

Transition-State Structure for the Neutral Water-Catalyzed Hydrolysis of Ethyl Trifluorothiolacetate

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Abstract: A chemical model is proposed for the transition-state structure for the neutral, water-catalyzed hydrolysis of ethyl trifluorothiolacetate. The transition-state model is consistent with the proton inventory which suggests three transition-state contributions to the observed solvent isotope effect.

Introduction

Several detailed studies of water-catalyzed hydrolyses of esters and related compounds have been recently reported.¹⁻⁴ The important role of water in the reactions of hydrolytic enzymes is well-known. Hence, an understanding of the detailed mechanism of the water-promoted hydrolysis (i.e., the neutral hydrolysis) of model reactions for these processes is extremely important. The importance of transition-state stabilization in enzymic catalysis further emphasizes the need to establish detailed transition-state structures for "simple" model reactions.⁵

We wish to report the results of proton inventory studies of the water-catalyzed hydrolysis of ethyl trifluorothiolacetate at two different temperatures. Possible transition-state structures consistent with the observed proton inventories are considered. The factors which led us to favor one structure for the transition state over the others will be discussed in detail. This discussion will illustrate the potential of the proton inventory technique for allowing certain mechanisms to be removed from consideration while providing confirmatory evidence for transition-state structures suggested by other experiments. As is true with most mechanistic probes, no single investigation allows one to pin down a mechanism. The cumulative information gained from numerous studies is required for mechanism verification. The proton inventory technique is shown to provide unique information about the transition state which when used in conjunction with other mechanistic information is of paramount importance in mechanistic studies. Fedor and Bruice presented a detailed kinetic study of ethyl trifluorothiolacetate hydrolysis which spurred the present investigation.⁶

Results

The hydrolysis of ethyl trifluorothiolacetate is pH-independent between pH 2.5 and 7.⁶ In the present study the rate constants for hydrolysis were obtained in two different ways. In one set of experiments the rate constants were obtained using potassium acetate-acetic acid buffers. Extrapolation of the observed rate constants to zero buffer concentration yielded the rate constant for the neutral hydrolysis. Alternatively, the rate constants were obtained directly using 10^{-3} M HCl (DCI) solutions. The agreement between the two methods was excellent. The rate constants obtained in H₂O using the two methods were 0.301 and 0.299 min⁻¹, respectively, at 25 °C. In D₂O the two methods yielded the identical value of 0.112 min⁻¹ at 25 °C. Table I lists the rate constants for the water-catalyzed hydrolysis at 25 and 30 °C as a function of the atom fraction of deuterium in the solvent. Figures 1 and 2 are plots of the observed rate constant, k_n , vs. the atom fraction of deuterium, n , in the solvent at 25 and 30 °C, respectively. The observed rate constants in the "pure" isotopic solvents at 25 and 30 °C are in good agreement with those reported in the

literature.⁶ The solvent-isotope effects, $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$, measured in our study were 2.67 and 2.72 at 25 and 30 °C, respectively. The single solvent-isotope effect measured by Bruice and Fedor was 2.74 at 30 °C.

Discussion

The proton inventory technique, which involves the measurement of rate constants in protium oxide, deuterium oxide, and mixtures of the two, has been applied recently to probe the transition-state structure of both enzymic and nonenzymic reactions.^{3,4,7} Details of the theory and method of application have been presented several times in recent years.^{3,4,7,8} Our discussion will be brief in this respect for this reason. The observed rate constant, k_n , in a mixture of H₂O and D₂O of the atom fraction of deuterium, n , is related to the rate constant, k_0 , in pure H₂O by eq 1. All exchangeable transition-state

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

protons, i , that contribute to the observed solvent-isotope effect contribute a term of the form shown in parentheses in the numerator of eq 1. Exchangeable reactant-state protons, j , that contribute to the observed solvent-isotope effect give rise to a like term in the denominator of eq 1. Each exchangeable proton is associated with an isotopic fractionation factor defined as in eq 2. These factors express the equilibrium deuterium

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

preference of the exchangeable site in question relative to the deuterium preference of an average solvent site.⁹ Fractionation factors less than unity indicate a greater preference for protium than deuterium relative to the solvent.

If all the isotopic reactants are solvent molecules, then, by definition, $\phi_j = 1$ and the denominator of eq 1 becomes unity. Such is the case here. Furthermore, if only one proton in the transition state contributes to the overall solvent-isotope effect, a plot of k_n vs. n will be linear (i.e., one-proton catalysis) except under unlikely conditions.¹⁰ A nonlinear plot of k_n vs. n indicates that two or more protons are contributing to the solvent isotope effect (i.e., multiproton catalysis).

The nonlinear dependence of k_n on n at both 25 and 30 °C for the hydrolysis of ethyl trifluorothiolacetate is apparent in Figures 1 and 2. Since there are no reactant-state contributions to the proton inventory (i.e., all exchangeable reactant-state sites are water sites), it is only necessary to formulate reasonable chemical models for the transition state and test them for consistency with the observed inventory and other available data. These interpretive models are usually based on other experimental data which suggest mechanistic features of the reaction. A general visual inspection of the shape of the observed inventory easily allows one to see whether multiple normal effects (downward bowing), inverse isotope-effect contributions (upward bowing), etc., are indicated. Polynomial

Table I. First-Order Rate Constants for the Hydrolysis of Ethyl Trifluorothiolacetate in Mixtures of 10^{-3} M HCl-H₂O and 10^{-3} M DCl-D₂O of Atom Fraction of Deuterium n at 25.00 ± 0.05 and 30.00 ± 0.05 °C^a

atom fraction of deuterium (n)	25 °C				30 °C			
	no. of runs	$10^3 k_n / \text{min}^{-1}$	$10^3 k_n / \text{min}^{-1}$ (calcd) ^b	no. of runs	$10^3 k_n / \text{min}^{-1}$	$10^3 k_n / \text{min}^{-1}$ (calcd) ^c		
0.000	5	299 ± 2^d	299	3	416	416		
0.246	4	243 ± 10	242	4	342 ± 3^d	339		
0.492	5	192 ± 5	192	5	267 ± 2	268		
0.739	4	146 ± 5	148	5	208 ± 1	206		
0.985 ^e	5	112 ± 1	110	3	153 ± 2	151		

^a Ionic strength was maintained at 1.0 M with KCl. ^b Calculated based on the model of eq 7. ^c Calculated based on the model of eq 9. ^d Error limits are standard deviations. ^e Atom fraction of deuterium in "100%" 10^{-3} M DCl-D₂O as determined by Mr. Josef Nemeth.¹⁵

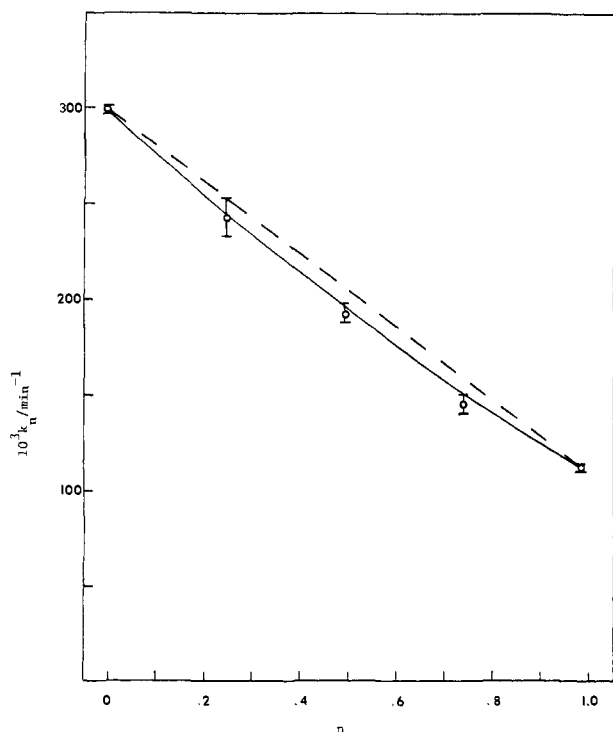


Figure 1. Plot of the rate constant for hydrolysis of ethyl trifluorothiolacetate, k_n , vs. the atom fraction of deuterium in the solvent at 25 °C. The solid line was calculated from eq 7.

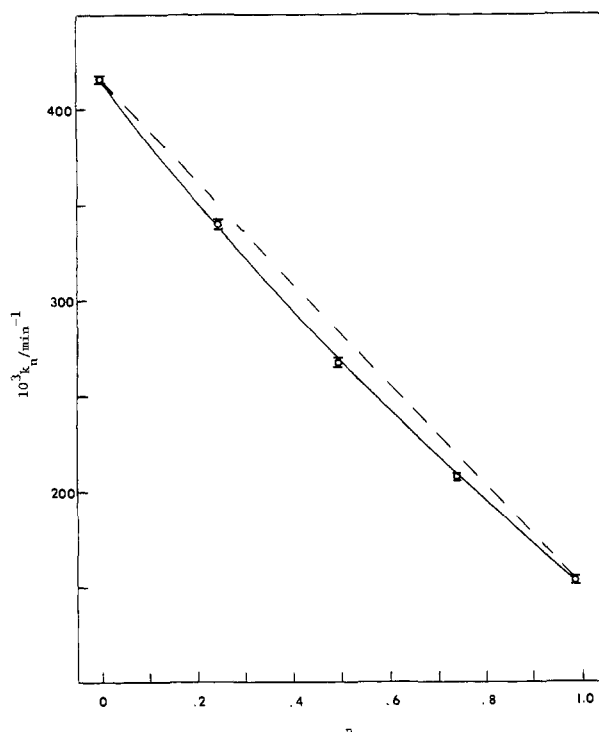
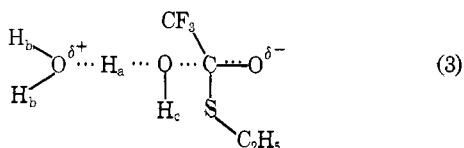


Figure 2. Plot of the rate constant for hydrolysis of ethyl trifluorothiolacetate, k_n , vs. the atom fraction of deuterium in the solvent at 30 °C. The solid line was calculated from eq 9.

regression analysis should then be used to check the fit of the data to the models.^{8d,e} Albery has recently suggested the use of the "gamma method" in data analysis.^{8c} In the final analysis a combination of all these methods will probably be necessary (and prudent) to fit the data to models. One must certainly bear in mind that the models must be chemically reasonable as well as mathematically consistent with the data. Neither criterion should be ignored in formulating models. The utilization of these approaches in formulating models will be illustrated for the hydrolysis of ethyl trifluorothiolacetate.

Fedor and Bruice have shown that the hydrolysis of ethyl trifluorothiolacetate is subject to general-base catalysis and that the water point lies on the Brønsted line ($\beta = 0.33$).⁶ This suggests that a reasonable chemical model for the transition state might be that shown in eq 3.



In this transition-state model one water molecule functions as a general base to remove a proton from the attacking water

molecule. This model has four protons which could contribute to the overall solvent-isotope effect. The proton H_c will be expected to have a fractionation factor of unity and thus should not contribute to the observed solvent-isotope effect. The "in flight" proton H_a will contribute a primary solvent-isotope effect and the two H_b protons will contribute secondary solvent-isotope effects. The H_b protons should exhibit fractionation factors between that for a simple -OH group ($\phi^* = 1$) and that for a full hydronium ion proton ($\phi^* = 0.69$) depending upon the extent of proton transfer. An estimate for the fractionation factor for each H_b proton can be made using the Brønsted β value and eq 4.⁹ Substituting unity for the reac-

$$\phi_b^{\text{TS}} = (\phi_b^{\text{RS}})^{1-\beta} (\phi_b^{\text{PS}})^{\beta} \quad (4)$$

tant-state fractionation factor for H_b (ϕ_b^{RS}), 0.69 for the product state (i.e., a full hydronium ion) fractionation factor for H_b (ϕ_b^{PS}), and the observed Brønsted β of 0.33 into eq 4, we calculate a transition-state fractionation factor (ϕ_b^{TS}) of 0.88 for the two H_b protons. This value and the experimentally observed values of the rate constant in protium oxide and deuterium oxide, coupled with the value of n for "pure" deuterium oxide, can be substituted into eq 5 to determine a ϕ_a^* consistent with the observed isotope effect. This gives a value

of 0.48 for ϕ_a^* which corresponds to a primary solvent-isotope effect contribution of 2.08 for the "in flight" proton H_a . A proton inventory for this transition-state

$$k_n = k_0(1 - n + n\phi_a^*)(1 - n + n\phi_b^*)^2 \quad (5)$$

$$k_n = 0.299(1 - n + 0.48n)(1 - n + 0.88n)^2 \quad (6)$$

model would then obey eq 6. Substitution of values of n into eq 6 allows the calculation of a theoretical proton inventory based on the model. Visual inspection of the inventory generated in this manner indicated a satisfactory fit to the experimental data. However, a nonlinear least-squares fitting of the experimental data to eq 5 using k_n/k_0 and n as experimental variables and ϕ_a^* and ϕ_b^* as disposable parameters gave best-fit values of 0.57 ± 0.05 and 0.80 ± 0.03 for ϕ_a^* and ϕ_b^* , respectively. These values are not significantly different from the original estimates for these fractionation factors which were based on a Brønsted β value measured at a different temperature (30 °C). Thus, the expression for the dependence of k_n on n at 25 °C determined by polynomial regression for the three-proton model of eq 3 is given in eq 7. The fit of the data to eq 7 and, hence, the transition-state model will be discussed shortly.

$$k_n = 0.299(1 - n + 0.57n)(1 - n + 0.80n)^2 \quad (7)$$

A similar analysis for the data obtained at 30 °C yields eq 8 based merely on the Brønsted β value. Nonlinear least-

$$k_n = 0.416(1 - n + 0.47n)(1 - n + 0.88n)^2 \quad (8)$$

squares fitting to the three-proton model of eq 3 yields eq 9 as

$$k_n = 0.416(1 - n + 0.48n)(1 - n + 0.86n)^2 \quad (9)$$

the best model. The agreement between eq 8 and 9 is remarkably good. The error limits on ϕ_a^* and ϕ_b^* of eq 9 were ± 0.03 and ± 0.02 , respectively.

The solid lines of Figures 1 and 2 were drawn based upon eq 7 and 9 for the data at 25 and 30 °C, respectively. The fit of the data is very good, as demonstrated by the sum of the squares after regression (0.79×10^{-4} and 0.96×10^{-4} for the 25 and 30 °C data, respectively). Thus the transition-state model of eq 3 is consistent with the proton inventory and is chemically reasonable. The differences in the transition states at 25 and 30 °C are probably not significant in terms of the available data.

An attempt to fit the proton inventories to a linear equation gave, for both 25 and 30 °C, a ϕ^* value of 0.33 with the sum of the squares after regression being 0.28×10^{-2} and 0.18×10^{-2} , respectively. This one-proton linear model (eq 10) ob-

$$k_n = k_0(1 - n + 0.33n) \quad (10)$$

viously does a poor job of duplicating the experimental data and was not considered further. Simple visual inspection of the downward bowing in the inventories leads to the same conclusion.

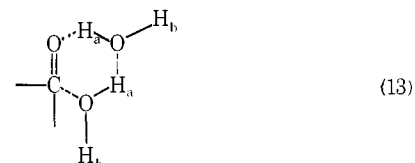
Another model which does generate theoretical proton inventories consistent with the data is a two-proton model. Equations 11 and 12 were generated by requiring the data to

$$25 \text{ }^\circ\text{C:} \quad k_n = 0.299(1 - n + 0.60n)(1 - n + 0.60n) \quad (11)$$

$$30 \text{ }^\circ\text{C:} \quad k_n = 0.416(1 - n + 0.52n)(1 - n + 0.69n) \quad (12)$$

be fit to the best possible two-term model. The sum of the squares after regression was 0.12×10^{-3} and 0.91×10^{-4} for eq 11 and 12, respectively. Although these equations represent the data less satisfactorily than the three-proton model, they are good enough to warrant further consideration. A possible two-proton transition state is that shown in the cyclic transition

state of eq 13. If the two protons H_a are being transferred in concert, then one could argue that these should be the only protons contributing to the isotope effect since both H_b should retain fractionation factors of unity. Thus, eq 11 and 12 could be consistent with this transition state and, hence, explain the proton inventories observed. A space-filling model of the cyclic transition shown in eq 13 involving two water molecules proved



to be unsuitable for the linear proton transfers thought to be important in such processes.¹¹ Several additional water molecules would be required to allow such linear proton transfers.

Another problem arises with the cyclic mechanism if one considers the implications of eq 12. Only if the two H_a protons are transferred in concert would the two H_b protons fail to contribute to the observed solvent-isotope effect. Therefore, unequal fractionation factors for the two H_a protons implies a different two-proton mechanism which cannot easily be imagined. Bruice and Benkovic have considered such cyclic transition states and come to the conclusion that "A choice between the cyclic and noncyclic mechanisms in ester solvolysis appears to be, at present, one of personal preference."¹² Based on the fact that water falls on the Brønsted line, the consistency of the proton inventory data with the noncyclic mechanism of eq 3, and the problems just mentioned, we strongly favor the transition state of eq 3.¹³

Conclusion

The observed proton inventories at 25 and 30 °C for the neutral hydrolysis of ethyl trifluorothiolacetate can be adequately described by a transition-state model based, in large part, on the experimental Brønsted β value. This transition-state model (eq 3) is chemically reasonable in view of the known general-base catalysis of hydrolysis. This study and earlier ones from this laboratory clearly indicate the importance of a catalytic proton bridge in the water-catalyzed hydrolysis of esters and amides. The potential of the proton inventory technique for providing supporting evidence, in terms of original data, for proposed mechanisms is amply illustrated.

Experimental Section

Materials. Ethyl trifluorothiolacetate (Aldrich) was purified by distillation before use. Potassium acetate was dried in the oven at 110 °C and stored in a desiccator until used. Glacial acetic acid (Fisher) was used as purchased. Water was glass distilled before use. Deuterium oxide (99.8 atom % deuterium, Aldrich) was purified by distillation before use.

Kinetics. Concentrated hydrochloric acid was used to prepare 10^{-3} M HCl and DCl solutions with H_2O and D_2O . The ionic strength was maintained at 1.0 M with potassium chloride. The amount of protium introduced in the 10^{-3} M DCl in this manner was very small. An analysis of the DCl solution by Mr. Josef Nemeth¹⁵ showed that the deuterium content was 98.5%. Reactions in H_2O - D_2O mixtures were done using appropriate volumes of the HCl and DCl stock solutions. The experiments conducted using potassium acetate-acetic acid buffers ($\mu = 1.0$; KCl) utilized separate stock solutions also.

The hydrolysis of ethyl trifluorothiolacetate was monitored by following the decrease in absorbance of the ester at 244 nm using a Cary 118C UV-vis spectrophotometer equipped with a constant temperature cell compartment and cell holder to control the temperature at 25.00 ± 0.05 or 30.00 ± 0.05 °C. Reactions were initiated by injecting 10 μ L of a stock solution which was 5×10^{-3} M in ethyl trifluorothiolacetate in acetonitrile into 3.00 mL of the appropriate HCl (DCl) solution. Reactions were followed to greater than 80%

