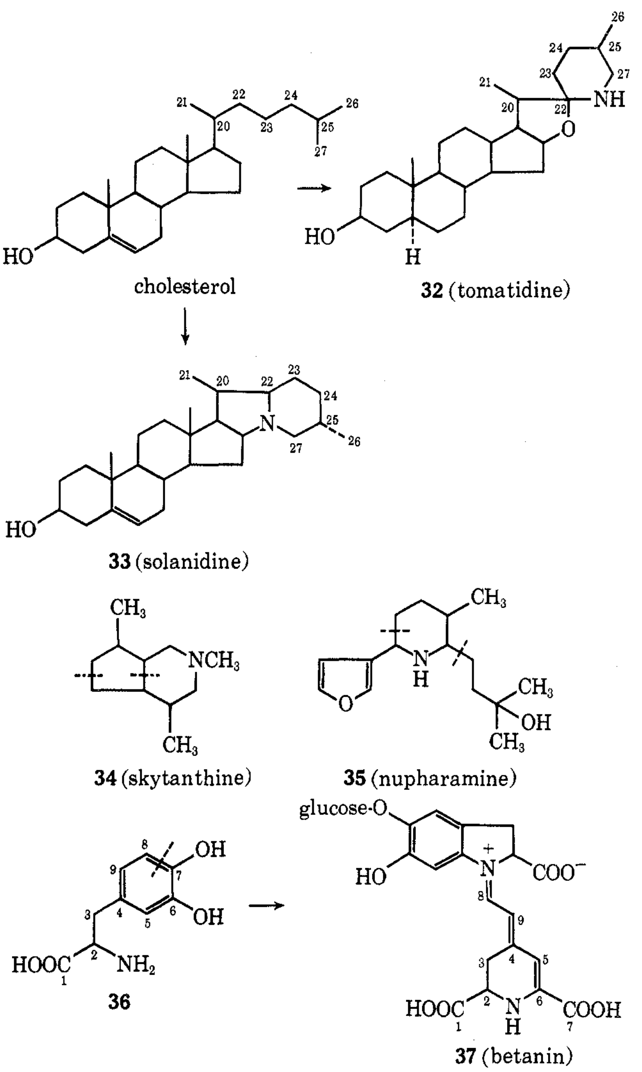
lost by a reversal of earlier steps in this biosynthetic pathway, *i.e.*, the transamination reaction involving 5-oxooctanal. 2-Methylpiperidine (**6**), a minor alkaloid of hemlock[4] and certain *Pinus* species,[57] is plausibly formed in an analogous manner from 5-oxohexanoic acid.

Little has been said about the origin of the hydroxylated alkaloids of hemlock, namely conhydrine and ψ-conhydrine. Compounds such as (**31**) may be intermediates between γ-coniceine and conhydrine. In fact the yield of conhydrine from hemlock is increased if the crude alkaloids are hydrogenated prior to separation,[49] favoring the presence of an unsaturated compound such as **31**.

Other Biosynthetic Routes to Piperidine Rings

In conclusion it should be mentioned that there are other known routes whereby piperidine rings are made in nature (Chart VI). Thus the alkaloids skytanthine (**34**) and nupharamine (**35**) are probably mono- and sesquiterpenes, respectively. It has been established that the former alkaloid is derived from mevalonic acid.[58] The dotted lines on the structures **34** and **35** indicate the dissection into isoprene units. The Δ^2-piperideine ring in betanin (**37**) is formed from dopa (**36**) by a sequence of reactions involving the opening of the catechol ring,[59] the atoms being numbered to illustrate the derivation of the carbons in betanin from dopa. A large group of alkaloids which contain the piperidine ring are those found in *Lycopodium* species, and it is considered that these are dimers of pelletierine.[60]

Chart VI



cholesterol

32 (tomatidine)

33 (solanidine)

34 (skytanthine)

35 (nupharamine)

36

37 (betanin)

I thank the National Science Foundation which supported our early work on the hemlock alkaloids; more recently I am indebted to the National Institutes of Health for support through Research Grant GM-13246.

---

(57) W. H. Tallent, V. L. Stromberg, and E. C. Horning, *J. Amer. Chem. Soc.*, **77**, 6361 (1955).

(58) H. Auda, H. R. Juneja, E. J. Eisenbraun, G. R. Waller, W. R. Keys, and H. H. Appel, *ibid.*, **89**, 2476 (1967).

(59) H. E. Miller, H. Rösler, A. Wohlpart, H. Wyler, M. E. Wilcox, H. Frohfer, T. J. Mabry, and A. S. Drieding, *Helv. Chim. Acta*, **51**, 1470 (1968).

(60) R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, and J. T. Wrobel, *J. Amer. Chem. Soc.*, **90**, 9360 (1968); M. Castillo, R. N. Gupta, D. B. MacLean, and I. D. Spenser, *Can. J. Chem.*, **48**, 1893 (1970); M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *J. Amer. Chem. Soc.*, **92**, 1074 (1970); *Can. J. Chem.*, **48**, 2911 (1970).

Kinetic Studies of Hydrogen-Bonded Solvation Complexes of Amines in Water and Hydroxylic Solvents

ERNEST GRUNWALD

Chemistry Department, Brandeis University, Waltham, Massachusetts 02154

EARLE K. RALPH

Chemistry Department, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

Received December 2, 1970

The familiar formula, NH_4OH, for ammonia in aqueous solution is correct in at least one respect: kinetic studies of proton exchange show clearly that amines form hydrates in aqueous solution. Thus, when the conjugate acid BH^+ of an amine B undergoes acid dissociation, the process is best represented by eq 1.

$$\mathrm{BH^+{\cdot}OH_2 + H_2O \rightleftarrows B{\cdot}HOH + H_3O^+} \tag{1}$$

That amines form hydrates in aqueous solution, and hence may be used as models to elucidate hydration in general, has been suspected for a long time. As far as we know, the first attempt to test this theory *experimentally* was reported by Moore and Winmill,[1] although their evidence would hardly seem conclusive today. However, it *is* possible to get conclusive evidence from kinetic studies of proton exchange: for many ammonium salts in dilute aqueous acid, proton exchange between BH^+ and water can be measured, at dynamic equilibrium, with high precision by nuclear magnetic resonance, and the rate of proton exchange owing to acid dissociation can be deduced. Let us see how such data can show that the amine is hydrated. If eq 1 is correct, then the detailed mechanism for proton exchange is that shown in eq 2–5, where we follow the fate of the italicized proton.

$$\mathrm{H_2O + B}\mathit{H}^+\mathrm{{\cdot}OH_2 \xrightarrow{k_a} B{\cdot}}\mathit{H}\mathrm{OH + H_3O^+} \tag{2}$$

$$\mathrm{B{\cdot}}\mathit{H}\mathrm{OH + H_3O^+ \xrightarrow[\text{no exchange}]{k_{-a}} B}\mathit{H}^+\mathrm{{\cdot}OH_2 + H_2O} \tag{3}$$

Proton-exchanging step (the italicized proton ends up in bulk water)

$$\mathrm{H_2O(aq) + B{\cdot}}\mathit{H}\mathrm{OH \xrightarrow{k_H} B{\cdot}HOH + }\mathit{H}\mathrm{OH(aq)} \tag{4}$$

Completion of the cycle (same as (3), but with a new proton)

$$\mathrm{B{\cdot}HOH + H_3O^+ \xrightarrow{k_{-a}} BH^+{\cdot}OH_2 + H_2O} \tag{5}$$

This reaction mechanism requires two distinct amines, those ($B{\cdot}\mathit{H}OH$) which still have the original (italicized) proton hydrogen bonded to the amino nitrogen atom, and those ($B{\cdot}HOH$) which have exchanged that proton. Since we measure exchange rates in dilute acid, the total concentration of amine is very small, and the steady-state approximations may be made. The rate law for proton exchange between BH^+ and water is then given by eq 6, where the quotient, $k_H/(k_H + k_{-a}[H^+])$, denotes the probability that the original $B{\cdot}\mathit{H}OH$ hydrogen bond is replaced before the hydrated amine reverts to hydrated BH^+.

$$\text{rate of proton exchange} = k_a[\mathrm{BH^+}]\{k_H/(k_H + k_{-a}[\mathrm{H^+}])\} \tag{6}$$

On the other hand, if the product of acid dissociation is the free amine rather than the hydrate, the reaction mechanism is that shown in eq 7–9, and the rate of proton exchange is given by eq 10.

$$\mathrm{B}\mathit{H}^+\mathrm{ + OH_2 \xrightarrow{k_a'} B + }\mathit{H}\mathrm{OH_2^+} \tag{7}$$

$$\mathit{H}\mathrm{OH_2^+ + H_2O \xrightarrow{fast} HOH_2^+ + }\mathit{H}\mathrm{OH} \tag{8}$$

$$\mathrm{B + HOH_2^+ \xrightarrow{k_{-a}'} BH^+ + OH_2} \tag{9}$$

$$\text{rate of proton exchange} = k_a'[\mathrm{BH^+}] \tag{10}$$

According to eq 10, the rate of proton exchange is kinetically first order in $[BH^+]$ and independent of $[H^+]$. According to eq 6, the rate is not independent of $[H^+]$, except when $[H^+] \ll k_H/k_{-a}$, but drops progressively below the first-order value as $[H^+]$ increases.

Although both rate laws have been observed—for instance, eq 10 fits the acid dissociation of $Al(OH_2)_6^{3+}$ as a Brønsted acid in water[2]—eq 6 applies to the process that interests us here. Equation 6 represents all known cases of proton exchange owing to acid dissociation of an ammonium salt in aqueous solution. For typical examples, see ref 3–10. The kinetic analysis is not always simple, sometimes because a parallel second-order reaction makes a significant contribution to the rate,[11] at other times because of the need to correct for kinetic salt effects,[12] but the chosen rate law is not in doubt. As an example, Figure 1 shows our results for the acid dissociation of tris(hydroxyethyl)ammonium ion in water at 30°. The fit to the smooth curve, which represents the rate law according to eq 6, is excellent.

Equation 6 has been found to apply also to the proton exchange of certain ammonium salts in hydroxylic solvents other than water. Indeed, the mechanism represented by eq 2–5 was first discovered for proton exchange of triethylammonium ion in *methanol*.[14] However, in certain other cases in methanol, the mechanism is still in doubt.[15]

Calculation of Rate Constants. If eq 6 is written in the equivalent form (eq 11), it becomes obvious that the rate measurements allow us to deduce two constants: the rate constant k_a and the quotient k_{-a}/k_H.

$$\text{rate of proton exchange} = k_a[\mathrm{BH^+}]/(1 + [k_{-a}/k_H][\mathrm{H^+}]) \tag{11}$$

Moreover, since measurements are made at dynamic equilibrium, the quotient k_a/k_{-a} is equal to the acid dissociation constant K_a, which can be measured independently. Thus it is possible to evaluate all three rate constants, k_a, k_{-a}, and k_H. Some representative

---

[1] T. S. Moore and T. F. Winmill, *J. Chem. Soc.*, **101**, 1635 (1912).

(2) D. W. Fong and E. Grunwald, *J. Amer. Chem. Soc.*, **91**, 2413 (1969).

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

(4) E. Grunwald, *J. Phys. Chem.*, **67**, 2211 (1963).

(5) M. Sheinblatt and H. S. Gutowsky, *J. Amer. Chem. Soc.*, **86**, 4814 (1964).

(6) E. Grunwald and E. K. Ralph, III, *ibid.*, **89**, 4405 (1967).

(7) R. J. Day and C. N. Reilley, *J. Phys. Chem.*, **71**, 1588 (1967).

(8) G. Fraenkel and Y. Asahi, *ibid.*, **71**, 1706 (1967).

(9) M. Cocivera, *ibid.*, **72**, 2520 (1968).

(10) (a) D. E. Leyden and W. R. Morgan, *ibid.*, **73**, 2924 (1969); (b) W. R. Morgan and D. E. Leyden, *J. Amer. Chem. Soc.*, **92**, 4527 (1970).

(11) E. Grunwald and M. Cocivera, *Discuss. Faraday Soc.*, **39**, 105 (1965).

(12) To keep the rates within a range accessible to measurement, it is sometimes necessary to work at fairly high concentrations of electrolyte, on the order of 1 *F*. We find it necessary, in general, to consider salt effects on K_a, on the solution viscosity, and—most importantly—on the acidity.[6,13] We believe that quite erroneous results can be obtained when these factors are neglected. Compare, for example, results for $(C_6H_5CH_2)_2NCH_3$ in Table I with those reported by Leyden and Morgan.[10]

(13) E. K. Ralph and E. Grunwald, *J. Amer. Chem. Soc.*, **89**, 2963 (1967).

(14) C. G. Swain, J. T. McKnight, and V. P. Kreiter, *ibid.*, **79**, 1088 (1957).

(15) See, for example, M. Cocivera, E. Grunwald, and C. F. Jumper, *J. Phys. Chem.*, **68**, 3234 (1964); M. Cocivera, *ibid.*, **72**, 2515 (1968).

Table I

Application of Equation 6 to Data for Amines with Nonpolar Substituents in Water

Amine	Temp, °C	pK_A for BH^+	k_a, sec^{-1}	k_{-a}, sec^{-1} M^{-1}	k_H, sec^{-1}
			Data in H_2O[a]		
NH_3	25	9.25	25	4.3×10^{10}	22×10^{10}
CH_3NH_2	25	10.62			6.2×10^{10}
$(CH_3)_3N$	25	9.80	4.7	3.0×10^{10}	1.0×10^{10}
$(C_2H_5)_3N$	25	10.81	(0.4)[b]	(2.7×10^{10})[b]	0.38×10^{10}
$(C_6H_5CH_2)_2NCH_3$	30	7.72	240	1.3×10^{10}	0.27×10^{10}
			Data in D_2O[c]		
$(CH_3)_3N$	33.2	10.32	1.0_8	2.3×10^{10}	0.85×10^{10}

[a] Reference 6. [b] These rate constants are not very accurate. [c] Reference 7.

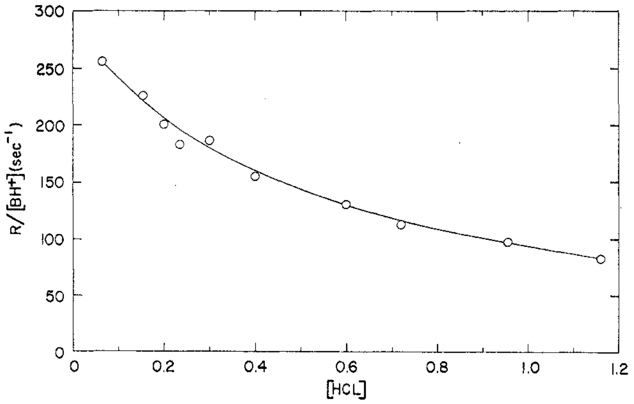
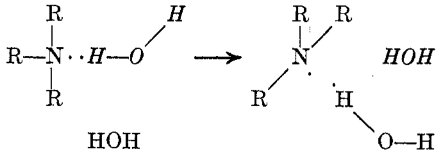


Figure 1. Proton exchange of 0.17 *F* tris(hydroxyethyl)ammonium chloride in water at 30°. The smooth curve is drawn according to eq 6 with $k_a = 283$ sec^{-1} and $k_{-a}/k_H = 1.88$ (M^{-1}).

results obtained in this way are listed in Table I. The validity of the reaction mechanism is indicated by the following. Values obtained for k_{-a} are precisely of the expected magnitude for diffusion-controlled reaction of hydrogen ion with the hydrated amine,[16] and in one case, where we have a direct comparison with results obtained by relaxation spectrometry, the agreement is within 10%.[17]

What We Hope to Learn from k_H. We are particularly interested in k_H, the rate constant for breaking the $R_3N \cdot HOH$ hydrogen bond between the amino nitrogen atom and the adjacent water molecule. Conceivably, this process could take place by rotation of the water molecule on its site (eq 12), or by a rotation of the R_3N molecule within its hydration shell (eq 13), or by a displacement process with Walden inversion of the nitrogen atom (eq 14), but for various reasons these models are not consistent with the facts.[6,18] Instead, it is highly probable that k_H is the rate constant for a dissociation process in which the HOH or the R_3N molecule surmounts an activation barrier and jumps to an adjacent "hole" in the liquid lattice.[19] On that basis, the magnitude of k_H, and its variation with the structure of the amine and with the solvent medium, can give us some rather direct insights into the peculiar blend of solvent–solute and solvent–solvent interactions whose total effect we customarily call "solvation."

$$R_3N \cdot \mathit{H}OH \longrightarrow R_3N \cdot HO\mathit{H} \qquad (12)$$


(13)

$$HOH + R_3N \cdot \mathit{HOH} \xrightarrow[\text{inversion}]{\text{Walden}} HOH \cdot NR_3 + \mathit{HOH} \qquad (14)$$

Amines with Nonpolar Substituents

Unimportance of Basicity. Deductions concerning solvation seem to be especially clear for amines with nonpolar substituents attached to pyramidal nitrogen. Values of k_H for such amines are summarized in Table I. The values are high, as expected, but they also show some features that are perhaps unexpected. First of all, the values are extraordinarily sensitive to the introduction of alkyl groups: k_H varies by almost two orders of magnitude for the limited range of substrates in Table I. Furthermore, k_H shows no obvious dependence on base strength. One might have expected that the strongest base forms the strongest, least readily dissociated, hydrogen bonds, yet in Table I the smallest k_H is observed with the weakest base. The unimportance of base strength is shown even more dramatically by the highest k_H value in Table I, 22×10^{10} sec^{-1} for $H_3N \cdot HOH$. This value is only slightly smaller than the rate constant for the separation of an adjacent pair of water molecules by diffusion, a plausible estimate of which is 80×10^{10} sec^{-1} at 1°,[20] in spite of the large difference in basicity between NH_3 and H_2O.

Effective Range of the Interaction. There is some justice in comparing the dissociation of $R_3N \cdot HOH$ to an elementary step in diffusion. For example, for ammonia, methylamine, and trimethylamine, k_H has

---

(16) E. Grunwald, *J. Phys. Chem.*, **67**, 2208 (1963).

(17) E. K. Ralph and E. Grunwald, *J. Amer. Chem. Soc.*, **91**, 2422 (1969).

(18) In a thought-provoking recent paper, Morgan and Leyden[10b] have indicated that Walden inversion (eq 14) may not be much slower than proton exchange and may thus account for all, or a substantial fraction, of k_H. However, their evidence is contrary to earlier work by M. Saunders and F. Yamada, *J. Amer. Chem. Soc.*, **85**, 1882 (1963), and by ourselves; see Figure 3 in ref 6.

(19) S. Glasstone, K. J. Laidler, and H. Eyring, "Theory of Rate Processes," McGraw-Hill, New York, N. Y., 1941, p 488.

(20) P. S. Leung and G. J. Safford, *J. Phys. Chem.*, **74**, 3696 (1970). According to these authors, the residence time, τ_0, of a water molecule in liquid water is 2.4×10^{-12} sec at 1°. Hence $2/\tau_0 = 80 \times 10^{10}$ sec^{-1}, and the jump distance (according to the Einstein–Smoluchowski theory[21]) is 1.45 Å.

(21) A. Einstein, "Investigations on the Theory of the Brownian Movement," Methuen and Co., Ltd., London, 1926.

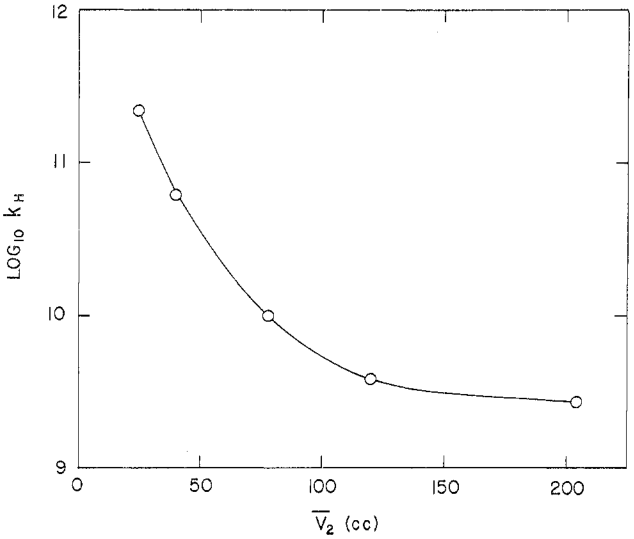


Figure 2. Plot of log k_H *vs.* partial molar volume, V_2, of the amine in water. Data points, from left to right, are for NH_3, CH_3NH_2, $(CH_3)_3N$, $(CH_3CH_2)_3N$, $(C_6H_5CH_2)_2NCH_3$.

been measured in sulfuric acid–water mixtures in which the viscosity, η, varies by an order of magnitude, and found to vary as $1/\eta$.[3,6] For trimethylamine, k_H has been measured not only in H_2O but also in the somewhat more viscous D_2O.[6,7] While $\eta_{H_2O}/\eta_{D_2O} = 0.81$, k_H(in D_2O)/k_H(in H_2O) = 0.85, in close agreement, thus suggesting that the *primary* isotope effect (k_H for $(CH_3)_3N \cdot DOD$ divided by k_H for $(CH_3)_3N \cdot HOH$, after correcting for medium effects) is practically unity. The temperature coefficient of k_H is of a typical magnitude for a diffusional process: for $(CH_3)_3N \cdot HOH$ in water, $\Delta H^{\ddagger} = 2.3$ kcal and $\Delta S^{\ddagger} = -5.0$ gibbs.[4]

If we treat the breaking of the hydrogen bond as a diffusional process, we shall want to know something about the nature of the diffusive jumps, and in particular about the mean jump distance. For most of the amine hydrates we may assume that the relatively small and light water molecule does nearly all of the actual moving. This simplifies matters, because the Brownian motion of water molecules has been well investigated by neutron scattering.[20] It has thus been deduced that the mean jump distance of a water molecule (in liquid water and in a series of concentrated salt solutions at 1°) is about 1.5 Å.[20] This distance is relatively long, being comparable to the radius of the water molecule, and we may therefore adopt a hole model for diffusion.[19] Thus we assume that the total activation free energy consists of two parts: the work required to form the hole, and the work required for the water molecule to move into that hole. Then, if k_H for a given amine varies as $1/\eta$, we may conclude that the internal pressure in the microscopic region in which the hole is formed varies in much the same way as does the internal pressure in the bulk solvent.

Let us risk the loss of some scientific precision and give a simple picture of what this conclusion seems to imply. Since pressure is force per unit area, when k_H varies as $1/\eta$, the force acting on the microscopic region in which the hole is formed is dominated by interactions with *solvent* molecules, and any specific forces due to the presence of the amine molecule are relatively small. Such a force diagram is credible only if the hole is formed *outside* the inner solvation sphere of the amine (the water molecule moves to an adjacent site in the next solvation sphere) and if any specific forces exerted by the amine molecule are of relatively short range.

When we examine the effects of nonpolar substituents on k_H we find, in support of this picture, that the dominant interaction of the departing water molecule with the substituents involves short-range forces. Thus Figure 2 shows a graph of log k_H *vs.* the partial molar volume, $\bar{V}_2$, of the amine. The relationship is smooth and appears to approach an asympototic limit horizontally as $\bar{V}_2$ becomes large. Figure 2 shows also that this limit is approached rapidly: substituent effects on k_H for $R_3N \cdot HOH$ seem to reach saturation when R $\approx$ ethyl. The interaction with the substituent is therefore of short range. We believe that it is primarily a London dispersion interaction.[22]

Nature of the Interaction. To show that van der Waals–London dispersion forces can account for the observed substituent effects, we have used the following model.[6] We treat the breaking of the hydrogen bond as a dissociation process with a ground state and a transition state. We then assume that the substituent effects of nonpolar groups are much larger in the ground state than in the transition state, owing to the short range of the London dispersion interaction and the relatively large jump distance of the departing water molecule—in fact, we neglect substituent effects in the transition state. We then calculate the interaction energy in the ground state to an approximation that is logically equivalent to an atomic additivity scheme. That is, we assume that the electronic oscillations whose interaction gives rise to the London dispersion forces are localized in atoms or groups.[6] The calculation shows that London dispersion forces can account for all, or most, of the observed substituent effects on k_H.

Variation of k_H with the Solvent. We have seen that introduction of alkyl substituents on the amino nitrogen atom reduces k_H for amine hydrates in water. If the preceding model is correct, then we expect that an increase in the size and polarizability of the hydrogen-bond *donor* molecule will likewise decrease k_H. This seems to be the case. Table II summarizes the available data for k_H in alcohols and alcohol–water mixtures. Strictly speaking, in comparing data in different solvents we must take into account any differences in the amounts of work required to make the "hole," but to a first approximation we shall neglect this relatively small quantity.

The data in Table II[6,13,14,23,24] show the expected decrease in k_H with increasing size of the hydroxylic mole-

---

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

(23) E. Grunwald, *ibid.*, **71**, 1846 (1967); R. L. Lipnick, Ph.D. Thesis, Brandeis University, 1969.

(24) E. Grunwald, R. L. Lipnick, and E. K. Ralph, *J. Amer. Chem. Soc.*, **91**, 4333 (1969).

Table II

Variation of k_H with the Solvent at 25°

Solvate	Solvent	k_H, sec^{-1}	Ref
$(CH_3)_3N \cdot HOH$	H_2O	1.0×10^{10}	6
$(CH_3)_3N \cdot HOCH_3$	CH_3OH	$(1.5 \pm 0.5) \times 10^{10}$	23
$(C_2H_5)_3N \cdot HOH$	H_2O	3.8×10^9	13
$(C_2H_5)_3N \cdot HOCH_3$[a]	CH_3OH	$\sim 1 \times 10^8$	14, *a*
DEMT·HOH[b]	HOH–HOC_4H_9-*tert*[c]	6.6×10^9	24
DEMT·$HOCH_3$[b]	CH_3OH	4.3×10^8	24
DMET·$HOC(CH_3)_3$[b]	HOH–HOC_4H_9-*tert*[c]	2.6×10^5	24

[a] $k_{-a}/k_H = 42$ (ref 14); k_{-a} is estimated as 4×10^9 sec^{-1} M^{-1} by analogy to data for amines of related structure. [b] DEMT = *N*,*N*-diethyl-*m*-toluidine. [c] 11.47 mole % *tert*-butyl alcohol–88.53 mole % water.

cule, except possibly for the trimethylamine–methanol complex. Indeed, for *N*,*N*-diethyl-*m*-toluidine (DEMT), the decreases in k_H are so strikingly large as to deserve special comment.

The kinetics of acid dissociation of DEMT was measured in methanol and also in a *tert*-butyl alcohol–water mixture.[24] In methanol eq 6 applies, and $k_H = 4.3 \times 10^8$ sec^{-1} at 25°. However, in the *tert*-butyl alcohol-water mixture we were able to identify two parallel processes, one with $k_H = 6.6 \times 10^9$ sec^{-1}, which we assigned to the amine hydrate, and the other with $k_H = 2.6 \times 10^5$ sec^{-1}, which we assigned to the amine–alcohol complex. The value of k_H for the hydrate is similar to values obtained for amines of comparable molar volume in water (Table I), while the value for the alcohol complex is more than 20,000 times smaller! However, even this very large difference can be accounted for on the basis of London dispersion interactions. If we construct a molecular model of the DEMT–HOC_4H_9-*tert* complex, we find a conformation, shown schematically in Figure 3, in which the N·HO hydrogen bond is nearly linear, and in which two methyl groups of the *tert*-butyl alcohol molecule are directly adjacent to the aromatic ring. We calculate 6.7–7.9 kcal as the difference in London dispersion energy for this particular alcohol complex relative to a hydrate,[24] while the experimental difference in $RT \ln k_H$ is 6.0 kcal. The close agreement supports our identification of k_H as a diffusion process: the entire *tert*-butyl alcohol molecule separates from the DEMT molecule, and the van der Waals interaction energy in the transition state is relatively small.

Table III lists the available data for k_H in glacial acetic acid. Because of extensive ionic association, the rate law and kinetic analysis are different from eq 2–6, but the identification of the process is again unambiguous.[25] The effects of *N*-alkyl substituents, the absolute values of k_H, and the lack of sensitivity to the base strength of the amine are entirely consistent with data in Tables I and II and provide further evidence that van der Waals–London dispersion forces are dominant.

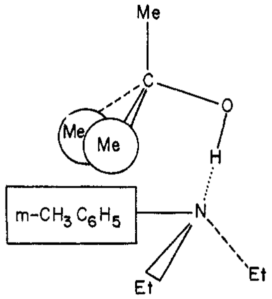


Figure 3. Schematic representation of the most stable conformation of the hydrogen-bonded complex between *N*,*N*-diethyl-*m*-toluidine and *tert*-butyl alcohol.

Table III

Rate Constants, k_H, and Base Ionization Constants, K_i, in Acetic Acid at or near 30° [25]

$C_6H_5NR_2$, NR_2 =	k_H, sec^{-1}	$K_i = [BH^+Ac^-]/[B]$
NH_2	2.0×10^9	7.9
$N(CH_3)_2$	1.3×10^9	12.7
$N(C_2H_5)_2$	0.60×10^9	109
$N(n\text{-}C_3H_7)_2$	0.27×10^9	30.5

Solvent–Solvent Interaction in Solvation. In any discussion of solvation we must, in principle, consider not only the solvent–solute interaction (as we did in the preceding sections) but also the solvent–solvent interaction. For organic solutes in water, there is a detailed set of theories in which the interaction among the water molecules is considered to be the dominant interaction in solvation. This point of view is based on an analysis of the highly irregular apparent molar entropies and heat capacities of many organic solutes in aqueous solution.[26,27] The introduction of the organic molecule is thought to induce a cooperative interaction among the water molecules which results in "patches of ice-like water" being formed adjacent to the solute molecules, or of clathrate-like cages being formed around the solute molecules.[27,28] While we do not believe that such cooperative interactions are always negligible, we *do* believe that they are much less important than has often been assumed.

Thus we have shown that it is possible to account for

---

[25] E. Grunwald and M. S. Puar, *J. Amer. Chem. Soc.*, **89**, 6842 (1967); M. R. Crampton and E. Grunwald, *Chem. Commun.*, 983 (1970).

[26] H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).

[27] H. S. Frank and W.-Y. Wen, *Discuss. Faraday Soc.*, **24**, 133 (1957).

[28] For early discussions of "clathrate water," see, for example, (a) R. L. Bohon and W. F. Claussen, *J. Amer. Chem. Soc.*, **73**, 1571 (1951); (b) W. F. Claussen and M. F. Polglase, *ibid.*, **74**, 4817 (1952); (c) D. D. Eley, *Trans. Faraday Soc.*, **35**, 1281 (1939); (d) D. N. Glew and E. A. Moelwyn-Hughes, *Discuss. Faraday Soc.*, **15**, 150 (1953).

the effects of nonpolar substituents on k_H in water solely on the basis of van der Waals interaction with the *solute*, without having to invoke the formation of cooperative water structures. Perhaps more important, we have shown that a change in the nature of the solvent from water, to *tert*-butyl alcohol–water, to methanol, and even to acetic acid, requires no modification of the view that the solvent–solute interaction is dominant, in spite of the marked change in any possible cooperative solvent–solvent interaction that must surely accompany these wide-ranging changes of the solvent.

Perhaps we may summarize our conclusions in terms of an anthropomorphic analogy. Most organic molecules have complex contours with protrusions and nooks and crannies. When solvent–solvent interactions are dominant, then the shape of the solvent shell is determined largely by interactions among the *solvent* molecules, and the solute molecule is "clothed" in a rigid suit of armor. However, when solvent–solute interactions are dominant, the solvent shell adapts its shape to that of the solute, and the solute molecule is "clothed" in a form-fitting sweater.

If we adopt the form-fitting sweater model, then the quality of the fit of the solvent molecule onto the surface of the solute molecule becomes very important to the solvation energy. For instance, in the case of *N,N*-diethyl-*m*-toluidine and *tert*-butyl alcohol, for the conformation shown in Figure 3, the matching of molecular contours is excellent and the interaction energy is therefore substantial. According to this point of view, the solvation phenomenon can become extraordinarily specific. If the solvation shell can assume many conformations of similar energy, then it is meaningful to treat the solvent as a continuum. However, if a specific conformation is of exceptionally low energy, then it is more meaningful to regard the solvent–solute interaction as a small-molecule analog of an enzyme–substrate complex.

Amines with Polar Substituents

Although our understanding of the solvation of amines with polar substituents is still rather unsatisfactory, it is already clear that two polar centers in close proximity can interact with the same solvent molecule.

Amines with an Ionic Charge. In our work to date, proximity effects owing to nearby polar groups have been shown most clearly by protonated ethylenediamines. Restricted rotation about the C–C bond in these molecules produces two conformational isomers, shown in Figure 4, in which the nitrogen atoms are trans or gauche, respectively. Accordingly, it has been possible to identify two parallel processes of proton exchange, one with k_H closely similar to that for the corresponding amine without the β-NH_3^+ group, the other with a much smaller k_H.[29] Because in the gauche isomer the departing water molecule can interact at close range with the β-NH_3^+ group, by charge–dipole interaction and perhaps by hydrogen bonding, we assign the smaller k_H value to the gauche isomer.

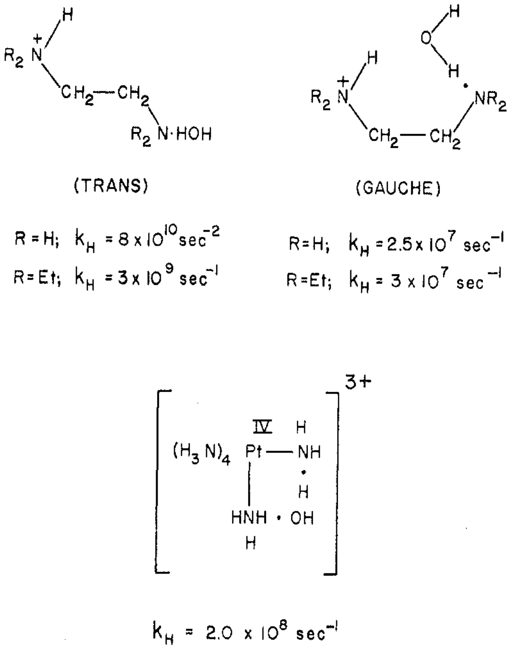


Figure 4. Kinetic results for amines with an ionic charge. Data in water at 25°.

Thus, for singly protonated *N,N'*-tetraethylethylenediamine (TEED), $k_H = 3 \times 10^7$ sec^{-1} for the gauche isomer and 3×10^9 sec^{-1} for the trans isomer (Figure 4). The latter value is remarkably similar to the value, $k_H = 3.8 \times 10^9$ sec^{-1}, obtained for the analogous nonpolar triethylamine (Table I). We interpret the near-equality as follows: van der Waals–London dispersion interactions with the departing water molecule, being of short range, are nearly the same, and the charge–dipole interaction of the trans β-NH_3^+ group with the departing water dipole is about the same in the ground state as in the transition state, an inference that is plausible in view of the relatively long distances and high effective dielectric constant.

Figure 4 also shows k_H for the hydrate of $(H_3N)_5$-$Pt^{IV}NH_2^{3+}$ in aqueous solution.[30] In this case, the existence of a cyclic hydrogen-bonded hydrate was demonstrated experimentally by the observation of fast proton transfer of *all* amino hydrogen atoms. The value obtained for k_H is 2×10^8 sec^{-1}, about six times larger than k_H for the *gauche* TEED hydrate. According to the geometry suggested in Figure 4, the charge–dipole interaction between the Pt^{IV} core of the ionic reactant and the departing water molecule should be small, because the water dipole is nearly perpendicular to the radius vector joining it to the platinum nucleus. This might explain the greater value of k_H compared to TEED.

Uncharged Polar Amines. Values of k_H for uncharged polar amines and for a series of methyl-substituted pyridines are listed in Table IV. The first

---

(29) E. K. Ralph and R. Davis, unpublished work.

(30) D. W. Fong and E. Grunwald, unpublished work.

Table IV
Uncharged Polar Amines and Methyl-Substituted Pyridines

Amine	Solvent	Temp, °C	k_H, sec^{-1}	Ref
$(HOCH_2CH_2)_3N$	H_2O	30	8.5×10^9	*a*
$(HOCH_2CH_2)_3N$	HOH–HOC_4H_9-*tert*[d]	25	5.3×10^9	*a*
$HO_2CCH_2NH_2$	H_2O	23	8.5×10^9	5
$CH_3O_2CCH_2NH_2$	H_2O	23	1.5×10^{10}	5
Sarcosine[e]	H_2O	21	2.3×10^{10}	*b*
Sarcosine methyl ester[f]	H_2O	21	1.1×10^{10}	*b*
Imidazole	H_2O	−0.4	0.9×10^9	17
Imidazole	H_2O	25	1.8×10^9	17
Imidazole	HOH–HOC_4H_9-*tert*[d]	25	$\approx 5 \times 10^8$	*c*
2-Picoline	H_2O	25.1	2.36×10^{10}	9
4-Picoline	H_2O	25.1	2.66×10^{10}	9
2,4-Lutidine	H_2O	25.1	2.78×10^{10}	9
2,6-Lutidine	H_2O	25.1	1.88×10^{10}	9

[a] D.-W. Fong, E. Grunwald, and E. K. Ralph, unpublished work. [b] M. Sheinblatt, *J. Chem. Phys.*, **36,** 3103 (1962). [c] E. K. Ralph and E. Grunwald, *J. Amer. Chem. Soc.*, **91,** 2429 (1969). [d] 11.47 mole % *tert*-butyl alcohol–88.57 mole % water. [e] $HO_2CCH_2NHCH_3$. [f] $CH_3O_2CCH_2NHCH_3$.

compound in Table IV, tris(hydroxyethyl)amine (Tris), again provides an opportunity for trans–gauche isomerism in each of the $HOCH_2CH_2$ groups. However, in contrast to the compounds listed in Figure 4, only one k_H value was observed.[31] This implies either that one isomer is dominant or that the k_H values for the different isomers are similar.

The substitution of $HOCH_2CH_2$ for CH_3CH_2 is a common device for changing a hydrophobic substituent into a hydrophilic one.[32] The fact that such substitution has only a rather small effect on k_H supports our previous conclusion that cooperative water–water interaction, leading to "patches of ice-like water" near hydrophobic groups, is relatively unimportant.

Proton exchange of Tris has also been studied in a *tert*-butyl alcohol–water mixture, and only one k_H value, similar to k_H in water, was found. We therefore assign that value to the dissociation of the Tris hydrate and conclude that hydrogen bonding between the amino nitrogen atom and a *tert*-butyl alcohol molecule is relatively unimportant.

k_H has also been measured for several amino acids in aqueous solution.[5,33] In these experiments it is clear from the method of measurement that k_H applies to the uncharged amino acids (as shown in Table IV) rather than to the zwitterions. The values obtained are quite high, of the order of 10^{10} sec^{-1}. They are probably not quite comparable with other values in Table IV because corrections for kinetic salt effects were made in a different way and because of the need to *estimate* the microscopic equilibrium constants for the uncharged amino acids. However, even with these limitations, it seems clear that the effect of the carboxyl group on k_H is small.

For imidazole, k_H is relatively small.[17,34] In this case the mechanism of acid dissociation is exceptionally complex and provides confirmatory evidence that the hydrate is unusually stable.

The uniformly high k_H values reported for methyl-substituted pyridines[9] are puzzling and are inconsistent with the reaction mechanism described for amines with nonpolar substituents. (We would have expected k_H to be of order 10^9 sec^{-1}.) Further work is currently in progress to test whether eq 6 is really the correct rate law.[35]

Conclusion

The preceding account of our research on the solvation of amines shows that, by studying the kinetics of fast proton-transfer reactions, we can obtain quite specific information about solvation at well-characterized sites. This is possible because the proton-transfer step itself is often so fast that solvation or desolvation steps become rate-determining. In principle, the same approach can be and has been applied not only to amines, but to a variety of acid–base reactions for which the proton-transfer step is very fast, and indeed to fast reactions in general. Results described here for the desolvation of amines justify the hope that further studies, using this approach, will give clear-cut explicit information about the forces involved in solvation and will dispel much of the uncertainty that too often surrounds this subject.

We express our appreciation to our respective universities, and to the following agencies who have given financial support: the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the National Research Council of Canada.

---

(31) See Table IV, footnote *a*.

(32) W.-Y. Wen and S. Saito, *J. Phys. Chem.*, **69,** 3569 (1965); **68,** 2639 (1964).

(33) See Table IV, footnote *b*.

(34) See Table IV, footnote *c*.

(35) D. Rosenthal and E. Grunwald, in progress.