Reactivity of Tetrahedral Intermediates

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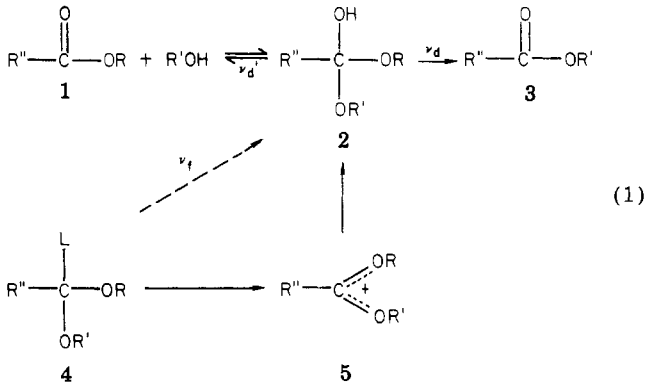
Received October 6, 1982 (Revised Manuscript Received May 5, 1983)

Nucleophilic acyl substitution reactions such as 1 → 3 have been recognized as proceeding via a tetrahedral intermediate (2) since the demonstration by Bender[1] that carbonyl oxygen exchange accompanies the hydrolysis of acid derivatives (eq 1). The presence of an



(1)

intermediate is supported by various kinetic observations,[2] such as a break in a rate–pH profile or a change in products not associated with a change in kinetic behavior. Some stable tetrahedral intermediates have also been found,[3] but these always contain some special structural feature that stabilizes the tetrahedral form relative to the carbonyl form.[4] In the vast majority of acyl transfer reactions the tetrahedral intermediate is of much higher energy and is not observed during the course of the reaction.

Recently Capon and his group at Glasgow[5-10] and our group at Toronto[11-19] have found ways of directly observing hemiorthoester tetrahedral intermediates of general formula 2. These are the intermediates of ester interchange reactions or of O,O-acyl transfer reactions, and they obviously bear a close resemblance to the intermediates formed in ester hydrolysis. The hemiorthoester is not actually observed in the acyl transfer reaction, but rather it is generated from some highly reactive precursor, in most cases some ortho acid derivative such as 4. As summarized in a recent Account,[5] the Capon group concentrated initially on low-temperature NMR spectroscopy[6-8] and have been able to provide assignments of tetrahedral intermediate structure to the observed intermediates. This Account summarizes work based on UV spectroscopy,[9-18] which allows for accurate kinetic measurements. This is important since not only have these studies established that intermediates of the hemiorthoester type can exist, they also provide direct kinetic data for the decomposition of such species. This type of information can never be obtained in the acyl transfer reaction itself where the intermediate is formed only in small stationary state amounts. Moreover rates of intermediate decomposition can be combined with rates of formation to give equilibrium constants. Such values are not accessible by direct measurement since the equilibrium concentration of the adduct is so low.

Change in Slow Step

Hemiorthoesters are formed as transient intermediates during the hydrolysis of an ortho acid derivative under conditions where the rate constant[20] for formation (ν_f of eq 1) is greater than the rate constant for decay (ν_d, ν_d'). Formation of the oxocarbocation (4 → 5) is generally expected to be the slow step in the hydrolysis of an ortho acid derivative,[21] but a number of systems have now been found where a changeover occurs. The formation of 2 from 4 is (usually) acid catalyzed, $\nu_f = k_1[H^+]$, reflecting the requirement for an acid to convert 4 to the cation 5. Decomposition proceeds with both acid and base catalysis, $\nu_d = k_2[H^+] + k_3[OH^-] + k_4$, where k_4 represents a pH-independent or water-catalyzed reaction that is also present. Given a situation where the constant k_1 for acid-catalyzed formation of the hemiorthoester is larger than the constant k_2 for its acid-catalyzed breakdown, ν_f and ν_d must cross over at some acidity, with breakdown being

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(1) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626–1629. Bender, M. L. *Chem. Rev.* **1960**, *60*, 53–113. Bender, M. L.; Heck, H. A. *J. Am. Chem. Soc.* **1967**, *89*, 1211–1220.

(2) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1968; p 465.

(3) (a) See for example tetrodotoxin[3] and 2-hydroxy-2-(trifluoromethyl)-1,3-dioxalane.[3c] (b) Woodward, R. B. *Pure Appl. Chem.* **1964**, *9*, 49–74. Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059–2088. (c) Hine, J.; Ricard, P.; Perz, R. *J. Org. Chem.* **1973**, *38*, 110–112.

(4) A detailed discussion of this can be found in ref 5.

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(8) Capon, B.; Ghosh, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 1765–1768.

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(17) McClelland, R. A.; Somani, R. *J. Chem. Soc., Chem. Commun.* **1979**, 407–408; McClelland, R. A.; Patel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6908–6911.

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(19) Santry, L. J.; McClelland, R. A. *J. Am. Chem. Soc.* **1983**, *105*, 3167–3172.

(20) The symbol ν is used to represent a pseudo-first-order rate constant that would be observed at constant pH, buffer concentration; for example, $-d[4]/dt = \nu_f[4]$ for a dilute solution of 4. The symbol k represents the true rate constant; for example, $-d[4]/dt = k_1[H^+][4]$.

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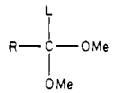
Table I
Rate Constants for Acid Catalysis of Hemiorthoester Decomposition and Formation from Ortho Acid Derivative (T = 25 °C, Water)

ortho acid derivative				formation, k_1, M^{-1} s^{-1}	decomp, k_2, M^{-1} s^{-1}	ref
struct	no.	R	L			
	6	H	OMe	2.6×10^2	2.8×10^4 [a]	9, 22
	7	H	OAc			
	8	Me	OMe	1×10^4	$>3 \times 10^4$	23
	9	Ph	OMe	56	1.9×10^4 [b]	17
	10	Ph	NMePh	8×10^6		
	11	cPr	OMe	8.1×10^4	5.3×10^3	24
	12	H	OMe	1.8×10^2	4.6×10^2 [a]	9, 13
	13	H	OAc			
	14	CH_3	OMe	2.0×10^4	1.4×10^3	25, 26
	15	$=CH_2$		$>10^6$		9
	16	Ph	OMe	5.4×10^3	3.0×10^2	13
	17	Ph	NMe_2	4×10^7		14

[a] 15 °C. [b] 50% dioxane.

the slow step in acids. The additional pathways available make breakdown faster at higher pH.

The changeover being discussed here is not the type of change in rate-determining step associated with a change in partitioning of a steady-state intermediate.[2] The kinetic system is one of two consecutive irreversible first-order reactions, **4** → **2** → products. There is no break in the kinetics associated with the disappearance of the ortho acid derivative. However, kinetic studies are usually based on product, and what limits product formation is the hemiorthoester decomposition. When $\nu_f >> \nu_d$, the intermediate **2** accumulates in nearly quantitative amounts before going on to products, and the kinetics of product formation refer directly to the decomposition process. The changeover can be seen in several ways, most notably by a break in the kinetic pattern between high pH and low pH and by the observation that rates in acid are independent of the nature of the leaving group L, since that group is not present in the kinetically important process. These examples are also typified by a short region of pH where strict adherance to first-order kinetics is not found. This represents the changeover region where $\nu_f \approx \nu_d$.

The requirement for a change in slow step is that k_1, the acid-formation rate constant, be greater than k_2, the acid-decomposition rate constant. If this requirement is not met, the dialkoxycarbocation-forming reaction is rate limiting in product formation at all acidities. Hemiorthoester does not accumulate in acids so that no kinetic information regarding its decomposition can be obtained. The change in slow step has now been observed in a number of cases; some examples are given in Table I. The dialkoxyalkyl acetates studied by Capon (**7**, **13**) differ slightly in their analysis, in that the dialkoxycarbocation forms in a simple ionization (no catalysis) that is faster than hemiorthoester decomposition.[5] In general these acetate derivatives, the ketene acetals (**15**) also studied by Capon,[8-10] and amide and anilide acetals (**10**, **17**) are all highly reactive and form hemiorthoester several orders of magnitude more rapidly than it decomposes under some conditions. Acyclic ortho esters (e.g., **6**, **8**, **9**) generally have $k_1 < k_2$ (see, however, the cyclopropyl derivative **11**[24]), and the dialkoxycarbocation-forming stage remains rate limiting throughout. The changeover is, however, observed with most cyclic ortho esters[11-13,15,25] and even bicyclic ones,[15,27,28] although cyclic orthoformates are borderline ($k_1 \approx k_2$)[29] A sulfur analogue of **16**, 2-methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane,[19] also exhibits the changeover. Ortho esters derived from lactones[16,30] have $k_1 \approx k_2$.[29] The occurrence of a changeover is not limited to ortho acid derivatives. Hemiacetals have been detected as transient intermediates in the hydrolysis of a number of acetal derivatives,[31] including benzaldehyde acetals.[31f]

Oxocarbocations

The previous discussion has focused on the dialkoxycarbocation-forming stage, but obviously the hydration of the cation must also be considered. We have measured rates of oxocarbocation hydrolysis in concentrated acids and, using an acidity function approach, extrapolated these to obtain the reactivity in water alone.[32] Our estimates for the cations $ArC^+(OMe)Me$ show excellent agreement with numbers obtained by a competition method.[33] The rates estimated are large. For example, half-lives in water for $PhC^+(OMe)Me$ and $PhC^+(OMe)_2$ are estimated as 10^{-8} and 10^{-5} s, respec-

(22) Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494–4499.
(23) Chiang, Y.; Kresge, A. J., personal communication.
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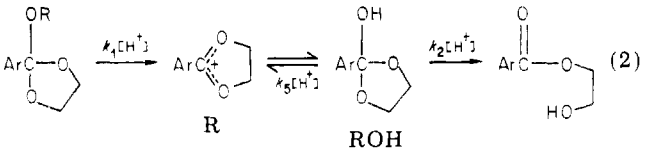
(27) Burt, R. A.; Chiang, Y.; Hall, H. K.; Kresge, A. J. *J. Am. Chem. Soc.* **1982**, *104*, 3687–3690.
(28) McClelland, R. A.; Lam, P. W. K. *Can. J. Chem.*, submitted for publication.
(29) Cases which have $k_1 \approx k_2$ within a factor of 3–5 exhibit in acids nonlinear first-order kinetic plots typical of two consecutive first-order reactions with nearly equal rate constants.[16] Information regarding hemiorthoester decomposition, although not as precise, is obtained by curve fitting to the appropriate equation.[16]
(30) McClelland, R. A.; Moreau, C., unpublished results.
(31) (a) Mori, A. L.; Porzio, M. A.; Schaleger, L. L. *J. Am. Chem. Soc.* **1972**, *94*, 5034–5039. (b) Mori, A. L.; Schaleger, L. L. *Ibid.* **1972**, *94*, 5039–5043. (c) Atkinson, R. F.; Bruice, T. C. *Ibid.* **1974**, *96*, 819–825. (d) Capon, B.; Nimmo, K.; Reid, G. P. *J. Chem. Soc., Chem. Commun.* **1976**, 871–873. (e) Capon, B. *Pure Appl. Chem.* **1977**, *49*, 1001–1007. (f) Jensen, J. L.; Lenz, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 1291–1293. (g) Finley, R. L.; Kubler, D. G.; McClelland, R. A. *J. Org. Chem.* **1980**, *45*, 644–648. (h) Przystas, T. J.; Fife, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 4884–4980. (i) Capon, B.; Grieve, D. M. A.; Nimmo, K.; Reid, G. P.; Sanchez, M. N. M., personal communication.
(32) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031–7036.
(33) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8248.

tively. Clearly the hydration process cannot in general be the slow step in the hydrolysis of an ortho acid derivative. There are a few examples[34] where hydration does become the slow step under some conditions and the oxocarbocation is observed as a transient intermediate. This occurs, however, only when some structural feature is present that stabilizes the cation, as, for example, in the aromatic methoxytropylium ion (half-life, 40 s) and in the sterically hindered dimethoxy 2,4,6-trimethylphenyl carbocation (half-life, 0.3 s).

In cyclic systems[11-15] oxocarbocation intermediates can frequently be observed, but the reason for this is different. The reverse of the hydration, the k_5 process in eq 2, is analogous to the process where the cation



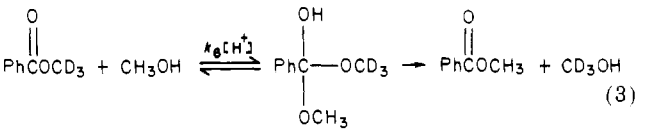
(2)

forms from an ortho ester, so that if k_2 is less than k_1, it is also likely to be less than k_5. This has the consequence that when hemiorthoester decomposition becomes the slow step in acids because $k_2 < k_1$, prior to decomposition it equilibrates with the cyclic cation precursor. The cation can be detected spectroscopically as an intermediate in equilibrium with the transient hemiorthoester, the amount of cation observed being dependent on acid concentration, since the equilibrium in question is acid dependent. Two kinetic stages for cation disappearance are expected, a rapid stage corresponding to the approach to equilibrium and a slower stage with a rate equal to the rate of product appearance as the equilibrating mixture of cation and hemiorthoester is converted to product. In most cases the equilibration is too rapid and only the slower stage is observed. The equilibrium in question is of the cation:pseudo-base type,[35] and an equilibrium constant can be defined in the normal way as $K_R = [ROH][H^+]/[R^+]$. Values for this constant have been determined from absorbance data and also from kinetic data since K_R appears in the kinetic expression. The pK_R values are typically in the range −1 to +2. For the 2-phenyl-1,3-dioxolan-2-ylium ion and its 4-methoxyphenyl analogue, for example, pK_R values are −0.5 and 1.1, respectively.

Oxocarbocation salts should themselves serve as highly reactive precursors of hemiorthoesters. As experienced by both Capon[5] and ourselves,[12] however, there are experimental difficulties with this approach, although we have used[12] 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolan-2-ylium borofluorate successfully.

Equilibrium Constants

The hemiorthoesters being observed are tetrahedral intermediates of ester interchange reactions, in most cases degenerate interchanges. Rate constants for the formation of these intermediates in the acyl transfer reaction have been obtained in two ways. The hemiorthoester **18** is the tetrahedral intermediate of the methanolysis of methyl benzoate. The degeneracy was destroyed by isotopic labeling and the exchange of eq 3 observed in acid solutions containing methanol.[18] The exchange rate constant was statistically corrected and

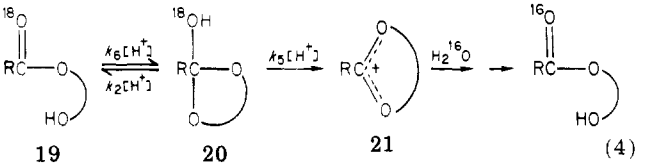


(3)

18

extrapolated to zero methanol concentration to give the rate constant for tetrahedral intermediate formation.

For intramolecular ester interchanges formation rate constants have been obtained by recognizing a further consequence of k_5 being greater than k_2 (see eq 2 and 4). Starting with a carbonyl oxygen labeled ester **19**,



19 20 21 (4)

cyclization produces the intermediate **20**, which in acid solutions loses its exocyclic labeled hydroxyl group through equilibration with the cation **21** before returning to the thermodynamically stable carbonyl form. The overall result is exchange of the carbonyl oxygen with solvent oxygen. This is the same process that Bender[1] observed in initially establishing the tetrahedral intermediate, but the mechanism is quite different. Exchange via the cyclization mechanism was demonstrated by the finding that β-hydroxy esters do exchange their carbonyl oxygen in acid solutions under conditions where they do not hydrolyze.[12] The rate constant for this exchange is equal to $k_5k_6[H^+]/(k_2 + k_5)$, which is equal to $k_6[H^+]$ with $k_2 < k_5$.

Both approaches provide k_6, the rate constant for acid-catalyzed formation of the tetrahedral intermediate in the ester interchange reaction. This constant can be combined with k_2, the rate constant for the microscopic reverse acid-catalyzed decomposition, to give the equilibrium constant K_f. Some representative values are given in Table II. The following general comments can be made. (a) The value for **18** can be compared with the value estimated by Guthrie using a thermodynamic approach[36,38] for **22**, the intermediate of the hydrolysis of methyl benzoate. (The actual number reported by Guthrie has been divided by 55 to convert to second-order units.) The almost exact agreement is probably fortuitous, but it does indicate that the methods are valid. There are a number of metastable species where the Guthrie approach has been applied for which a measurement, either direct or through kinetics, is not likely to be possible. (b) As expected, tetrahedral intermediates of intramolecular reactions are more stable than those of intermolecular reactions, with additional stability resulting on introduction of methyl groups (as in **24**) or some degree of conformational rigidity (as in **25**). These effects have been well-documented through kinetic studies of intramolecular acyl transfer reactions, for example, in the lactonization reactions studied by Milstein and Cohen[39]

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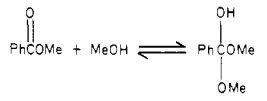
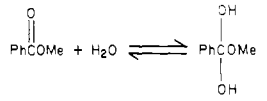
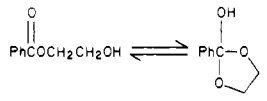
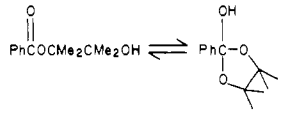
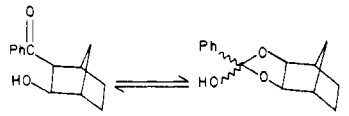
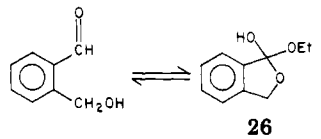
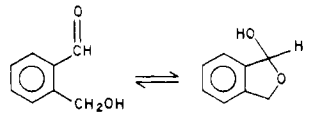
(35) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1–82.
(36) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1980**, *58*, 1281–1294.
(37) Harron, J.; McClelland, R. A.; Thankachan, C.; Tidwell, T. T. *J. Org. Chem.* **1981**, *46*, 903–910.
(38) Guthrie, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6999; *Acc. Chem. Res.* **1983**, *16*, 122–129.
(39) Milstein, S.; Cohen, L. *J. Am. Chem. Soc.* **1970**, *92*, 4377–4382; **1972**, *94*, 9158–9165. See also Caswell, M.; Schmir, G. L. *Ibid.* **1980**, *102*, 4815–4821.

Table II
Equilibrium Constants for the Formation of Tetrahedral Intermediates (Water, 25 °C)

system	K_f, M^{-1}	ref
 **18**	2.2×10^{-12} [a]	18
 **22**	1.5×10^{-12}	36
 **23**	2.7×10^{-9}	12
 **24**	3.7×10^{-5}	12
 **25**	3.1×10^{-5}	26
 **26**	1×10^{-6}	16
 **27**	8.1	37

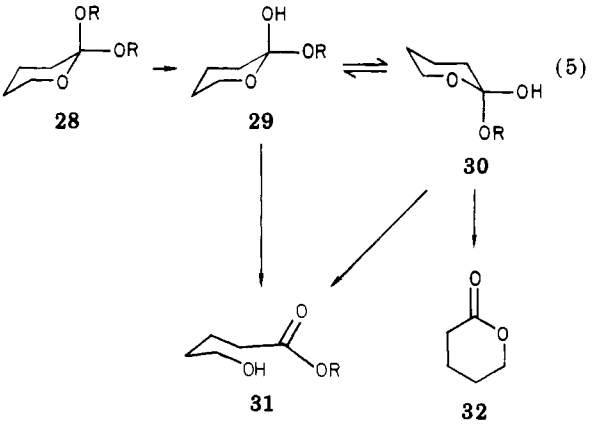
[a] 50% dioxane.

and by Storm and Koshland,[40] and arise through a combination of steric and entropic factors.[41] (c) Entries **26** and **27** illustrate the well-recognized difference between acyl and aldehyde derivatives, the cyclic hemiacetal **27**, in fact, being thermodynamically stable relative to its carbonyl form. The 10^7 difference in K_f observed here is about that estimated by Fastrez[42] for any comparison involving equilibrium constants for addition to aldehydes and esters and corresponds to a resonance energy in the ester form of about 12–15 kcal/mol.[42] (This takes into account a small electrostatic destabilization of the ester form.[42])

Intermediate Lifetime and Lone-Pair Orientation

Of the hemiorthoesters studied to date, rate constants have been found in the range 10^0–10^5 M^{-1} s^{-1} for the H^+-catalyzed breakdown (k_2), in the range 10^{-1}–10^1 s^{-1} for the pH-independent breakdown (k_4), and in the range 10^7–10^{11} M^{-1} s^{-1} for the OH^--catalyzed breakdown (k_3). Rate profiles are U-shaped with minimum rates typically around pH 4, the minimum occurring in acid because of the much greater rate for OH^- catalysis. The half-life of the hemiorthoester at this rate minimum lies within an order of magnitude of 1 s. Lifetimes are obviously significantly decreased in stronger acids and even in weakly basic solutions and become exceedingly short in strongly basic solutions.

Deslongchamp's theory of stereoelectronic control[43] states that in the decomposition of a tetrahedral intermediate, the two remaining heteroatoms must each have a lone pair antiperiplanar to the breaking bond. Although this theory is undoubtedly correct,[44] an important question in these considerations, as illustrated by the following example, is whether the intermediate has sufficient lifetime to undergo conformational change. The hemiortho ester **29** is formed from the ortho ester precursor **28** in the specific conformation shown[45] and from that conformation can only produce hydroxy ester **31**, since the ring oxygen does not have a lone pair antiperiplanar to the exocyclic alkoxy group (eq 5). Ring-flip gives **30**, which can produce both


(5)

products **31** and **32**. Hydroxy ester **31** is the major product,[45] although contrary to the original report,[45] some lactone also forms[46] even under conditions of kinetic control. Although the original interpretation[45] involved breakdown with lone-pair orientation control prior to conformational change, the experiments were conducted in mild acids, and the intermediate should achieve conformational equilibrium prior to breakdown. The intermediate **29** has, in fact, recently been detected,[30] and its rates of breakdown are normal. The half-life at pH 2–4 for example ranges from 0.01 to 0.5 s. Ring-flip should occur in 10^{-5}–10^{-6} s.[44] Deslongchamps has how proposed[47] a "secondary stereoelectronic effect," namely, that the hydroxy ester forms in the more stable *Z* configuration while the lactone is limited to the less stable *E* configuration.

Mechanism

Hemiorthoester decomposition, like that of aldehyde hydrates and acetals,[48] is catalyzed by all available acid–base species, including general acids and bases. A feature of our approach is that direct mechanistic in-

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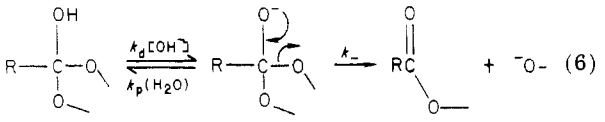
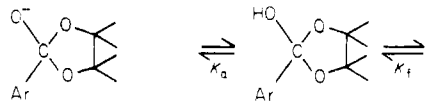
formation is provided for the decomposition and obviously also for the microscopic reverse, the formation. As pointed out recently by De Tar,[49] the study of an acyl transfer reaction is always complicated by the question as to whether tetrahedral intermediate formation or breakdown is rate limiting. This ambiguity is obviously not present when the breakdown is directly followed.

(a) Base Catalysis. The general-base reaction has proved the most difficult to study, for the reason that in solutions where this catalysis occurs the pH is such that hemiorthoester decomposition is usually not the slow step. Gravitz and Jencks[50] have argued that the general-base-catalyzed decomposition of a tetrahedral intermediate derived from a phthalimidium cation occurs by a kinetically equivalent mechanism with general-acid catalysis of the breakdown of the deprotonated intermediates. Such a mechanism is also proposed with aldehyde hydrates and hemiacetals.[48b,51] The limited data available with the hemiorthoesters are also consistent with this mechanism,[9,18] although others admittedly cannot be ruled out.

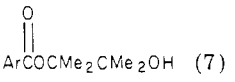
The hydroxide ion reaction is characterized by very large rate coefficients k_3, often of the order of 10^{10}–10^{11} M^{-1} s^{-1} typical of a diffusion-limited process.[52] The mechanism most likely[48,50] involves deprotonation as shown in eq 6. The pK_a value (for normal R) is esti-



mated as 11–12,[8,36,53] hemiorthoesters being more acidic than simple alcohols because of the additional oxygens. We have recently observed[54] a hemiorthoester anion **33** in equilibrium with its ring-opened form **35**. The apparent acidity constant (**33**[H⁺]/**35**) is 13.5 (as pK), and since $K_f \approx 10^{-3.5}$, p$K_a \approx 10$, in agreement with the estimates considering the NO_2 substituent.



33, Ar = 4-nitrophenyl 34



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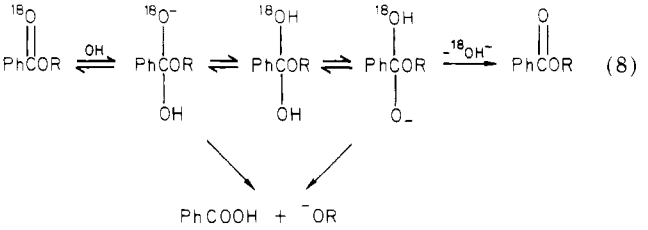
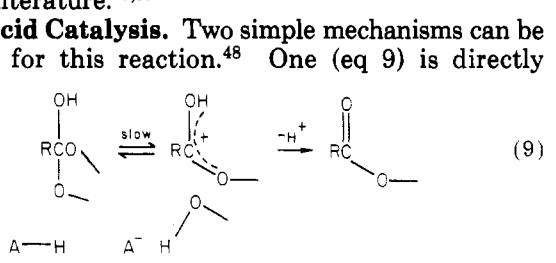
The deprotonation step in eq 6 is thermodynamically favored and therefore $k_d \approx 10^{10}$ M^{-1} s^{-1} and $k_p \approx 10^7$–10^8 s^{-1}.[52,55] Catalytic coefficients k_3 for OH^- of 10^{10} correspond to rate-limiting deprotonation. This arises if the anion falls apart faster than it is reprotonated or if $k_- > k_p$. Catalytic coefficients less than 10^{10} corresponds to reversible deprotonation, but even in these cases values of k_- must be quite large. The general conclusion is that the lifetime of an anionic hemiorthoester is short, and the question as to whether it forms reversibly or irreversibly from neutral hemiorthoester is delicately balanced. For example, PhC(OMe)$_2$OH has $k_3 = 5 \times 10^8$ M^{-1} s^{-1} and the anion forms reversibly. The dioxolane analogue of this (**23**, Table II) has $k_3 = 5 \times 10^{10}$ M^{-1} s^{-1} and deprotonation is probably rate limiting.

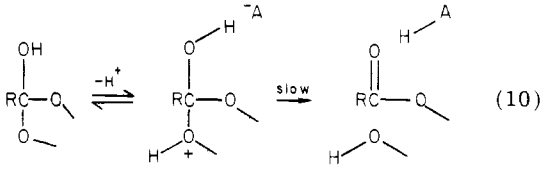
The situation with $k_- > k_p$ implies that an intermediate that is generated in its anionic form, as in base ester hydrolysis, would break down before being protonated. This has been suggested by Bender[56] on the basis of ^{18}O-exchange measurements during benzoate ester saponification, although some of the experimental numbers in this study are in error.[57] There is very little carbonyl ^{18}O exchange during the base hydrolysis of simple benzoates.[57] This could be caused by very rapid breakdown rates, since the exchange process requires protonation of an initially formed intermediate, while hydrolysis does not. The interesting possibility also



arises that in certain cases, perhaps when good leaving groups such as aryloxide ions are involved, the lifetime of the intermediate anion would be so short that it could not exist,[58] and the nucleophilic displacement would have to be regarded as being concerted. Some suggestions of this possibility have, in fact, appeared in the recent literature.[49,59]

(b) Acid Catalysis. Two simple mechanisms can be written for this reaction.[48] One (eq 9) is directly





analogous in its rate-determining step to the oxocarbocation-forming step of a general-acid-catalyzed ortho ester hydrolysis. This can be rejected on several grounds. (i) Rates of H^+-catalyzed decomposition of acyclic hemiorthoesters are significantly larger in general than rates of H^+-catalyzed formation of an oxocarbocation from the corresponding ortho ester (Table

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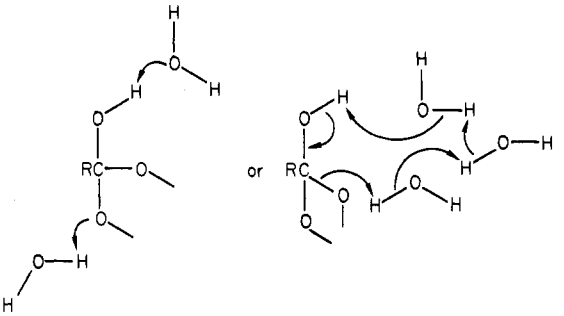
I). (ii) The Brønsted α value for decomposition of dimethyl hemiorthobenzoate is 0.46,[18] whereas trimethyl orthobenzoate hydrolysis is not buffer catalyzed[60] ($\alpha >$ 0.8). (iii) With ortho esters a significant increase in rate is observed on substituting H by Me, as expected since the methyl stabilizes the cation. Hemiorthoformates on the other hand show a very similar reactivity to hemiorthoacetates (Table I). It can be noted that rejection of this mechanism implies also a rejection of the mechanism normally written for acid-catalyzed ester alcoholysis (and hydrolysis). This involves a preequilibrium protonation of the ester, followed by addition of alcohol (or water), and this is the reverse of eq 9.

The eq 9 mechanism has also been rejected for aldehyde hydrates and hemiacetals[48b,51] and the mechanism of eq 10 favored. This reaction, however, seems also to be ruled out for the hemiorthoesters in that for certain catalysts rate constants for the slow step considerably larger than the diffusion limit are required.[18] We considered the possibility of a "1-encounter" mechanism,[61] in which the acid that donates the proton then acts as a base to deprotonate the hydroxy group before diffusional separation. This suggestion has the drawback that in the previous system for which this mechanism was proposed,[61] the addition of hydrogen peroxide to aldehydes, Brønsted α values were near unity. Capon[9] has proposed a fully concerted mechanism, with a proton being simultaneously donated to the departing alkoxy group by the acid catalyst and removed from the hemiorthoester hydroxyl by water solvent. This mechanism, however, appears entropically difficult, particularly in the reverse direction. We conclude that the acid mechanism is not yet established, and further work is needed.

The Water Reaction

The possibility that water is simply acting as another general acid or general base can be rejected on the grounds that even after correction to second-order units, the points for this catalyst lie well above the acid and base Brønsted lines.[18] Other experimental observations include (a) a near zero ρ value (for dimethyl hemiorthobenzoates[18] and for 2-hydroxy-2-aryl-1,3-dioxolanes),[13] (b) very little effect of substituting methyl by CH_2Cl and $CHCl_2$,[9] (c) k_{H_2O}/k_{D_2O} = 4.5 (for 2-hydroxy-2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane),[26] and (d) $\Delta S^{\ddagger}$ = −22 eu for the pH-independent ring opening of 2-hydroxy-2-phenyl-1,3-dioxolane.[26] The last two observations suggest a highly structured transition state with a considerable proton-transfer component, and the mechanism favored by both us[18] and Capon[9] involves a concerted process with water molecules simultaneously donating and removing protons, perhaps in a cyclic fashion through a solvent bridge.[62]



Concluding Remarks

Tetrahedral intermediates of the hemiorthoester type have now been shown to have a sufficient lifetime to be observed in aqueous solution, providing that they are generated from more reactive precursors. These observations not only establish that these are reasonable intermediates for O,O-acyl transfer reactions but they also permit direct kinetic and mechanistic study of the decomposition process. Further work should provide a detailed understanding of mechanistic behavior not only for the decomposition process but also for the microscopic reverse, an ester alcoholysis or hydrolysis.

The continued support of the Natural Sciences and Engineering Research Council of Canada is acknowledged. Grants from the Research Corp. and the J.. P.. Bickell Foundation are also acknowledged.

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Metal–Ammonia Reductions of Cyclic Aliphatic Ketones

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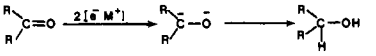
Received December 2, 1982 (Revised Manuscript Received June 27, 1983)

The reduction of aliphatic cyclic ketones by alkali metals in liquid ammonia was first employed about 30 years ago as an alternative to the sodium–alcohol procedure for the stereoselective conversion of 11-keto steroids to the 11α-(equatorial) alcohols.[1] Subsequently this reaction has found limited use as a method for the reduction of ketonic carbonyl groups in other steroids and in the synthesis of various natural products.

Scheme I



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