anhydrides,[6] and the entropies of activation would become correspondingly more negative. An alternative possibility is that these variations in kinetic form of the acid hydrolysis and in the entropy of activation arise not from the extent of nucleophilic involvement of the incoming water molecule, but upon the necessity of one or more water molecules being oriented around the transition state, so that they can transfer a proton from one oxygen atom to another and so assist making of a new or breaking of an existing bond.[20] Thus, if breaking of the existing carbon–oxygen bond were less important in forming the transition state for acetic than for trimethylacetic anhydride, we should except fewer water molecules to be involved in the transition state. The entropy of activation should then be less negative, and, as noted by Bunnett, the w-values should be smaller[8] and reaction rate increase more sharply with increasing acidity.

The Hydrolysis of Carboxylic Ortho Esters

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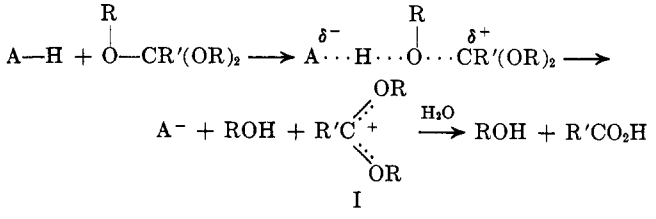
Estimates of the probable basicities of carboxylic ortho esters suggest that their conjugate acids are not reactive intermediates in their hydrogen ion catalyzed hydrolyses, but that proton transfer to oxygen is involved in the rate-limiting step. The proposed mechanism accords with the relative insensitivity of rate to α-substituents.

In developing his theory of proton acids and bases Brønsted[1] pointed out that general acids, *i.e.* acids other than the solvated hydrogen ion, should be able to catalyze reactions. Both the solvated hydrogen ion and general acids can transfer protons to bases in equilibria, and therefore should be able to transfer protons to basic sites in the transition state of a reaction. Hydrolyses of aliphatic ortho esters were the first general acid catalyzed reactions to be found; although the hydrolysis of ethyl orthoformate is catalyzed specifically by hydronium ions in water,[2] it is catalyzed by both hydronium ion and general acids in aqueous dioxane,[3] and the hydrolysis of most of the other ortho esters is general acid catalyzed even in water.[2]

The general acid catalyzed hydrolysis of an ortho ester could involve a slow proton transfer from the weak acid to an oxygen atom of the ortho ester, concerted with or followed by carbon–oxygen bond cleavage, or a slow carbon–oxygen bond cleavage of a hydrogen-bonded complex of the acid and ester.[4] Both of these mechanisms lead to identical rate laws, and both may be considered examples of bimolecular electrophilic displacements (SE2) upon oxygen, giving dialkoxycarbonium ion intermediates (I). We exclude

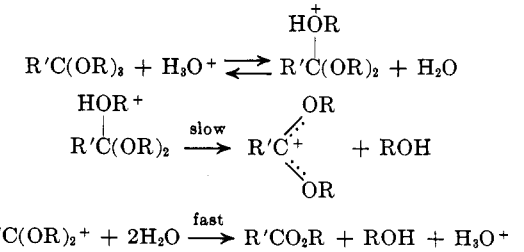


nucleophilic attack by the conjugate base of the acid upon the conjugate acid of the ortho ester as a possible mechanism, because it is inconsistent with observed structural effects in either the catalyst or the substrate upon reactivity.

Conversion of I to products must be fast, because for both proton and general acid catalyzed reaction there is no evidence for its accumulation in aqueous solution: the reaction can be followed either dilatometrically,[2] *i.e.*, by following a bulk property of the solution, or by following the formation of the carboxylate ester spectrophotometrically,[5a] and the rates of disappearance of methyl orthobenzoate and appearance of methyl benzoate, followed by n.m.r. spectroscopy, are identical.[5b]

Hydrogen ion catalyzed ortho ester hydrolysis almost certainly involves reactive dialkoxycarbonium ion intermediates. Ortho esters are known to form stable dialkoxycarbonium salts,[6] and Fullington and Cordes recently produced convincing evidence for a cationic intermediate by an intervention experiment using hydroxylamine as the trapping agent.[7]

If the usual assumption is made that proton transfer from hydronium ion to an oxygen atom of a substrate cannot be the rate-limiting step of an acid hydrolysis,[8] the most reasonable mechanism of formation of the dialkoxycarbonium ion intermediate is the A-1 mechanism of Winstein and Buckles.[9]



(1) For leading references, see R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, Chapter 4.

(2) J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

(3) R. H. DeWolfe and R. M. Roberts, *J. Am. Chem. Soc.*, **76**, 4379 (1954).

(4) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2d Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 213.

(5) (a) R. H. DeWolfe and J. L. Jensen, *J. Am. Chem. Soc.*, **85**, 3264 (1963); (b) A. M. Wenthe and E. H. Cordes, *Tetrahedron Letters*, 3163 (1964).

(6) H. Meerwein, V. Hederich, H. Morschel, and K. Wunderlich, *Ann.*, **635**, 6 (1960).

(7) J. G. Fullington and E. H. Cordes, *J. Org. Chem.*, **29**, 970 (1964).

(8) For an early discussion of this problem as applied to hydrolysis of esters and related compounds, see (a) J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941); (b) R. P. Bell, *ibid.*, **37**, 705 (1941); (c) ref. 1, p. 148.

(9) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **65**, 613 (1943).

This mechanism is similar to the accepted A-1 mechanism for the acid hydrolysis of acetals and ketals,[10,11] which are structurally similar to ortho esters. It explains the specific hydrogen ion catalysis, and the solvent deuterium isotope effect, $k_{H_3O}/k_{D_2O} \simeq 0.5$, in the acid hydrolysis of ethyl orthoformate,[12] ethyl orthobenzoate,[5,7] and acetals. These explanations imply that hydronium ions and weak acids catalyze ortho ester hydrolyses in different ways.

The effects of substituents on ortho ester hydrolytic reactivity are difficult to rationalize in terms of the A-1 mechanism. The rate-limiting step in this mechanism is assumed to be dissociation of the ortho ester conjugate acid into a mesomeric dialkoxycarbonium ion and alcohol. All other reactions which are known to involve rate-limiting carbonium ion formation, either from a neutral substrate or its conjugate acid, are strongly accelerated by electron-releasing substituents which stabilize the positively charged ion. These substituents presumably also stabilize the transition state, which itself has carbonium ion character, and hence lower the free energy of activation. The effect of alkyl and aryl substitution at the reaction site in SN1 reactions is well known, and similar substituent effects are observed for acetal hydrolysis, which almost certainly occurs by the A-1 mechanism (Table I).

TABLE I

RELATIVE RATES OF HYDROLYSIS OF ACETALS AND KETALS IN 50% DIOXANE AT 25°

Compd.	Relative hydrolysis rate[a]
$CH_2(OC_2H_5)_2$	1.00[b]
$CH_3CH(OC_2H_5)_2$	6.00×10^3
$C_6H_5CH(OC_2H_5)_2$	1.71×10^5
$(CH_3)_2C(OC_2H_5)_2$	1.83×10^7

[a] Data from M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, **77**, 5590 (1955). [b] $k_2 = 4.13 \times 10^{-5}$ mole^{-1} sec.$^{-1}$ l.

Substituent effects on ortho ester hydrolysis are not only very much smaller than would be predicted by analogy with acetal hydrolysis, but in some cases are in the opposite direction (Table II). Thus, ethyl orthocarbonate and ethyl orthobenzoate, which are known from exchange experiments to form the most stable carbonium ions,[6,13] are hydrolyzed more slowly than either ethyl orthoformate or ethyl orthoacetate.

TABLE II

RELATIVE REACTIVITIES OF ORTHO ESTERS

R in $R\text{-}C(OC_2H_5)_3$	Relative hydrolysis rate
H[a]	1.00[b]
CH_3[a]	38.5
C_2H_5[a]	24.3
C_6H_5[c]	0.62
C_2H_5O[a]	0.17

[a] Data from ref. 2. [b] $k_2 = 5.38 \times 10^2$ mole^{-1} sec.$^{-1}$ l. [c] Data from ref. 5a.

Further, the logarithms of the rate constants of hydrolysis of 4-substituted methyl orthobenzoates in aqueous methanol correlate well with σ-constants, but not with σ^+-constants,[14] suggesting again that there is little carbonium ion character in the transition state, whereas for arylmethyl halide hydrolysis there is a good correlation with σ^+-constants.[15] Substituent effects in ortho ester hydrolyses tend to follow an inductive, rather than a mesomeric, order.

One way out of this dilemma would be to abandon the carbonium ion mechanism for hydronium ion catalyzed hydrolysis of ortho esters—*e.g.*, we might assume that water attacks the conjugate acid of the ester in the rate-limiting step—but such an A-2 mechanism is unlikely in view of the very high reactivity of ortho esters and the known stability of dialkoxycarbonium ions[6,13] and is excluded by the recent finding that hydroxylamine captures a cationic intermediate without affecting the rate of hydrolysis of methyl orthobenzoate.[7]

If it is assumed that ortho ester hydrolysis occurs by the A-1 mechanism, the data could be rationalized by invoking a saturation effect: perhaps the transition state for dialkoxycarbonium ion formation is so stabilized by the two alkoxy groups that the alkyl or aryl substituent does not significantly further stabilize it. This argument does not appeal to us either, since such a saturation effect has not been previously observed in carbonium ion reactions. For example, in solvolyses of $C_6H_5CH_2Cl$, $(C_6H_5)_2CHCl$, and $(C_6H_5)_3CCl$, relative reactivities are approximately $1:10^5:10^9$.[16]

A third explanation, previously offered by one of us,[5a] assumes that because dialkoxycarbonium ions are very much more stable than ordinary carbonium ions the transition state for their formation could be such a short distance along the reaction coordinate that the central carbon atom remains tetrahedral, or nearly so, and hence is not geometrically suited for resonance interaction with a substituent. This idea was arrived at in desperation, because the formation of very stable triarylmethyl cations is aided by electron-releasing substituents, and there are good linear free-energy relationships between σ^+-constants and rate or equilibrium constants in arylalkyl systems, which demonstrate the additivity of substituent effects.[16,17]

All this experimental evidence, and the very rapid hydrolysis of ortho esters in solutions of low hydrogen ion concentration, in which the conjugate acid of the ortho ester could be present in only vanishingly small concentration, suggests that the A-1 mechanism does not apply to these reactions. Instead, we agree with Cordes' suggestion that hydronium ion catalyzed ortho ester hydrolysis, like general acid catalyzed ortho ester hydrolysis, occurs by the SE2 mechanism.[7] That is, the rate-limiting step of the reaction involves slow proton transfer to an oxygen atom of the ortho ester, which may be concerted with displacement of a dialkoxycarbonium ion.

Since the nonoccurrence of rate-determining proton transfers from hydronium ion to oxygen has been ac-

(10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 344.
(11) D. McIntyre and F. A. Long, *J. Am. Chem. Soc.*, **76**, 3240 (1954).
(12) See ref. 1, p. 146.
(13) R. H. DeWolfe, unpublished experiments.
(14) H. Kwart and M. B. Price, *J. Am. Chem. Soc.*, **82**, 5123 (1960). Two reactions occur in aqueous methanol, hydrolysis and methanolysis, the latter giving no chemical change, although its importance has been demonstrated by isotopic labeling.[5b] This fact should not affect the correlations between rate and structure, provided that partitioning of a carbonium ion intermediate between hydrolysis and methanolysis is independent of the structure of the ortho ester.
(15) H. L. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).
(16) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956).
(17) R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

cepted generally by physical organic chemists,[8,14] it is important to consider whether this proposed SE2 mechanism is reasonable in terms of expected rates of proton transfer to oxygen compounds and the basicities of oxygen bases, or whether an A-1 mechanism can be accommodated to these properties. So far as we know, there has been no direct measurement of the basicities of ortho esters; their high reactivity in aqueous acid excludes the more obvious methods of measurement. It may be reasonably assumed that structural effects on basicity of oxygen bases parallel structural effects on the basicity of nitrogen bases. The basicities of aliphatic amines fit linear free-energy relations using Taft's σ^*-values.[18] The value of ρ^* is *ca.* -3 and varies slightly for primary, secondary, and tertiary amines. If we assume that the basicities of ethers, acetals, and ortho esters are described by the same relation, using $\rho^* = -3$, we can calculate the basicities of ortho esters using $\sigma^* = 0.52$ for a methoxy or ethoxy group, 0.215 for a phenyl group, and -0.100 for a methyl or ethyl group. Taking $pK_a = -3.8$ for dimethyl and -3.6 for diethyl ether,[19] and using the σ^*- and assumed ρ^*-values, the estimated pK_a values are -5.4 for dimethyl acetal, -7 for triethyl orthoformate, -7.6 for triethyl orthobenzoate, and -8.5 for ethyl orthocarbonate.

Qualitative support for these estimates of basicity comes from the measurement of the O–H stretching frequency in the hydrogen-bonded complex between phenol and several ethers, diethyl ketal, ethyl orthoformate, triethyl orthoacetate, and ethyl orthocarbonate. The shift in the stretching frequency decreases with decreasing basicity of the base, and measurements of it lead to the expected basicity sequence[13,20]: $(C_2H_5)_2O > (CH_3)_2C(OC_2H_5)_2 > CH_3C(OC_2H_5)_3 > CH(OC_2H_5)_3 > C(OC_2H_5)_4$.

We did not attempt to calculate basicities from the stretching frequencies, because Arnett notes that the uncertainty of pK_a values determined in this way is *ca.* 2 units, due to the effect of adventitious impurities, π-bonding, and steric hindrance.[19]

Ortho ester and acetal hydrolysis in mineral acid can be represented by the following reaction scheme, assuming that the conjugate acid is the reactive intermediate, where S is the substrate and SH^+ is its conjugate acid. Application of the steady-state approximation to this scheme leads to

$$S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ + H_2O$$

$$SH^+ \xrightarrow{k_2} \text{products}$$

$$k_\psi = k_1k_2(H_3O^+)/(k_{-1} + k_2)$$

$$k_{H^+} = k_1k_2/(k_{-1} + k_2)$$

where k_ψ is the experimentally observed first-order rate constant and $k_{H^+} = k_\psi/(H_3O^+)$.

If ortho ester hydrolysis occurs by the A-1 mechanism, *i.e.*, if $k_{-1} >> k_2$

$$k_{H^+} = k_1k_2/k_{-1} = k_2/K_a$$

$$k_2 = k_{H^+}K_a$$

Values of k_2 required by the A-1 mechanism can therefore be calculated, using known values of k_{H^+} and our estimated values of K_a.

For the acid hydrolysis of dimethyl acetal,[11] $k_{H^+} \simeq 3 \times 10^{-5}$ sec.$^{-1}$ mole^{-1} l. at 25°, and therefore $k_2 \simeq 7$ sec.$^{-1}$. This value is much less than the expected value for loss of a proton from a strong conjugate acid, and the conventional A-1 mechanism is applicable to acetal hydrolysis, *i.e.* $k_{-1} >> k_2$.

The situation is generally different for the hydronium ion catalyzed hydrolysis of ortho esters. For hydrolysis of ethyl orthoformate at 20°, $k_{H^+} = 5.4 \times 10^2$ sec.$^{-1}$ mole^{-1} l., and a calculation similar to that described above shows that, if the conjugate acid is in equilibrium with the reactants, $k_2 \simeq 5 \times 10^9$ sec.$^{-1}$. It is unlikely in this case that $k_{-1} >> k_2$, because the value of k_{-1} would then be improbably high, even though it concerns a proton transfer from a strong acid to water. This would require a value of k_{-1} similar to, or larger than, measured rates of proton transfer between strong acids and strong bases.[21] In contrast, the rate constant for the transfer of a proton between ethanol and its conjugate acid or base is only 10^6–10^8 sec.$^{-1}$ mole^{-1} l.[22] For ethyl orthoformate hydrolysis k_{-1} and k_2 may have similar values, and the mechanism of this reaction may be on the borderline between A-1 and SE2. The solvent deuterium isotope effect,[5,7,23] $k_{H_2O}/k_{D_2O} \simeq 0.4$, shows that transfer of the proton from the hydronium ion to the substrate must be complete, or nearly so, in the transition state.[24]

If a similar treatment is applied to hydronium ion catalyzed hydrolysis of ethyl orthoacetate, where $k_{H^+} = 2 \times 10^4$ sec.$^{-1}$ mole^{-1} l. at 20°, we calculate $k_2 \simeq 2 \times 10^{11}$ sec.$^{-1}$. It is difficult in this case to see how the rate of loss of the proton from the conjugate acid could then be faster than the rate of its breakdown to products. A similar situation applies to the hydrolysis of ethyl orthopropionate. For ethyl orthobenzoate $k_{H^+} = 3.4 \times 10^2$ sec.$^{-1}$ mole^{-1} l. at 20°, and a similar calculation gives $k_2 \simeq 3 \times 10^9$ sec.$^{-1}$, and for ethyl orthocarbonate, where $k_{H^+} = 90$ sec.$^{-1}$ mole^{-1} l. at 20°, $k_2 \simeq 10^{10}$ sec.$^{-1}$. Proton transfer to the substrate must be complete, or nearly so, in the transition states of hydrolysis of methyl orthobenzoate and ethyl orthocarbonate, although the value of k_{H_2O}/k_{D_2O} for the latter is significantly higher than for ethyl orthoformate. For methyl orthobenzoate,[7] $k_{H_2O}/k_{D_2O} = 0.45$, and, for ethyl orthocarbonate, [23b] 0.7.

If our estimates of the basicities of ortho esters are of the right order of magnitude, the A-1 mechanism requires that heterolysis of the hypothetical ortho ester conjugate acids should occur at rates comparable to those for proton transfers from strong acids to strong bases. It seems much more reasonable to assume that heterolysis of a conjugate acid cannot be

(18) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(19) E. M. Arnett in "Progress in Physical Organic Chemistry," Vol. 1, S. G. Cohen, A. Streitwieser, and R. A. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 223.

(20) R. West, L. S. Whatley, and K. J. Lake, *J. Am. Chem. Soc.*, **83**, 761 (1961).

(21) M. Eigen, *Angew. Chem., Intern. Ed. Engl.*, **3**, 1 (1964).

(22) (a) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 118; (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 113.

(23) (a) F. Brescia and V. K. LaMer, *J. Am. Chem. Soc.*, **62**, 612 (1940); (b) W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **34**, 245 (1938).

(24) C. A. Bunton and V. J. Shiner, *J. Am. Chem. Soc.*, **83**, 3207, 3214 (1961).

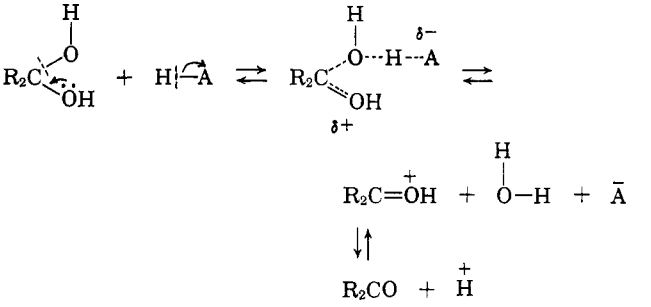
the rate-limiting step for the hydrogen ion catalyzed hydrolysis of *all* these ortho esters. Indeed estimates of the various rate constants for these hypothetical reactions suggest that *none* of these hydrolyses follow this course (except possibly that of ethyl orthoformate).

An SE2 mechanism of ortho ester hydrolysis is reasonable in terms of expected rates of proton transfers from hydronium ion to weak bases. The second-order catalytic coefficients, k_{H^+}, for ortho ester hydrolyses are in the range 10^2–10^4 sec.$^{-1}$ mole^{-1} l. at 20° in water.[2,5] These rate constants are not much smaller than those quoted for proton transfer between ethanol and its conjugate acid (*ca.* 10^6),[22] and proton transfer from hydronium ion to carbonate ion is even slower.[21] An approximate estimate of the expected value of k_1 for proton transfer from hydronium ion to an ortho ester can be made by using the values estimated for K_a, and the maximum probable values of k_{-1}. For triethyl orthoacetate we calculate $K_a \simeq 10^7$, and, if k_{-1} were about 10^{11} sec.$^{-1}$, then k_1 would be *ca.* 10^4 sec.$^{-1}$ mole^{-1} l., which is very close to the observed value of $k_{H^+} = 2 \times 10^4$ sec.$^{-1}$ mole^{-1} l. at 20° in water. Again the estimates of probable rate constants depend upon assumptions of the basicity of the ortho esters, but it is unlikely that they can be out by more than an order of magnitude.

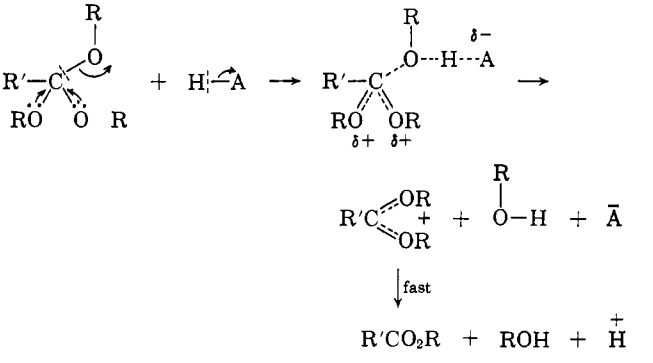
Other evidence supports an SE2 mechanism for the hydronium ion catalyzed hydrolysis of ortho esters. The observed substituent effects show that the transition states have little carbonium ion character.[5,14] The relative reactivities recorded in Table II clearly require that the inductive effect of substituents on rate of hydronium ion attack at ortho ester oxygen outweigh their mesomeric effect on the stability of the incipient carbonium ion transition state. This is also suggested by the data of Kwart and Price for hydrolysis of *para*-substituted ethyl orthobenzoates.[14] The hydronium ion catalyzed reaction gives an excellent Hammett $\rho\sigma$ plot of slope −2.0, but, if carbonium ion stability were the factor influencing reactivity, the rates should correlate better with Brown's σ^+-constants.[15]

It is probable that addition of the proton is concerted with breaking of the C–O bond. Hydrolysis of an ortho ester is similar mechanistically to mutarotation of glucose, or dehydration of an aldehyde hydrate, and in these reactions proton transfer to oxygen is concerted with carbon–oxygen bond heterolysis in either the forward or reverse step,[25] and there are considerable similarities between the transition states for these various reactions. In particular an acid and its conjugate base are included in the transition state, and electron release from oxygen is important.

Substituent effects show that there is very little carbonium ion character in the transition state, and we should not expect always to observe simple relations between rate and the electron-releasing power of substituents, as can be seen from comparison of the reactivities of the orthoformates, orthoacetates, and orthobenzoates in aqueous mineral acid. A methyl substituent (R = CH_3) at the reaction center should assist both proton transfer to oxygen (a) and alkyl–

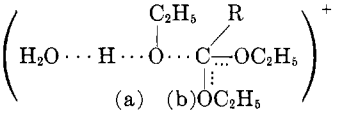


dehydration
(a similar mechanism can be written for mutarotation)



ortho ester hydrolysis

oxygen fission (b), but a phenyl group should inductively withdraw electrons, and so retard proton transfer (a), but should mesomerically donate electrons, and so assist bond breaking (b). It seems that these two



effects approximately cancel, because orthobenzoates are only slightly less reactive than orthoformates, but the strong inductive electron withdrawal of an ethoxy group, as evidenced by its large σ^*-value, more than offsets its mesomeric electron release, and orthocarbonates are relatively unreactive.

It seems that bond breaking plays a more important role in the general acid catalyzed component of hydrolysis as compared with the hydronium ion catalyzed component. For that part of the hydrolysis of 4-substituted methyl orthobenzoates which is catalyzed by chloroacetic acid a simple linear free-energy relation between rate and either σ- or σ^+-constants is not followed.[14] Relative to the hydronium ion the catalytic power of chloroacetic acid decreases sharply with decreasing electron release from the *para* substituent. This result is intelligible for an SE2 reaction at oxygen. The driving force for such a reaction comes from two main sources: (i) formation of a new O–H bond, and (ii) release of bond electrons from the existing C–O bond to form this new O–H bond. With a strong acid formation of the new O–H bond can occur without much breaking of the existing C–O bond, *i.e.*, the transition state will have little carbonium ion character, but with a weak acid C–O bond breaking will become much more important, and therefore hydrolysis of a *para*-substituted orthobenzoate should become more sensitive to general acids (relative to strong acids) as the *para* substituent favors C–O bond breaking by stabilizing the incipient carbonium ion. Except for methyl

(25) Ref. 1, Chapter 4; R. P. Bell and B. deB. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950); R. P. Bell and J. C. Clunie, *Proc Roy. Soc.* (London), **212A**, 33 (1952); ref. 10, p. 689.

p-nitroorthobenzoate the catalytic coefficient of chloroacetic acid correlates fairly well with σ, but with a small value of ρ.

Because O–H bond making and C–O bond breaking are both important, we should not expect to see clear and simple substituent effects, although inductively electron-releasing groups should always speed reaction by assisting both O–H bond making and C–O bond breaking.

The solvent deuterium isotope effect for the hydronium ion catalyzed reaction and the observation of general acid catalysis will depend upon the extent of H–O bond making in the transition state. If the proton is transferred completely to oxygen in the transition state the reaction will be faster in D_2O than in H_2O, whether or not there is a pre-equilibrium proton transfer, or concerted C–O bond breaking. Similarly the observation of general acid catalysis depends upon the extent of proton transfer. If the Brønsted exponent $\alpha \simeq 1$, the hydronium ion will be far and away the most effective catalyst, and we will not observe any general acid catalysis.[1] (One should consider general acid catalysis on an operational rather than a theoretical basis, *e.g.*, solvolysis of methyl orthobenzoate is catalyzed by chloroacetic acid in aqueous methanol,[14] whereas that of ethyl orthobenzoate is not catalyzed by acetic acid in aqueous dioxane,[5a] and in any event Eigen has recently shown how the experimental value of α can depend upon the pK values of the catalysts.[21]) The relative importance of bond making and bond breaking will depend upon the structure of the ortho ester, the nature of the catalyzing acid, and their environment.

The value of the entropy of activation is often used to distinguish between hydronium ion catalyzed A-1 and A-2 mechanisms,[26] but it is unlikely to be of much help in distinguishing between a conventional A-1 mechanism of hydrolysis of an ortho ester and one involving rate-limiting proton transfer to oxygen. In both reactions the proton is almost wholly transferred to the substrate, and in any event there is a broad spectrum of values of the entropy of activation which is regarded as characteristic of an A-1 mechanism. The values of the entropy of activation which are zero or positive for the hydronium ion catalyzed hydrolysis are therefore reasonable in terms of the proposed mechanism.

(26) L. L. Schaleger and F. A. Long in "Advances in Physical Organic Chemistry," Vol. 1, V. Gold, Ed., Academic Press, Inc., New York, N. Y., 1963, p. 1.

Fluorothiocarbonyl Compounds.[1] I. Preparation of Thio Ketones, Thioacyl Halides, and Thio Esters

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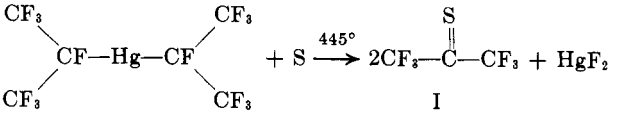
General methods for preparing fluoro thio ketones, fluorothioacyl halides, and fluoro thio esters are described. Reaction of perfluoro-*sec*-alkyl mercurials with sulfur leads to perfluoro thio ketones. For example, hexafluorothioacetone is obtained by passing bis(perfluoroisopropyl)mercury through the vapors of boiling sulfur. This thio ketone dimerizes spontaneously to tetrakis(trifluoromethyl)-1,3-dithietane. Pyrolysis of the dimer regenerates the fluoro thio ketone. Perfluoro thio ketones are also obtainable by reaction of perfluoro-*sec*-alkyl iodide with phosphorus pentasulfide at 550°. A third synthesis is photolytic reduction of a bis(perfluoro-*sec*-alkyl) disulfide to a mercaptan followed by dehydrofluorination with sodium fluoride. Perfluorothioacyl fluorides and chlorides, including trifluorothioacetyl fluoride and chloride, can be synthesized by similar methods. Certain members of this class can also be obtained from fluoro olefins and sulfur. The simplest fluoro thio acid fluoride, thiocarbonyl fluoride, is easily made by pyrolysis of the dithietane formed by fluorination of thiophosgene dimer. In addition, the preparation of fluoro thio esters by reaction of fluorothioacyl halides with thiols and a description of several special thio ester syntheses are given.

In earlier communications,[1] we have reported briefly on our investigation of the chemistry of perfluorothiocarbonyl compounds. In the course of this investigation, we have devised a number of approaches to the preparation of these compounds. Many of these approaches represent new synthetic methods that are generally applicable to the preparation of a large variety of fluorine-containing thiocarbonyl compounds, including thio ketones, thioacyl halides, and thio esters.

Fluoro Thio Ketones.—Hexafluorothioacetone has been prepared in 60% yield by the reaction of bis(perfluoroisopropyl)mercury[2] with refluxing sulfur vapor. The thio ketone is a deep blue compound boiling at 8°. It was identified by its mass spectrum, which showed a parent ion of m/e 182, and by its fluorine n.m.r. spectrum, which consisted of a single unsplit peak.



The reaction of perfluoromercurials with boiling sulfur appears to have wide applicability, and we have used it to prepare 4H-perfluorobutane-2-thione and 4-chloroperfluorobutane-2-thione from bis(4H-octafluoro-2-butyl)mercury and bis(4-chlorooctafluoro-2-butyl)mercury, respectively.

If bis(perfluoroisopropyl)mercury comes into contact with sulfur at lower temperatures, the reaction takes a different course. At 200°, a mixture of perfluoroisopropyl di- and polysulfides is formed. The disulfides

(1) Part of the work included in this series of papers was reported in a Communication to the Editor [W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Am. Chem. Soc.*, **83**, 2589 (1961)] and later at the 140th Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) P. E. Aldrich, E. G. Howard, W. J. Linn, W. J. Middleton, and W. H. Sharkey, *J. Org. Chem.*, **28**, 184 (1963).