Kinetic Isotope Effects for Reactions of Methyl Formate-*methoxyl*-^{18}O[1]

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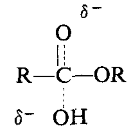
Abstract: Values of $k_{^{16}O}/k_{^{18}O}$ have been measured for several reactions of methyl formate-*methoxyl*-^{18}O. The ratios for acid-catalyzed hydrolysis, alkaline hydrolysis, and general base catalyzed hydrolysis in succinate buffer are 1.0009 ± 0.0004, 1.0091 ± 0.0002, and 1.0115 ± 0.0002, respectively. The maximum expected effect, 1.052, for rate-determining scission of the acyl carbon–methoxyl oxygen bond was calculated from the observed difference in the stretching frequencies between ^{16}O and ^{18}O ester. The observed isotope effect for hydrazinolysis under conditions of rate-determining breakdown of the tetrahedral intermediate at low pH is 1.0621 ± 0.0008, while at high pH, where attack of hydrazine on the ester or a proton transport step is rate determining, it is only 1.0048 ± 0.0006. The values of the ratios of the rates of hydrolysis to carbonyl oxygen exchange for methyl formate are 11.4 ± 0.1 in acid and 18.3 ± 0.4 in alkaline solution. The extremely small kinetic isotope effect observed for acid-catalyzed hydrolysis suggests a mechanism in which equilibrium protonation of the ester is counterbalanced by the normal kinetic isotope effect for the attack of water on the oxocarbonium ion. The small but significant isotope effects observed for alkaline hydrolysis, general base catalyzed hydrolysis, and hydrazinolysis at high pH suggest a transition state in which the order of the acyl carbon–methoxyl oxygen bond of 1.15 in the ester is only slightly reduced in the transition state.

Extreme transition-state geometries for acyl transfer reactions of esters are represented by that reached very early along the reaction coordinate in alkaline hydrolysis, perhaps en route to a tetrahedral intermediate (I), and by the late transition state in which the breakdown of a tetrahedral intermediate is rate determining (II).[2] The transition states for other simple nucleophilic displacements of OR′ would be intermediate between I and II. It was demonstrated that for the particular case of the hydrazinolysis of methyl formate, an early transition state obtains at high pH while the rate of decomposition of an anionic tetrahedral intermediate imposes the kinetic barrier at low pH (II).[3] The mechanism postulated at that time, omitting terms not relevant to the present study, is shown in eq 1.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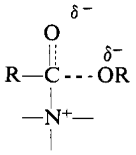
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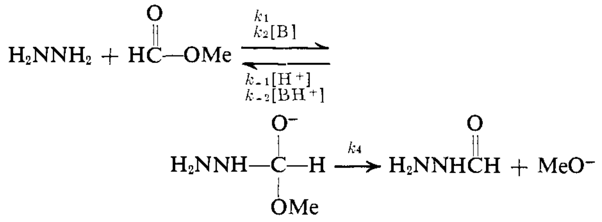

$$H_2NNH_2 + HC(=O)OMe \underset{k_{-1}[H^+],\ k_{-2}[BH^+]}{\overset{k_1,\ k_2[B]}{\rightleftharpoons}} H_2NNH\text{–}C(O^-)(OMe)\text{–}H \xrightarrow{k_4} H_2NNHC(=O)H + MeO^- \qquad (1)$$

More complex reactions of esters involving more than two species in the transition state such as acid-catalyzed hydrolysis or general acid–base catalyzed displacement reactions have not yet provided sufficient data from which quantitative conclusions about the degree of bond making and breaking between the acyl carbon atom and the entering and leaving groups in the transition states can be drawn.

We have approached this problem by measuring the rate ratios, $k_{^{16}O}/k_{^{18}O}$ (Δ), for several reactions of methyl formate specifically enriched with oxygen-18 in the methoxyl position. It is expected that reactions with late transition states involving significant acyl carbon–methoxyl oxygen bond loosening will exhibit large kinetic isotope effects while only small or negligible isotopic discriminations should accompany reactions having transition states resembling I or complex reactions where some step preceding the expulsion of methanol is rate determining.

Experimental Section

Materials. Glass-distilled water was used for all kinetic determinations. Water containing about 60 atom % and about 10 atom % oxygen-18 (Bio-Rad) was used as supplied. *tert*-Butylamine (Matheson Coleman and Bell) was redistilled and stored in the dark under nitrogen where it remained colorless. Di-*n*-butyl phthalate (Matheson Coleman and Bell) was redistilled at 15 mm over a 1° range. Diglyme (Matheson Coleman and Bell) was dried over calcium hydride, distilled from lithium aluminum hydride, and stored under nitrogen. Hydrazine hydrochloride, prepared in methanol from hydrazine dihydrochloride and 95+% hydrazine (both Eastman), was crystallized from methanol, stored in a dessicator, and recrystallized within 1 week before use. Succinic acid (Eastman) was recrystallized from water. Sodium succinate was recrystallized from water–ethanol, dried at 110° (250 mm), and stored in a dessicator. Trimethyl and triethyl orthoformates were distilled through a Vigreux column and protected from moisture. Lithium aluminum hydride (Ventron) was used in lumps as supplied. All other compounds and solvents were reagent grade.

Methyl formate-*methoxyl*-^{18}O material of 60 atom % was prepared as described.[4] Ester of lower ^{18}O content was prepared similarly, except that triethyl orthoformate was used instead of tributyl orthoformate, thus requiring a different purification procedure. In a typical preparation, a mixture of 1 ml of $H_2{}^{18}O$ (about 10 atom %), 10 ml of triethyl orthoformate, and 1 ml of anhydrous HCl was distilled through a Vigreux column, giving a quantitative yield of ethyl formate-*carbonyl*-^{18}O (bp 53–54°, mass spectrum showing (P + 2)/P = 0.1154 corresponding to 10.2 atom % carbonyl label). This ester was slowly dropped into a suspen-

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(1) Supported by National Science Foundation Grant Number GB 35573X. Abbreviations used are: MF, methyl formate; Δ, $k^{16}O/k^{18}O$.

(2) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(3) G. M. Blackburn and W. P. Jencks, *ibid.*, 90, 2638 (1968).

(4) C. B. Sawyer, *J. Org. Chem.*, 37, 4225 (1972).

sion of 1.5 g of lithium aluminum hydride in 50 ml of diglyme at 0° under nitrogen. After 20 min of stirring and addition of 5 ml of ordinary water, the mixture was distilled through a Vigreux column. All materials boiling over the range of 64–78° were collected together and mixed with about four times their volume of 98% formic acid and three drops of concentrated sulfuric acid. Distillation through a Vigreux column yielded a mixture of esters boiling over the range 31–55°. Redistillation through a small glass-helix-filled column (addition of anhydrous diglyme to small fractions before distillation facilitated the separation) yielded methyl formate-*methoxyl*-^{18}O (bp 31.5–32°, mass spectrum showing $(P + 2)/P = 0.111$ corresponding to 9.85 atom % methoxyl-^{18}O, base peak (derived from the methoxyl group) at m/e 31 (m/e 33 = 0.12 of base peak[5]), yield 3.01 g (90% based on starting $H_2{}^{18}O$). If necessary, the ester was redistilled through the same column until the content of ethyl formate (as determined by mass spectrometry) was less than 0.05%.

Methyl Formate-*carbonyl*-^{18}O. To a mixture of 7 ml of trimethyl orthoformate at 0° in an apparatus protected from atmospheric moisture, 1 ml of $H_2{}^{18}O$ (about 10 atom %, from a different lot than the above), and 10 ml of anhydrous diglyme was added 1 ml of anhydrous HCl from a syringe. Distillation through a small helix-packed column afforded methyl formate-*carbonyl*^{18}O (bp 31.5–32.0°, mass spectrum showing $(P + 2)/P = 0.1025$ indicating 9.1 atom % carbonyl-^{18}O, base peak at m/e 31, peak at m/e 33 less than 0.005 of base peak[5]) in quantitative yield.

Apparatus. A Unicam Model SP800A spectrophotometer equipped with a separate recorder and a thermostated cuvette holder was used for all directly monitored kinetic determinations. All mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-614 residual gas analyser modified for use as a mass spectrometer. A Radiometer Model PHM4c pH meter equipped with a B type glass electrode was used for pH determinations. Ester assays involving hydroxamates were read on a Gilford spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Model 257 grating spectrophotometer in CaF_2 cells.

Kinetics. All buffers except 0.5 N HCl were 0.1 mM EDTA. Hydrazine buffers were prepared from hydrazine hydrochloride and KOH, and, if above pH 9.9, *tert*-butylamine, and were 0.2 M in free hydrazine. Buffers above pH 9.9 were 0.1 M in total *tert*-butylamine. Succinate buffers were either prepared from succinic acid and sodium hydroxide or from anhydrous disodium succinate and succinic anhydride; buffers in D_2O were prepared by the latter method. Buffers made with succinic anhydride were incubated at 80° overnight following solution.

All reactions were initiated either by the addition from a syringe at 25° of 12.5 ml of a freshly prepared 1.97 M aqueous solution of methyl formate to 750 ml of stirred buffer in a water bath at 25 ± 0.05°, or by the addition of 50 μl of the ester solution to 3 ml of buffer in a cuvette. Reactions involving hydrazine were followed by the change in absorbance at 242 nm, acid-catalyzed hydrolysis at 228 nm, and alkaline hydrolysis at 236 nm. Hydrolysis experiments in succinate buffers were performed in stoppered containers and were monitored by the hydroxamate assay[3] except that only 0.1 ml of the reaction mixture was used and the ferric chloride solution was 0.6 N in HCl. The total change in absorbance in the ultraviolet absorbance assays was 0.1–0.8. Reactions performed on the larger scale used labeled ester. For all such reactions except hydrolysis in succinate buffer and hydrazinolysis at pH 10, an aliquot of the reaction mixture was transferred to a cuvette as soon as possible after mixing for kinetic monitoring, the time for transfer amounting to 10–40% of the total reaction time. In addition, the kinetics of all reactions except succinate-catalyzed hydrolysis were determined separately on a small scale using the same buffer and ester solutions. Hydroxamate assays involving labeled ester were performed in quintuplicate. The zero points were determined by extrapolation over not more than 15% of the reaction and the percentage of ester remaining at the times of taking of aliquots for isotopic analysis was determined directly from the progress curves. All reactions were done under pseudo-first-order conditions except hydrazinolysis at pH 7.85 and hydrolysis at pH 10.6.

Recovery of Esters for Isotopic Analysis. At about 1 half-life and 2 half-lives aliquots of about 110 and 220 ml, respectively, were removed from the reaction mixture and the time of quenching was noted. The remaining solution was quenched at about 3 half-lives. The first two aliquots of reaction mixtures containing hydrazine or *tert*-butylamine were rapidly drawn into previously evacuated flasks containing a predetermined amount of 10 N H_2SO_4 and Bromophenol Blue indicator, and the pH was quickly adjusted to 3–4 if necessary. The transfer and quench were completed in about 0.4 and 0.7 sec for the smaller and larger volumes, respectively. This did not consume an appreciable part of the reaction time except during hydrazinolysis at pH 10, for which the half-life was 5 sec. A few per cent of the ester was hydrolyzed by acid during the mixing. Reactions in 0.5 N HCl were quenched by addition of 5 N NaOH from a pipet with vigorous stirring, to bring the pH to 4. Reactions in succinate were not quenched before work-up, since the half-life was about 42 hr. Aliquots were stored in ice until used.

For isolation of the ester, the aliquot was warmed to 30° and 5–10 ml, depending on the aliquot volume, was rapidly distilled at reduced pressure. A cold trap immersed in Dry Ice and acetone was inserted between the receiver and the vacuum line. The contents of the cold trap were extracted with 5 ml of dibutyl phthalate. The remaining distillate was saturated with ammonium sulfate and extracted with 3 ml of dibutyl phthalate. The combined extracts were dried twice ($MgSO_4$). During recovery of carbonyl-labeled material, significant depletion of label was observed unless the total exposure time to $MgSO_4$ was less than 5 min. The dried extract was warmed to 40° and directly distilled at 15 mm into a small receiver immersed in Dry Ice–acetone, until the rate of boiling became slow. Recovery of ester was 30–50%.

To determine the change (if any) in the isotopic content of ester during recovery, the following control experiments were performed. A mixture of 400 ml of hydrazine buffer (pH 10) and 1 ml of unlabeled MF was allowed to react to completion. After adjustment of pH to 3 with H_2SO_4, 0.12 ml of methoxyl- or carbonyl-labeled MF (10 atom %) was dissolved in the buffer and recovered as above. The measured oxygen-18 excess in the recovered sample of methoxyl-labeled ester was about 0.1% lower than the starting material. When the experiment was repeated without the initial aminolysis of unlabeled ester, or with initial aminolysis of labeled ester, the oxygen-18 excess of recovered ester had not changed measurably. The change mentioned above is therefore probably due to transesterification with free methanol during recovery. If so, the corresponding error introduced into the values found for Δ is within the reported experimental error.

The recovered ester was analyzed directly by mass spectrometry. Each sample was scanned from m/e 60 to 62 at least 15 times and the resulting $(P + 2)/P$ ratio was compensated for natural abundance of isotopes in other positions[6] and for the drop in sample pressure during analysis. The reproducibility for samples of 10 atom % label was about 0.01 atom % during the same day and 0.1 atom % otherwise. All samples from a given experiment were analyzed on the same day. The isotope effect, $\Delta = k/k^*$, was calculated[7] from the slope of a plot of $\ln E^*/E_0^*$ *vs.* $\ln E/E_0$ for

$$-kt = \ln\left[\frac{f(1 + r_0)}{1 + r}\right] = \ln E/E_0 \qquad (2)$$

$$-k^*t = \ln\left[\frac{f(1 + 1/r_0)}{1 + 1/r}\right] = \ln E^*/E_0^* \qquad (3)$$

where f = fraction of total ester remaining at time t, $r = E^*/E$, and $r_0 = E_0^*/E_0$; and E, E_0, E^*, and E_0^* are the concentrations of unlabeled and labeled ester at time 0 and t. In order to present the magnitude of the isotope effect more clearly, Figures 1, 3, and 5 are plots of

$$\log(100E^*/E_0^*) - \log(100E/E_0) = (1 - \Delta)\log(100E^*/E_0^*) \qquad (4)$$

which follows directly from eq 2 and 3 and the definition of Δ.

Results

The oxygen-18 content of unreacted methoxyl-labeled MF during hydrolysis at 25° in 0.5 N HCl, and at pH 10.6 in 0.1 M *tert*-butylamine buffer, is plotted according to eq 4 in Figure 1. The low value of 1.0091 observed for Δ in alkaline hydrolysis is a direct confirmation of

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[5] H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 174–175.

[6] R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 20 ff.

[7] J. Bigeleisen, *J. Chem. Phys.*, 17, 675 (1949).

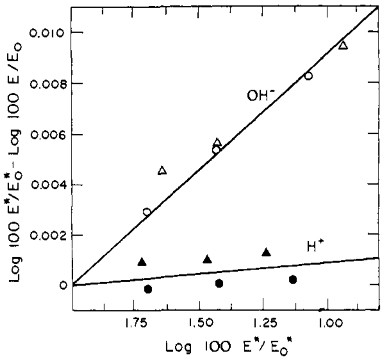

Figure 1. Oxygen-18 kinetic isotope effects in the alkaline and acid-catalyzed hydrolysis of methoxyl-labeled methyl formate: (△, ○) duplicate experiments at pH 10.6 in 0.1 *M* *tert*-butylamine buffer; (▲, ●) same as above except in 0.5 *N* HCl.

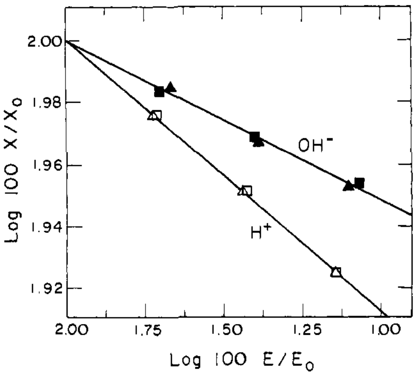

Figure 2. Concurrent hydrolysis and carbonyl-oxygen-18 exchange of methyl formate at 25°: (■, ▲) duplicate experiments in 0.1 *M* *tert*-butylamine buffer at pH 10.6; (□, △) same as above except in 0.5 *N* HCl. X_0 and X are the atom per cent label in the carbonyl position at time 0 and *t*, respectively.

Table I. Ratios of the Rate Constants of Hydrolysis to Carbonyl-Oxygen Exchange for Methyl Formate[a]

Conditions	k_h/k_e
0.5 *N* HCl	11.4 ± 0.1
pH 10.6[b]	18.3 ± 0.4

[a] In water at 25°. [b] In 0.1 *M* *tert*-butylamine buffer.

previous kinetic evidence[2] that the formyl-C–methoxyl-O bond is not broken in the rate-limiting step. During acid-catalyzed hydrolysis, there is almost no measurable isotope effect ($\Delta = 1.0009 \pm 0.0004$). This result almost certainly shows the presence of a compensating inverse isotope effect (see Discussion). The alkaline and acid hydrolysis of MF was further investigated under the same reaction conditions as above, using carbonyl-labeled ester. The data are plotted as previously described[8] in Figure 2. The value of the ratio of the rates of hydrolysis to the rates of ^{18}O exchange, k_h/k_e, for alkaline hydrolysis is 18.3, comparable to the value of 27.7 previously reported for methyl benzoate at low ionic strength[8] (Table I). The value obtained for k_h/k_e in acid-catalyzed hydrolysis is 11.4, which is of the same order of magnitude as literature values for acid catalyzed k_h/k_e ratios for other esters.[9,10]

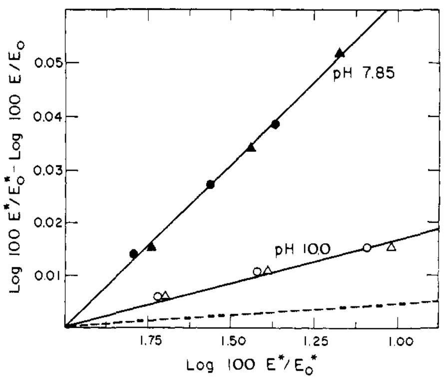

Figure 3. Oxygen-18 kinetic isotope effects for the hydrazinolysis of methoxyl-labeled methyl formate under conditions of (closed symbols) rate-determining tetrahedral intermediate breakdown (pH 7.85, 25°, initial ester, 0.03 *M*, initial free hydrazine, 0.2 *M*, ionic strength, 0.2), and (open symbols) predominantly rate-determining tetrahedral intermediate formation or proton transfer (same conditions as above except at pH 10.0). Circles and triangles denote duplicate experiments. The dashed line is calculated for an isotope effect of 1.0048 (see text).

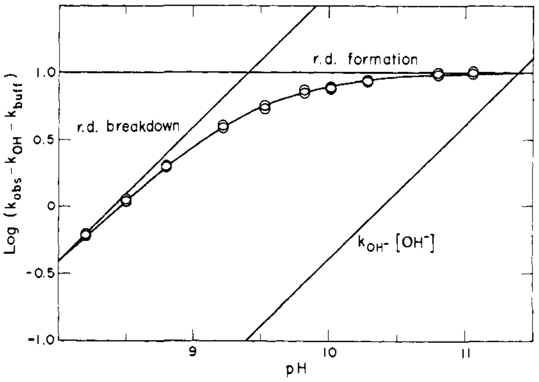

Figure 4. Pseudo-first-order rate constants for the hydrazinolysis of methyl formate as a function of pH with free hydrazine constant at 0.2 *M*, at 25° and ionic strength maintained at 0.2 with tetramethylammonium chloride. *tert*-Butylamine buffers (0.1 *M*) were used above pH 10 and no added buffer below pH 10. The theoretical curve is calculated from eq 5. The horizontal line is drawn for the rate constant for rate-determining intermediate formation from hydrazine and methyl formate and also applies for a rate-determining proton transfer preceding intermediate breakdown (see text). The two lines of slope 1 are drawn for alkaline hydrolysis and for rate-determining intermediate breakdown of the hydrazine reaction as indicated.

The behavior of methoxyl-labeled MF during hydrazinolysis at ionic strength 0.2, free hydrazine 0.2 *M*, at 25° is shown in Figure 3. The values obtained for Δ are 1.0167 at pH 10 and 1.0621 at pH 7.85. The latter value is by far the largest observed in this study, demonstrating unambiguously that the formyl–methoxyl bond is broken during the rate-determining step.[3] The lower value for Δ at pH 10 shows that the change in rate-determining step with increasing pH previously deduced from kinetic studies[3] is a change from rupture of the formyl-C–methoxyl-O bond to an earlier step. To determine the proportions of ester reacting by these pathways in the above experiments, the pH dependence of the rate of hydrazinolysis of unlabeled MF was determined under these conditions and is plotted in Figure 4. The curve is constructed from a least-squares fit to eq 5 by nonlinear regression and is valid at pH >8.[3]

[8] S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, **90**, 5848 (1968).
[9] M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
[10] C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Amer. Chem. Soc.*, **90**, 6492 (1968).

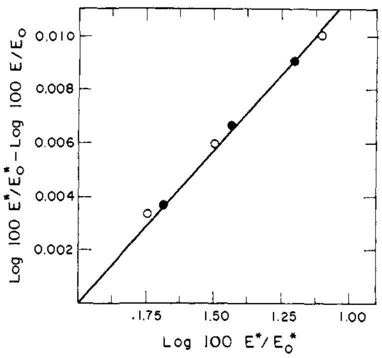

Figure 5. Kinetic oxygen-18 isotope effects in the general base catalyzed hydrolysis of methoxyl-labeled methyl formate: (○, ●), duplicate experiments at 25° in sodium succinate buffer, 0.8 M, 70% free base, pH 5.12, and 0.0001 M EDTA.

rate/[N_2H_4][ester] =

$$k_4(k_1 + k_2[N_2H_4])/(k_4 + k_{-2}[N_2H_5^+]) \quad (5)$$

The rate of hydrazinolysis at pH 10.0, taken from the fitted curve, is 0.792 of that of the limiting value at high pH. This means that at pH 10.0, 20.8% of the reaction proceeds *via* rate-limiting rupture of the formyl-C–methoxyl-O bond. The value of 1.0048 for the isotope effect under conditions where hydrazinolysis of MF proceeds with rate-limiting formation of an anionic tetrahedral intermediate was derived from

$$\Delta_a = (\Delta_{obsd} - f_b\Delta_b)/(1 - f_b) \quad (6)$$

where Δ_a, Δ_b, and Δ_{obsd} are the kinetic isotope effects arising from rate-limiting formation and breakdown of the intermediate, and the observed isotope effect, and f_b is the fraction of the reaction proceeding by rate-limiting breakdown of this anionic tetrahedral intermediate (T^-).

This value, indicated by the dashed line in Figure 3, could not be measured directly under conditions of 100% rate-determining formation of T^- because of experimental difficulties which include appreciable rates of hydrolysis above pH 10, as shown in Figure 4. The rate of hydrazinolysis at pH 7.85 is more than 99.9% limited by breakdown of the intermediate, that is, by formyl–methoxyl bond rupture. Buffer-catalyzed hydrazinolysis was negligible when *tert*-butylamine buffers were used.

Infrared spectra of methyl formate-*methoxyl*-^{18}O (60 atom %), 2.5% in CCl_4, and unlabeled MF were compared directly and by difference in the region of 1150–1250 cm^{-1}. The results are shown in Table II. The absorption at 1208.3 cm^{-1} has been ascribed to formyl-C–methoxyl-O stretching.[11]

Table II. Infrared Absorption Frequencies of Unlabeled and Oxygen-18 Methoxyl-Labeled Methyl Formate

	Absorption frequency, cm^{-1} [a]			
Mode	^{16}O ester	^{18}O ester	Difference	Lit.[b] (^{16}O ester)
Methyl rock	1162.3	1144.8	17.5	1156
Formyl-C–methoxyl-O stretch	1208.3	1187.4	20.9	1203

[a] 2.5% in CCl_4, path length, 0.5 mm. [b] Reference 11, 1% in CS_2.

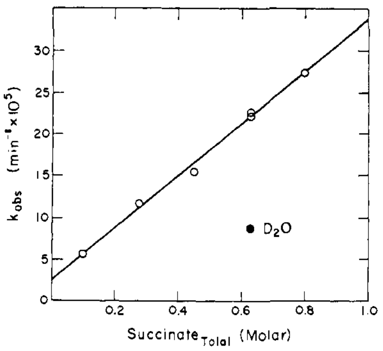

Figure 6. Pseudo-first-order rate constants for the general base catalyzed hydrolysis of methyl formate in succinate buffer, 70% free base, containing 0.0001 M EDTA, at 25°: (○) in H_2O; (●) in D_2O.

The behavior of methoxyl-labeled MF during the course of succinate-catalyzed hydrolysis at pH 5.12 is plotted as above in Figure 5. The value obtained for Δ, 1.0115, is somewhat larger than that for alkaline hydrolysis, suggesting some loosening of the formyl-C–methoxyl-*O* bond in the transition state. Pseudo-first-order rate constants for the hydrolysis of unlabeled MF in varying concentrations of total succinate, 70% free base, pH 5.12, are shown in Figure 6. The reaction at 0.625 M total succinate was measured in H_2O and in D_2O, giving a solvent isotope effect, k_H/k_D, of 2.55. This is in agreement with previously reported values[12] for general base catalyzed hydrolysis of esters.

The kinetic oxygen-18 isotope effects for the acyl transfer reactions of methoxyl-labeled methyl formate reported above are summarized in Table III. The values range from 1.0009 for acid-catalyzed hydrolysis to 1.0621 for hydrazinolysis at pH 7.85.

Table III. Summary of Oxygen-18 Kinetic Isotope Effects for Methoxyl-Labeled Methyl Formate[a]

Reaction	Kinetic isotope effect
Acid catalyzed hydrolysis[b]	1.0009 ± 0.0004
Alkaline hydrolysis[c]	1.0091 ± 0.0004
General base catalyzed hydrolysis[d]	1.0115 ± 0.0002
Hydrazinolysis	1.0048 ± 0.0006[e]
Hydrazinolysis	1.0621 ± 0.0008[f]

[a] In water at 25°. [b] Measured in 0.5 N HCl. [c] Determined at pH 10.0 in 0.1 M *tert*-butylamine buffer. [d] Determined in 0.8 M sodium succinate buffer (pH 5.12). [e] For rate-determining formation of T^- at high pH. The value is calculated from observations made at pH 10 as described in the text. [f] For rate-determining breakdown of the tetrahedral intermediate. Measured at pH 7.85.

Discussion

Hydrazinolysis. The hydrazinolysis reaction of MF is an excellent system with which to quantitate the kinetic isotope effects due to oxygen-18 substitution in the methoxyl position, since both early and late transition states with respect to the breaking of the C–OMe bond can be achieved for this one reaction by a simple change in pH.[3] As pointed out by Blackburn and Jencks, the leveling exhibited by the plot of Figure 4 is indicative only of a change in rate-determining step. It does not provide information about which steps are

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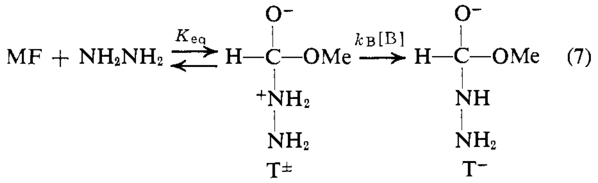
(11) J. K. Wilmshurst, *J. Mol. Spectrosc.*, 1, 201 (1957).

(12) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **83**, 1743 (1961).

rate limiting at high and low pH. From the fact that methoxymethylenemorpholinium cation hydrolyzed to MF at low pH and to *N*-formylmorpholine at high pH, they reasoned that in the reactions of MF with amines attack would be rate determining at high pH and cause breakdown of the tetrahedral intermediate at low pH (eq 1).[3] More recently Jencks[13] has concluded that the rate-determining step at high pH is the loss of a proton to a base, B, from the dipolar intermediate, T±, to form T⁻ (eq 7).



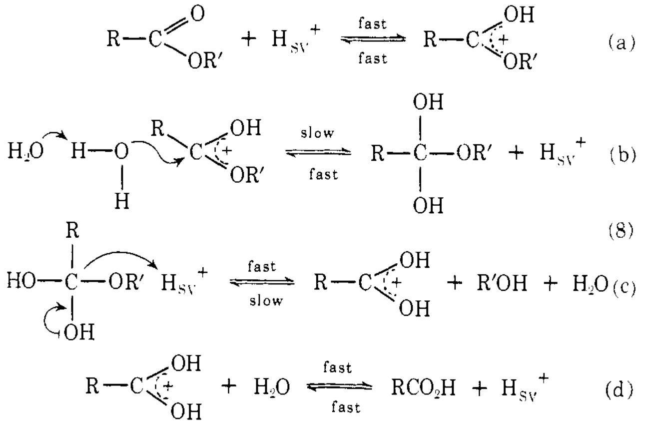
$$\mathrm{MF} + \mathrm{NH_2NH_2} \overset{K_{eq}}{\rightleftharpoons} \underset{\mathrm{T^{\pm}}}{\mathrm{H{-}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\underset{\displaystyle NH_2}{|}}{\displaystyle {}^+NH_2}}{\underset{|}{C}}}{-}OMe}} \xrightarrow{k_B[B]} \underset{\mathrm{T^-}}{\mathrm{H{-}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\underset{\displaystyle NH_2}{|}}{\displaystyle NH}}{\underset{|}{C}}}{-}OMe}} \qquad (7)$$

Because the formation of T± results in a slight reduction of bond order of the C–OMe bond of MF, the equilibrium slightly favors the tetrahedral intermediate formed from the ^{16}O ester relative to that from the ^{18}O (see discussion of acid-catalyzed hydrolysis below), and since the proton transfer step is, because of the two intervening atoms, independent of the isotope, the net overall result should be a $k_{^{16}O}/k_{^{18}O}$ ratio of slightly greater than one for this mechanism as well as for direct rate-determining formation of T⁻. The small observed isotope effect is thus compatible with both proposals.

Decomposition of the proposed intermediate requires scission of the bond to the labeled oxygen, while attack of the amine on the ester merely involves rehybridization of this bond from sp^2 to sp^3. A large isotope effect is expected only when a bond to the labeled atom is broken in the rate-determining step, which occurs in the above mechanism only at low pH. The present results confirm this and quantitate the expected large effect. The observed value of 1.062 at low pH is about the same as the largest previously reported values for the breaking of a bond to oxygen; 1.08 ± 0.02 for solvolysis of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate ether-^{18}O,[14] and 1.06 for reduction of H_2O_2 by ferrous ion.[15] These values are still much less than the theoretical maximum value of 1.19 calculated by Bigeleisen.[7] At pH 10, decomposition of the intermediate is still 20.8% rate determining (see Figure 4). This figure together with the observed isotope effect of 1.0167 at this pH leads to the value 1.0048 for the isotope effect under conditions where T-formation is fully rate limiting (eq 6). This secondary isotope effect may most reasonably be assigned to the equilibrium rehybridization of the carbon–oxygen bond from sp^2 to sp^3. The approximate theoretical maximum kinetic isotope effect to be expected for acyl transfer reactions of methyl formate could be derived from the difference in the formyl-C–methoxyl-O stretching frequencies for the labeled and unlabeled esters, with the assumption that the difference in the bond energies vanishes in the transition state.[16] The stretching frequencies near 1200 cm^{-1} of this bond for labeled and unlabeled ester in CCl_4 are given in Table II. The bending modes at 767 and 325 cm^{-1} observed by Wilmshurst[11] may also contribute to the total energy difference, but were not measured. The stretching frequency difference ($^{16}O - {}^{18}O$) is 20.9 cm^{-1}, which is equivalent to an energy difference of 29.9 cal mol^{-1} and a calculated isotope effect of 1.052. Since the maximum observed isotope effect is 1.062, it is likely that the two lower frequency bending modes also contribute to the total kinetic isotope effect.

Alkaline Hydrolysis. Structure–reactivity studies show that the alkaline hydrolysis of alkyl esters generally proceeds with rate-determining attack of hydroxide ion on the acyl carbon atom and that the transition state is reached at an early point on the reaction path;[2] that is, the transition state for the reaction of hydroxide ion with methyl formate resembles I and not II ($N = OH^-$). The kinetic isotope effect measured for the alkaline hydrolysis of methyl formate is 1.0091. This is much less than the large value of 1.0621 measured for hydrazinolysis with rate-determining breakdown of T⁻ and is close to 1.0048 which was obtained for hydrazinolysis at high pH. Thus the transition state must resemble I, where the bond to the leaving group is not substantially weakened.

Acid-Catalyzed Hydrolysis. The mechanism of ester hydrolysis in dilute acid is more complicated than are the second-order direct nucleophilic displacements considered so far. Yates[17] and Kirby[18] have summarized the evidence supporting the mechanism shown in eq 8 in which the protonated ester formed in a rapid preequilibrium step (8a) is subject to general base catalyzed attack by water to form a neutral tetrahedral intermediate (8b), whose breakdown to give the alcohol and protonated carboxylic acid is aided by general acid catalysis from the solvated proton, H_{SV} (8c). The support for this mechanism derives from the interpretation of results of experiments on carbonyl oxygen exchange, ortho ester hydrolysis, solvent deuterium isotope effects, and structure–reactivity correlations.[18] The very small methoxyl oxygen-18 kinetic isotope effect of 1.0009 ± 0.0004 observed in this study can be accommodated within the framework of eq 8 with the aid of the transition state diagram shown in Figure 7. The initial step, protonation of the ester, results in an increase in order of the C–OMe bond. This bond order in the ester itself has been assigned a value of 1.15 from infrared and microwave spectroscopic measurements.[19] In the



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(17) K. Yates, *Accounts Chem. Res.*, 4, 136 (1971).

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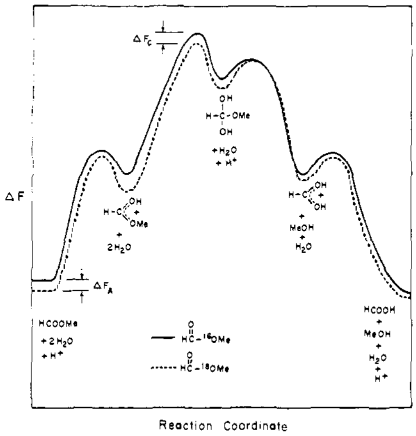
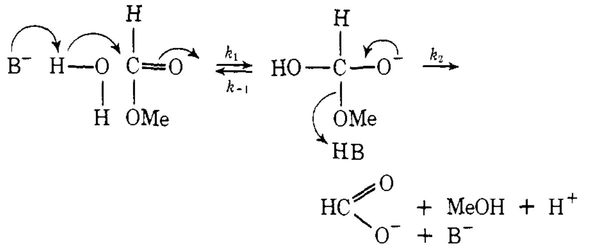


Figure 7. Reaction coordinate diagram for acid-catalyzed hydrolysis according to eq 8. Reaction pathways are shown for the ^{16}O (—) and ^{18}O (- - -) esters. The small kinetic isotope effect is the result of the very similar differences in free energy for the starting materials, ΔF_A, and the rate-limiting transition states, ΔF_C. See text.

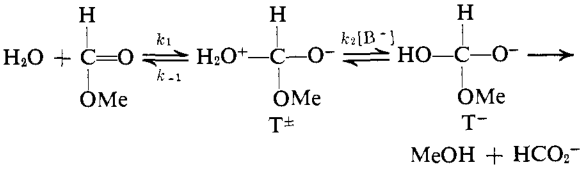
protonated ester, an oxocarbonium ion, the bond order has been shown to be the same as for protonated formic acid in HSO_3F–SbF_5,[20] which should be 1.5. Bonds to ^{18}O are stronger than to ^{16}O because of the larger reduced mass. Hence equilibrium protonation of the ester, which involves increasing the bond order to the ether oxygen, should favor the ^{18}O compound; that is, the labeled ester is more basic. The fraction of protonated oxygen 18 compound in the reaction mixture should therefore be higher than that of the protonated oxygen-16 ester. Attack on the protonated ester by water leads to the tetrahedral intermediate. If the bond to attacking water is almost fully formed in the transition state (late transition state), the C–OMe bond order will be reduced nearly to that of a single bond. Reduction of bond order to a heavy isotopic atom proceeds with discrimination against the compound containing that atom, that is, with a normal kinetic isotope effect, as shown for example by Mitton and Schowen for the reaction of methoxide ion with carbonyl oxygen labeled *p*-bromophenyl benzoate, which proceeds with a Δ of about 1.02.[21] In the overall reaction leading to the tetrahedral intermediate, the protonation of the ester produces a higher concentration of the protonated labeled ester, which in turn is kinetically discriminated against in the attack by water. The total kinetic isotope effect in proceeding from ester to the tetrahedral intermediate should therefore be quite small, the result of a reduction in bond order of 0.15. The expulsion of methanol from the intermediate should, however, be accompanied by a large kinetic isotope effect, perhaps similar in magnitude to the 6% measured for hydrazinolysis at low pH. The observed lack of an overall isotope effect argues that the energy barrier for expulsion of methanol must be significantly smaller than that for water. This contention is consistent with the fact that the ratios of the rates of acid-catalyzed hydrolysis to carbonyl-oxygen exchange are always substantially greater than unity (this work and ref 9, 10, and 17). The small observed methoxyl oxygen kinetic isotope effect and the large ratios of the rates of hydrolysis to carbonyl oxygen exchange do argue against any proposed mechanism involving rate-determining acyl carbon–methoxyl oxygen bond scission.

General Base Catalyzed Hydrolysis. For the simplified symmetrical mechanism shown in eq 9, the base


(9)

catalyses attack by water in the first step to form an anionic tetrahedral intermediate. If the intermediate has such a short lifetime that there is insufficient time for the catalyst to diffuse away, the same molecule will catalyze the second step and the reaction is termed one encounter.[22] If the second step is rate limiting, a substantial ether oxygen isotope effect should be observed since this step involves breaking the carbon–oxygen bond. General acid catalysis during breakdown does not affect this argument. The observed kinetic isotope effect is small, 1.0115, as compared to 1.062 observed during hydrazinolysis with rate-determining breakdown. This is consistent only with mechanisms in which the final step, breakdown, is not rate limiting.

Before further discussion of the mechanism shown in eq 9, it is worth considering the possible implications of the completely stepwise mechanism for general base catalyzed hydrolysis which avoids all termolecular collisions[13,23] (eq 10).


$$H_2O + \underset{OMe}{\overset{H}{C}}{=}O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{T^{\pm}}{H_2O^+{-}\underset{OMe}{\overset{H}{C}}{-}O^-} \overset{k_2[B^-]}{\rightleftharpoons} \underset{T^-}{HO{-}\underset{OMe}{\overset{H}{C}}{-}O^-} \longrightarrow MeOH + HCO_2^- \quad (10)$$

Catalysis may occur through this mechanism if $T^{\pm}$ has a sufficiently great lifetime to be trapped by B^-. Moreover, the rate constant, k_2, will be that for a diffusion controlled reaction if $T^{\pm}$ is a stronger acid than BH. The pK_a of $T^{\pm}$ has been estimated as follows:

$$\underset{\text{III}}{CH_3OCH_2OH} \qquad \underset{\text{IV}}{CH_3OCH(OH)_2} \qquad \underset{\text{V}}{CH_3OC\underset{O^-}{H}OH}$$

The nearly identical polar substituent effects of CH_3O^- and HO^- [24] suggest that the pK_a of III, omitting the statistical factor, will be similar to that of 1,1-dihydroxyethane which is 13.5.[25] The ΔpK_a for III and IV is assumed to be the same as for ethanol and 1,1-dihydroxyethane[25] which is 2.5, thus giving a pK_a = 11.0 for IV. Compound IV is a diprotic acid with both hydroxyl groups bonded to the same atom. Since the second pK_a for such compounds is generally greater

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[20] G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).

[21] C. G. Mitton and R. L. Schowen, *Tetrahedron Lett.*, **55**, 5803 (1968).

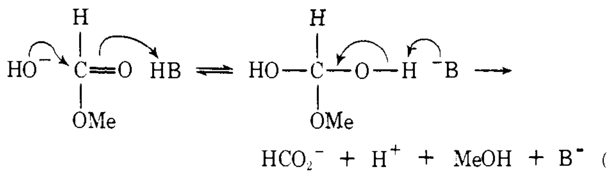
[22] (a) M. Eigen, *Discuss. Faraday Soc.*, No. **39**, 7 (1965); (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 211.

[23] R. J. Zygmunt and R. E. Barnett, *J. Amer. Chem. Soc.*, **94**, 1996 (1972).

[24] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 222.

[25] R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 2983 (1960).

than the first by *ca.* 5 units,[26] the pK_a of V (T^-) may be estimated at 16.0. Finally, taking the ΔpK_a between $T^\pm$ and V as equal to that existing between H_3^+O and H_2O gives a pK_a of *ca.* -1 for $T^\pm$. Since this value is considerably less than the pK_2 of succinic acid, the k_2 step in eq 10 should be diffusion controlled. While data sufficient to generate a Brønsted plot for the general base catalyzed hydrolysis of MF do not exist, extrapolations from the literature make it appear unlikely that the coefficient would approach 0. The β value for general base catalyzed hydrolysis of ethyl dichloroacetate, an ester considerably more reactive than MF, in general base catalyzed hydrolysis, is 0.47.[12] The β decreases to ≈ 0.2 for ethyl trifluorothiolacetate which has a much better leaving group than MF, and is equal to 0 only for the hydrolysis reactions of relatively basic catalysts with methyl *S*-trifluoroacetylmercaptoacetate which has an even better leaving group.[23] The mechanism of eq 10 can therefore be ruled out.


(11)

The mechanism of eq 9 is kinetically indistinguishable from that of eq 11 involving specific base, general acid catalysis.[27] Such a mechanism would predict a methoxyl-^{18}O kinetic isotope effect that is less than that obtained for alkaline hydrolysis, since the attack by hydroxide ion on the ester stabilized by proton donation from BH should result in an earlier transition state than in unassisted attack. The observed isotope effect while small is significantly larger for general base catalyzed than for alkaline hydrolysis and thus argues against the mechanism of eq 11. Leaving group kinetic isotope effects thus provide a new means for resolving kinetic ambiguity in general acid–base catalysis reactions.[27]

The remaining mechanism for consideration is that shown in eq 9. The present results provide no information on whether or not the anionic tetrahedral intermediate depicted is stable enough to be at equilibrium with respect to transport processes.[28] They do require that k_1 be rate determining if the intermediate exists, and, in either case, an early transition state involving little C–OMe bond loosening for the rate-determining step.

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[26] Reference 19, p 324.

[27] Reference 22b, p 182.

[28] M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8828 (1972); W. P. Jencks and K. Salvesen, *ibid.*, **93**, 1419 (1971).

Kinetics of the Reaction of Cyclohexyl Bromide with Tetra-*n*-propylammonium Thiophenoxide in Methanol, Dimethylformamide, and Molten Triethyl-*n*-hexylammonium Triethyl-*n*-hexylboride

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Abstract: The reaction of cyclohexyl bromide with tetra-*n*-propylammonium thiophenoxide ($N_{3333}SPh$) follows approximately a second-order rate law in each of three solvents. Relative rates as a function of solvent at 25° and 0.1 *M* $N_{3333}SPh$ are: methanol, 1.00; triethyl-*n*-hexylammonium triethyl-*n*-hexylboride ($N_{2226}B_{2226}$), 41.0; and dimethylformamide (DMF), 492. In DMF at 10–35° and in $N_{2226}B_{2226}$ at 25–45° the reaction products consist of $57 \pm 1\%$ cyclohexene and $43 \pm 1\%$ cyclohexyl phenyl sulfide. In methanol the per cent elimination ranges from 46% at 24° to 54% at 73°. The insensitivity of product distribution to solvent and temperature suggests that the substitution and elimination transition states are very similar. Mechanisms which may explain this similarity are discussed with emphasis on a possible tight ion pair intermediate.

Preparation of molten tetraalkylammonium tetraalkylborides[1] on a large scale in high purity makes available a totally new class of solvents.[2] These salts may be liquid at or near room temperature and are miscible with most common organic materials. Each ion consists of a charged core surrounded by aliphatic hydrocarbon groups. This character permits electrostatic, ion–dipole, ion-induced dipole, and dispersion interactions but prevents hydrogen bonding or any Lewis acid–base interactions between solvent ions and between solutes and molten salt solvent. We report here the first study of the influence of a molten tetraalkylammonium tetraalkylboride solvent on a chemical reaction.[3]

As a solvent we chose triethyl-*n*-hexylammonium triethyl-*n*-hexylboride ($N_{2226}B_{2226}$) because of its relatively low viscosity at room temperature and its ease of preparation. To test its influence on both the rate and the product distribution of a reaction, we have

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[1] By IUPAC nomenclature these anions are tetraalkylbor*ates*. We prefer tetraalkylbor*ide* because it avoids possible confusion with borate esters.

[2] W. T. Ford, R. J. Hauri, and D. J. Hart, *J. Org. Chem.*, in press.

[3] For references to previous uses of other kinds of molten salt solvents, see footnotes 1–7 of ref 2.