J. Org. Chem. **1980**, *45*, 307–310

Immature Hydronium Ion as a General Transition-State Catalytic Entity in Water Reactions[1,2]

Mohamed Hegazi, Julio F. Mata-Segreda,[3] and Richard L. Schowen*

Department of Chemistry, The University of Kansas, Lawrence, Kansas 66045

Received July 25, 1979

The "water terms" for the hydrolysis of ethyl trifluoroacetate (which is subject to protolytic general-base catalysis) and for the hydrolysis of ethyl *o*-nitrophenyl oxalate (which shows nucleophilic general-base catalysis) produce solvent isotope effects and dependences of rate constant on atom fraction of deuterium ("proton inventories") which are consistent with the presence of an "immature hydronium ion" in the transition state, bridging to the remainder of the structure through an unusually strong type of hydrogen bond. A number of other reactions are probably subject to this kind of catalysis.

Catalysts accelerate chemical reactions by favorable interaction with the activated complex so that its free energy and thus the free-energy barrier for the reaction are lowered.[4] The understanding of the phenomenon of catalysis is therefore equivalent to an elucidation of the factors governing interactions among the catalyst-derived and substrate-derived regions of catalytic transition states. We can imagine the transition state for a catalytic process as dissected into three regions: (a) the *core*, or entity derived largely from substrate structure, (b) the *catalytic entity*, derived from catalyst, and (c) *bridges*, representing structures through which the core and catalytic entity interact. Bridges may cause increases or decreases in free energy, but if catalysis is to occur, the sum of bridging interactions must represent stabilization. In many cases of acid–base catalysis, the bridges may be made of protons, either in hydrogen bonds or in the process of undergoing transfer between the core and catalytic entity.

A particularly interesting case is presented by the "water terms" in general acid–base catalyzed reactions. Here, some entity derived from the structure of liquid water is participating in a manner presumably related to the role of a general catalyst. The highly structured nature of water suggests that, in some cases, a form of cooperativity may be involved. Furthermore, these "water terms" are found for reactions which proceed by both of the recognized modes of general-base catalysis, viz., protolytic catalysis ("proton-transfer" catalysis or "classical general-base" catalysis) and nucleophilic catalysis. The hydrolysis reactions of many esters which have strong electron-withdrawing groups next to carbonyl, such as the haloacetates, exhibit general-base catalysis, and several lines of evidence combine to indicate that a protolytic process is at work.[5,6]

Table I. Observed First-Order Rate Constants[a] for the "Water" Hydrolysis of Ethyl Trifluoroacetate at 25 ± 0.1 °C and $\mu = 0.1$ in Mixtures of Protium and Deuterium Oxides

n[b]	10^4k_n, s^{-1}	n[b]	10^4k_n, s^{-1}
0.000	34.96 ± 0.55	0.543	19.63 ± 0.30
0.082	31.27 ± 1.05	0.616	17.60 ± 0.50
0.219	28.53 ± 0.23	0.670	16.37 ± 0.58
0.257	26.35 ± 0.80	0.901	12.27 ± 0.75
0.476	19.83 ± 0.10	0.993	9.69 ± 0.28
0.514	18.95 ± 0.07		

[a] Mean of three or four determinations. Error limits are standard deviations from the mean. Ionic strength maintained with sodium perchlorate. [b] Atom fraction of deuterium determined by NMR technique.

These esters generally undergo a reasonably rapid spontaneous hydrolysis corresponding to the "water term". Typically the spontaneous reaction is slower in deuterium oxide[6] by a factor of 2–4, suggesting some cooperative role of water molecules in the transition state.[5-21] On the other hand, the hydrolysis of ethyl *o*-nitrophenyl oxalate, studied in great detail by Bruice and Holmquist,[22] appears to prefer a nucleophilic mode of general-base catalysis. Thus the data initially obtained suggested that the reaction catalyzed by acetate ion might be slightly faster in deuterium oxide than in protium oxide.[22] Here again, however, the "water term" was prominent and showed a normal

---

[1] Catalysis in Ester Hydrolysis. VII. For part VI, see: Gandour, R. D.; Schowen, R. L. *J. Am. Chem. Soc.* **1974**, 96, 2231.

[2] This research was supported by the National Institutes of Health and the National Science Foundation. Part of the data reduction was carried out at the University of Kansas Computation Center.

[3] On leave from the Department of Chemistry, University of Costa Rica, San José, Costa Rica.

[4] It is on occasion suggested that catalysts might also accelerate reactions by increasing the free energy of the reactant state. To see that this is fallacious, one need only consider interaction of catalyst and substrate. If the interaction is endergonic, so that the catalyst–substrate complex is minor in concentration compared to its limiting component, then the increased reactivity of the low-concentration species will be precisely compensated by its lower concentration, with no attendent change in reaction rate (Curtin-Hammett Principle: Hammett, L. P. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1970; p 119). If the interaction is exergonic, then the catalyst in fact stabilizes the reactant state, and clearly the stabilization of the transition state must exceed this effect to produce net acceleration. For further discussion, see Schowen, R. L. In "Transition States of Biochemical Processes"; Gandour, R. D.; Schowen, R. L., Eds.; Plenum: New York, 1978; Chapter 2.

[5] The classic study is that of: Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743–50. Subsequent developments are reviewed in: Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; Bender, M. L. "Mechanisms of Homogeneous Catalysis from Protons to Proteins"; Wiley-Interscience: New York, 1971.

[6] Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237.

[7] Klinman, J. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1968**, *90*, 4390.

[8] Batts, B. P.; Gold, V. *J. Chem. Soc. A* **1969**, 984.

[9] Euranto, E. K.; Cleve, N. J. *Suom. Kemistil. B* **1970**, *43*, 147–53.

[10] Barnes, D. J.; Cole, M.; Lobo, S.; Winter, J. G.; Scott, J. M. W. *Can. J. Chem.* **1972**, *50*, 2175–81.

[11] Engbersen, J. F. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1974**, *96*, 1231–3; **1975**, *97*, 1563–8.

[12] Choi, M.; Thornton, E. R. *J. Am. Chem. Soc.* **1974**, *96*, 1428.

[13] Kurz, J. L.; Farar, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 2250–4.

[14] Kurz, J. L.; Wexler, D. N. *J. Am. Chem. Soc.* **1975**, *97*, 2255–8.

[15] Kurz, J. L.; Erhardt, G. L. *J. Am. Chem. Soc.* **1975**, *97*, 2259–63.

[16] Menger, F. M.; Venkatasubban, K. S. *J. Org. Chem.* **1976**, *41*, 1868–70.

[17] Hogg, J. L.; Phillips, M. K.; Jergens, D. E. *J. Org. Chem.* **1977**, *42*, 2459–61.

[18] Hogg, J. L.; Phillips, M. K. *Tetrahedron Lett.* **1977**, 3011–14.

[19] Venkatasubban, K. S.; Davis, K. R.; Hogg, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 6125–8.

[20] Gandour, R. D.; Coyne, M.; Stella, V. J.; Schowen, R. L. In press.

[21] Schowen, K. B. In "Transition States of Biochemical Processes"; Gandour, R. D.; Schowen, R. L., Eds.; Plenum: New York, 1978; Chapter 6.

[22] Bruice, T. C.; Holmquist, B. *J. Am. Chem. Soc.* **1967**, *89*, 4028.

0022-3263/80/1945-0307$01.00/0

Table II. Observed First-Order Rate Constants ($10^4 k_{obsd}^n$, s^{-1})[a] for Acetate-Catalyzed Hydrolysis of 2×10^{-4} M Ethyl *o*-Nitrophenyl Oxalate at 25.0 ± 0.1 °C and $\mu = 0.1$ in Mixtures of Protium and Deuterium Oxides

	$[CH_3CO_2Na]$,[b] M			
n^c	0.02	0.03	0.04	0.05
0.000	249 ± 5 (237 ± 14)	288 ± 14 (287 ± 9)	316 ± 7 (330 ± 4)	342 ± 9 (372 ± 6)
0.197	208 ± 7	246 ± 5	279 ± 5	306 ± 8
0.249	212 ± 8	242 ± 6	263 ± 9	293 ± 6
0.481	177 ± 3	201 ± 6	231 ± 10	259 ± 14
0.750	139 ± 6	166 ± 11	197 ± 10	228 ± 4
0.789	139 ± 3	169 ± 10	196 ± 8	231 ± 11
0.993	117 ± 2	142 ± 6	177 ± 7	200 ± 10

[a] Mean of four determinations. Error limits are standard deviations from the mean. [b] Buffer ratio is unity for all runs, except for those in parentheses, for which $[CH_3CO_2H] = 0.1[CH_3CO_2Na]$. Ionic strength was maintained constant with sodium perchlorate. [b] Atom fraction of deuterium, determined by NMR technique.

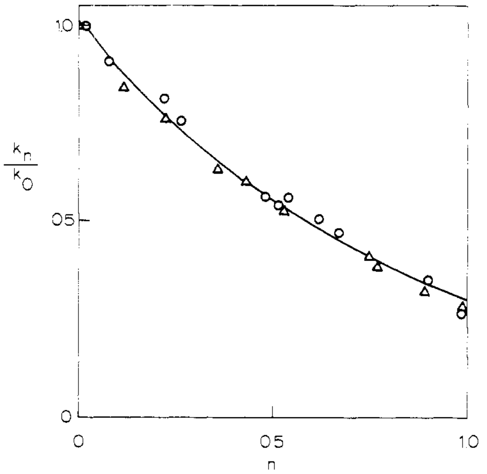


Figure 1. The kinetic solvent isotope effect for hydrolysis of ethyl trifluoroacetate in mixtures of protium oxide and deuterium oxide (atom fraction of deuterium *n*). The triangular points are those of Barnes et al.[10] for 10 °C and the circular points are for 25 °C, taken from Table I. The solid line is a plot of the best-fit cubic equation.

solvent isotope effect of $k_H/k_D = 3$.

To illuminate the structure of the solvent-derived catalytic entity in the "water" transition states for nucleophilic and protolytic catalysis, we examined a typical reaction from each class by the *proton inventory method*, which produces a list of active protons in the transition state and the solvent isotope-effect contribution from each (which is a measure of its binding state).[21,23] As an example of protolytic catalysis, we chose the hydrolysis of ethyl trifluoroacetate; for nucleophilic catalysis, we chose the hydrolysis of ethyl *o*-nitrophenyl oxalate.

The hydrolysis of ethyl trifluoroacetate in isotopic solvent mixtures has been studied before[10] at a temperature of 10 °C. Extension to 25 °C seemed most desirable because of the recent, complete elucidation of the mechanism of hydrolysis of the related compound, ethyl trichloroacetate, by Kurz and his group.[13-15] They found excellent evidence for a tetrahedral intermediate and observed further that, whereas in H_2O it reverted to reactants threefold faster than it formed products, this ratio was increased to fivefold in D_2O.

Results

Water Term in Protolytic Catalysis. Table I shows first-order rate constants k_n for hydrolysis of ethyl trifluoroacetate in mixtures of protium and deuterium oxides at 25 °C. Figure 1 contains a plot of these data, together with the data of Scott and his group[10] for the same reaction at 10 °C. As can be seen, there is no observable difference, the temperature effect on both the magnitude of the overall isotope effect ($k_{H_2O}/k_{D_2O} = 3.6 \pm 0.1$) and the curvature of the *n*-dependence being indetectable for this temperature range and level of precision.

Table III.[a] Dependency of k_{AcO} and k_w for the Hydrolysis of Ethyl *o*-Nitrophenyl Oxalate upon the Atom Fraction of Deuterium (*n*) in Mixtures of Protium and Deuterium Oxides at 25.0 ± 0.1 °C and $\mu = 0.1$

n	$10^4 k_w$, s^{-1}	$10^3 k_{AcO}$, $M^{-1}\ s^{-1}$
0.000	195 ± 7	306 ± 19
0.197	145 ± 5	323 ± 13
0.249	157 ± 5	269 ± 15
0.481	121 ± 7	275 ± 18
0.750	78 ± 7	299 ± 18
0.789	78 ± 6	303 ± 16
0.993	64 ± 7	267 ± 18

[a] Rate constants determined by linear least-squares fit of the data of Table II to eq 1. Error limits are standard deviations.

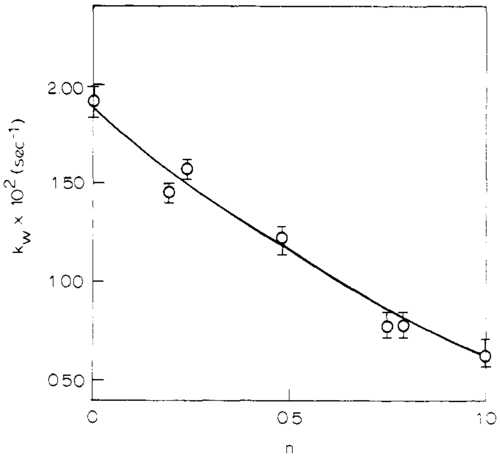


Figure 2. Rate constants for "water-catalyzed" hydrolysis of ethyl *o*-nitrophenyl oxalate in mixed isotopic solvents as a function of atom fraction of deuterium *n*. The solid line represents the best-fit cubic equation.

Water Term in Nucleophilic Catalysis. Table II gives first-order rate constants k_{obsd}^n for hydrolysis of ethyl *o*-nitrophenyl oxalate in buffers of acetic acid and sodium acetate in mixtures of protium and deuterium oxides. The data are described by eq 1, as previously found by Bruice

$$k_{obsd}^n = k_w^n + k_{AcO}^n[CH_3CO_2Na] \qquad (1)$$

and Holmquist for protium oxide.[22] Values of the catalytic constant for acetate ion and for water in each isotopic solvent were found by a linear least-squares fit to eq 1 and are given in Table III. The data are plotted in Figure 2. The solvent isotope effect k_{H_2O}/k_{D_2O} for the k_w term is 3.0 ± 0.3, and for the acetate term, 1.15 ± 0.06. The data for

---

(23) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275.

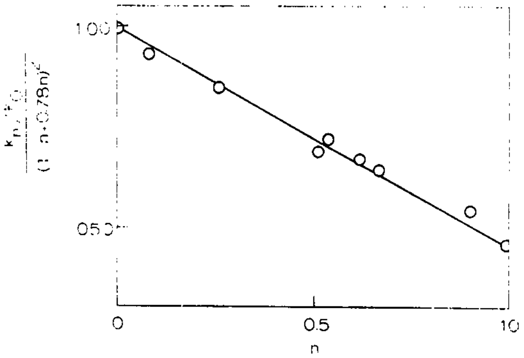


Figure 3. A plot of eq 3 with $\phi_a = 0.78$, with slope $\phi_b = 0.47$. The data are from Table I for the hydrolysis of ethyl trifluoroacetate at 25 °C.

the water term will be treated in this paper, but discussion of the acetate term will be reserved for a later publication.

Discussion

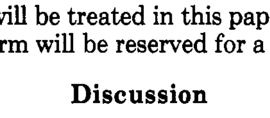
Water Term in Hydrolysis of Ethyl Trifluoroacetate. To analyze the dependence of k_n on n (Figure 1) and relate it to transition-state structure, we assume that ethyl trifluoroacetate is equally stable in H_2O and D_2O so that the dependence of eq 2 is expected.[21] Here, the $\phi^T{}_i$

$$k_n = k_0 \prod_i^{\nu} (1 - n + n\phi^T{}_i) \tag{2}$$

represent the transition-state isotopic fractionation factors.

Figure 1 shows that the data of Scott and his group[10] for 10 °C are entirely congruent with our own for 25 °C when both are expressed as k_n/k_0 to eliminate the temperature dependence of the individual rate constants. As described by Schowen,[21] the data were fitted to polynomials of increasing order. Linear and quadratic terms were significant at the 99.9% confidence level, the cubic at 95%, and the quartic term only at 80%. We conclude that at least two, probably three, and perhaps four protons must be active (i.e., contributing to the isotope effect).

The most reasonable 3–4 proton structure is 1, previously deduced for water terms[7-21] and given particularly powerful support by Kurz and his collaborators.[13-15] This is the structure for decomposition of the tetrahedral intermediate to products, a transition state which determines the rate to the extent of 76% in H_2O and 84% in D_2O in the case of the related substrate ethyl trichloroacetate.[24]



1

A hydronium-ion-like moiety is shown catalyzing the departure of the leaving alkoxy group. The fractionation factors for the H_a sites should be between 1.00 (water) and 0.69 (hydronium ion),[21,23] that for the H_b site should be in the general neighborhood of $(2.2)^{-1} \sim 0.45$ if "solvation catalysis" is involved,[26] and that for the H_c site should be between about 1.25 (tetrahedral adduct[27]) and 1.00. Because statistical justification for the fourth proton is very marginal, we assume $\phi_c \sim 1.00$ and write eq 3. This

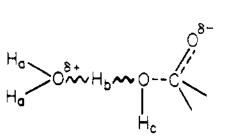
$$k_n = k_0(1 - n + n\phi_a)^2(1 - n + n\phi_b) \tag{3}$$

$$[k_n/k_0(1 - n + n\phi_a)^2] = 1 - n + n\phi_b \tag{4}$$

expression can be rearranged to eq 4, in which a plot of the left-hand side vs. n will be linear if the proper values of ϕ_a and ϕ_b are employed. Figure 3 shows that a good fit to the data at 25 °C is obtained with $\phi_a = 0.78$ and $\phi_b = 0.47$. No change is introduced by including the data for 10 °C. The solvation–catalysis model therefore accounts adequately for these data, in agreement with one of the conclusions of Kurz and Ehrhardt.[15] Although a more complex model involving the transition states for both steps (formation and decomposition of the tetrahedral intermediate) should in principle be used, apparently the small shift[24] in importance of the two transition states with added D_2O makes this unnecessary. It is also true that the reactant may be unequally stable in the isotopic solvents, rendering the fractionation factors less quantitatively reliable. Some part of this inequality, arising from structures unchanged on activation, may be preserved into the transition state, producing an amelioration of the error.

Water Term for Nucleophilic Catalysis. On the assumption of an equal stability for ethyl *o*-nitrophenyl oxalate in light and heavy water, eq 2 may also be employed to treat the k_w term for this substrate. Here the excellent leaving-group capacity of *o*-nitrophenoxide essentially guarantees that formation of the tetrahedral intermediate will limit the rate if the mechanism is at all simple.

Because of the difficulty in obtaining k_w (the intercept of k_{obsd} vs. [acetate]), the proton-inventory results are rather disappointing. Figure 2 shows the plot of $k_w{}^n$ vs. n. It is apparently nonlinear (a line drawn through the central values of $k_w{}^0$ and $k_w{}^1$ would leave all other points below it), but this is hard to support statistically. The quadratic term is significant only at the 80% confidence level, whereas the cubic and quartic terms are not significant even at this level. This result thus yields only a marginal indication of a multiproton ($\nu > 1$) mechanism. If two equivalent transition-state protons were assumed, as in a transition state for simple nucleophilic attack by water, then the average fraction factor would have to be $(3.0)^{-1/2} = 0.58$. This is unreasonably smaller than the value of 0.69 for hydronium ion, as noted above, and essentially rules out the simple nucleophilic mechanism. It remains then to ask whether the data are consistent with a transition state such as 2 in which we take $\phi_c \sim 1.00$.



2

---

(24) For a process

$$\mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{T} \xrightarrow{k_2'} \mathrm{P}$$

the observed rate constant k_0 is given by $k_0{}^{-1} = k_1{}^{-1} + k_2{}^{-1}$, where $k_2 = k_1k_2'/k_{-1}$. Noting that $\Delta G_0{}^* = RT \ln (e^{\Delta G_1{}^*/RT} + e^{\Delta G_2{}^*/RT})$, we can apply a Leffler–Grunwald operator δ_I for small additions of D_2O near $n = 0$ or for small additions of H_2O near $n = 1$. In the former case, we obtain[25]

$$\delta_I\Delta G_0{}^* = f_{-1}{}^H\delta_I\Delta G_2{}^* + f_2{}^H\delta_I\Delta G_1{}^* \tag{i}$$

and in the latter case,

$$\delta_I\Delta G_0{}^* = f_{-1}{}^D\delta_I\Delta G_2{}^* + f_2{}^D\delta_I\Delta G_1{}^* \tag{ii}$$

where $f_{-1}{}^H = 1/(1 + [k_2{}^H/k_1{}^H])$, $f_2{}^H = 1/(1 + [k_1{}^H/k_2{}^H])$ and $f_{-1}{}^D = 1/(1 + [k_2{}^D/k_1{}^D])$, $f_2{}^D = 1/(1 + [k_1{}^D/k_2{}^D])$. From the finding of Kurz and Wexler[14] that $k_1{}^H/k_2{}^H = 3.18$ and $k_1{}^D/k_2{}^D = 5.42$, we have $f_{-1}{}^H = 0.76$, $f_2{}^H = 0.24$; $f_{-1}{}^D = 0.84$, $f_2{}^D = 0.16$.

(25) Schowen, R. L.; Latham, K. S. *J. Am. Chem. Soc.* **1967**, *89*, 4677.

(26) Minor, S. S.; Schowen, R. L. *J. Am. Chem. Soc.* **1973**, *95*, 2279.

(27) Mata-Segreda, J. F.; Wint, S.; Schowen, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 5608.

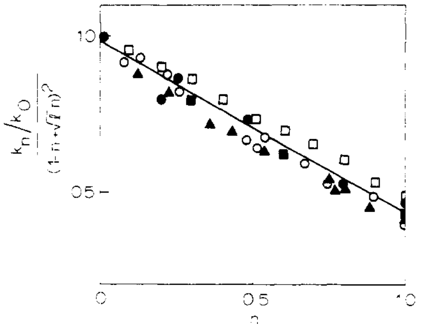


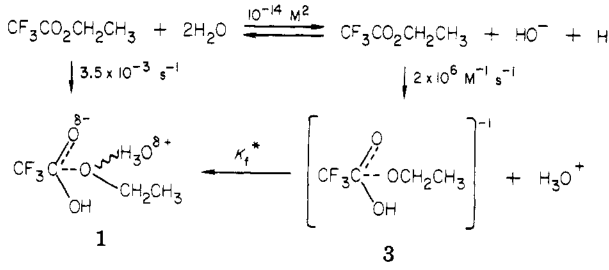
Figure 4. Plot of eq 3 according to the immature hydronium ion hypothesis incorporating data for ethyl *o*-nitrophenyl oxalate at 25 °C (●), ethyl trifluoroacetate at 10 °C (▲, ref 10) and 25 °C (○), chloromethyl chloroacetate at 25 °C (■, ref 9) and acetic anhydride at 25 °C (□, ref 8).

Calculation shows agreement of the data with a model having $\phi_a = 0.83$ ($\doteq[0.69]^{1/2}$, corresponding to the arbitrary assumption that $\delta^+ \approx {}^1/_2$ in **2**) and $\phi_b = 0.45$, although the agreement constitutes no real test.

The rough conclusion, chiefly from the large magnitude of the overall isotope effect and secondarily from the proton inventory, is that a transition-state structure such as **2**, for a form of protolytic catalysis, is the most reasonable one for the "water term" in a process in which other general bases function as nucleophiles.

The Immature Hydronium Ion as Catalytic Entity. The analysis of the "water term" for both nucleophilic and protolytic catalysis, as we have just seen, yields very similar transition-state structures in which the core of the catalytic transition state interacts by means of a *one-proton solvation bridge*[26] with a catalytic entity resembling a partially formed hydronium ion. It may be useful to consider this as a general catalytic entity associated with structured water. It might be denoted an "immature hydronium ion". If the charge on the oxygen of this entity were always near $+{}^1/_2$ and if a one-proton solvation bridge always connected it to the core of the transition state, we would expect proton-inventory data for reactions involving the immature hydronium ion to obey eq 3 with $\phi_a = l^{1/2}$ ($l = 0.69$, the fractionation factor for the fully formed hydronium ion[23]) and $\phi_b \sim 0.45$. That this is approximately the case is shown by Figure 4, incorporating data from the present paper, from Euranto and Cleve[9] (for chloromethyl chloroacetate), from Barnes et al.[10] and from Batts and Gold[8] (for acetic anhydride).

If the small isotope effect for the bridging proton is taken as evidence that it has only a small amplitude in the reaction coordinate and is therefore to be regarded as forming a type of hydrogen-bonding bridge in the transition state,[23,26] the question arises, what force binds the core of the transition state to the catalytic entity? We can formulate this question more precisely in terms of the scheme of eq 5. The rate constant of $2 \times 10^6\ M^{-1}\ s^{-1}$ for basic hydrolysis of ethyl trifluoroacetate at 25 °C is estimated from the data of Bender and Heck.[28] The formation constant of the hydrogen-bonded transition state **1** from its components **3** and H_3O^+ is $K_f^* = (3.5 \times 10^{-3})/(10^{-14})(2 \times 10^6)\ M^{-1} \simeq 10^{5.3}\ M^{-1}$.



(5)

This is an enormous formation constant for a hydrogen-bonded complex with hydronium ion in aqueous solution. It clearly requires the postulation of some unusual special stabilizing feature, perhaps peculiar to transition states. Swain, Kuhn, and Schowen[29] suggested that an enhanced polarizability of reacting-orbital electrons might give rise to large association constants between activated complexes and other molecules. Another suggestion has been made by Jencks,[30] who notes that activated complexes may generate momentary sites of extreme acid–base character, which might therefore produce extremely strong hydrogen-bonded complexes. For longer-lived species, proton transfer and dissociation of the conjugate acids and bases would have become complete. Current quantum-mechanical investigations may emerge as capable of discriminating among these and other postulates.

In summary, the present study and previous work suggest that the immature hydronium ion frequently may be a catalytic entity, deriving from the structured character of water solvent and stabilizing catalytic transition states by unusually strong hydrogen bonding.

Experimental Section

Materials. Ethyl *o*-nitrophenyl oxalate was synthesized from ethyl oxalyl chloride and the potassium salt of *o*-nitrophenol in dry dioxane according to reported methods,[22] sublimed three times using horizontal-zone sublimation, and kept under nitrogen in a small vial until used. Ethyl trifluoroacetate was purchased from Aldrich. Mixed isotopic solvents and acetate buffers in them were prepared gravimetrically.[21] Deuterium oxide was obtained from Stohler Isotope Chemicals. Protium concentrations were determined in pure and mixed solvents using their NMR signals, with sodium acetate as internal standard. Chlorophenol Red indicator was obtained from Fisher Scientific Co.

Kinetic Measurements and Data Treatment. Kinetic runs were carried out on a Cary 16 spectrophotometer equipped with a thermocirculator accessory for temperature control within the cell to 25.0 ± 0.1 °C. Cells and solutions (3 mL) were thermostated for at least 15 min before the runs were initiated. In the oxalate case, the reaction was followed by recording the increase of absorbance at 372.5 nm. In the trifluoroacetate case, the reaction was carried out in the presence of Chlorophenol Red, and the release of hydrogen ions was followed by recording the disappearance of the red form at 590 nm. First-order rate constants were determined by submitting the absorbance–time data to a nonlinear least-squares computer program written by Dr. Maw-Song Wang.

Registry No. Ethyl *o*-nitrophenyl oxalate, 17318-84-2; ethyl oxalyl chloride, 4755-77-5; *o*-nitrophenol potassium salt, 824-38-4; ethyl trifluoroacetate, 383-63-1; water, 7732-18-5.

---

[28] Bender, M. L.; Heck, H. d'A. *J. Am. Chem. Soc.* **1967**, *89*, 1211.

[29] Swain, C. G.; Kuhn, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 1553.

[30] Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–32.