Secondary α-Deuterium Kinetic Isotope Effects and Transition-State Structures for the Hydrolysis and Hydrazinolysis Reactions of Formate Esters[1]

Zayn Bilkadi, Robert de Lorimier, and Jack F. Kirsch*

Contribution from the Department of Biochemistry, University of California, Berkeley, California 94720. *Received October 12, 1974*

Abstract: The transition-state structures for several formyl transfer reactions from methyl formate have been examined by measuring the secondary α-deuterium kinetic isotope effects. The value of k_D/k_H for alkaline hydrolysis is 1.05 ± 0.01. This figure taken together with previously determined data on the methoxyl-O-18 kinetic isotope effect and a simple theoretical estimate of the important vibrational frequencies of the anionic tetrahedral intermediate leads to a moderately precise description of the bond orders in the transition state. These are 1.0, 1.54 ± 0.07, 0.98 ± 0.01, and 0.48 ± 0.07 for the C–H, carbonyl, acyl carbon–methoxyl oxygen, and acyl carbon–hydroxide oxygen bonds, respectively. The value of the α-deuterium kinetic isotope effect for the alkaline hydrolysis of ethyl formate is $k_D/k_H = 1.10 \pm 0.01$, implying a more nearly tetrahedral configuration in the transition state for that reaction of this ester. Other values of k_D/k_H are 1.23 ± 0.02 for acid hydrolysis of methyl formate, 1.23 ± 0.01 for acid hydrolysis of ethyl formate, 1.38 ± 0.01 for rate-determining formation of the anionic tetrahedral intermediate (T^-) in the hydrazinolysis reaction of methyl formate, and 1.02 ± 0.01 for the rate-determining breakdown of T^- to give formyl hydrazide. The former figures are indicative of tetrahedral and the last one of a trigonal transition state.

The acyl transfer reactions of MF have recently been the subject of intensive kinetic investigation and analysis.[2-4] These studies support the conclusion that the alkaline hydrolysis of carboxylic esters proceeds through transition states corresponding to rate-determining attack of hydroxide ion and in which there is little breaking of the bond to the leaving group.[5-7] Recent methoxyl-O-18 kinetic isotope effect measurements on MF have lent further confirmation by showing that the acyl-methoxyl bond is only slightly weakened in the transition state.[8]

Furthermore, kinetic studies of the hydrazinolysis reaction of MF indicated[2,3] that, at high pH, the rate-determining step is a proton-transfer step from a dipolar tetrahedral intermediate, $T^{\pm}$, to a base to form the anionic tetrahedral intermediate, T^-, while, at lower pH, the rate-determining step is the breakdown of the tetrahedral intermediate, T^-, to products. Methoxyl-O-18 kinetic isotope effect measurements have confirmed the assignment of rate-determining steps at high and low pH.[8]

Kinetic isotope effects offer the further possibility of delineating precisely transition-state structures. In acyl transfer reactions where a hydrogen atom is directly attached to the acyl carbon, the change in the out-of-plane bending mode that occurs when a trigonally bonded $-C(=O)H$ is converted to a tetrahedral $>C(-O)H$ group leads to rather large α-deuterium isotope effects.[9,10] In principle therefore a measure of the secondary (α-C-D/α-C-H) isotope effect for various acyl transfer reactions of MF, taken together with the known methoxyl-O-18 and structure-reactivity data,[6-8] should lead to self-consistent detailed structures of the transition states involved. In the present paper, we report the values of the α-deuterium kinetic isotope effects for the hydrolysis and hydrazinolysis reactions of MF and undertake their analyses in terms of differences in the zero-point energies between hydrogen atoms attached to acyl and tetrahedral carbon atoms. These data allow the construction of a detailed quantitative model of the transition state for the alkaline hydrolysis reaction of MF.

Experimental Section

Materials. Methyl formate-α-*d* (98+ atom % D) was purchased from Bio-Rad Laboratories and distilled at 4° through a Vigreux column. Mass spectrometric analysis (Consolidated Electrodynamics Corp. Model 21-614 modified residual gas analyzer) of the distilled deuterated ester indicated an isotopic purity of at least 98 atom % and no chemical impurities. Unlabeled methyl formate was the redistilled commercial product (bp 32–33°). Triethylamine hydrochloride, *tert*-butylamine hydrochloride, and hydrazine hydrochloride were each recrystallized at least twice and stored in desiccators prior to use. Glass-distilled water was used for all kinetic determinations. Ethyl formate-α-*d* (bp 53–54°) was synthesized from ethanol and 99 atom % formic acid-α-*d* (Merck).

Apparatus. A Radiometer TTT 11 Titrator equipped with a pH meter (type PHA 925a, combined glass electrode type G202B), an ABU 1b syringe buret, and a type SBR 2c titrigraph recorder was used to follow the alkaline hydrolysis reactions. All other reactions were monitored spectrophotometrically using a Unicam Model SP800A double-beam spectrophotometer equipped with a thermostated cuvette holder and a slave recorder. Values of pH were determined at the temperature of the kinetic runs using a Radiometer Model PHM4c pH meter equipped with a GK 2302C glass electrode.

Kinetics. Measurements of individual rate constants were always made alternately on labeled and unlabeled samples in order to minimize systematic errors. Saponification rates of MF and MF-α-*d* were determined at pH 9.52 and 9.80. The electrode was standardized before and after hydrolysis with pH 7.00 buffer (Matheson Coleman and Bell), pH 9.91 buffer (Fisher Scientific), and with 0.01 *N* KOH solution (pH 11.94 at 25°). Solutions consisting of 25 ml of glass-distilled water maintained at an ionic strength of 1.0 with KCl were placed in a thermostated 30-ml glass vessel with a magnetic stirring bar. The electrode and capillary tube from the microburet were inserted into the reaction mixture through a Bakelite cover fitted with an O-ring to ensure a tight seal. The reaction mixture was first brought to a pH slightly higher than that desired by the addition of 0.30 *N* KOH which served as the titrant. After temperature equilibration, the experiments was initiated by the addition of 0.1 ml of 1 *M* aqueous ester solution from a micropipet. pH fluctuations during the reaction did not exceed 0.02 pH units. A control experiment showed that there was negligible evaporation of the ester from this apparatus over the requisite time period. The rate constants for saponification of ethyl formate and ethyl formate-α-*d* were measured at pH 10.00 and 10.20 in the same manner. Pseudo-first-order rate constants were obtained by least-squares fitting of the observed data to a first-order rate equation using the computer program LYSKIN1[11] and a CDC 6400 computer. This program was also used to compute rate constants for all spectrophotometrically monitored reactions. Acid-catalyzed hydrolyses of MF and EF were followed spectrophotometrically at 236 and 222 nm, respectively. Reactions were carried out by placing 3 ml of 1.00 *N* HCl solution into 4-ml cuvettes maintained at 25°. For MF the reactions were initiated after equilibration by adding 0.05 ml of 1.0 *M* ester solution from a micropipet. For EF the reactions were initiated by adding 0.025 ml of 1.35 *M* ester solution from a micropipet. Immediately following the addition of ester, the reaction mixture was thoroughly mixed and the cuvette stoppered. The hydrazinolysis reaction at pH 10.00 ± 0.02 was studied in 0.1 *M* *tert*-butylamine hydrochloride buffer solution which was 0.2 *M* in free hydrazine and 0.2 m*M* in EDTA. The ionic strength was kept at 1.1 with KCl. Absorbance changes were recorded at 225 nm with the buffer solution used as reference. Reactions were initiated by adding 0.01 ml of 1 *M* MF to 3 ml of buffer solution with a micropipet. Addition and mixing required 3-4 sec. The half-life of these reactions at pH 10.00 is 5.1 sec (see Results section).

The kinetic measurements on the hydrazinolysis reactions at pH 8.00 were carried out in hydrazine hydrochloride buffer solution which was 0.2 *M* in free hydrazine and 0.4 m*M* in EDTA. Ionic strength was maintained at 1.5 with tetramethylammonium chloride. The change in absorbance was followed at 242 nm using the buffer solution as reference. Reactions were initiated by adding 0.010 ml of 1 *M* ester to 3 ml buffer solution in 4-ml cuvettes which were stoppered immediately after addition and mixing. The observed total changes in absorbance were in the range 0.04-0.08 for most of the reactions.

Results

The observed rate constants and kinetic isotope effects for the reactions studied are shown in Tables I, II, III, and IV. Rate constants for the hydrolysis of MF in concentrated aqueous solutions of HCl containing small amounts of sodium nitrate were measured by Bell, Dowding, and Noble[12] at 25° in the range 2.5-6.5 *M* HCl. To our knowledge no measurements at lower acid concentration are available. Very close agreement between our results and those of Bell et al. would obtain if a linear variation of log $k_{\text{obsd}}/[\text{HCl}]$ with acid concentration is assumed up to 3.5 *M* HCl. A linear extrapolation based on Bell's values at the two lowest HCl concentrations yields ~0.20 min^{-1} for the rate constant in 1.0 *M* HCl solution, to be compared with the value 0.189 min^{-1} given in Table II. Guthrie[13] calculates a value $k = 0.177\ \text{min}^{-1}$ for this reaction based on the value for the acid hydrolysis of ethyl formate in water and the ratio of rate constants for ethyl and methyl formates measured in 40% aqueous acetone.

Table I. Values of the Kinetic α-Deuterium Isotope Effect k_D/k_H for Alkaline Hydrolysis[a]

	Methyl formate	Ethyl formate
k_D/k_H	1.05 ± 0.01	1.10 ± 0.01

[a] Values of alkaline hydrolysis and standard errors were determined from least-squares plots of four to seven determinations of k_{obsd} vs. a_{OH} forced through the origin.

The rate constant for hydrazinolysis of MF at pH 10.00 (Table III) is some 15% higher than that obtained by Blackburn and Jencks,[2] possibly because of different salt conditions. The rate constant for hydrazinolysis at pH 8.00 is virtually identical with that calculated from the proposed steady-state equation[2] which was deduced from the kinetic parameters at an ionic strength of 1.5. The errors reported in the tables are the standard errors of the means, and the errors in k_D/k_H were determined from the formula:

$$\left(\frac{1}{k_H^{\,2}}\Delta_D^{\,2} + \left(\frac{k_D}{k_H^{\,2}}\right)^2 \Delta_H^{\,2}\right)^{1/2}$$

where Δ_D and Δ_H are the standard errors on k_D and k_H, respectively. The kinetic isotope effect in all cases is inverse ($k_D > k_H$); this is in the expected direction for reactions involving an sp^2 (trigonal) ground state in equilibrium with a transition state possessing some sp^3 character.[9] The magnitude of the isotope effect is taken as a measure of the deviation of the transition state from the trigonal configuration. Within this framework, our results indicate that the transition states for the alkaline hydrolysis and hydrazinolysis of MF at pH 8.00 have very little sp^3 character, whereas the transition states associated with the acid-catalyzed hydrolysis and hydrazinolysis at pH 10.00 are very nearly tetrahedral. The value of k_D/k_H for the alkaline hydrolysis of ethyl formate is slightly higher than that for MF.

Discussion

Alkaline Hydrolysis. It is generally agreed that the structure of the transition state in the reactions of oxygen nucleophiles with carboxylic esters is a function of the relative basicity of the nucleophile and the leaving group.[6,7] Attack is primarily rate determining, and the transition state is reactant-like when the nucleophile is more basic than the leaving group, whereas acyl-oxygen scission is largely rate determining, and the transition state is product-like when the nucleophile is less basic than the leaving group. Within this framework, it has been argued that the alkaline hydrolysis of carboxylic esters should proceed through an early transition state retaining much of the trigonal configuration of the reactant.[6,7] The determination of the α-deuterium isotope effect in the saponification of methyl and ethyl formate was undertaken with the understanding that a small observed kinetic isotope effect would indicate a nearly trigonal transition state, and a relatively large effect would be consistent only with a transition state well advanced toward tetrahedral geometry. The observed kinetic α-deuterium isotope effect for the saponification of MF is 1.05 ± 0.01 (Table I). The interpretation of this value in terms of the

Table II. Kinetic α-Deuterium Isotope Effect for Acid-Catalyzed Hydrolysis of Ethyl and Methyl Formate at 25°

Methyl formate[a]				Ethyl formate[b]			
Run	k_D, min^{-1}	Run	k_H, min^{-1}	Run	k_D, min^{-1}	Run	k_H, min^{-1}
1	0.231	2	0.173	1	0.660	2	0.517
3	0.239	4	0.201	3	0.636	4	0.525
5	0.235	6	0.187	5	0.630	6	0.533
7	0.235	8	0.189	7	0.630	8	0.513
9	0.235	10	0.182	9	0.642	10	0.525
					0.642 ± 0.006		0.523 ± 0.003
11	0.231	12	0.190				
13	0.231	14	0.201				
15	0.228						
	0.233 ± 0.001		0.189 ± 0.003				
	k_D/k_H = 1.23 ± 0.02				k_D/k_H = 1.23 ± 0.01		

[a] Hydrolysis in 1.0 *N* HCl. [b] Hydrolysis in 2.0 *N* HCl.

Table III. Kinetic α-Deuterium Isotope Effect for the Hydrazinolysis of Methyl Formate at pH 10.00[a]

Methyl formate-α-*d*			Methyl formate		
Run	k_{obsd}, sec^{-1}	$k_{obsd} - k_{OH}$	Run	k_{obsd}, sec^{-1}	$k_{obsd} - k_{OH}$
1	0.174	0.166	2	0.135	0.127
3	0.175	0.167	4	0.135	0.127
5	0.175	0.167	6	0.128	0.120
7	0.175	0.167	8	0.135	0.127
9	0.172	0.164	10	0.136	0.128
		0.166 ± 0.001			0.126 ± 0.001
					k_D/k_H = 1.32 ± 0.01

[a] Ionic strength = 1.1 (KCl), 25°, 0.1 *M* *tert*-butylamine hydrochloride buffer.

Table IV. Kinetic α-Deuterium Isotope Effect for the Hydrazinolysis of Methyl Formate at pH 8.00[a]

Methyl formate-α-*d*		Methyl formate	
Run	k_{obsd}, min^{-1}	Run	k_{obsd}, min^{-1}
1	0.189	2	0.186
3	0.186	4	0.175
5	0.186	6	0.187
7	0.189	8	0.188
	0.187 ±.0.001		0.184 ± 0.003
			k_D/k_H = 1.02 ± 0.01

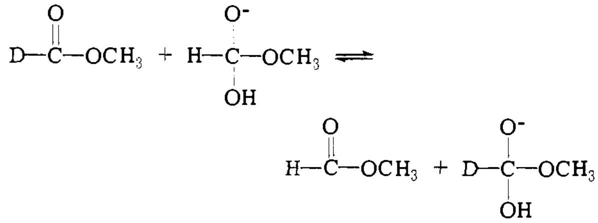
[a] Ionic strength = 1.5 (tetramethylammonium chloride), 0.2 *M* hydrazine hydrochloride buffer, 25°.

Table V. C–H Stretching and Bending Frequencies (cm^{-1}) of Compounds Related to $HC(OH)_2OCH_3$

	C–H stretch[a]	C–H bend[b]
$CH_2(OCH_3)_2$	2903[b]	1391[b]
$CH_2(OC_2H_5)_2$	2885[c]	1390[c]
$CH(OCH_3)_2CH_3$	2902[d]	1396[e]
$CH(OC_2H_5)_2CH_3$	2900[d]	1396[e]
$CH(OH)_2CH_3$	2874[f]	1353[f]
$CH(OH)_2CCl_3$	2860[f]	1348[f]
$CH_3CH(OCH_3)CH_3$		1345[e]
$CH(OCH_3)_3$	2888[g]	1370[g] 1353[e]
$CH(OC_2H_5)_3$	2899[g]	1350[h,i] 1370[g]
$CH(O(CH_2)_3CH_3)_3$	2890[g]	1361–1377[g]
$CH(SC_2H_5)_3$		1180[h]
$CH(SC_2H_5)_2CH_3$		1190[h]

[a] For methylene groups, the stretch frequencies are those for the symmetric stretch mode, and the bending frequencies are those for the wagging motion. [b] K. Nukada, *Spectrochim. Acta*, 18, 745 (1962). [c] K. Nukada, *Bull. Chem. Soc. Jpn.*, 34, 1624 (1961). [d] K. Nukada, *J. Chem. Soc. Jpn.*, 80, 977 (1959). [e] B. Wladislaw, A. Giora, and G. Vicentini, *J. Chem. Soc.* B, 586 (1966). [f] M. Matsushima, *Bull. Chem. Soc. Jpn.*, 36, 954 (1963). [g] K. Nukada, *J. Chem. Soc. Jpn.*, 81, 1028 (1960). [h] B. Wladislaw, P. R. Olivato, and O. Sala, *J. Chem. Soc.* B, 2037 (1971). [i] H. Lee and J. K. Wilmshurst, *Spectrochim. Acta*, 23, 347 (1967).

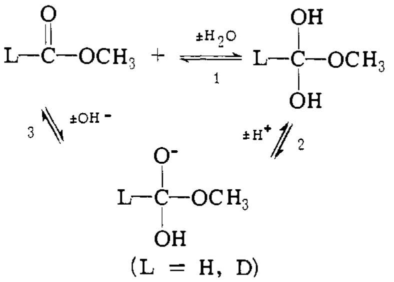
precise structure of the transition state is only possible if K_D/K_H for the formation of a fully tetrahedral transition state can be determined accurately, i.e., only if the α-D effect on the (hypothetical) equilibrium I is known. Since it is



$$\mathrm{D{-}C({=}O){-}OCH_3 + H{-}C(O^-)(OH){-}OCH_3 \rightleftharpoons H{-}C({=}O){-}OCH_3 + D{-}C(O^-)(OH){-}OCH_3}$$

(I)

not possible to determine the ratio K_D/K_H for reaction I experimentally, the only alternative is to attempt to estimate it theoretically. Routine statistical mechanical methods[14] allow rather accurate estimates of equilibrium isotope effects, on the condition that these equilibria involve stable molecular species, with known vibrational spectra. Unfortunately sufficient vibrational spectra resembling the anions in I are not available, but those of a number of compounds resembling the neutral tetrahedral intermediate $HC(OH)_2OCH_3$ are (Table V), and therefore an approach to the determination of the equilibrium constant for I was made through the thermodynamic cycle II, from which the equi-



(II)

librium isotope effect for the formation of the tetrahedral anion through step 3 is equal to the product of the equilibrium effect for the formation of the geminal diol (step 1) and its ionization (step 2). The secondary deuterium isotope effect on the first step is largely a result of the rehybridization of the acyl-hydrogen bond from sp^2 in MF to sp^3 in the geminal diol.[15] This rehybridization is accompanied by changes in the vibrational frequencies of the C-H bond[10] which can be related to the equilibrium isotope effect by the method of Streitwieser et al.[9]

The vibrational frequencies of the methine group in $H-C(OH)_2OCH_3$ can be estimated with the aid of the observed vibrational frequencies associated with the motion of hydrogen atoms directly attached to the central carbon in several stable tetrahedral molecules that resemble the geminal diol in (II) (Table V). These frequencies remain surprisingly constant throughout the series. Apparently, the nature of the RO (R = H, CH_3, C_2H_5) substitutents on the central carbon has very little or no effect on the force constants of the C-H bond. The C-H (or CH_2) stretching frequency remains in the neighborhood of 2900 cm^{-1}, whereas the bending frequencies are ~1390 cm^{-1} for the acetals and 1350-1370 cm^{-1} for the aldehyde hydrates and the orthoesters. These latter frequencies do change considerably when the substituents are changed from RO to RS, as seen for example in the last two entries of Table V. On the basis of Table V and other literature values,[16] we estimate 2900 and 1370 cm^{-1} as the stretching and bending frequencies, respectively, of the methine group for $HC(OH)_2OCH_3$. The latter frequencies and those of the acyl-hydrogen bond in MF are listed in Table VI, together with the individual contribution of each mode to the overall isotope effect. As expected, the bulk of the effect is determined by a C-H deformation frequency which increases from ~1030 cm^{-1} in MF to ~1370 cm^{-1} in $HC(OH)_2OCH_3$. The natural logarithm of the overall equilibrium isotope effect is 0.19 corresponding to a ratio K_D/K_H = 1.21. The α-D isotope effect on the ionization constant of the geminal diol in (II) is almost certainly in the range 1.05-1.07, judging from very similar effects observed on the ionization constants of some amines[17] and a carboxylic acid.[18] Thus the ratio $K_a(H)/K_a(D)$ is 1.05 per single deuterium substitution on the carbon atom of methylamine,[17] 1.07 in trimethylamine,[17] and 1.08[18] for formic acid. The ratio for formic acid is slightly higher than those

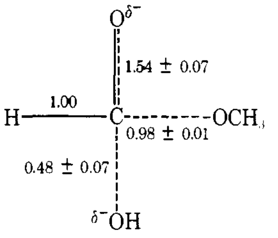
Table VI. C–H Stretching and Bending Frequencies (cm^{-1}) in Methyl Formate and Its Hydrate $HC(OH)_2OCH_3$ and the Resulting α-D Isotope Effect at 25°

Mode	$HCOOCH_3$ [a]	$HC(OH)_2$-OCH_3 [b]	$\Delta\nu$	$\ln (K_D/K_H)$ [c]
C–H stretch	2943	2900	−43	−0.02
C–H bend	1032 (OP)	1370	+338	+0.21
C–H bend	1371 (IP)	1370		
			Sum:	+0.19

[a] T. Shimanouchi, "Tables of Molecular Vibrational Frequencies Consolidated Volume I", NSRDS-NBS 39, June 1972. [b] See text for discussion of these assignments. [c] $\ln (K_D/K_H) = (0.187/T)\Delta\nu$ (ref 9).

for the amines possibly because of charge delocalization over the entire carboxylate anion and vibrational coupling.[18] The calculated isotope effect on step 3 of (II) is thus 1.21/1.06 = 1.14. This is by definition the α-D effect that would be expected were the transition state for the alkaline hydrolysis of MF fully tetrahedral. The observed value 1.05 ± 0.01 suggests that the progress toward tetrahedral geometry in the transition state is only about (5/14 = 0.36) complete. The significance of this finding in terms of the degree of nucleophilic attachment to carbon and the detailed structure of the transition state will now be considered.

One approach to this problem would be to conduct a thorough vibrational analysis of the reactants and transition state using the computer methods developed by Wolfsberg and Stern.[19] We feel, however, that useful qualitative deductions concerning the nature of bonding in the transition state are possible even without such a detailed analysis. We adopt the view, supported by recent X-ray evidence,[20] that the partial double-bond character of the carbonyl group in the transition state is a sensitive indicator of the extent of transition state progress along the reaction coordinate toward tetrahedral geometry. As this advancement toward tetrahedral geometry proceeds, the bond order of the carbonyl group decreases from 1.85 in MF[21] to 1.0 in the tetrahedral configuration. This loss of 0.85 bond order would be reflected in a rate constant ratio of 1.14 corresponding to the equilibrium α-deuterium isotope effect. Since the observed kinetic isotope effect is only 36% of the maximum value, the amount of partial double-bond character lost in going from the ester to the transition state is 0.31. On this basis the bond order of the slightly weakened double bond of the carbonyl group in the transition state is (1.85 − 0.36 × 0.85 = 1.54). An estimate of the bond order of the acyl-methoxyl bond in the transition state may be made on the basis of primary O-18 kinetic isotope effects determined previously.[8] A methoxyl-O-18 effect of 1.0621 ± 0.0008 was observed for the reaction of hydrazine with MF under conditions of 100% rate-determining breakdown of the anionic tetrahedral intermediate, T^-. This value of the methoxyl-O-18 isotope effect corresponds to nearly complete scission of the acyl-methoxyl bond in the transition state for that reaction and therefore to a decrease in the bond order of that bond from 1.15 in MF[21] to near zero in the transition state. Any secondary methoxyl-O-18 kinetic isotope effect on the rate of loss of the proton from the zwitterionic tetrahedral intermediate, $T^{\pm}$, should be negligibly small and will not be considered. The observed value of the methoxyl-O-18 isotope effect in the alkaline hydrolysis reaction is 1.0091 ± 0.0004 indicating by simple proportion with the effect in the hydrazinolyss reaction a 0.17 ± 0.01 decrease in the bond order of the acyl-methoxyl bond from its original value. Assuming a constant C-H bond order of 1.00 throughout, a picture of the transition state may now be drawn with the following bond orders:



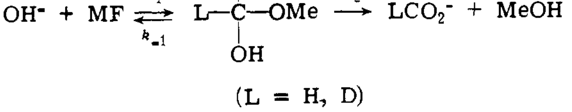
A

where the sum of the bond orders around the central carbon is four, and the uncertainties are calculated from the standard errors of the experimental isotope effects.

After submission of this manuscript, Dr. R. L. Schowen kindly sent us results of detailed computer calculations of the α-D isotope effect for the addition of hydroxide ion to acetaldehyde-L (L = H, D).[22] These Wolfsberg-Stern type calculations revealed that the α-D isotope effect is indeed approximately linear with the bond order *n* of the hydroxide oxygen-carbonyl carbon bond. For acetaldehyde-L, this indicates that the α-D isotope effect is also nearly linear with the bond order (2 − *n*) of the carbonyl double bond, thus providing theoretical support for the assumption adopted here.

Since the final product of the alkaline hydrolysis of carboxylic esters is the carboxylate anion with C-O bond orders of 1.5, these calculations indicate that the carbon-nucleophile bond in the transition state is only about 0.32 of the way between reactant and ionized product or 0.48 of the way to un-ionized formic acid. The model structure A of the transition state is qualitatively in agreement with results from several other lines of evidence. Structure-reactivity studies[6,7] on various phenyl acetates have yielded values of the Brønsted coefficient near 0.3 for oxyanion nucleophiles and for the leaving group when the pK_a of the nucleophile is higher than that of the leaving group. This value of β was interpreted as indicating that the attacking group lost some 0.3 of its charge in the transition state and had proceeded less than 0.3/1.7 of the way to completion.[6,7] Similarly, a value of 0.3 for the leaving group was interpreted as indicating that the acyl-alcohol bond had proceeded about 0.3/1.7 = 0.18 of the way to product.[6] β values for both entering and leaving groups increase as their pK_a values become more nearly equal.[7]

The above discussion of bond order is framed in terms of a single rate-limiting transition state. It is likely, although not proved, that the alkaline hydrolysis reaction of some esters proceeds through a tetrahedral addition intermediate (eq 1).[23] This intermediate is only 4.3 kcal/mol less stable



$$OH^- + MF \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} L{-}\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}}{-}OMe \xrightarrow{k_2} LCO_2^- + MeOH \qquad (1)$$

(L = H, D)

than $OH^- + MF$.[13] If it is at equilibrium with respect to proton-transport processes, then the ratio of the hydrolysis to carbonyl oxygen exchange rates gives the partitioning ratio of the intermediate ($k_h/k_{ex} = 2k_2/k_{-1}$).[24] The value of k_h/k_{ex} for MF is 18.3[8] and thus, in terms of eq 1, the attack step is about 90% rate limiting. The steady-state rate expression for the kinetic isotope effect arising from eq 1 is given in eq 2. The observed kinetic isotope effect thus con-

$$\frac{k_{obsd}}{k^*_{obsd}} = \frac{K_1}{K^*_1} \frac{(k_2/k_2^*) + (k_2/k_{-1}^*)}{1 + k_2/k_{-1}} \qquad (K_1 = k_1/k_{-1}) \quad (2)$$

sists of contributions from all three rate constants. Since the attack step is about 90% rate determining, the bond orders shown in structure A are a composite of the attack and decomposition steps but weighted about 9 to 1 toward the former.

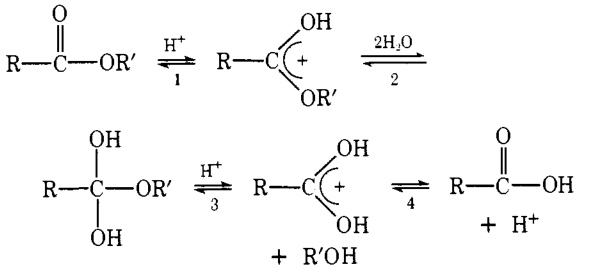
Mitton and Schowen reported a *carbonyl*-O-18 kinetic isotope effect of 1.024 ± 0.013 for the methoxide-catalyzed methanolysis of phenyl benzoate.[25] They have attributed this effect to a change in the carbonyl stretching frequency which decreases from ~1700 cm^{-1} in the ester to ~1300 ± 200 cm^{-1} in the transition state. There are numerous empirical relationships correlating frequency (or force constant) changes to bond orders. That proposed by Pauling[26]

$$b_{ij} \log \left(\frac{F}{F_{\text{single}}}\right) = 0.71 \log n$$

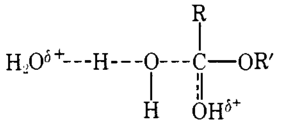
is perhaps the most widely used and could serve our purpose here. The bond order n of the C-O bond in the transition state may be calculated if the force constants F in the transition state and F_{single} for a single C-O bond are known. The constant b_{ij} for a C-O bond is not known but is traditionally set at 0.71 which is the value for a C-C bond.[20,26] The stretching frequency for a single C-O bond is usually[27] near 1100 cm^{-1}, and $F = 4\pi^2\nu^2\mu$ in the harmonic approximation. Within the limits of these approximations, the results of Mitton and Schowen lead to n = 1.39 ± 0.18 for their reaction which can be compared with the 1.54 ± 0.07 calculated here for the alkaline hydrolysis of MF.

The observed α-D isotope effect for the alkaline hydrolysis of ethyl formate is significantly larger than that of MF (Table I). This is a reflection of both the more nearly equal partitioning of the tetrahedral intermediate between starting materials and products for the ethyl ester,[23] and of a slightly later transition state for the attack step for this ester.

Acid-Catalyzed Hydrolysis. The mechanism of acid-catalyzed hydrolysis of carboxylic esters has been a subject of debate for many years. Recently mechanism III has been proposed.[28] The proposed rate-determining step is step 2 which involves water-catalyzed attack of water on the protonated ester to form a neutral tetrahedral intermediate. The transition state thus includes two water molecules in addition to the protonated ester and may resemble[28]



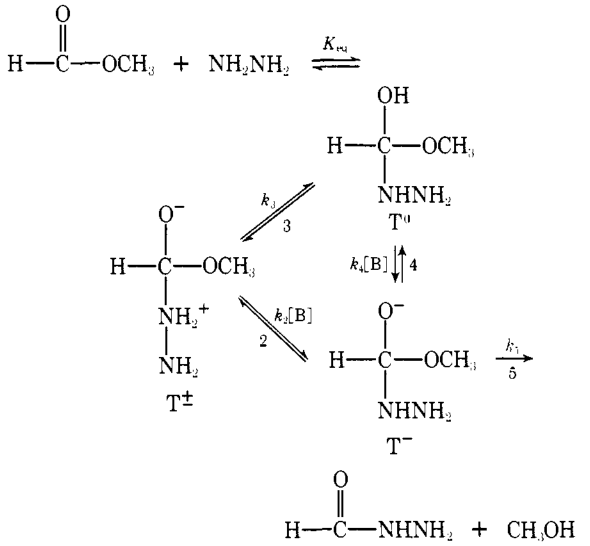
(III)



$$H_2O^{\delta+}\text{---}H\text{---}O\text{---}\overset{\overset{\Large R}{|}}{\underset{\underset{\Large OH^{\delta+}}{\vdots}}{C}}\text{—}OR' \quad (\text{O bears } \underset{H}{|})$$

According to this mechanism, there should be no contribution to the α-deuterium isotope effect from the post rate-determining steps 3 or 4. The magnitude of the effect should be determined solely by that on the equilibrium protonation, step 1, and the rate-determining step 2. The observed values of the deuterium isotope effect for methyl and ethyl formate are 1.23 ± 0.02 and 1.23 ± 0.01, respectively (Table II). These figures are very close to the maximum effect of 1.21 calculated in the previous section and thus represent complete sp^2-sp^3 rehybridization of the bonds to the formyl carbon in ethyl and methyl formate. The α-D isotope effects on the individual steps 1 and 2 of (III) have not been measured. It is perhaps reasonable to estimate an α-D isotope effect $K_1(D)/K_1(H)$ of 1.10 on the first step, by comparison with the observed α-D isotope effect of 1.10 on the equilibrium constant for the protonation of *p*-chlorophenylaldehyde.[29] The ratio $K_2(D)/K_2(H)$ for the second step would thus be 1.23/1.10 = 1.12. The large value of the observed isotope effect provides a definite indication that the transition state for this reaction is very close to tetrahedral.

Hydrazinolysis. Detailed kinetic investigations of the hydrazinolysis of MF in the pH range 8-11 have established that a change in the rate-determining step occurs within this region, as well as the existence of a tetrahedral intermediate in the reaction. As a result of these studies, the mechanism IV was proposed.[2,3] The precise nature of the rate-determining step was shown to be the proton transfer (step 2) from the dipolar intermediate, $T^{\pm}$, to a base at high pH, and the breakdown of T^- to products at lower pH[2-4] (step 5). Oxygen-18 primary kinetic isotope effect measurements have confirmed this conclusion by showing that the acyl-methoxyl bond is broken in the rate-determining transition state at pH 7.85 but not above pH 10.[8] At high pH the rate-determining deprotonation of $T^{\pm}$ is preceded by an equilibrium step that changes the hybridization of the C-H bond from sp^2 (in MF) to sp^3 (in $T^{\pm}$). Neglecting for the moment the isotope effect on the rate of deprotonation of $T^{\pm}$ (see below), the α-D isotope effect on the overall rate at high pH would be expected to be equal to the isotope effect on the preequilibrium. That is



(IV)

$$\left(\frac{k_D}{k_H}\right)_{\text{obsd}} = \frac{K_{eq}(D)}{K_{eq}(H)}$$

The observed α-D effect for the reaction of hydrazine with MF at pH 10.00 is 1.32 ± 0.01 (Table III). At this pH the proportion of reaction proceeding via rate-determining breakdown of T^- and via rate-determining proton transfer from $T^{\pm}$ are 17.7 and 83.3%, respectively.[30] Extrapolation of the observed value of the isotope effect to conditions of 100% rate-determining proton transfer is effectuated through the equation[8]

$$\Delta_a = (\Delta_{\text{obsd}} - f_b\Delta_b)/(1 - f_b)$$

where Δ_a and Δ_b are the secondary deuterium isotope effects for conditions of 100% rate-determining proton transfer from $T^{\pm}$ and 100% rate-determining breakdown of T^-, respectively, and f_b is the fraction of reaction proceeding through rate-determining breakdown of T^-. The calculated value of Δ_a is thus 1.38. This value, representing the α-D isotope effect for the equilibrium addition of hydrazine to acyl carbon is considerably larger than the figure of 1.21 calculated for water addition. The values of k_D/k_H should, however, be sensitive to the nature of the nucleophilic atom. This can be seen by comparison of the CH frequencies for RS- vs. RO- substitution in Table V, the difference in K_D/K_H for the addition of HCN vs. hydroxylamine to aldehydes,[31] and from the theoretical calculations of Wolfsberg et al. for the solvolysis of various halides.[32]

A more nearly complete analysis of the hydrazinolysis reaction at high pH would allow for the weaker acidity of deuterated $T^{\pm}$ when the rate of proton transfer in step 2 is not diffusion controlled. Hydrazine is the predominant trapping agent for $T^{\pm}$ under the conditions of these experiments, and the proton transfer to hydrazine is thus slightly unfavorable thermodynamically.[4] This means that, for the reaction $T^{\pm} + NH_2NH_2 \rightarrow T^- + NH_2NH_3^+$, k_H/k_D is slightly greater than 1 but perhaps does not exceed 1.07.[17] The value 1.38 ± 0.01 for the deuterium isotope effect on the equilibrium constant for the formation of $T^{\pm}$ is thus a maximum one and could be as low as $1.38/1.07 = 1.29$.

At pH values below 8, the hydrazinolysis of MF proceeds through rate-determining breakdown of the tetrahedral intermediate T^-. The observed α-D isotope effect for the reaction of hydrazine and MF at pH 8.0 is 1.02 ± 0.01 (Table IV). This value may be accommodated within scheme IV as follows. At pH 8.0 approximately 98% of the reaction proceeds through rate-determining breakdown of T^-.[2] The isotope effect for the formation of T^- is inverse and near 1.38. The breakdown of T^- to products results in a normal isotope effect, which compensates for the inverse effect on its formation and leads to the small effect on the overall rate observed at pH 8.0.[33] The present results taken together with the O-18 data[8] provide clear evidence that the transition state for the k_5 step in (IV) is very product-like. These data, as pointed out to us by Professor W. P. Jencks, are somewhat surprising since they require that the thermodynamically highly unfavorable reaction,[34] the attack of MeO^- on the neutral hydrazide to give T^-, has an extremely early transition state, in contrast to the general predictions of the Hammond postulate.[35]

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References and Notes

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