The Mechanism of Hydrolysis of Ortho Esters[1]

A. J. Kresge and R. J. Preto

Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616. Received April 19, 1965

The hydrolysis of ethyl orthocarbonate in cacodylic acid buffers at 30° occurs at the same rate in the presence of sodium iodide as in the presence of sodium perchlorate. Since, under the conditions of these experiments, nucleophilic attack of the iodide ion on the conjugate acid of the ortho ester would be expected to increase the rate of reaction by more than 100%, nucleophile catalysis is absent and an A2 mechanism for this reaction can be ruled out. Because the reaction is catalyzed by general acids, its mechanism must therefore involve rate-determining proton transfer from the catalyst to the substrate. Though proton transfer is probably concerted with carbon-oxygen bond breaking and proton attack occurs on the electrons of this bond, even proton addition to an unshared electron pair of oxygen (proton transfer between two oxygen atoms) could be slow in this case since ethyl orthocarbonate is only very weakly basic. This mechanism is also consistent with the solvent isotope effect on this reaction.

Introduction

Ortho esters of carboxylic acids react readily with aqueous acids to give ordinary esters as the normal products. This reaction is subject to general acid catalysis, though the Brønsted α is large and catalysis by undissociated acids cannot always be detected in aqueous solution. Thus, general acid catalysis has been observed in the hydrolysis of ethyl orthocarbonate,[2] ethyl orthoacetate,[2,3] and ethyl orthopropionate,[2] but not in the hydrolysis of ethyl orthoformate[2] and ethyl orthobenzoate.[2,4] With the latter two substrates, however, general acid catalysis has been detected in aqueous dioxane[5] and aqueous methanol,[6] respectively.

Two commonly occurring reaction mechanisms are consistent with general acid catalysis: (1) rate-determining proton transfer from catalyzing acid to substrate (A-SE2 reaction) (eq. 1) and (2) pre-equilibrium proton

$$S + HA \longrightarrow products \qquad (1)$$

transfer from catalyzing acid to substrate followed by rate-determining reaction of the substrate conjugate acid with the conjugate base of the catalyst (A2 reaction) (eq. 2). For ortho ester hydrolysis by the A2

$$S + HA \rightleftharpoons SH^+ + A^- \text{ (rapid)} \qquad (2)$$

$$A^- + SH^+ \longrightarrow products \text{ (slow)}$$

mechanism, the rate-determining step would consist of

(1) This investigation was supported by Public Health Service Research Grant GM 09369-03 from the National Institute of General Medical Sciences.

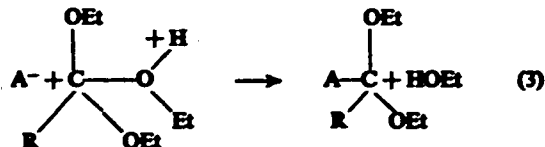(2) J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 25, 59 (1929).

(3) R. H. DeWolfe and J. L. Jensen, *J. Am. Chem. Soc.*, 85, 3264 (1963).

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

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

(6) H. Kwart and M. Price, *ibid.*, 82, 5123 (1960).

nucleophilic attack by A^- on the protonated ortho ester in a bimolecular substitution reaction (eq. 3).


$$(3)$$

Rates of this process, therefore, would reflect the nucleophilic power of A^- as well as the Brønsted acidity of HA, and characteristic deviations from the Brønsted relation should be observed; i.e., nucleophile catalysis ought to be found. In the case of the A-SE2 mechanism, however, A^- serves only as a proton transfer agent; it does not function as a nucleophile, and nucleophile catalysis will be absent. This then, constitutes a test whereby the A-SE2 and A2 mechanisms of ortho ester hydrolysis might be differentiated.

Nucleophile catalysis has already been shown to be absent in one example of ortho ester hydrolysis. The strongly nucleophilic reagents hydroxylamine and semicarbazide have no effect on the rate of reaction of methyl orthobenzoate even though they do prevent appreciable amounts of the substrate from appearing as the normal hydrolysis product, methyl benzoate.[4] Though this does provide evidence against an A2 mechanism with nucleophile catalysis, it cannot, strictly speaking, be taken as proof of the A-SE2 mechanism for ortho ester hydrolysis. In aqueous solution, the medium in which these experiments were carried out, methyl orthobenzoate, does not show general acid catalysis.[2,4] The rate of reaction is proportional only to the concentration of hydronium ion, and undissociated acids have no effect on reaction velocity. It might be argued, therefore, that the rate of this reaction is not sensitive to the presence of nucleophiles, or, what is equivalent, that it occurs by an A1 mechanism: pre-equilibrium protonation of the substrate is followed by a unimolecular rate-determining step (eq. 4). The product of the slow step is an alkoxy-

$$S + HA \rightleftharpoons SH^+ + A^- \text{ (rapid)}$$
$$SH^+ \longrightarrow products \text{ (slow)} \qquad (4)$$
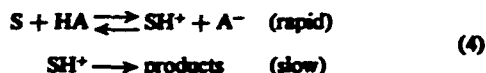
carbonium ion which can react rapidly either with the solvent or with an added nucleophile (eq. 5). Since

$$(5)$$
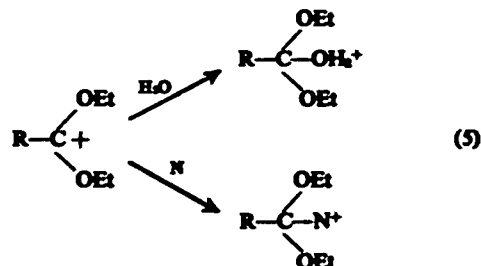
the reaction with the nucleophile occurs after the

rate-determining step, this additional process will not raise the rate of disappearance of the ortho ester, and nucleophile catalysis will not be manifest.

This objection can be circumvented by looking for nucleophile catalysis in the hydrolysis of an ortho ester which is subject to general acid catalysis. Ethyl orthocarbonate would seem to be the substrate of choice for this purpose, for, of all the ortho esters so far examined, this substance gives the lowest value of Brønsted's α.[2] On the assumption, therefore, that ortho ester hydrolysis occurs through the A2 mechanism, the conjugate acid of ethyl orthocarbonate would be the most sensitive to attack by nucleophilic reagents and nucleophile catalysis would be most easily detected in this case. We have, accordingly, examined this reaction for nucleophile catalysis.

Results

Rates of reaction of ethyl orthocarbonate were determined dilatometrically by following the increase in volume of the reaction mixtures with time. This method measures a bulk property of the solutions and so gives the rate of the over-all reaction; since intermediates do not accumulate in ortho ester hydrolysis,[7] this is equivalent to determining the rate of disappearance of ortho ester. The reactions were accurately first order throughout their course. Infinity readings were taken after at least 10 half-lives and rate constants were calculated graphically.

Reactions were carried out at 30° in cacodylic acid buffer solutions at a buffer ratio of 2.00 ([HA]/[A⁻]). As the buffer concentration was varied, ionic strength was maintained at 0.050 by the addition of various salts. The pH of a solution 0.020 M in cacodylic acid, 0.010 M in sodium cacodylate, and 0.040 M in sodium chloride was found to be 5.67 ± 0.01 (30°), which gives 1.07×10^{-6} M as the dissociation constant of this acid under these conditions. This is in agreement with the reported value of 5.33×10^{-7} M for an infinitely dilute solution at 25°.[8]

Rate constants at five buffer concentrations are presented in Table I. Least-squares analysis of this gives the following relationship

Table I. Rates of Hydrolysis of Ethyl Orthocarbonate in Cacodylic Acid Buffers at 30°

[HA], M	[NaA], M	[NaX], M	$10^2 k_1$, min.$^{-1}$
0.100	0.050	0.000	4.72
0.100	0.050	0.000	4.74
NaX = NaCl			
0.080	0.040	0.010	4.60
0.080	0.040	0.010	4.58
0.060	0.030	0.020	4.38
0.060	0.030	0.020	4.34
0.020	0.010	0.040	4.05
0.020	0.010	0.040	4.12
NaX = NaClO₄			
0.040	0.020	0.030	4.34
0.040	0.020	0.030	4.28
NaX = NaI			
0.040	0.020	0.030	4.26
0.040	0.020	0.030	4.23

(7) A. M. Wenthe and E. H. Cordes, *Tetrahedron Letters*, 3163 (1964).
(8) M. L. Kilpatrick, *J. Am. Chem. Soc.*, 71, 2607 (1949).

$$k_{\text{obsd}} = 0.0393 \pm 0.0003 + (0.0802 \pm 0.0055)[\text{HA}] \quad (6)$$

where the uncertainties are standard deviations. The catalytic coefficient of cacodylic acid is therefore 8.0×10^{-2} M^{-1} min.$^{-1}$, and, using the dissociation constant measured for these solutions (1.07×10^{-6}), a catalytic coefficient of 1.8×10^4 M^{-1} min.$^{-1}$ can be calculated for the hydronium ion. The value of Brønsted's α based on these two points is 0.69. These results are consistent with values measured earlier at 20° in buffer solutions of the same acid at a different buffer ratio and a different ionic strength ($k_{\text{HA}} = 1.7 \times 10^{-2}$, $k_{\text{H}^+} = 5.0 \times 10^3$, and $\alpha = 0.68$).[2]

Discussion

Nucleophile Catalysis. It can be seen from Figure 1 that rates of hydrolysis of ethyl orthocarbonate in cacodylic acid buffers are a linear function of the buffer acid concentration, and that a single relation serves to correlate all the data well. This is also apparent from the fact that the limits of error in the slope and intercept of the least-squares line through all the data are small (eq. 6). Since these rates were measured in the presence of various salts, the nucleophilic activities of whose anions varied over a considerable range (on the Swain–Scott scale, from $n < 0$ for ClO_4^- to $n = 5.04$ for I^-),[9] it would seem that these salts have little effect on the reaction velocity and that nucleophile catalysis is absent.

This conclusion can be supported by the following quantitative argument. Let us suppose that the hydrolysis of ethyl orthocarbonate does occur by an A2 mechanism in whose rate-determining step various nucleophiles compete for reaction with the substrate conjugate acid. Then by application of the Swain–Scott equation,[9] we can calculate the increase in rate to be expected when sodium perchlorate, a salt whose anion has very low nucleophilic activity, is replaced by sodium iodide, a salt whose anion is a very reactive nucleophile. On the assumption that the perchlorate ion has negligible nucleophilic activity, two sets of experiments of Table I refer to conditions where water and the cacodylate ion are the only nucleophiles present in the reaction mixtures; these are the kinetic runs with no added salt (0.10 M HA and 0.050 M NaA) and the runs with added sodium perchlorate (0.040 M HA, 0.020 M NaA, and 0.030 M NaClO₄). From these data, $k_{\text{H}_2\text{O}}$, the specific rate constant for the hydrolysis of ethyl orthocarbonate at pH 5.67 with water acting as the nucleophile, and k_{A^-}, the rate constant for the corresponding reaction with cacodylate ion acting as the nucleophile, can be calculated as 7.3 $\times 10^{-4}$ l. M^{-1} min.$^{-1}$ and 1.4×10^{-1} l. M^{-1} min.$^{-1}$, respectively. With this information, the substrate parameter (s) in the Swain–Scott equation (7) could be

$$\log (k/k_{\text{H}_2\text{O}}) = sn \quad (7)$$

calculated if the nucleophilic constant, s_{A^-}, of the cacodylate ion were known. Unfortunately, this constant has not been measured.

A reasonable estimate of the nucleophilic constant of the cacodylate ion can, however, be made in a straightforward manner. It has been observed in cases of

(9) C. G. Swain and C. B. Scott, *ibid.*, 75, 141 (1953).

genuine nucleophile catalysis, that, although the data for different nucleophiles do not in general give a single, good Brønsted plot, the data for catalysts which are sufficiently similar often do obey the Brønsted relation quite well.[10] For example, the rates of reaction of p-nitrophenyl acetate with acetate ion, monohydrogen phosphate ion, and several phenolate ions (all nucleophiles which attack through an oxygen atom) can be correlated well by a single Brønsted relation.[10a] This can be understood in terms of the recent demonstration that nucleophilic power is a function of the pK_A of the conjugate acid of the nucleophile and only two other factors, polarizability and the α effect[11]: for the oxygen-containing nucleophiles mentioned above, these other factors must contribute a constant amount to nucleophilic activity. Since the cacodylate ion is also an oxygen-containing nucleophile whose structure is not unlike that of the acetate ion or the monohydrogen phosphate ion, its nucleophilic constant can be estimated from the known nucleophilic constants of these other ions. When this is done using a scale proportional to the pK_A values of the nucleophile conjugate acids, the nucleophilic constant for cacodylate ion is found to be 3.4.

We are now in a position to evaluate the substrate parameter for the hypothetical A2 reaction of ethyl orthocarbonate at pH 5.67

$$\log (k_A/k_{H_2O}) = sn_{A^-}$$

$$\log (1.4 \times 10^{-1}/7.3 \times 10^{-4}) = s \times 3.4$$

$$s = 0.67$$

and the rate constant for this reaction with iodide ion acting as the nucleophile

$$\log (k_{I^-}/k_{H_2O}) = sn_{I^-}$$

$$\log (k_{I^-}/7.3 \times 10^{-4}) = 0.67 \times 5.04$$

$$k_{I^-} = 1.7 \ M^{-1} \ min.^{-1}$$

In a reaction mixture containing 0.030 M sodium iodide, the iodide ion will therefore contribute an increment of $1.7 \times 0.030 = 0.054$ min.$^{-1}$ to the rate of disappearance of ethyl orthocarbonate. Since the rate observed in the presence of 0.030 M sodium perchlorate is 0.043 min.$^{-1}$, replacement of perchlorate ion with iodide ion at this concentration will increase the rate of reaction by 125%. Of course, no increase at all is actually observed: the rate of disappearance of ethyl orthocarbonate in the presence of 0.030 M sodium iodide is 0.042 min.$^{-1}$ (Table I). Nucleophile catalysis therefore is not occurring, and the reaction cannot be taking place by the A2 mechanism.

Reaction Mechanism. The present study, as well as an earlier investigation,[2] shows that the hydrolysis of ethyl orthocarbonate is subject to general acid catalysis. But, because Brønsted's α is large, in both cases only a small fraction of the reaction occurred through catalysis by undissociated acids. In the present case, the amount was 5 to 20% (10% in the case of the experiments which demonstrate the absence of nucleophile catalysis).

(10) (a) T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, **80**, 2265 (1958); (b) M. L. Bender and W. A. Glasson, *ibid.*, **81**, 1590 (1959); M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(11) J. O. Edwards, *J. Am. Chem. Soc.*, **78**, 1819 (1956); J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).
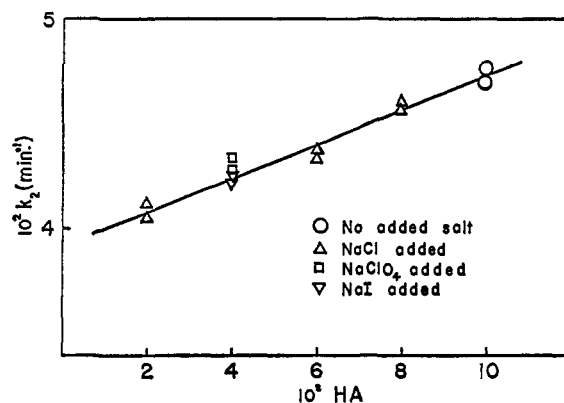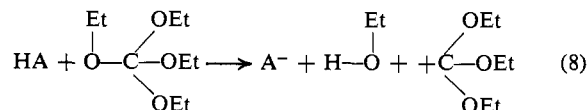
Figure 1. Variation of the rate of hydrolysis of ethyl orthocarbonate with cacodylic acid buffer concentration in the presence of various salts.

The rest of the reaction occurred through catalysis by dissociated acid, *i.e.*, the hydronium ion. It might be argued, therefore, that this portion of the reaction (that catalyzed by the hydronium ion) takes place by an A1 mechanism and the two simultaneous reactions are really occurring (one catalyzed by general acids and one catalyzed by the hydronium ion in which the catalyst serves only to control the concentration of the protonated substrate). But such a situation is quite unlikely in view of the fact that the over-all reaction obeys the Brønsted relation quite well: the catalytic coefficient for the hydronium ion falls on a line defined by the catalytic coefficients of acetic and codacylic acids.[2] It has been shown quite recently, moreover, that an A1 mechanism for this reaction is not consistent with the observed rates and an estimate of the basicity constant of ethyl orthocarbonate.[12] It seems justifiable to conclude, therefore, that the reaction is mechanistically homogeneous, and that the hydronium ion, like the undissociated acids, is functioning as a general acid.

Only two mechanisms of acid catalysis are consistent with general acid catalysis: the A-SE2 and the A2. Since we have ruled out the A2 mechanism for this case on the basis of no nucleophile catalysis, the hydrolysis of ethyl orthocarbonate must occur by an A-SE2 mechanism. The rate-determining step then involves transfer of a proton from the catalyzing acid to an oxygen atom of the orthe ester; this process could give the protonated ortho ester as a reaction intermediate, or, more likely, it could be concerted with carbon–oxygen bond breaking. In the latter case, an alkoxycarbonium ion is formed directly (eq. 8) and this

$$\text{HA} + \underset{\displaystyle \overset{|}{\text{OEt}}}{\overset{\displaystyle \overset{\text{Et} \quad \text{OEt}}{\diagdown \diagup}}{\text{O} - \text{C}}} - \text{OEt} \longrightarrow \text{A}^- + \text{H} - \underset{\displaystyle \overset{|}{\text{OEt}}}{\overset{\displaystyle \overset{\text{Et}}{|}}{\text{O}}} + \underset{\displaystyle \overset{|}{\text{OEt}}}{\overset{\displaystyle \overset{\text{OEt}}{\diagup}}{+\text{C}}} - \text{OEt} \quad (8)$$
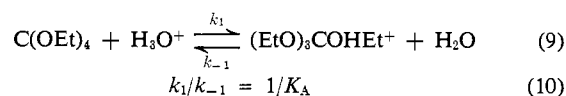
carbonium ion reacts in further rapid steps either with the solvent or with other nucleophiles which happen to be present.

This mechanism might seem to be at variance with a widely held axiom of mechanistic chemistry which states that proton transfers between oxygen atoms are very fast and that such processes therefore cannot be rate-

(12) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).

determining steps of reactions which proceed at rates measurable by conventional methods. But proton transfers between oxygen atoms cannot always be very fast. When they occur between bases of different strength, they must have a free energy of activation in one direction at least equal to the free energy difference between the two conjugate acids involved in the transfer. For example, in the present situation for the case of proton transfer from the hydronium ion to ethyl orthocarbonate

$$C(OEt)_4 + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (EtO)_3COHEt^+ + H_2O \qquad (9)$$

$$k_1/k_{-1} = 1/K_A \qquad (10)$$

and

$$k_1 = k_{-1}/K_A \qquad (11)$$

The acidity constant of ethyl orthocarbonate (K_A) has been estimated at $3 \times 10^8 \ M$.[12] Assuming, therefore, that k_{-1} has the largest value it can possibly have, $10^{11} \ sec.^{-1}$ (this is the order of magnitude of the rate actually observed in reactions of this kind when the process is diffusion controlled[13]), $k_1 = 3 \times 10^2 \ M.^{-1} \ sec.^{-1}$. A rate constant of this magnitude can easily be measured by conventional methods.

The catalytic coefficient actually found for the hydrolysis of ethyl orthocarbonate by the hydronium ion is also $3 \times 10^2 \ M^{-1} \ sec.^{-1}$, but this agreement with the value calculated above may not be significant for the rate-determining step in hydrolysis could be different from the simple protonation shown in eq. 9. If, as is quite likely, proton transfer in hydrolysis is concerted with carbon–oxygen bond breaking, then the proton very probably attacks the electrons of the carbon–oxygen bond, whereas in simple protonation, proton addition must occur to one of the unshared electron pairs of oxygen. The calculation does serve, however, to show that a route leading to hydrolysis does exist in which proton transfer between oxygens is relatively slow.

Another piece of information which might seem to argue against an A–SE2 mechanism for this reaction is the solvent isotope effect: $k_{H_2O}/k_{D_2O} = 0.7$ for the hydronium ion catalyzed hydrolysis of ethyl orthocarbonate.[14] It has been generally assumed that only pre-equilibrium proton transfer reactions (A1 and A2 mechanisms) will have faster rates in D_2O than in H_2O, and that rate-determining proton transfer will show a solvent isotope effect in the normal direction.[15] In the present case, however, as the discussion in the paragraph above shows, proton transfer is very nearly complete at the transition state. The transition state is therefore quite unsymmetrical, and the primary isotope effect (that contribution to the over-all rate ratio which is produced by oxygen–hydrogen bond breaking) should be close to unity.[16] It is now established that proton transfer from the hydronium ion is accompanied also by an inverse secondary isotope effect,[17] and this secondary effect will, in the present case of a product-like transition state, be near its maximum value of about 0.5. The over-all solvent isotope effect, there-

fore, can easily be less than unity, and the observed value of 0.7 does, in fact, support the picture of this reaction drawn above.

Hydrolysis of Other Ortho Esters. The arguments presented here are strictly applicable to the hydrolysis of ethyl orthocarbonate. The general behavior of other ortho esters upon hydrolysis, however, is similar to that of ethyl orthocarbonate: all have inverse solvent isotope effects, all can be made to show general acid catalysis only with some difficulty, and all have entropies of activation near 0. The hydrolysis of these substances, therefore, seems to form a mechanistically homogeneous set of reactions, and it may not be too far wrong to say that all the reactions occur by the A–SE2 mechanism.

Experimental Section

Materials. Ethyl orthocarbonate (K & K Laboratories) was fractionally distilled through an efficient column; a center cut had b.p. 161.0–161.5°, $n^{25}D$ 1.3880. This material gave rate constants which were identical with those obtained with the substance before purification, and the distilled and undistilled samples were therefore used interchangeably. Cacodylic acid and sodium cacodylate were Merck reagent grade; all other chemicals were the best available analytical reagents.

Kinetic Method. Rate constants were determined by measuring the expansion of reaction mixtures in a dilatometer with a spiral bulb of about 12-ml. capacity. The dilatometer arm used for filling was made of ordinary 2-mm. capillary with a glass tap which was closed during a kinetic run; the total expansion therefore took place in the other arm, which was made of precision-bore, fine capillary. Substrate concentrations of about $5 \times 10^{-2} \ M$ gave changes in height of the order of 1.0 cm. which were read to 0.05 mm. with a cathetometer. The reactions had half-lives of 15 to 20 min.; infinity readings were taken after 2 to 4 hr. The kinetic experiments were carried out in a bath at 30.0° which was controlled to ±0.001°.

Buffer solutions were made up by weighing out the components and dissolving them in distilled water to make a known total volume. To start a reaction, 0.2 ml. of ethyl orthocarbonate was added to 20 ml. of buffer solution which had previously been equilibrated with the constant temperature bath, the mixture was shaken for 30 sec. to effect solution, and this was then forced into the dilatometer by nitrogen gas at a pressure a few pounds above atmospheric. Readings were taken every minute for 2 to 3 half-lives.

pH Measurements. Hydrogen ion activities were measured at 30.00 ± 0.05° using a Borax buffer as the standard with glass and calomel electrodes in conjunction with a Beckman Model G pH meter. The method was checked by measuring the pH of a 0.050 M potassium acid phthalate buffer. The observed pH was 4.01 ± 0.01 (lit.[18] pH 4.011).

(13) R. P. Bell, *Quart. Rev.* (London), **13**, 169 (1959).
(14) W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **34**, 245 (1938).
(15) K. Wiberg, *Chem. Rev.*, **55**, 713 (1955); F. A. Long and J. G. Pritchard, *J. Am. Chem. Soc.*, **78**, 6008 (1956); F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959).
(16) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961); J. Bigeleisen, *Pure Appl. Chem.*, **8**, 217 (1964).
(17) A. J. Kresge and D. P. Onwood, *J. Am. Chem. Soc.*, **86**, 5014 (1964).
(18) V. Gold, "pH Measurements," Methuen and Co. Ltd., London, 1956, p. 118.