structure and solvation. That is, only the intermediate shown in eq 1 leads to products; however, as the amount of water decreases in the medium, the concentration of that intermediate decreases; other intermediates need to be transformed into that intermediate before product can be formed. So this phenomenon becomes essentially a probability effect and it shows up in the entropy part of the activation parameters. Part of the problem may be reversion of intermediates to starting materials in competition with intermediates forming product. Higher solvation is required to form products as discussed previously.[2a] One can also describe the entropy barrier as a decreased probability of adequate numbers of water molecules in the solvation shell of the intermediate that forms the product transition state.

In contrast to eq 1, Bender and Komiyama have concluded from a proton-inventory study that solvation of the pNTA reaction requires only two water molecules.[6] Because of the assumptions inherent in the equation which is the basis of the interpretation of isotope effects,[12] on which the proton-inventory method is based, we tend toward the view that our simple method based on rate effects in acetonitrile-water may have greater reliability in assessing solvation. However, the principle finding in this paper, entropy control, is independent of the exact number of waters involved in solvation of the transition state.

A major part of enzymic catalysis appears to be due to the lack of an entropy barrier: the "Circe effect".[4] Our observation in this paper of the entropy barrier to solvation of transition states indicates that functional groups on enzymes will not only play critical roles such as that of nucleophile but they will also have to solvate the intermediates and transition states along the reaction pathway. In the function of enzymes, a knowledge of the way the amino acid residues are involved in solvating the substrate must be a major part of the total understanding of enzymic binding and catalysis.

These results also demonstrate that water as a solvent provides a minimum energy pathway to products in many reactions in a way that is somewhat similar to the mechanism of action of enzymes. That is, the acidic and basic properties of water provide catalysis and solvation with little entropy barrier when a reaction is carried out in pure water.

Registry No. 1, 404-27-3; imidazole, 288-32-4.

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Influence of Water Concentration in Acetonitrile upon the Transition-State Structure for 1-Acetyl-3-methylimidazolium Ion Hydrolysis[1]

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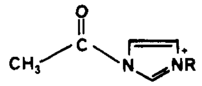
Received July 27, 1982

The hydrolysis of 1-acetyl-3-methylimidazolium ion has been investigated in water and water–acetonitrile mixtures with the proton-inventory technique. The influence of the solvent composition upon the β-deuterium secondary isotope effect and upon the thermodynamic activation parameters has been investigated as well. The relatively large solvent deuterium isotope effects (k_{H_2O}/k_{D_2O}) of about 2.5–2.8 at water concentrations greater than 1 M in acetonitrile were shown to be consistent with a transition-state structure in which one water molecule acts as a general base to abstract a proton from the nucleophilic water. At low concentrations of water (i.e., <1 M) in acetonitrile the solvent deuterium isotope effect drops to 1.17 and the proton inventory is consistent with a transition-state structure involving a single nucleophilic water molecule.

Our recent studies[2,3] on the pH-independent, water-catalyzed hydrolysis of the reactive acyl compounds 1-acetylimidazolium ion (**1a**) and 1-acetyl-3-methylimidazolium ion (**1b**) have shown that the rate-limiting transition-state structure involves a water dimer (**2**) with one water molecule serving as a nucleophile and the other as a general base. The studies on the hydrolysis of **1a** in acetonitrile and water mixtures have revealed that a quite drastic alteration in environmental conditions has little or no influence on the structure of the transition state **2**.[4]



1a R = H
1b R = CH_3

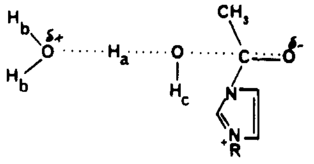


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Table I. First-Order Rate Constants for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion as a Function of Water Concentration (<1 M) in Acetonitrile at 50.00 ± 0.05 °C

$[H_2O]$, M	10^5k_1,[a] s^{-1}	10^4k_2,[b] $M^{-1}\ s^{-1}$
0.327	4.88 ± 0.06	1.49 ± 0.02
0.516	7.51 ± 0.31	1.46 ± 0.06
0.654	9.47 ± 0.08	1.45 ± 0.01
0.794	11.62 ± 0.39	1.46 ± 0.05
0.892	12.77 ± 0.25	1.43 ± 0.03

[a] Error limits are standard deviations. [b] These values were obtained by dividing the first-order rate constant by the water concentration.

Table II. First-Order Rate Constants for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion as a Function of Water Concentration (>2 M) in Acetonitrile at 48.50 ± 0.05 °C

$[H_2O]$, M	10^4k_1,[a] s^{-1}	$[H_2O]$, M	10^4k_1,[a] s^{-1}
2.04	1.78 ± 0.02	4.07	6.28 ± 0.03
2.64	2.75 ± 0.01	4.75	8.32 ± 0.02
3.06	3.55 ± 0.03	5.65	11.74 ± 0.17

[a] Error limits are standard deviations.

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[1] This research was supported by the Robert A. Welch Foundation and, in part, by the National Institutes of Health (Grant No. 1 R01 GM25433).

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Table III. First-Order Rate Constants for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion in 0.5 Volume Fraction of Acetonitrile (Before Mixing) in H_2O-D_2O Mixtures of Atom Fraction of Deuterium n at 25.00 ± 0.05 °C[a]

atom fraction of deuterium (n)	no. of runs	10^5k_n,[b] s^{-1}	10^5k_n, s^{-1} (calcd[c])
0.000	5	1305 ± 18	1305
0.249	5	1050 ± 10	1056
0.498	5	834 ± 8	833
0.747	4	636 ± 6	637
0.996[d]	4	461 ± 5	464

[a] Ionic strength was maintained at 0.23 M with sodium chloride and, the pH (pD) was maintained at 3.0 with HCl (DCl). [b] Error limits are standard deviations. [c] Calculated on the basis of the model of eq 3 with $\phi_a = 0.491$ and $\phi_b = 0.849$. [d] Atom fraction of deuterium determined by Josef Nemeth.[23]

Table IV. First-Order Rate Constants for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion in 0.9 Volume Fraction of Acetonitrile (Before Mixing) in H_2O-D_2O Mixtures of Atom Fraction of Deuterium n at 25.00 ± 0.05 °C[a]

atom fraction of deuterium (n)	no. of runs	10^7k_n,[b] s^{-1}	10^7k_n, s^{-1} (calcd[c])
0.000	5	5402 ± 3	5402
0.249	5	4394 ± 3	4352
0.499	4	3412 ± 1	3425
0.748	4	2629 ± 3	2623
0.997[d]	4	1935 ± 1	1932

[a] Ionic strength was not maintained, but the pH (pD) was maintained at 3.0 with HCl (DCl). [b] Error limits are standard deviations. [c] Calculated on the basis of the model of eq 3 with $\phi_a = 0.53$ and $\phi_b = 0.82$. [d] Atom fraction of deuterium determined by Josef Nemeth.[23]

Table V. First-Order Rate Constants for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion in Acetonitrile Containing 0.8 M H_2O, D_2O, or H_2O-D_2O of Atom Fraction of Deuterium n at 48.50 ± 0.05 °C[a]

atom fraction of deuterium (n)	no. of runs	10^7k_n,[b] s^{-1}	10^7k_n, s^{-1} (calcd[c])
0.000	5	915 ± 12	915
0.249	5	877 ± 10	879
0.499	4	840 ± 7	843
0.748	5	811 ± 3	809
0.997[d]	4	779 ± 11	775

[a] pH (pD) and ionic strength were not controlled. [b] Error limits are standard deviations. [c] Calculated on the basis of eq 5 with $\phi^* = 0.92$. [d] Atom fraction of deuterium determined by Josef Nemeth.[23]

Table VI. Temperature Dependence of the First-Order Rate Constants and of the β-Deuterium Secondary Isotope Effect for Hydrolysis of 1-Acetyl-3-methylimidazolium Ion at pH 3.0 and $\mu = 0.2$[a]

temp, °C	$10^2k_{CH_3}$,[b] s^{-1}	$10^2k_{CD_3}$,[b] s^{-1}	k_{CH_3}/k_{CD_3}
40.33	10.43 ± 0.06	11.20 ± 0.02	0.931 ± 0.006
35.77	8.12 ± 0.20	8.75 ± 0.12	0.928 ± 0.026
30.43	6.35 ± 0.01	6.91 ± 0.06	0.919 ± 0.008
25.00	4.66 ± 0.01	4.95 ± 0.05	0.941 ± 0.010
25.00[c]	1.44 ± 0.03	1.53 ± 0.001	0.941 ± 0.020
25.00[d]	0.0539 ± 0.001	0.0576 ± 0.001	0.931 ± 0.024
20.33	3.42 ± 0.02	3.66 ± 0.07	0.934 ± 0.018
15.04	2.42 ± 0.02	2.58 ± 0.02	0.938 ± 0.011

[a] Ionic strength maintained with potassium chloride. [b] Average of two or more determinations. Error limits are standard deviations. [c] In 0.5 volume fraction of acetonitrile; ionic strenght not maintained. [d] In 0.9 volume fraction of acetonitrile; ionic strength not maintained.

Table VII. Thermodynamic Activation Parameters for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion as a Function of Volume Fraction of Acetonitrile in Water

volume fraction of CH_3CN[a]	$\Delta G^\ddagger$, kcal/mol	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
0.00	19.3	10.1	−30.5
0.25	19.7	9.9	−32.3
0.50	20.0	9.7	−34.3
0.75	20.7	8.2	−41.5
0.90	22.1	6.3	−52.2

[a] The pH was maintained at 3.0 with HCl. The ionic strength was not controlled.

The present study which is an extension of the earlier work[3,4] lends further confirmation to the transition-state structure and allows us to locate the position of the transition state on the reaction coordinate by probing the influence of solvent composition on the solvent isotope effect and the proton-inventory curve. Both solvent and temperature effects on the β-deuterium secondary isotope effect for deuteration of the acetyl groups are also discussed.

Results

The hydrolysis of 1-acetyl-3-methylimidazolium ion (**1b**) has been investigated in acetonitrile–water mixtures containing low concentrations of water, and the first-order rate constants are collected in Tables I and II. The results (Figure 1) clearly indicate a first-order dependence on water at $[H_2O] < 1.0$ M and a second-order dependence on water at $[H_2O] > 1.0$ M. While the observed second-order dependence on water is consistent with the transition state **2**, the first-order dependence at low water concentrations is not.

The hydrolysis of 1-acetyl-3-methylimidazolium ion has also been studied in 0.5 and 0.9 volume fraction of acetonitrile in protium oxide and deuterium oxide mixtures of atom fraction of deuterium n. The first-order rate constants are collected in Tables III and IV. Also included in Tables III and IV are calculated values of the observed rate constants based on a chemical model discussed below. Figure 2 shows the dependence of the observed first-order rate constants on the isotopic composition of the solvent. The solid lines drawn through the data points in these figures are based on the chemical model proposed below.

The hydrolysis of **1b** has also been studied in acetonitrile containing only 0.8 M H_2O, D_2O, or H_2O–D_2O of atom fraction of deuterium n. The solvent isotope effect in this case is found to be very small (i.e., $k_{H_2O}/k_{D_2O} = 1.17$). The rate constants, k_n, corresponding to various atom fractions of deuterium, n, are collected in Table V, and a plot of k_n vs. n in this case (Figure 2 inset) is almost linear.

Table VI contains first-order rate constants for the hydrolysis of protiated and 1-acetyl-d_3-imidazolium ion in water buffered at pH 3.0 with HCl at temperatures from 15.0 to 40.3 °C, together with the corresponding secondary β-deuterium isotope effects. The isotope effects reported in Table VI are all inverse and very near the mean value of $k_H/k_D = 0.93 \pm 0.007$ calculated for the entire temperature range.

The effect of temperature on the rate of hydrolysis of **1b** was investigated in acetonitrile–water solvent mixtures. Rate constants were measured at six different tempera-

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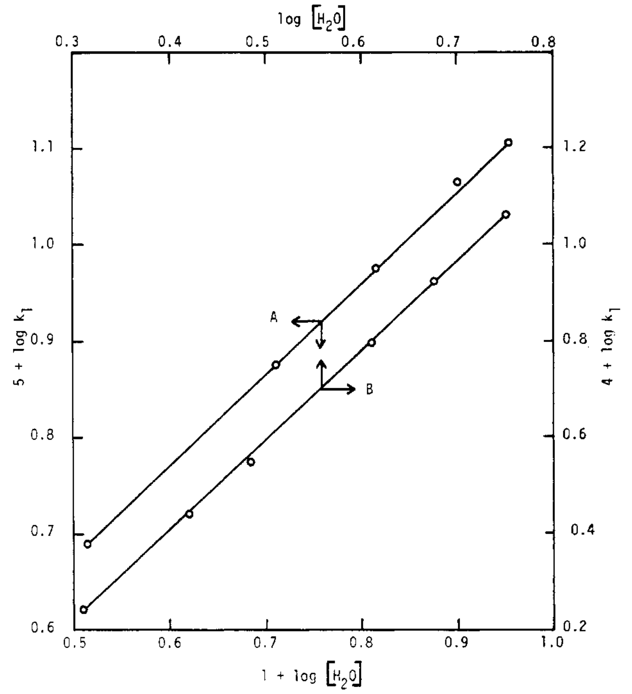

Figure 1. Plot of log k_1 vs. log $[H_2O]$ for $[H_2O] < 1.0$ M at 50 ± 0.05 °C (A) and for $[H_2O] > 1.0$ M at 48.5 ± 0.05 °C (B). The slope of the least-squares lines (A) shown is 0.97 ($r = 0.9998$), and that for line B is 1.86 ($r = 0.9995$). Data are taken from Tables I and II.

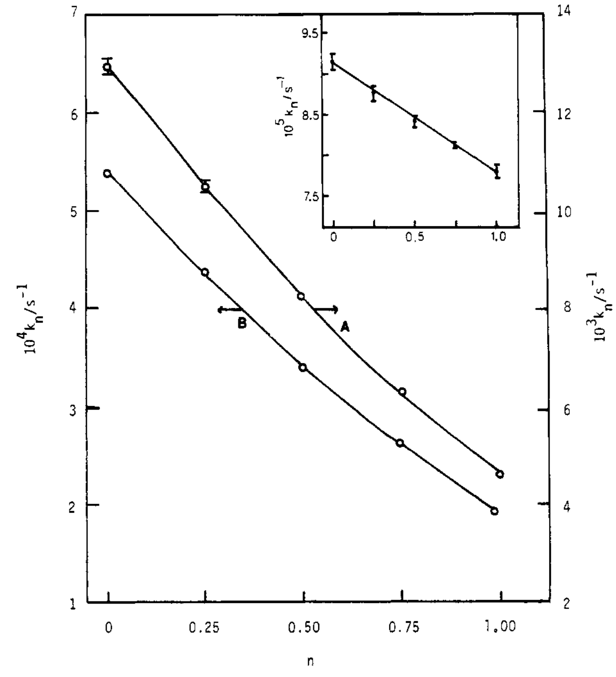

Figure 2. Proton-inventory plots for the water-catalyzed hydrolysis of 1-acetyl-3-methylimidazolium ion in 0.5 volume fraction of acetonitrile in water (A), in 0.9 volume fraction of acetonitrile in water (B), and in acetonitrile containing 0.8 M water (inset). The solid lines of A and B were calculated from eq 3 with ϕ_a = 0.491 and ϕ_b = 0.849 for A and ϕ_a = 0.53 and ϕ_b = 0.822 for B. The data are taken from Tables III and IV. Where error bars are omitted the circles encompass them.

tures (15.0, 20.3, 25.0, 30.4, 35.8, and 40.3 °C) and used to calculate the values for the enthalpy and entropy of activation which are collected in Table VII.

Discussion

Proton Inventories. The utility of solvent isotope effects in helping to delineate the role of proton transfers is well documented.[5-11] A recent development in this area is the proton-inventory technique. This involves the measurement of reaction rates (k_n) in mixtures of protium oxide and deuterium oxide of atom fraction of deuterium n and relates the observed rate constant, k_n, to the rate constant, k_0, in pure protium oxide by eq 1. All exchangeable transition-state protons, i, and exchangeable reactant-state protons, j, that contribute to the observed solvent isotope effect contribute a term of the form shown in parentheses in the numerator and denominator of eq 1, respectively. Each exchangeable proton is associated with an isotopic fractionation factor defined as in eq 2. This expresses the equilibrium deuterium preference of the exchangeable site in question relative to the deuterium preference of an average solvent site.[9] If all isotopic reactants are solvent molecules, then, by definition, ϕ_j = 1, and the denominator of eq 1 becomes unity. Such is the case here. Since the theory of the proton inventory has been the subject of several recent reviews and papers,[5-11] only this brief discussion is given here.

$$k_n = k_0 \prod_{i}^{\mathrm{TS}}(1 - n + n\phi_i^*)/\prod_{j}^{\mathrm{RS}}(1 - n + n\phi_j) \qquad (1)$$

$$\phi_k = [(\mathrm{D})/(\mathrm{H})]_k/[(\mathrm{D})/(\mathrm{H})]_{\mathrm{solvent}} \qquad (2)$$

The data obtained in proton-inventory studies can be analyzed either by polynomial regression analysis as described by Schowen[13] or by the "gamma method" as suggested by Albery.[9] If the Brønsted coefficient for the reaction is available and if the water point falls on the Brønsted plot, the Brønsted coefficient can be utilized as an aid in analyzing the data as illustrated in ref 2.

Transition State. The transition-state model, **2**, proposed for the neutral, water-catalyzed hydrolysis of the compounds **1a** and **1b** is largely supported by proton inventories,[2,3] Brønsted plots,[12] and solvent isotope effects.[2,3] In proton-inventory studies[2,3] support for **2** arises from the nonlinear dependence of k_n on n as illustrated by eq 3, the appropriate form of the Gross-Butler equation (eq 1) for this system. In eq 3, ϕ_a and ϕ_b are fractionation factors for H_a and H_b in **2**. These ϕ_a and ϕ_b values were found to be 0.55 and 0.83 for the hydrolysis of **1a** and 0.56 and 0.83 for the hydrolysis of **1b**, respectively.[2,3] As usual, the fractionation factor of the H_c proton was assumed to be unity.

$$k_n = k_0\,(1 - n + n\phi_a)(1 - n + n\phi_b)^2 \qquad (3)$$

In transition state **2** the "in flight" proton H_a will contribute a primary solvent isotope effect, and the two H_b protons will contribute secondary solvent isotope effects. An estimate of the fractionation factor for each H_b proton (ϕ_b) was made[3] by using the Brønsted β value, and an estimate of the fractionation factor for the H_a proton was made[3] by using the calculated value of ϕ_b and the exper-

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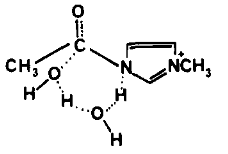
Table VIII. Values of the Curvature Parameter, γ, and the Range of Isotopic Fractionation Factors for the Hydrolysis of 1-Acetyl-3-methylimidazolium Ion in H_2O-D_2O Mixtures for Fitting Data to Eq 3

volume fraction of CH_3CN	γ	ϕ_a (range)	ϕ_b (range)
0.00	0.51	0.528 (0.473–0.632)	0.859 (0.786–0.908)
0.50	0.52	0.491 (0.463–0.526)	0.849 (0.820–0.874)
0.90	0.46	0.530 (0.507–0.559)	0.822 (0.800–0.840)

imentally determined values of k_n and k_o in eq 3. But in the present studies, the use of the Brønsted β value observed in water fails to generate the proton-inventory data acquired from the studies in 0.5 and 0.9 volume fraction of acetonitrile in water. This is probably due to a change in the Brønsted β value with the solvent composition.

The γ values (Table VIII) generated for the proton inventories suggest that at least two and probably three protons contribute to the observed solvent isotope effect. This is a result of the Albery analysis[9] which showed that the numbers of isotopically exchangeable sites contributing to the solvent deuterium isotope effect is greater than γ^{-1}.

The most reasonable "two-proton" transition-state structure, which is consistent with the observed second-order dependence on water, is **3**. This has two protons



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which could contribute equally to the overall solvent isotope effect. The expected fractionation factors for the protons in such a model are 0.62, 0.59, and 0.61 for the reaction in 0.0, 0.5 and 0.9 volume fraction of acetonitrile. These were calculated from the γ values. Such a model fails to generate the proton-inventory data.

The probable three-proton models are (a) a cyclic transition state similar to **3** involving three water molecules and, thus, three contributing protons and (b) the acyclic transition state **2**. The former is unacceptable because (i) it requires a third-order dependence on water concentration, (ii) it fails to account for the observed solvent isotope effects as the calculated fractionation factors are 0.68, 0.65, and 0.67, and (iii) it fails to generate the proton inventory data. This leaves the transition state model **2** as the most reasonable one.

Further, in the present investigation the observed proton-inventory plots of the hydrolysis of **1b** in 0.5 and 0.9 volume fractions of acetonitrile in water are almost identical with those for the reaction in water containing no acetonitrile. The values of the solvent isotope effects are almost identical (2.57 in water, 2.83 in 50% CH_3CN, and 2.80 in 90% CH_3CN). The values of γ, the curvature parameter, are 0.51 ± 0.14, 0.52 ± 0.06, and 0.46 ± 0.04, respectively. Lastly, the values of k_n/k_o calculated are almost identical. This suggests that the transition states of the reaction in 0.5 and 0.9 volume fractions of acetonitrile in water are not significantly different from that of the reaction in pure water (i.e., transition-state model **2**).

The fractionation factors for the two kinds of protons, H_a and H_b, in transition-state model **2** as calculated from γ values are $\phi_a = 0.53$ and $\phi_b = 0.86$, $\phi_a = 0.49$ and $\phi_b = 0.85$, and $\phi_a = 0.53$ and $\phi_b = 0.82$ in 0.0, 0.5, and 0.90 volume fraction of acetonitrile in water, respectively. H_c has again been assumed to have a unit fractionation factor. These values successfully generate the proton-inventory data when they are used in eq 3. The values of k_n thus calculated are collected in Tables III and IV and were used to draw the solid lines in Figure 1. This again lends confirmation to our earlier inference that the structure of the transition state is the same for the reactions in 0.0, 0.5, and 0.9 volume fraction of acetonitrile in water.

Having established the nature of the transition state structure as being **2**, we can make further deductions about the degree of proton transfer from the size of the secondary factor, ϕ_b. Kresge[7] suggested that the fractionation factors for H_b-type protons can be related to the degree of proton transfer by eq 4. Here l is the fractionation factor of

$$\phi_b = l^{\alpha} \tag{4}$$

protons in a hydronium ion (i.e., 0.69), and α is the measure of the degree of proton transfer from the nucleophilic water to the general base water. Depending on the degree of proton transfer, the secondary factor changes from the value of 1.0, appropriate for neutral water protons, to that appropriate for hydronium ion. For the hydrolysis of **1b** in water, the estimated value of ϕ_b is 0.86. This corresponds to a degree of proton transfer of 0.41. Thus, the maturity of the hydronium ion is about 41% based on this estimate of the degree of proton transfer in the transition-state structure.

Secondary Isotope Effects. The β-deuterium secondary isotope effect for this reaction in water at 25 ± 0.05 °C is $k_H/k_D = 0.94$. This is indicative of the degree of tetrahedral character developed at the carbonyl carbon since the effect is thought to arise almost entirely from changes in the β-CH (CD) force constants induced by variations in hyperconjugation of the electrons of the β-CH (CD) bonds into the carbonyl group.[15,16] The degree of tetrahedral character at carbonyl carbon in the transition state is calculated from the β-deuterium secondary isotope effect to be about 41%, based on a value of $k_H/k_D = 0.863$ for the equilibrium β-deuterium secondary effect for ketone hydration.[3,16-18] Such a value can be used to estimate the isotope effect for complete sp^2 to sp^3 conversion at the carbonyl carbon. The exact agreement between the degree of tetrahedral character (41%) at the transition state as measured by the β-deuterium secondary isotope effect on one hand and the degree of proton transfer (41%) and degree of maturity of hydronium ion as measured by the proton inventory data on the other hand is really remarkable.

Although the exact values of the fractionation factors of each kind, ϕ_a and ϕ_b, obtained for the reactions in different solvent compositions do differ a little, they remain essentially the same within the ranges calculated by using the limits of each γ value (Table VIII and Figure 3). This, coupled with the essentially equal values of the β-deuterium secondary isotope effects observed in different solvent composition, again ascerts that, with respect to charge distributions, the transition states for the reaction in 0.5 and 0.9 volume fraction of acetonitrile in water are not different from that in pure water.

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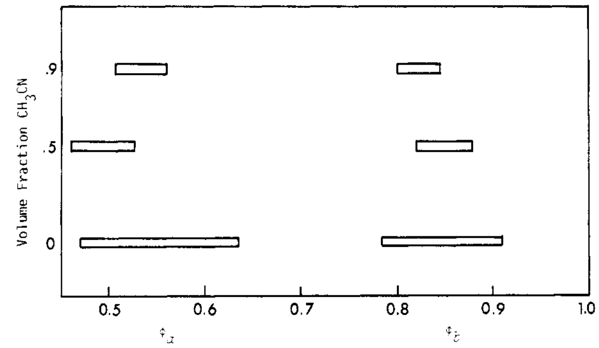

Figure 3. Representation of the ranges of ϕ_a and ϕ_b calculated from the γ method by using $k_n/k_{H_2O} = (1 - n + n\phi_a)(1 - n + n\phi_b)^2$ for the water-catalyzed hydrolysis of 1-acetyl-3-methylimidazolium ion in 0.0, 0.5, and 0.9 volume fraction of acetonitrile in water.

As the solvent composition changes from 0.0 to 0.9 volume fraction of acetonitrile, water loses its function as the solvent. Hence, solvation of the reactants and transition state must be essentially by water in the water-rich solvent mixtures and by acetonitrile in acetonitrile-rich solvent mixtures. Water and acetonitrile differ in their ability to solvate reactants and transition states as evident from the difference in their dielectric constants, 78.4 and 36.0, respectively, at 25 °C.[19] Hence, we expect some effect of changing the solvent composition either on structure of the transition state or on the distribution charge at the transition state or on both. The fact that no significant change is observed is curious.

The generally accepted mechanism of this type of reaction involves the following typical steps: (I) approach of the nucleophile toward the carbonyl group, (II) passage through a first transition state, (III) formation of a tetrahedral intermediate, (IV) passage through a second transition state, and (V) formation of the products. For most cases, the intermediate is of very low stability, and it is often thought that both transition states should resemble the intermediate and, thus, each other closely. But in the present case, as inferred above, the transition state occurs at a point where the tetrahedral character is less than half, shows more trigonal character like the reactant and product than tetrahedral character like the intermediate, and preserves its nearly trigonal character against the influences of the protic/aprotic character of the solvent. These deductions, especially the last one, imply that the requirement for desolvation of the nucleophile or electrophile is, therefore, not responsible for this structural feature of the transition state. Considerable desolvation of the partially positive carbonyl carbon should increase the hyperconjugation of C–H bonding electrons into the carbonyl group and, thus, should propel the observed β-deuterium secondary isotope effect even more in the inverse direction in 0.5 and 0.9 volume fraction of acetonitrile. This is not observed.

The thermodynamic parameters reported in Table VII make it clear that in the hydrolysis of 1-acetyl-3-methylimidazolium ion there are some striking changes in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ which can be attributed to effects of solvent cage structure. The observed values of entropy of activation at different volume fractions of acetonitrile are all negative and large and indicate an increase in structuring of the solvent as the reaction proceeds from the reactant state to the transition state. In the present reaction the nucleophile is the solvent water, and the transition state is found to occur when the tetrahedral character of carbonyl carbon is less than half. Hence, the region between the unquenched charges of the nucleophile and electrophile remains as a concentrated region of high polarity and exerts a nonspecific dipolar attraction for solvent molecules which results in a constriction of the nearby solvent and a net increase in tightness of solvation (i.e., a compression of the solvent cage and an increase of solvent structure around the transition state). The entropy of activation exhibits little change as the solvent composition changes from 0.0 to 0.5 volume fraction of acetonitrile. This is probably an indication of the dominance of water in the formation of the solvent cage. But as one proceeds from 0.5 to 0.9 volume fraction of acetonitrile, there is a striking change in $\Delta S^\ddagger$. This is probably due to the preferential solvation by water which is favored by either a low activity of H_2O in the solvation cage or a high activity of water in the bulk mixture. Since a small preference for water in the solvation cage is adequate to produce strong preferential solvation and since this preferential solvation will be magnified by the nonideality of the bulk liquid mixture,[20] the observed decrease in $\Delta S^\ddagger$ from −34.3 to −52.2 eu may be taken as due to the magnification of the increase in structure of the solvent cage. Thus, the observed enthalpy and entropy of activation serve as more sensitive indicators of effects of solvent composition on the transition state than the rate constants directly.

In acetonitrile the partial negative dipole charge is localized on the nitrogen while the positive charge of the dipole is diffused onto the methyl group. Hence, it can solvate positive centers much more strongly than negative centers. But water is capable of solvating both effectively.

The partial positive and negative charges of the polar carbonyl group of the substrate are localized on carbon and oxygen, respectively, in the reactant state. Hence, the reactive center (i.e., the partially positive carbon) is solvated by water in water and by both acetonitrile and water in the acetonitrile–water mixtures. In both cases the composition of the solvent cage is almost the same as that of the bulk solvent. On going from the reactant to the transition state, since only water molecules of the solvent cage separate out and function as nucleophile and general base, desolvation of the substrate is not required.

But, in the transition state **2** the partial negative charge is still localized at the carbonyl oxygen while the positive charge is diffused throughout the transition state. This situation gives rise to preferential solvation by water.

The observed decrease in $\Delta H^\ddagger$ from 10.1 to 6.3 kcal/mol suggests that the reactant is more destabilized than the transition state on changing the solvent from water to an acetonitrile-rich mixture. This is quite reconciliable with the normal solvation of the reactant and preferential solvation of the transition state by water. The observed increase in $\Delta G^\ddagger$ is the net result of changes in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ opposing each other. Hence, the observed decrease in rate with an increase in the percentage of acetonitrile in the solvent is due to the dominating effect of the decrease of $\Delta S^\ddagger$ from −30.5 to −52.2 eu.

The solvent isotope effect is reduced to 1.17 when the water is a dilute solute (i.e., $[H_2O] = 0.8$ M) in acetonitrile, and the order dependence of the reaction on water is reduced to unity when $[H_2O] < 1.0$ M. This suggests either a change of mechanism or a change in transition-state structure, probably the second. Infrared spectra and other evidence[21,22] reveal that water exists as monomers in ace-

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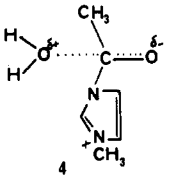
tonitrile when $[H_2O] < 1.0$ M. In that case the transition state of the reaction may be **4**. The water molecule bound to the positive site should produce fractionation factors for both of its hydrogenic sites with values between $\phi = 1$ (the reactant value) and $\phi = 0.69$ (the product value). A value of $\phi^* = 0.92$ substituted into eq 5, the appropriate form of the Gross–Butler equation for **4**, reproduces the isotope effect. The proton inventory should show some slight curvature, but it is beyond the limits of detection with our experimental data (Figure 1 inset).



4

$$k_n = k_0\,(1 - n + n\phi^*)^2 \tag{5}$$

Conclusion

We have shown that the transition-state structure for the hydrolysis of 1-acetyl-3-methylimidazolium ion varies little as a function of the composition of an acetonitrile–water solvent system over a wide range. However, at very low water concentrations the transition-state structure does change due to a change in the molecularity of the reaction with respect to water. This result may be of importance in mechanistic studies of enzymes with very hydrophobic active sites.

Experimental Section

Materials. 1-Acetyl-3-methylimidazole was prepared and purified by the method of Wolfenden and Jencks.[12] 1-Acetyl-d_3-3-methylimidazole was prepared by the same method by using acetyl-d_3 chloride (Aldrich). Acetonitrile was distilled twice from phosphorus pentoxide and stored under nitrogen. Deuterium oxide (99.75 atom % deuterium, Bio-Rad) was used as obtained. Water was doubly distilled. Sodium chloride (Fischer certified) was dried in an oven at 120 °C for 24 h.

Reaction Solutions. The solutions containing 0.5 and 0.9 volume fraction of acetonitrile in water were prepared by mixing appropriate volumes of acetonitrile and water, adjusting their pH to 3.0 by the addition of HCl, and dissolving the required amount of NaCl. Similarly, solutions of acetonitrile in D_2O were prepared as above except that the solutions were adjusted to pD 3.0 (pH meter reading 2.6). The solutions for proton-inventory studies in 0.5 and 0.9 volume fractions of acetonitrile in H_2O–D_2O of atom fraction of deuterium n were prepared by mixing appropriate volumes of H_2O and D_2O solutions in CH_3CN. The atom fraction of deuterium of exchangeable protons was calculated from the results of an analysis by Joseph Nemeth[23] on a sample of "100%" D_2O–acetonitrile solution. The solvent mixtures for the water order studies were prepared gravimetrically.

Kinetics. The instrumentation employed has been described elsewhere.[4] Experiments were conducted in thermostated cell holders and were initiated after thermal equilibration. Initiation of reaction was accomplished by injection of 25 μL of a 9.0×10^{-3} M 1-acetyl-3-methylimidazole in acetonitrile solution into 3.00 mL of buffer contained in a cuvette. A decrease in absorbance was monitored at 245 nm by directly registering the absorbance at 1-s intervals with a microcomputer interfaced with a Cary 118C UV-vis spectrophotometer. The rate constants were calculated by using a nonlinear least-squares program.

Registry No. 1b, 31399-05-0; deuterium, 7782-39-0.

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Pyridinium Halide Promoted Ring-Opening Reactions of *exo*-Norbornene Oxide

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Received June 8, 1982

Ring opening of **1** with pyridinium chloride or pyridinium iodide in chloroform and/or pyridine gives significant amounts of halohydrins **2a** or **2b**, reflecting partial suppression of the Wagner–Meerwein rearrangement that occurs on ring-opening with hydrogen halides. Opening with pyridinium iodide (but not with pyridinium chloride) in acetonitrile gave considerable amounts of the 2-*endo*-iodohydrin **4b**. Pyridinium poly(hydrogen fluoride) or triethylammonium tris(hydrogen fluoride) gave only rearranged products.

Vicinal *trans*-norbornane halohydrins are difficult to obtain by treatment of epoxides with either hydrochloric or hydrobromic acid because of the tendency of this bicyclic system to undergo the Wagner–Meerwein rearrangement.[1] In fact, several processes can be observed in the acid-induced ring opening of *exo*-norbornene oxide (**1**), as shown in Figure 1.

Suppression of the Wagner-Meerwein rearrangement has been reported where R (Figure 1) is CH_2Cl, presumably because this group leads to formation of a relatively stable chloronium ion intermediate (route d),[2] and via a stable dioxolenium ion in related systems.[3] We have reported that this rearrangement is also partly suppressed in the reaction of **1** with pyridinium chloride (PyHCl), with **2a** being one of the products (Table I, entries 2 and 4).[4]

We here report on the ring opening of **1** with several pyridinium halides and with the corresponding hydrogen halides. The results are summarized in Table I. Product

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