

# Ethyl Trichloroacetate Hydrolysis. I. Kinetic Evidence for a Common Tetrahedral Intermediate in the Acid-Catalyzed and Water-Catalyzed Hydrolyses

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**Abstract:** The rates of hydrolysis of ethyl trichloroacetate and ethyl trifluoroacetate increase nonlinearly with increasing hydronium ion concentration at constant ionic strength. For ethyl trichloroacetate, this rate increase is shown to be a consequence of unsymmetrically catalyzed partition of the intermediate which is formed from the water-catalyzed addition of water to the carbonyl group of the ester. The value of the partitioning ratio in the limit of zero hydronium ion concentration is calculated from the kinetic data and found to be identical with the value derived from measurements of the oxygen-18 exchange which accompanies the water-catalyzed hydrolysis. It is further shown that for esters which are sufficiently weakly basic, if acid catalysis of hydrolysis is observed, then this unsymmetric partition is expected to be the mechanism for the catalysis instead of the  $A_{AC}2$  mechanism commonly observed for unsubstituted carboxylic esters.

Several previous reports have shown that acid-catalyzed hydrolysis rates for weakly basic carboxylic esters are often not linearly related to the hydronium ion concentration.<sup>1</sup> Most of these investigations were not carried out at constant ionic strength, and the nonlinearity has commonly been attributed to salt effects. In their investigation of *o*-nitrophenyl oxalate hydrolysis, Bruice and Holmquist<sup>2</sup> did keep ionic strength constant but attributed the nonlinear increase in rate which results from an increase in  $[H^+]$  to differences between the specific effects of  $H^+$  and  $Li^+$  on the activity coefficients of water and ester.

During our investigations of acyl-activated carboxylic ester hydrolysis,<sup>3,4</sup> we observed that the hydrolysis rates of ethyl trichloroacetate and ethyl trifluoroacetate also increase nonlinearly with increasing  $[H^+]$  at constant ionic strength. This paper presents evidence that, for these trihaloacetate ester hydrolyses, this nonlinearity does *not* arise from specific salt effects but is instead the result of unsymmetrically catalyzed partition of a tetrahedral intermediate.

## Experimental Section

**Materials.** Ethyl trichloroacetate (Eastman), ethyl trifluoroacetate (Aldrich), ethyl difluoroacetate (Columbia), and ethyl chloroacetate (Eastman) were each purified by distillation through a Nester/Faust annular Teflon spinning-band column; for each ester, the center fraction (boiling range  $\leq 0.2^\circ$ ) was collected. Water was ordinary distilled water which had been passed through a Barnsted mixed bed (0808) ion-exchange resin column. Ethyl acetate (Fisher certified 99 mol %), anhydrous sodium perchlorate and lithium perchlorate (both G. F. Smith), deuterium oxide (ICN, 99.75 atom % D), and other commercially available reagents were used without further purification. Perchloric acid-*d* ( $\geq 97$  atom % D) was prepared from 70%  $HClO_4$  by repeatedly adding portions of  $D_2O$  and distilling off the excess mixed waters *in vacuo*.

**Kinetic Measurements.** Four methods were used for determining the hydrolysis rate constants: direct uv spectrophotometry using a Cary 16K spectrophotometer, conversion of unhydrolyzed ester to the hydroxamic acid followed by measurement of the absorbance of the ferric complex (procedure based on that of Jencks and Carriuolo),<sup>5</sup> dilatometry, and titration with standard NaOH of the total acid content of aliquots taken from the reaction mixture. The solvent in all hydrolyses was purely aqueous ( $H_2O$  or  $D_2O$ ); mixed solvents were not used. Good adherence to first-order kinetics was observed over several half-lives for all hydrolyses reported here.

Low solubility limited the concentrations of the trihaloacetate esters to ca.  $1 \times 10^{-3} M$  so that their hydrolysis rates could be measured only by uv spectroscopy (at 215 nm for ethyl trichloroacetate and 196 nm for ethyl trifluoroacetate) and by the hydroxamic acid method. The greater solubility of the other esters allowed use of the titrimetric and dilatometric methods. Since  $\Delta V^\circ$  is small for these hydrolyses (ca.  $1 \text{ cm}^3 \text{ mol}^{-1}$ ), the dilatometric method requires temperature control to  $\pm 0.002^\circ$  in order to avoid significant errors from thermal expansion of the solution when ester concentrations are in the range used here (0.05–0.1 *M*). Temperature control in the spectrophotometric method was  $\pm 0.1^\circ$  (measured in the cell) and was  $\pm 0.05^\circ$  in the baths used when the other two methods were employed.

## Results

Figure 1 shows the dependences of the observed pseudo-first-order rate constant,  $k_h$ , for ethyl trichloroacetate hydrolysis on the hydronium ion concentrations at constant ionic strength in  $H_2O$  and  $D_2O$ . The deviations of these plots from linearity are far outside of experimental scatter. It should be noted that the values observed for  $k_h$  are independent both of which method is used to measure  $k_h$  (spectrophotometric or conversion of ester to hydroxamic acid) and of which cation ( $Li^+$  or  $Na^+$ ) is used to complement the  $H^+$  (or  $D^+$ ) in bringing the ionic strength up to 1.0. The values of  $k_h$  measured for the  $Na^+/H^+$  solutions were fitted to eq 1 by least-squares. The resulting values and standard deviations are given in Table I; the correlation matrices<sup>6</sup> for the errors in  $k_a$ ,  $k_b$ , and  $k_c$  in that order are

$$k_h = (k_a + k_b[H^+]) / (1 + k_d[H^+]) \quad (1)$$

tions are given in Table I; the correlation matrices<sup>6</sup> for the errors in  $k_a$ ,  $k_b$ , and  $k_c$  in that order are

$$\mathbf{R} \text{ (for } H_2O) = \begin{pmatrix} 1 & -0.55 & -0.66 \\ -0.55 & 1 & 0.98 \\ -0.66 & 0.98 & 1 \end{pmatrix} \quad (2)$$

and

$$\mathbf{R} \text{ (for } D_2O) = \begin{pmatrix} 1 & -0.55 & -0.67 \\ -0.55 & 1 & 0.98 \\ -0.67 & 0.98 & 1 \end{pmatrix} \quad (3)$$

Measurements of  $k_h$  for ethyl trifluoroacetate were significantly less reproducible than were the measurements for the trichloro ester. Although the data were in qualitative agreement with a nonlinear dependence of  $k_h$  on  $[H^+]$  in aqueous  $HClO_4/NaClO_4$  at an ionic strength of 1.0, the scatter in the  $k_h$  values was large enough to prevent us from obtaining sufficiently precise values of  $k_a$ ,  $k_b$ , and  $k_c$ ; the

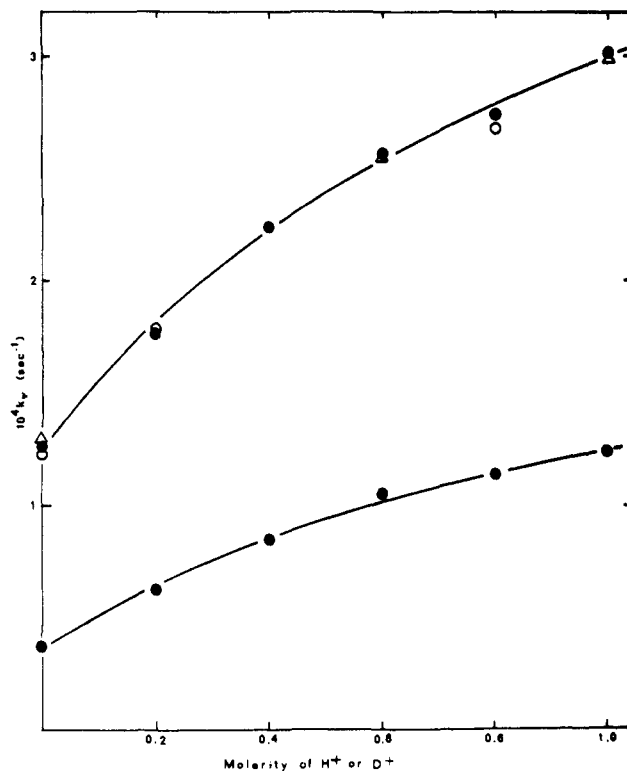


Figure 1. Pseudo-first-order rate constants for ethyl trichloroacetate hydrolysis at 25.0° as a function of lyonium ion concentration at an ionic strength of 1.00 in H<sub>2</sub>O and D<sub>2</sub>O. ● denotes a mean value of two or more spectrophotometrically measured values for a solution containing HClO<sub>4</sub> (or DClO<sub>4</sub>) and/or NaClO<sub>4</sub>. ○ denotes a single spectrophotometrically measured value for a solution containing HClO<sub>4</sub> and LiClO<sub>4</sub>. Δ denotes a single value determined by the hydroxamic acid method for a solution containing HClO<sub>4</sub> and/or NaClO<sub>4</sub>. Curves are best fits of eq 1 to the ● values and correspond to the parameters in Table I.

Table I. Rate Constants<sup>a</sup> for Hydrolysis of Ethyl Trichloroacetate in H<sub>2</sub>O and D<sub>2</sub>O at 25° and an Ionic Strength 1.0<sup>b</sup>

	$k_{\text{H}_2\text{O}}$	$k_{\text{D}_2\text{O}}$	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$
$10^4 k_a, \text{sec}^{-1}{}^c$	$1.24 \pm 0.04$	$0.359 \pm 0.024$	
$k_b, M^{-1}{}^c$	$0.87 \pm 0.07$	$0.85 \pm 0.09$	
$10^4 k_c, M^{-1} \text{sec}^{-1}{}^c$	$4.37 \pm 0.40$	$1.96 \pm 0.19$	
$10^4 k_1, \text{sec}^{-1}{}^d$	$5.03 \pm 0.11$	$2.31 \pm 0.05$	$2.18 \pm 0.07$
$k_{-1}/k_2{}^e$	$3.06 \pm 0.20$	$5.42 \pm 0.49$	$0.56 \pm 0.06$

<sup>a</sup>The uncertainties shown are standard deviations. <sup>b</sup>The ionic solutes present were HClO<sub>4</sub> and NaClO<sub>4</sub>; the sum of their molarities was always 1.0. <sup>c</sup>From the least-squares fit of the Na<sup>+</sup>/H<sup>+</sup>  $k_h$  values (Figure 1) to eq 1. <sup>d</sup>From eq 9. <sup>e</sup>From eq 10.

values of these parameters are therefore not reported for ethyl trifluoroacetate.

In contrast to the nonlinear dependence of  $k_h$  on [H<sup>+</sup>] shown by the trihaloacetate esters, Figure 2 shows that  $k_h$  at constant ionic strength is precisely described as a linear function of [H<sup>+</sup>] (eq 4) when the ester being hydrolyzed is ethyl acetate, chloroacetate, or difluoroacetate.

$$k_h = k_a + k_c'[\text{H}^+] \quad (4)$$

## Discussion

**Kinetic Salt Effects.** Before this difference between the dependences on [H<sup>+</sup>] of the rate constants for the hydrolyses of these two sets of esters can be ascribed confidently to a difference in mechanism, it is necessary to consider the possibility that it arises trivially from a difference in specific salt effects. It is possible in principle that the dependence of  $k_h$  on [H<sup>+</sup>] in the absence of salt effects could be given by

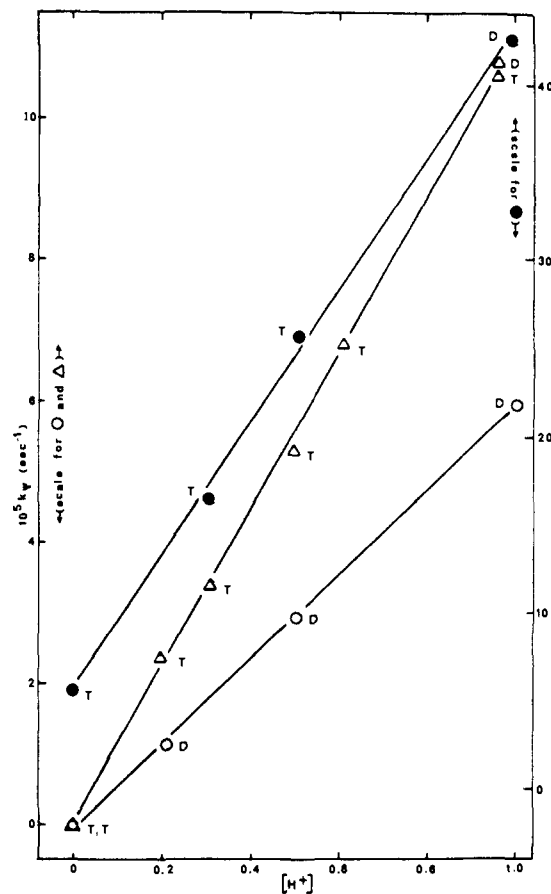


Figure 2. Pseudo-first-order rate constants for ester hydrolysis at 25.0° at an ionic strength of 1.00 in H<sub>2</sub>O. Electrolytes present are HClO<sub>4</sub> and/or NaClO<sub>4</sub>. ● denotes F<sub>2</sub>CHCO<sub>2</sub>Et. ○ denotes ClCH<sub>2</sub>CO<sub>2</sub>Et. Δ denotes CH<sub>3</sub>CO<sub>2</sub>Et. D denotes dilatometric measurement. T denotes titrimetric measurement.

Table II. Salt Effects on  $k_a$  at 25°

Added salt	$10^4 k_a, \text{sec}^{-1}$
None	2.404 <sup>b</sup>
1F NaClO <sub>4</sub>	1.27
1F LiClO <sub>4</sub>	1.20
1F KCl	2.07
1F LiCl	1.98

<sup>a</sup>When [H<sup>+</sup>] = 0,  $k_h = k_a$  (eq 1). <sup>b</sup>Reference 4.

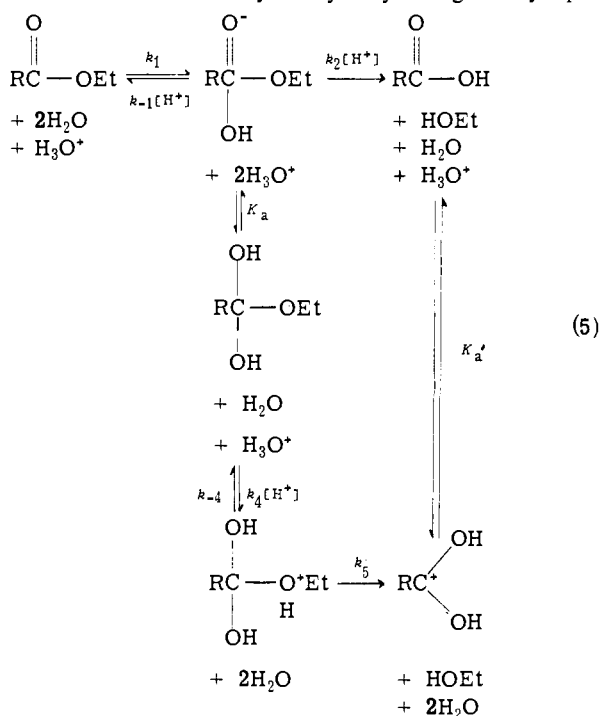
eq 4, and that the observed curvature arises from salt effects on  $k_a$  and/or  $k_c'$  instead of from a nonzero value of  $K_b$  in eq 1. Since the value of [ClO<sub>4</sub><sup>-</sup>] remains constant, any such salt effects could arise only from a difference between the specific effects of H<sup>+</sup> on one hand and of Na<sup>+</sup> and Li<sup>+</sup> on the other.

The possibility that specific salt effects on  $k_a$  are responsible for the curvature can be rejected for two reasons. First, for salt concentrations in the range studied here, salt effects on reactions between uncharged reactants are expected to be approximately linear in the salt concentration,<sup>7</sup> and this linearity has been verified for water-catalyzed ester hydrolysis.<sup>5,8</sup> If the effects of [Na<sup>+</sup>] and [H<sup>+</sup>] on  $k_a$  are both linear, then it is impossible for such effects to result in a nonlinear dependence of  $k_h$  on [H<sup>+</sup>] at constant ([H<sup>+</sup>] + [Na<sup>+</sup>]); the extreme nonlinearity actually observed would require salt effects on  $k_a$  whose deviation from linearity is larger than any previously reported for reactions of this charge type. Second, the data in Table II imply that the rate of hydrolysis via the water-catalyzed mechanism is not sensitive to the identity of the cation in univalent salt solutions (although it is sensitive to the identity of the anion).

If it is assumed that individual ionic contributions to salt effects on  $k_a$  are approximately additive, then those data show that the effects of  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$  are identical within a range of ca. 5%. It is thus reasonable to expect that the difference between the effects of  $\text{H}^+$  and  $\text{Na}^+$  would be comparably small.

Salt effects on  $k_c'$  are also expected to be linearly related to the salt concentration.<sup>7</sup> However, these effects could give rise to a nonlinear dependence of  $k_h$  on  $[\text{H}^+]$  since linear dependences of  $k_h$  on  $[\text{H}^+]$  and  $[\text{Na}^+]$  (i.e.,  $1 - [\text{H}^+]$ ) could lead to a term proportional to  $[\text{H}^+]^2$  in the expression for  $k_h$ . However, the strict linearity shown in Figure 2 demonstrates that no significant difference exists between the effects of  $\text{Na}^+$  and  $\text{H}^+$  on the acid-catalyzed (presumably  $\text{A}_{\text{Ac}2}$ )<sup>1</sup> mechanism for the hydrolysis of those three esters; it is thus improbable that the curvature observed for the closely related trihalo esters originates in differing specific effects of  $\text{H}^+$  and of  $\text{Na}^+$  (and  $\text{Li}^+$ ) on the rate constants for their hydrolysis via a "normal"  $\text{A}_{\text{Ac}2}$  path.

**Proposed Mechanism.** A mechanism which both predicts the form of eq 1 and is consistent with the accepted mechanism<sup>9,10</sup> for the water-catalyzed hydrolysis is given by eq 5.



In that equation, the complete stoichiometry of each state is shown, and the order (omitting  $\text{H}_2\text{O}$ ) of each kinetically significant step is indicated by the algebraic form of the pseudo-first-order rate constant written over the arrow. (E.g., the rates of the  $k_1$  and  $k_{-1}$  steps are  $k_1[\text{RCO}_2\text{Et}]$  and  $k_{-1}[\text{H}_3\text{O}^+][\text{RC}(\text{OH})(\text{OEt})\text{O}^-]$ , respectively.)

In this mechanism, the water-catalyzed reaction follows the  $k_1, k_2$  sequence of steps, while the observed acid catalysis is the result of unsymmetrically catalyzed partition of the intermediate in the water-catalyzed reaction and follows the  $k_1, K_a^{-1}, k_4, k_5$  sequence. At low acidity, both the  $k_1$  and  $k_2$  steps are partially rate determining; as the acidity increases, the rate of the  $k_4$  step increases until  $k_1$  becomes rate determining.

The empirical rate constants in eq 1 are related to the mechanistic rate constants in eq 5 by eq 6–8, and the values

$$k_a = k_1 k_2 / (k_{-1} + k_2) \quad (6)$$

$$k_b = k_4 k_5 / (k_{-1} + k_2)(k_4 + k_5) K_a \quad (7)$$

$$k_c = k_1 k_4 k_5 / (k_{-1} + k_2)(k_4 + k_5) K_a \quad (8)$$

of  $k_1$  and  $k_{-1}/k_2$  can be calculated from the empirical rate constants<sup>11</sup> by eq 9 and 10. The resulting values of  $k_1$  and

$$k_1 = k_c / k_b \quad (9)$$

$$k_{-1}/k_2 = (k_c / k_a k_b) - 1 \quad (10)$$

$k_{-1}/k_2$  are given in Table I. It should be noted that errors in  $k_a, k_b,$  and  $k_c$  are not independent so that the propagation of their standard deviations to obtain the uncertainties in  $k_1$  and  $k_{-1}/k_2$  must take into account<sup>6</sup> the error correlation coefficients given in matrices 2 and 3.

The excellent agreement between the value of  $k_{-1}/k_2$  obtained here for hydrolysis in light water ( $3.06 \pm 0.20$ ) and that calculated independently from the oxygen-18 exchange which is observed to accompany the water-catalyzed hydrolysis ( $3.18 \pm 0.06$ )<sup>3</sup> strongly supports the mechanism shown in eq 5.<sup>12</sup> The only previously studied hydrolyses of which we are aware in which both oxygen-18 exchange and the effect of unsymmetrically catalyzed partition have been shown to agree in their estimates of  $k_{-1}/k_2$  (and thus to require both that there be an intermediate and that the intermediate be tetrahedral) are the water-catalyzed hydrolysis of ethyl trifluorothiolactate<sup>9,13</sup> and the alkaline hydrolysis of acetanilide.<sup>14,15</sup>

In their classic study of oxygen-18 exchange accompanying the hydrolysis of ethyl trifluorothiolacetate in 25% aqueous acetonitrile, Bender and Heck<sup>9</sup> found that the extent of that exchange was independent of  $[\text{H}^+]$  for values of  $[\text{H}^+]$  up to ca. 0.1 M, and thus that partition of any intermediate which is formed during the hydrolysis must be symmetrically catalyzed. That report is in qualitative agreement with our observations that the hydrolysis rates of ethyl trichloroacetate and trifluoroacetate in a purely aqueous medium are not significantly dependent on  $[\text{H}^+]$  unless  $[\text{H}^+] \geq 0.1 \text{ M}$ . Had they been able to extend their exchange measurements to higher values of  $[\text{H}^+]$ , it seems likely that Bender and Heck would have obtained evidence for unsymmetrically catalyzed partition of the intermediate in their solvent also.

**Kinetic Deuterium Solvent Isotope Effect.** Further evidence that the nonlinear dependence of  $k_h$  on  $[\text{H}^+]$  arises from a change in rate-determining step (as in eq 5) rather than from specific salt effects or experimental artifacts is provided by the observed solvent isotope effect. The  $\text{A}_{\text{Ac}2}$  mechanism which is followed in the hydrolysis of more basic aliphatic esters<sup>1</sup> leads to an inverse solvent isotope effect; for example, the observed values of  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$  for the specific acid-catalyzed hydrolyses of methyl acetate and ethyl formate are 0.62 and 0.73.<sup>16,17</sup> Therefore, if the acid-catalyzed hydrolysis of ethyl trichloroacetate followed the  $\text{A}_{\text{Ac}2}$  mechanism, then as the acid concentration increased, the fraction of the total hydrolysis which followed the  $\text{A}_{\text{Ac}2}$  mechanism would approach unity, and the observed value of  $(k_h)_{\text{H}_2\text{O}}/(k_h)_{\text{D}_2\text{O}}$  would approach a value less than 1. Instead, this ratio remains greater than 1 and approaches a value near 2.

The observed values of this isotope effect on  $k_h$  are shown in Figure 3. Extrapolation of the data obtained at unit ionic strength gives a limiting value of 2.18. Values measured at an ionic strength of 2 are shown to be in consonance with that value. From eq 1 and 9, it follows that if the mechanism given in eq 5 is correct, then this limiting value is equal to  $(k_1)_{\text{H}_2\text{O}}/(k_1)_{\text{D}_2\text{O}}$ . This value for the solvent isotope effect on the water-catalyzed addition of water to the carbonyl group of ethyl trichloroacetate is consistent with the expected structure of the activated complex.<sup>4</sup>

**Effect of Ester Basicity on Hydrolysis Mechanism.** The principal difference between the  $\text{A}_{\text{Ac}2}$  mechanism for acid-catalyzed ester hydrolysis and that proposed in eq 5 lies in

the timing of the protonation and addition steps. In the  $A_{Ac2}$  mechanism, prior equilibrium proton transfer to the carbonyl oxygen is followed by addition of water; in the  $k_1, K_a^{-1}, k_4, k_5$  mechanistic sequence in eq 5, addition of water occurs first and proton transfer second.

In principle, an additional term in eq 1 corresponding to an  $A_{Ac2}$  pathway should be observable even for the trihaloacetate esters if the value of  $[H^+]$  were sufficiently high. This conclusion follows from the algebraic form of an  $A_{Ac2}$  term; a rate law which includes both the mechanism of eq 5 and the  $A_{Ac2}$  path would have the form of eq 11. The  $k_d$

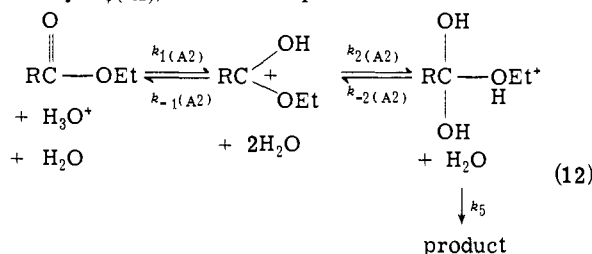
$$k_h = \frac{k_a + k_c[H^+]}{1 + k_d[H^+]} + k_d[H^+] \quad (11)$$

term corresponds to the  $A_{Ac2}$  path and is proportional to  $[H^+]$ , while the first term becomes independent of  $[H^+]$  at large values of  $[H^+]$ .

If the data shown in Figure 1 are fitted to eq 11 by least-squares, the fit is *not* significantly more precise than is the fit to eq 1, and small *negative* values are found for  $k_d$  for the reactions in both  $H_2O$  and  $D_2O$ . This implies that the hydrolysis of ethyl trichloroacetate via an  $A_{Ac2}$  mechanism is not kinetically significant when  $[H^+] \leq 1 M$ ; therefore the value of  $k_d$  must be much lower than  $10^{-4} M^{-1} sec^{-1}$ .

In order for the mechanism of eq 5 to provide an acid-catalyzed path at lower values of  $[H^+]$  than are required for the  $A_{Ac2}$  mechanism, it is necessary that proton transfer from the cationic intermediate in eq 5 to solvent (the  $k_{-4}$  step) be faster than elimination of water from that intermediate to give the protonated ester. The reason for this necessity follows from the principle of detailed balance;<sup>18</sup> the breakdown of the cationic intermediate to form starting material and the formation of that intermediate from starting materials must follow the same path. Thus if elimination of water from the cationic intermediate were kinetically significant, then formation of that intermediate by hydration of the protonated ester (i.e., by the  $A_{Ac2}$  path) would necessarily also be kinetically significant. However, the form of the observed rate law (eq 1 rather than eq 11) has been shown above to exclude this  $A_{Ac2}$  path.

The necessity of this inequality can be demonstrated more rigorously by the following algebraic argument. Compare the path for acid catalysis in eq 5 (with overall pseudo-first-order rate constant denoted by  $k_\psi$ ) with the  $A_{Ac2}$  mechanism (with overall pseudo-first-order rate constant denoted by  $k_{\psi(A2)}$ ) shown in eq 12. The ratio of the rate



constants for these two mechanisms is given by eq 13. The

$$\frac{k_\psi}{k_{\psi(A2)}} = \left( \frac{k_1 k_4}{k_{-1} K_a (k_{-4} + k_5) + k_4 k_5 [H^+]} \right) \times \left( \frac{k_{-1(A2)} (k_{-2(A2)} + k_5) + k_2(A2) k_5}{k_1(A2) k_2(A2)} \right) \quad (13)$$

equilibrium constant for formation of the cationic intermediate,  $\text{RC}(\text{OH})_2\text{OEt}^+$ , which is common to both mechanisms can be expressed in terms of the rate constants as  $k_1 k_4 / k_{-1} k_{-4} K_a$  (for eq 5) and also as  $k_1(A2) k_2(A2) / k_{-1(A2)} k_{-2(A2)}$  (for eq 12). These two expressions for the same equilibrium constant must be equal. Combination of this equality with eq 13 gives eq 14.

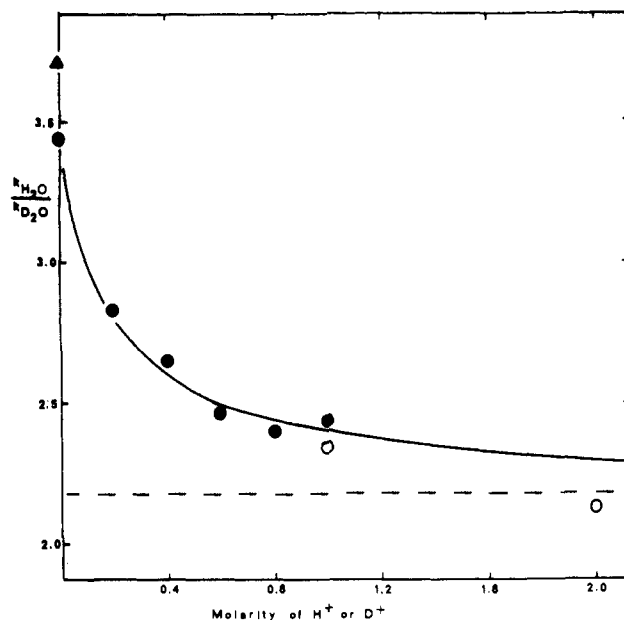


Figure 3. Solvent deuterium isotope effect on the rate of hydrolysis of ethyl trichloroacetate at 25.0° as a function of lyonium ion concentration. Each point represents a mean ratio calculated from two or more determinations of each rate constant. All rate constants except those for the zero ionic strength point were measured spectrophotometrically.  $\blacktriangle$  denotes zero ionic strength (ref 4).  $\bullet$  denotes an ionic strength of 1.00 in a solution containing  $\text{HClO}_4$  (or  $\text{DClO}_4$ ) and/or  $\text{NaClO}_4$ .  $\circ$  denotes an ionic strength of 2.00 in a solution containing  $\text{HClO}_4$  (or  $\text{DClO}_4$ ) and/or  $\text{NaClO}_4$ . The solid curve is calculated from eq 1 using the parameters in Table I. The dashed line represents the high lyonium ion concentration asymptote for an ionic strength of 1.00.

$$\frac{k_\psi}{k_{\psi(A2)}} = \frac{k_{-1} k_{-4} K_a}{k_{-1(A2)} k_{-2(A2)}} \left( \frac{k_{-1(A2)} (k_{-2(A2)} + k_5) + k_2(A2) k_5}{k_{-1} K_a (k_{-4} + k_5) + k_4 k_5 [H^+]} \right) \quad (14)$$

Even for esters as weakly basic as the trihaloacetate esters, it is expected that  $k_{-(A2)} \gg k_2(A2)$ .<sup>19</sup> If it is also true that  $k_{-4} \gg k_{-2(A2)}$ , then substitution of these two inequalities into eq 14 gives inequality 15.

$$\frac{k_\psi}{k_{\psi(A2)}} \gg \left( 1 + \frac{k_4 k_5 [H^+]}{k_{-1} K_a (k_{-2(A2)} + k_5)} \right)^{-1} \quad (15)$$

Consider the value of the right-hand side of inequality 15 for very weakly basic esters. As R is made more electronegative (e.g., by the successive substitution of Cl for H), there will be increases in  $K_a$ ,  $k_5$ , and  $k_{-2(A2)}$  together with decreases in  $k_4$  and  $k_{-1}$ . Both  $k_5$  and  $k_{-2(A2)}$  refer to elimination from a cationic tetrahedral intermediate so that the ratio,  $k_5 / (k_{-2(A2)} + k_5)$ , should remain approximately constant. Also, for any fixed value of  $[H^+]$ , the  $k_4 [H^+] / k_{-1} K_a$  ratio should decrease<sup>25</sup> so that the net effect of introducing electronegative substituents into R will be to make the right-hand side of inequality 15 approach 1. Therefore, for sufficiently weakly basic esters,  $k_{5A} \gg k_{12}$ .

The critical requirement in the above argument is that  $k_{-4} \gg k_{-2(A2)}$ . The  $k_{-4}$  step is another example of a proton transfer which probably is ultrafast,<sup>19,23,24</sup> while the  $k_{-2(A2)}$  step is an elimination of water from a tetrahedral intermediate and thus could be significantly slower as is required by the present observations. However, this inequality is not necessary a priori; the probability that such eliminations sometimes have rates which are competitive with fast proton transfer has been well documented by Barnett.<sup>28</sup>

In summary, the above argument predicts that for esters which are sufficiently weak bases, if acid catalysis is observed, it is likely that the mechanism of the catalysis is that

shown in eq 5 and not the  $A_{Ac}2$  mechanism. There are limitations on the generality of this conclusion in addition to the requirement that  $k_{-4} \gg k_{-2(A2)}$ . First, the maximum rate acceleration possible from the unsymmetric partition mechanism (eq 5) is a factor of  $(1 + k_{-1}/k_2)$ ; if the partition of the intermediate in the water-catalyzed reaction strongly favored formation of product, acceleration of the hydrolysis by hydronium ion via this mechanism might not be observable. Second, a borderline ester which was sufficiently non-basic for acid catalysis of its hydrolysis to proceed by this mechanism at moderate values of  $[H^+]$  might also show additional hydrolysis rate enhancement at still higher acidities from the incursion of an ordinary  $A_{Ac}2$  mechanism.

One further connotation of the unsymmetric partition mechanism is worthy of comment. This mechanism includes proton transfer to the OEt group in the uncharged intermediate but makes no mention of proton transfer to the OH groups. However, this formulation does *not* imply that OEt protonation must be faster than OH protonation. As shown above, the principle of detailed balance<sup>18</sup> in combination with the observed form of the rate law excludes the reverse of the  $A_{Ac}2$  path. Therefore, a cationic "intermediate" which results from proton transfer to an OH group [i.e.,  $RC(OH)(OEt)OH_2^+$ ] cannot return to ester by loss of  $H_2O$  and has no choice but to lose the extra proton and regenerate the uncharged intermediate. Unsymmetrically catalyzed partition of an intermediate does not require that the leaving groups have different basicities. The only requirements for this conclusion are that the ester be of sufficiently low basicity and that  $k_{-4} \gg k_{-2(A2)}$ . The possible relationship between the existence of this unsymmetric catalysis and the inverse solvent isotope effect on  $\alpha$  (Table I) is discussed elsewhere<sup>4</sup> in the context of evidence concerning the structures of the activated complexes in the  $k_{-1}$  and  $k_2$  steps.

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## References and Notes

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- (10) This mechanism is discussed in greater detail in ref 3 and 4.
- (11) A slightly more simple mechanism which also leads to eq 9 and 10 can be written by setting  $k_{-4} = 0$ . However, this assumption about  $k_{-4}$  is shown to be unrealistic later in the discussion.
- (12) This agreement also implies that salt effects on  $k_{-1}$  and  $k_2$  must be very similar so that the negative salt effects observed for  $K_a$  (Table II) very probably reflect salt effects on  $k_1$ .
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- (19) This inequality is well established for the  $A_{Ac}2$  hydrolysis of unsubstituted aliphatic esters.<sup>1</sup> However, since less basic esters will have smaller values for  $k_{1(A2)}$ , it is possible in principle that an ester might be so weakly basic that  $k_{1(A2)}$  would be rate determining so that  $k_{-1(A2)} < k_{2(A2)}$ . The value of  $k_{1(A2)}$  for ethyl trichloroacetate can be estimated from the predicted  $pK_a$  of the conjugate acid of that ester. Recent estimates of the corresponding  $pK_a$  for ethyl acetate range from 3.4<sup>20</sup> to 6.2<sup>21</sup> correction of these numbers for the substituent effect of the  $CCl_3$  group [estimated from  $\sigma^*$  ( $CCl_3$ ) = 2.65 and  $\rho^* \approx 1.7$  (the value for  $RCO_2H$  dissociation)]<sup>22</sup> predicts  $pK_a \approx -8$  or  $-11$ . Since the reverse of the  $k_{1(A2)}$  step is a simple proton transfer from an oxygen base to solvent and has  $\Delta G^\ddagger < 0$ , it should be very fast, probably ultrafast.<sup>23,24</sup> Therefore the value of  $k_{1(A2)}$  should be given approximately by  $(kT/h) \exp(pK_a \ln 10) = 6 \times 10^4$  or  $6 \times 10^1 M^{-1} sec^{-1}$ . Both of these estimates are much larger than the upper limit ( $10^{-4} M^{-1} sec^{-1}$ ) obtained above for  $k_d$  (in eq 11). Thus  $k_{1(A2)} \gg k_d$ , and since  $k_d = k_{1(A2)}k_{2(A2)}/(k_{-1(A2)} + k_{2(A2)})$ , it follows that  $k_{-1(A2)} \gg k_{2(A2)}$ .
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