Ethyl Trichloroacetate Hydrolysis. II. Oxygen-18 Exchange Accompanying the Water-Catalyzed Hydrolysis

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Abstract: Values of k_e/k_h (the oxygen-18 exchange/hydrolysis rate constant ratio) have been measured as a function of temperature for the water-catalyzed hydrolysis of ethyl trichloroacetate in dilute aqueous solution. It was found that $k_e/k_h = 1.59 \pm 0.03$ (25°), $\Delta H_e^{\ddagger} - \Delta H_h^{\ddagger} = -1.7 \pm 0.3$ kcal mol^{-1} and $\Delta S_e^{\ddagger} - \Delta S_h^{\ddagger} = -5 \pm 1$ cal deg^{-1} mol^{-1}. This is the first report of a carboxylic ester for which $k_e > k_h$; the contrary order reported for other esters may arise from the fact that most previous studies of ester exchange and hydrolysis have used mixed solvents. Comparison of this 25° value of k_e/k_h to the kinetically measured value of k_{-1}/k_2 (the rate constant ratio for partition of the intermediate between elimination of water and elimination of ethanol, respectively) implies that proton transfer to the initially formed anionic intermediate is faster than elimination from that intermediate and allows calculation of the following parameters for that partition: $k_{-1}/k_2 = 3.18 \pm 0.06$ (25°); $\Delta H_{-1}^{\ddagger} - \Delta H_2^{\ddagger} = -1.7 \pm 0.3$ kcal mol^{-1}; $\Delta S_{-1}^{\ddagger} - \Delta S_2^{\ddagger} = -3 \pm 1$ cal deg^{-1} mol^{-1}.

Nearly all previous studies of carbonyl oxygen exchange during water-catalyzed hydrolyses of carboxylic acid derivatives have used mixed solvents; the results of those investigations have been reviewed.[1-5] Among those results is the observation[6] that k_e/k_h, the exchange/hydrolysis first-order rate-constant ratio, varies when the solvent composition is changed so that the known values for reaction in mixed solvents are not necessarily relevant to investigations of mechanisms of hydrolysis in a purely aqueous medium.

This paper reports values of k_e/k_h as a function of temperature for the water-catalyzed exchange and hydrolysis of ethyl trichloroacetate in dilute aqueous solution near zero ionic strength. These measurements were undertaken, because such values were needed for the interpretation of our data on the temperature dependence of the water-catalyzed hydrolysis rate[7] and to provide an independent test of our proposed mechanism for the hydronium ion-catalyzed hydrolysis.[8] That mechanism requires that $k_e > k_h$ for the water-catalyzed reaction, whereas until the data reported here were obtained, all investigations of water-catalyzed hydrolyses of alkyl carboxylates had agreed that $k_e < k_h$.

Experimental Section

Materials. Trichloroacetic-^{18}O acid was prepared by hydrolysis of trichloroacetonitrile (Eastman, purified by distillation through a Nester/Faust annular Teflon spinning-band column) with aqueous 20 *F* Na^{18}OH [from ca. 4% sodium amalgam[9] and $H_2{}^{18}O$ (Volk, 1.59 atom % ^{18}O)], followed by acidification with anhydrous HCl, evaporation of the water, and vacuum distillation of the product. Ethyl trichloroacetate-^{18}O was prepared from this acid by reaction with diazoethane[10] in dry ether and purified by distillation through a Nester/Faust annular Teflon spinning-band column; product was collected over a 0.2° range at ca. 75° (30 mm). Other reagents were either as elsewhere described[8] or were of the best commercially available grade and used without further purification.

Oxygen-18 Exchange Measurements. Oxygen-18 analyses were carried out by conversion of the oxygen into CO_2 followed by analysis of that gas using a Consolidated-Nier Model 21-201 isotope ratio mass spectrometer. Analyses with an analytical mass spectrometer of CO_2 samples resulting from the procedures described below showed no extraneous peaks which could interfere with the mass ratio determinations.

The extent of oxygen exchange in the ester during hydrolysis was measured by analysis of the trichloroacetate hydrolysis product. Each hydrolysis was carried out by allowing 500 ml of water in a flask to become thermally equilibrated with the constant-temperature bath (described elsewhere)[7] and then adding 20 μl of ethyl trichloroacetate-^{18}O (giving an initial ester concentration near 2.9×10^{-4} *M*), while the water was stirred vigorously. One minute after addition of the ester, stirring was discontinued and the hydrolysis allowed to proceed for 8 half-times. The pH of the reaction mixture was then adjusted to near 6 with sodium hydroxide and the water removed by rotary evaporation under vacuum; the temperature of the reaction mixture was kept below 25° during the evaporation. The residue was dissolved in 0.1 ml of water, transferred to a microfilter, and mixed with 0.1 ml of saturated aqueous mercurous perchlorate. The resulting precipitate of mercurous trichloroacetate was immediately separated from the mother liquor by filtration, washed twice with 0.1-ml portions of water, and dried at room temperature under high vacuum ($<10^{-4}$ mm). The dry precipitate was transferred to a tube connected to the vacuum line and heated by an oil bath at 90-110°; the CO_2 produced was condensed in a U tube cooled in methanol slush (−98°). Natural abundance CO_2 reference samples were prepared from Fisher certified trichloroacetic acid via the mercurous salt procedure described above. Control experiments in which the labeled mercurous trichloroacetate precipitate was allowed to remain in contact with the acidic mercurous ion solution for 30 min gave no evidence of oxygen exchange with the medium.

The extent of exchange of the labeled trichloroacetate ion hydrolysis product with the medium during the ester hydrolysis and work-up was measured by applying the above described hydrolysis procedure (at several different temperatures and pH values) to samples of labeled trichloroacetic acid.

The ^{18}O content of the labeled ester was determined by two methods: by the usual $HgCl_2$ procedure[11] and by decarboxylation of the lithium salt produced from reaction of the ester with LiI. In the latter procedure, a small sealed bulb containing ca. 20 mg of ester was placed in a tube with excess anhydrous LiI. The LiI was dried further by heating the tube at about 140° for at least 8 hr, while the contents was maintained under high vacuum; the tube was then sealed off; the ester bulb was broken; the tube was heated at 205° for at least 6 hr and the resulting CO_2 separated from most of the ethyl iodide by distillation on the vacuum line from methanol slush (−98°). There was no significant difference between the results of the two methods, but the LiI procedure was more easily reproducible.

Results

Values of the k_e/k_h ratio were calculated from the measured oxygen-18 abundances using procedures described by previous workers.[12,13] Under the conditions of these experiments, the measured values of atom percent excess ^{18}O in the ester (R^E) and in the trichloroacetate ion (R^I) are related to the first-order rate constants for ester hydrolysis (k_h), ester oxygen exchange (k_e), and trichloroacetate ion oxygen exchange (k_x) for ester hydrolysis experiments by eq 1 and

$$2\frac{R^I}{R^E{}_0} = \frac{e^{-k_x t}}{1 + k_e/k_h + k_x/k_h} \tag{1}$$

for trichloroacetate ion oxygen exchange experiments by eq

Table I. Rate Constants as Functions of Temperature

T, °C	$10^4 k_h$,[a,f] sec^{-1}	$10^4 k_x$,[b,c] sec^{-1}	k_e/k_h[d-f]
25.00	2.404	<0.0025	1.59 ± 0.03
35.00	4.154	<0.004	1.49 ± 0.05
45.00	6.75	<0.007	1.30 ± 0.06
55.00	10.38	<0.012	1.30 ± 0.08
65.00	15.19	<0.02	1.11 ± 0.05

[a] From ref 7. [b] Upper limit on k_x calculated from the assumption that pH 2.7 (the highest pH for which k_x was measured) persisted throughout the experiment. In actuality, the pH decreased throughout each run from near 7 to near 3.5. Since k_x increases as pH decreases, the average value of k_x during a run is well below the listed value. [c] From eq 2. [d] From eq 1. [e] The listed values are the mean (and the standard deviation of the mean) of between two and six determinations. [f] The ionic strength was $\leqslant 3 \times 10^{-4}$ during measurements of k_e/k_h and $\leqslant 1 \times 10^{-3}$ during measurements of k_h (ref 7).

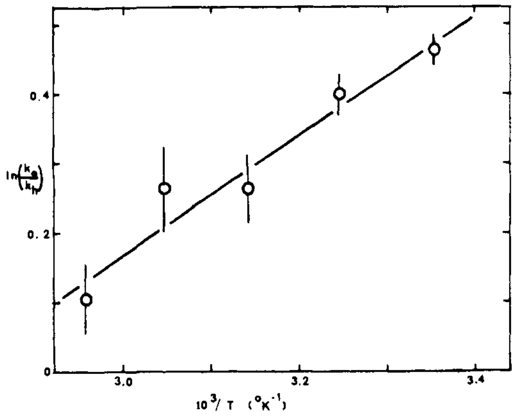


Figure 1. Temperature dependence of the exchange/hydrolysis rate constant ratio. The line shown is the least-squares line of best fit [$\ln(k_e/k_h) = -2.414 + 861(1/T)$]; the standard deviation of a point from the line is ±0.04.

2, where the subscript zero denotes initial time. The factor

$$\frac{R^I}{R^I_0} = e^{-k_x t} \tag{2}$$

of 2 in eq 1 arises from the fact that the ester is labeled in both oxygens together with the assumption that the hydrolysis proceeds via acyl-oxygen cleavage. The validity of this assumption is proved by the observation that all observed values of the R^I/R^E_0 ratio are less than 0.5; if the hydrolysis proceeded via alkyl-oxygen cleavage, loss of ^{18}O from the alkoxyl oxygen could occur only after hydrolysis to trichloroacetate ion, and the value of k_x is too small to allow that exchange mechanism to account for the data.

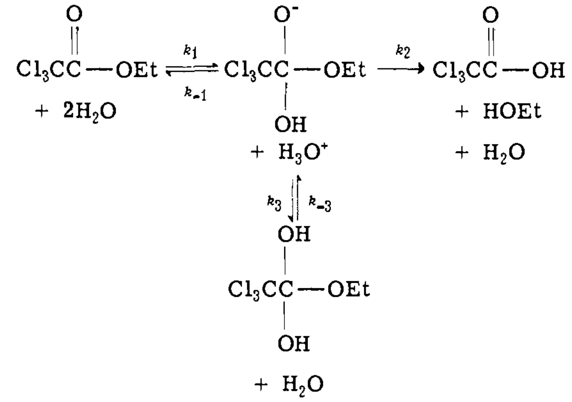
The derived values of k_e/k_h are summarized in Table I. It should be noted that at all temperatures k_x is sufficiently small to make no significant contribution to the value of k_e/k_h computed from eq 1. (For example, at 25°, $k_x/k_h < 0.001$ and $[1 - \exp(-k_x t)] < 0.006$, when t equals 8 hydrolysis half-times.)

Figure 1 shows the observed k_e/k_h values as a function of the reciprocal absolute temperature. From the illustrated functional dependence, it follows that $\Delta H_e^\ddagger - \Delta H_h^\ddagger = -1.71 \pm 0.26$ kcal mol^{-1} and $\Delta S_e^\ddagger - \Delta S_h^\ddagger = -4.8 \pm 0.9$ cal deg^{-1} mol^{-1}, where the indicated uncertainties are standard deviations. The data are too imprecise to give any indication even of the sign of $\Delta C_{p,e}^\ddagger - \Delta C_{p,h}^\ddagger$.

To our knowledge, the results reported here provide the first example of a hydrolysis of an alkyl carboxylate for which $k_e > k_h$. The only related reactions for which it has previously been reported that oxygen exchange is faster than hydrolysis were hydrolyses of compounds with very poor leaving groups such as $Co^{2+}(NH_3)_5O^-$ [5,14] and RNH^-.[15] The present observation should be contrasted with that of Bender and Heck[12] ($k_e/k_h = 0.6$) for the uncatalyzed hydrolysis of the closely related ester, ethyl trifluoroacetate, in 25% aqueous acetonitrile. The difference between these two reports is consistent with the observations of Bender and Ginger[6] concerning the effect of solvent composition on k_e/k_h values and emphasizes the desirability of avoiding mixed solvents, when the goal of an investigation is an increased understanding of reactions in aqueous solution.

Discussion

The hydrolysis of ethyl trichloroacetate is general-base catalyzed, and the observed rate of the formally "uncatalyzed" (or water-catalyzed) hydrolysis is consistent with a mechanism for the first step in which one water molecule plays the role of general base by abstracting a proton from another water molecule which acts as a nucleophile and adds to the carbonyl group.[3,16] The tetrahedral intermediate formed in that addition can either eliminate ethanol to form product or eliminate water to regenerate ester. Protonation of the intermediate can make equivalent the two oxygen atoms which originally were in the ester carbonyl group and in the nucleophilic water molecule. After such protonation has taken place, elimination of water from the intermediate provides a path for regeneration of an ester molecule which has exchanged its original carbonyl oxygen with the water. The most simple mechanism which includes these paths for hydrolysis and exchange was proposed by Bender and Heck;[12] their mechanism is given in abbreviated form by eq 3. (This mechanism appears as part of the more complete mechanism shown in eq 5 of the preceding paper.[8] The first-order rate constants, k_{-1} and k_2, used here are equal to $k_{-1}[H^+]$ and $k_2[H^+]$ in the more complete mechanism, and $k_{-3}/k_3 = K_a$.)



(3)

In this mechanism, exchange of the ester carbonyl oxygen with solvent oxygen occurs with 50% probability each time an ester molecule traverses the sequence of steps with first-order rate constants k_1, k_3, k_{-3}, k_{-1} in that order, and ester hydrolysis occurs via the k_1, k_2 sequence. For this mechanism, the observable parameters, k_h and k_e (eq 1), are related to the mechanistic rate constants by eq 4 and 5,

$$k_h = k_1/(1 + \alpha) \tag{4}$$

$$\frac{k_e}{k_h} = \frac{\alpha}{2}\left(\frac{k_3}{k_{-1} + k_2 + k_3}\right) \tag{5}$$

where $\alpha = k_{-1}/k_2$, the ratio for partition of the anionic intermediate between return to ester and advance to product.

Evaluation of k_{-1}/k_2. Since the exchange reaction passes through the k_3 and k_{-3} proton-transfer steps, while the hydrolysis does not, the relationship between α and the observed k_e/k_h ratio depends on whether those proton-transfer steps are rapid enough to establish equilibrium between the anionic and uncharged intermediates. If proton transfer is sufficiently fast, then

$$k_3 >> k_{-1} + k_2$$

and

$$\alpha = 2(k_e/k_h) \qquad (6)$$

If proton transfer is slow enough to be at least partially rate determining in the exchange, then $k_3 < k_{-1} + k_2$ and $\alpha > 2k_e/k_h$.

From the value of k_e/k_h at 25° (Table I), eq 6 predicts that $\alpha = 3.18 \pm 0.06$. An independent estimate of α at 25° (3.06 ± 0.20)[8] has been obtained from the dependence of k_h on [H^+]. The close agreement between this independent estimate and the prediction of eq 6 argues strongly both that protonation of the anionic intermediate in eq 3 is faster than elimination from that intermediate (i.e., that $k_3 \gg k_{-1} + k_2$), and that the mechanism which has been proposed[8] to account for the dependence of k_h on [H^+] is correct.

The question of whether proton transfer or elimination is rate determining for the oxygen exchange which often accompanies carboxylic ester hydrolysis has been the subject of much discussion. For example, Bender and Heck[12] have suggested that their observation that $(k_e/k_h)_{H_2O}/(k_e/k_h)_{D_2O} \approx 2$ or 3 for a reaction which is closely related to that studied here (water-catalyzed hydrolysis and exchange of ethyl trifluoroacetate in aqueous acetonitrile) implies that $k_3 \approx k_{-1} + k_2$; however, Jencks[5] has pointed out that this observation can be explained equally plausibly as a solvent isotope effect on k_{-1}/k_2. A difference between the solvent isotope effects on k_2 and k_{-1} as large as a factor of 2 (the value of $\phi_{OL^-}{}^{-1}$)[17] in the observed direction could arise from the fact that a lyon is bound to the expelled oxygen in the k_{-1} step, and no such lyon is present in the k_2 step.

Independently of the experimental evidence, there are theoretical grounds for expecting rate-determining proton transfer to be much less probable in water-catalyzed exchange (e.g., the reaction under study here) than in OH^--catalyzed exchange. Since the k_1 step proceeds with general-base catalysis by H_2O, the k_{-1} step must occur with general-acid catalysis by H_2O, the k_{-1} step must occur with general-acid catalysis by H_3O^+. Furthermore, the similarity between H_2O and EtOH makes is highly probable that the k_2 step also proceeds with general-acid catalysis by H_3O^+. Thus all three possible reactions of the anionic intermediate (the k_{-1}, k_2, and k_3 steps) involve proton transfer to the intermediate, and each of these three first-order rate constants contains the concentration of H_3O^+ as a factor. Since the anionic oxygen which accepts the proton in the k_3 step should be about 10^{12} times as basic[18] as the uncharged sites which accept the proton in the k_{-1} and k_2 steps, it is expected[20] that $k_3 > k_{-1} + k_2$ on the basis of this difference in basicity alone. The fact that changes in carbon-oxygen bonding and transfer of charge through a longer series of bonds accompany proton transfer in the k_{-1} and k_2 steps might further enhance this inequality.[23,24]

Application of a similar argument to the hydroxide ion-catalyzed reaction leads to a quite different conclusion. Catalysis by OH^- almost certainly takes place by direct nucleophilic attack of OH^- on the carbonyl carbon and not by a general-base catalyzed mechanism in which OH^- abstracts a proton from a water molecule.[12,25] Thus the tetrahedral intermediate has the same structure as that shown for the anionic intermediate in the water-catalyzed reaction (eq 3); however, under the conditions which lead to OH^--catalyzed exchange and hydrolysis, this intermediate does *not* require general-acid catalysis in order to return to ester or proceed to product. In the OH^--catalyzed reaction, the analogs of the k_{-1} and k_2 steps in eq 3 are uncatalyzed first-order decompositions of the intermediate and might very well be faster than protonation of the intermediate.[26]

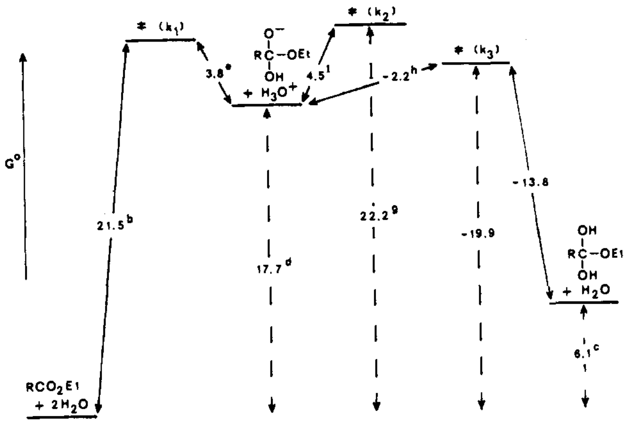


Figure 2. Relative standard Gibbs free energies[a] of transition states and intermediates in the water-catalyzed exchange and hydrolysis of ethyl trichloroacetate in dilute aqueous solution at 25°. [a] All numerical values are in kcal mol^{-1}, and all species (including H_3O^+) are in their standard states (1 *M* for solutes, mole fraction = 1 for H_2O). [b] From the values of k_h and k_e/k_h in Table I together with eq 4 and 6. [c] From Guthrie's estimate[22] that $\Delta G° = 12.1$ kcal mol^{-1} for $H_2O + CH_3CO_2CH_3 \rightarrow CH_3C(OH)_2OCH_3$ together with the assumptions that the substitution of C_2H_5O for CH_3O has a negligible effect on $\Delta G°$ (this substitution has an effect on $\Delta G_h^‡$ of only 0.1 kcal mol^{-1}),[22] and that the substitution of CCl_3 for the acyl CH_3 will have the same effect as the analogous known substituent effect on the aldehyde hydration equilibrium ($\Delta G° = 0.0$ kcal mol^{-1} for CH_3CHO hydration,[22] and $\Delta G° = -6.0$ kcal mol^{-1} for CCl_3CHO hydration).[28] [d] Calculated from the result of *c* and an estimate that for $CCl_3C(OH)_2OEt$, $pK_a = 8.5$ (from $pK_a = 10.2$ for $CCl_3CH(OH)_2$,[29] $pK_a = 12.2$ for CCl_3CH_2OH,[30] and the assumption that the symmetry-corrected substituent effects on pK_a of OH and OEt are identical). [e] The difference between $\Delta G_1^‡$ (from *b*) and $\Delta G_1°$ (from *d*). [f] From $k_2 = k_{-1}/\alpha$ together with eq 6, k_e/k_h (from Table I) and $\Delta G_{-1}^‡$ (from *e*). [g] The sum of $\Delta G_2^‡$ (from *f*) and $\Delta G_1°$ (from *d*). [h] Average of the upper and lower limits estimated in the text. [i] The sum of $\Delta G_3^‡$ (from *h*) and $\Delta G_1°$ (from *d*). [j] The sum of $\Delta G_1°$ (from *d*), $\Delta G_3^‡$ (from *h*) and $-\Delta G°$ for $H_2O + CCl_3CO_2Et \rightarrow CCl_3C(OH)_2OEt$ (from *c*).

The value of α together with other known rate and equilibrium constants allows the recent analysis of hydration equilibria by Guthrie[22] to be extended to the construction of a reaction profile for the uncatalyzed exchange and hydrolysis of ethyl trichloroacetate (Figure 2).

Note that in Figure 2 the value of $\Delta G^‡$ for the k_{-1} step is obtained by difference and is required to be near 3.8 kcal mol^{-1} which corresponds to $k_{-1} = 1 \times 10^{10}$ sec^{-1} when [H^+] = 1. This predicted value suggests that k_{-1} is on the borderline of being encounter controlled; however, because of uncertainties in the prediction of $\Delta G_{-1}^‡$ of approximately 1 or 2 kcal mol^{-1},[22] the question of whether k_{-1} and k_2 are encounter controlled remains open. The answer to this question is further complicated by its dependence on whether the H_3O^+ required in the k_{-1}, k_2, and k_3 steps must be supplied from the bulk solution (as has been assumed implicitly in the above discussion) or whether, as has sometimes been suggested,[3] the H_3O^+ produced in the k_1 step participates in the k_{-1}, k_2, or k_3 step before it diffuses away from the newly formed anionic intermediate. If this latter suggestion is correct, then the correct formulation of k_{-1}, k_2, and k_3 would be as true first-order rate constants whose values are independent of the H_3O^+ concentration; those values could be well above 10^{10} sec^{-1}.[26] Even in such a case, however, the expectation that $k_3 > k_{-1}$ remains valid so long as $1/k_{-1}$ is greater than the mean time required for rearrangement of hydrogen bonds within the solvated $CCl_3CH(OH)O^-,H_3O^+$ ion pair out of the orientation which results from the k_1 step into the orientations required for the k_2 and k_3 steps. This mean time should be of the order of the dielectric relaxation time or the proton spin-lattice relaxation time of water (8×10^{-12} and 2×10^{-12} sec, respectively at 25°).[27]

These relaxation times suggest an upper limit on k_3 of ca. 5×10^{11} sec^{-1} which corresponds to a lower limit on $\Delta G_3^\ddagger$ of 1.5 kcal mol^{-1}. An approximate upper limit on $\Delta G_3^\ddagger$ can be estimated from the agreement of the observed value of $2k_e/k_h$ with the kinetically determined[8] value of α. Since that α was evaluated at an ionic strength of 1.0, the correct value for comparison to $2k_e/k_h$ would differ from the measured value if the salt effects on k_{-1} and k_2 were not identical. If an upper limit of ca. 20% is guessed for this possible error, then the $k_3/(k_{-1} + k_2 + k_3)$ ratio in eq 5 could be as low as ca. 0.8; this ratio together with the estimates of $\Delta G^\ddagger$ for k_{-1} and k_2 in Figure 2 gives an upper limit of $\Delta G_3^\ddagger \leq 2.9$ kcal mol^{-1}. This corresponds to a lower limit on k_3 of ca. 4×10^{10} sec^{-1}, when H_3O^+ is in its standard state of 1 *M*. Thus the k_3 step could be *either* a "unimolecular" recombination of the anion and H_3O^+ within the solvent cage (with a true first-order rate constant in the range $4 \times 10^{10} \lesssim k_3 \lesssim 5 \times 10^{11}$ sec^{-1}) *or* a bimolecular reaction of the anion with H_3O^+ from the bulk solution (with an encounter-limited second-order rate constant, $k_3/[H^+] \approx 4 \times 10^{-10}$ M^{-1} sec^{-1}, the value expected for a reaction between oppositely charged ions.

Temperature Dependence of k_e/k_h. The observed temperature dependence of the exchange/hydrolysis rate constant ratio (Figure 1) was used above to derive values for the differences between the corresponding empirical enthalpies and entropies of activation. From eq 5, it follows that the general relationships between these observed differences and the differences between the corresponding activation parameters for the k_{-1} and k_2 steps in the mechanism (eq 3) are given by eq 7 and 8. The last terms on the right-hand sides of both of these equations vanish when $k_3 \gg k_{-1} + k_2$. This inequality has been shown to be true at 25°; assuming it to be true over the entire temperature range gives $\Delta H_{-1}^\ddagger - \Delta H_2^\ddagger = -1.71 \pm 0.26$ kcal mol^{-1} and $\Delta S_{-1}^\ddagger - \Delta S_2^\ddagger = -3.4 \pm 0.9$ cal deg^{-1} mol^{-1}.

$$\Delta H_{-1}^{\neq} - \Delta H_2^{\neq} = (\Delta H_e^{\neq} - \Delta H_h^{\neq}) + \frac{(\Delta H_3^{\neq} - \Delta H_2^{\neq}) + \alpha(\Delta H_3^{\neq} - \Delta H_{-1}^{\neq})}{1 + \alpha + k_3/k_2} \tag{7}$$

$$\Delta S_{-1}^{\neq} - \Delta S_2^{\neq} = (\Delta S_e^{\neq} - \Delta S_h^{\neq}) + R \ln 2 + \frac{(\Delta H_3^{\neq} - \Delta H_2^{\neq}) + \alpha(\Delta H_3^{\neq} - \Delta H_{-1}^{\neq})}{T(1 + \alpha + k_3/k_2)} \tag{8}$$

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