oxide solutions used were prepared by dissolving sodium metal (thoroughly washed with anhydrous ethanol) in an appropriate volume of ethanol. Aliquots were removed, diluted 1:3 with water, and titrated with standardized HCl using bromothymol blue as indicator.

Determination of Phenol.—When the reactions of triesters Ia and Id had reached completion, 2–3-ml. aliquots containing 0.2–0.4 μmole of products were evaporated to dryness. The residue was dissolved in water and free phenol was estimated colorimetrically at 650 mμ by the Folin–Ciocalteu[32] method using a standard curve for phenol.

Kinetics in Potassium *t*-Butoxide.—*t*-Butyl alcohol (Eastman) was purified by refluxing overnight over exsiccated barium oxide and distilling twice from sodium through a 30-cm. Vigreux column. Repeated distillation did not completely free the *t*-butyl alcohol of an impurity absorbing between 240 and 260 mμ.

Potassium *t*-butoxide was prepared by dissolving potassium metal (prewashed with anhydrous *t*-butyl alcohol) in the purified *t*-butyl alcohol and was titrated as described for the ethoxide solutions. The Beckman Model DU spectrophotometer used for the kinetic measurements was converted to a linear direct reading instrument by a Gilford Model 220 optical density converter. The absorbances were recorded continuously by means of a Honeywell Brown electronic recorder. The reaction mixture was kept at 28° using Beckman thermospacers maintained at constant temperature by means of a circulating bath. The temperature of the reaction solutions in the cuvette was checked occasionally with a microprobe connected to a Thermistor thermometer. Solutions ($1–2 \times 10^{-4}$ *M*) of compounds Ia–Id and IIIa in anhydrous *t*-butyl alcohol were equilibrated in a 28° constant temperature bath. For each kinetic run, the solution of the compound was transferred into a 4-ml. Beckman cell using a 3-ml. volumetric pipet calibrated for *t*-butyl alcohol. The appropriate amount of potassium *t*-butoxide (5–1000 μl.) was added rapidly using a Carlsberg pipet followed by immediate manual mixing with a glass–stainless steel Hershberg-type microstirrer. The cell was stoppered and the increase in absorbance at 310 mμ or the decrease in absorbance at 340 mμ was recorded. The instrument was nulled against the appropriate *t*-butoxide solution. At the end of the reaction, a sample was removed by means of a 2-ml. calibrated pipet. These samples, after addition of 4 ml. of water, were titrated with standard 0.1 *N* HCl to the yellow color of bromothymol blue using an Agla microburet. The *t*-butoxide concentrations ($2–50 \times 10^{-3} M$) determined by titration were in close agreement with the expected values calculated from the dilution of the *t*-butoxide stock solution. Concentrations of *t*-butoxide lower than 2×10^{-3} *M* were calculated from the appropriate dilution factor. Pseudo-first-order rate constants were calculated either from the integrated first-order rate equation or by the Guggenheim method.[33] In the latter case, Δt was chosen to be over 2.5 half-lives. The wave length selected (310 or 340 mμ) was the one where the value ($D_f - D_i$) was the larger.

Solvolysis of Ethyl Diphenyl Phosphate.—The procedure described above for the kinetics of cyclization in sodium ethoxide was employed here. Appearance of phenoxide ion was followed by measuring the increase in absorbance at 290 mμ. The pseudo-first-order rate constant k_6 was estimated by plotting the rate data obtained in the initial portion of the reaction (*ca.* 0–20% completion) according to the integrated first-order rate equation. The rate constant k_7 was similarly estimated by using the data obtained at 60–100% completion of reaction (at which time release of the first mole of phenol was more than 99% complete). The results of these experiments are summarized in Table VII.

TABLE VII

SOLVOLYSIS OF ETHYL DIPHENYL PHOSPHATE[a]

$[NaOC_2H_5]$, *M*[b]	$k_6 \times 10^2$, min.$^{-1}$	$k_7 \times 10^2$, min.$^{-1}$
0.180	12.90	0.90
.075	5.25	.37
.030	2.08	.14
.015	1.03	.06
.0075	0.50	

[a] In ethanol at 30°; ethyl diphenyl phosphate at 2.5×10^{-4} *M*. [b] All reaction mixtures made up to 0.36 ionic strength with $LiClO_4$.

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Acid-Catalyzed Hydrolysis of Carboxylic Acid Orthoesters

BY ROBERT H. DEWOLFE AND JAMES L. JENSEN[1]

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Several empirical mechanistic criteria indicate that hydrogen ion-catalyzed aliphatic orthoester hydrolysis occurs by a unimolecular (A-1) mechanism, involving formation of resonance-stabilized carboxonium ion intermediates. In view of this, it is suprising that the influence of acyl substituents on the reactivity of orthoesters toward hydrogen ion-catalyzed hydrolysis depends almost entirely on their inductive effects. Substituents, such as phenyl and ethoxy, which should increase the stability of the carboxonium ion intermediate actually decrease the reactivity of the orthoester. This fact, together with a recent suggestion that methyl orthobenzoates hydrolyze by a bimolecular (A-2) mechanism, prompted a study of the energies and entropies of activation for hydrogen ion-catalyzed hydrolysis of ethyl orthoformate, ethyl orthoacetate, and ethyl orthobenzoate in aqueous dioxane acetate buffers. These data, as well as the deuterium solvent isotope effect on ethyl orthobenzoate hydrolysis, support the A-1 mechanism for hydrolysis of all three of these orthoesters. The apparently anomalous substituent effects are rationalized by assuming that, owing to the greater stability of carboxonium ions than carbonium ions, the acyl carbon atom is so far from attaining a trigonal configuration in the transition state that resonance stabilization of the transition state by acyl substituents is not a significant factor in determining reactivity. The data on general acid-catalyzed orthoester hydrolysis are consistent with a mechanism involving rate-determining dissociation of a hydrogen-bonded complex of the ester and acetic acid into a carboxonium ion, ethanol, and acetate ion.

Kinetic studies of the hydrolysis of aliphatic orthoesters played an important role in the development of modern theories of acid catalysis. The first examples of general acid catalysis to be discovered were hydrolysis reactions of ethyl orthoacetate, ethyl orthopropionate, and ethyl orthocarbonate.[2]

The most extensively studied orthoester hydrolysis reaction is that of triethyl orthoformate

$$HC(OC_2H_5)_3 + H_2O \longrightarrow HCO_2C_2H_5 + 2C_2H_5OH \quad (1)$$

This reaction is specific acid-catalyzed in aqueous buffer solutions.[3–9] The hydrogen ion catalytic coefficient for ethyl orthoformate hydrolysis is more than twice as large in deuterium oxide buffer solutions than in protium oxide buffers,[6–9] and the hydrogen ion-catalyzed reaction has a small positive entropy of activa-

(1) Abstracted in part from the M.A. Thesis of James L. Jensen.

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

(3) A. Skrabal and O. Ringer, *Monatsh.*, **42**, 9 (1921).

(4) A. Skrabal, *Z. Elektrochem.*, **33**, 322 (1927).

(5) H. S. Harned and N. T. Samaras, *J. Am. Chem. Soc.*, **54**, 1 (1932).

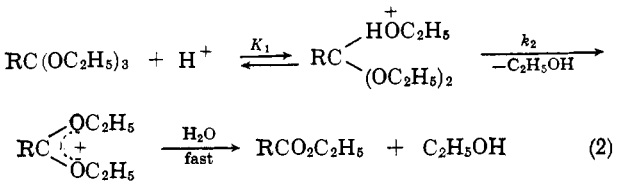
(6) J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.*, 1360 (1936).

(7) F. Brescia and V. K. La Mer, *Ann. N. Y. Acad. Sci.*, **39**, 395 (1940).

(8) F. Brescia and V. K. La Mer, *J. Am. Chem. Soc.*, **62**, 612 (1940).

(9) F. Brescia and V. K. La Mer, *ibid.*, **60**, 1962 (1938).

tion and a small positive volume of activation.[10] All of these observations are consistent with an A-1[11] mechanism involving rate-determining dissociation of the protonated orthoester into ethanol and a reactive carboxonium ion intermediate (eq. 2, R = H). The



fact that ethyl orthoformate hydrolysis is general acid-catalyzed in aqueous dioxane acetate buffers (in which the hydronium ion concentration is much less than that of aqueous buffers) indicates that the reaction in aqueous solution is general acid-catalyzed, but has a Brönsted catalysis law α-value too close to unity for general catalysis to be detectable.[12,13]

The hydrolysis of ethyl orthoacetate has not been so thoroughly studied. Brönsted and Wynne-Jones[2] demonstrated that the reaction is general acid-catalyzed. The data of Kilpatrick and Kilpatrick[14] show that the hydrogen ion-catalyzed reaction has a positive entropy of activation, which suggests but does not require an A-1 mechanism for this portion of the reaction.[15]

The rate-determining step in the A-1 mechanism of hydrogen ion-catalyzed orthoester hydrolysis presumably involves formation of a resonance-stabilized carboxonium ion. In uncatalyzed unimolecular solvolysis (SN1) reactions, substituents which stabilize the intermediate carbonium ion almost invariably increase the reactivity of the substrate. That this is not always the case in orthoester solvolyses was suggested to us by Brönsted's observation[2] that ethyl orthocarbonate is less reactive than ethyl orthoformate, even though it forms a more stable carboxonium ion,[16] and by data which indicated that methyl orthobenzoate is also less reactive than ethyl orthoformate.[17] In addition, hydrolysis of methyl orthobenzoates in 70% methanol correlates very well with Hammett's σ-substituent constants, but not with Brown's σ^+-constants,[17-19] which suggests that resonance stabilization of the transition state by interaction with acyl substituents is an insignificant factor in determining orthoester reactivity. On the basis of this and other evidence, Kwart and Price suggested that orthobenzoates hydrolyze by an A-2 mechanism.[17]

The unimolecular mechanism for ethyl orthoformate hydrolysis receives support from three independent criteria of mechanism, as well as from theoretical considerations. That ethyl orthoacetate hydrolyzes by the same mechanism is suggested by its fortyfold greater reactivity than ethyl orthoformate and by the expectation that it should form a more stable carboxonium ion than ethyl orthoformate. The lower reactivity of ethyl orthocarbonate and methyl orthobenzoate than ethyl orthoformate is surprising, since both of these esters should form more stable carboxonium ions than ethyl orthoformate, and the A-2 mechanism suggested by Kwart and Price for orthobenzoate hydrolysis is clearly contrary to theoretical predictions based on aliphatic orthoester hydrolysis In an effort to resolve these apparent discrepancies, we have measured the entropies and energies of activation for acid-catalyzed hydrolysis of ethyl orthoformate, ethyl orthoacetate, and ethyl orthobenzoate in solvents of differing polarity. These quantities, and the deuterium oxide solvent isotope effect on ethyl orthobenzoate hydrolysis, provide additional support for the A-1 mechanism of aliphatic orthoester hydrolysis and strongly indicate that orthobenzoate hydrolysis occurs by the same mechanism. We have also examined the mechanism of general acid-catalyzed orthoester hydrolysis in more detail than has been done previously.

Experimental

Materials.—Triethyl orthoformate and triethyl orthoacetate were obtained from Kay–Fries Chemical Co. Triethyl orthobenzoate was prepared by the procedure of McElvain[20]; b.p. 132–133° at 20 mm. *p*-Dioxane from Matheson Coleman and Bell was redistilled from sodium immediately before use. Reagent grade chemicals were used in preparing the buffer solutions. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories.

Buffer Solutions.—Acetic acid–sodium acetate buffer solutions of constant ionic strength were prepared from standardized solutions of acetic acid, sodium hydroxide, and sodium chloride. Reaction solutions were usually prepared by pipetting 5 ml. of the stock buffer solution and the desired quantity of dioxane into a 25-ml. volumetric flask and filling the flask to the calibration mark with distilled water. For the hydrolysis runs in deuterium oxide, a stock buffer was prepared from 5 ml. of glacial acetic acid, 4 g. of 40% sodium hydroxide solution, and 5 ml. of water. The reaction solutions were prepared by adding 25 λ of stock buffer to 5.00 ml. of H_2O or D_2O. The resulting aqueous buffer had a pH of 5.02. The deuterium oxide buffer contained about 99.5% D_2O.

Kinetic Measurements.—The hydrolysis reactions are experimentally first order. The reactions were followed spectrophotometrically, using a Cary Model 14 recording spectrophotometer equipped with a thermostated cell holder. The wave lengths used were 220 mμ for ethyl orthoacetate and ethyl orthoformate and 231 mμ for ethyl orthobenzoate. In the case of the aliphatic orthoesters, a run was started by allowing 3 ml. of the buffer solution in a silica absorption cell to reach thermal equilibrium with the spectrophotometer, then adding 10 λ of orthoester to the cell, shaking the cell vigorously, and replacing the cell in the holder. After thermal equilibrium had been reestablished, optical absorbance was recorded as a function of time. A similar procedure was used with ethyl orthobenzoate, except that 4 λ of a dilute solution of the ester in dioxane was added to the buffer solution.

Calculations.—First-order rate constants were calculated graphically from plots of $\log (A_\infty - A_t)$ *vs.* t, or by the Guggenheim method.[21] All rate constants are expressed in reciprocal seconds and natural logarithms. All rate constants listed in the tables of data are averages of two or more runs, with agreement between runs usually being within 3% or better. Energies of activation were calculated by the least squares method from the rate constants, using the Arrhenius equation. Entropies of activation were calculated for 25° from the relationship: $\Delta S^\ddagger = 2.303\,R\,(\log A - RT/Nh)$, where A is the pre-exponential term of the Arrhenius equation.[22] Catalytic coefficients of hydrogen ion and acetic acid were evaluated by the procedure of Brönsted and Wynne-Jones,[2] using ionization constants for aqueous dioxane solutions of acetic acid interpolated from the data of Harned and Owen.[23] Owing to lack of the necessary data, ionization constants were not corrected for ionic strength effects. The catalytic coefficient of deuterium ion for ethyl orthobenzoate hydrolysis was calculated on the assumption that the ionization constant of protoacetic acid is 3.33 times that of deuterioacetic acid at 25°.[8] The rate of hydrolysis of ethyl orthobenzoate in the H_2O buffer (see above) was 6.22×10^{-3} sec.$^{-1}$ and the rate of hydrolysis in the D_2O buffer was 4.33×10^{-3} sec.$^{-1}$.

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Errors are estimated for quantities calculated from slopes of lines (E_a, k_{HOAc}) and from intercepts of lines (k_{H^+}, $\Delta S^{\pm}$) as: Errors in slopes are quoted as $\pm 2\sigma(x_2 - x_1)$, while errors in intercepts are estimated by $\pm\sigma(x_2 + x_1)/(x_2 - x_1)$, where σ is the standard deviation of points from the regression line and x_1 and x_2 are the extreme experimental values of the quantities plotted on the x-axis. The number of points in each case was too small for these deviations to have any statistical significance, but they do indicate the precision with which the experimental points fit the least squares lines.

Results and Discussion

Experimental rate constants for the hydrolysis of ethyl orthoformate and ethyl orthoacetate in aqueous dioxane acetate buffers are recorded in Table I. Similar data for hydrolysis of ethyl orthobenzoate are collected in Table II. Catalytic coefficients of hydrogen ion and acetic acid for these orthoester hydrolyses, calculated from the rate constants, are given in Table III. In Table IV are the Arrhenius activation energies and the entropies of activation for the hydrogen ion and the acetic acid-catalyzed portions of each reaction, calculated from the catalytic coefficients.

Hydrogen Ion-Catalyzed Orthoester Hydrolysis.—The entropies of activation for hydrogen ion-catalyzed hydrolysis of ethyl orthoformate in aqueous dioxane are positive This fact lends further support to the conclusion, reached on the basis of several kinds of experimental evidence,[6-10] that this reaction proceeds by an A-1 mechanism. The facts that hydrogen ion-catalyzed hydrolysis of ethyl orthoacetate also has a positive entropy of activation, and that this ester is 35–50 times more reactive than ethyl orthoformate, provide strong support for an A-1 mechanism for this reaction also. The simplest mechanism consistent with the facts is that outlined in eq. 2 (R = CH_3) The increase in the hydrogen ion catalytic coefficient with increasing dioxane concentration for both of these reactions is in accord with a mechanism in which charge is dispersed in forming the transition state of the rate-determining step. This would be predicted by either the A-1 or the A-2 mechanism, however.

The apparently clear-cut case for a unimolecular mechanism of orthoester hydrolysis is clouded by the data of Kwart and Price[17] on acid-catalyzed hydrolysis of substituted methyl orthobenzoates, which they interpreted as providing support for a bimolecular mechanism for these reactions. Kwart applied his empirical solvent composition criterion[24] to the hydrochloric acid-catalyzed hydrolysis of methyl ortho-*p*-nitrobenzoate in aqueous methanol and concluded that the curvature of the resulting graph ruled out the A-1 mechanism and hence supported the A-2 mechanism. The criterion used is based on two assumptions: first, that the change in extent of protonation of the orthoester with changing solvent composition parallels

(24) (a) H. Kwart and I. B. Weisfeld, *J. Am. Chem. Soc.*, **80**, 4670 (1958); (b) H. Kwart and A. Goodman, *ibid.*, **82**, 1947 (1960).

TABLE I

HYDROLYSIS OF ALIPHATIC ORTHOESTERS IN AQUEOUS DIOXANE ACETATE BUFFERS

Dioxane,[a] %	T, °C.	$10^4 k_1$, sec.$^{-1}$, R = 0.50[b] 10^2(HA) = 0.819	1.67	2.46	R = 1.00 10^2(HA) = 0.819	1.67	2.46
Ethyl orthoformate							
0	10.0	30.0	30.7	31.2	60.3	60.5	64.1
0	30.0	..	188	188	...	360	...
0	40.0	..	394	...	...	761	...
20.5	10.0	11.5	11.0	10.7	22.1	21.5	21.1
20.5	30.0	59.9	61.8	63.5	11.3	12.8	11.8
20.5	40.0	..	131	...	...	25.2	...
40.5	10.0	..	2.01	...	...	4.06	...
40.5	30.0	12.0	12.1	12.3	...	23.3	23.4
40.5	40.0	..	26.7	...	...	...	50.1
60.4	30.0	1.03	1.16	1.36	1.73	1.91	2.03
60.4	40.0	2.14	2.49	2.72	4.19	4.44	4.73
60.4	50.0	4.61	5.16	5.63	8.40	9.06	9.63
Ethyl orthoacetate							
20.5	10.0	..	582	...	...	...	...
20.5	20.0	..	735	...	...	...	...
20.5	30.0	..	...	...	...	...	...
40.5	10.0	..	103	...	...	209	...
40.5	20.0	..	240	...	...	459	...
40.5	30.0	..	457	...	...	944	...
60.4	10.0	8.31	10.0	11.5	15.9	17.4	19.3
60.4	30.0	40.6	49.5	58.3	74.5	81.3	91.2
60.4	40.0	81.4	98.8	116	145	161	176
80.2	10.0	0.399	0.683	0.890	0.587	0.863	1.04
80.2	40.0	5.29	8.30	11.2	7.10	10.2	13.4
80.2	50.0	10.8	16.4	23.3	15.3	21.0	27.8

[a] Weight per cent. [b] $R = (HOAc)/(OAc^-)$.

TABLE II

HYDROLYSIS OF ETHYL ORTHOBENZOATE IN AQUEOUS DIOXANE ACETATE BUFFERS

T, °C.	(HOAc)	$10^3 k_1$, sec.$^{-1}$
20.5% dioxane,[a] $R = 0.5$,[b] $\mu = 0.048$		
39.8	0.0240	4.47
39.8	.0080	4.62
30.0	.0080	2.22
20.0	.0080	1.04
Water, $R = 0.5$, $\mu = 0.024$		
40.0	0.0040	13.6
30.0	.0040	6.80
20.0	.0040	2.95

[a] Weight per cent. [b] $R = (HOAc)/(OAc^-)$.

TABLE III

CATALYTIC COEFFICIENTS OF HYDROGEN ION AND ACETIC ACID FOR ORTHOESTER HYDROLYSIS IN AQUEOUS DIOXANE

Dioxane, %	T, °C.	$10^{-3}k_{H^+}$	$10^3 k_{HOAc}$
Ethyl orthoformate			
0	10.0	0.346	..
0	30.0	2.03	..
0	40.0	4.30	..
20.5	10.0	0.480	..
20.5	30.0	2.67	..
20.5	40.0	5.60	..
40.5	10.0	0.541	..
40.5	30.0	3.12	..
40.5	40.0	6.68	..
60.4	30.0	6.3	1.93
60.4	40.0	15.7	3.54
60.4	50.0	31.3	6.88
Ethyl orthoacetate			
40.5	10.0	27.8	..
40.5	20.0	61.2	..
40.5	30.0	126	..
60.4	10.0	56.5	20.1
60.4	30.0	263	105
60.4	40.0	519	201
80.2	10.0	1140	2.89
80.2	40.0	16400	37.3
80.2	50.0	37400	76.4
Ethyl orthobenzoate			
0	20.0	0.336	..
0	30.0	0.779	..
0	40.0	1.60	..
20.5	21.1	0.46	..
20.5	30.0	0.99	..
20.5	39.8	2.10	..

TABLE IV

ENERGIES AND ENTROPIES OF ACTIVATION FOR ACID-CATALYZED ORTHOESTER HYDROLYSIS IN AQUEOUS DIOXANE

Dioxane, %	R in $RC(OC_2H_5)_3$	E_a	$\Delta S^{\pm}$
Specific H^+-ion catalysis			
0	H	14.8 ± 0.1	3.4 ± 0.7
20.5	H	14.4 ± .2	2.9 ± .6
40.5	H	14.8 ± .2	4.1 ± .5
60.4	H	15.5 ± .1	8 ± 5
40.5	CH_3	12.9 ± .2	5.5 ± 0.6
60.4	CH_3	13.0 ± .1	7.1 ± .2
80.2	CH_3	15.7 ± .2	23 ± .5
0	C_6H_5	14.3 ± .4	−0.3 ± 1.2
20.5	C_6H_5	14.6 ± .3	1.4 ± 1.1
Catalysis by HOAc			
60.4	H	11.4 ± 1.4	−35 ± 4
60.4	CH_3	13.5 ± .5	−20 ± 1.5
80.2	CH_3	14.9 ± .2	−19 ± 0.5

the change in extent of protonation of an indicator base, and, second, that the rate of hydrolysis by the A-1 mechanism depends on the concentration of the protonated ester, but not on the composition of the solvent. The first of these assumptions is reasonable though approximate. The second, however, is certainly erroneous in the present case. Regardless of the mechanism, the rate of solvolysis of a methyl ester in aqueous methanol is not determined by the concentration of protonated ester alone, since reaction with methanol regenerates starting material, while reaction with water yields hydrolysis products. The departure of observed rate from proportionality to concentration of orthoester conjugate acid may be due entirely to competition between methanol and water in the product-forming step. This competition should be quite serious at high methanol concentrations (the reaction was studied in 20–97.5% methanol). The solvent effect data therefore do not exclude an A-1 mechanism for this reaction.

Another of Kwart's observations, however, also seems to support an A-2 mechanism for orthobenzoate hydrolysis. Hydrogen ion-catalyzed methyl orthobenzoate hydrolysis gives an excellent linear Hammett $\rho\sigma$ plot[18] ($\rho = -2.02$ in 70% methanol), although most solvolyses proceeding through intermediates having positively charged carbon attached to the aromatic ring show departures from linearity in log k *vs.* σ plots, but give nearly linear plots of log k *vs.* σ^+.[19]

In order to obtain additional data pertinent to the mechanism of orthobenzoate hydrolysis, ethyl orthobenzoate was hydrolyzed in aqueous and aqueous 20% dioxane–acetate buffers and in a deuterium oxide–acetate buffer. The entropy of activation for hydrogen-ion catalyzed hydrolysis is approximately zero in water and has a small positive value in 20% dioxane. The ratio of catalytic coefficients for D^+ and H^+ (k_{D^+}/k_{H^+}) is 2.3 at 25°.

The entropy of activation for ethyl orthobenzoate hydrolysis is in the borderline between the ranges of values empirically correlated with the A-2 and the A-1 mechanisms. As Whalley has pointed out,[15] the experimental entropy of activation for an acid-catalyzed solvolysis is a composite quantity which includes the entropy change associated with the pre-equilibrium protonation of the substrate. This fact renders difficult the interpretation of entropies of activation, and values near zero suggest an A-1 mechanism but do not exclude an A-2 mechanism.

The solvent isotope effect clearly supports an A-1 mechanism for ethyl orthobenzoate hydrolysis. A value of 2.3 for k_{D^+}/k_{H^+} is well in the range of values correlated empirically with the A-1 mechanism and is also in the range of values predicted for this mechanism from theoretical considerations.[25] For comparison, Brescia and La Mer[8] reported that k_{D^+}/k_{H^+} for ethyl orthoformate hydrolysis has a value of 2.7 at 15° and 2.3 at 35°.

The entropy of activation is not incompatible with an A-1 mechanism for ethyl orthobenzoate hydrolysis, and the solvent isotope effect provides support for this mechanism. Two observations appear to be inconsistent with the unimolecular mechanism, however. Ethyl orthobenzoate is less reactive even than ethyl orthoformate (see Table V), and there appears to be no rate-accelerating resonance interaction between electron-donating substituents such as *p*-methoxy and the carboxonium carbon atom in the transition state for formation of the reactive intermediate assumed to be involved in the A-1 mechanism. We believe that these two observations are consistent with the A-1 mechanism and that the explanation of them resides in the stability of carboxonium ions.

(25) C. A. Bunton and V. J. Shiner, *J. Am. Chem. Soc.*, **83**, 3211 (1961).

TABLE V

RELATIVE REACTIVITIES OF ORTHOESTERS

R in R-C(OC$_2$H$_5$)$_3$	k_{H^+} (20°)	$k_{H^+}^R/k_{H^+}^H$
H[a]	5.38×10^2	1.00
CH_3[a]	2.07×10^4	38.5
C_2H_5[a]	1.31×10^4	24.3
C_6H_5	3.36×10^2	0.62
C_2H_5O[a]	9.02×10^1	0.17

[a] Data from reference 1.

The effect of structure on reactivity in orthoester hydrolysis is anomalous only by comparison to structural effects on rates of SN1 solvolyses. In SN1 solvolyses, substituents which stabilize carbonium ions powerfully accelerate the reaction. The intermediate carbonium ion plus the leaving group is several kilocalories less stable than the substrate. Because of this, the transition state of an SN1 reaction will resemble the carbonium ion more closely than it resembles the substrate.[26] That is, the substituted carbon atom is nearly trigonal in the transition state, which makes possible resonance interactions with substituents; such interactions stabilize the transition state and hence lower the activation energy of the reaction.

The situation in acid-catalyzed orthoester solvolysis differs from that in typical SN1 solvolyses in two important ways. First, substituents influence not only the rate-determining step, but also the equilibrium concentration of the conjugate acid of the ester. Second, there is much less difference in free energy between the conjugate acid of an orthoester and the resonance-stabilized carboxonium ion plus alcohol formed in the rate-determining step than there is between, say, an alkyl halide and the carbonium ion and halide ion formed from it by heterolysis. It is even conceivable that the carboxonium ion plus ethanol are lower in energy than the ester conjugate acid, since the bond broken here is a weak one, and considerable stability is gained owing to resonance in the ion. In any event, the transition state for heterolysis of the orthoester conjugate acid will look more like the substrate and less like the intermediate ion than is the case in SN1 solvolyses. The effects of substituents on reactivity indicate that the orthoester carbon atom in the transition state is so far from a trigonal configuration that there is little or no resonance interaction between it and the rest of the molecule.

Carboxonium ions are isoelectronic with carboxylate ions, in which the carboxyl group apparently has little tendency to enter into direct conjugation with aromatic systems

I

It is possible that carboxonium ions also are not significantly stabilized by resonance with aromatic systems

II

Lack of data on the relative stabilities of substituted carboxonium ions makes it impossible to state whether benzoxonium ions are more stable relative to orthobenzoates than aliphatic carboxonium ions are relative to aliphatic orthoesters. However, canonical struc-

(26) G. S. Hammond, *ibid.*, **77**, 335 (1955).

tures such as II are much more reasonable than structures such as I, in which there is both separation of opposite charge and concentration of like charge on neighboring atoms. Indirect evidence for resonance interaction between the acyl carbon atom and the aromatic ring in benzoxonium ions is afforded by the observation of Stewart and Yates that the pK_a's of protonated benzoic acids correlate better with σ^+ than with σ.[27] This was interpreted as evidence for the carboxonium structure

for the conjugate acids.

It appears that the influence of acyl substituents on the rate of orthoester hydrolysis is due predominantly or entirely to their inductive effects and that the observed reactivities are not markedly influenced by the stabilities of the postulated carboxonium ion intermediates. This is demonstrated by the data of Table V, which show that ethyl orthobenzoate and ethyl orthocarbonate are both less reactive than ethyl orthoformate. Ethyl orthobenzoate is expected to form a more stable carboxonium ion than ethyl orthoformate on theoretical grounds, and ethyl orthocarbonate has been shown to do so experimentally.[16]

The data in Table V show that the influence of acyl substituents on the rate of hydrogen-ion catalyzed hydrolysis of orthoesters closely parallels their inductive effects. If the mechanism outlined in eq. 2 is correct, and if the rate-determining step involves a transition state in which there is little or no resonance interaction between the acyl carbon atom and the substituent R, the relative reactivities are easily rationalized. Electron-releasing substituents, by increasing the value of K_1 and by facilitating the dissociation of the conjugate acid into a carboxonium ion and ethanol, should increase the observed reaction rate. The converse would be true of electron-attracting substituents.

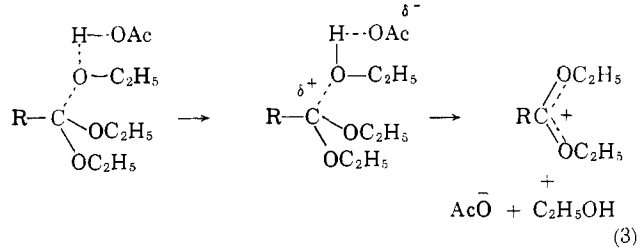
General Acid-Catalyzed Orthoester Hydrolysis.—In the case of aliphatic orthoester hydrolysis, two of the three possible mechanisms of general acid catalysis can be ruled out with considerable confidence. The first of these, rate-determining proton transfer from a non-hydrogen bonded acid catalyst molecule to the substrate, conflicts with a widely accepted principle of solution kinetics which holds that proton transfer from an acid to oxygen is too rapid to be rate determining in an acid-catalyzed reaction,[28] unless the transfer is to an intermediate present in extremely low concentration.[29]

A mechanism involving bimolecular nucleophilic attack by acetate ion on the conjugate acid of the orthoester seems equally unlikely, in view of the fact that ethyl orthoacetate is about 55 times more reactive toward acetic acid-catalyzed hydrolysis than is ethyl orthoformate in aqueous 60% dioxane. While the acetate methyl group should render the orthoacetate somewhat more basic than ethyl orthoformate, so that its conjugate acid would be present in higher concentration, the methyl group should also exert considerable steric hindrance to nucleophilic attack on the acyl carbon. The retarding effect of methyl substitution on SN2 reactions is well known, and acetate esters are much less reactive than formate esters toward A-2 hydrolysis.[30]

(27) R. Stewart and K. Yates, *J. Am. Chem. Soc.*, **82**, 4059 (1960).
(28) R. P. Bell and B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).
(29) A. R. Butler and V. Gold, *J. Chem. Soc.*, 2305 (1961).
(30) R. P. Bell, A. L. Dowding, and J. A. Noble, *ibid.*, 3106 (1955).

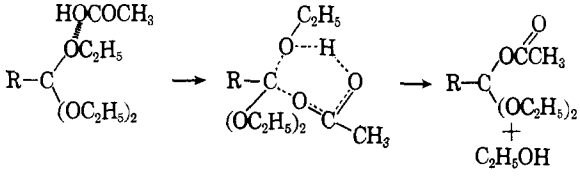
It seems likely that the steric effect of the orthoacetate methyl group would outweigh its electronic effect in orthoester hydrolysis also, if the reaction occurred by a bimolecular mechanism. It is also significant that the difference in reactivity between ethyl orthoacetate and ethyl orthoformate for hydrogen ion-catalyzed hydrolysis, for which several lines of evidence exclude a bimolecular mechanism, is similar to that for acetic acid-catalyzed hydrolysis.

If rate-determining proton transfer and rate-determining nucleophilic attack on orthoester conjugate acid are excluded as mechanisms of general acid-catalyzed hydrolysis, only one mechanism remains for serious consideration. This is rate-determining conversion of a hydrogen-bonded complex of the ester and the acid to reaction products. The rate-determining step could conceivably involve dissociation of the complex into acetate ion, ethanol, and a carboxonium ion



(3)

Or, as suggested by Kwart,[17] it might involve a cyclic transition state which, in the extreme case, would lead to a reactive diethoxyacetyl intermediate



(4)

Either of these mechanisms would account for the observed negative entropies of activation for general acid-catalyzed orthoester hydrolysis. The transition state in the dissociation mechanism has several atoms with partial charges and hence should be more strongly solvated than the hydrogen-bonded complex, while the transition state for the cyclic mechanism is a much more rigid system than the complex.

Two observations suggest that the formation of the transition state for general acid-catalyzed hydrolysis involves substantial charge separation. The first of these is the fact that the catalytic coefficient of the weak acid decreases with increasing dioxane content of the solvent (Table III and ref. 12), as would be expected if charge separation occurs in forming the transition state from the complex. Second, the entropy of activation for acetic acid-catalyzed hydrolysis of ethyl orthoformate is more than 10 e.u. more negative than that for ethyl orthoacetate hydrolysis. The acetate methyl group should hinder solvation of the partially charged acyl carbon of the orthoacetate, and it is also possible that the partial positive charge on the acyl carbon of the orthoformate transition state causes an increase in hydrogen bonding of solvent molecules to the acyl hydrogen atom. Both of these factors would tend to make the entropy of activation of the orthoformate more negative than that of the orthoacetate. These observations are more consistent with the dissociation mechanism than with a cyclic concerted mechanism.