[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Ortho Esters, Imidic Esters and Amidines. V. General Acid Catalyzed Hydrolysis of Ethyl Orthoformate[1]

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Hydrolysis of ethyl orthoformate, a reaction hitherto believed to be catalyzed specifically by oxonium ion, is found to be catalyzed by general acids in aqueous dioxane–acetic acid buffer solutions. It is suggested that for this reaction general acid catalyzed hydrolysis is unobservable in aqueous buffer solutions because of the much higher oxonium ion concentration of such solutions. The theoretical implications of these results are discussed briefly.

The hydrolysis of ethyl orthoformate

$$HC(OC_2H_5)_3 + H_2O = HCOOC_2H_5 + 2C_2H_5OH$$

has been studied by a number of investigators,[3–9] all of whom reported that the reaction is specific acid catalyzed. The observed specific oxonium ion catalysis might be due either to the reaction involving a mobile and reversible proton transfer followed by a rate-determining non-protolytic reaction, or a rate-determining proton transfer with the catalytic constant for oxonium ion so large that catalysis by other acids is not detectable.[10] In the latter case, ethyl orthoformate hydrolysis would properly be considered to be general acid catalyzed.

Attempts to decide between the two possible reaction mechanisms from kinetic data determined in deuterium oxide solutions have not been notably successful.[6–8] It was found that the specific rate is greater in heavy water than in ordinary water. This indicated that a true specific oxonium ion catalyzed reaction is involved, since on the basis of theoretical considerations a general acid catalyzed reaction should be slower in heavy water than in light.[11] Doubt was shed on this criterion of mechanism when it was found that in the case of ethyl orthocarbonate hydrolysis, a reaction which is known to be general acid catalyzed,[5] the catalytic coefficient for oxonium ion is increased, although that for acetic acid is decreased, by changing from H_2O to D_2O.[12] It is reasonable to expect ethyl orthoformate hydrolysis to be general acid catalyzed, since the hydrolysis reactions of ethyl orthoacetate, ethyl orthopropionate and ethyl orthocarbonate are known to be general acid catalyzed.[5] One would not expect the reaction of the closely related ethyl orthoformate to be fundamentally different. If the reaction is general acid catalyzed, available experimental evidence indicates that oxonium ion is tremendously more effective as a catalyst than weak acids. The experimental problem, then, was to devise a method of reducing oxonium ion catalysis without proportionately reducing catalysis by weak acids.

Swain[13] has recently suggested that reactions classified as examples of specific oxonium ion catalysis may be made to exhibit general acid catalysis simply by using higher buffer concentrations, and demonstrated that this can be done for the reaction of epichlorohydrin with iodide ion. This procedure involves using inordinately high concentrations of weak acids and electrolytes in the buffer solutions, which considerably complicates the task of interpreting the experimental results. It is doubtful that this method could be applied to a reaction as sensitive to oxonium ion catalysis as is ethyl orthoformate hydrolysis, for which a low buffer ratio ($[HA]/[A^-]$) would be desired in order to minimize this catalysis. Another approach to the detection of general acid catalysis would be to carry out the reaction in aqueous dioxane solutions. The ionization constants of carboxylic acids are smaller in such solutions than in pure water. By using aqueous dioxane buffer solutions it would be possible to lower the oxonium ion concentration without affecting the concentration of the buffer acid. For example, the oxonium ion concentration of an aqueous dioxane–acetic acid buffer solution containing 70% dioxane is less than 1/1000 that of an aqueous buffer of the same buffer ratio. If the catalytic coefficient of acetic acid toward ethyl orthoformate hydrolysis were not decreased to the same extent as its ionization constant by increasing the dioxane concentration of the reaction solution, it should be possible to reduce the rate of the oxonium ion catalyzed reaction enough to allow catalysis by molecular acetic acid to be observed. In the present work the rate of hydrolysis of ethyl orthoformate was measured in aqueous dioxane–acetic acid buffer solutions containing 50, 58 and 70% dioxane by weight at 35°.

Experimental

The dioxane used was purified by the procedure of Fieser.[14] Reagent grades of acetic acid, anhydrous sodium acetate, and sodium chloride were used. The ethyl orthoformate was redistilled shortly before use, b.p. 143–144°.

Stock solutions of sodium acetate, acetic acid and sodium chloride were prepared by dissolving weighed quantities of the anhydrous compounds in distilled water. The aqueous dioxane–acetic acid buffer solutions were prepared by pipetting the desired volumes of acetic acid, sodium chloride and sodium acetate solutions, and anhydrous dioxane into a 100-ml. volumetric flask and filling the flask to the calibration mark with distilled water. In a series of runs enough sodium

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(1) (a) For the previous article in this series, see R. M. Roberts and R. H. DeWolfe, THIS JOURNAL, **76**, 2411 (1954); (b) this work was taken from the Ph.D. thesis of Robert H. DeWolfe, 1953.

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

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

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

(6) J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.*, 1361 (1936).

(7) F. Brescia and V. K. LaMer, THIS JOURNAL, **60**, 1962 (1938).

(8) F. Brescia and V. K. LaMer, *ibid.*, **62**, 612 (1940).

(9) H. S. Harned and N. T. Samaras, *ibid.*, **54**, 1 (1932).

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 241.

(11) W. F. K. Wynne-Jones, *Chem. Revs.*, **17**, 115 (1935).

(12) W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **34**, 245 (1938).

(13) C. G. Swain, THIS JOURNAL, **74**, 4108 (1952).

(14) L. F. Fieser, "Experiments in Organic Chemistry," Part II, D. C. Heath and Co., New York, N. Y., 1941, p. 368.

chloride solution was used in each run to maintain the ionic strength of the reaction solutions constant. The weight percentage dioxane in these solutions was calculated from the refractive indices of blank solutions containing the same amount of dioxane, using the data of Stallard and Amis.[15]

Reaction rates were determined dilatometrically. The dilatometer consisted of a reaction chamber of approximately 120-ml. capacity to the bottom of which was sealed a capillary tube having a uniform bore of about 0.6 mm. diameter and a stopcock-equipped sidearm connected by means of a rubber tube to a mercury-filled leveling bulb. To the top of the reaction chamber was attached a wide-bore capillary tube leading to a stopcock-equipped receiving tube of approximately 200-ml. capacity (see Fig. 1). A scale graduated in millimeters was attached to the small-bore capillary.

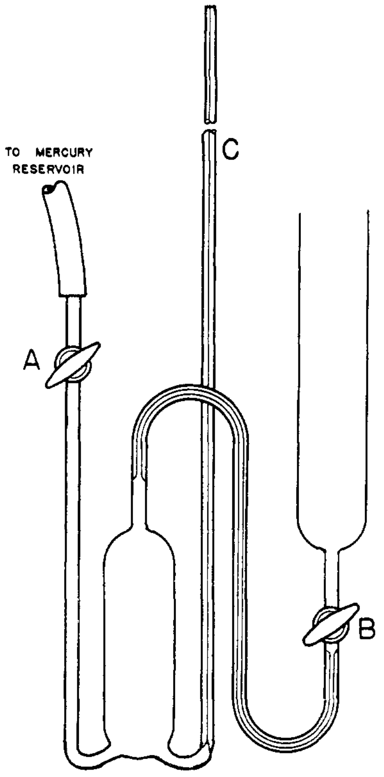

Fig. 1.—Dilatometer.

Before starting a run, the buffer solution is refluxed briefly to expel dissolved gases and then allowed to reach thermal equilibrium with a thermostat (which maintained the temperature constant to ±0.002°). Stopcocks A and B of the dilatometer, which is also immersed in the thermostat, are opened, and the reaction chamber and the lower part of the receiver are filled with mercury by raising the leveling bulb. Stopcock A is closed, and the reaction solution is poured into the receiver. To start a run, the sample of ethyl orthoformate (0.5 ml.) is dissolved in the solution in the receiver. Then the mercury reservoir is lowered and stopcock A is opened, allowing the mercury to flow back into the reservoir and the solution to flow from the receiver into the reaction chamber. When the mercury level approaches the bottom of the reaction chamber or when most of the reaction solution has entered the chamber, 3 or 4 ml. of mercury is poured into the receiver to seal stopcock B. The mercury in the receiver outlet is worked up and down to remove any solution trapped under stopcock B by raising and lowering the mercury reservoir. Stopcock B is closed, and the mercury level in the capillary C is raised until it is about an inch from the top and held there for two or three minutes. (Stopcock B is lubricated only very lightly, and the initial pressure of the mercury forces any solution trapped below stopcock B to flow out around the stopcock. Mercury, since it does not wet glass, will not escape.) The mercury level in the capillary is then lowered until it is even with the bottom of the scale, and stopcock A is closed. The entire filling operation takes less than five minutes. Readings of the mercury level in the capillary tube are then made at regular intervals until the reaction has gone almost to completion.

The first-order reaction rate constant, *k*, for a hydrolysis run was calculated from the slope of the line obtained by plotting the data according to the method of Guggenheim,[16] using the equation

$$k = -2.303 \text{ d} \log (r_2 - r_1)/\text{d}t$$

in which r_1 and r_2 are dilatometer readings at times t_1 and t_2, with the interval $t_2 - t_1$ being constant throughout a run. Times were measured in seconds.

Results and Discussion

A series of hydrolysis runs was made at 35° in 70% dioxane–acetic acid buffers of three different buffer ratios, three runs being made at different acetic acid concentrations for each buffer ratio. The ionic strength of the reaction solutions was the same for all runs. It was found that when the first-order rate constants were plotted against acetic acid concentration of the buffer, three parallel straight lines of positive slope were obtained. The fact that these lines have a definite positive slope means that the reaction is measurably catalyzed by acetic acid in 70% dioxane. The data for this series of runs appear in Table I and in Fig. 2.

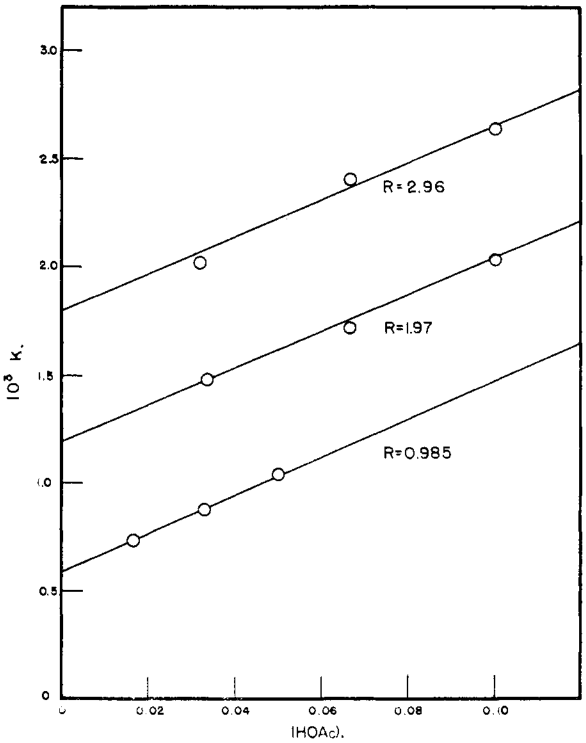

Fig. 2.—Hydrolysis of ethyl orthoformate in 70% dioxane–acetic acid buffers at 35°; R = (HOAc)/(OAc⁻).

Two series of three runs each were made at 35° in 50 and 58% dioxane–acetic acid buffers. General acid catalysis was also evident in these solutions. The data appear in Table I.

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[15] R. D. Stallard and E. S. Amis, This Journal, **74**, 1781 (1952).

[16] E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

TABLE I

HYDROLYSIS OF ETHYL ORTHOFORMATE IN AQUEOUS DIOXANE–ACETIC ACID BUFFER SOLUTIONS AT 35°

Ionic strength = 0.05

Wt. % dioxane	(HOAc)	(HOAc)/(OAc$^-$)	10^4k
70	0.0493	0.985	1.04
70	.0328	.985	0.873
70	.0164	.985	0.718
70	.0985	1.97	2.03
70	.0656	1.97	1.72
70	.0328	1.97	1.48
70	.0985	2.96	2.63
70	.0656	2.96	2.40
70	.0328	2.96	2.02
50	.0123	0.246	3.13
50	.00820	.246	2.99
50	.00410	.246	2.86
58[a]	.0995	1.17	10.7
58[a]	.0664	1.17	10.0
58[a]	.0332	1.17	9.2

[a] Ionic strength = 0.085.

The results described above show conclusively that ethyl orthoformate hydrolysis is a general acid catalyzed reaction in aqueous dioxane–acetic acid buffer solutions containing from 50 to 70% dioxane. It seems almost certain that the reaction is general acid catalyzed in aqueous solutions also, since the catalytic coefficient of acetic acid is found to *increase* as the dioxane concentration decreases.

Values of k_{HA} and k_H (the catalytic coefficients of acetic acid and oxonium ion, respectively) for ethyl orthoformate hydrolysis, together with K_i of acetic acid, are given in Table II for different concentrations of dioxane. (K_i was calculated from the data of Harned and Fallon.[17] The value of k_H for 0% dioxane was calculated from the data of Harned and Samaras.[9])

TABLE II

CATALYTIC COEFFICIENTS FOR ETHYL ORTHOFORMATE HYDROLYSIS IN DIFFERENT CONCENTRATIONS OF DIOXANE AT 35°

Ionic strength = 0.05

Wt. % dioxane	K_i	k_H	k_{HA}
0	1.8×10^{-5}	2.16×10^3	....
49.9	2.3×10^{-7}	4.8×10^3	3.4×10^{-3}
58[a]	4.8×10^{-8}	1.7×10^4	2.3×10^{-3}
70.2	3.8×10^{-9}	1.6×10^4	8.4×10^{-4}

[a] Ionic strength = 0.085.

The available data do not cover a wide enough range of dioxane concentrations to permit an accurate value of k_{HA} in aqueous solutions to be determined by extrapolation, but this can be estimated to lie between 1×10^{-2} and 3×10^{-2} at 35°. Taking the upper limit, $k_{HA} = 3 \times 10^{-2}$, it can be shown that in an aqueous acetic acid buffer solution having $R = 0.01$ and a maximum ionic strength of 0.05, the rate of hydrolysis at 35° will be approximately 4×10^{-4}/sec.; less than 4% of this rate will be due to catalysis by acetic acid. Therefore, general acid catalysis has never been observed in aqueous solutions simply because under ordinary experimental conditions it is negligible in comparison to catalysis by oxonium ions. It is observable in aqueous dioxane solutions because the acetic acid catalytic coefficient decreases less rapidly than the oxonium ion concentration when the dioxane concentration increases, and because the catalytic coefficient of oxonium ion is not greatly affected by changes in dioxane concentration.

It would seem, as suggested by Swain,[13] that general acid catalysis is much more common than formerly supposed. The results of this investigation, together with those on ethyl orthocarbonate hydrolysis discussed by Wynne-Jones,[12] show that care must be taken in using experiments in deuterium oxide to decide between "true" and "apparent" specific oxonium ion catalysis.

It does not seem likely that the rate-determining step in ethyl orthoformate hydrolysis is a simple proton transfer of the type

$$HA + S = SH^+ + A^-$$

for if this were the case the catalytic coefficient of acetic acid would probably decrease about as much as its ionization constant when dioxane concentration is increased; actually, k_{HA} decreases by about one power of ten while K_i decreases by about three powers of ten in going from aqueous solution to 70% dioxane solution. The mechanism of Winstein and Buckles,[18] with a concerted process such as that suggested by Swain operating in the rate-determining step,[19] would seem to be a satisfactory explanation of the course of ortho ester hydrolysis. If a concerted process is operating, the kinetic data do not permit one to decide whether molecular acetic acid is the electrophilic and water the nucleophilic catalyst, or whether oxonium ion and acetate ion serve in these capacities. Lowering the dielectric constant of the medium should facilitate a concerted process involving oxonium ion and acetate ion, but since this would also decrease the oxonium ion concentration it is difficult to predict how dioxane concentration would influence the importance of this process.

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(17) H. S. Harned and L. D. Fallon, THIS JOURNAL, **61**, 2374 (1939).

(18) S. Winstein and R. E. Buckles, *ibid.*, **65**, 613 (1943).

(19) C. G. Swain, *ibid.*, **72**, 4582 (1950).