Studies in Solvolysis. Part V. Further Investigations Concerning the Solvolysis of Primary, Secondary, and Tertiary Trifluoroacetates¹

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The rate of solvolysis of ethyl trifluoroacetate has been investigated in a series of H_2O/D_2O mixtures at 9.97 °C. The secondary isotope effects related to the hydrolysis of the isotopic pairs, methyl/methyl- d_3 , ethyl/ethyl- d_5 , *i*-propyl/*i*-propyl- β - d_6 and *t*-butyl/*t*-butyl- d_9 trifluoroacetates have been established as well as the temperature dependence for the hydrolysis of *t*-butyl trifluoroacetate. The significance of all these measurements with respect to the mechanism of these reactions is discussed.

La vitesse de la solvolyse du trifluoroacétate d'éthyle a été étudiée dans divers mélanges H_2O/D_2O à 9.97 °C. Les effets isotopiques secondaires concernant les paires isotopiques des trifluoroacétates de méthyle/méthyl- d_3 , d'éthyle/éthyl- d_5 , d'*i*-propyle/*i*-propyl- β - d_6 et de *t*-butyle/*t*-butyl- d_9 , ont été établis ainsi que l'influence de la température sur l'hydrolyse du trifluoroacétate de *t*-butyle. La signification de toutes ces mesures, quant au mécanisme de ces réactions, est discutée.

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Introduction

In a previous communication (1) the temperature dependence for the rates of uncatalyzed (neutral) hydrolysis of a series of esters CF₃-COOR(R = Me, Et, i-Pr and t-Bu) was reported in water and deuterium oxide. An examination of the thermodynamic parameters ΔH^{\dagger} , ΔS^{\dagger} , and ΔC_{p}^{*} which characterize the thermal activation of these molecules suggested that the methyl, ethyl, and *i*-propyl esters all react by a B_{Ac}2 acyloxygen cleavage mechanism whereas the tertiary ester reacts by an S_N1 alkyl-oxygen fission path or a mechanism which involves mixed kinetics, *i.e.* both the B_{Ac}^2 and S_N^1 routes. The mechanistic pattern based on the thermodynamic parameters was completely substantiated by the kinetic solvent isotope effects (k.s.i.e.) measured in light and heavy water.

The designations B_{Ac}^2 and S_N^1 for these reactions are, however, only partly adequate. The former description merely emphasizes the fact that the "basic" or nucleophilic properties of the solvent are important driving forces for the reaction with at least one water molecule in the transition state for the rate determining step. The latter (S_N^1) description offers no indication as to whether the ester itself or the tetrahedral intermediate postulated for the B_{Ac}^2 reaction reacts further by an alkyl-oxygen fission mechanism and also leaves the question of the incursion of ion pairs etc. unresolved.

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The inadequacy of the B_{Ac}^2 description is apparent when a more detailed specification of the overall reaction is attempted. A simplified mechanistic description for the B_{Ac}^2 process is

[1] Ester + N $\stackrel{k_1}{\rightleftharpoons}$ sp³ intermediate + E $\stackrel{k_3}{\rightarrow}$ products²

where N and E are respectively nucleophilic and electrophilic reagents which, in the case of the uncatalyzed hydrolysis, are provided by the solvent acting in both roles.

In the two step mechanism represented by reaction 1 the observed kinetic behavior for any particular ester will depend on the relative magnitudes of the rate constants associated with the individual steps. With strong nucleophiles e.g. the lyate ion, the observed kinetics provide a standard example of a second order reaction and presumably k_1 is the rate determining step. On the other hand, if the nucleophilic strength of N is reduced as is the case when water replaces the hydroxide ion, the kinetic behavior may be modified in such a way as to make k_1 , k_2 and k_3 all kinetically significant. In cases where k_3 is kinetically significant the B designation of the $B_{Ac}2$ category will be only partly justified. The indeterminacy of the reaction order with respect to the solvent in the neutral hydrolysis excludes the possibility of locating the rate determining step in the overall process. Indeed, the

¹For Part IV, see ref. 20.

²We regard reaction 1 as a minimal mechanistic description for the $B_{Ac}2$ process.

CANADIAN JOURNAL OF CHEMISTRY. VOL. 50, 1972

CD₂CD₃

CH(CH₃)₂

 $CH(CD_3)_2$

C(CH₃)₃

C(CD₃)₃

[2]

92 N

pseudo first order hydrolyses of the trifluoroacetate esters raise all the classical conundrums associated with processes where the reaction medium also provides the attacking reagent or reagents. In spite of these difficulties we hope to show that mixed k.s.i.e.'s and secondary isotope effects provide useful probes to examine these perennial questions. As a prerequisite to some resolution of the problems posed above we report below the rates of hydrolysis of ethyl trifluoroacetate in H₂O/D₂O mixtures as well as the secondary isotope effects for the isotopic ester pairs methyl/methyl- d_3 , ethyl/ethyl- d_5 , *i*propyl/*i*-propyl- d_6 , and *t*-butyl/*t*-butyl- d_9 . A more detailed investigation of the temperature variation of the rate of hydrolysis of t-butyl trifluoroacetate is also reported and this particular study suffices to establish the temperature dependence of the enthalpy of activation for this substance.

Experimental

Materials and Methods

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The experimental methods for rate determinations were identical to those described in Part I of the present series. The isotopic solvent mixtures were prepared by weight from deuterium oxide of known water content. The ethyl trifluoroacetate used in this study was the same sample used previously (1). Deuterium oxide was obtained from the Atomic Energy of Canada Ltd. and deuterated materials used in the preparation of the esters were obtained from Merck, Sharp, and Dohme Ltd.

The methyl and ethyl trifluoroacetates and their respective deuterated analogs were prepared by reacting the appropriate methyl or ethyl halide with silver trifluoroacetate in purified benzonitrile (1). The i-propyl and t-butyl trifluoroacetates and the related deuterium compounds were prepared by reacting trifluoroacetic anhydride and the appropriate alcohol in the presence of a small amount of silver trifluoroacetate (2). The i-propyl alcohol used was purified with magnesium in the usual way. The t-butyl alcohol was purified by fractional freezing and the commercial *t*-butyl alcohol-do was used without further purification. The *i*-propyl alcohol- d_6 was obtained in good yield (ca. 90%) by the reduction of acetone-d₆ with lithium aluminum hydride using n-butyl carbitol to decompose the alcoholate (3). The usual physical and spectroscopic properties indicated that the eight esters were sufficiently pure for meaningful kinetic studies. The b.p.'s and n.m.r. τ values are recorded in Table 1. When supersaturation of the ester solution was avoided (see below) the excellent Guggenheim plots obtained provided a further check of the homogeneity of the substrates. The rate constants obtained from these studies are recorded in Tables 2, 3, and 4. The rate vs. composition profile for ethyl trifluoroacetate reacting in a series of H2O/D2O mixtures is illustrated graphically in Fig. 1.

The agreement between the rate constants reported here

I ABLE 1. Some physical properties of esters derived from trifluoroacetic acid			
R (CF ₃ COOR)	Boiling point* (°C at 760 mm)	τ value† (n.m.r.)	
СН3	43 (43)	6.04 (6.02)	
CD_3	42.5-43		
CH ₂ CH ₃	59 (61.3)	8.68, 5.60 (8.58, 5.54)	

8.66, 4.81

(8.64, 4.83)

8.45 (8.45)

4.85

*Literature values in parentheses are from ref. 4. †Literature values in parentheses are from ref. 1.

73

85

59.2-60

72.5-73 (73)

and those reported previously (1) is generally satisfactory and where minor differences are apparent the new results are to be preferred.

84 (45 °C at 145 mm)

The temperature dependence of the rates of hydrolysis of the methyl, ethyl, and *i*-propyl trifluoroacetates and their deuterated analogs can be represented over a short temperature range by the equation

$$\log k/T = A/T + B$$

The parameters ΔH^* and ΔS^* were determined from least squares values of A and B in the usual way (1) and the thermodynamic quantities so calculated are reported in Table 5.

For the *t*-butyl trifluoroacetate the temperature dependence of the rates could be expressed by the equation

[3]
$$\log k = -10612/T - 38.35 \log T + 127.63$$

The numerical coefficients were determined by a least squares method using the individual rates rather than the average experimental rates quoted in Table 3. The least squares calculation and the evaluation of the thermodynamic parameters from the numerical coefficients in eq. 3 were carried out using a computer program available in Dr. Robertson's laboratory at the University of Calgary.

As mentioned above the supersaturation of the substrate is a bothersome feature in the determination of the rates of hydrolysis of the esters of trifluoroacetic acid. In consequence the yield of reproducible rate constants obtained in the present study is less than that obtained with other substrates such as sulfonates and halides. The supersaturation problem also probably accounts for the relatively large error in the heat capacity of activation reported for *t*-butyl trifluoroacetate.

Discussion

(a) Mixed Solvent Isotope Effects

The theory of rate and equilibrium processes in H_2O/D_2O mixtures has been developed by Kresge, Long, and co-workers and others (4–9) and has been reviewed by Robertson and

2176

BARNES ET AL.: STUDIES IN SOLVOLYSIS, PART V

TABLE 2. Rate constants and secondary isotope effects for the solvolysis of trifluoroacetates at 5, 10, 15, and 25 °C.

Ester	T (°C)	$k (\mathrm{H})^*$ (× 10 ⁴ s ⁻¹)	$k (D)^*$ (× 10 ⁴ s ⁻¹)	k (H)/k (D)
CF ₃ COOCH ₃	4.963	23.42 ± 0.015 (16)	22.30 ± 0.015 (4)	1.050 ± 0.001
(CD ₃ —)	10.007	33.45 ± 0.026 (5)	31.74 ± 0.016 (5)	1.054 ± 0.001
	15.001	46.51 ± 0.000 (4)	44.13 ±0.016 (6)	1.050 ± 0.004
CF ₃ COOCH ₂ CH ₃	5.001	8.837 ± 0.008 (8)	8.531 ± 0.004 (6)	1.036 ± 0.0010
(CD ₃ CD ₂)	10.002 15.000	$\begin{array}{rrrr} 12.69 & \pm 0.013 \ \text{(6)} \\ 17.69 & \pm 0.008 \ \text{(4)} \end{array}$	$\begin{array}{r} 12.24 \ \pm 0.015 \ \text{(4)} \\ 17.07 \ \pm 0.019 \ \text{(5)} \end{array}$	$\begin{array}{c} 1.037 \pm 0.0016 \\ 1.036 \pm 0.0012 \end{array}$
CF ₃ COOCH(CH ₃) ₂	5.001	2.465 ± 0.005 (7)	2.402 ± 0.007 (6)	1.026 ± 0.0036
((CD ₃) ₂ CH—)	10.000 15.001	3.554 ± 0.010 (6) 4.993 ± 0.008 (7)	3.473 ± 0.0003 (5) 4.844 ± 0.006 (5)	$\begin{array}{c} 1.023\pm 0.0027\\ 1.031\pm 0.0021 \end{array}$
$CF_3COOC(CH_3)_3$ ((CD_3) ₃ C—)	25.001	14.09 ±0.007 (7)	6.478 ± 0.053 (11)	2.175 ± 0.018
			· · · · · · · · · · · · · · · · · · ·	

*Number of rate determinations in parentheses.

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TABLE 3. Temperature dependence of the rate of hydrolysis of t-butyl trifluoroacetate				
 (°С)	k^* (× 10 ⁴ s ⁻¹)			
4.986 8.919 12.003 15.001 19.082 21.782 24.777 27.509	$\begin{array}{c} 0.5493 \pm 0.0106 \ (17) \\ 1.021 \ \pm 0.047 \ (15) \\ 1.871 \ \pm 0.044 \ (8) \\ 2.970 \ \pm 0.073 \ (17) \\ 5.586 \ \pm 0.122 \ (9) \\ 8.540 \ \pm 0.162 \ (12) \\ 13.20 \ \pm 0.43 \ (11) \\ 17.53 \ \pm 1.35 \ (10) \end{array}$			

*Number of rate determinations in parentheses.

TABLE 4. Rates of solvolysis of ethyl trifluoroacetate in H₂O/D₂O mixtures at 9.97 °C

Atom fraction deuterium	k*	$\frac{k(n)}{k(n)}$
(<i>n</i>)	$(\times 10^4 \text{ s}^{-1})$	<i>k</i> (H)
1.000	······································	0.275
		(extrapolated)
0.993	3.503 ± 0.006 (7)	0.281
0.892	4.061 ± 0.008 (4)	0.326
0.773	4.821 ± 0.012 (4)	0.387
0.751	5.101 ± 0.015 (4)	0.409
0.543	6.547 ± 0.013 (4)	0.525
0.434	$7.498 \pm 0.010(4)$	0.601
0.358	7.913 ± 0.018 (4)	0.634
0.225	9.505 \pm 0.026 (4)	0.762
0.122	10.532 ± 0.030 (4)	0.844
0.000	12.476 ± 0.021 (4)	1.000
(pure H ₂ O)	- ()	

*Number of rate determinations in parentheses.

by the equation

$\phi = ([D]/[H])_{substrate}/([D]/[H])_{solvent}$ [4]

In applications of the Kresge-Long theory no attempt is made to relate the various ϕ parameters to the more fundamental statistical quantities (vibrational frequencies etc.) which must ultimately determine their magnitude. Rather, the ϕ 's are considered as disposable parameters which can be estimated from the rate or equilibrium constants observed in the pure isotopic solvents. The ϕ values so calculated are then

Laughton (10). The more recent developments in the theory use the fractionation factor (ϕ) formalism which provides a means of considering the variation of the ratios k(n)/k(H) (rates) or K(n)/K(H) (equilibria) in terms of "n", the atom fraction deuterium in the solvent and the fractionation factors (ϕ) mentioned previously. The "n" parameter requires no further discussion but some explanatory remarks concerning the ϕ parameter are helpful.

Essentially the fractionation factors (ϕ) are isotopic equilibrium constants for all the labile protons associated with each equilibrium state, either ground or activated, which define any particular rate or equilibrium process. The fractionation factor for each labile proton is defined ∆¢,

300

200

100

0

-+ 001-3.0

20

T.0

TABLE 5. Thermodynamic parameters (at 10 °C) for the solvolysis of deuterated and non-deuterated trifluoroacetates in water

R (CF ₃ COOR)	ΔH^+ (kcal mol ⁻¹)	ΔS^{\dagger} (cal mol ⁻¹ deg ⁻¹)	
CH ₃ CD ₃ CH ₂ CH ₃ CD ₂ CD ₃ CH(CH ₃) ₂	$10.35 \pm 0.02 \\ 10.26 \pm 0.02 \\ 10.53 \pm 0.04 \\ 10.49 \pm 0.03 \\ 10.68 \pm 0.05 \\ 10.62 \pm 0.07 \\ 10.74 \\ 10.74 \\ 10.74 \\ 10.74 \\ 10.75 \\ 10$	$-33.2 \pm 0.2 -33.6 \pm 0.2 -34.5 \pm 0.4 -34.7 \pm 0.4 -36.5 \pm 0.6 -36.5 \pm 0.2 -36.5 \pm 0.2 \\ -36.5 \pm 0.4 \\ $	

represented by reaction 1 with the further assumption that the nucleophile (N) and the electrophile (E) are respectively represented by "p" and "q" water molecules, *i.e.* the bonding of 2p labile protons is modified in the first step to give an intermediate containing 2p labile protons which then decomposes into the products.

The application of the Kresge-Long theory to this model is straightforward and gives

[5]
$$\frac{k(n)}{k(H)} = \frac{(1-n+n\overline{\phi}_1^+)^{2p}(1-n+n\overline{\phi}_2^+)^{2q}(1+\gamma)}{\gamma(1-n+n\overline{\phi}_1^+)^{2p}+(1-n+n\overline{\phi}_2^+)^{2q}}$$

in which $\overline{\phi}_1^{\dagger}$ and $\overline{\phi}_2^{\dagger}$ are respectively mean fractionation factors for the first and second transition states in reaction 1. The parameter γ is related to the rate constants k_2 and k_3 by the equations

[6]

with [7]

$$k_2/(k_2 + k_3) = \gamma/(1 + \gamma)$$

 $k_2/k_3 = \gamma$

and [8]

$$k_3/(k_2 + k_3) = 1/(1 + \gamma)$$

To simplify the present theoretical treatment it was assumed that the fractionation factors are all equal (ϕ), and that 2q = 2p + 2, *i.e.* one water molecule is involved in the k_3 step. Equation 5 is then reduced to

[9]
$$\frac{k(n)}{k(H)} = \frac{(1-n+n\phi)^{2q}(1+\gamma)}{\gamma+(1-n+n\phi)^2} = R$$

FIG. 1. Correlation between the rate ratios, k(n)/k(H) and the atom fraction, n, of D₂O for the solvolysis of ethyl trifluoroacetate in H₂O/D₂O mixtures.

0.0

logβ

1.0

2.0

3.0

used to establish the variation of the rate or equilibrium constants as a function of the isotopic composition of the solvent.

Fractionation factors which are less than unity correspond to normal isotope effects and those greater than unity inverse effects.³ In processes which involve the cooperative attack of several water molecules, and in which both the nucleophilic and hydrogen bonding (electrophilic) properties of the solvent are important, the net weakening of hydrogen–oxygen bonds compared with those of bulk water should lead, on the basis of a simple zero-point treatment (11, 12), to normal effects. This implies that the appropriate fractionation factors will be less than unity.

The application of the Kresge-Long theory requires some assumptions concerning the path between the reactants and products for the chemical reaction studied. In the case of ethyl trifluoroacetate, we have adopted the mechanism

³This is a consequence of the fact that the Kresge-Long theory considers isotopic ratios with the light atom quantities in the denominator. The opposite convention is more usual.



2

		$\delta \times 10^3$ for $\gamma =$					
q	10-3	10-2	10-1	1	10	10 ²	10 ³
1	432	367	224	81.3	84.0	29.9	29.6
2	29.6	30.3	32.0	23.2	15.4	14.3	14.3
3	14.3	14.3	14.7	13.7	12.8	12.7	12.7
4	12.7	12.7	12.9	13.0	13.4	13.6	13.5
5	13.5	13.6	13.6	13.6	14.2	14.3	14.3

Table	6.	A comparison of the theoretical and observed dependence of		
	the	rate of hydrolysis of ethyl trifluoroacetate in light and		
heavy water mixtures				

When $\gamma < 10^{-2}$ eq. 9 reduces to

[10]
$$\frac{k(n)}{k(H)} = (1 - n + n\phi)^{2q-2} = R$$

and when $\gamma > 10^2$ eq. 8 becomes

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[11]
$$\frac{k(n)}{k(H)} = (1 - n + n\phi)^{2q} = R$$

Equations 10 and 11 are identical in form but are out of phase with respect to the variable q. This has important consequences when eq. 9 is used to analyze the experimental data (see below).

For n = 1, which corresponds to the pure isotopic rate ratio $k(D_2O)/k(H_2O)$, values of ϕ were determined for five integral values of q in the range 1 < q < 5 and six integral values of log γ in the range $-3 < \log \gamma < 3$ together with $\log \gamma = 0$ giving a total of seven different values of γ . This leads to thirty five values of ϕ appropriate to n = 1. Each of these values ϕ with the appropriate values of q and γ gives rise to a family of theoretical curves relating $k(n)/k(H_2O)$ to n. The derived theoretical curves may be compared with the experimental curve using a least squares criterion such as

12]
$$\delta = \{\sum (R_{\text{calc}} - R_{\text{obs}})^2\}^{1/2}$$

to search for the best values of γ and q in the $\gamma-q$ grid (Table 6). Minima in δ are evident in the grid at q = 4 and $\gamma = 10^{-2}$ or 10^{-3} and at q = 3 with $\gamma = 10^2$ or 10^3 . The identity of the values of δ at these minima arises merely from the fact that the exponents of eqs. 10 and 11 are out of phase. Since eq. 9 does not provide a unique minimum, mechanistic conclusions based on this criterion are of limited significance. However, of the two alternatives suggested by

TABLE 7. Thermodynamic parameters for the hydrolysis of *t*-butyl trifluoroacetate in water at various temperatures

Т (°К)	ΔH_T^+ (kcal/mol)	ΔS_T^* (e.u.)	
273.15	27.20	19.9	
298.15	25.24	13.0	
323.15	23.29	6.75	
348.15	21.33	0.92	
373.15	19.38	-4.58	

 $^{*}\Delta C_{\mu 0}^{*} = -78 \pm 16 \text{ cal mol}^{-1} \text{ deg}^{-1}$. The conversion of the numerical coefficients of eq. 3 to enthalpies, entropies, and heat capacities of activation was made in the usual way (see ref. 1).

the above analysis we find the sequential attack of a total of three water molecules (q = 3) on both the substrate and the intermediate involved in a pre-equilibrium mechanism ($\gamma = 10^2$ or 10^3) to be more likely than the attack of four water molecules on the substrate in a unitary step $(q = 4 \text{ and } \gamma = 10^{-2} \text{ or } 10^{-3})$. The pre-equilibrium model is also in accord with Bender's mechanistic description of ester hydrolysis involving a tetrahedral intermediate (13).

(b) The Thermodynamic Parameters

The new thermodynamic parameters reported here include the ΔH^{+} and ΔS^{+} for the deuterated primary and secondary esters and the heat capacity of activation for *t*-butyl trifluoroacetate (see Tables 5 and 7). The ΔH^{+} and ΔS^{+} values for the deuterated esters do not call for any particular comment but the ΔC_{p0}^{+} for the tertiary ester is of considerable interest.

The observed heat capacity of activation ΔC_{p0}^{\dagger} for a process proceeding simultaneously by

two distinct mechanisms with rate constants k_1 and k_2 is given by the expression

[13]
$$\Delta C_{p0}^{*} = \frac{1}{1+\beta} \Delta C_{p1}^{*} + \frac{\beta}{1+\beta} \cdot \Delta C_{p2}^{*} + \frac{\beta}{(1+\beta)^{2}} \cdot \frac{(\Delta H_{2}^{*} - \Delta H_{1}^{*})^{2}}{RT^{2}}$$

where $\beta = k_1/k_2$ and ΔC_{p1}^+ , ΔC_{p2}^+ , ΔH_1^+ , and ΔH_2^+ are respectively the heat capacities and enthalpies of activation associated with the individual paths. Thus if a situation exists in which both paths contribute to the observed rate such that⁴ $0.01 < \beta < 100$ then the observed heat capacity of activation will be made up of real and spurious terms. The first two terms of the r.h.s. of eq. 13 are real and the final term is spurious (see ref. 14). If the "average" heat capacities of activation for B_{Ac}^2 and S_N^1 processes are respectively -65 and -80 cal mol⁻¹ deg⁻¹ (1, 15) and the difference in the enthalpies of activation for the two processes is taken as $15 \text{ kcal mol}^{-1}(1)$, then the calculated expression for ΔC_{p0}^{\dagger} as a function of β *i.e.* mechanism, is illustrated in Fig. 2. The strongly positive heat capacities of activation calculated for the region $0.01 < \beta < 100$ suggest that the *t*-butyl ester reacts primarily by an S_N l mechanism which agrees with other evidence presented in this paper and elswehere (1).

(c) Secondary Isotope Effects

The secondary isotope effects reported in Table 2 are considered in the light of previous mechanistic conclusions based on other evidence. Since the alkyl group is the reaction seat in the S_N1 process and is relatively remote from the reaction center in the $B_{Ac}2$ process, deuteration of the alkyl group is likely to be more potent in the former reaction. This analysis is consistent with the experimental observations. The rate ratio for the normal and d_9 t-butyl trifluoroacetates is very similar to that of the related chlorides and is fully consistent with the S_N1 description based on ΔH^+ , ΔS^+ , and k.s.i.e. parameters.

The isotope effects observed with the primary esters are more complex. We first draw attention to the fact that deuteration in the methyl groups of the methyl halides or sulfonates leads



22

FIG. 2. Variation of the observed heat capacity of activation for a reaction proceeding partly by the $B_{Ac}2$ and $S_{N}1$ routes.

to inverse effects (16). Thus the normal effect in the case of methyl trifluoroacetate is entirely consistent with attack at a position other than the methyl group. Any further analysis of the isotope effects observed with the primary and secondary esters must be made in terms of the Bender (13) pre-equilibrium mechanism mentioned above, which is

[14]
$$k_{\rm o} = K_{\rm e} k_3$$
 where $K_{\rm e} = k_1 / k_2$

It may be readily shown that the observed isotope effect for the pre-equilibrium mechanism is influenced only by vibrational-force constant changes between the initial state and the second transition state. We assume reasonably that the vibrational changes in the alkyl group of the ester arise primarily from the increasing oxonium character of the alkyl oxygen in the second transition state as a consequence of electrophilic attack at this position. Since bond angles in oxonium compounds are similar to those involving divalent oxygen the isotope effects are primarily a consequence of electronic changes rather than changes which derive from concomitant electronic and geometrical alterations. Differential hydrogen-deuterium inductive electron release (17) to the incipient oxonium center should lead to the increased reactivity of the deuterium compounds in the case of the methyl/ methyl- d_3 and the ethyl/ethyl- d_5 esters, assuming that the net isotope effect in the ethyl compounds is dominated by the deuterium atoms on the carbon adjacent to the alkyl oxygen atom. Since

2180

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⁴These limits define the mixed region. Outside the limits the mechanisms are not mixed. The limits are, of course, quite arbitrary.

the isotopic methyl esters demonstrate a normal effect and the net effect in the case of the ethyl esters is also normal, the inductive hypothesis is reasonably rejected. The decreasing isotope effect with increasing homology of the alkyl group in the case of the primary and secondary esters is more consistent with the hyperconjugation hypothesis developed by Shiner and coworkers (17, 18). However, such an interpretation is not clear-cut because γ contributions are present in the case of both the ethyl and *i*-propyl esters and the hyperconjugation hypothesis is only applicable to deuteration which is β to the reaction site.

Isotopic substitution γ to the reacting center has been shown to lead to inverse effects in reactions which involve substitution at a saturated carbon atom (19). In contrast, complete deuteration of the γ positions in the *i*-propyl esters, *i.e.*, deuteration of the two methyl groups, leads to a normal effect. Thus there is no correlation between the influence of γ isotopic substitution in nucleophilic substitution reactions and ester hydrolyses. This is not surprising. Although reacting oxygen and carbon centers become more positive in the transition state in both types of reaction, any further resemblance between the two processes is slight, particularly with respect to geometrical reorganization which is virtually absent in the case of ester hydrolyses (see above).

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Clearly the main value of the secondary isotope effects in the present study is to further emphasize the distinction between the primary and secondary esters on the one hand and the tertiary ester on the other. The finer differences displayed within the primary and secondary esters as a group are less amenable to unequivocal theoretical interpretation.

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