTE ADDED IN PROOF. A recent study (R. J. Day and C. N. Reilly, *J. Phys. Chem.*, 71, 1588 (1967)) of deuterium exchange between $(CH_3)_3ND^+$ and D_2O has led to a value for $k_H\eta/\eta_0$ in heavy water that is in good agreement with values listed in the final column of Table II.

[24] D. W. McCall and D. C. Douglass, *J. Phys. Chem.*, **69**, 2001 (1965).

[25] This estimate is based Einstein's formula for Brownian movement, $t = s^2/6D$, where t is the mean time required for a molecule to travel a distance s in an arbitrary direction and D is the diffusion coefficient. For two water molecules, $D = 2 \times 2.44 \times 10^{-5}$ cm^2 sec^{-1} at 25°; for s we use 2.9 A.

[26] S. Brunauer, P. H. Emmett, and E. Teller, *J. Am. Chem. Soc*, 60, 309 (1938).

solution[12] that postulate the formation of ordered ice-like agregates extending over more than a single layer.

Since η/η_0 is a smooth function of solvent composition in sulfuric acid–water mixtures, it follows that k_H' is a smooth function also. This fact alone seems to us to argue against any model that depicts the solvation shell as consisting of a substantial number of water molecules acting in cooperation. If the formation of a solvation shell were a cooperative phenomenon, its "melting" or any change of composition would be cooperative also and would resemble a change of phase. As a result, k_H' would show a sudden, step-like change at the critical solvent composition. Table II shows no evidence that step-like changes occur up to 58 wt % H_2SO_4.

k_H' for Ammonia. An acidity function $H_0°$ for ammonia has not been constructed. However, it has been shown that acidity functions in general are linearly related.[27] We have therefore represented $H_0°$ as a linear combination of H_0' and H_0''' (eq 14).

$$H_0° = H_0' - x(H_0''' - H_0') \qquad (14)$$

Assuming the constancy of $k_H'\eta/\eta_0$, it then follows from (13) that the plot of log $(h_0'k_e g\varphi_1\eta/\eta_0 K_A)$ *vs.* $(H_0''' - H_0')$ is a straight line, with slope equal to x and intercept equal to log k_H' in water. The result of this treatment is shown in Table II. "Best values" are: x = 0.191, $k_H' = 2.2 \times 10^{11}$ sec^{-1} in water. Because $H_0°$ is not known *a priori*, the treatment does not test the constancy of $k_H'\eta/\eta_0$ so much as it provides a rational method for evaluating k_H' in water. The new value differs by a factor of two from an earlier estimate, based on the same k_e values,[3] and is probably more accurate.

Effect of Nonpolar Substituents

Table III summarizes the substituent effect on k_H for a variety of amines in water. It is seen that the free energy quantity, $-RT\delta_R$ ln k_H, amounts to nearly 3 kcal/mole as the amine changes from ammonia to dibenzylmethylamine. In this section we wish to show that the effect of nonpolar substituents on k_H may be attributed largely to the London dispersion interaction.

Table III. Correlation of Substituent Effects on k_H

Amine	$-RT\delta_R$ ln k_H, cal	δ_RpK_B	$\Sigma\sigma^*$	$\bar{V}_2$, ml	$\delta_R F_{disp}$, cal eq 15,17	eq 16,17
NH_3	(0)	(0.00)	1.47	25.1[b]	0	0
CH_3NH_2	750	−1.37	0.98	40.0[a]	200	840
$(CH_3)_3N$	1840	−0.97	0.00	77.9[a]	630	2520
$(C_2H_5)_3N$	2410	−1.56	−0.30	119.7[a]	710	4350
$(PhCH_2)_2NCH_3$	2650	+1.36	+0.43	204[c]	1050	3900

[a] R. E. Verrall and B. E. Conway, *J. Phys. Chem.*, **70**, 3961 (1966). [b] Computed from density of ammonia–water solutions. [c] Molar volume of pure liquid.

We begin by considering a plausible alternative theory, that k_H measures the strength of the $R_3N \cdot HOH$ hydrogen bond: the stronger that bond, the smaller the rate constant k_H for breaking it. Hydrogen-bond strength can be predicted. For a fixed donor and a series of structurally related acceptors, it tends to increase with the basicity of the acceptor.[28] This linear free energy relationship has its limitations, especially if there is a change in the hybridization of the acceptor electron orbital in the series,[29] but in the present case it ought to apply. For the measure of basicity we could try either pK_B, which measures basicity in water, or Taft's polar substituent constant σ^*,[30] which measures electron supply to nitrogen and correlates certain data for base strength and hydrogen bonding in nonpolar solvents.[28b,31,32]

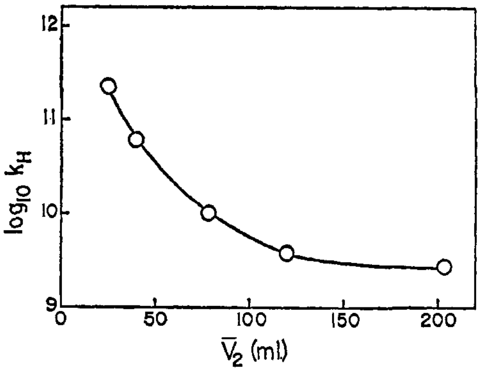

Figure 1. Plot showing monotonic relationship between log k_H and $\bar{V}_2$. Points are for (left to right) NH_3, CH_3NH_2, $(CH_3)_3N$, $(C_2H_5)_3N$, $(PhCH_2)_2NCH_3$.

Values of δ_R pK_B and $\Sigma\sigma^*$ are listed in Table III. It can be seen at once that log k_H does not vary simply with pK_B. The variation with $\Sigma\sigma^*$ is monotonic for the series NH_3 to $N(C_2H_5)_3$ but fails decisively in the case of dibenzylmethylamine, which provides a more sensitive test. It is clear that $R_3N \cdot HOH$ hydrogen-bond strength can account at most for part of the substituent effect on k_H.

However, there does exist a smooth relationship between log k_H and the partial molar volume, $\bar{V}_2$, of the amine, as shown in Figure 1. Moreover, as the size of the alkyl groups increases, the slope in Figure 1 decreases rapidly and approaches zero near the point for triethylamine. Thus the dominant interaction seems to be of short range and seems to reach saturation at or near R = ethyl. Qualitatively, Figure 1 is the sort of relationship that one expects when the substituent effect is dominated by the London dispersion interaction. There is a strong resemblance between the present phenomenon and previous measurements of neighboring molecule effects on acid strength in systems where London dispersion effects are known to be important.[33]

Calculation of the London Dispersion Interaction. We now wish to calculate the London dispersion interaction between the water molecule and the nonpolar R groups in $R_3N \cdot HOH$. Our model will be simple and the results semiquantitative. Nevertheless, we shall

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(27) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899 (1966).

(28) (a) J. E. Gordon, *J. Org. Chem.*, **26**, 738 (1961); (b) see, for example, J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y. 1963, pp 257, 311.

(29) E. Grunwald and W. C. Coburn, *J. Am. Chem. Soc.*, **80**, 1322 (1958).

(30) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

(31) R. P. Bell and J. W. Bayles, *J. Chem. Soc.*, 1518 (1952); J. W. Bayles and A. Chetwyn, *ibid.*, 2328 (1958).

(32) C. G. Cannon, *Spectrochim. Acta*, **10**, 429 (1958).

(33) E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **86**, 4517 (1964).

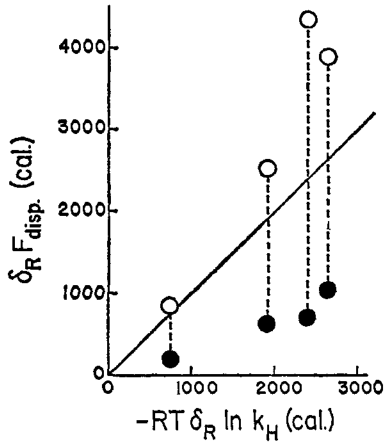

Figure 2. Plot showing that $-RT\delta_R \ln k_H$ is of the same order of magnitude as the change in the London dispersion interaction. Based on data in Table III. Solid circles based on eq 15, 17; open circles based on eq 16, 17. Solid line is drawn with unit slope.

show that the London dispersion interaction is of the correct magnitude to make an important, and possibly a dominant, contribution to the substituent effect on k_H.

Our calculation is based on London's concept that complex molecules contain many independent centers of van der Waals attraction.[10] It applies this concept to an approximation that is logically consistent with an atomic additivity scheme, that is, a scheme in which molecular electronic properties such as the polarizability[34] or diamagnetic susceptibility[35] are represented as additive functions of independent terms assignable to individual atoms or groups. To this approximation, we represent the complex molecule as a collection of isotropic electronic oscillators, each tied to a specific atomic nucleus. The properties of the oscillators are given by the appropriate independent terms in the additive schemes, and their locations are those of the central nuclei.

In the actual calculation, we treated the water molecule as a single oscillating dipole, located at the oxygen nucleus, and the molecule of amine as a collection of oscillating atomic dipoles. We used precision-made space-filling atomic models[36] to predict the most probable conformation of the $R_3N \cdot HOH$ complex and obtained the interatomic distances accordingly. We then calculated the interaction energy between the water molecule and each oscillating dipole in the R_3N molecule separately and added the results to obtain the total for $R_3N \cdot HOH$. Each calculation was made by two methods: (a) London's original approximation, which utilizes polarizabilities (α_i, α_j) and ionization potentials ($h\nu_i$, $h\nu_j$), as shown in eq 15; (b) an approximation suggested by Linder,[37] which utilizes diamagnetic susceptibilities (χ_i, χ_j) and ionization potentials, as shown in eq 16. In (15) and (16), ϵ_{ij} is the interaction energy of a pair of isotropic oscillating dipoles (in ergs/molecule) separated by a distance R_{ij} cm.

$$\epsilon_{ij} = \frac{-3h}{2}\frac{\alpha_i\alpha_j\nu_i\nu_j}{(\nu_i + \nu_j)R_{ij}^6} = 9.94 \times 10^{-27}\frac{\alpha_i\alpha_j\nu_i\nu_j}{(\nu_i + \nu_j)R_{ij}^6} \quad (15)$$

$$\epsilon_{ij} = \frac{-24m^2c^4}{N^2h}\frac{\chi_i\chi_j}{(\nu_i + \nu_j)R_{ij}^6} = 6.69 \times 10^{-33}\frac{\chi_i\chi_j}{(\nu_i + \nu_j)R_{ij}^6} \quad (16)$$

Finally, we calculated the substituent effect by each method according to (17), where $F_{R_3N \cdot HOH}$ denotes the total dispersion energy (a free-energy quantity) between R_3N and HOH in the complex, in calories per

$$\delta_R F_{disp} = F_{R_3N \cdot HOH} - F_{H_3N \cdot HOH} - F_{\delta V} \quad (17)$$

mole. A term, $F_{\delta V}$, is included in (17) because R_3N is a larger molecule than H_3N. Let δV denote the volume of water displaced when R_3N is substituted for H_3N. Then $F_{\delta V}$ allows for the dispersion interaction between the water molecule in $H_3N \cdot HOH$ and water molecules in δV.

Details of the calculations are summarized in Table IV. Final results for $\delta_R F_{disp}$ are included in Table III and plotted *vs.* $-RT\delta_R \ln k_H$ in Figure 2. We find, as did Linder,[37] that results obtained by the two methods differ considerably, though not in order of magnitude, in spite of the fact that the two methods represent very similar approximations. Nevertheless, it is clear that $\delta_R F_{disp}$ is comparable in magnitude to $-RT\delta_R \ln k_H$. In fact, the line of unit slope drawn in Figure 2 lies well within the area of uncertainty defined by the two methods of calculation. It is assumed in this comparison that in the transition state of the process measured by k_H, the water molecule is sufficiently far removed from R_3N so that $\delta_R F^{\mp}{}_{disp}$ may be neglected.

Table IV. Data for Calculation of $\delta_R F_{disp}$

Atom or group	$10^{-15}\nu_i$,[a] sec^{-1}	R_{ij}, A	$10^{24}\alpha_i^D$, cm^3[g]	$-10^6 \cdot \chi_i$[h]
N (NH_3)	3.77	2.84[b]	0.858	5.55
Primary N	3.77	2.84	0.920	5.55
Tertiary N	3.77	2.84	1.126	5.55
1st (α) CH_2	2.4	3.57[c]	1.83	11.86
2nd (β) CH_3	2.4	5.08, 3.70 4.4[d]	2.27	14.79
H (NH_3)	3.73	3.27	0.43	2.93
C_6H_5	2.24	3.52, 6.04[e]	9.58	51.1
H_2O	3.04	2.84, 3.70, 4.8[f]	1.477	10.46

[a] Based on data in ref 37 and in A. Streitwieser, *Progr. Phys. Org. Chem.*, **1**, 23 (1963). [b] G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, p 285. [c] Or distance H_2O–(α)CH_3. [d] In triethylamine. [e] $(\Sigma R_{ij}^{-6}/6)^{-1/6}$ for two phenyl groups in $(PhCH_2)_2NCH_3$. [f] Distances used in calculation of $F_{\delta V}$. For CH_3NH_2, 0.8H_2O molecule at 4.8 A; for $(CH_3)_3N$, 2.95 H_2O molecules at 4.8 A; for $(CH_3CH_2)_3N$, 3.6 H_2O molecules at 4.8 A and 0.5 H_2O molecule at 3.70 A; for $(PhCH_2)_2NCH_3$, 1.0 H_2O molecule at 2.84 A and 3.6 H_2O molecules at 4.8 A. [g] From ref 34 and J. W. Smith, "Electric Dipole Moments," Butterworth and Co. (Publishers), Ltd., London, 1955, p 261. [h] From ref 35 and 37.

Experimental Section

In this section we report new measurements of pK_A and of NH-OH proton exchange rates for dibenzylmethylammonium chloride at 30° in water at pH <4. Data for imidazole listed in Table I

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[34] K. Fajans in "Physical Methods of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1949, p 1163.

[35] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 19.

[36] CPK models, sold by the Ealing Corp., Cambridge, Mass.

[37] B. Linder, *J. Chem. Phys.*, 33, 668 (1960).

were obtained by similar techniques and will be reported in detail when current work on imidazole and its derivatives reaches completion.

pK_a Measurements. Because of the low solubility of dibenzylmethylamine (*ca.* 7 × 10^{-4} M at 30°) it was necessary to measure K_A at pH <4, near the equivalence point, and a differential potentiometric method[38] was used. The concentration of R_3NHCl in six independent experiments ranged from 0.02 to 0.2 M; pK_A appeared to be independent of concentration and was 7.72 ± 0.04 at 30°. Saunders and Yamada[17] have reported that pK_A = 7.5 ± 0.1 at 25°, somewhat lower than our value.

Kinetic Results. Rates of NH–OH proton exchange between dibenzylmethylammonium chloride and water were measured by nmr techniques described previously[7,39] in the presence of 10^{-4} to 1 M HCl. The NH–HOH chemical shift used in the interpretation was 4.48 ppm. The rate law was found to be (18).

$$R = k[R_3NH^+]/(1 + Q[H^+]) + k_2[R_3NH^+][R_3N] \quad (18)$$

Because of the low solubility of the amine, the accuracy of k_2, which depends on measurements in the high pH end of the pH range, was less than usual. The accuracy of k and Q and the test of the rate law at pH <3 were satisfactory. On interpreting k and Q by the mechanism in eq 3 and 4, we obtained at 30°: $k_a = (2.4 \pm 0.3) \times 10^2$ sec^{-1}; $k_{-a} = (1.25 \pm 0.16) \times 10^{10}$ sec^{-1} M^{-1}; $k_H = (2.7 \pm 0.5) \times 10^9$ sec^{-1}; $k_2 = (1.5 \pm 0.4) \times 10^7$ sec^{-1} M^{-1}.

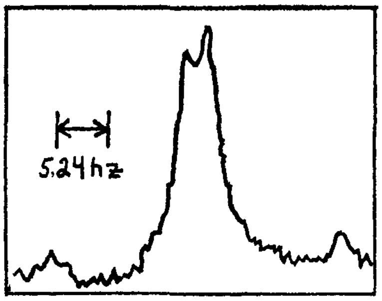

Figure 3. CH_2 proton resonance spectrum of dibenzylmethylammonium chloride at 56.4 MHz in 0.134 M DCl in D_2O. The scale of the abscissa is 5.24 Hz per large division.

Confirmation of the Rate Constant for Walden Inversion about Nitrogen. Saunders and Yamada, in their measurement of $k_{\text{inversion}}$, treat the nuclear magnetic resonance of the CH_2 protons as a partially exchange-averaged AB spectrum.[17] Unfortunately, because of the strong background nmr absorption due to the water protons, they could not show that an AB spectrum is actually obtained in the absence of exchange, in strong acid. In Figure 3 we show our measurement of the CH_2 proton resonance at 56.4 MHz of dibenzylmethylammonium chloride in 0.134 M DCl in D_2O. The resonance is in good agreement with prediction for an AB spectrum for which δ = 0.132 ppm and J = 13.1 Hz.

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(38) E. Grunwald, *J. Am. Chem. Soc.*, 73, 4934 (1951).

(39) E. Grunwald and E. Price, *ibid.*, **86**, 2965, 2970 (1964).

Aromatic Protonation. III. Kinetic Hydrogen Isotope Effects on Acid-Catalyzed Aromatic Hydrogen Exchange in 1,3,5-Trimethoxybenzene[1]

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Abstract: Rates of aromatic hydrogen exchange in 1,3,5-trimethoxybenzene catalyzed by dilute aqueous perchloric acid were measured for four systems which used the three isotopes of hydrogen as tracers in different pairwise combinations. Kinetic analysis of the results in terms of the known two-step mechanism of this reaction shows that secondary isotope effects must be taken into account and that the Swain relation between deuterium and tritium isotope effects is valid. The product of primary and secondary isotope effects on hydrogen ion transfer from the hydronium ion to isotopically identical substrates is 3.59 ± 0.11 (k_H/k_D), and the secondary isotope effect produced by hybridization changes in the nonreacting bond of the aromatic substrate in this step of the reaction is 0.90 ± 0.03 (k_H/k_D). The quotient of primary and secondary isotope effects on hydrogen ion loss from the phenonium ion intermediate is 8.1 ± 0.3 (k_H/k_D). The secondary isotope effect on this step of the reaction is also produced by hybridization changes in the nonreacting bond of the aromatic substrate, and there is reason to expect it to be the reciprocal of the corresponding isotope effect on the other step of the reaction. This gives the primary isotope effect on hydrogen ion loss from the phenonium ion intermediate the value 9.0 ± 0.4 (k_H/k_D).

Ever since Melander's pioneering work,[3] kinetic hydrogen isotope effects have played a prominent role in mechanistic investigations of electrophilic aromatic substitution.[4] Acid-catalyzed aromatic hydrogen exchange is the most elementary electrophilic aromatic substitution, and isotope effects on this reaction are therefore of special significance in this respect. Quite apart from their value to electrophilic aromatic substitution, however, isotope effects on aromatic hydrogen exchange are important because one of the rate-determining steps of this reaction is slow proton transfer from the catalyzing acid to the substrate. Proton

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(1) (a) This research was supported by the U. S. Atomic Energy Commission under Contract No. AT(11-1)-1025 to the Illinois Institute of Technology. (b) Part I: A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961). (c) Part II: A. J. Kresge, L. E. Hakka, S. Mylonakis, and Y. Sato, *Discussions Faraday Soc.*, **39**, 75 (1965).

(2) (a) Guggenheim Fellow. (b) Guest of the Institute, Massachusetts Institute of Technology.

(3) L. Melander, *Arkiv Kemi*, **2**, 213 (1950).

(4) For recent reviews, see H. Zollinger, *Advan. Phys. Org. Chem.* **2**, 164 (1964); E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964).