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Transition State Structure for the Water-Catalyzed Hydrolysis of *p*-Nitrophenyl Trifluoroacetate in Acetonitrile

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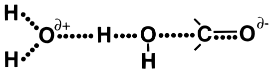
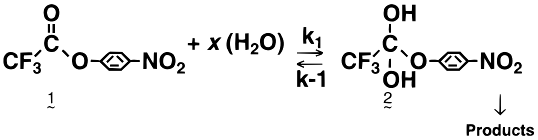
The neutral hydrolysis of *p*-nitrophenyl trifluoroacetate in acetonitrile solvent has been studied by varying the molarities of water from 1.0 to 5.0 at 25 °C. The reaction is found to be third order in water. The reaction is also third order in D_2O and in methanol when D_2O and methanol replace water as the solvent. The kinetic solvent isotope effect is $(kH_2O/kD_2O) = 2.90 \pm 0.12$. Proton inventories at each molarity of water studied are consistent with an eight-membered cyclic transition state model. In this model, three protons undergo bonding changes. Such an eight-membered transition state model can easily accommodate linear hydrogen bonds for the three transferred protons. These results are consistent with the experimental findings of Bell and Critchlow[1] on the reversible addition of water to 1,3-dichloroacetone in dioxane and the theoretical findings of Wolfe and co-workers[2] on the hydration of formaldehyde.

The water-catalyzed hydrolysis of esters and related carboxylic acid derivatives in aqueous solutions is thought to proceed via a three-proton transition state involving two water molecules as shown below.[3]



Proton transfers through a set of ordered water molecules between two active site residues seem to play a critical role at the active site of the enzyme carbonic anhydrase.[4] Do such ordered molecules of water play a role in proton transfers in a nonaqueous medium for simple organic reactions? There is considerable interest in the role of hydrogen bonds in such proton transfer mechanisms in view of the recent suggestions that low barrier hydrogen bonds (LBHB) may play an important role in enzyme catalysis.[5] We have studied the neutral hydrolysis of *p*-nitrophenyl trifluoroacetate, 1, in acetonitrile with water concentrations ranging from 1.0 to 5.0 M in order to characterize the transition state structure for water reactions in a nonaqueous medium (Table 1). We have also conducted proton inventories at different molarities of water to test whether there is any variation in the transition state structure with increasing water content. Interest in the mechanism of water-catalyzed reactions of organic substrates at low concentrations of water in a predominantly nonaqueous medium was spurred by the pioneering work of Hammett and his co-workers.[6]

Scheme 1



Results

A simple kinetic pathway for the neutral hydrolysis of **1** in acetonitrile is shown in Scheme 1. The decomposition of the tetrahedral intermediate **2** to products should be considerably faster than the reversal of **2** to reactants because *p*-nitrophenoxide is a better "leaving group" than hydroxide ion. Thus, the kinetic information obtained in this study pertains to the addition step rather than the elimination step.

For Scheme 1:

$$\begin{aligned} \text{rate} &= k_1[\mathbf{1}][H_2O]^x \\ &= k_{obs}[\mathbf{1}], \text{ since } [H_2O] \gg [\mathbf{1}] \end{aligned}$$

Hence, $k_{obs} = k_1[H_2O]^x$ and $\log k_{obs} = \log k_1 + x \log[H_2O]$. A plot of $\log k_{obs}$ versus $\log[H_2O]$ should be linear, and the slope of such a plot should give x, an apparent order with respect to water. Figure 1 shows such a plot.

Figure 1 also includes plots of $\log k_{obs}$ versus $\log [D_2O]$ and the plot of $\log k_{obs}$ versus $\log [CH_3OH]$. All these plots are linear and parallel suggesting that the apparent order in H_2O, D_2O and methanol are the same. The apparent orders are 3.22 for both H_2O and D_2O, and 2.87 for CH_3OH.

The water reaction is 2.96 times slower in D_2O than in H_2O, and the measured kinetic solvent isotope effect is the same, within experimental error, for the different molarities of water studied. The rates were also measured in mixtures of H_2O and D_2O for each molarity of water employed. The plot of k_n, the measured rate constant at an atom fraction of deuterium n of the solvent, is nonlinear against n and gives a bowl-shaped

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Table 1. Observed First-Order Rate Constants for the Neutral Hydrolysis of *p*-Nitrophenyl Trifluoroacetate in Acetonitrile at Various Molarities of Water, D_2O, and Mixtures of H_2O/D_2O at 25 ± 0.10 °C

atom fraction of deuterium	10^4k_{obs}, s^{-1}				
	1.0 M L_2O^a	2.0 M L_2O	3.0 M L_2O	4.0 M L_2O	5.0 M L_2O
0	3.03 ± 0.62	2.81 ± 0.50	107.7 ± 0.66	308.4 ± 2.0	545.1 ± 2.0
0.249	2.32 ± 0.10	23.5 ± 0.32		221.9 ± 1.6	414.3 ± 4.1
0.499	1.83 ± 0.16	18.4 ± 0.50	68.1 ± 0.58	178.6 ± 0.87	316.5 ± 2.4
0.748	1.33 ± 0.14	14.2 ± 0.22		134.5 ± 1.54	253.1 ± 2.3
0.998	1.06 ± 0.14	10.4 ± 0.41	36.8 ± 0.87	101.9 ± 1.00	184.1 ± 0.87
(kH_2O/kD_2O)	2.86	2.70	2.92	3.03	2.96

[a] L = H or D.

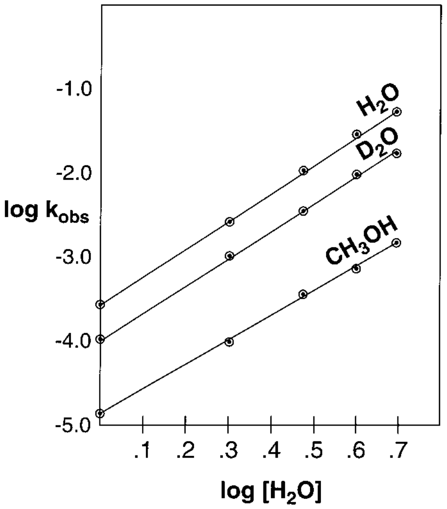

Figure 1. Plots of log k_{obs} vs log[H_2O], log[D_2O], and log[CH_3OH].

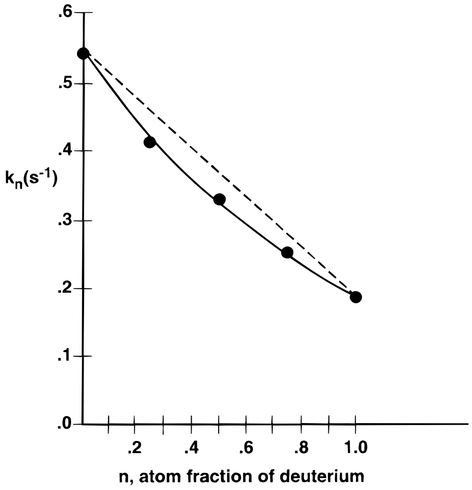

Figure 2. Plots of log k_n vs n at [H_2O] = 5.0. The solid line is based on $k_n = k_0(1 - n + 0.697n)^3$. The broken line is drawn to emphasize the nonlinearity of the solid line.

proton inventory for each molarity of water studied.[7] Figure 2 shows the proton inventory plot at a water molarity of 5.0. No solvent isotope effect was measured for the methanol reaction because the reaction is too slow to make any accurate rate measurements at 25 °C.

Discussion

The kinetic orders in H_2O, D_2O, and CH_3OH, are 3.22 ± 0.25, 3.22 ± 0.25, and 2.87 ± 0.18, respectively. While the exact values of these orders are not critical they suggest that three molecules of H_2O, (D_2O or CH_3OH) are involved in the rate-limiting transition state. The fact that the reaction is approximately three times slower in D_2O compared to water suggests that proton transfers occur as part of the rate-determining step.

In proton inventory experiments rates are measured in H_2O and D_2O and mixtures of H_2O and D_2O. The measured rate constants (k_n) are plotted against the atom fractions of deuterium (n) of the solvent. The relationship between k_n and n was first derived for special cases by Gross and Butler[8] and later put into the currently used general form of eq 1 by Kresge.[9] Equation 1 relates the rate constant k_n for a given n value to the rate constant k_0 in pure H_2O as shown below.

$$k_n = k_0 \frac{\prod_i^{\mathrm{TS}}(1 - n + n\phi_i^*)}{\prod_j^{\mathrm{RS}}(1 - n + n\phi_j)} \qquad (1)$$

where ϕ_i^* and ϕ_j are the isotopic fractionation factors for each exchangeable hydrogenic site present in the transition state and the reactant state, respectively. The isotopic-fractionation factor ϕ for any given site is the ratio of the preference of that site for protium compared to deuterium relative to similar preference of a solvent site. For sites that show a greater preference for protium than deuterium relative to the solvent, the fractionation factor will be less than unity. The application of the Gross−Butler equation to characterize proton transfers has been amply illustrated by Gold,[10] Kresge,[11] and Schowen.[12] Schowen's group has been mainly instrumental in utilizing this technique to its full advantage.

For the system under study the only exchangeable protons in the reactant state are those of solvent water, and the isotopic fractionation factor for water protons is 1.0. Therefore, eq 1 reduces to eq 2, which contains terms from the transition state only.

$$k_n = k_0 \prod_i^{\mathrm{TS}}(1 - n + n\phi_i^*) \qquad (2)$$

If more than one transition state site contributes to the isotope effect, then the plot of k_n versus n will be

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Table 2. List of Partial Solvent Isotope Effect (k_n/k_0) Values at Different Molarities of Water

n, atom fraction of deuterium	(k_n/k_0)					
	1.0 M H_2O	2.0 M H_2O	3.0 M H_2O	4.0 M H_2O	5.0 M H_2O	(k_n/k_0) (mean)
0	1.0	1.0	1.0	1.0	1.0	1.0
0.249	0.766	0.837		0.719	0.760	0.771 ± 0.049
0.499	0.605	0.655	0.632	0.579	0.598	0.614 ± 0.030
0.748	0.439	0.504		0.436	0.464	0.461 ± 0.031
0.998	0.350	0.370	0.342	0.330	0.338	0.346 ± 0.015
(kH_2O/kD_2O)	2.86	2.70	2.92	3.03	2.96	2.90 ± 0.124
γ	0.169	0.610	0.547	0.052	0.190	0.314 ± 0.249

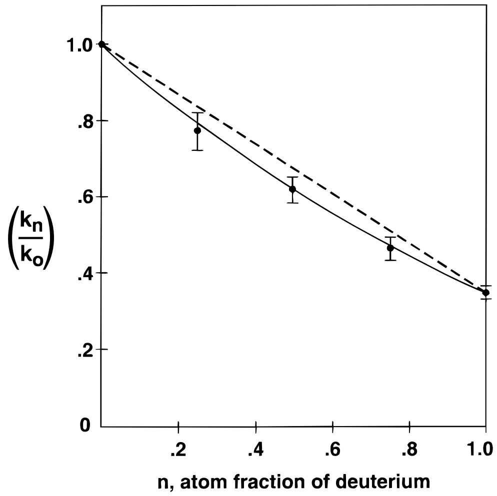


Figure 3. Plot of (k_n/k_0) vs n. The plot includes the data for five different molarities of water ranging from 1.0 to 5.0 M. The error bars are standard deviations based on five different (k_n/k_0) values at each value of n.

nonlinear and bowl shaped. Such a bowl-shaped plot implies a rate-determining transition state where multiple proton transfers are occurring. Figure 2 is a plot of k_n vs n for the hydrolysis of **1** in water molarity of 5.0 M. The solid line in Figure 2 is based on a three-proton model with each proton having an identical fractionation factor of 0.697 ± 0.005. Thus, the experimental proton inventory data can be described by eq 3:

$$k_n = k_0(1 - n + 0.697n)^3 \tag{3}$$

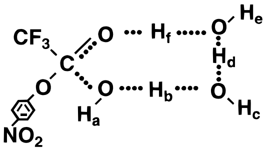
Equation 3 can be rearranged to eq 4:

$$\frac{k_n}{k_0} = (1 - n + 0.697n)^3 \tag{4}$$

The advantage of eq 4 is that all the proton inventory data for different molarities of water can be included in a single plot. Figure 3 shows the plot of (k_n/k_0) against n. The solid line is based on the right-hand side of eq 4. Thus, all the proton inventory data for all the molarities of water are adequately described by the three-proton model. The transition state structure is independent of the molarity of water in the acetonitrile. Hence, a transition state model involving three water molecules wherein only three protons contribute to the isotope effect is favored.

Albery has suggested the evaluation of a quantity called γ, which is a measure of solvent isotope effect curvature.[13] Kresge has illustrated with specific examples the usefulness of the γ method in delineating reaction mechanisms.[11] The reciprocal of γ serves to specify the minimum number of protons that are responsible for a given isotope effect curvature. The γ values for each of the five proton inventories we conducted at different molar concentrations of water were calculated using the (k_n/k_0) values at $n = 0.998$ and 0.499 (Table 2). The γ values calculated vary quite a bit, but not in a monotonic way. Hence, we calculated a mean γ value from the five values obtained, which is 0.31 ± 0.25. This implies that there are a minimum of three protons (1/0.31 $\approx$ 3) that contribute to the isotope effect.

A three-proton model for the transition state is shown below. In this model, protons H_b, H_d, and H_f undergo



major bonding changes and therefore contribute to the overall isotope effect. For these protons the fractionation factor changes from a reactant state value of 1.0 to a transition state value of 0.697. Protons H_a, H_c, and H_e undergo minimal bonding changes, and their fractionation factor remains unaltered at a value of 1. This model is essentially the same as the one suggested for the hydration of 1,3-dichloroacetone in dioxane.[1] A similar model is suggested by Wolfe and co-workers for the hydration of formaldehyde based on theoretical calculations.[2] Eigen was the first one to suggest such a cyclic cooperative mechanism for the hydration of a carbonyl group.[14] A similar cyclic transition state involving a cooperative mechanism has been proposed for the water-catalyzed decomposition of nitramide by Cox.[15]

The advantage of this eight-membered transition state over a six-membered transition state involving two water molecules is that it accommodates linear hydrogen bonds as suggested by Gandour.[16] Wolfe and co-workers have argued that the linearity of hydrogen bonds formed in the transition state balances the entropic disadvantage of bringing four molecules together.[2] A reviewer suggested that a plot like the one in Figure 1 be done, but using the activity (partial pressure) of water in acetonitrile. Such a plot (not shown) yields a slope of about 11.[17]

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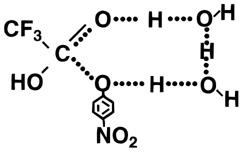
(17) We thank one of the reviewers for suggesting this plot.

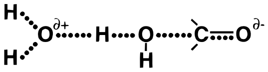
This suggests that a large number of water molecules are involved in the rate-determining step. A mechanism involving such a large number of water molecules is presumably a general solvation effect. Such a mechanism may be operating, but we believe the simplest mechanism consistent with the experimental data is the cyclic cooperative mechanism involving three water molecules. The reaction in methanol apparently involves three methanol molecules. Thus, the transition state model is the same as that of the water reaction except that protons H_a, H_c, and H_e are replaced by the CH_3 groups of methanol.

There is yet another model for the water reaction thaat is consistent with the experimental data. In this model the substrate is rapidly hydrated by a single molecule of water, followed by a rate-limiting decomposition of the hydrate involving two additional water molecules. The hydrates of trifluoromethyl derivatives of carbonyl compounds are known to be formed rather readily. The transition state again involves a cyclic eight-membered ring with three protons undergoing bonding changes as shown below.



In order to test the validity of the three-proton model for the transition state, we analyzed our data using a general nonlinear least squares program. In this analysis we used all the individual (k_n/k_0) values instead of using only the mean (k_n/k_0) value for each n value. Statistically, using all the (k_n/k_0) values is more representative of the true situation than using the mean values. This analysis revealed that there is improvement at the 99.7% confidence level (F-test) in going from a single fractionation factor model to two fractionation factor model and there is improvement at the 90% confidence level in going from a two fractionation factor model to a three fractionation factor model. In the three fractionation factor model the errors in the ϕ values are more reasonable when the fractionation factors are identical ($\phi_i^* = 0.697 \pm 0.005$) than when the fractionation factors are different. For the later situation the errors become ridiculously large. Thus, both statistical analysis of our data and the γ method seem to validate the three-proton model with identical fractionation factors for the transition state.

The cyclic transition state model for water reaction in acetonitrile is in contrast to an acyclic three-proton transition state model proposed for water reactions of esters and related compounds in aqueous solutions as shown earlier.[3] We believe that this difference is due to



the stabilization of the developing charges on the oxygens by hydrogen bonds to bulk water in aqueous solution. This kind of stabilization by bulk water is difficult to achieve in a predominantly nonaqueous medium, which forces a cyclic transition state with minimal development of charges. In order to achieve the cyclic transition state a third water molecule is necessary to accommodate linear hydrogen bonds.

Experimental Section

p-Nitrophenyl trifluoroacetate, deuterium oxide, HPLC grade water, and HPLC grade acetonitrile were all purchased from Aldrich and were used as obtained. A stock solution of the substrate ($\sim 1.3 \times 10^{-2}$ M) in acetonitrile was prepared fresh for every set of runs. All the solutions prepared were bubbled with nitrogen for 15 min and kept in a 20 mL serum tube in a desiccator until use. All D_2O solutions were prepared in a glovebox flushed with nitrogen to minimize any contamination with H_2O. H_2O (3 mL) (or D_2O) in acetonitrile was thermostatted in a cuvette placed in a constant temperature cell holder of a Varian DMS 90 spectrophotometer at 25 ± 0.1 °C. Then 20 μL of a 1.3×10^{-2} M stock solution of the substrate was mixed with the H_2O/acetonitrile solution to initiate the reaction. The reaction was followed by monitoring the appearance of the product *p*-nitrophenol that was released at 320 nm for about 3−5 half-lives. First-order rate constants were calculated using a kinetics calculation program designed for the DMS-90 spectrophotometer and the Varian DS-15 data station. Each rate constant reported is an average of five kinetic runs.

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