Kinetic and Mechanistic Studies on the Hydration of 2-Acetyl-3,4-dimethylthiazolium Ion

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The equilibrium hydration of 2-acetyl-3,4-dimethylthiazolium ion has been investigated in water–acetonitrile mixtures by using the proton inventory technique and by measuring thermodynamic activation parameters. The solvent isotope effect, $k(H_2O)/k(D_2O)$, on the rate constant, k_f, for the forward step of the equilibrium hydration varied from 3.10 to 2.58 as the volume fraction of acetonitrile was increased from 0.25 to 0.90. The solvent isotope effects were found to be consistent with a transition state consisting of two water molecules in which one water molecule acts as a general base to abstract a proton from the nucleophilic water molecule. The transition state was found to be invariant within this range of solvent composition.

Introduction

Thiamine pyrophosphate 1 is an essential cofactor for numerous enzymes which catalyze the formation and cleavage of carbon–carbon bonds adjacent to carbonyl groups.[1] Many of these transformations are catalyzed in the absence of enzyme by thiamine and simple thiazolium salts, albeit at much slower rates.[2] Since the properties of 2-acylthiazolium salts are known to mimic those postulated for the enzymatic systems,[3] the study of these compounds should provide insight into the mechanism of the biological reactions.

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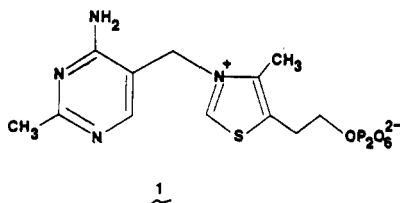
In the hydrolysis of the 2-acetyl-3,4-dimethylthiazolium ion, 2, the two steps of the reaction (Scheme I) may be followed directly because the intermediate hydrate accumulates to a significant extent.[3a] To gain information on the structure of the transition state for the hydrolysis of 2-acylthiazolium compounds, we have studied the kinetics of the equilibrium hydration of 2 in water–acetonitrile mixtures by using the proton inventory technique. Thermodynamic activation parameters for the hydration have also been determined.

Results

The equilibrium hydration of 2 has been studied in acidic solutions of pH 2 or less, or the equivalent point on the pH(D) rate profile, in 0.25, 0.50, 0.75, and 0.90 volume fractions of acetonitrile in protium oxide and deuterium oxide mixtures of atom fraction of deuterium *n*. The rate constants for the forward step of the equilibrium hydration were calculated from the observed first-order rate constants as described elsewhere[3a] and are collected in Table I. The observed solvent isotope effect on k_f at each volume fraction of acetonitrile, given in Table II, varied from 3.10
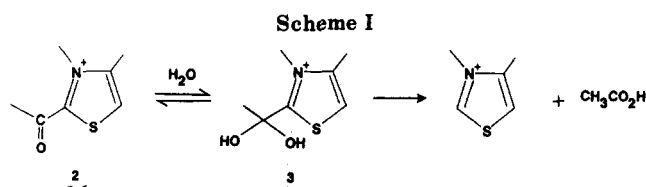
Scheme I

Table I. First-Order Rate Constants for the Forward Step of the Equilibrium Hydration of 2-Acetyl-3,4-dimethylthiazolium Ion in Different Volume Percentages of Acetonitrile at 25.00 ± 0.05 °C[a]

atom fraction of deuterium (n)[b]	$10^4 k_f$[c] s⁻¹ (vol % CH₃CN)			
	25	50	75	90
0.00	175.0 ± 2.0	145.0 ± 1.0	49.9 ± 1.2	6.45 ± 0.05
0.25	148.0 ± 1.0	110.0 ± 1.0	38.3 ± 0.2	5.36 ± 0.02
0.50	107.0 ± 6.0	89.0 ± 1.0	31.4 ± 0.3	4.28 ± 0.06
0.75	76.0 ± 4.0	61.0 ± 8.0	21.8 ± 0.7	3.23 ± 0.03
1.00	56.0 ± 1.0	48.0 ± 1.0	17.3 ± 0.1	2.50 ± 0.02

[a] The pH (pD) was maintained at 1.78, 1.90, 1.70, and 0.56 with HCl (DCl) in 25, 50, 75, and 90 vol % of acetonitrile, respectively. Ionic strength was not controlled. [b] The actual values of the atom fraction of deuterium were determined by Josef Nemeth, Urbana, IL 61801, and varied slightly from the values reported in the table. The actual values are: 25% acetonitrile 0.000, 0.196, 0.490, 0.783, and 0.979; 50% acetonitrile 0.000, 0.290, 0.484, 0.774, and 0.967; 75% acetonitrile 0.000, 0.285, 0.475, 0.760, and 0.950; 90% acetonitrile atom fraction of deuterium was not analyzed. [c] Average of three runs. Error limits are standard deviations.

Table II. Solvent Deuterium Isotope Effect on the Forward Step of the Equilibrium Hydration of 2-Acetyl-3,4-dimethylthiazolium Ion as a Function of the Volume Fraction of Acetonitrile in Water at 25.00 ± 0.05 °C[a]

volume fraction of CH₃CN	$k(H_2O)/k(D_2O)$
0.25	3.10
0.50	3.02
0.75	2.88
0.90	2.58

[a] The pH (pD) was maintained constant at each volume fraction of acetonitrile at ≤2.0 with HCl (DCl). Ionic strength was not controlled.

to 2.58 as the fraction of acetonitrile in the solvent was increased from 0.25 to 0.90. The plot of k_f versus *n* at 0.25 volume fraction of acetonitrile is shown in Figure 1 and is representative of the proton inventories obtained at other volume fractions of acetonitrile. The effect of temperature on the forward step of the equilibrium hydration of 2 was investigated at each volume fraction of acetonitrile in the solvent. Rate constants were measured at four different temperatures over the range 16–32 °C and were

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$$k_n = k_o \prod_i^{TS}(1 - n + n\phi_i)/\prod_j^{RS}(1 - n + n\phi_j) \qquad (1)$$

This means that 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.

The fractionation factors of the exchangeable protons in the transition state can be evaluated from the experimental data and the reactant state fractionation factors either by polynomial regression analysis[6] or by Albery's "γ method".[4d] Our analysis will center on the use of the γ method. This γ method requires the calculation of the curvature parameter, γ, defined by eq 2

$$\gamma = 8 \ln \left[(y_{0.5}/y_{1.0}^{1/2})\right]/\left[\ln (y_1)^2\right] \qquad (2)$$

in which

$$y_n = k_n/k_o \prod_j^{RS}(1- n + n\phi_j) = \prod_i^{TS}(1 - n + n\phi_i) \qquad (3)$$

The γ values calculated in the present study range between 0.407 and 0.546 for the water-catalyzed hydration of 2 in solvent mixtures of water–acetonitrile containing different volume fractions of acetonitrile. These values suggest that the transition state of the equilibrium hydration of 2 involves at least two and most probably three active protons (i.e. protons contributing to the observed solvent isotope effect).

Probable transition states that involve three active protons are 4 and 5. In 4, one water molecule acts as a nucleophile and the other as a general base. There are three protons in this model which could contribute to the overall solvent isotope effect. The "in-flight" proton, H_a, will contribute a primary effect and the two H_b protons will contribute secondary solvent isotope effects. The H_c proton is expected to have a fractionation factor of unity and therefore contributes nothing to the observed solvent isotope effect. This transition-state structure resembles those proposed earlier for the hydrolysis of acetylimidazole[7] and N-methylacetylimidazole.[8]
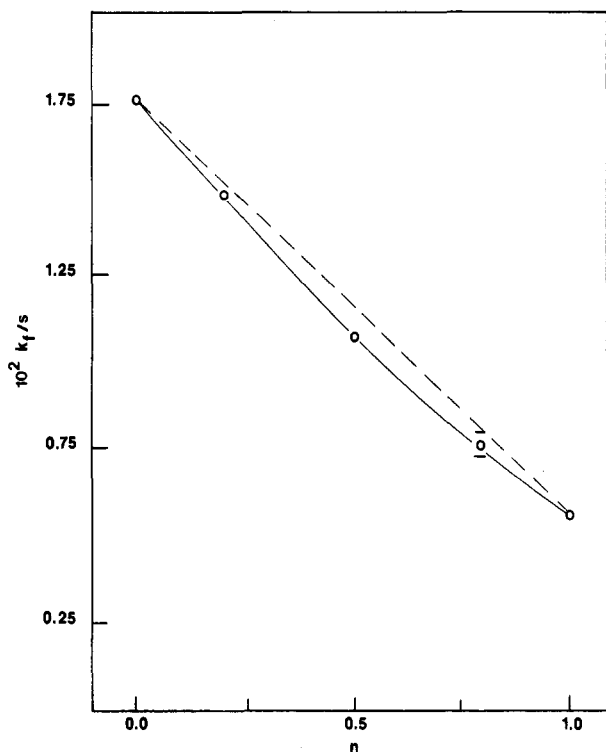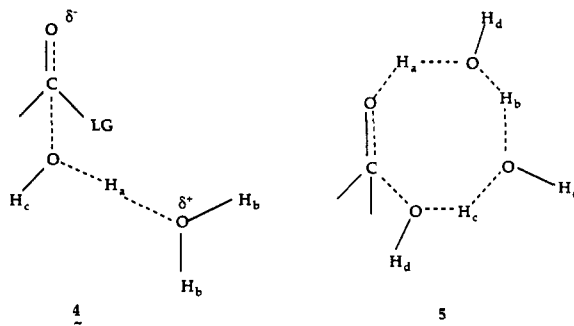

Figure 1. Proton inventory plot for the forward step of the equilibrium hydration of 2-acetyl-3,4-dimethylthiazolium ion at 25.00 ± 0.05 °C in 0.25 volume fraction of acetonitrile in water. The solid line was calculated from eq 2 with $\phi_a = 0.509$ and $\phi_b = 0.872$. Data are taken from Table I. Where error bars are omitted the circles encompass them. The dashed line is included merely to emphasize the nonlinearity of the plot.

Table III. Thermodynamic Activation Parameters for the Forward Step of the Equilibrium Hydration of 2-Acetyl-3,4-dimethylthiazolium Ion as a Function of the Volume Fraction of Acetonitrile in Water at 25.00 ± 0.05 °C[a]

volume fraction of CH_3CN	$\Delta G^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$-\Delta S^{\ddagger}$, eu
0.25	19.6	7.08	41.9
0.50	19.7	7.37	41.9
0.75	20.6	6.79	46.2
0.90	21.8	5.12	56.9

[a] The pH (pD) was maintained at each volume fraction of acetonitrile at ≤2.0 with HCl. Ionic strength was not controlled.

used to calculate the thermodynamic activation parameters shown in Table III.

Discussion

The theory of the proton inventory technique is well documented in the literature.[4] This technique has recently been used to help elucidate transition-state structures for a number of organic and enzyme-catalyzed reactions.[5] This technique includes the measurement of reaction rate constants (k_n) in mixtures of protium oxide and deuterium oxide of varying atom fraction of deuterium, n, and relates k_n to the rate constant in pure protium oxide (k_o) by the Gross–Butler equation (eq 1).

4

5

The transition state 5 involves eight atoms in the cyclic transition state and thus has proton donor–acceptor arrangements much closer to linearity in accord with the preferred requirement for intramolecular proton transfer postulated by Gandour.[9] The H_d protons in 5 should each have a fractionation factor of unity as do the H_c protons of 4 mentioned earlier. The H_a, H_b, and H_c protons may have equal or unequal fractionation factors and contribute equally or unequally to the observed solvent isotope effect. This transition state (5) is similar to that proposed by Bell

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(8) Hogg, J. L.; Phillips, M. K. *Tetrahedron Lett.* **1977**, 3011.

(9) Gandour, R. D. *Tetrahedron Lett.* **1974**, 295.

Table IV. Rate Constants and Equilibrium Constants for the Equilibrium Hydration of 2-Acetyl-3,4-dimethylthiazolium Ion as a Function of the Volume Fraction of Acetonitrile in Water at 25.00 ± 0.05 °C[a]

volume fraction of CH_3CN	$10^2 k_f$ (H_2O), s^{-1}	$10 K_{hyd}$		$K(H_2O)/K(D_2O)$
		H_2O	D_2O	
0.25	1.75	9.86	9.86	1.00
0.50	1.45	8.06	8.34	0.97
0.75	0.50	6.79	7.31	0.93
0.90	0.64	4.43	4.87	0.91

[a] The pH (pD) was maintained constant at each volume fraction of acetonitrile at ≤2.0 with HCl (DCl). Ionic strength was not controlled.

and Critchlow[10] for the water-catalyzed hydration of 1,3-dichloroacetone.

The transition states **4** and **5** contain two and three water molecules, respectively. If the reaction occurs through transition state **4**, the rate constants should exhibit a second-order dependence on the water concentration. Similarly, if it proceeds through transition state **5**, the rate constants should exhibit a third-order dependence on the water concentration.

In the present work, the rate constant for the forward step of the equilibrium hydration, k_f, decreases moderately as the solvent composition is changed from 25 to 50 volume fraction of acetonitrile. In solvents of higher volume fraction of acetonitrile, k_f decreases dramatically (Table IV). This decrease in k_f is reflected in the equilibrium constant for the hydration, K_{HYD}, that decreases by a factor of approximately two over the range of solvent compositions studied (Table IV).

The observed trend in k_f upon changing the solvent composition (curve A in Figure 2) is significantly different from the trends expected from a second-order (curve B) and a third-order (curve C) dependence of the reaction rate on water concentration. Furthermore, a plot of log k_f versus log $[H_2O]$ exhibits a break at approximately 35 vol % of water. The slope of the limb corresponding to greater than 50 vol % of water is approximately 0.5, while that corresponding to lower water concentration (less than 35 vol % of water) is approximately 2.0. It is pertinent to point out that similar plots of other acyl transfer reactions, such as the hydrolyses of 1-acetylimidazolium ion and 1-acetyl-3-methylimidazolium ion, show no such break. This clearly indicates that the break observed in Figure 2 and in the water order plot (i.e. the double log plot) is not due to the change in the solvent structure.

The proton inventory plots generated from the data obtained in the present work in different solvent mixtures have almost the same degree of curvature. This clearly suggests that the observed break in the log k_2 versus log $[H_2O]$ plot is not due to any change in the rate–determining step or in the mechanism of the reaction.

The plot of k_f versus volume percentage of water (curve A in Figure 2), as well as the plot of log k_f versus log $[H_2O]$, suggests that in lower concentrations of water the reaction has a second-order rate dependence on water concentration. Hence, hydration probably occurs via the transition state **4** under these conditions. The comparison of curves A and B in Figure 2 suggests that some compensatory process must be taking place at higher concentrations of water so that the expected decrease in the rate constant (curve B or C in Figure 2) on decreasing water concentration is masked.
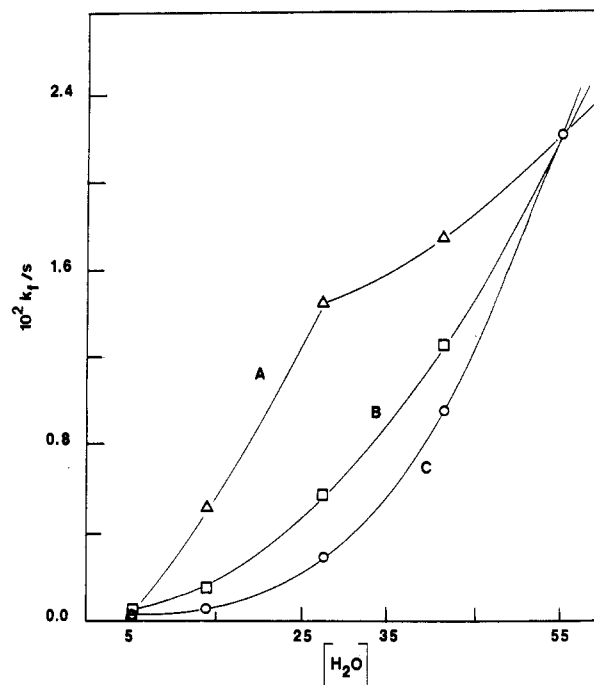
(10) Bell, R. P.; Critchlow, J. E. *Proc. R. Soc. A* **1971**, *325*, 5.
(11) Huskey, W. P.; Hogg, J. L. *J. Org. Chem.* **1981**, *46*, 2459.
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Figure 2. Plot of k_f for the water-catalyzed hydration of **2** versus the molar concentration of water in acetonitrile (curve A). Also shown are the theoretical plots for a second- and third-order dependence of reaction rate on water concentration (curves B and C, respectively).

A change in the reaction rate is normally due to a change in either the free energy of activation or in the concentration(s) of the reactant(s). In the present investigation, the free energy of activation for the forward step of the equilibrium hydration remains almost constant as the volume percentage of acetonitrile increases from 25 to 50% (Table III). This constancy in $\Delta G^\ddagger$ is not due to any compensating changes in enthalpy and entropy of activation. This clearly shows that the suspected compensatory effect comes not from changes in the activation energy nor from changes in solvent structure but rather from changes in the concentration of **2**.

The positive charge in **2** may be localized either on nitrogen or on the sulfur of the ring, and the carbonyl group of the side chain may be coplanar with the thiazolium ring or may be twisted out of the coplanarity (**6** and **7**). In
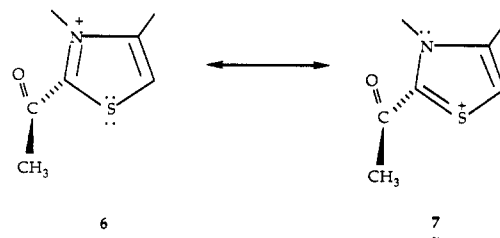
aqueous solutions **2** will be solvated as in **8** or **9** depending upon the location of the positive charge in the ring and the solvated species will be in equilibrium with their unsolvated counterparts. Further, in **8** and **9** the acyl side chain is coplanar with the thiaziolium ring and the π electron pair of the carbonyl group is in conjugation with the π system of the ring. The stabilization resulting from solvation and the extension of the π system provides the energy to surmount the barrier to rotation from the twisted to the coplanar conformation.
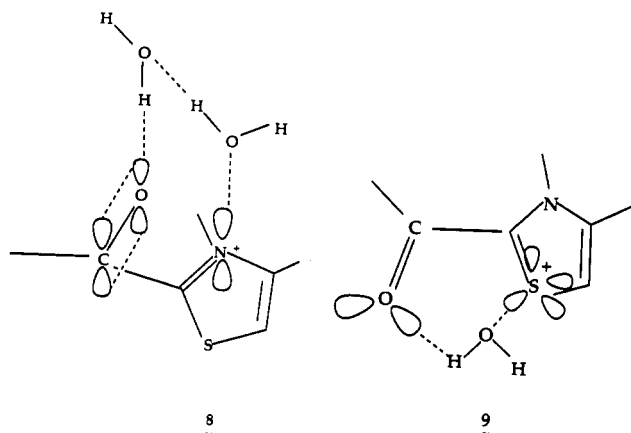
In **8** and **9**, the conjugation of the ring's π electron system with the acyl side chain reduces the electrophilicity of the carbonyl carbon and makes **8** and **9** less reactive

than **6** and **7**. However, the decrease in water concentration in the solvent mixture decreases the effective solvation in **8** and **9**, allowing the twisting of the carbonyl group out

8   **9**

of coplanarity with the ring and reducing the conjugation at the carbonyl carbon. This compensates the expected decrease in rate upon decreasing the water concentration in the solvent mixture. Such enhancement of rates due to the twisting of the coplanar conformation to unconjugate the π-systems is not uncommon. Stable,[13] Fife and Marburg,[14] and Jencks[15] have identified this effect in the hydrolyses of *N*-acetylimidazole and *N*-benzoylimidazole.

Although both the transition states **4** and **5** look reasonable, the following reasons prompt us to exclude **5** as a viable transition-state model. First, the rate of the water-catalyzed hydration of 1,3-dichloroacetone in acetonitrile–water mixtures exhibit a third-order dependence on water,[16] but in the hydration of **2** a second-order dependence on water is observed. Second, the proton inventory plots obtained in the water-catalyzed hydration of 1,3-dichloroacetone have a deeper bowing than the ones obtained for the hydration of **2**. This is evident from the comparison of the γ value of 0.26 ± 0.05[10] for the hydration of 1,3-dichloroacetone with the γ values of 0.41–0.55 obtained in the present investigation. Third, Bell and Sorensen[17] have reported an increase in activation energy of the hydration of 1,3-dichloroacetone with an increase in water concentration in water–dioxane solvent mixtures. The activation energy of the hydration of **2** exhibits the opposite trend.

An interesting observation in the present investigation is that the kinetic solvent isotope effect on k_f decreases as the concentration of water in the solvent mixture is decreased. The solvent isotope effect arises from the ratio of the fractionation factors of the reactant and transition-state protons (eq 1). The observed decrease in the magnitude of the solvent isotope effect is possible only if there is a decrease in the reactant state fractionation factors or an increase in the transition–state fractionation factors or both.

The transition state of any catalytic process can be dissected into three parts:[18] (i) the core, or entity derived largely from substrate structure, (ii) the catalytic entity, derived from catalyst, and (iii) bridges, through which the core and the catalytic entity interact. In transition state **4** the two water molecules represent the catalytic entity and the bridge. In the reactant state, the fractionation factors of these water protons are unity. In the transition state they depend upon the degree of the tetrahedral character at the carbonyl carbon which in turn depends upon the polarization of the carbonyl group. The hydration of **2** is a pH-independent reaction and exhibits no significant hydronium ion catalysis.[3a] This suggests that any solvation change at the carbonyl oxygen can have no significant effect on the polarization and on the fractionation factors of the water protons in **4**. So, the decrease in the observed kinetic solvent isotope effect on decreasing the water content of the solvent mixture should come from the changes in the core.

Although most simple cations have fractionation factors reasonably close to unity, some cations have fractionation factors significantly different from unity. This is rationalized by the different orientation of the solvent water toward cations. A cationic species with the positive charge located on sulfur has a fractionation factor of 1.13–1.15,[19] and $(n\text{-}B_u)_4N^+$ has a fractionation factor of 0.70.[19] We can assume that **2** in the form of **6** and **8** will have a fractionation factor of about 0.70 and that in the form of **7** and **9** will have a fractionation factor of 1.15 in the reactant state. If the population ratio of the species that have the positive charge localized on nitrogen and that have positive charge on sulfur in the reactant state increases in the transition state, then there will be a decrease in the core's contribution to the solvent isotope effect.

We already postulated that **6** and **7** are more reactive than **8** and **9**. In **6** and **7**, the p-π orbital of the carbonyl carbon lies in a plane that is coplanar with the ring (**10**).

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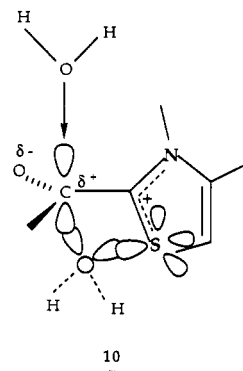
In both cases, the *N*-methyl group will cause steric and hydrophobic hindrance to the nucleophilic attack of water on the carbonyl carbon from the *N*-methyl side. So the nucleophilic attack can occur only from the sulfur side of the ring. If positive charge is localized on the sulfur, i.e., if **7** is the major resonance contributor as the reactant, the positive sulfur will compete with the carbonyl carbon for the lone pairs of the nucleophilic water. This will not only decrease the effectiveness of water as a nucleophile but also affect its proper orientation toward the carbonyl carbon. This clearly suggests that for the effective hydration of the carbonyl group in **2**, the ring and the acyl group must be in a noncoplanar conformation and the positive charge must be on the ring nitrogen rather than sulfur. In other words, **6** is the effective resonance contributor as the reactant in the hydration.

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The two structures, **6** and **7**, are resonance forms of **2**. They are not as distinctive as represented. However, in aqueous solutions, the solvation locks the charges as shown in **8** and **9** and they are in equilibrium with each other through the twisted form(s) of **2**. The solvated species **9** involves only one water molecule that bridges a filled n orbital of oxygen with an empty σ orbital of sulfur and has greater order than that in **8**. It is therefore more stable than **8**, which involves two molecules of water that bridge a positive p-π orbital of the nitrogen and a p-π orbital of the carbonyl oxygen. Thus, the population of **9** in aqueous solution should be higher than that of **8**. When the twisted form of **2** (i.e. **6**) is hydrated, the equilibrium between the solvated species and **6** shifts in favor of **6**.

Since **6** is the effective reactant and the positive charge localized on nitrogen remains through the transition state, its fractionation factor of 0.7 undergoes no change and therefore makes no contribution to the solvent isotope effect. However, since **9** transforms into **6** and reacts with water to reach the transition state, its fractionation factor changes from 1.15 in the reactant state to 0.70 in the transition state. As a result, eq 1 for the solvent isotope becomes eq 4.

$$k(H_2O)/k(D_2O) = x\frac{(1 - n + 1.15n)}{(1 - n + 0.7n)} \frac{1}{\prod_i^{TS}(1 - n + n\phi_i)} \quad (4)$$

The fractionation factors of cationic species are due to the different orientations of the solvent water toward the cations.[4d] Hence they tend to approach unity as the water molecules are replaced by aprotic solvent molecules. This results in the decrease of the value of the second term in eq 4. Further, the fraction of **2** in the form of **9** (i.e. *x*) also decreases with the decrease of water content in the solvent mixture. These decreases are the causes of the decrease in the observed solvent isotope effect. If we assume that at 90 vol % of acetonitrile the fractionation factors of the cationic species approach the unit value, eq 4 becomes eq 5 and the observed solvent isotope effect of 2.58 will be the isotope effect contributed by the transition state protons of the hydration process. As an example, assume

$$k(H_2O)/k(D_2O) = \frac{1}{\prod_i^{TS}(1 - n + n\phi_i)} \quad (5)$$

that about 65% of **2** exists as **9** in pure water. Then eq 4, coupled with eq 5, gives a solvent isotope effect of 3.31. Instead, if we assume that only 60% of **2** exists as **9**, eq 4 gives a solvent isotope effect of 3.1. The contribution from the first two terms of eq 4 to the observed solvent isotope effect is small, viz. 1.20, 1.17, and 1.12 at 75, 50, and 25 vol % of water, respectively.

The Gross–Butler equation that relates the different rate constants (k_n) obtained at different atom fraction of deuterium, *n*, in 90 vol % of acetonitrile is eq 6. Since we

$$k_n = k_0\prod_i^{TS}(1 - n + n\phi_i) \quad (6)$$

favor transition state **4** over **6**, this equation becomes eq 7 with ϕ_a = 0.509 and ϕ_b = 0.872. These values generate the observed proton inventory data at 90 volume percent of water.

$$k_n = k_0(1 - n + n\phi_a)(1 - n + n\phi_b)^2 \quad (7)$$

The Gross–Butler equation for the reactions in water containing different volume percent of acetonitrile (eq 8) can be obtained by combining eq 4 and 7.

$$k_n = k_0\frac{(1 - n + 0.7n)}{x(1 - n + 1.15n)}(1 - n + n\phi_b)^2 \quad (8)$$

In this equation, the contribution from the second term to the observed solvent isotope effect is 1.0, 1.12, 1.17, and 1.20 in 10, 25, 50, and 75 vol % of water, respectively; ϕ_a and ϕ_b are 0.509 and 0.872, respectively. This equation generates the observed proton inventory data at 75, 50, and 25 vol % of water.

Incorporation of the transition-state features of **4** into the structure of **2** gives the full structure of the transition state (**11**). In **11** a filled σ orbital on carbonyl oxygen is in proper orientation with the vacant p-π orbital of the ring nitrogen so that these two can be bridged by solvating water molecules. This solvation not only stabilizes the transition state but also accounts for the observed absence of acid catalysis in the hydration of **2**.

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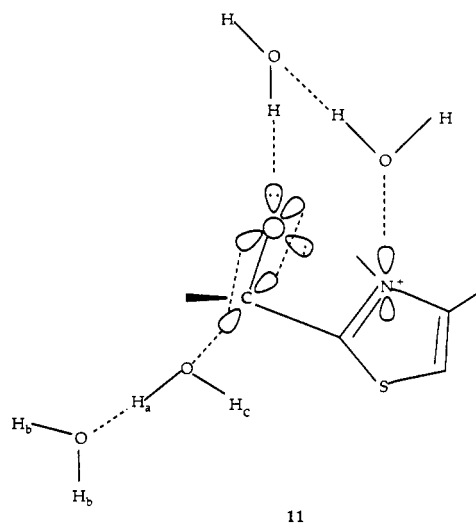
Conclusion

We have shown that the transition state for the hydration of 2-acetyl-3,4-dimethylthiazolium ion resembles the transition states of the acyl transfer reactions and involves two water molecules, one functioning as a nucleophile and the other functioning as a general base. The transition state varies little as a function of the composition of the acetonitrile–water solvent system over a wide range. Further, we have shown that the thiazolium ring plays an important role in steering the water molecules toward the carbonyl carbon in the hydration and also in stabilizing the transition state.

Experimental Section

Materials. 2-Acetyl-3,4-dimethylthiazolium iodide **2** was synthesized by using the method of Lienhard[3a] with the following modifications. 2-(1-Hydroxyethyl)-4-methylthiazole was oxidized to 2-acetyl-4-methylthiazole with pyridinium dichromate following the procedure of Schmidt and Corey.[20] The final product **2** was purified by repeated recrystallization from acetonitrile–ether; mp 145–145.8 °C (lit.[3a] mp 138–139 °C). NMR analysis on a Varian EM390 spectrometer confirmed the identity of the desired compound.

Deuterium oxide (99.8 atom % D, Aldrich), deuterium chloride (20% solution in D_2O, Aldrich), and hydrochloric acid (1 M, Fisher) were used as obtained. Acetonitrile was distilled over phosphorus pentoxide and stored under nitrogen. Water was doubly distilled. Sodium chloride was dried in an oven before use.

Reaction Solutions. The solutions containing 0.25, 0.5, 0.75, and 0.9 volume fraction acetonitrile in water were prepared by mixing the appropriate volumes of water and acetonitrile, adjusting the pH to 2.0 by addition of HCl while monitoring with a Corning

130 pH meter with combination electrode, and then dissolving the needed amount of NaCl to achieve the desired ionic strength. The solutions of acetonitrile in deuterium oxide were prepared as above except that the solutions were adjusted to pD 2.0 (pH meter reading 1.6) with deuterium chloride. The solutions for the proton inventory studies at each volume fraction of acetonitrile in H_2O-D_2O mixtures of atom fraction deuterium n were prepared by mixing appropriate volumes of the corresponding H_2O-CH_3CN and D_2O-CH_3CN solutions. The atom fraction of deuterium of exchangeable protons was calculated from the results of an analysis by Josef Nemeth (see footnote in Table I) on a sample of "100%" D_2O-CH_3CN solution.

Kinetics. The equilibrium hydration of 2-acetyl-3,4-dimethylthiazolium iodide was monitored by following the decrease in absorbance at 295 nm on a Cary 118C UV-vis spectrophotometer equipped with a constant temperature cell compartment and cell holder. Runs were initiated by 100-μL injections of a stock solution of 2 (4×10^{-3} M in CH_3CN) into a cuvette containing 3.0 mL of the appropriate $HCl-DCl-CH_3CN$ solution. A timer was started at the moment of injection to allow extrapolation

back to time zero. Runs were followed for at least 5 half-lives and exhibited good first-order kinetics. First-order rate constants were determined from linear regression analysis of plots of (A_t-A_∞) versus time using the linear regression program on an HP-11C. Equilibrium constants and rate constants for the hydration of 2 were determined from these first-order rate constants by using the equation described previously.[3a] Thermodynamic activation parameters were calculated from the rate constants of the forward step of the equilibrium hydration obtained at four temperatures between 16 and 32 °C. The activation parameters were determined from Eyring plots of ln (k/T) versus $1/T$.

The Steric Effect of Ortho Substituents on the Acidic Hydrolysis of Benzamides

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The rate constant, k, for the acidic hydrolysis of a number of substituted benzamides in water and in a dioxane–water mixture (1:1, v/v) was measured. The reaction conditions were selected to exclude the electronic effects of substituents on the overall rate as far as possible. The log k value for meta derivatives was almost independent of the electronic effects of substituents. Although the log k value for para derivatives was weakly affected by the through-resonance effect of electron-donating substituents, the value for ortho derivatives was almost linear with the Taft–Kutter–Hansch (TKH) E_s steric parameter except for NO_2 and Ph. The effective steric effects of these π-bonded planar substituents were approximated by the averaged value of the two TKH E_s constants estimated from the thickness and width of each group. The log k value was also analyzed by using the Charton v steric parameter. The differences in definition of the v from the TKH E_s parameter seriously distorted the analysis of the ortho substituent effects on the hydrolytic reaction.

We have proposed a procedure to analyze the effects of ortho substituents on the reactivity of aromatic compounds on the same basis as those of para and meta substituents. In this procedure, the Taft–Kutter–Hansch (TKH) E_s parameter was used to represent the steric effect of ortho substituents.[1,2] The original Taft E_s parameter for mostly alkyl substituents is defined by the reactivity data of the acidic hydrolysis of aliphatic esters.[3] For such substituents as halogens, alkoxy, alkylthio, and π-bonded planar groups, the E_s value cannot be evaluated experimentally under the same conditions as that for alkyls. Charton has found that the Taft E_s value of alkyl groups of a similar structural type is quantitatively related to their van der Waals dimensions.[4] On the basis of this finding, Kutter and Hansch have extended the E_s value to non-alkyl substituents by using their appropriate van der Waals dimensions.[5] The TKH E_s is a combined set of parameters of

the original Taft E_s and those extended by Kutter and Hansch. Although the Taft E_s is defined for aliphatic substituents, the TKH E_s has been shown to apply in certain cases to substituents at various positions of aromatic molecules in correlation analysis of biological activities with structural properties[5–8] besides the above-mentioned aromatic ortho substituent effects.

Two types of TKH E_s values are estimated from the half-width and the half-thickness of each π-bonded planar substituent.[5] In our previous analysis of ortho effects, either of the two E_s parameters was selected, depending upon the situation, but the criterion for the selection was somewhat arbitrary.[2] We also noticed that occasionally neither of the two parameters rationalizes the ortho steric effect satisfactorily. In addition, the TKH E_s value for OR, NHR, and SR groups, which is evaluated from the van der Waals radius (r_v) of O, N, and S atoms, sometimes does not predict the reactivity well, especially when the R group

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