Immature Hydronium Ion Implicated in Water-Catalyzed Immonium Ion Hydrolysis[1]

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The water-catalyzed hydrolysis of the dimethylimmonium ion of benzophenone exhibits a solvent deuterium isotope effect of $k_{H_2O}/k_{D_2O} = 2.19$. Proton inventory studies in protium oxide–deuterium oxide mixtures of atom fraction deuterium n indicate identical contributions of three protons to the observed effect. Each proton exhibits an isotope effect of about 1.30. The downwardly curved proton inventory can be fit to the equation $k_n/k_0 = (1 - n + n\phi^*)^3$ where $\phi^* = 0.768$. The data support a transition-state structure involving an immature hydronium ion.

Several detailed studies of the base-catalyzed and water-catalyzed hydrolysis of Schiff bases have been reported.[3-9] Much of the impetus for these studies derives from the occurrence of such compounds in the catalytic mechanism of several enzymes, including acetoacetate decarboxylase[10] and aldolase[11] among others. Since proton transfer and solvent participation are of major importance in the hydrolysis of such compounds, we felt that proton inventory studies would be useful in elucidating the details of the transition-state structure for such a reaction. The compound chosen for study models the protonation state of Schiff bases at low-pH values and has been the object of much investigation.[3,4,9] The dimethylimmonium ion of benzophenone (1) exhibits a pH-independent region for

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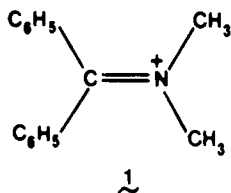
hydrolysis between pH 2 and 6.5 due to the cationic nature of the compound (i.e., further protonation of nitrogen is prevented). Previous studies have shown that this pH region corresponds to water-catalyzed hydrolysis of 1.[3,4,9]

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Table I. First-Order Rate Constants for the Water-Catalyzed Hydrolysis of 1 at 50.00 ± 0.05 °C in H₂O–D₂O Mixtures of Atom Fraction of Deuterium n[a]

deuterium atom fraction (n)	no. of runs	$10^6 k_n$, s⁻¹ obsd	$10^6 k_n$, s⁻¹ calcd[b]
0.000	5	1409 ± 6[c]	1409
0.248	5	1179 ± 8	1180
0.495	4	978 ± 3	978
0.743	5	801 ± 4	800
0.990[d]	4	644 ± 3	645

[a] The pH(D) was maintained at 3.0 by using 10⁻³ M HCl (DCl). Ionic strength was kept at 0.5 M with KCl. [b] Calculated on the basis of eq 8 for transition state 6 with $\phi_a^* = 0.768$. [c] Error limits are standard deviations. [d] Atom fraction of deuterium in "pure" 10⁻³ M DCl solution as determined by Josef Nemeth.[31]

Table II. First-Order Rate Constants for the Water-Catalyzed Hydrolysis of 1 as a Function of Volume Fraction of Acetonitrile in the Solvent at 25.00 ± 0.05 °C[a]

volume fraction of CH₃CN[b]	$10^6 k$, s⁻¹
0.0	220 ± 3[c]
0.1	270 ± 5
0.2	336 ± 4
0.3	414 ± 4
0.4	493 ± 4
0.5	536 ± 5
0.6	568 ± 2

[a] The pH was maintained at 3.0 by using 10⁻³ M HCl, and the ionic strength was kept at 0.5 M with KCl. [b] Before mixing. [c] Average of at least two determinations. Error limits are standard deviations.

Results

Table I summarizes the data obtained for the hydrolysis of 1 at 50 °C in protium oxide, deuterium oxide, and mixtures of atom fraction of deuterium n of the two at pH 3.0 or the equivalent pD. This table also contains the calculated rate constants predicted on the basis of a chemical model to be discussed. The proton inventory plot (Figure 1) for the data of Table I is clearly downwardly
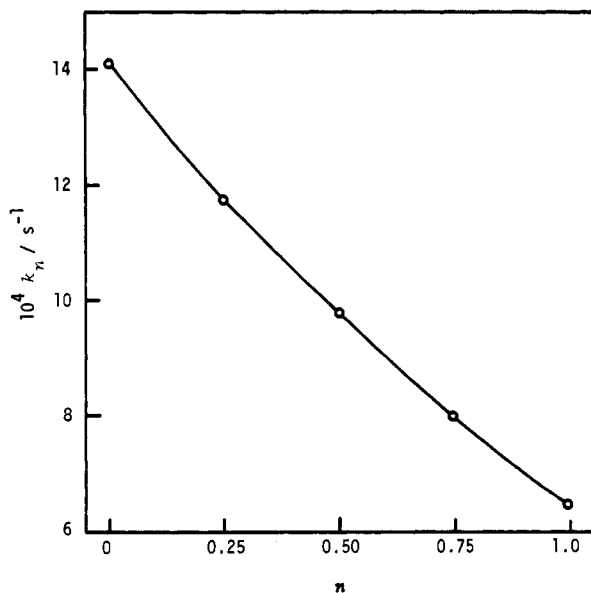
Figure 1. Proton inventory plot of the first-order rate constants, k_n, for the hydrolysis of 1 as a function of the atom fraction of deuterium (n) in the solvent. The data are taken from Table I. The solid line is calculated for transition state 6 (assuming H_a approximates H_b) based on eq 8 with $\phi_a{}^* = 0.768$.

Table III. First-Order Rate Constants for the Water-Catalyzed Hydrolysis of 1 as a Function of Ionic Strength at 50.35 ± 0.05 °C[a]

ionic strength, M	$10^6 k$, s^{-1}
0.0	1726 ± 35[b]
0.5	1465 ± 32
1.0	1260 ± 19
1.5	1089 ± 39
2.0	1008 ± 2
2.5	897 ± 21

[a] The pH was maintained by using 10^{-3} M HCl, and the ionic strength was kept at 0.5 M with KCl. [b] Average of at least two determinations. Error limits are standard deviations.

curved, indicating multiple proton contributions to the observed solvent deuterium isotope effect of k_{H_2O}/k_{D_2O} = 2.19.

Table II shows the dependence of the observed first-order rate constants for hydrolysis on the volume fraction of acetonitrile in the solvent water. Experimental problems with the solvent absorbance at 300 nm prevented the use of higher volume fractions of acetonitrile. The rate constant increases by more than 2.5-fold as the solvent is changed from pure water to 0.6 volume fraction acetonitrile. Table III and Figure 2 show the approximately 2-fold decrease in rate constant as the ionic strength is changed from zero to 2.5 M in water. Table IV contains rate constants as a function of temperature in the range 25.0 to 50.35 °C. This study allowed determination of the activation parameters: $\Delta H^{\ddagger}$ = 15.2 kcal/mol, $\Delta S^{\ddagger}$ = -24.5 e.u., and $\Delta G^{\ddagger}$ = 22.9 kcal/mol.

Discussion

The proton inventory technique involves the measurement of reaction rate constants (k_n) in mixtures of protium oxide and deuterium oxide of atom fraction deuterium n.[12-14] The observed rate constant, k_n, is related to the
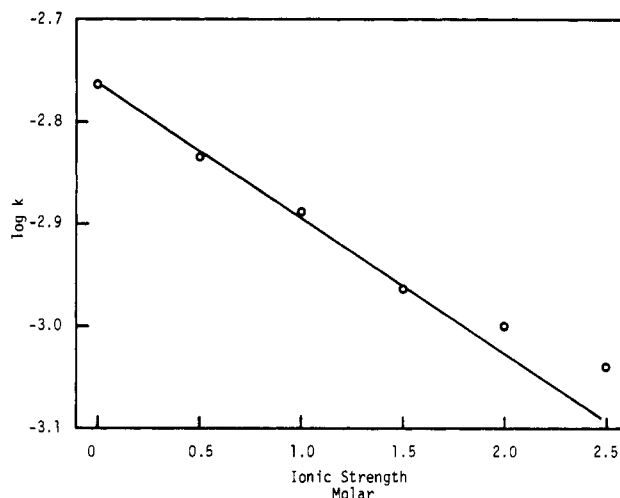

Figure 2. Influence of ionic strength upon the first-order rate constants for the hydrolysis of 1. The data are taken from Table III. The solid line in the figure is drawn merely to emphasize the nonlinear dependence.

Table IV. Temperature Dependence of the First-Order Rate Constants for the Water-Catalyzed Hydrolysis of 1[a]

T, °C	$10^6 k$, s^{-1}
25.00	178 ± 5[b]
31.55	314 ± 3
38.06	543 ± 1
45.35	978 ± 7
50.35	1465 ± 32

[a] The pH maintained at 3.0 by using 10^{-3} M HCl. Ionic strength was maintained at 0.5 M with KCl. Reaction solutions contained 0.8% CH_3CN. [b] Error limits are standard deviations for average of two or more runs.

rate constant, k_0, in pure protium oxide by the Gross–Butler expression (eq 1) where the contributions of i exchangeable transition-state (TS) protons and j exchangeable reactant-state (RS) protons are characterized by their

$$k_n = [k_0 \prod_i^{TS} (1 - n + n\phi_i{}^*)] / [\prod_j^{RS} (1 - n + n\phi_j{}^*)] \quad (1)$$

changeable transition-state (TS) protons and j exchangeable reactant-state (RS) protons are characterized by their respective isotopic fractionation factors $\phi_i{}^*$ and $\phi_j{}^*$. The present case is one in which all of the isotopically exchangeable reactant-state sites are solvent sites with $\phi_j{}^*$ = unity. Additional details of the proton inventory technique can be found in several reviews.[12-14]

The magnitude of the solvent deuterium isotope effect and the observed curvature of the proton inventory plot (Figure 1) suggests that multiple protons contribute to the isotope effect. Quantitative analysis of the data in Table I by Albery's γ method[14] yields a γ value of 0.33 ± 0.05. Since γ^{-1} is an indication of the number of protons involved, a tentative assumption is that we are dealing with contributions to the solvent isotope effect from at least three protons.

A "three-proton" transition-state structure for the hydrolysis of 1 is very reasonable, based on numerous analogies for the hydrolysis of several acyl compounds.[15-19]

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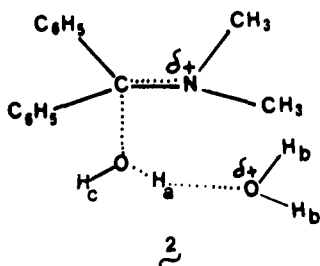
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Such a transition-state structure in which one water molecule acts as a base to abstract a proton from the nucleophilic water molecule is shown as **2**. On the basis of

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proton inventory studies, one expects the "in-flight" H_a to contribute a primary isotope effect and both H_b's to contribute secondary isotope effects. The proton H_c has generally been assumed to make no contribution to the observed isotope effect since it is likely that its fractionation factor remains unity as it undergoes transition from a water proton to an alcohol-like proton during the reaction.[13] Both of these species have unit fractionation factors for the proton bonded to oxygen. The Gross–Butler equation for a structure such as **2** is shown as eq 2, in a

$$y_n = \frac{k_n}{k_0} = (1 - n + n\phi_a^*)^a (1 - n + n\phi_b^*)^b \qquad (2)$$

form put forth by Albery,[14] with $a = 1$ and $b = 2$. Albery has shown that the γ value defined by eq 3 is related to his Λ_A value by eq 4 and that $\Lambda_B = 1 - \Lambda_A$.[14] These

$$\gamma = 8 \ln [y_{0.5} y_{1.0}^{-0.5}][\ln y_{1.0}]^{-2} \qquad (3)$$

$$a\gamma = \Lambda_A{}^2 + \frac{a}{b}(1 - \Lambda_A)^2 \qquad (4)$$

equations can be used to determine Λ_A and Λ_B, which can then be used to arrive at estimates of the fractionation factors ϕ_a^* and ϕ_b^* from eq 5 and 6. This was done by

$$\phi_a^* = \exp\left[\frac{1}{a}(\ln y_{1.0})\Lambda_A\right] \qquad (5)$$

$$\phi_b^* = \exp\left[\frac{1}{b}(\ln y_{1.0})\Lambda_B\right] \qquad (6)$$

using a computer program, GAMISO I, provided by Albery. This analysis yielded two possible but not very different sets of values: (i) $\phi_a^* = 0.753$, $\phi_b^* = 0.779$ and (ii) $\phi_a^* = 0.788$, $\phi_b^* = 0.762$.

In transition-state structure **2**, one would expect the "in-flight" proton H_a to exhibit a fractionation factor near 0.5.[15–20] The analysis above yields values closer to 0.75–0.79. These values are unrealistic for such a proton. Kresge has argued that the size of the secondary factors ϕ_b^* can be used as a measure of the extent of proton transfer to the basic water molecule.[21] Equation 7 relates

$$\phi_b^* = \phi_{H_3O^+}^\alpha \qquad (7)$$

the fractionation factor ϕ_b^* to the fractionation factor of 0.69 for a hydronium ion ($\phi_{H_3O^+}$) and the extent of proton transfer (α). Use of $\phi_b^* = 0.779$ or 0.762 gives α values of 0.67 and 0.73, representing roughly 70% transfer of H_a to the basic water molecule. This contrasts sharply with the extent of proton transfer estimated from the Brønsted β

Table V. Comparison of the Observed Ratios of k_n/k_0 with Those Predicted by eq 2 and 8 for the Water-Catalyzed Hydrolysis of **1** in H_2O–D_2O Mixtures of Atom Fraction of Deuterium n

atom fraction of deuterium (n)	k_n/k_0 obsd[a]	k_n/k_0 calcd		
		eq 2 $\phi_a^* = 0.753$ $\phi_b^* = 0.779$	eq 2 $\phi_a^* = 0.788$ $\phi_b^* = 0.762$	eq 8 $\phi_a^* = 0.768$
0.000	1.000	1.000	1.000	1.000
0.248	0.837	0.839	0.839	0.838
0.495	0.694	0.696	0.697	0.694
0.743	0.568	0.571	0.571	0.568
0.990	0.457	0.461	0.462	0.458

[a] Calculated from the rate constants in Table I.

value of 0.24 for general-base catalysis by bases with pK_a values between 1.03 and 7.06.[4,9] However, it should be noted that the water point falls below the Brønsted line for catalysis by carboxylate and other oxygen bases. Both of these observations tend to disfavor transition state **2** as written, although the mathematical fit (Table V) is very good for eq 2 with the calculated ϕ_a^* and ϕ_b^* values.

Another possible transition-state structure one should consider on the basis of the near equivalence and magnitude of the ϕ_a^* and ϕ_b^* values calculated by GAMISO I is a cyclic one in which three protons contribute equally to the solvent isotope effect. Such transition states have been proposed before.[22,23] A representation of this transition state is shown as **3**. The Gross–Butler equation for this

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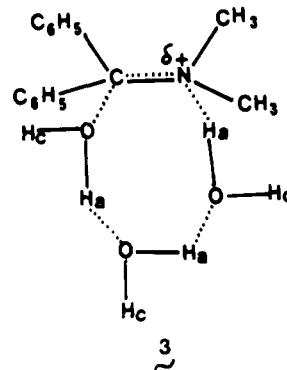
structure is given by eq 8. In **3** the protons labeled H_c

$$k_n/k_0 = (1 - n + n\phi^*)^3 \qquad (8)$$

are assumed to contribute nothing to the solvent isotope effect. Rearrangement of eq 8 to eq 9 indicates that a plot of $(k_n/k_0)^{1/3}$ vs. n should give a straight line whose slope

$$(k_n/k_0)^{1/3} = (\phi_a^* - 1)n + 1 \qquad (9)$$

is $\phi_a^* - 1$. Such a plot yields a straight line with a correlation coefficient equal to 0.9999 and a ϕ_a^* value of 0.768. Table V also shows that eq 8 reproduces the experimental data very well when this value is used.

We are again faced with another transition-state structure that is mathematically possible but seems chemically unreasonable. Cordes and co-workers[4] previously showed that the rate of hydrolysis of **1** increases if one replaces the N-methyls by hydrogen. If structure **3** is the correct transition-state structure, one might expect opposing influences on the reaction rate upon substitution of hydrogen by methyl. Although the electron-releasing ability of the methyl groups should stabilize the reactant state due to

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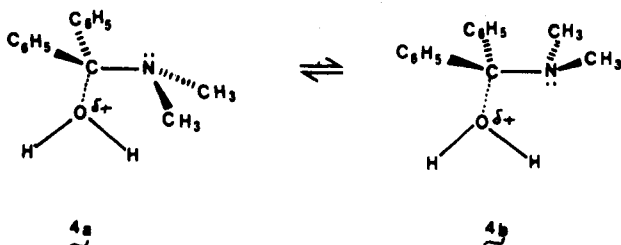(19) Karzijn, N.; Engberts, J. B. F. N. Tetrahedron Lett. 1978, 1787.
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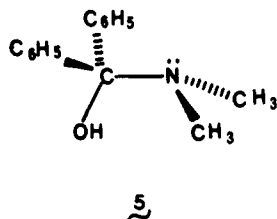(23) Gopalakrishnan, G.; Hogg, J. L. Bioorg. Chem. 1981, 10, 243.

its positive charge, one would expect additional electron release to nitrogen to enhance its basicity in a transition state such as 3. The former effect would reduce reactivity while the latter would increase reactivity if a transition state like 3 is involved. In fact, compound 1 reacts more rapidly when the methyl groups are replaced by hydrogen. Thus, the bearing of this result on the structure of the transition state is debatable, but it possibly disfavors transition state 3 since the reactant-state nitrogen is nonbasic and an increase in basicity does not appear to enhance reactivity. Jencks et al. have considered bifunctional acid–base catalysis in the hydrolysis of such compounds.[9,24] Compound 1 did not exhibit such catalysis presumably because of the unfavorable nonbonded interactions between the two phenyl groups and the two methyl groups shown in 4b. This interaction must pro-

hibit rotation or inversion of the dimethylamino group. Such rotation or inversion would be required for the cyclic transition-state structure 3 to be important if the proton transfer is to be linear. Thus, the absence of bifunctional catalysis in the hydrolysis of 1 argues against transition-state structure 3.

Albery has argued that the value of the fractionation factor for H_a in 2 provides information about the nature of the proton transfer.[14] If ϕ is less than 0.3, the proton transfer is simple; if it is between 0.4–0.7, the proton transfer is concerted; and if it is greater than 0.7, the proton is not transferring in the transition state.[14] The values required in the present study for $\phi_a{}^*$ are all greater than 0.7, indicating the proton H_a is not "in-flight".

The groups of Cordes and Jencks have established that the formation of the carbinolamine (5) is the rate-deter-

mining step in the water-catalyzed hydrolysis of 1.[3,4] If the proton is not transferring in the rate-determining step, then we can expect that more than one transition state precedes the formation of the carbinolamine. It is likely that the formation of carbinolamine occurs through a series of three different transition states in which major portions of the heavy-atom motion and proton transfer occur in different transition states. Thornton has elegantly considered such a possibility in two fine papers[25,26] and suggested that the coupling of proton motions with those of heavy atoms, a generally avoided phenomenon,[27] may be avoided by the hypothesis of two consecutive transition states. He suggested a first transition state similar to 2

in which H_a is in a strong, approximately symmetrical (half-transferred) hydrogen bond. The reaction-coordinate motion is primarily nucleophilic attack of water on the carbonyl carbon atom. The second transition state would be one in which the reaction-coordinate motion is that due to significant transfer of H_a from the nucleophilic water to the general-base water with no change in the C–O distance. This would give the nucleophilic water considerable hydroxide character and the general-base water considerable hydronium ion character and reduce the mutual repulsion of positive charges. Schowen has referred to this as an immature hydronium ion transition state.[18] The premature hydronium ion forming in this transition state would be solvated by solvent water. The third and rate-determining transition state would be one in which completion of formation of the C–O bond occurs with completion of breakage of the C–N π bond. The premature hydronium ion would still be present and is shown to be solvated by two additional waters as shown in 6. The
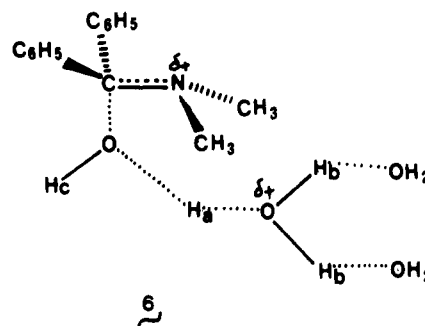
greater nucleophilicity of the partially developed hydroxide ion would aid in allowing the π electrons of the C–N bond to swim against the inductive effect of the methyl groups on nitrogen and quench the positive charge on nitrogen.

In the proposed rate-determining transition state 6, the three protons, H_a and two H_b's, are in similar bonding states and their isotopic fractionation factors depend upon the amount of positive charge developed on the basic water oxygen atom. Thus, all three protons exhibit a fractionation factor of 0.768, which correlates with approximately 71% of a full positive charge on oxygen, on the basis of the relation between extent of proton transfer and fractionation factor developed by Kresge.[21] Thus, this water molecule fits the requirements for a premature hydronium ion. As we have already seen, eq 8 and 9, which would be consistent with 6, reproduce the experimental data very well. The two solvating water molecules are isotopically equivalent to solvent water and make no contribution to the observed isotope effect but are consistent with the observed fourth-order dependence of the reaction rate on the water concentration in formic acid.[6] In fact, this transition state is not very different from that proposed by Jencks and Hand.[6]

The influence of added acetonitrile (Table II) upon the reaction can be explained in the following way. The cationic reactant 1 will experience a destabilization as the percentage of acetonitrile in the solvent system is increased. The less polar acetonitrile should be less capable of solvating the immonium ion but should exert a positive influence on transition states in which charge is delocalized. Just as one sees an increase in rate as the methyl groups on nitrogen are switched to hydrogen, due in part to less stabilization of the positive charge by hydrogen, one expects less solvation of the positive charge on nitrogen to allow for a more facile transfer of the π electrons to nitrogen. This will, in turn, increase the partial charge on carbon, making it more susceptible to nucleophilic attack.

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This should shift the rate-determining transition state to 2 in which the attacking water molecule has less hydroxide ion character than in 6 where a better nucleophile is required. Thus, the rate increase in the solvent with increasing amounts of acetonitrile is attributed to (i) desolvation of the reactant, which raises its energy, and (ii) stabilization of the transition state in which charge is more delocalized.

Formation of transition state 2 involves heavy-atom motion for the formation of the C–O bond. This requires removal of solvent molecules from the region between the nucleophilic oxygen and the electrophile carbon and more favorable reorganization of the solvent around the reaction center. In acetonitrile–water mixtures, both centers are less solvated to begin with than in pure water. Hence, less desolvatioin is required in these solvent mixtures, and due to the effects discussed above, transition state 2 is rate determining.

In pure water there is a high degree of solvation and, consequently, more solvent reorganization is required. The removal of more solvent molecules from the area around the nucleophilic and electrophilic centers leaves unsolvated regions of high polarity. This results in nonspecific dipolar attractions for solvent molecules and causes a net constriction of the surrounding solvent cage to produce a net increase in general solvation. This exerts a parallel effect on the structure of the transition state, shifting it from 2 to 6 with greater solvent release. The opposite situation holds in acetonitrile–water mixtures, and we see a shift in structure of the transition state from 6 to 2.

The formation of 6 involves both heavy-atom motion and solvent reorganization. Heavy-atom motion requires a release of solvent molecules, but this very solvent release causes a constriction of the solvent cage due to the dipolar attractions. The result is a net increase of solvent structure, which accounts for the observed $\Delta S^* = -24.5$ eu. The bonding changes coupled with the required desolvation energy account for $\Delta H^* = 15.2$ kcal/mol.

The observed inhibition of rate caused by the increase in ionic strength (Table III) is similar to the effect observed in the hydrolysis of cationic acyl compounds such as 1-acetylimidazolium ion[28] and acetylpyridinium ion.[29] The plot of log k vs. salt concentration (Figure 2) in nonlinear, and, hence, it is not possible to determine the Setschenow constant for the inhibition. It is likely that the inhibition can be attributed to the formation of an unreactive ion pair at high salt concentrations although other explanations are possible.

Experimental Section

Materials. The iodide salt of the dimethylimmonium ion of benzophenone (1) was prepared by the method of Hauser and Lednicer,[30] purified by continuous Soxhlet extraction with anhydrous ether for 6 h, and dried over P_2O_5 under vacuum. Deuterium oxide (99.75 atom % deuterium; Bio-Rad) and deuterium chloride (20% solution in D_2O; Aldrich) were used as obtained. Potassium chloride was oven-dried before use.

Kinetics. The hydrolysis of 1 was monitored by following the increase in absorbance at 250 nm on a Cary 118C UV–Vis spectrophotometer equipped with a constant-temperature cell compartment and cell holder to control the temperature at 50 ± 0.05 °C.

Reactions were initiated by injections of 25 μL of a stock solution, which was 1.44×10^{-2} M in 1, in acetonitrile into 3.00 mL of the appropriate HCl, DCl, or HCl–DCl solution. Stock 10^{-3} M HCl and DCl solutions in H_2O and D_2O, respectively, were prepared from concentrated hydrochloric acid and 20% DCl solution in D_2O, respectively. The amount of protium introduced into the 10^{-3} M solution in D_2O in this manner was determined by Josef Nemeth.[31] This factor has been considered in the data analysis. Reactions in H_2O–D_2O mixtures were carried out by using appropriate volumes of HCl–H_2O and DCl–D_2O stock solutions.

Reactions were followed for more than 3 half-lives. Absorbance values at 20-s intervals were collected by using a Micromation computer interfaced to the Cary 118C spectrophotometer. The data were then analyzed by using a nonlinear least-squares computer program. Plots of log $(A_t - A_\infty)$ vs. time were used in a confirmatory fashion.

Registry No. 1·I, 1209-96-7; D, 16873-17-9.

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