An excellent overall agreement is seen between the experimentally determined spin density distributions and those predicted by the molecular orbital calculations.

Several theoretical accounts have been reported concerning a bent structure, hence the nonequivalence of the β protons, of the vinyl radical,[20-22] and the sign of the isotropic coupling constant to its α proton.[3] The results of the present esr study show that, while the vinyl radical is bent, the propargyl and butatrienyl radicals possess a linear acetylenic section -C-C-H. This conclusion is not surprising since any bending of the latter radicals would have to occur at the expense of the optimum delocalization in the π-electron system. We have carried out INDO molecular orbital calculations of these radicals and examined the dependency of the total energy as well as those of the isotropic coupling constants of the protons upon the angle ϕ. The results are depicted in Figure 7. The calculations clearly show the energy minimum for the vinyl radical at $\phi = 30°$. Also, although the calculated isotropic coupling constant to the α proton is still negative at this angle, the predicted dependency of the coupling constant upon ϕ provides a strong support to our experimental assignment of positive sign to this coupling. The dependency upon ϕ of the isotropic coupling constants to β protons is essentially the same as those given by valence bond or CNDO type calculations.[20,22]

As expected, no energy minima were found for the propargyl and butatrienyl radicals away from the linear configuration. Surprisingly the calculations also showed that, for these radicals, neither the isotropic coupling constant of the acetylenic proton nor those of the methylene protons change appreciably when the acetylenic section -C-C-H is bent.[23]

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(20) F. J. Adrian and M. Karplus, *J. Chem. Phys.*, **41**, 56 (1963).

(21) W. T. Dixon, *Mol. Phys.*, **9**, 201 (1965).

(22) N. M. Atherton and A. Hinchliffe, *ibid.*, **12**, 349 (1967).

(23) This aspect on propargyl had been reported by Kochi and Krusic in ref 2.

Quatermolecular Proton Transfer of 2,4-Lutidine and Its Conjugate Acid in Aqueous Solution[1a]

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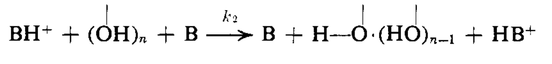
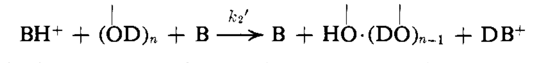
Abstract: Symmetrical proton exchange between 2,4-lutidine and its conjugate acid in aqueous solution proceeds with participation of (on the average) 1.74 water molecules in H_2O and 1.8 water molecules in $HOD-D_2O$ (5 atom % H). Within the experimental error both processes could be precisely quatermolecular; second-order rate constants at 25° are 1.05×10^8 sec^{-1} M^{-1} in H_2O and 0.26×10^8 sec^{-1} M^{-1} in $HOD-D_2O$. The high values of these rate constants, in spite of the quatermolecular nature of the reaction, indicate strong hydrogen-bonded solvation of at least one of the reactant solutes. The mechanism of acid dissociation of 2,4-lutidinium ion has been reexamined on the basis of kinetic $HOD-D_2O$ solvent isotope effects and salt effects. The initial product of acid dissociation may be a lutidine molecule that is *not* hydrogen bonded to a water molecule at the nitrogen atom.

We wish to report a kinetic study, using nuclear magnetic resonance (nmr), of proton exchange in aqueous solutions of 2,4-lutidine (2,4-dimethylpyridine, B) and 2,4-lutidinium ion (BH^+). We find that proton transfer involving BH^+, B, and water is largely quatermolecular. For reaction 1 in H_2O at 25°, the (second-order) rate constant k_2 is 1.05×10^8 sec^{-1} M^{-1}, and $n = 1.74$.

 (1)

$$\mathrm{BH^+ + (\overset{H}{O}H)_n + B \xrightarrow{k_2} B + H{-}\overset{H}{O}{\cdot}(\overset{H}{H}O)_{n-1} + HB^+} \qquad (1)$$

For reaction 2 in 5% $HOD-D_2O$ (5 atom % H) at 25°, $k_2' = 2.6 \times 10^7$ sec^{-1} M^{-1} and $n = 1.8$.

 (2)

$$\mathrm{BH^+ + (\overset{D}{O}D)_n + B \xrightarrow{k_2'} B + H\overset{D}{O}{\cdot}(\overset{D}{D}O)_{n-1} + DB^+} \qquad (2)$$

Within the experimental error, n could be precisely 2 in both cases. Our kinetic results in H_2O overlap in part with earlier work,[2] and the agreement is satisfactory.

For fast symmetrical proton-exchange reactions involving an acid, its conjugate base, and water or alcohol, previous *direct measurements* had led to the result that $n > 1$ only for the reaction of imidazolium ion with imidazole in water, where $n = 1.42 \pm 0.19$ at 25°.[3] There is indirect evidence (from reaction diameters and rate equations) that $n > 1$ for the reactions, in water, of H_3O^+ with OH^-, SO_4^{2-}, and $(CH_3)_3N$ and for the reaction of $H_2PO_4^-$ with HPO_4^{2-}.[4-7]

The participation of two or more water molecules in a fast proton-transfer reaction indicates that the hydrogen-bonded solvation of the reactants is strong.

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(2) M. Cocivera, *J. Phys. Chem.*, **72**, 2520 (1968).

(3) E. K. Ralph and E. Grunwald, *J. Amer. Chem. Soc.*, **90**, 517 (1968).

(4) M. Eigen and L. DeMaeyer, *Proc. Roy. Soc., Ser. A*, **247**, 505 (1958).

(5) H. Chen and D. E. Irish, *J. Phys. Chem.*, **75**, 2672 (1971).

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

(7) Z. Luz and S. Meiboom, *J. Amer. Chem. Soc.*, **86**, 4764 (1964).

This is because processes of high molecularity (quatermolecular or higher) are inherently improbable and will proceed rapidly only if the water molecules are "*locked*" (by strong interaction with B and/or BH^+) *into configurations permitting rapid proton transfer.* It has been proposed in previous publications from this laboratory[8] that London dispersion forces play an important role in hydrogen-bonded solvation. The present results are consistent with this proposal because the molecules of 2,4-lutidine and of its conjugate acid may be said to be strong centers of van der Waals attraction for the hydrogen-bonded water molecule at the 1 position, owing to the presence of the polarizable π-electron system and the nearby 2-methyl group.

In describing reactions 1 and 2 as largely quatermolecular, we have made the tacit assumption that these reactions take place in a single step, that is, the transfer of the $n + 1$ hydrogen ions (H^+ or D^+) is a concerted process. The magnitude of the $HOD-D_2O$ solvent isotope effect is consistent with this assumption. For 2,4-lutidinium ion we find that $k_2'/k_2 = 0.25$. For the analogous reactions of trimethylammonium ion, where $n = 1$,[9] k_2'/k_2 has been reported to be 0.6,[10] substantially closer to unity.[11]

We have also examined the $HOD-D_2O$ solvent-isotope effect on the rate constant for acid dissociation of 2,4-lutidinium ion and have obtained evidence that the reaction mechanism may be different from that for aliphatic ammonium ions.[12]

Experimental Section

Reagents and Solutions. Aldrich 2,4-lutidine (2,4-dimethylpyridine) was examined for impurities by gas chromatography and estimated to be about 99% pure. The reagent was diluted with two parts by volume benzene. Hydrogen chloride (from sodium chloride and sulfuric acid) was bubbled through the solution. The precipitated hydrochloride was recovered, dried, and recrystallized from ethanol. The final product was dried and stored in a desiccator. Stock solutions were prepared by weighing the recrystallized reagent into a volumetric flask, adding H_2O or D_2O to volume, and weighing the solution. All concentrations were known on a molar and moles per gram of solution basis. At the beginning, in the middle, and toward the end of these investigations new stock solutions were prepared and the titer was checked by titration with sodium hydroxide. The titer was 100.6, 101.0, and 100.5% of the theoretical value. Silver nitrate titration of the final solution gave 100.1% of the theoretical value. The titer obtained by titration was employed.

New England Nuclear deuterium oxide (99.7 atom % deuterium) was distilled prior to use, as was the Yeda-Miles ^{17}O enriched water.

DCl in D_2O was prepared from Aldrich dichlorodimethylsilane[13] and D_2O. NaOD was prepared from a very concentrated solution of NaOH in D_2O. All NaOH, NaOD, HCl, and DCl solutions were standardized.

Solutions for the nmr measurements were prepared from stock solutions and pure solvent by quantitative dilution. If water enriched in ^{17}O and/or D was used, the isotopic composition of the final solutions was calculated from the amounts of natural and enriched water used, the isotopic composition of natural water, and the isotopic composition of the enriched water as supplied by the manufacturer.

p_cH and p_cK_A Determinations. Method A. Initially p_cH measurements were made by using a Beckmann 39030 combination glass electrode with a 4 M KCl silver-silver chloride reference electrode having a ceramic junction. To determine p_cH ($= -\log c_H$) for the solutions used in the nmr measurements, the Beckmann Research pH meter was adjusted to a pH of 4.008 for a solution of 0.05 F NBS potassium acid phthalate, and the pH of the solutions was measured on the same scale. However, the pH scale differs from the p_cH scale owing to activity coefficients and differences in liquid junction potentials. The difference is a function of the lutidine hydrochloride (BH^+Cl^-) concentration and appeared also to depend on the pH. Assuming a linear dependence on pH, we calculated p_cH for each series (at fixed $[BH^+Cl^-]$) from eq 3, where a and b are "constants" characteristic of the given lutidine hydrochloride concentration. To evaluate a and b, pH measurements

$$p_cH = pH + [a + b(pH)] \qquad (3)$$

were made on: (a) a solution containing the desired concentration of BH^+Cl^- and a known concentration (usually 2.50×10^{-2} or $5.00 \times 10^{-3} M$) of excess HCl; (b) a 2,4-lutidine buffer having practically the same total ($B + BH^+$) buffer concentration and ionic strength. Since the buffer ratio and p_cK_A (determined by method B) were known, p_cH could be calculated.

The correction term $[a + b(pH)]$ was checked frequently during the course of each series of nmr measurements, using solution (a). Whatever small changes occurred were used to adjust the value of a. The magnitude of $[a + b(pH)]$ was less than 0.1; that of b was 0.02 or less. Method A was somewhat unsatisfactory because equilibrium across the liquid junction was established slowly (15–30 min) and because of the need for a pH-dependent correction term which appeared to be due to the liquid junction.

Method B. A Beckman General Purpose glass electrode was used together with a silver-silver chloride reference electrode. Both electrodes were immersed directly into the solution to be measured, so that there was no liquid junction. The silver-silver chloride electrode was made from 18 or 22 gauge silver wire. The end immersed in the solution was shaped into a coil (five or six turns of 0.5-in. diameter) and was covered electrolytically with a thin coating of silver chloride. In most cases, electrode equilibrium was reached in 10 min.

The cell emf, E, was measured with a Corning Model 112 research pH meter. At 25°, E is given by eq 4, where E^* is a constant for the

$$E = E^* - 0.059155 \log c_{Cl} - 0.059155 \log y_H y_{Cl} + 0.059155\ p_cH \qquad (4)$$

electrodes. The molar concentration of chloride was known and the molar activity coefficients y_H and y_{Cl} were calculated using appropriate modifications of the Debye-Hückel equation.[14] The validity of eq 4 was checked with known solutions of HCl, HCl + NaCl, and HCl + BH^+Cl^-. E^* was found to be constant within 0.3 mV. Moreover, E^* was checked frequently during the course of each series of experiments with a known solution of type (a) described in method A. In most cases, the values did not vary by more than ±0.3 mV, and there were no systematic drifts. E^* changed by about 1 mV during the 5 months in which the electrodes were used.

The acid dissociation constant, K_A, of 2,4-lutidinium ion was measured at 25.0° in H_2O and also in an $HOD-D_2O$ solvent having 0.0567 atom fraction of H. In H_2O, 12 sets of measurements were made on solutions in which $[B]/[BH^+]$ varied from 0.5 to 2 and $[B] + [BH^+]$ varied from 0.06–0.12 M. p_cH was determined as described above. There was no significant variation of p_cK_A ($= p_cH - \log [B]/[BH^+]$) with concentration or buffer ratio. The mean p_cK_A was 6.716 and the standard deviation from the mean was 0.004. In $HOD-D_2O$, seven sets of measurements were made in which $[B] + [BH^+]$ was 0.06 M. Under these conditions, p_cK_A was found to be 7.096 ± 0.003.

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[8] (a) E. Grunwald and E. Price, *J. Amer. Chem. Soc.*, **86**, 4517 (1964); (b) E. Grunwald and E. K. Ralph, *ibid.*, **89**, 4405 (1967); (c) E. Grunwald, R. L. Lipnick, and E. K. Ralph, *ibid.*, **91**, 4333 (1969); (d) D.-W. Fong and E. Grunwald, *J. Phys. Chem.*, 73, 3909 (1969).

[9] Z. Luz and S. Meiboom, *J. Chem. Phys.*, **39**, 366 (1963).

[10] R. J. Day and C. N. Reilly, *J. Phys. Chem.*, **71**, 1588 (1967).

[11] In calculating the value of k_2', Day and Reilly[10] have assumed a reaction mechanism in which rotation of the water molecule in the termolecular complex $BH^+ \cdot OD_2 \cdot B$ is fast compared to proton transfer. We have assumed in our calculations that, on the contrary, rotation of the water molecule(s) is slow compared to proton transfer in the reactive complex. If we recalculate Day and Reilly's results on the basis of our mechanism, we find that (in their notation) $\rho = 2$, and $k_2'/k_2 = 0.85$.

[12] E. Grunwald and E. K. Ralph, *Accounts Chem. Res.*, **4**, 107 (1971). These authors use the symbol k_a' to denote reaction by the process shown in our eq 14 while we use primed symbols to denote rate constants in $HOD-D_2O$.

[13] W. H. Greive and K. F. Sporek, *J. Chem. Educ.*, **43**, 381 (1966).

[14] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 469.

Rate Measurements. Rates of proton exchange were measured at 25.2° with a Varian HR-60 nmr spectrometer operating at 56.4 MHz, which had been modified to permit the measurement of longitudinal (T_1) and transverse (T_2) relaxation times by pulsed nmr techniques. This equipment has been in use in this laboratory for a number of years. Midway through the present measurements, the energizing coils around one pole of the electromagnet shorted out and had to be replaced. At the same time, the preamplifier tube in the detector was replaced and repairs were made to the superstabilizer. These changes resulted in a marked improvement in the signal-to-noise ratio, but unfortunately the changes also brought on a slight but significant (and unexplained) change in the measured rates of proton exchange. In the following, "condition A" will refer to measurements made before the repair, and "condition B" to results obtained afterward.

Rates of proton exchange were determined (1) between OH protons of water and NH protons of BH^+, and (2) in ^{17}O enriched water among the water molecules. As in previous publications,[15] T_1 and T_2 were measured[16] for the dominant (OH or coalesced OH + NH) proton nmr line.[2,17] The broadening due to exchange, Δ, was calculated from T_2 and T_1 according to eq 5, where ϵ is a

$$\Delta = 1/T_2 - 1/T_1 - \epsilon \tag{5}$$

small correction term which amounted to less than 5% of Δ.[18] For measurements in H_2O, ϵ was taken as equal to $(1/T_2 - 1/T_1)$ for 0.0125 F HCl where Δ is known to be practically zero. For measurements in $HOD-D_2O$, ϵ was taken similarly as $(1/T_2 - 1/T_1)$ for 0.0025 F DCl. In the H_2O experiments, both T_2 and T_1 were measured for each reaction mixture. In the $HOD-D_2O$ experiments, T_2 was measured for each reaction mixture, but direct measurement of T_1 was difficult in the presence of BH^+Cl^- owing to interference beats from the nmr of the methyl protons, and T_1 was assumed to have the value obtained for 0. 0025 F DCl. This approximation introduced no appeciable error because $1/T_1$ is small (0.095 sec^{-1} at 25.2°) and the solutions were dilute.

Rate Calculations. Because of double isotopic labeling (D and ^{17}O), more variables are involved than in previous rate calculations.[15] We shall use the following symbols.

L	any hydrogen isotope, H or D.
p	$[BL^+]/([BL^+] + 2[L_2O])$, site fraction of BL^+ in the L_2O-BL^+ hydrogen-exchanging system.
f	atom fraction of H in the L_2O-BL^+ hydrogen-exchanging system.
g	atom fraction of ^{17}O in the water (L_2O).
τ_{NH}	mean time a proton resides on BH^+ during one cycle of proton exchange between BH^+ and water.
τ_w	mean lifetime of an OH bond of a water molecule during one cycle of $^{17}OH-OH$ exchange.

On the basis of previous experience[19] we shall assume a random distribution of hydrogen isotopes between BL^+ and L_2O; hence $f = [BH^+]/[BL^+]$. Moreover, in the present experiments p and g are quite small (<0.01). We may therefore represent the exchange broadening, Δ, of the dominant (OH or coalesced OH + NH) proton resonance as the sum of additive contributions from NH-OH and $^{17}OH-OH$ exchange.

$$\Delta = \Delta_{NH} + \Delta_{^{17}OH} \tag{6}$$

Since $(1 - p) \approx (1 - g) \approx 1$, these contributions are given in good approximation by eq 7-9.

$$\Delta_{NH} = p\delta^2\tau_{NH}/(1 + \delta^2\tau^2_{NH}) \tag{7}$$

$$\Delta_{^{17}OH} = \frac{g}{3}\sum_{i=1}^{3} j_i^2\tau_w \Big/ (1 + j_i^2\tau_w^2) \tag{8}$$

$$2j_i = (2i - 1)J(T^1/[T^1 + \tau_w]) \quad i = 1, 2, 3 \tag{9}$$

Equation 7 is the familiar expression for exchange broadening due to two-site exchange when $p << 1$; δ is the NH-to-OH chemical shift, in radians per sec. This equation neglects the effect of $^{14}N-H$ spin-spin interaction,[20] which is indeed negligible in the present case.

Equation 8 was derived by Meiboom[17] for proton exchange among water molecules. The parameters j_i are defined in (9), where J is the $^{17}O-H$ spin-spin interaction, in radians per sec, and T^1 is the longitudinal relaxation time of ^{17}O.

In practice, Δ was always measured under conditions where either Δ_{NH} or $\Delta_{^{17}OH}$ was quite small. To evaluate Δ_{NH} (and hence τ_{NH}), measurements were made in water of ordinary ^{17}O abundance at pH <5, where $\Delta_{^{17}OH}$ is well below the experimental error. To measure $\Delta_{^{17}OH}$ (and hence τ_w), measurements were made in water containing 0.2-1.0 atom % ^{17}O at pH >6, where Δ_{NH} is at most of the order of the experimental error. In the latter case, Δ_{NH} could be predicted well enough by means of the rate law for $1/\tau_{NH}$ established at pH <5.

The value of δ (eq 7) was determined by varying the pH (thus changing τ_{NH}) until the maximum value of Δ_{NH}/p was determined. The latter equals $\delta/2$. In H_2O, this maximum occurred at 0.4-0.5 F HCl, and the corresponding result for δ was corrected for the presence of HCl.[21] Results at 56.4 MHz and 25.2° were: in H_2O, $\delta = 3376 \pm 60$ rad/sec; in $HOD-D_2O$, $\delta = 3300 \pm 60$ rad/sec when $f = 0.05$. A value of 3313 rad/sec in H_2O at 56.4 MHz is calculated from results reported by Cocivera.[2]

The value of J (eq 9) was determined similarly by fitting $\Delta_{^{17}OH}/g$ in the vicinity of its maximum. The result, which gave "best fit" in H_2O and close to "best fit" in $HOD-D_2O$, is 606 ± 30 rad/sec at 25.2°. The value used for T^1 was 0.0069 sec in H_2O and 0.0067 sec in $HOD-D_2O$.[22] Our result is in good agreement with the value, J = 612 rad/sec in H_2O, reported by Luz and Meiboom.[9]

Results

NH-to-OH Proton Exchange. Using the nmr methods described in the preceding section, $1/\tau_{NH}$ was obtained as a function of 2,4-lutidinium ion concentration and pH at 25.2°. For purposes of kinetic analysis, $1/\tau_{NH} = R_{NH}/[BH^+]$, where R_{NH} is the *rate* of NH-to-OH exchange. In H_2O, R_{NH} is simply the rate of H-H exchange, but in $HOD-D_2O$, it is the sum of the rates of H-H and H-D exchange.[23] However, if the proton fraction $f \ll 1$, the rate of H-H exchange is relatively small, and R_{NH} in $HOD-D_2O$ is essentially the rate of H-D exchange. In our experiments, $f = 0.0541$. Although this is not quite as small as we would like, the approximation that R_{NH} is equal to the rate of H-D exchange is tolerable and will be made throughout this paper. Consistently with this approximation we shall assume that $(1 - f) \approx 1$. Thus, rate constants reported for H-D exchange may be too high by as much as 15%, but this error will tend to cancel in the calculation of n.

Kinetic results at p_cH values between 1.7 and 4.3 in H_2O and p_cL values between 2.0 and 5.0 in $HOD-D_2O$ could be represented satisfactorily by the rate laws (10) and (11). For H-H exchange in H_2O

$$1/\tau_{NH} = k_a + k_2[B] = k_a + k_2K_A[BH^+]/[H^+] \tag{10}$$

For H-D exchange in $HOD-D_2O$

$$1/\tau_{NH} = k_a' + k_2'[B] = k_a' + k_2'K_A'[BL^+]/[L^+] \tag{11}$$

We interpret these rate laws as follows: k_2 and k_2' are rate constants for reactions 1 and 2; k_a and k_a' are rate

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(15) See, for example (a) E. Grunwald and M. S. Puar, *J. Phys. Chem.*, **71**, 1842 (1967); (b) D.-W. Fong and E. Grunwald, *J. Amer. Chem. Soc.*, **91**, 2413 (1969).

(16) T_2 was measured by the spin-echo method described by S. Meiboom and D. Gill, *Rev. Sci. Instrum.*, **29**, 688 (1958). T_1 was measured using the null method of H. Y. Carr and E. M. Purcell, *Phys. Rev.*, **94**, 630 (1954).

(17) Nmr line broadening due to exchange between a dominant line and one or a number of weak lines has been treated by S. Meiboom, *J. Chem. Phys.*, **34**, 375 (1961).

(18) Equation 5 is equivalent to Cocivera's eq 6 since $1/T_1 + \epsilon = 1/T_2^0$, as defined by Cocivera.[2]

(19) (a) C. G. Swain and M. M. Labes, *J. Amer. Chem. Soc.*, **79**, 1084 (1957); (b) P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Phys. Chem.*, **68**, 410 (1964); (c) unpublished experiments for $Pt(NH_3)_6^{4+}$ in water by D.-W. Fong and E. Grunwald.

(20) E. Grunwald and E. Price, *J. Amer. Chem. Soc.*, **86**, 2965 (1964).

(21) G. C. Hood, O. Redlich, and C. A. Reilly, *J. Chem. Phys.*, **22**, 2067 (1954).

(22) B. B. Garrett, A. B. Denison, and S. W. Rabideau *J. Phys. Chem.*, **71**, 2606 (1967).

(23) For a full discussion, see ref 19a.

constants for acid dissociation of BH^+ (*i.e.*, the transfer of a proton from BH^+ to H_2O).[12]

There is evidence, from studies of nucleophilic reactivity, that pyridine and methyl-substituted pyridines undergo self-association in aqueous solution.[24] However, it was not necessary to postulate the existence of such association complexes to explain the kinetic and potentiometric data obtained in this study.

Our kinetic results for NH-proton exchange are summarized in Table I. Rate constants obtained under conditions A (nmr instrument before modification; pH measurements by method A) and under conditions B (nmr instrument after modification; pH measurements by method B) are listed separately; *s* denotes the number of different solutions for which τ was measured. The differences between the two sets of results are somewhat larger than expected on the basis of the experimental precision, as mentioned earlier. We feel that the two sets should be given equal weight and shall adopt the mean of the two sets of rate constants for our final average. Our final value for k_a in H_2O, 4.71 $\times 10^3$ sec^{-1}, is in good agreement with the value, 4.81 $\times 10^3$ sec^{-1}, reported by Cocivera.[2]

Table I. NH Proton Exchange of 2,4-Lutidinium Ion in Water at 25.2°

Conditions[a]	$[BH^+]$	p_cH or p_cL	$10^{-3}k_a$,[b] sec^{-1}	$10^{-8}k_2$,[b] sec^{-1} M^{-1}
		HOH		
A, $s = 23$	0.06–0.12	1.7–4.3	5.25	1.09
B, $s = 15$	0.06–0.12	2.3–4.2	4.17	1.00
		Av	4.71	1.05
		HOD–D_2O ($f = 0.0541$)		
A, $s = 16$	0.046–0.12	2.6–5.1	1.36	0.29
B, $s = 13$	0.06	2.0–5.2	1.58	0.23
		Av	1.47	0.26

[a] See text for explanation of symbols. [b] For HOD–D_2O, read: $10^{-3}k_a'$, $10^{-8}k_2'$. See eq 10 and 11.

^{17}OH-to-OH Proton Exchange. The mean lifetime of a water OH bond, τ_w, was measured in 2,4-lutidine buffers of pH 6–7 over a wide range of buffer concentrations. In agreement with Cocivera,[2] we found that τ_w in H_2O is represented satisfactorily by the rate law (12). Analogously, in HOD–D_2O the data were represented by (13).

For H–H exchange in H_2O

$$1/\tau_w = k_+[H^+]/3 + k_-K_w/2[H^+] + nk_2[BH^+][B]/2[H_2O] \quad (12)$$

For H–D exchange in HOD–D_2O

$$1/\tau_w = k_+'[L^+]/3 + k_-'K_w'/2[L^+] + nk_2'[BL^+][B]/2[L_2O] \quad (13)$$

k_+, k_+', k_-, and k_-' denote the rate constants for hydrogen ion and hydroxide ion catalyzed proton exchange,[25] respectively, and *n*, k_2, and k_2' are characterized in eq 1 and 2. Under the conditions of measurement, the total rate of ^{17}OH-to-OH proton exchange is fast compared to the rate of acid dissociation of BH^+, so that the kinetic term due to the latter cannot be resolved. As before, we shall interpret the results in HOD–D_2O as rate constants for H–D exchange and assume that $(1 - f) \approx 1$.

Our experiments were designed so that we could evaluate nk_2 and (with lesser accuracy) k_+. The lyoxide-catalyzed reaction was not too important under the conditions of the measurements and k_-k_w was evaluated from data reported by others.[25–27] The kinetic results are summarized in Table II. By comparison, Cocivera[2] found that in H_2O, $nk_2 = 1.5 \times 10^8$ sec^{-1} M^{-1}, and his result for k_+ is 9.0×10^9 sec^{-1} M^{-1} if hydrogen ion concentrations are calculated from our K_A value for BH^+ (1.92×10^{-7}).

Table II. Kinetic Analysis of τ_w at 25.2° According to Eq 12 and 13

Solvent	H_2O[a]	HOD–D_2O[b]
Conditions[c]	A, $s = 12$	B, $s = 6$
$[B] + [BH^+]$	0.002–0.2	0.06–0.3
$[B]/[BH^+]$	0.18–1.0	0.56–1.2
k_+, sec^{-1} M^{-1} [d]	8.1×10^9	8.0×10^9
k_-K_w, sec^{-1} M[d,e]	3.8×10^{-5}	3.6×10^{-6}
nk_2, sec^{-1} M^{-1} [d]	1.82×10^8	0.47×10^8
n[f]	1.74	1.8

[a] $g = 0.0035$–0.0072. [b] $g = 0.0022$–0.0098; $f = 0.0546$. [c] See text for explanation of symbols. [d] For HOD–D_2O, read: k_+', $k_-'K_w'$, nk_2'. [e] Based on ref 25–27. [f] Based on $k_2(k_2')$ as given in Table I.

HOD–D_2O Solvent Isotope Effects. Our results are summarized in Table III.

Table III. HOD–D_2O Solvent Isotope Effects for Reactions of 2,4-Lutidinium Ion at 25.2°

Constant	H_2O	HOD–D_2O	Ratio
$k_2 \times 10^{-8}$	1.05	0.26	0.25
n	1.74	1.8	1.0
$K_A \times 10^7$ [a]	1.92	0.802	0.42
$k_a \times 10^{-3}$	4.71	1.47	0.31
$k_{-a} \times 10^{-10}$	2.45	1.83	0.75
$k_+ \times 10^{-9}$	8.1	8.0	1.01

[a] 25.0°.

Discussion

Quatermolecular Reaction Mechanism. The most remarkable result of this study, in our opinion, is that proton transfer involving 2,4-lutidinium ion, water, and 2,4-lutidine is largely quatermolecular. In H_2O, $n = 1.74$, with a standard error of about ±0.25. In principle, this value could be the average number of water molecules for two or more parallel reactions; for instance, 74% of the elementary reactions proceed with $n = 2$ and 26% with $n = 1$. However, because *n* is practically unchanged in HOD–D_2O ($n = 1.8 \pm 0.3$), we consider it likely that the "true" value in both solvents is 2.0 and that the reaction is quite uniformly quatermolecular.

Our argument is as follows. If *n* in H_2O were the resultant of two or more parallel reactions, we would

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(24) A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3209 (1965); A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5432 (1970), and references cited therein.

(25) S. Meiboom, *J. Chem. Phys.*, **34**, 375 (1961).

(26) E. K. Ralph, private communication, for k_-'. In estimating $k_-'K_w'$, the value of K_w' for 100% D_2O was used.[27]

(27) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966).

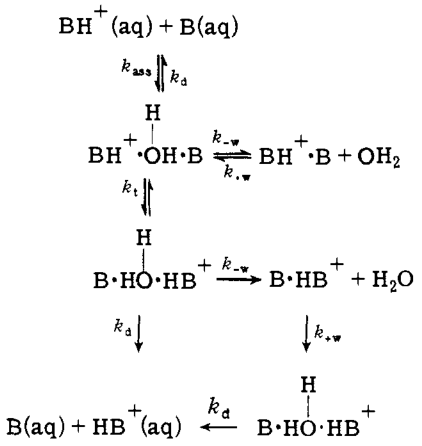

Figure 1. Proton transfer can be termolecular with $n > 1$ if $k_d < k_t$, k_{-w}. As explained in the text, we do not think this scheme is consistent with our observations when B is 2,4-lutidine. It is conceivable that $n > 1$ even if bimolecular proton transfer ($BH^+ \cdot B \rightleftarrows B \cdot HB^+$) is added to the scheme.

expect n to be much closer to 1.0 in HOD–D$_2$O, or else we could not rationalize the HOD–D$_2$O solvent isotope effect on k_2. For definiteness, suppose that in H$_2$O, 74% of the reaction events occur with $n = 2$ and 26% with $n = 1$. Suppose further that the HOD–D$_2$O kinetic isotope effect on the reaction component with $n = 1$ is 0.6, the same as for the analogous reaction of $(CH_3)_3NH^+$ where n is known to be 1.[9,10] To fit the experimental value of 0.25 for k_2'/k_2 (Table III), we then infer that the kinetic isotope effect on the reaction component with $n = 2$ is 0.12. This leads to the prediction that $n = 1.36$ in HOD–D$_2$O. The statistical probability that a predicted value of 1.36 could be consistent with our experimental value of 1.8 ± 0.3 is about 0.15.

Another reaction mechanism which could give $n > 1$ without involving quatermolecular reaction is shown in Figure 1. In this scheme, proton transfer involving water is termolecular, but the formation of $BH^+ \cdot OH_2 \cdot B$ leads (on the average) to the exchange of more than one water proton per NH proton because the rate of dissociation of $BH^+ \cdot OH_2 \cdot B$ is smaller than the rate of proton transfer and of $BH^+ \cdot B$ formation ($k_d < k_t$, k_{-w}; see Figure 1). We believe this mechanism can be ruled out not only because n would decrease in HOD–D$_2$O (the isotope effect on k_t would be the dominant effect), but also because our pH and kinetic measurements provide no evidence that complex formation of BH$^+$ with B is unusually important. That is to say, we have no evidence that k_d/k_{ass} (Figure 1) is unusually small.

Hydration of Reactants. If an acid BH$^+$ and a base B$'$ can each form a hydrogen bond to a water molecule, the water molecules in these solvated species can form hydrogen bonds with additional water molecules so that each of these species has long "tentacles" consisting of hydrogen-bonded water molecules reaching out into the solution. As BH$^+$ and B$'$ approach each other in solution, these "tentacles" can lock together to form a species $BH^+ \cdot (OH_2)_n \cdot B'$ where n can be a large number. There will be a distribution of such species with different values of n in any solution. The possibility exists that proton transfer through such a chain of water molecules can occur. We believe that proton transfer will occur to a significant extent only if all hydrogen bonds in the chain are quite strong and if the stereochemical conformation is both favorable to proton transfer and prescribed within narrow limits. The reason that proton transfer rarely occurs in such long chains is that at least some of the hydrogen bonds in the chain are weak and the species is much too "floppy."

In the present case where quatermolecular proton transfer is rapid, we infer that the conditions of strong hydrogen bonding and well-defined conformation are satisfied in the dihydrated complex $BH^+ \cdot (OH_2)_2 \cdot B$. If this be granted, then it becomes probable that the original reactants, BH$^+$(aq) and B(aq), between them also bind two water molecules with exceptional firmness. The possible combinations of reactants with tightly bound water molecules are: (a) $BH^+ \cdot OH_2$ + $B \cdot HOH$, (b) $BH^+ \cdot (OH)H \cdot OH_2$ + B, (c) BH$^+$ + $B \cdot H(OH) \cdot HOH$. In case b or c one would expect to find that the lutidinium ions can also undergo quatermolecular *hetero*proton transfer with other bases.

Our results indicate that symmetrical proton transfer (eq 1) is largely quatermolecular. Is the more common termolecular process[3] slow due to steric hindrance of the 2-methyl groups in $BH^+ \cdot OH_2 \cdot B$? When we built a molecular model of this complex from CPK space-filling atomic models,[28] we found that such a complex can exist with linear NH:O and OH:N hydrogen bonds without any obvious steric crowding. We believe, therefore, that steric hindrance is not a factor. The most likely alternative explanation is that the *rate of formation* of $BH^+ \cdot OH_2 \cdot B$ is exceptionally slow because it involves the displacement of a tightly bound water molecule. In this way, the turnover rate of protons by the termolecular mechanism would be slow even though, intrinsically, proton transfer within the termolecular complex might be quite rapid.

Acid Dissociation of 2,4-Lutidinium Ion. Two reaction mechanisms for acid dissociation can be distinguished on the basis of proton exchange rates.[12] In one of these, eq 14, the acid proton of BH$^+$ is transferred directly to an OH site of H$_3$O$^+$, and the corresponding rate of proton exchange is given by (15). In the other,

$$BH^+ + OH_2 \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} B + HOH_2^+ \qquad (14)$$

$$R_{NH}\ (\text{eq } 14) = k_a[BH^+] \qquad (15)$$

the acidic proton remains hydrogen bonded to the conjugate base of the substrate (eq 16) and becomes transferred to bulk water only in a subsequent reaction step (17). The corresponding rate of proton exchange is given by (18). Further discussion of these mechanisms

$$BH^+ \cdot OH_2 + H_2O \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} B \cdot HOH + HOH_2^+ \qquad (16)$$

$$B \cdot HOH + HOH(aq) \xrightarrow{k_H} B \cdot HOH + HOH(aq) \qquad (17)$$

$$R_{NH}\ (\text{eq } 16, 17) = k_a k_H[BH^+]/(k_H + k_{-a}[H^+]) \qquad (18)$$

will be found in a recent review.[12] The distinguishing feature is that in strongly acid media ($k_{-a}[H^+] \gg k_H$), the rate of proton exchange according to (18) becomes inversely proportional to [H$^+$]. Equation 18 appears to be consistent with the facts for the acid dissociation of aliphatic ammonium ions.[12]

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[28] Ealing Corporation, Cambridge, Mass. 02140.

Cocivera[2] has measured τ_{NH} for methyl-substituted pyridinium salts in aqueous HCl solutions up to moderately high HCl concentrations. His results for 2,4-lutidinium ion are listed in Table IV. The apparent rate "constant" for acid dissociation, k_a^* (obtained by applying a small correction for symmetrical proton exchange with rate constant k_2), shows a substantial decrease with increasing HCl concentration. Accordingly, Cocivera treated his data according to (18) and obtained $k_a = 4.81 \times 10^3$ and $k_H = 1.7 \times 10^{10}$ sec^{-1}.[2] However, the value obtained for k_H is unexpectedly high.[12] We wish to show that eq 15 can also fit the kinetic data if we make plausible corrections for medium and salt effects.

Table IV. Kinetic Analysis of NH Proton Exchange of 0.3 *F* 2,4-Lutidinium Ion in Aqueous HCl on the Basis of Eq 20

[HCl]	$1/\tau_{NH}$[a]	k_a^*	k_a^* (calcd)[b]	Discrepancy, %
2.310	667	664	710	−6.9
1.155	2190	2180	1770	+18.8
0.0722	4210	4120	4160	−1.0
0.0361	4520	4340	4290	+1.2

[a] Data at 25.1°; ref 2. [b] $k_a^* = 4410(\eta_0/\eta)10^{-0.32[HCl]}$.

Let $K_A^* = k_a^*/k_{-a}^*$ and $K_A = k_a/k_{-a}$ denote acid dissociation and rate constants in the given medium and in the infinitely dilute aqueous reference state, respectively. Medium effects on k_a^* are then given by (19).

$$k_a^*/k_a = (K_A^*/K_A) \cdot (k_{-a}^*/k_{-a}) \qquad (19)$$

The reaction of B with hydrogen ion appears to be diffusion controlled. We shall therefore assume that $k_{-a}^*/k_{-a} = \eta_0/\eta$, where η is the bulk viscosity.[29] We shall further assume that acid dissociation of 2,4-lutidinium ion is reproduced by the acidity function for tertiary anilines, H_0''' (in the notation of Arnett and Mach.)[30] On this basis, it has been shown[29] that in aqueous HCl, log $(K_A^*/K_A) = -0.32$ [HCl]. As a result, the medium effect on k_a^* is given by (20). Table IV shows that when k_a is evaluated from the data at 0.072 and 0.036 *F* HCl, eq 20 will reproduce the substantial decrease of k_a^* at 1.16 and 2.31 *F* HCl quite well.

$$k_a^* = k_a(\eta_0/\eta)10^{-0.32[HCl]} \qquad (20)$$

Another method for distinguishing between the two mechanisms for acid dissociation makes use of HOD–D$_2$O kinetic isotope effects. Again we assume that the reaction of B with hydrogen ion is diffusion controlled. On the basis of a theory due to Fong and Grunwald,[31] we then predict that $k_a'/k_a = 0.364$ at 25° for the mechanism represented in (14) and that $k_a'/k_a = 0.245$ at 25° for the mechanism represented in (16). The experimental value, 0.31 (Table III), is unfortunately not clearly one or the other of these predicted values, but it is also clear that the mechanism represented in (14) cannot be ruled out.

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

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

[31] D.-W. Fong and E. Grunwald, *ibid.*, **91**, 2413 (1969).