

Fig. 2. —NH— proton resonance spectrum for (a) 0.388 *M* and (b) 1.19 *M* methylammonium chloride in acetic acid at 25°. Solid curves are calculated for (a) $1/T^1 = 230 \text{ sec.}^{-1}$; (b) $1/T^1 = 360 \text{ sec.}^{-1}$.

viscosimeter. The measurements were made at $25 \pm 0.05^\circ$ and were precise to $\pm 0.5\%$.

N.m.r. Measurements.—All n.m.r. measurements were made on the high resolution n.m.r. spectrometer of Meiboom, operating at 60 Mc./sec. A brief description of the instrument and of methods of frequency stabilization, temperature control, and spin-echo determination of T_1 and T_2' relaxation times has been

given elsewhere.²⁷ In measurements of T_1 and T_2' of the carboxyl protons, the radiofrequency field was adjusted according to the method of Alexander²⁸ so as to eliminate interference from the CH_3 - protons of acetic acid. Values of $1/T_2'$ were precise to $\pm 0.012 \text{ sec.}^{-1}$, up to about 4 sec.^{-1} , but the precision decreased rapidly above this value. Values of $1/T_1$ were usually precise to $\pm 0.005 \text{ sec.}^{-1}$. Typical values of Δ ranged from 0.3 to 3 sec.^{-1} .

The CH_3 - proton resonance of methylammonium ion (present largely in the form of ion pairs) was recorded under conditions of slow passage and negligible saturation. $1/T_2$, the effective line width in the absence of exchange, was taken as equal to the actual line width of the C^{13}H_3 - proton satellite of acetic acid.

The T^1 relaxation time of N^{14} in the methylammonium salts was obtained from slow passage records of the NH- proton resonance under conditions of negligible saturation. In spite of the low signal-to-noise ratio, results were sufficiently precise even at concentrations as low as 0.2 *M*. Typical data are shown in Fig. 2. The interpretation of the NH- proton spectra was based on Pople's theory,²⁹ and allowance was made for spin-spin interaction with the CH_3 - protons and for chemical exchange. Pople assumes in his theory that in the absence of T^1 relaxation, the NH- proton resonance is a 1:1:1 triplet of extremely sharp lines. (Line width approaches zero as $1/T^1$ approaches zero.) Chemical exchange can be introduced into the theory by assuming that in the absence of T^1 relaxation the width of each triplet line equals $R/(\text{NH})$, where R is the known rate of exchange and (NH) is the number of gram-atoms of NH- protons per liter. For any given value of T^1 and $R/(\text{NH})$, a theoretical curve that allows for spin-spin interaction with the CH_3 - protons can then be constructed by adding a 1:3:3:1 quadruplet of curves, calculated as described above, and separated by the known CH-NH spin-spin interaction of 6.17 c.p.s. The fit of theoretical curves calculated in this way to some data for methylammonium chloride is illustrated in Fig. 2. In this case, $R/(\text{NH}) = 0$, and T^1 is defined by the data with a precision of about 10%. However, for methylammonium acetate the precision is less (about ± 25) because of the relatively large value of $R/(\text{NH})$.

(27) E. Grunwald, C. F. Jumper, and S. Meiboom, *J. Am. Chem. Soc.*, **84**, 4646 (1962).

(28) S. Alexander, *Rev. Sci. Instr.*, **32**, 1066 (1961).

(29) J. A. Pople, *Mol. Phys.*, **1**, 168 (1958).

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Ionization and Proton Exchange of Amines in Acetic Acid. II. Effect of Structure on Reactivity and the Reaction Mechanism

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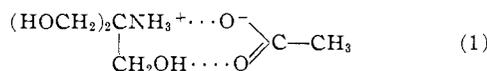
Rates of exchange of NH- with COOH- protons have been measured over a wide temperature range for a series of amines in dilute solution in acetic acid by precise nuclear magnetic resonance techniques. The ionization of these amines is nearly complete in acetic acid, the actual reactant being $\text{R}_3\text{NH}^+\text{OAc}^-$. Reaction rates were calculated from the n.m.r. data by a rigorous method that requires the data: (i) the exchange broadening of the dominant line in the NH-COOH proton system, (ii) the chemical shift of NH- relative to COOH- protons, (iii) the N^{14} -H spin-spin coupling constant of $\text{R}_3\text{NH}^+\text{OAc}^-$, and (iv) the T^1 relaxation time of N^{14} in $\text{R}_3\text{NH}^+\text{OAc}^-$. The rates of proton exchange in all cases were first order in $\text{R}_3\text{NH}^+\text{OAc}^-$, and the rate constant, k , appeared to decrease slightly with increasing concentration. The following kinetic results are reported: for $\text{NH}_4^+\text{OAc}^-$, $k(25^\circ) = 6080 \text{ sec.}^{-1}$, $\Delta H^* = 19.75 \text{ kcal.}$, $\Delta S^* = 25.0 \text{ e.u.}$; for $(\text{CH}_3)_3\text{NH}^+\text{OAc}^-$, $k(25^\circ) = 945 \text{ sec.}^{-1}$, $\Delta H^* = 16.95 \text{ kcal.}$, $\Delta S^* = 11.9 \text{ e.u.}$; for $(\text{HOCH}_2)_3\text{CNH}_3^+\text{OAc}^-$, $k(25^\circ) = 41,000 \text{ sec.}^{-1}$, $\Delta H^* \approx 20.7 \text{ kcal.}$, $\Delta S^* \approx 32 \text{ e.u.}$ Previously reported values for $\text{CH}_3\text{NH}_3^+\text{OAc}^-$, $k(25^\circ) = 230 \text{ sec.}^{-1}$, $\Delta H^* = 18.41 \text{ kcal.}$, $\Delta S^* = 14.0 \text{ e.u.}$, were also included in the analysis of the effect of structure on reactivity. The preceding rate constants for proton exchange of $\text{R}_3\text{NH}^+\text{OAc}^-$ in acetic acid are very nearly proportional to both rate and equilibrium constants for the acid dissociation of R_3NH^+ in water. Moreover, the variations with structure of ΔH and ΔS for the two processes follow similar patterns. These remarkably simple relationships suggest a close analogy of reaction mechanism. Thus in acetic acid the mechanism 13, with $\text{B} = \text{R}_3\text{N}$ and with $k_2 > k_H$, seems to fit these facts as well as some data concerning diffusion control of the reaction of acetic acid with strongly basic amines in water. The order of magnitude of k_H is estimated as 10^8 sec.^{-1} ; k_2 appears to be so large that the interactions with the surrounding dielectric in the activation step of this reaction cannot be described by a reversible electrostatic model. As a result, it is probable that k_2 is greater in acetic acid than in water, in spite of the smaller static dielectric constant of acetic acid.

In water, equilibrium and rate constants for the acid dissociation of the methyl-substituted ammonium ions

are in the well-known and peculiar sequence, $\text{NH}_4^+ \gg \text{CH}_3\text{NH}_3^+ \approx (\text{CH}_3)_2\text{NH}_2^+ < (\text{CH}_3)_3\text{NH}^+$, which

deviates from the order expected for a purely inductive effect.^{1a,b} In this paper we extend the previously reported² nuclear magnetic resonance (n.m.r.) measurements of proton exchange rates in glacial acetic acid so as to provide first-order rate constants and activation parameters for NH-COOH proton exchange for the series of substrates $\text{NH}_4^+\text{OAc}^-$, $\text{CH}_3\text{NH}_3^+\text{OAc}^-$, $(\text{CH}_3)_3\text{NH}^+\text{OAc}^-$, and $(\text{HOCH}_2)_3\text{CNH}_3^+\text{OAc}^-$ (TRIS·OAc). We find that for ammonium acetate and the methyl derivatives, the rate constants in acetic acid are in precisely the same sequence as the equilibrium and rate constants for acid dissociation in water and are, in fact, nearly proportional to the latter. Changes of enthalpy and entropy obtained for the two processes likewise display closely similar patterns of substituent effects. We believe that these simple relationships are the result of a close analogy of the reaction mechanisms and on this basis propose a plausible mechanism for proton exchange in acetic acid.

Kinetic results obtained for the highly polar substrate, TRIS·OAc, in acetic acid fit into the pattern established by the methylamines, suggesting that the cyclic complex 1, in which there are two intramolecular hydrogen bonds, is not a major subspecies.



Results

Calculation of Reaction Rates from N.m.r. Data.—

Since in our systems the ratio $[\text{B}]/[\text{BH}^+\text{OAc}^-]$ of un-ionized to ionized amine is very small, we treat the proton exchange as involving two chemical shifts, that of the carboxyl protons of acetic acid and that of the NH- protons of the ionized amine. We define the proton fraction p_B as $(\text{NH})/[(\text{NH}) + (\text{COOH})]$, where () denotes proton gram-atoms per liter and (NH) is computed on the assumption of complete ionization. Since acetic acid is the solvent, $p_B \ll 1$, and the treatment simplifies to the special case of one dominant line,³ the broadening of which is measured. The NH- protons are split into a 1:1:1 triplet by spin-spin interaction with the N^{14} nucleus, the N-H coupling constant being J .⁴ However, the quadrupole relaxation of the N^{14} nucleus, with characteristic time T^1 , has some effect on the width of the dominant line, and this is allowed for in Meiboom's treatment³ by using an *effective* coupling constant, J_{eff} (to be defined below), instead of J . Thus in the absence of exchange we have four relevant lines, the dominant carboxyl line, of intensity $1 - p_B$ and resonance frequency ω_0 ; and three NH- lines, each of intensity $p_B/3$, whose resonance frequencies differ from ω_0 by $\delta - J_{\text{eff}}$, δ , and $\delta + J_{\text{eff}}$ radians/sec., respectively. δ is the chemical shift of the NH- protons relative to the COOH- protons. Then, in the presence of exchange and for small p_B , the broadening, Δ , of the dominant line is given to a very good approximation by eq. 2.

(1) (a) H. C. Brown, *J. Am. Chem. Soc.*, **67**, 378 (1945); (b) E. Grunwald, P. J. Karabatsos, R. A. Kromhout, and E. L. Purlee, *J. Chem. Phys.*, **33**, 556 (1960).

(2) E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **86**, 2965 (1964).

(3) S. Meiboom, *J. Chem. Phys.*, **34**, 375 (1961), especially pp. 387, 388.

(4) Further splitting of the NH- proton resonance of $(\text{CH}_3)_3\text{NHOAc}$ by spin-spin interaction with the CH- protons will be neglected throughout this discussion.²

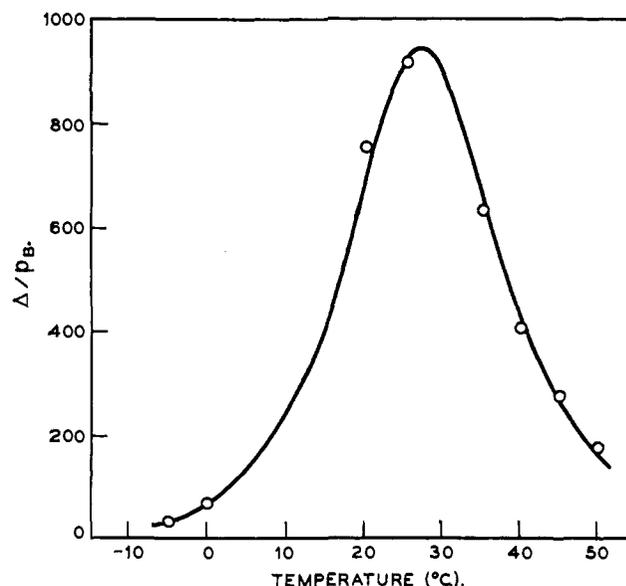


Fig. 1.—Exchange broadening as a function of temperature for 0.111 *M* ammonium acetate in acetic acid. Circles represent experimental points. Smooth curve is calculated from eq. 2, using $\delta = 1915$ radians/sec., $J = 330$ radians/sec., $T^1 = 0.01$ sec., $\log \tau T = 4318/T - 15.200$.

$$\Delta = \frac{1}{T_2'} - \frac{1}{T_2} = \frac{p_B \tau}{3} \left[\frac{(\delta - J_{\text{eff}})^2}{1 + (\delta - J_{\text{eff}})^2 \tau^2} + \frac{\delta^2}{1 + \delta^2 \tau^2} + \frac{(\delta + J_{\text{eff}})^2}{1 + (\delta + J_{\text{eff}})^2 \tau^2} \right] \quad (2)$$

$$\tau = R^{-1} \times (\text{COOH})(\text{NH})/[(\text{NH}) + (\text{COOH})]$$

R = rate of exchange, in g.-atom/l.

T_2' = exptl. value of transverse relaxation time for the dominant line

T_2 = hypothetical value, exclusive of exchange broadening; as before,² we obtained T_2 from the longitudinal relaxation time T_1 of the dominant line, using the empirical relation, $T_2 = T_1/1.14$

The *effective* coupling constant is defined by eq. 3.

$$J_{\text{eff}} = JT^1/(T^1 + \tau) \quad (3)$$

As a result of eq. 2 and 3, τ (and hence R) can be derived from Δ/p_B provided that the n.m.r. parameters δ , J , and T^1 are known. For our systems, δ is in the range 700 to 2000 radians/sec., J is about 330 radians/sec., and T^1 is in the range 0.01 to 0.0001 sec. With these values of the parameters τ is much more sensitive to error in δ than to error in J , and τ is rather insensitive to error in T^1 , a semiquantitative estimate for the latter being sufficient. Moreover, for a given error in Δ/p_B the accuracy of τ and its sensitivity to δ varies greatly for different values of $\delta\tau$.

For definiteness, consider the experimental data, Δ/p_B , obtained for ammonium acetate in acetic acid over a wide temperature range, plotted as circles in Fig. 1. The smooth curve is calculated from eq. 2, the values of the relevant parameters being stated in the figure caption. As the reaction rate and hence $1/\tau$ increases with increasing temperature, Δ/p_B increases with temperature at low temperatures, goes through a maximum near 27°, and decreases again at higher temperatures.

The broadening observed at the lowest temperatures is "lifetime broadening." When $\delta\tau \gtrsim 10$, eq. 2 reduces to 4 in good approximation, and $1/\tau$ is therefore independent of δ , J , and T^1 in this range.

$$\Delta/p_B = 1/\tau \quad (4)$$

At the temperature where Δ/p_B is at a maximum

$$1/\tau_{\max} = \delta[1 + x^2/3 + 0(x^4)] \quad (5)$$

where $x = J_{\text{eff}}/\delta$ ($< 1/2$ in our systems), and $0(x^4)$ is a small residual of order of magnitude x^4 . However, the curve calculated from eq. 2 is rather flat near the maximum. For example, when τ differs from τ_{\max} by a factor of 1.5, the decrease in Δ/p_B below the maximum value is only slightly less than 10% on either side of the maximum. Thus, near the maximum, values of τ are very sensitive to error in Δ/p_B , and this region of the curve is not particularly useful for rate measurements. However, the lack of sensitivity to τ in this region implies that Δ/p_B is essentially a function of δ and x alone, and data obtained in this region afford a convenient and rather accurate determination of δ . According to eq. 5, J and T^1 enter into this calculation only through the factor $(1 + x^2/3)$, and since $x^2/3 < 0.1$, rather large errors in J and T^1 can be tolerated.

At temperatures above that of maximum broadening, $\tau\delta$ is less than unity and decreases continuously with increasing temperature. Eventually, when $\tau\delta \lesssim 0.1$, eq. 2 reduces to

$$\Delta/p_B = \delta^2\tau[1 + 2x^2/3 + 0(x^4)] \quad (6)$$

J and T^1 enter into (6) through x . However, in our experiments $1/T^1 \lesssim \delta$; hence $1/T^1 < 0.10/\tau$ and, according to (3), $J_{\text{eff}} \approx J$. Thus Δ/p_B becomes virtually independent of T^1 as $\tau\delta$ becomes < 0.1 .

Values of J and T^1 .—For practical reasons we were constrained to obtain J and T^1 from the NH- proton resonance; J can be measured in this way only if the NH- proton resonance is a resolved triplet, and T^1 can be deduced only if τ is sufficiently long, that is, if the effect of T^1 relaxation of N^{14} is not hidden by that of NH- proton exchange. Fortunately for these measurements, solutions in acetic acid can be supercooled readily as much as 15 to 20° below their equilibrium freezing points.

Of the compounds used in this study, J could be measured in glacial acetic acid only for NH_4OAc , where the value obtained at 0° was 52 ± 1 c.p.s. However, J is apparently quite insensitive to change of solvent and to alkyl substitution on nitrogen. Thus we observed a value of 50 ± 3 c.p.s. for J of 2 M $(CH_3)_3NHCl$ in methanol at 50°, and values of 54 c.p.s. have been reported for NH_4Cl and CH_3NH_3Cl in water at 25°. ^{1b,5} We therefore adopted the single value, $J = 52$ c.p.s. (330 radians/sec.) in all calculations.

T^1 of N^{14} could also be measured for ammonium acetate in acetic acid at 0°. After correction for the effect of NH- proton exchange (Table I), line widths of the T^1 -broadened NH- proton triplet were found to be in the 3:2:3 ratio predicted by Pople's theory.⁶ T^1 is apparently not sensitive to concentration. "Best

values" obtained for T^1 in acetic acid were 0.0094 sec. for 0.11 M NH_4OAc at 0° and 0.0099 sec. for 0.74 M NH_4OAc at -10°.

We did not succeed in observing the NH- proton resonance of $(CH_3)_3NHOAc$, but we were able to make moderately precise measurements of T^1 ($\pm 30\%$) for $(CH_3)_3NHCl$. Here the NH- proton resonance is a single broad line due to the combined effects of T^1 relaxation of N^{14} and of spin-spin interaction with nine equivalent CH_3 - protons. Theoretical line shapes for comparison with the experimental records were obtained as follows. (i) We calculated theoretical NH- proton resonance curves⁶ for various T^1 , neglecting the spin-spin interaction with the CH_3 - protons. (ii) Spin-spin interaction with the CH_3 - protons produces a decuplet (ten-line multiplet) with adjacent line intensities proportional to adjacent terms in the binomial expansion of $(1/2 + 1/2)^9$. We therefore constructed a similarly weighted decuplet of the curves calculated in (i), making the spacing equal to the known CH-NH spin-spin coupling constant of 5.14 c.p.s., and then added the intensities of the ten curves to obtain the theoretical line shape for the given T^1 . Results obtained at 25° for 0.6 to 6 M $(CH_3)_3NHCl$ in acetic acid are represented within experimental error by

$$-\log T^1 = 2.60 + 0.11c \quad (7)$$

Extrapolation of (7) to $c = 0$ gives the value 0.0025 sec., for T^1 of N^{14} in $(CH_3)_3NHCl$ in acetic acid at 25°.

We estimated T^1 for $(CH_3)_3NHOAc$ from the above result and from known data² for the methylammonium system, according to eq. 8.

$$\frac{T^1_{(CH_3)_3NHOAc}}{T^1_{(CH_3)_3NHCl}} \approx \frac{T^1_{CH_3NH_3OAc}}{T^1_{CH_3NH_3Cl}} = 0.6 \quad (8)$$

Equation 8 is plausible in view of the similar molecular structures of the two cations and should be at least semi-quantitatively correct. The resulting value of T^1 for $(CH_3)_3NHOAc$ is 0.0015 sec. at 25°. To estimate T^1 at other temperatures, we assumed that $1/T^1$ is proportional to the viscosity of the solvent.⁷

For TRIS·OAc the NH- proton resonance at -5° is a single broad line, but most of the line width is due to proton exchange. To estimate T^1 , a 0.9 M solution was irradiated at -5° with a strong radio-frequency field at 4335.6 Mc., the resonance frequency of N^{14} in the given magnetic field. Irradiation induces rapid transitions between the N^{14} nuclear spin states and thus averages out the N^{14} -H spin-spin interaction to zero.⁸ Application of the radiofrequency field gave a small, barely significant reduction in the NH- proton line width of 10 ± 10 radians/sec. Thus T^1 is quite short; that is, in the absence of proton exchange the resonance would be a single, rather narrow, line. We may therefore assume that the contributions to the line width due to T^1 relaxation and chemical exchanges are very nearly additive, and that the observed reduction in width on irradiation is equal to the line broadening resulting from T^1 relaxation in the

(7) See footnote 21 of ref. 2.

(8) 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. 229.

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

(6) J. A. Pople, *Mol. Phys.*, **1**, 168 (1958).

absence of irradiation; T^1 , as calculated⁶ from this result, is $(1.4 \pm 1.4) \times 10^{-4}$ sec.

Kinetic Results for Ammonium Acetate.—The experimental results are summarized in Table I. At 25°, values obtained for Δ/p_B were almost exactly the same in 0.1 and 0.3 *M* ammonium acetate, thus showing that the proton exchange is first order in NH_4OAc to a good approximation. We therefore introduced a first-order rate constant, k , as in eq. 9, and represented the temperature dependence of k according to transition-state theory as shown in that equation.

$$R/c = k = \frac{kT}{h} e^{\Delta S^*/R} e^{-\Delta H^*/RT} \quad (9)$$

c is the formal concentration of ammonium acetate, k is the Boltzmann constant, h is the Planck constant, and ΔH^* and ΔS^* are the enthalpy and entropy of activation. For the 0.1 *M* solution, data were obtained over a wide temperature range. These data were interpreted on the basis of eq. 2 and 9, treating the quantities δ , ΔH^* , and ΔS^* as temperature-independent adjustable parameters. In this treatment, J_{eff} could be equated to J since T^1 was sufficiently long compared to τ . "Best values" obtained for the parameters are: $\delta = 1915$ radians/sec., $\Delta H^* = 19.75$ kcal., and $\Delta S^* = 25.03$ e.u. Values of Δ/p_B and of k calculated from these parameters are listed in columns 4 and 5 of Table I. The r.m.s. derivation of observed and calculated Δ/p_B for the entire 55° temperature range is only 3.9%, which we regard as very satisfactory. The parametric value of δ is also in good agreement with the corresponding chemical shift, 1955 radians/sec., obtained by direct measurement of the n.m.r. spectrum for this solution at 0°.

TABLE I
N.M.R. EXCHANGE BROADENING AND RATE CONSTANTS FOR
AMMONIUM ACETATE IN GLACIAL ACETIC ACID

c, M	Temp., °C.	Δ/p_B		$10^{-2}k$, sec. ⁻¹ ^b
		Obsd.	Calcd. ^a	
0.111	-5	33.4	33.6	1.31
	0	67.4	67.2	2.62
	20	754	711	33.8
	25	915	926	60.8
	35	631	656	185
	40	404	426	315
	45	274	265	526
0.325	50	172	163	870
	25	922	...	64.4

^a $\delta = 1915$ radians/sec., $J_{\text{eff}} = 330$ radians/sec., $R = kc$.
^b $k = 4/\tau$, $\Delta H^* = 19.75$ kcal., $\Delta S^* = 25.03$ e.u., $\log(k/T) = 15.791 - 4318/T$.

Kinetic Results for Trimethylammonium Acetate.—Rate measurements for trimethylammonium acetate were more difficult than for ammonium acetate because the chemical shift, δ , is much smaller. Results are given in Table II. Values of Δ/p_B appeared to be nearly independent of c throughout the experimental temperature range, showing that the proton exchange is very nearly first order in BH^+OAc^- . However, the small differences observed in the values were, at all temperatures, in the direction that k decreases with increasing c . The qualitative statement that k tends to decrease with increasing c is therefore probably correct, and such a trend would be consistent with results obtained for methylammonium acetate.²

The data were interpreted on the basis of eq. 2, 3, and 9, using values for J and T^1 as described in a preceding section. The following values of the required additional parameters gave "best fit": $\delta = 690$ radians/sec., $\Delta H^* = 16.95$ kcal., $\Delta S^* = 11.93$ e.u. The fit is reasonably good, as shown in Table II.

TABLE II
N.M.R. EXCHANGE BROADENING AND RATE CONSTANTS FOR
TRIMETHYLAMMONIUM ACETATE IN GLACIAL ACETIC ACID

c, M	Temp., °C.	Δ/p_B		k , sec. ⁻¹ ^b
		Obsd.	Calcd. ^a	
0.0207	15	273	272	339
.0438	15	262		
.0442	18	312	316	464
.0442	22	309	339	700
.0207	25	360	325	945
.0442	25	307		
.0553	25	331		
.0761	25	330		
.1101	25	338		
.1520	25	349		
.0207	30	254	262	1,540
.0207	35	165	190	2,470
.0438	35	172		
.0438	45	98	86	6,090
.0207	75	23	8	67,000
.0438	75	21		

^a $\delta = 690$ radians/sec., $J = 330$ radians/sec., $T^1 = 0.0015$ sec. (25°), $R = kc$. ^b $\Delta H^* = 16.95$ kcal., $\Delta S^* = 11.93$ e.u., $\log(k/T) = 12.972 - 3705/T$.

In view of the relatively small value obtained for the parameter δ , we thought it desirable to verify this value by an independent method. We did not succeed in observing the NH^- proton resonance directly for $(\text{CH}_3)_3\text{NHOAc}$. We did succeed, however, in observing this resonance for $(\text{CH}_3)_3\text{NHCl}$ and for a 4:1 mixture of the chloride and acetate at 25°. Chemical shifts⁹ of NH^- vs. COOH^- protons, obtained at several concentrations above 0.4 *M* were then analyzed according to

$$\delta_{\text{mix}} = \delta_{\text{Cl}} + p_{\text{OAc}}(\delta_{\text{OAc}} - \delta_{\text{Cl}}) \quad (10)$$

where p_{OAc} denotes the fraction of acetate in the mixture, δ_{Cl} is the chemical shift observed directly for the pure chloride at the same concentration, and δ_{OAc} is the apparent shift of the acetate. Values observed for δ_{Cl} can be represented by the empirical equation, $\delta_{\text{Cl}} = -880 + 50c$. To obtain the desired chemical shift, δ , values of δ_{OAc} were plotted vs. electrolyte concentration and the resulting relationship, which was linear, extrapolated to infinite dilution. The result was 720 ± 50 radians/sec., in good agreement with the value of 690 radians/sec. that gives "best fit" to the exchange-broadening data in Table II.

We shall now digress briefly to present a few additional kinetic results of interest. In one experiment, rate measurements based on Δ/p_B were compared directly with rate measurements based on the CH_3^- proton resonance of trimethylammonium ion (or rather, of its ion pairs). The two results agreed to better than 3%, thus showing that NH^- protons exchange at a significant rate only with COOH^- protons.

(9) The observed line positions were corrected by small amounts, as required, to allow for the effect of proton exchange. H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

The CH_3^- resonance of pure trimethylammonium chloride in acetic acid at 25° is a sharp spin-spin doublet, thus showing that proton exchange of free trimethylammonium ion or of its association products with chloride ion is negligibly slow.

Some kinetic salt effects observed for trimethylammonium acetate are listed in Table III. The effect of sodium acetate is found to be insignificant; that of trimethylammonium chloride is significant but smaller than the analogous effect found in the methylammonium system.²

TABLE III
KINETIC SALT EFFECTS ON PROTON EXCHANGE OF
TRIMETHYLAMMONIUM ACETATE IN ACETIC ACID AT 25°

<i>c</i> , M	Added salt, M	<i>k</i> , sec. ⁻¹
Dilute	None	945
0.0438	(CH_3) ₃ NHCl, 0.0209	890
.0438	.0444	870
.0438	.0986	760
.0799	.0182	960
.0799	.0430	880
.0799	.0804	800
.0206	NaOAc, .0841	930

Kinetic Results for Tris(hydroxymethyl)methylammonium Acetate.—Rate measurements for this compound are complicated by the fact that the NH^- and OH^- protons both exchange, in parallel reactions, with the COOH^- protons of acetic acid. In order to characterize the exchange of the OH^- protons, we investigated dilute solutions of the following alcohols in acetic acid: neopentyl alcohol, 2,2-dimethylpropane-1,3-diol, and pentaerythritol. Results obtained for these model substances will now be summarized: (1) Proton exchange is sufficiently fast so that the resonance of the OH^- and COOH^- protons is a single line. (2) Measurements of T_2' and T_1 show that there is significant exchange broadening. (3) The amount of exchange broadening for a given alcohol is proportional to the alcohol concentration, showing that the exchange is a first-order process. (4) The amount of exchange broadening per OH^- -equivalent per liter is roughly the same for all three alcohols. (5) The chemical shift, $|\delta_{\text{OH}} - \delta_{\text{COOH}}|$, is evaluated approximately as 2000 radians/sec. Using that value, the first-order rate constant for OH^- - COOH^- proton exchange is calculated from the exchange broadening to be 3×10^5 sec.⁻¹ per OH^- group at 25° .

The exchange broadening observed for TRIS·OAc was in all experiments much larger than that obtained for the model alcohols under comparable conditions. We analyzed the data according to eq. 11, which involves the assumptions that exchange broadening due to OH^- - COOH^- exchange is a small additive term, and that this term can be evaluated with sufficient accuracy from the actual exchange broadening, Δ_{diol} , observed for 2,2-dimethylpropane-1,3-diol under equal conditions of temperature and molar concentration. The

$$\begin{aligned}\Delta_{\text{TRIS}} &= \Delta_{\text{NH-COOH}} + \Delta_{\text{OH-COOH}} \\ &= \Delta_{\text{NH-COOH}} + \frac{3}{2}\Delta_{\text{diol}}\end{aligned}\quad (11)$$

coefficient of Δ_{diol} in (11) is a statistical factor equal to the ratio of the number of OH^- groups per molecule in the two substances. The validity of eq. 11 could be tested at -1° , at which temperature the NH^- proton

resonance is directly observable at sufficiently high concentrations as a separate, exchange-broadened line. Results obtained for *k* are: 1200 ± 300 sec.⁻¹ from the NH^- proton resonance in 0.2 M TRIS·OAc, and 1530 ± 50 sec.⁻¹ from Δ_{TRIS} and Δ_{diol} in 0.05 M TRIS·OAc.

The relevant data are summarized in Table IV. The values obtained for $\Delta_{\text{NH-COOH}}$ were interpreted on the basis of eq. 2. Instead of treating δ as an adjustable parameter as before, we used the value 1480 ± 60 radians/sec., obtained by direct measurement of $|\delta_{\text{NH}} - \delta_{\text{COOH}}|$ for 0.2 M TRIS·OAc at -1° .¹⁰ Values of *k* calculated for each experiment are listed in the final column of Table IV. At 25° , the data show a slight decrease of *k* with increasing concentration. Activation parameters, calculated according to eq. 9 from the data for the 0.05 M solution, are $\Delta H^* = 20.7$ kcal., $\Delta S^* = 32$ e.u. The error of the results for TRIS·OAc is greater than that for the other substrates, partly because of the approximations introduced through the use of eq. 11, and partly because the experimental temperatures in this series are less accurately known, being uncertain by as much as 1° .

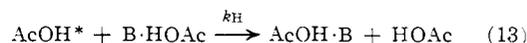
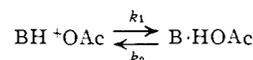
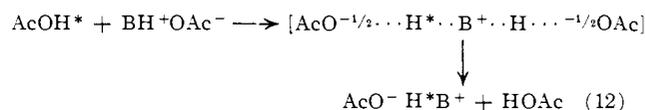
TABLE IV
N.M.R. EXCHANGE BROADENING FOR
TRIS(HYDROXYMETHYL)METHYLAMMONIUM ACETATE AND
2,2-DIMETHYLPROPANE-1,2-DIOL IN ACETIC ACID

<i>c</i> , M	Temp., °C.	Δ_{TRIS}	Δ_{diol}	$10^{-4}k$, sec. ⁻¹
0.0518	-1	4.49	0.283	1.53
.0518	14.5	3.63	.137	17.3
.0518	25	1.56	.092	41
.0891	25	2.83	.190	40
.0998	25	3.22	.207	39
.123	25	4.29	.251	35
.155	25	5.31	.320	36
.0518	35	0.475	.079	168

^a Eq. 2, 3, 11. $\delta = 1480$ radians/sec., $J = 330$ radians/sec., $T_1 = 1.4 \times 10^{-4}$ sec., $k = 3/\tau$.

Reaction Mechanism

Ammonia and the Methylamines.—The data presented in this and the preceding paper² show clearly that the reaction whose rate we have measured is the proton exchange between the ion pair BH^+OAc^- and the carboxyl group of acetic acid. The relevant kinetic results are collected in Table V. We wish to consider two possible reaction mechanisms: (i) direct electrophilic displacement (eq. 12), and (ii) a complex mechanism involving the reversible formation of unionized amine and exchange of acetic acid between the solvation shell of the amine and the bulk solvent (eq. 13).



(10) Strictly speaking, the measured chemical shift is $|\delta_{\text{NH}} - \delta_{\text{COOH,OH}}|$, where $\delta_{\text{COOH,OH}}$ refers to the single line resulting from rapid exchange of OH^- and COOH^- protons. However, for 0.2 M TRIS·OAc the resulting determinate error is less than the indeterminate error of measurement.

TABLE V
PROTON EXCHANGE IN GLACIAL ACETIC ACID COMPARED
WITH ACID DISSOCIATION IN WATER

Value at 25°	Sol- vent	-BH ⁺			
		NH ₄ ⁺	CH ₃ NH ₃ ⁺	(CH ₃) ₃ NH ⁺	TRIS ^a
<i>k</i> , sec. ⁻¹	HOAc	6080	230	945	41,000
10 ¹⁰ <i>K</i> _A , <i>M</i> ^b	HOH	5.69	0.238	1.58	84.0
<i>k</i> ₄ , sec. ^{-1c}	HOH	24.4	0.90	4.70	...
Δ <i>H</i> [*] , kcal.	HOAc	19.75	18.41	16.95	~20.7 ^d
Δ <i>S</i> [*] , e.u.	HOAc	25.0	14.0	11.9	~32 ^d
Δ <i>H</i> ^o , kcal. ^b	HOH	12.48	13.09	8.82	11.6
Δ <i>S</i> ^o , e.u. ^b	HOH	-0.5	-4.7	-15.2	+1.8
<i>K</i> _i ^e	HOAc	4 × 10 ⁴	8 × 10 ⁵	1.3 × 10 ⁵	2.4 × 10 ²
<i>K</i> _i / <i>k</i> , sec. ⁻¹	HOAc	2.2 × 10 ⁸	1.9 × 10 ⁸	1.2 × 10 ⁸	1.0 × 10 ⁸

^a TRIS = (HOCH₂)₃CNH₃⁺. ^b R. G. Bates and G. D. Pinching, *J. Res. Natl. Bur. Std.*, **42**, 419 (1949); **43**, 519 (1949); D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc. (London)*, **A177**, 499 (1941). ^c Ref. 1b and 14. The value of *k*₄ for CH₃NH₃⁺ is estimated from *K*_A, assuming that the reaction of CH₃NH₂ with H⁺ is diffusion controlled. We believe that this estimate is reliable to ±30%. ^d Result of lower accuracy. ^e *K*_i = 2 × 10⁹*K*_B, where *K*_B is the base dissociation constant in water; see footnote 11.

Application of mechanism i to our kinetic results presents problems. First of all, the ammonium or alkyl ammonium ion, BH⁺, is a poor electron donor, and we would hardly expect direct electrophilic displacement to proceed with a rate constant as high as *k*. Secondly, the kinetic data do not show any of the manifestations of steric hindrance resulting from methyl substitution on nitrogen that we would have expected for this mechanism. We therefore believe that mechanism i can be ruled out.

On the other hand, the data provide strong evidence that a mechanism involving the formation of un-ionized amine is probably correct. Perhaps the most striking feature of the data is the extraordinary analogy between the effects of methyl substitution on *k* for proton exchange in acetic acid and the corresponding effects on equilibrium constants (*K*_A) and rate constants (*k*₄) for acid dissociation in water. Not only do the values of *k*, *K*_A, and *k*₄ (Table V) all fall in the same sequence, NH₄⁺ >> CH₃NH₃⁺ < (CH₃)₃NH⁺, but these quantities are very nearly proportional to each other, as shown in Fig. 2. In addition, there is a qualitative resemblance of substituent effects on Δ*H* and Δ*S* that is unmistakable in spite of the larger experimental errors. Values of Δ*S*^{*} for proton exchange in acetic acid and Δ*S*^o for acid dissociation in water are both in the sequence, NH₄⁺ > CH₃NH₃⁺ > (CH₃)₃NH⁺, which is different from that of *k* and *K*_A. And values of Δ*H*^{*} and Δ*H*^o for the two processes are at least approximately in the common sequence, NH₄⁺ ≈ CH₃NH₃⁺ > (CH₃)₃NH⁺.

Relative Magnitude of *k*₂ and *k*_H.—Using rate constants as defined in (13), the observed value of *k* is given according to mechanism ii by

$$k = k_1 k_H / (k_2 + k_H) \quad (14)$$

There are two limiting cases: (a) *k*_H >> *k*₂, which implies that *k* = *k*₁. In case (a), proton transfer within the hydrogen-bonded acid-base pair, BH⁺OAc⁻ → B·HOAc, is rate determining. (b) *k*₂ >> *k*_H, which implies that *k* = (*k*₁/*k*₂)*k*_H = *K*_i⁻¹*k*_H, where *K*_i is the ionization constant of the amine in acetic acid.

It has been suggested that *K*_i for amines can be estimated by simple proportion from the base dissociation constants in water, the ratio *K*_i/*K*_B being

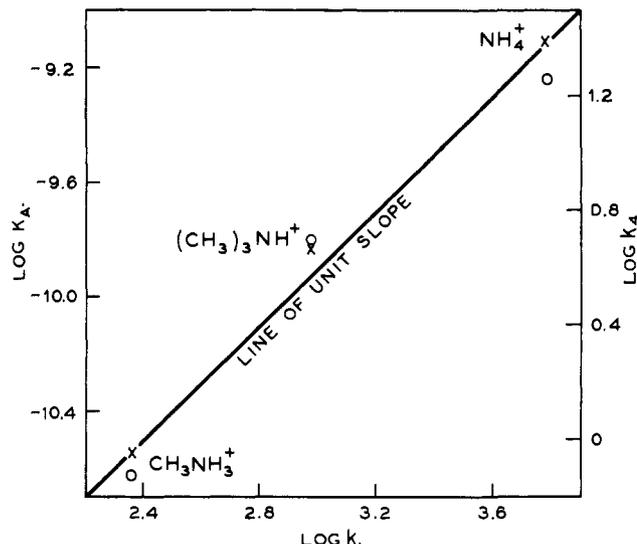
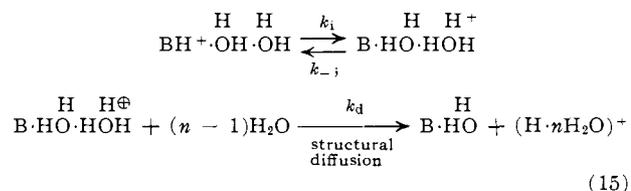


Fig. 2.—Rate constants (*k*) for proton exchange in acetic acid compared with equilibrium constants (*K*_A) and rate constants (*k*₄) for acid dissociation in water: O, *K*_A; X, *k*₄.

about 2 × 10⁹.^{2,11} Values of *K*_i estimated in this way and the corresponding values of *kK*_i are listed in Table V. In case a the values obtained for *kK*_i, which are of order 10⁸ sec.⁻¹, measure *k*₂; in case b they measure *k*_H.

We believe that case b represents reality and shall present two independent arguments to support this belief. The first is an argument by analogy. We infer from the marked resemblance of substituent effects, noted above, that the reaction mechanisms for proton exchange in acetic acid and for acid dissociation in water are closely similar. The mechanism of acid dissociation in water is represented best by an ionization-dissociation model¹² such as that shown in eq. 15, which is closely analogous to that shown in eq. 13.



The first step in both eq. 13 and 15 is a proton transfer within a hydrogen-bonded complex to produce a conjugate acid-base pair; the second step in both is a diffusional process. The ratio *k*_{-i}/*k*_d in (15) is therefore analogous to *k*₂/*k*_H in (13). Now it is probable that *k*_{-i}/*k*_d > 1. This follows from microscopic reversibility because the reverse reaction, between amine and hydrogen ion, appears to take place rapidly at each encounter,

(11) In view of the enormously high rate constants associated with proton transfer in some cases, it is possible that the ratio *K*_i/*K*_B changes from one constant value for small *K*_i to a higher constant value for large *K*_i, as *K*_i passes through unity. Suppose that the shorter of the two lifetimes in the mobile prototropic system B·HOAc = BH⁺OAc⁻ is shorter than the dielectric relaxation time of the solvent. It then follows that the interaction of the system with the surrounding dielectric cannot be reversible in the electrostatic sense. If BH⁺OAc⁻ is the species with the very short life (*K*_i << 1), the effective dielectric constant of the solvent will be that resulting from distortion polarization alone. If B·HOAc is the species with the very short life (*K*_i >> 1), the dielectric interaction will resemble the model shown in Fig. 3b. Thus, if the irreversible model applies, the stabilization of BH⁺OAc⁻ by interaction with the dielectric is greater when *K*_i >> 1. Since the factor 2 × 10⁹ for *K*_i/*K*_B is based on data with *K*_i ≈ 1, the correct factor for *K*_i >> 1 could be larger, and the estimates of *K*_i in Table V could be too small.

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

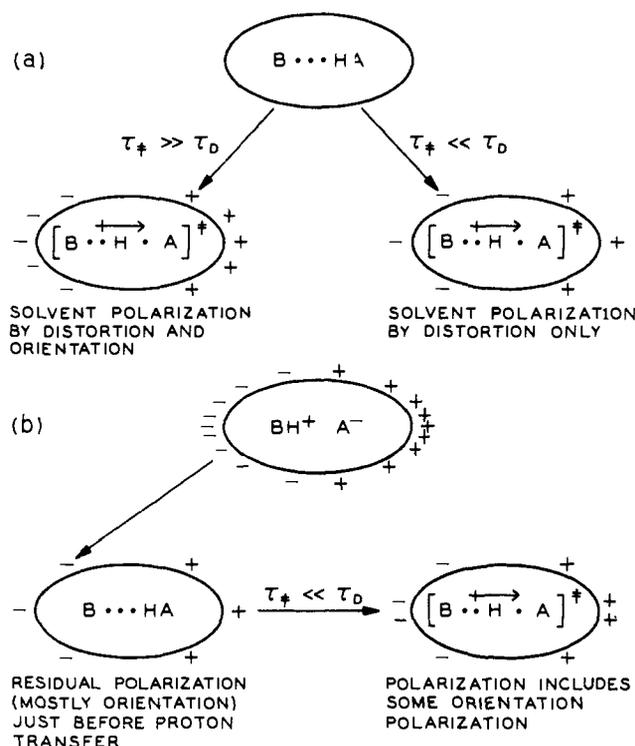


Fig. 3.—Models for the interaction of reactants and transition state in the prototropic system $B \cdot HOAc = BH^+ \cdot OAc^-$ with a surrounding dielectric.

provided only that the reaction zones are appropriately juxtaposed.^{13,14} Analogy then requires that k_2/k_H is also greater than unity.

Medium Effect on k_2 . Irreversible Aspects of Dielectric Interaction.—The second argument begins with some kinetic data in water and considers the medium effect on k_2 . Eigen and Maas¹⁵ have measured rate constants between acetic acid and a series of amines in water. They find that for weakly basic amines the rate constant increases with the base dissociation constant, but when K_B exceeds about 10^{-7} , the reaction rate becomes limited by the number of encounters. This means that for ammonia and the alkylamines in water, for which $K_B \gg 10^{-7}$, the quantity $k_2\tau_e$ (which is the analog of k_2/k_H) is much greater than unity, where τ_e is the mean duration of the appropriate encounter and k_2 , as before, is the probability *per second* of proton transfer during the existence of the encounter.

Since k_H in acetic acid is not likely to be much greater than $1/\tau_e$ in water (acetic acid is more viscous than water), we may infer that $k_2/k_H > 1$ in acetic acid if the medium effect on k_2 is relatively small. This is probably the case.

The simplest argument makes use of a reactivity-selectivity relationship.¹⁶ We have seen that in water k_2 must be very large, almost certainly greater than 10^{10} sec.⁻¹. Such a high rate constant implies, with a high probability, that the transition state closely resembles

(13) M. Eigen and L. De Maeyer, *Proc. Roy. Soc. (London)*, **A247**, 505 (1958); in "Structure of Electrolytic Solutions," W. J. Hamer, Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, Chapter 5.

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

(15) M. Eigen and G. Maas, data cited by M. Eigen and L. De Maeyer, "Investigation of Rates and Mechanisms of Reactions," S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1040.

(16) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, pp. 162-168.

the initial un-ionized state with respect to structure and charge distribution.¹⁷ Medium effects, which reflect differences of the two states with the solvent, should therefore be small.

In view of the occasional failure of the reactivity-selectivity relationship,¹⁶ we shall develop an alternative argument that does not require the transition state to be essentially un-ionized. Medium effects on the rate constants of polar reactions are normally dominated by interactions depending on the dielectric properties of the solvent. The magnitude of such interactions will depend, among other variables, on the relative values of τ_D , the dielectric relaxation time of the solvent, and of τ_* , the mean time required for transition from the initial state to the transition state of the reaction. If $\tau_* \gg \tau_D$, then the interaction with the dielectric can be treated as reversible and the solvent polarization as being in equilibrium with the charge distribution of the reacting system both in the initial state and in the transition state. If $\tau_* < \tau_D$, then the permanent dipoles of the solvent molecules do not have time to come into equilibrium with the changing charge distribution of the reacting system and the solvent polarization due to orientation is essentially constant. These relationships are illustrated in Fig. 3a for a model of ionization in which the initial state, $B \cdot HA$, is nonpolar, and the transition state has a dipole moment between zero and that of the product, BH^+A^- . We now wish to discuss the medium effect on k_2 due to dielectric interactions according to this model, allowing the transition state to be polar.

Dielectric relaxation times are about 10^{-11} sec. for water¹⁸ and 10^{-10} sec. for glacial acetic acid.¹⁹ The time required for activation cannot exceed the lifetime of the initial state, and τ_* must therefore be less than $1/k_2$. In water, $1/k_2 < \tau_e$, the lifetime of the appropriate encounter, and we therefore have the inequalities $\tau_* < 1/k_2 < \tau_e$. Since relaxation times for diffusional processes in liquids are normally not longer than those for rotational processes, τ_e is probably at most of the order of magnitude of τ_D , and τ_* is therefore probably less than τ_D . In terms of Fig. 3a, this implies that the model on the right, in which the transition state is stabilized only by distortion polarization, is probably correct. If we adopt this model, then the transition state will be more stable in acetic acid than in water because acetic acid, which has the greater optical refractive index, will develop more distortion polarization than will water.

Figure 3b shows that the dielectric effect of acetic acid might, in the reactions studied in this investigation, be even more favorable than one would expect on the basis of Fig. 3a, because the un-ionized complex $B \cdot HA$ is formed directly from the highly polar ion pair, $BH^+ \cdot A^-$. The lifetime of $BH^+ \cdot A^-$ is sufficiently long for the polarization of the acetic acid solvent to reach the equilibrium value. On the other hand, the lifetime, $1/k_2$, of $B \cdot HA$ is probably not longer than τ_D . When $B \cdot HA$ is formed from $BH^+ \cdot A^-$, the solvent shell surrounding it will still have some of the orientation polarization originally associated with $BH^+ \cdot A^-$, and this polarization will not have time to decay to zero

(17) J. E. Leffler, *Science*, **117**, 340 (1953).

(18) G. H. Haggis, J. B. Hasted, and T. J. Buchanan, *J. Chem. Phys.*, **20**, 1452 (1952).

(19) P. Girard and P. Abadie, *J. chim. phys.*, **44**, 313 (1947).

