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Rate-Limiting Deprotonation in Tetrahedral Intermediate Breakdown

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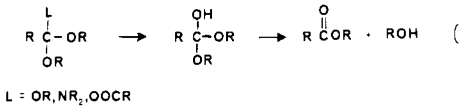
Abstract: A kinetic study in acetate and formate buffers is reported of the breakdown to β-hydroxyethyl benzoate of the hemiorthoester-type tetrahedral intermediate 2-phenyl-2-hydroxy-1,3-dioxolane. This species is generated as a transient intermediate in acid solutions in the hydrolysis of the amide acetals 2-phenyl-2-(dimethylamino)-1,3-dioxolane and 2-phenyl-2-(1-imidazolyl)-1,3-dioxolane. Plots of observed rate constant vs. buffer concentration exhibit pronounced curvature in dilute buffers suggestive of a change in rate-limiting step with changing buffer concentration. A mechanism is proposed involving deprotonation of the hydroxy group of the hemiorthoester to produce a highly reactive anion. In the absence of buffer and in very dilute buffers the deprotonation step is rate limiting, the anionic hemiorthoester going on to product at a rate faster than it is reprotonated. In more concentrated buffers the deprotonation step becomes reversible because of the availability of the acid component of the buffer for the reprotonation. A kinetic analysis is presented, providing a rate constant of approximately 5×10^7 s^{-1} for breakdown of the anionic hemiorthoester. This intermediate is comparable to that which would be encountered during the hydrolysis of a benzoate ester, and some consequences of the large reactivity are discussed. This is suggested to be a contributing factor behind the small amount of carbonyl ^{18}O exchange observed during the base hydrolysis of esters. It is also pointed out that with leaving groups significantly better than alcoxide, the lifetime may become so short that the tetrahedral intermediate anion could not exist. In this case an acyl transfer reaction proceeding via this anion would have to be regarded as being concerted with the anion as a transition state, not an intermediate.

A number of examples have recently been reported[1,2] of the observation of hemiorthoesters $R'C(OR)_2OH$ as transient intermediates in the hydrolysis of some ortho acid derivative. Hemiorthoesters are tetrahedral intermediates of [O,O]-acyl transfer reactions, and the generation from the ortho acid derivative has allowed direct kinetic study of their breakdown. This decomposition is invariably general acid–base catalyzed, and a particularly interesting finding has been that of very large rate constants for hydroxide ion catalysis (k_{OH}), in many instances numbers approaching and even exceeding the diffusion limit. The commonly accepted mechanism[1-4] for the reaction with hydroxide involves deprotonation of the hydroxyl group of the hemiorthoester followed by expulsion of alcoxide ion from the anion. A value for k_{OH} at the diffusion limit implies the deprotonation step is rate limiting. The situation is clouded, however, by the presence of buffer in the solutions where k_{OH} is measured, since the buffer acid:base species can participate in the initial proton transfer reaction.[3]



(1)

This paper presents a study of the effect of buffers on the decomposition of a cyclic hemiorthoester, 2-phenyl-2-hydroxy-1,3-dioxolane (**1**). We have previously reported[5,6] a value of k_{OH} of 6×10^{10} M^{-1} s^{-1} for this compound. This is a number perhaps about an order of magnitude too large for a diffusion-limited rate constant. Its determination was based on extrapolation to zero buffer concentration of data obtained in quite concentrated buffers,[5,6] and we suspected that curvature might occur in the buffer dilution plots in dilute buffers. Significant curvature is indeed observed, implicating a change in rate-determining step with changing buffer concentration. This allows a kinetic analysis to be carried out which furnishes a measure of the lifetime of the anionic tetrahedral intermediate.

Experimental Section

Amide Acetals. 2-Phenyl-2-(dimethylamino)-1,3-dioxolane was from a previous study.[5] 2-Phenyl-2-(1-imidazoyl)-1,3-dioxolane was prepared as follows. 2-Phenyl-1,3-dioxolan-2-ylium tetrafluoroborate[6] (0.05 mol) and the sodium salt of imidazole (0.08–0.10 mol) (prepared from imidazole and sodium hydride in dry tetrahydrofuran) were isolated in their solid forms under anhydrous conditions in a glovebag, and the solids were mixed (no apparent reaction). The mixture was cooled in a dry ice:acetone bath and 20 mL of cooled (−30 °C) acetonitrile freshly distilled from P_2O_5 added all at once. The mixture was then stirred and allowed to come to room temperature, 20–50 mL of dry ether added, and the mixture filtered (to remove unreacted imidazole salt and $NaBF_4$). The filtrate was evaporated on a rotary evaporator and the remaining solid purified by dissolving in benzene and precipitation with hexane. The imidazole amide acetal had mp 85 °C and NMR δ 7.74 (1 H, br s), 7.36 (5 H, s), 7.08 (2 H, br s), 4.24 (4 H, symmetrical m). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.59; H, 5.71; N, 12.88.

Kinetics. These were performed essentially as previously described[5] by using a Durrum Gibson stopped-flow spectrophotometer. The amide acetals were added to an 0.01 M NaOH solution which had been thermostated at 25 °C in an external water bath. This solution was placed in one syringe of the stopped-flow apparatus and mixed with acetate (or formate) buffers containing 0.01 M HCl. In order to ensure that pH was remaining constant upon buffer dilution the pH of all mixtures was immediately recorded with use of solutions mixed on the stopped-flow apparatus. A variation of ±0.02 was considered satisfactory; results outside of this range were discarded. Rate constants were evaluated from the absorbance increase at 230 nm. The photomultiplier output of the stopped-flow was digitized to give 118 absorbance points per kinetic run, plus 4 infinity values. Eight–ten kinetic runs were performed for each buffer. Excellent linearity was observed in all plots of ln ($A_\infty - A$) vs. time; observed rate constants were calculated as the slopes of these plots.

Results

Hemiorthoester Generation. The approach for generating the hemiorthoester with amide acetals as precursors is summarized in eq 2. The key feature of the chemistry is that the protonated forms of these compounds undergo loss of the exocyclic amine or imidazole extremely rapidly. Hydration of the 1,3-dioxolan-2-ylium ion **4** is also very rapid.[6] Thus in acid solutions where the protonated form of the amide acetal is favored in the initial equilibrium, the steps leading to the hemiorthoester are faster than its decomposition. This means that the hemiorthoester forms in

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[1] Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Acc. Chem. Res.* **1981,** *14,* 306–312.

[2] McClelland, R. A.; Santry, L. J. *Acc. Chem. Res.* **1983,** *16,* 394–399.

[3] Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974,** *96,* 489–499.

[4] Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978,** *100,* 5444–5459. McClelland, R. A.; Coe, M. *Ibid.* **1983,** *105,* 2718–2725.

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[6] Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1979,** *101,* 2669–2677.

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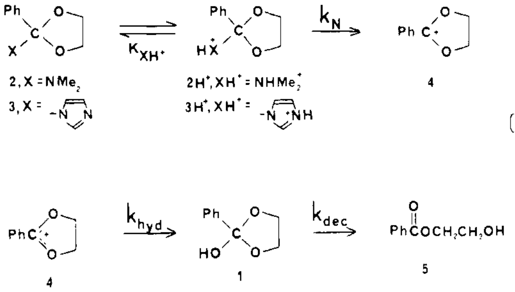

(2)

nearly quantitative amounts before undergoing further reaction. Moreover, since the kinetics are based upon the appearance of the benzoate ester **5**, they measure directly the rate of the hemiorthoester decomposition process. The detailed analysis has been presented in a previous study[5] for the dimethylamino compound. Investigations on imidazole amide acetals have just recently begun in our laboratories, and the pertinent results obtained with the dioxolane **3** are presented in the next section. What is important to note here is that the dimethylamine and imidazole systems exhibit identical rate behavior in solutions with pH <5.5. It is in these solutions that hemiorthoester decomposition is proposed to be the slow step in product formation, and the two compounds must, of course, produce the same hemiorthoester.

Imidazole Amide Acetal Hydrolysis. Examples of imidazole amide acetals have only recently been prepared by Brown and co-workers,[8] using exchange reactions of ortho esters and imidazoles. This reaction fails with 2-phenyl-2-methoxy-1,3-dioxolane and imidazole. The preparation of **3**, however, was accomplished by combining the 2-phenyl-1,3-dioxolan-2-ylium cation as its borofluorate salt with the imidazole anion as its sodium salt.

Brown has also recently reported a kinetic study of the hydrolysis of some formic acid derived imidazole amide acetals.[9] A single reaction was observed, involving equilibrium protonation of the imidazole followed by loss of this group to produce the dialkoxycarbocation and eventually ester and alcohol products. This is the mechanism outlined in eq 2. Unlike the situation with **3** the kinetic study with the formic acid derivatives was based[9] upon changes in the imidazole chromophore, so that at all pH the rate of the formation of the dialkoxycarbocation is measured. The rate–pH profile is thus quite straighforward, with rate constants at high pH being proportional to H^+ concentration because of the protonation requirement and the rate constants leveling in acid solution when protonation is complete.

The basic chemistry of the hydrolysis of the imidazole amide acetal **3** is the same, with imidazole and the hydroxy ester **5** being the only products at all pH. In base solutions observed rate constants are linear in H^+ concentration with a slope (k_H) of 8×10^9 M^{-1} s^{-1}. This represents rate-limiting formation of the cation **4**, and k_H can be set equal to k_N/K_{XH^+} with the latter terms as defined in eq 2. Brown found $pK_{XH} = 5.97$ for imidazole protonation in his study, and a similar value is likely here since the substituent differences are quite remote from the protonation site. Therefore k_N should be of the order of 10^4 s^{-1}. The rate of formation of the cation **4** in acids is equal to k_N. Rate constants for the hemiorthoester decomposition are, however, considerably smaller,[2,5,6] so that a change in slow step in product formation occurs. The decomposition becomes rate limiting, and the measured rate constants represent directly this decomposition.

Rate Constants. Rate constants for this hemiorthoester decomposition have been measured in a series of acetate buffers and one formate buffer. Emphasis was placed on dilute buffer solutions, and particular care was taken to ensure constant pH on buffer dilution. As noted previously the two precursors give identical rate constants in the same solution. The majority of the measurements were made with the imidazole system. This has the advantage of undergoing only the one reaction; the dimethylamino derivative in solutions above pH 4.5 begins to undergo a competing C–O cleavage.[5] First-order rate constants for the hemiorthoester decomposition are listed in Table S1 and are plotted against buffer concentration in Figure 1. Pronounced curvature is found in dilute buffers. This had been missed in our previous study[5] where only more concentrated buffers had been employed. As seen in Figure 1, rate constants in the more concentrated buffers are approximately linear in buffer concentration. The zero intercept of such plots which we had previously used to calculate k_{OH} is obviously not the true rate constant in the absence of buffer.

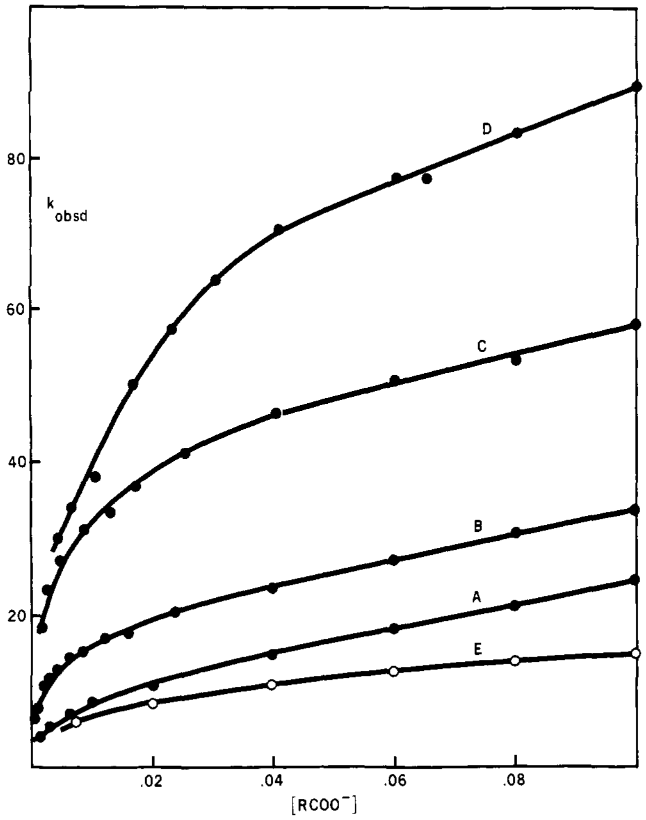

Figure 1. First-order rate constants (25 °C, ionic strength 0.1 s^{-1}) for the decomposition of the tetrahedral intermediate 2-phenyl-2-hydroxy-1,3-dioxolane in acetate buffers [(A) α(HA) = 0.8, pH 3.92; (B) α(HA) = 0.6, pH 4.38; (C) α(HA) = 0.4, pH 4.72; (D) α(HA) = 0.2, pH 5.12] and in formate buffer [(E) α(HA) = 0.2, pH 4.09].

The rate law which has previously been applied[1,2,5,6] to hemiorthoester decomposition is that of eq 3, with catalysis by H^+,

$$k_{obsd} = k_H[H^+] + k_0 + k_{OH}[OH^-] + k_{HA}[HA] + k_A[A^-] \quad (3)$$

OH^-, buffer acids, and bases and a pH-independent term. This equation is obviously not completely satisfactory in the present case. We can note from our previous work[5,6] that the terms in k_H and k_{HA} are not important in the solutions employed in the present study since pH >4. The pH-independent term k_0 has a value[6,10] of 1.5 s^{-1} so that it does make a contribution. In the analysis the assumption will be made that that contribution is constant, so that it is the variation in $k_{obsd} - k_0 \equiv k'_{obsd}$ which is determining the shapes of the buffer profiles in Figure 1. A brief analysis of the k_0 reaction will be presented at the end of the discussion section.

Discussion

Kinetic Analysis. Curved plots of rate vs. buffer concentration usually mean that a change in rate-limiting step occurs with changing buffer concentration. The reaction of the present study is a particularly simple one, since it involves the breaking of one C–O bond and two proton transfers. The occurrence of a change in rate-limiting step in this case signifies that (a) there must be at least two steps in the reaction and (b) a simple proton transfer step must be rate limiting under some conditions. The reaction

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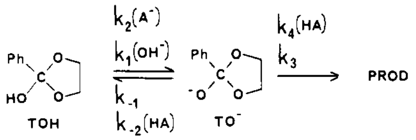
(7) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–72.
(8) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038–4040.
(9) Brown, R. S.; Ulan, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 2382–2388.

sequence of eq 4 can be proposed, with the hemiorthoester being



(4)

converted to its conjugate base prior to breakdown. This deprotonation occurs with hydroxide ion as the base or with the conjugate base form of the buffer. The microscopic reverses of these whereby the neutral hemiorthoester is regenerated involve protonation by water and protonation by the acid component of the buffer. Decomposition of the anion occurs by a pH-independent (or water catalyzed) reaction and by a reaction catalyzed by the buffer acid. The actual mechanisms of these reactions and the question of the involvement of a second intermediate $PhCO_2CH_2CH_2O^-$ will be discussed later. The acidity constant of the hemiorthoester will be defined as K_a, and the following relationship can be noted,

$$K_a = \frac{k_1 K_W}{k_{-1}} = \frac{k_2 K_{HA}}{k_{-2}} \tag{5}$$

where K_{HA} is the acidity constant of the buffer acid ($pK_{HA} = 4.56$ for acetic acid and 3.56 for formic acid[12]) and K_W is the autoprotolysis constant ($pK_W = 13.7$).[12] As will be discussed later, pK_a is expected to have a value near 11. This means that for the equilibrium $TOH + OH^- \rightleftharpoons TO^- + H_2O$ it is the deprotonation step which is thermodynamically favored, while for $TOH + A^- \rightleftharpoons TO^- + HA$ with acetate and formate buffers it is the protonation step. Consequently, the constants k_1 and k_{-2} are expected[7] to have values near 10^{10} M^{-1} s^{-1}. The possibility of deprotonation occurring with a water molecule as the base, and its microscopic reverse, protonation of the anion by H_3O^+, is ignored in our analysis. Although the rate constant for the latter is also expected to be near 10^{10} M^{-1} s^{-1}, in solutions with pH >4 its contribution is relatively unimportant compared to the contribution from the buffer acid and even protonation by water.[11]

The stationary state assumption in TO^- produces the following rate expression,

$$k'_{obsd} = \frac{a[OH^-] + b[A^-] + c[H^+][A^-]^2}{1 + d[H^+][A^-]} \tag{6}$$

where $a = k_1k_3/(k_{-1} + k_3)$, $b = (k_2k_3 + k_1k_4(K_W/k_{HA}))/(k_{-1} + k_3)$, $c = k_2k_4/K_{HA}(k_{-1} + k_3)$, and $d = (k_{-2} + k_4)/K_{HA}(k_{-1} + k_3)$. Experimental data for the acetate buffers were fitted to this equation to yield values of the constants: $a = (5 \pm 2) \times 10^9$, b $(5.5 \pm 1) \times 10^3$, $c = (1.2 \pm 0.2) \times 10^9$, and $d = (8.0 \pm 2) \times 10^{-4}$. Errors in these coefficients are quite large because of the difficultly of measuring accurately rate constants in very dilute buffer. The constant a is the OH^--dependent intercept at zero buffer concentration and is particularly difficult to obtain accurately. Although six individual rate constants appear in the kinetic scheme of eq 4, because of the relationships of eq 5, there are only five which are independent. From the experimental fit the four constants a–d are obtained, so that there is not sufficient information to place a value on all of the rate constants. With the appropriate rearrangement of the expressions for a–d,[13] it can be seen that the two constants k_1 and k_2 stand on their own and thus can be assigned a value while the other four can be expressed as ratios,[14] for example, as k_{-1}/k_3 and k_{-1}/k_4. Values of the constants or ratios determined from the experimental values of a–d are listed in Table I.

Table I. Rate Constants at 25 °C, Ionic Strength 0.1 for the Decomposition of 2-Phenyl-2-hydroxy-1,3-dioxolane in Acetate Buffers

constant	values		
k_1, M^{-1} s^{-1}		6×10^9	
k_2, M^{-1} s^{-1}		6×10^3	
(k_{-1}/k_3)		1.4	
(k_{-1}/k_4)		0.024	
pK_a	10.50		10.80
k_{-1}, s^{-1}	4×10^6		7×10^6
k_{-2}, M^{-1} s^{-1}	5×10^9		1.1×10^{10}
k_3, s^{-1}	2.5×10^7		5×10^7
k_4, M^{-1} s^{-1}	1.5×10^8 [a]		3×10^8 [b]

[a] $k_4 = 4.5 \times 10^8$ for formic acid as catalyst and $pK_a = 10.50$. [b] $k_4 = 9.1 \times 10^8$ for formic acid and $pK_a = 10.80$.

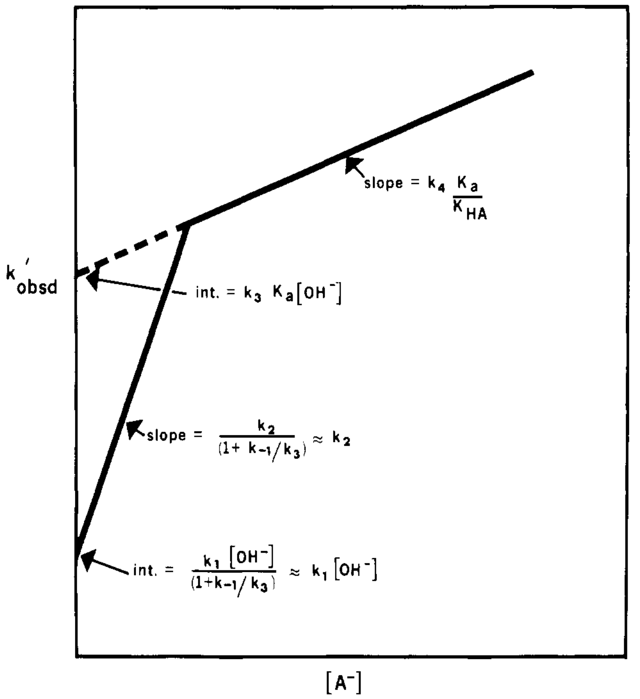


Figure 2. Schematic representation of the effect of buffer concentration on the decomposition of the tetrahedral intermediate 2-phenyl-2-hydroxy-1,3-dioxolane.

A schematic representation of the rate buffer profile is given in Figure 2. The change in rate-limiting step can be explained as follows. Since k_{-1}/k_3 is less than unity or k_3 is greater than k_{-1}, in the absence of buffer formation of the anionic intermediate is essentially irreversible. That is, the anion once formed goes on to product rather than being reprotonated by water. The deprotonation step is rate limiting, and since this is occurring with hydroxide ion, the intercepts of the rate–buffer curve are equal to $k_1[OH^-]$. (This is actually only approximate since with $k_{-1} = 0.14k_3$ there is some reversal of the deprotonation.) The addition of a small amount of buffer results in a significant increase in the rate. This is due to the presence of the base component of the buffer and its participation in the deprotonation reaction. Although the rate constant for the reaction with A^- is numerically much smaller than that for OH^-, deprotonation via the buffer can occur since the hydroxide ion concentration is so low. At this stage, very dilute buffers, the proton transfer step is still rate limiting (or mainly rate limiting), but as the buffer concentration continues to increase, the rate of protonation of TO^- is significantly increased

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(10) This value is measured in HCl solutions where no buffer is present.

(11) For example at pH 4, the most acidic pH of this study, protonation of TO^- by H_3O^+ will occur with a rate constant of $10^{10} \times 10^{-4} = 10^6$ s^{-1}. Protonation by water occurs with a rate constant of 5×10^6 s^{-1}–10^7 s^{-1} (see analysis).

(12) (a) Values for the constants at 0.1 ionic strength. (b) Harned, H. S.; Owen, B. B. "The Physical Chemistry of Electrolytic Solutions", 3rd ed.; Rheinhold Publishing Co.: New York, 1958.

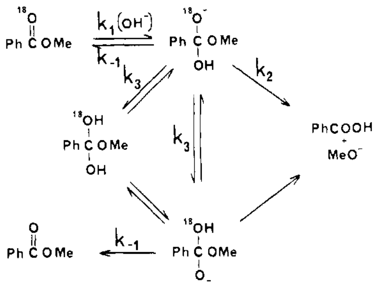
(13) $a = k_1/(1 + (k_{-1}/k_3))$, $b = (k_2 + k_1(k_4/k_{-1})(k_{-1}/k_3)(K_W/K_{HA}))/(1 + (k_{-1}/k_3))$, $c = k_2(k_4/k_{-1})(k_{-1}/k_3)/K_{HA}(1 + (k_{-1}/k_3))$ and $d = ((k_2/k_1)(K_{HA}/K_W)(k_{-1}/k_3) + (k_4/k_{-1})(k_{-1}/k_3))/K_{HA}(1 + (k_{-1}/k_3))$.

(14) This is typical of a system of this sort, involving a change in rate-determining step for a reaction with an unstable intermediate. The appropriate kinetic analysis is capable of providing absolute rate constants for intermediate formation, but rate constants for the return of this intermediate to reagent and for the further reaction can only be expressed as ratios.

through reaction with the acid component of the buffer. The stage is ultimately reached where k_{-2}[HA] becomes greater than k_3, and a change in rate-limiting step must occur. Formation of the anionic intermediate becomes reversible with its breakdown being rate limiting. Rate constants do continue to increase with increasing buffer concentration due to a buffer acid catalyzed breakdown. The non-catalyzed breakdown process also occurs in this region. Intercepts of plots of k_{obsd} vs. [A$^-$] have values of k_3K_a[OH$^-$]. This corresponds to the hypothetical situation where breakdown is rate limiting and occurs with no buffer catalysis, but the buffer maintains the initial equilibrium. The buffer acid catalyzed breakdown appears in the overall kinetics as general base catalysis, $k'_{\text{obsd}} = k_4K_a[\text{A}^-]/K_{\text{HA}}$, because of the pre-equilibrium deprotonation. It is in fact now commonly accepted that the general base catalysis which is observed for the decomposition of aldehyde hydrates, hemiacetals, and hemiorthoacid derivatives is occurring by the kinetically equivalent specific base–general acid route.[3,4]

Absolute values of the rate constants k_{-1}, etc., can be obtained if one further piece of information is available, for example, the acidity constant K_a for acid dissociation of the hemiorthoester. Two approaches based on linear–linear free energy relationships have been suggested for estimating tetrahedral intermediate acidities. Guthrie[15] uses an equation originally proposed by Hine[16] for carbonyl hydrates and estimates[17] a pK_a of 10.7 for $C_6H_5C(OH)_2OMe$. Fox and Jencks[18] use a simple alcohol as a starting point; with their approach a value of 10.9 is estimated for the same species. We have recently been able to measure a value for the cyclic hemiorthoester, 2-(*p*-nitrophenyl)-2-hydroxy-4,4,5,5-tetramethyl-1,3-dioxolane.[19] The pK_a value obtained is 10.4, in reasonable agreement with the estimates, particularly considering the presence of the acid-strengthening nitro substituent. The pK_a value for the hemiorthoester of concern here is predicted therefore to lie in the range 10.5–11.0. In Table I values are listed for the various constants[20] obtained by using pK_a values of 10.5 and 10.8. That a pK of this order of magnitude is reasonable can be seen in the fact that values of the rate constant k_{-2} are produced of the correct order of magnitude,[21] that is somewhere near 10^{10} M^{-1} s^{-1}.

Tetrahedral Intermediate Lifetimes. The lifetime of the hemiorthoester anion in its breakdown reactions is obviously extremely short, about 10 ns even in the absence of buffer. This finding of enormous reactivity for a tetrahedral intermediate anion has several implications. As shown in eq 7, for example, the base hydrolysis of an ester can take place in two steps, hydroxide addition to the ester carbonyl followed by elimination of alkoxide.



(7)

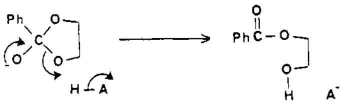
The carbonyl oxygen exchange which accompanies this hydrolysis requires protonation of the initial intermediate (or perhaps a direct proton switch). In terms of eq 7, a stationary state assumption for the tetrahedral intermediates produces the following equation for the ratio of hydrolysis to exchange.

$$\frac{k_{\text{H}}}{k_{\text{E}}} = \left(\frac{2k_2}{k_{-1}}\right)\left(\frac{k_{-1} + k_2 + k_3}{k_3}\right) \tag{8}$$

Very little exchange is in fact observed for alkyl benzoates in base, $k_{\text{H}}/k_{\text{E}}$ values ranging from 20 to 100.[22] As seen in eq 8, there are two factors which could be responsible for this, an unfavorable partitioning ($k_2 > k_{-1}$) and tetrahedral intermediate breakdown faster than proton transfer (k_{-1}, $k_2 > k_3$). The latter factor has been suggested as being important,[22,23] although its contribution is frequently ignored. The results of the present study suggest that it is a very real possibility.

It is also interesting to speculate on the lifetimes of tetrahedral intermediate anions with leaving groups such as aryloxide, carboxylate, or even halide. If the expulsion of alkoxide can occur with a rate constant of the order of 10^7–10^8 s^{-1}, the situation could easily be reached with these significantly better leaving groups where the lifetime of the intermediate becomes so short that it does not exist.[24] In such a case the tetrahedral species becomes a transition state and the nucleophilic displacement reaction would be regarded as being concerted. The possibility of a one-step acyl-transfer reaction has recently been raised for several quite different systems.[25-28] In one case[27] arguments were based on tetrahedral intermediate lifetimes. Experiments are currently underway to investigate this possibility.

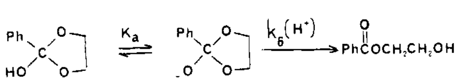
Nature of Anion Breakdown. The acid-catalyzed decomposition of the hemiorthoester anion (k_4 process) has a Brønsted α value of 0.5, calculated by using data for the two buffers—acetic acid and formic acid.[29] This intermediate α value implies a concerted reaction with proton transfer and C–O bond breaking occurring simultaneously. The rate constant k_3 for the pH-independent breakdown lies four orders of magnitude above the extrapolated line for these two acids. Although this extrapolation is a lengthy one, the implication is that the reaction is mechanistically different. Possibly in this case the alkoxide anion is formed as a discrete intermediate.



(9)

(10)

The possibility of catalysis by H_3O^+ can also be considered.



(11)

This reaction would correspond overall to a pH-independent process in the decomposition of the neutral hemiorthoester, and it is thus a possible candidate for the observed noncatalyzed reaction (k_0 term in eq 3). The pH-independent rate constant for eq 11 is equal to k_6K_a and the observed k_0 is 1.5. Therefore, since pK_a = 10.5–11.0, k_6 is required to be near 10^{11} M^{-1} s^{-1}, that is slightly greater than diffusion limited. This suggests that the

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(18) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449.

(19) McClelland, R. A.; Seaman, N. E.; Cramm, D. *J. Am. Chem. Soc.* **1984**, *106*, 4511–4515.

(20) $k_{-1} = k_1K_W/K_a$; $k_{-2} = k_2K_{HA}/K_a$; $k_3 = k_{-1}/(k_{-1}/k_3)$; $k_4 = k_{-1}/(k_{-1}/k_4)$.

(21) An alternative approach is to set the value of k_{-2} at 10^{10} M^{-1} s^{-1} and then calculate the other constants, including pK_a. This obviously results in a pK_a value of the expected order.

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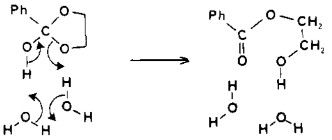
reaction of eq 11 does not make a significant contribution to k_0. The possibility has been raised[1,2] of a concerted process for this reaction, with solvent water molecules acting as acid and base to transfer protons to and from the neutral hemiorthoester.



(12)

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Supplementary Material Available: Table SI listing observed rate constnts for the breakdown of 2-phenyl-2-hydroxy-1,3-dioxolane in acetic and formate buffers (1 page). Ordering information is given on any current masthead page.

Mechanisms of Elimination Reactions. 38. Why Is the Effect of Successive β-Alkyl Substitution on the Rates of Elimination from Quaternary Ammonium Salts Nonadditive?[1]

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Abstract: Possible reasons are examined for the nonadditivity of the effect of successive β-methyl substitution on the rates of elimination reactions of quaternary ammonium salts. The temperature dependences of the deuterium isotope effects in E2 reactions of $R_1R_2NMe_2^+$ show that tunneling is not a significant source of nonadditivity. Neither is a change of gross mechanism or stereochemistry, for studies with $C_4H_9CHDCHDNMe_3^+$ and $C_4H_9(CH_3)CHCHDNMe_3^+$ show the reactions to be very predominantly (>88%) anti-E2 in both cases. Secondary tritium isotope effects with $R_1R_2CHCHTNMe_3^+$ increase, however, in the order ethyl (1.108 ± 0.002), propyl (1.150 ± 0.015), isobutyl (1.216 ± 0.012). This result suggests increasing rehybridization at the α-carbon in the transition state and therefore a shift toward less E1cB and more central-E2 character. Since methyl substitution is expected to favor a developing double bond, the much smaller rate-depressing effect of the second β-methyl is accounted for by such a shift in transition-state character.

Substituent effects on rates and equilibria in organic reactions are usually assumed to be approximately additive. This assumption is often valid for remote substituents; e.g., the Hammett σ for 3,4-dichlorophenyl is well represented by $\sigma_{p\text{-Cl}} + \sigma_{m\text{-Cl}}$.[3] When substituents are closer to the reaction center, saturation effects may be observed. Chloroacetic acid is 79 times as acidic as acetic acid, but dichloroacetic acid is only 37 times as acidic as chloroacetic acid.[4] This saturation effect is still modest. When successive substituents affect each other's ability to undergo resonance interaction with the reaction center, dramatic effects often result. Diphenylmethane is 10^8 times as acidic as toluene, but triphenylmethane is less than 10^2 times as acidic as diphenylmethane.[4]

We have been intrigued for some time by a pattern of nonadditive substituent effects for certain E2 reactions. In the Hofmann elimination at 85–150 °C of quaternary ammonium hydroxide, $R_1R_2NMe_2^+OH^-$, the ethylene/propylene ratio when R_1 = Et and R_2 = *n*-Pr is 41, but the propylene/isobutylene ratio when R_1 = *n*-Pr and R_2 = *i*-Bu is only 2.7.[5] In other words, the effect of the second β-methyl group is only one-fifteenth that of the first. A similar, though somewhat less dramatic effect persists in direct rate measurements. The relative rates of the elimination reactions of $RNMe_3^+$ with ethoxide in ethanol at 104.2 °C run Et/*n*-Pr = 13.8 and *n*-Pr/*i*-Bu = 3.1.[6] To get the true chemical effects, the above values should be corrected for symmetry number differences. The corrections can most simply be understood from the fact that there are three indistinguishable anti-E2 transition states for loss of ethyl, two enantiomeric ones for loss of propyl, but only one for loss of isobutyl. The ratios from $R_1R_2NMe_2^+OH^-$ then become ethylene/propylene 27.3 and propylene/isobutylene 1.35, while the relative rates from $RNMe_3^+$ become Et/*n*-Pr 9.20 and *n*-Pr/*i*-Bu 1.55.

Table I. Temperature Dependence of the Product Ratios for the Reactions of $R_1R_2NMe_2^+Br^-$ with Sodium 1-Butoxide in 50% 1-Butanol–Dimethyl Sulfoxide

	ethylene/ propylene		propylene/isobutylene		
T, °C	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**5**[a]
50	68.12				
60	59.80	19.88	2.594	0.7072	11.59
70	49.65	16.20			
80			2.696	0.8458	10.80
90	38.42	13.20	2.764	0.8748	10.65
100		12.50	2.892	0.9059	10.12

[a] See text for structures of these compounds. Each product ratio is the average of two runs. Derivations from mean ran usually 1–2% and never above 4%.

Even more interesting is the fact that this nonadditivity is almost completely absent in the reactions of the corresponding sulfonium ions, $RSMe_2^+$. Here the relative rates of reaction with ethoxide

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