an Aerograph 1520 chromatograph with flame ionization detector and a 20% silicone elastomer (D.C. 550) on Gas-Chrom P column (7 ft × 0.05 in.). The column temperature was raised during 50 min from 185 to 225°. Under these conditions **1b** did not rearrange. The chromatograph was calibrated using pure sample with 4-bromobiphenyl as an internal standard. Reactions were followed to at least 95% conversion of **1b**. First-order rate constants were found by a least-squares fit to the individual points.

B. Nematic Solvent. A mixture (% by weight) of **1b** (2.14), phenyl benzoate (0.853) as internal standard, and **3** (97.007) was heated to 202° (*i.e.*, above the nematic → liquid transition), vigorously stirred, and then rapidly cooled. The resulting solid was pulverized and homogenized. The resulting mixture was homogeneous to glc and the nematic → liquid transition temperatures of various samples were identical (200°). The reactions were carried out as before with samples (2 mg) in evacuated ampoules. In the case of the experiments in a magnetic field, the samples were held between the pole pieces of an electromagnet in an aluminum container through which thermostated oil was circulated. The samples were dissolved in benzene for analysis by glc as before.

Clathrate of 1b in 21. The clathrate was prepared from a mixture of **1b** (0.25 g) and **22** (0.75 g) by crystallization from acetone (125 ml) forming dark yellow prisms. *Anal.* Calcd for $C_{63}H_{46}N_8O_{17}$ (*i.e.*, **1b**, $(\mathbf{22})_4$): C, 63.74; H, 3.91; N, 9.44; O, 22.91. Found: C, 63.67; H, 3.88; N, 9.35; O, 22.86. Material of the same composition crystallized from solutions of **1b** and **22** even when the ratio of the components was varied. For the kinetic experiments crystals *ca.* 3 mm in diameter were sealed in evacuated ampoules and heated in a thermostat as before. For glc analysis solutions in hot acetone were injected into the chromatograph.

Concurrent General Acid–Electrostatic Catalysis in Vinyl Ether Hydrolysis and Aspartic-52 of Lysozyme

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Abstract: The hydrolyses of various ring-substituted α-methoxystyrenes have been studied across the acidic pH region, and proceed by an initial, rate-limiting proton transfer to the vinyl ether double bond. The hydrolysis of the *p*-methoxy analog may represent an exception to this mechanism. The products of these reactions are the corresponding acetophenones, except in the case in which the ring bears an *o*-carboxyl substituent (**1a,b**). In this case, 3-methoxy-3-methylphthalide (**2**) is formed, and is, to a good approximation, an obligatory intermediate in the hydrolysis reaction at all pH values. Arguments are presented which show that the presence of the *o*-carboxyl group evidently does not alter the rate-determining process in the hydrolysis mechanism leading to **2**. Ionization of the *o*-carboxyl group accelerates the hydronium ion catalyzed reaction by a factor of only 11.6, and the formic acid catalyzed reaction by only 7.9; these numbers are shown to represent upper limits on electrostatic facilitation of general acid catalyzed α-oxycarbonium ion formation in aqueous solution *via* vinyl ether hydrolysis. These results suggest that the electrostatic role postulated for aspartic acid-52 of hen lysozyme in a very similar process is yet to be demonstrated. The trapping of the carbonium ion intermediate by the intramolecular carboxyl group, even when it is un-ionized, shows that covalent interaction of such a carboxyl with carbonium ion intermediates does not require ionization of the carboxyl group. Other roles for Asp_{52} are considered.

The ready availability of hen egg-white lysozyme presents the chemist with a remarkable opportunity to study the chemical details of enzymatic catalysis. Lysozyme rapidly hydrolyzes β-1,4-linked 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) polymers of five residues or greater, as well as alternating copolymers of *N*-acetylglucosamine and *N*-acetylmuramic acid, to yield smaller saccharides with β stereochemistry retained at the point of cleavage. The X-ray crystallographic structure of Phillips' group[2] and kinetic investigations in model systems have suggested at least four factors which might be crucial for catalytic activity of the enzyme.

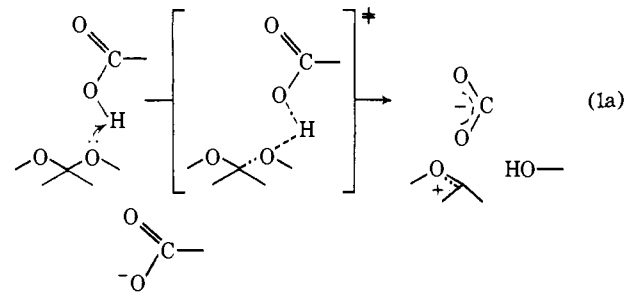
Distortion of the saccharide ring at the point of cleavage into a half-chair conformation more like that of the transition state can result in relief of strain upon hydrolysis, and therefore a large rate acceleration. The synthesis of strained model ketals has led to small rate accelerations,[3] although it has not been possible to sort the observed effect into contributions due to altered substrate basicity and acceleration of bond breaking. The ingeniously designed transition state analog of Lienhard's group[4] has been found to bind more tightly to lysozyme than tetra-*N*-acetylglucosamine, but the actual site of binding was not proved.

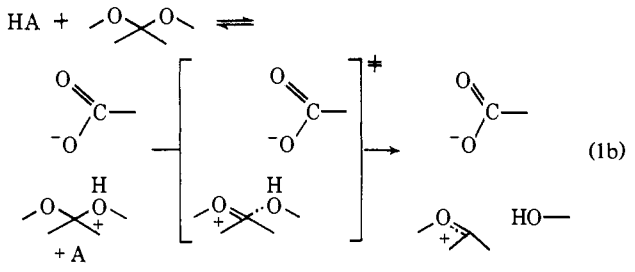
There is kinetic evidence that β anomers of 2-acetamido-2-deoxyglucopyranosides are more rapidly hydrolyzed in aqueous solution than their glucose counterparts, and that this acceleration is due to nucleophilic participation of the acetamido group at the developing carbonium ion.[5] It has been shown, however, that the presence of the acetamido group in the substrate is not an absolute requirement for lysozyme-catalyzed hydrolysis.[6]

The finding of two carboxylic acid residues, aspartic acid-52 (Asp_{52}) and glutamic acid-35 (Glu_{35}), at the presumed site of cleavage of chitin oligosaccharides in the lysozyme active site suggested that these residues might be crucial for the activity of the enzyme. The carboxylic acid side chain of Glu_{35} has been suggested

(1) (a) National Science Foundation Undergraduate Research Participant, 1972; (b) Undergraduate, Cornell University.
(2) C. C. F. Blake, L. N. Johnson, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Proc. Roy. Soc., Ser. B*, 167, 378 (1967).
(3) E. Anderson and T. H. Fife, *J. Amer. Chem. Soc.*, **93**, 1701 (1971).
(4) I. I. Secemski and G. E. Lienhard, *J. Amer. Chem. Soc.*, **93**, 3549 (1971).
(5) D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 6237 (1967).
(6) M. A. Raftery and T. Rand-Meir, *Biochemistry*, 7, 328 (1968).

as an acid catalyst for proton transfer to the oxygen of the incipient leaving group, whereas the corresponding ionized carboxyl of Asp_{52}, because of its more remote location (*ca.* 3 Å) from the presumed point of cleavage, and because there is evidence for the involvement of carbonium ions in lysozyme-catalyzed reactions,[7] has been thought to stabilize a developing carbonium ion at the point of cleavage by a through-space, electrostatic interaction, a phenomenon to which we shall refer for brevity as "electrostatic catalysis."[8] The kinetically equivalent role of nucleophilic participation by this carboxyl group to form an intermediate acylal which we shall call "nucleophilic catalysis," is of course not rigorously excluded, but a covalent intermediate in lysozyme catalysis has never been demonstrated. The effects of proximal carboxyl groups on the generation of α-oxycarbonium ions have been studied in a number of ketal hydrolysis reactions.[10] In many of these examples, ionization of the proximal carboxyl group formally accelerates the reaction by several 100-fold, but it is difficult to distinguish between the two kinetically indistinguishable roles for the carboxyl group, that of an intramolecular acid catalyst (eq 1a) or that of an electrostatic or nucleophilic catalyst (eq 1b).[11] Indeed, there may be a substantial electrostatic component to general acid catalysis. Solvent isotope effects are often of no help in distinguishing between these two mechanisms, for they are often near unity for this type of reaction, and occasionally inverse, even for demonstrated cases of catalysis by external buffers. The isotope effects observed in these reactions, as Bruice and Piszkiewicz have pointed out,[5] are equally consistent with either mechanism. It is worth noting that general acid catalysis is reasonable, but not required, by a postulate recently advanced by Jencks.[12]





Recently, Fife and Anderson[13,14] were able to decide clearly between these two mechanistic alternatives in two examples, and demonstrated that large rate accelerations of 10^4–10^9 may occur because of participation of a proximal carboxylic acid function as a proton transfer catalyst in ketal hydrolyses. Thus, the postulated role of Glu_{35} in lysozyme has good analogy in the study of model compounds.

There is a certain amount of modification[15] and affinity label work[16] on lysozyme which is interpretable in terms of the essentiality of Asp_{52}. Obviously, Asp_{52} may be an "essential residue" without acting as an electrostatic or nucleophilic catalyst, nor do the protein experiments require the essentiality of Asp_{52} for reasonable interpretation. The effect of a carboxyl group acting as an electrostatic catalyst in general acid catalyzed oxycarbonium ion formation has not been well characterized in a model system. Reports of such an effect recently appeared,[14] and the resulting catalysis appears to be quite weak. Thus, we undertook this work to investigate the effect of electrostatic or nucleophilic catalysis in α-oxycarbonium ion formation occurring concurrently with general acid catalysis using a different but closely related system in which kinetic ambiguities would be minimized.

The hydrolysis of vinyl ethers and related compounds[17] has in general been shown to proceed with rate-determining protonation of the carbon–carbon multiple bond to give as a presumed first intermediate the corresponding α-oxycarbonium ion. If this mechanism is retained when an *o*-carboxyl substituent is present, then one expects to see either intramolecular or intermolecular general acid catalysis; observation of strong catalysis of the reaction by external buffers would rule out the former possibility, and the effect of the carboxyl group as an electrostatic or nucleophilic catalyst, uncomplicated by the possibility of intramolecular proton transfer, may be observed. Therefore, we synthesized and studied the hydrolysis of enol ethers **1a–k** and the related compound **2**. We have found that the electrostatic facilitation of the general acid catalyzed reaction of **1a** by the ionized carboxyl group is indeed quite weak.

Experimental Section

All melting points are uncorrected, and were obtained on a Büchi Melting Point Apparatus. Proton nmr spectra were taken at 60

(7) F. W. Dahlquist, T. Rand-Meir, and M. A. Raftery, *Biochemistry*, **8**, 4214 (1969).

(8) This effect is, of course, a well-known phenomenon in chemistry, and the use of this terminology is not meant to imply a new effect never before observed. The term has also been used in a slightly different way[9] to mean an electrostatic attraction of two reactants in a bimolecular reaction leading to enhanced probability of collision.

(9) T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, **89**, 4028 (1967); **90**, 7136 (1968); **91**, 2982, 2985 (1969).

(10) (a) T. C. Bruice and D. Piszkiewicz, *J. Amer. Chem. Soc.*, **89**, 3568 (1967); (b) B. M. Dunn and T. C. Bruice, *ibid.*, **92**, 2410 (1970); (c) *ibid.*, **92**, 6589 (1970); (d) *ibid.*, **93**, 5725 (1971); (e) T. H. Fife, *Accounts Chem. Res.*, **5**, 264 (1972).

(11) In some cases it is possible to rule out nucleophilic catalysis, as the hydrolysis of the intermediate which would be formed in such a situation may be studied independently and ruled out on kinetic grounds. See, for example, B. Capon and M. C. Smith, *Chem. Commun.*, 523 (1965).

(12) W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972); (b) *Chem. Rev.*, **72**, 705 (1972).

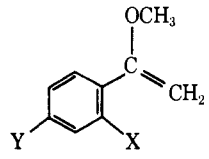
(13) T. H. Fife and E. Anderson, *J. Amer. Chem. Soc.*, **93**, 6610 (1971).

(14) (a) E. Anderson and T. H. Fife, *Chem. Commun.*, 1470 (1971); (b) *J. Amer. Chem. Soc.*, **95**, 6437 (1973).

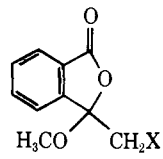
(15) (a) T.-Y. Lin and D. E. Koshland, Jr., *J. Biol. Chem.*, **244**, 505 (1969); (b) S. M. Parsons and M. A. Raftery, *Biochemistry*, **8**, 4199 (1969).

(16) E. W. Thomas, J. F. McKelvey, and N. Sharon, *Nature (London)*, **222**, 485 (1969).

(17) (a) A. J. Kresge and Y. Chiang, *J. Chem. Soc. B*, 53 (1967); (b) M. M. Kreevoy and R. Eliason, *J. Phys. Chem.*, **72**, 1313 (1968); (c) E. J. Stamhuis and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **80**, 797 (1961); (d) *ibid.*, **80**, 1285 (1961); (e) *ibid.*, **80**, 1289 (1961); (f) R. D. Frampton, T. T. Tidwell, and V. A. Young, *J. Amer. Chem. Soc.*, **94**, 1271 (1972); (g) A. J. Kresge and H. I. Chen, *J. Amer. Chem. Soc.*, **94**, 2819 (1972), and references therein.



1a, X = CO_2^-; Y = H
b, X = CO_2H; Y = H
c, X = H; Y = CO_2^-
d, X = H; Y = CO_2H
e, X = Y = H
f, X = CO_2CH_3; Y = H
g, X = H; Y = CO_2CH_3
h, X = H; Y = OCH_3
i, X = H; Y = CH_3
j, X = H; Y = Br
k, X = H; Y = NO_2



2, X = H
2-d, X = D

MHz on a Varian A60A nmr spectrometer. Mass spectral analyses were performed on an AEI MS 902 instrument operating in the electron impact mode unless otherwise noted. Ir spectra were taken on a Perkin-Elmer 137 prism spectrophotometer.

Synthetic Procedures. 1-Methoxyvinylbenzene (α-**methoxystyrene**) (**1e**) was synthesized by two independent routes. The first procedure involved the synthesis, in 54% yield, of β-methoxy-β-phenylethyl iodide,[18] which was dehydrohalogenated immediately after preparation[19] in $NaOCH_3/CH_3OH$. The product was distilled at 85–87° (13 mm)[19] to give a clear, colorless liquid in 90% yield. In a procedure which proved to be more general, and typical for other enol ethers, acetophenone (24 g, 200 mmol) was converted to the dimethyl ketal in the presence of trimethyl orthoformate (25 g, 238 mmol), 150 ml of anhydrous methanol, and 5 drops of concentrated H_2SO_4 with stirring. The ketal (10 g, 61 mmol) was cracked at 135° in 150 ml of boiling chlorobenzene containing 50 mg of *p*-toluenesulfonic acid monohydrate, dried sufficiently for this purpose by azeotropic distillation of the chlorobenzene solution. Following completion of the reaction (conveniently monitored by nmr) the acid was neutralized with LiH. Concentration of the chlorobenzene and distillation at reduced pressure afforded the vinyl ether as a clear, colorless oil at 85–87° (13 mm)[19] in 55% yield. The ir spectrum showed the absence of carbonyl absorption, and the nmr was definitive: δ_{CCl_4} (ppm downfield from TMS) 3.34 (s, 3 H), 4.12 (d, J = 3 Hz, 1 H), 4.60 (d, J = 3 Hz, 1 H), 7.1–7.7 (m, 5 H). High resolution mass spectrum, 134.0728 (calcd for $C_8H_{10}O$, 134.0732). Occasionally, small amounts of impurities identified by nmr and gas chromatography (glpc) as ketone and ketal corresponding to the enol ether were present to the extent of $\leq$5%. These were easily removed from kinetic and analytical samples by preparative gas chromatography on an 8 ft × 0.25 in. column of 20% Carbowax 20M on neutral 60–80 Chromosorb W at a temperature of 100–180°, depending on the particular enol ether. Enol ethers were stored in evacuated sealed tubes at −20°, but even under these conditions slowly polymerized.

4-Methoxy-(1-methoxyvinyl)benzene (**1h**) was prepared by the ketal cracking method just described: nmr δ_{CCl_4} 3.67 (s, 3 H), 3.71 (s, 3 H), 4.04 (d, J = 2.7 Hz, 1 H), 4.48 (d, J = 2.7 Hz, 1 H), 7.3–7.7 (A_2B_2 pattern typical of para substitution, 4 H); high resolution mass spectrum 164.0840 (calcd for $C_{10}H_{12}O_2$, 164.0836).

4-Methyl-(1-methoxyvinyl)benzene (**1i**) was synthesized by the ketal cracking method: nmr δ_{CCl_4} 2.30 (s, 3 H), 3.66 (s, 3 H), 4.07 (d, J = 2.8 Hz, 1 H), 4.53 (d, J = 2.8 Hz, 1 H), 6.9–7.6 (A_2B_2 pattern, 4 H); high resolution mass spectrum, 148.0889 (calcd for $C_{10}H_{12}O$, 148.0888).

4-Bromo-(1-methoxyvinyl)benzene (**1j**) was prepared both by the ketal cracking method and from *p*-bromostyrene (Aldrich) by the first procedure described for **1e**: nmr δ_{CCl_4} 3.65 (s, 3 H), 4.13 (d, J = 3.0 Hz, 1 H), 4.58 (d, J = 3.0 Hz, 1 H), 7.40 (apparent s, 4 H); high resolution mass spectrum, 211.9837 (calcd for C_9H_9OBr, 211.9835).

Methyl 4-(1-Methoxyvinyl)benzoate (**1g**). *p*-Bromoacetophenone was converted to the dimethyl ketal by the procedure used above for acetophenone. The Grignard reagent was readily formed from 26 g (106 mmol) of *p*-bromoacetophenone dimethyl ketal with Mg in dry (distilled from $LiAlH_4$) tetrahydrofuran (THF), and it was added to a rapidly stirred slurry of Dry Ice chunks in dry THF. The mixture was allowed to warm to room temperature, and was acidified with 5% HCl. The aqueous layer was saturated with NaCl and drawn off, and the THF layer, to which ether was added, was saturated with 5% Na_2CO_3 solution. The carbonate extracts were combined, chilled, and acidified with concentrated HCl to yield, after drying *in vacuo* over P_2O_5, 12.0 g of *p*-acetylbenzoic acid (69%), mp 208–210.5° (lit.[20] mp 207–209°). The acid was esterified on a 50-mmol scale in THF with 100 mmol of diazomethane generated from Aldrich *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) to yield, after recrystallization from hexanes, 86% yield of methyl *p*-acetylbenzoate, mp 94–96° (lit.[21] mp 92–95°). This material was treated as the foregoing acetophenones to give sequentially the dimethyl ketal and the enol ether. The latter was isolated in 10% yield by crystallization from petroleum ether at low temperature instead of distillation, and had mp 72–73°: nmr δ_{CCl_4} 3.73 (s, 3 H), 3.86 (s, 3 H), 4.25 (d, J = 3.0 Hz, 1 H), 4.73 (d, J = 3.0 Hz, 1 H), 7.5–8.1 (A_2B_2 pattern, 4 H); high resolution mass spectrum (chemical ionization, giving P + 1 ion), 193.0854 (calcd for $(C_{11}H_{13}O_3)^+$, 193.0864).

4-Nitro-(1-methoxyvinyl)benzene (**1k**) was prepared by the ketal cracking method. *p*-**Nitroacetophenone dimethyl ketal**, recrystallized from hexanes to mp 60–61.5°, was treated as previously described ketals, except that no attempt was made to distill the product. After removal of chlorobenzene, the pot residue was triturated with hexanes and the resulting hexane triturates were crystallized. Recrystallization after decolorization with Norit yielded 31% of the desired product as yellow needles: mp 83–86°; nmr δ_{CDCl_3} 3.76 (s, 3 H), 4.42 (d, J = 3.5 Hz, 1 H), 4.84 (d, J = 3.5 Hz, 1 H), 7.7–8.3 (A_2B_2 pattern, 4 H); high resolution mass spectrum, 179.0577 (calcd for $C_9H_9O_3N$, 179.0582).

Sodium 4-(1-Methoxyvinyl)benzoate (**1c**). Methyl 4-(1-methoxyvinyl)benzoate (**1g**), 1.0 g (5.2 mmol), was suspended in 6.0 ml of standard 0.971 *M* NaOH (5.82 mmol of NaOH) with a few drops of methanol and stirred until the solution was clear. The resulting solution was extracted with ether, and the aqueous layer was lyophilized. The resulting powder was suspended in about 15 ml of boiling acetone, and the minimum amount of water necessary for dissolution of the powder was added. A volume of acetone equal to the total volume of liquid was added, and the solution was placed in the freezer. A white solid crystallized which did not melt below 275°, and whose nmr defined the proposed structure: $\delta_{D_2O/NaOD}$ (ppm upfield from HDO) 1.20 (s, 3 H), 0.52 (d, J = 3.2 Hz, 1 H), 0.12 (d, J = 3.2 Hz, partially buried under HDO resonance, but apparently 1 H), −2.6 to −3.1 (A_2B_2 pattern, 4 H). This material was contaminated with small amounts of *p*-acetylbenzoic acid (sodium salt), whose aromatic proton resonance was evident as an apparent singlet at $\delta_{D_2O/NaOD}$ 3.08 ppm downfield from HDO. Since this material is the product of the enol ether hydrolysis reaction of **1c**, it did not interfere with the hydrolysis kinetics, which were strictly first order for >5 half-lives (see below).

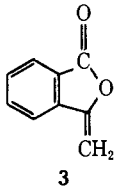
Methyl 2-(1-Methoxyvinyl)benzoate (**1f**). 2-Acetylbenzoic acid (Aldrich) was esterified with either diazomethane or dimethyl sulfate in a refluxing acetone-K_2CO_3 slurry. The resulting oil, bp 108° (0.4 mm), was then treated as other acetophenones. Upon conversion to the ketal, a few per cent of 3-methoxy-3-methylphthalide (**2**) was obtained, but this could be removed after the ketal cracking by preparative glpc. The ketal was cracked to yield **1f**, a clear oil, in 95% yield: nmr δ_{CCl_4} 3.57 (s, 3 H), 3.74 (s, 3 H), 4.19 (d, J = 2.4 Hz), 4.29 (d, J = 2.4 Hz), total of 2 H; 7.1–7.7 (m, 4 H); high resolution mass spectrum (chemical ionization, giving P + 1 ion), 193.0856 (calcd for $(C_{11}H_{13}O_3)^+$, 193.0865).

Sodium 2-(1-Methoxyvinyl)benzoate (**1a**). Methyl 2-(1-methoxyvinyl)benzoate (**1f**) was treated exactly in the manner of the para isomer, **1g**, in the preparation of **1c**. The product obtained was not contaminated with 2-acetylbenzoic acid. It was later shown that the first product of hydrolysis of **1a** is **2** (see below); any of this material which was formed in the saponification reaction is evidently removed in the ether extraction: nmr $\delta_{D_2O/NaOD}$ (ppm downfield from HDO) 1.13 (s, 3 H), 0.40 (d, J = 2.4 Hz), 0.30 (d, J = 2.4 Hz), total of 2 H, −2.6 (apparent s, 4 H).

3-Methoxy-3-methylphthalide (**2**). Stirring 2-acetylbenzoic acid

(18) K. B. Wiberg, R. R. Kitner, and E. I. Mottell, *J. Amer. Chem. Soc.*, **85**, 450 (1963).
(19) S. Winstein and L. I. Ingraham, *J. Amer. Chem. Soc.*, 77, 1738 (1955).
(20) J. K. Detweiler and E. D. Anstutz, *J. Amer. Chem. Soc.*, **72**, 2882 (1950).
(21) W. S. Emerson and C. F. Deebel, *Org. Syn.*, **32**, 81 (1952).

with 6 weight equiv of purified thionyl chloride at room temperature for 2 hr, followed by removal of the excess thionyl chloride at 30° and reduced pressure, gave a quantitative yield of a fuming white solid, which could be recrystallized from hexanes or petroleum ether to a mp of 55–56°. Literature melting point for **2-acetylbenzoyl chloride (3-methoxy-3-chlorophthalide)** is 54°,[22] 57–58°.[23] This compound was added directly to a rapidly stirred solution of anhydrous methanol (15 ml per gram of 2-acetylbenzoic acid used) containing 2.5 g of dry pyridine per gram of 2-acetylbenzoic acid used. The mixture was stirred for 5 min, poured into water, and extracted with ether. The ether extracts were backwashed with 5% HCl, 5% $NaHCO_3$, and H_2O, dried, and concentrated. Distillation afforded a 51% yield of the desired compound, bp 105° (0.5 mm). This was, however, contaminated with 5–10% of two impurities readily observable in the nmr spectrum. One was the ester **1f**, which could be easily separated and detected by glpc on the Carbowax column noted above in the preparation of **1e**, at 200°. The other impurity, which cochromatographed on glpc with the desired compound, appeared to be, from its nmr, 3-methylenephthalide (**3**). This material, the desired compound, and the ester



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impurity, running in that order, were resolved on preparative thin-layer chromatography (tlc) using multiple elutions with 15 vol % of ethyl acetate in hexanes on 1 mm × 20 × 20 cm plates on silica gel PF-254 (Brinkmann-Merck). The desired compound, from the pooling of the results of several such plates, was pure by both analytical glpc and analytical tlc: ir carbonyl absorption at 1770 ± 5 cm^{-1}; nmr δ_{CCl_4} 1.74 (s, 3 H), 3.00 (s, 3 H), 7.4–8.0 (m, 4 H); high resolution mass spectrum (chemical ionization, giving P + 1 ion), 179.0704 (calcd for $(C_{10}H_{11}O_3)^+$, 179.0708).

Kinetic Procedures. The solvent system used in the kinetic determinations was "5% dioxane"-water, 1 *M* ionic strength. For a typical buffer whose conjugate acid is HA, the amount of HA corresponding to the maximum total buffer concentration desired for a given series of determinations was pipetted into a 25-ml volumetric flask from a *ca.* 1 *M* standardized solution of HA, except when the acid was $H_2PO_4^{2-}$; in this case, KH_2PO_4 was weighed into the flask. An amount of *ca.* 0.5 *M* standard KOH was added, corresponding to the concentration of A desired. A weight of KCl was added such that the final total ionic strength, μ, would be 1.0 *M*; 1.25 ml of dioxane, freshly stirred over and distilled from $LiAlH_4$, was added, and the solution was brought to volume with doubly distilled, deionized water. For subsequent serial dilutions of the same buffer, this master solution was diluted with a "5% dioxane"-1.0 *M* KCl solution. For pH values of <3, solutions of the desired pH were made up by dilutions of standard HCl solutions; "5% dioxane" was then added, as well as sufficient KCl so that the ionic strength was maintained at 1.0 *M*.

pH meter readings (Radiometer PHM 26, Combination Electrode GK 2302B) of standard HCl solutions in the concentration range 0.001–0.1 *M* in this solvent system revealed that the pH meter reading equals $-\log [H^+]$, within the tolerance of the meter reading (±0.02 pH unit); pH = the pH meter reading, and a_H = the hydrogen ion activity based on the one molar, dilute solution reference state in a particular medium of a given ionic strength and organic solvent composition. Bates[24] and Van Uitert and Haas[25] have shown that the pH meter reading in many mixed solvent systems is equal to pH within a constant, δ, which itself is independent of pH and dependent only on the composition of the medium in question.

$$pa_H = pH - \delta \quad (2)$$

Our observations with dilute HCl solutions indicate that, if one can assume that activity coefficients based on the 1 *M* dilute solution reference state in *this solvent system* approach unity for these HCl solutions, δ is essentially zero. Thus, we shall assume that

$$pa_H = pH \quad (3)$$

in this study.

pK_a values of buffers in this solvent system were assumed to be equal to the pH of a half-neutralized solution of the acidic buffer component in the most concentrated solution of that buffer used in the kinetic study. For acetic acid buffers, for example, the pK_a was therefore measured as the pH of a 1:1 [HOAc]/[OAc] solution, with the stoichiometric concentration of acetate (*i.e.*, [HOAc] + [OAc]) = 0.2 *M*. The pH meter readings changed negligibly with sequential dilution of buffers at a constant ratio of the buffer components, and the difference in pH values at different buffer ratios was that predicted from the mass action law, taking as the buffer acid dissociation constant antilog $[-pK_a]$. Thus, the pK_a values used here are operationally useful in this solvent system.

pH values at elevated temperatures were measured in jacketed vessels thermostated at the appropriate temperature. For pD determinations in D_2O, the use of standardized DCl/D_2O solutions, made up from 20% DCl/D_2O ampoules, after the manner of Fife and Bruice's[26] procedure for aqueous solution, established that, for the solvent system used here

$$pa_D = pH + 0{,}36 \quad (4)$$

Isotope effects were determined in the acidic region of pD with these standard DCl solutions, and in the buffer region with acetate buffers made up from standard CH_3CO_2D (98 mol %)/D_2O solutions and dried potassium acetate.

Kinetic determinations were carried out spectrophotometrically in the usual manner on either a Cary Model 1605 spectrophotometer, or a Beckman DU spectrophotometer, both thermostated at the appropriate temperature. The pH of the kinetic solution before and after the kinetic determination was found to be invariant throughout the course of all determinations. A scan of the uv spectrum during all reactions as a function of time revealed that in all reactions except that of **1a**, as detailed below, invariant isosbestic points were observed, and kinetics were cleanly first order throughout the reaction for >5 half-lives. Pseudo-first-order rate constants were calculated either from the slopes of semilogarithmic plots of $A_\infty - A_t$ *vs.* time, or by the method of Kézdy, Jaz, and Bruylants.[27]

For the reaction of **1a**, the time rate of change in absorbance was observed to change sign after a period of time, so that stable "infinity" readings were not obtained; likewise, clearly defined isosbestic points were also not observed. It was subsequently shown (see below, and Results) that this behavior was due to the intermediacy of **2** in the **1a** → 2-acetylbenzoic acid (**4**) conversion. The **2** → **4** reaction was sufficiently slow at the pH values used in the study of the **1a** → **2** reaction that rates of reaction of **1a** in its conversion to **2** could be obtained reproducibly by treating the data by the Kézdy method,[27] which does not require a stable infinity reading. In selected cases, the rate constants so obtained were verified by a nonlinear least-squares fitting of the entire progress curve of the **1a** → **4** conversion to the expression for two consecutive first-order reactions (see eq 7, below). The argument of the more rapidly changing exponential was always identical with that obtained by the more approximate method. The problem of the incursion of the **2** → **4** reaction became less serious as the pH was lowered, because the rate of the more rapid process increased with decreasing pH, whereas that of the slower process was pH-invariant, and because the electronic spectrum of **2** and **4** becomes essentially identical at pH values which are less than the pK_a of **4**.

The presence or absence of buffer catalysis was assessed by the usual method of measuring the rates of the reaction at varying total buffer concentration at constant ionic strength and pH. Buffers were used at rather low concentrations in order to obtain more accurate extrapolations to zero buffer concentration, and in order to minimize contributions of the buffer to the total ionic strength. The ionic strength contribution from buffer was never greater, and was usually less, than 18% of the total ionic strength. Linearity in plots of the observed pseudo-first-order rate constant *vs.* total buffer was obtained for all compounds across the range of buffer concentration studied. Some reactions were run with 0.5 *M*

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(25) L. G. Van Uitert and C. G. Haas, *J. Amer. Chem. Soc.*, 75, 451, 455 (1953); 76, 5887 (1954).
(26) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, 65, 1079 (1961).
(27) F. J. Kézdy, J. Jaz, and A. Bruylants, *Bull. Soc. Chim. Belg.*, 67, 687 (1958).

KBr replacing an equivalent amount of KCl as the inert electrolyte. This substitution did not affect the pH at a given buffer ratio.

Product Determinations. For the reactions of compounds **1c-k** and **2**, infinity spectra were quantitatively matched to those of the corresponding acetophenone in the same solvent. The complex behavior of **1a** and **1b** on hydrolysis, however, necessitated more detailed considerations. Preparative scale reactions of **1a**, not possible with **1e-2**, could be carried out because of increased solubility of the acid of its anion. Two different types of experiments were conducted, one in the pH region well below the pK_a of both **1a,b** and **4**, and one in the pH region above the pK_a of both **1a,b** and **4**.

For the experiments in the acid region, 36 mg of **1a** (0.18 mmol) was placed in 10 ml of 0.1 *M* KCl and "5% dioxane" so that the final concentration of the substrate was 0.018 *M*. After 5 min (> 10 half-lives, according to a parallel kinetic experiment) the solution was extracted with ether. The ether extract was backwashed with water and concentrated to 10–15 ml. This solution was treated with diazomethane generated from a magnetically stirred, 1:1 v/v 50% KOH-ether mixture and 0.9 g of *N*-methyl-*N*-nitrosourea in a small scale generator. The residue after drying and concentrating was analyzed by glpc ($^1/_8$ in. × 8 ft, 20% Carbowax 20M on neutral 60–80 mesh Chromosorb W at 170°) for relative amounts of methyl 2-acetylbenzoate (**5**) derived from CH_2N_2 treatment of 2-acetylbenzoic acid (**4**) and 3-methoxy-3-methylphthalide (**2**), presumably unaffected by the CH_2N_2 treatment. Artificially concocted mixtures of **2** and **4**, on the same scale as the experiment, were subjected to reaction conditions, and to the isolation and CH_2N_2 treatment. Glpc analysis revealed that the **5**:**2** molar ratio recovered was exactly identical with the **4**:**2** ratio subjected to the reaction conditions. Corrections for relative thermal conductivity detector sensitivity were made by analysis of standard mixtures of **5** and **2**; such corrections, however, proved to be negligible. The controls showed that this method was sensitive to **5**:**2** molar ratios of 1:100; that is, 1% **5** could easily be detected. The precision of the method is estimated as ±0.1% in the absolute amount of **5** present. Finally, the species emerging from the detector of the chromatograph were identified as **5** and **2**, respectively, by mass spectral comparison with authentic samples.

For experiments above the pK_a of **1a,b**, the results of the deuterium incorporation studies below may be cited in which excellent recoveries of **2**-*d* were obtained. However, any **4** present in the reaction mixture would remain as the anion at the higher pH employed, and would not be extracted into ether. Therefore, we sought another method to estimate the amount of **4** formed concurrently with **2**. At pH 6.60, in phosphate buffer (total phosphate = 0.500 *M*), the reactions **1a** → **2** and **2** → **4** are both rather slow. The uv spectrum of **1a** was determined immediately after injection into the solvent. Complete conversion to **4** was then allowed to proceed (several days) and the uv spectrum of **4** was then determined. Extremely accurate *relative* extinction coefficients of **1a** and **4** could thus be determined. In a similar manner, relative extinction coefficients of **2** and **4** could be measured. The progress curve for the complete **1a** → **4** conversion was then recorded at the wavelength at which **1a** and **2**, and **2** and **4**, show a maximum difference in their uv spectra, 260 nm. The infinity point, A_∞, in this progress curve was assumed to equal $\epsilon_4[\mathbf{1a}]_T$, where ϵ_4 is the extinction coefficient of **4** at 260 nm, and $[\mathbf{1a}]_T$ is the stoichiometric amount of substrate present in solution; highly accurate values of ϵ_{1a} and ϵ_2 relative to this ϵ_4 were available from the above experiments. The value of ϵ_4 thus calculated agreed well with the value determined independently from authentic **4**, but the important feature in what follows is the availability of the accurate relative extinction coefficients. The absorbance *vs.* time data for the entire progress curve were fitted to alternate mechanisms discussed below and enabled us to determine to what extent **4** was produced directly from **1a**, and how much came from **2** in the overall reaction **1a** → **4**.

Deuterium incorporation into **2** was assessed by the isolation of **2** from the reaction of **1a,b** in either D_2O/DCl solution (acidic region) or in CH_3CO_2D-potassium acetate-D_2O, 0.2 *M* total acetate, at a pD approximately 1 unit above the pK_a of **1a,b** in D_2O (basic region). The scale of the experiments was identical with that of the product identification experiments, and the isolation procedure was identical with that for the experiments in the acidic region. For experiments in the basic region, the **2** was extracted directly into ether from the reaction mixture. Glpc showed that **2** was the only detectable component present in the residue from the dried ether extract. Deuterium content was analyzed by nmr by repeated integration of the CH_2D signal relative to the OCH_3 signal. The

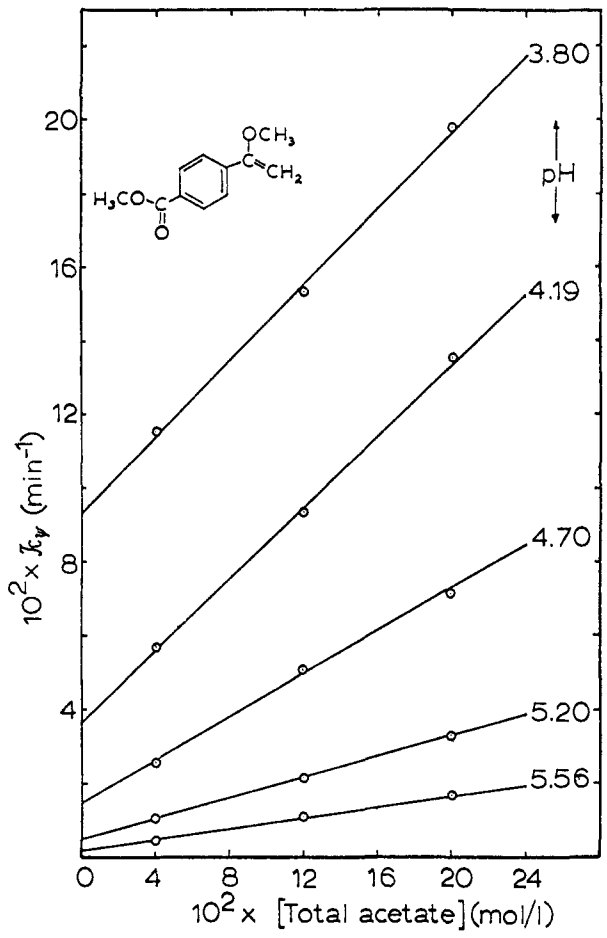


Figure 1. The buffer and pH dependence of the hydrolysis of 4-carbomethoxy(1-methoxyvinyl)benzene. The points are experimental, and the lines are the linear least-squares best fit.

reproducibility of this method was ±1–2% of the amount of deuterium present, and the accuracy, limited by the integration techniques used, is about ±10%. We also attempted to analyze for the amount of deuterium incorporated into **2** using chemical ionization mass spectrometry, since electron impact operation fails to yield a parent ion for this compound. The results on a given sample were highly variable, a fact suggesting that an exchange process was occurring in the mass spectrometer; reasonable mechanisms may be written for such a process.

Deuterium exchange from solvent into unreacted starting material was studied by following the progress of the reaction of **1a** in an nmr tube. Dioxane, which would have interfered with the spectral analysis, and KCl were omitted from this reaction mixture, and the buffer was a 1.0 *M* total acetate buffer, $[CH_3CO_2D]$ = 0.250 *M*, [KOAc] = 0.750 *M*, pD 5.76 (well above the pK_a of **1a,b** in D_2O). The concentration of substrate in the reaction mixture was 0.30 *M*; thus, the substrate concentration was about equal to the general acid concentration. Since the **1a** → **2** reaction consumes 1 equiv of protons, this means that pseudo-first-order conditions no longer apply in this experiment. As the reaction proceeded, the pD rose as **2** oiled out of solution, and the reaction became progressively slower; under these conditions, the reaction was effectively stopped at 69% completion by the high pD (8.03) of the solution. Careful spectral analysis of the remaining **1a** could then be carried out at leisure; the relative integration of the vinyl and methoxy signals of **1a**, by both spectrometer integration and planimeter methods, enabled us to assess the amount of exchange into the vinyl protons of unreacted **1a**. The interpretation of this experiment is obviously contingent on certain assumptions, namely, that the omission of dioxane and KCl results in no mechanistic alteration, and that the higher buffer concentration used also does not result in mechanistic change. The high concentrations used in this study are obviously necessary to achieve reasonable sensitivity with the nmr technique used.

Calculations. Nonweighted, linear least-squares fitting of data

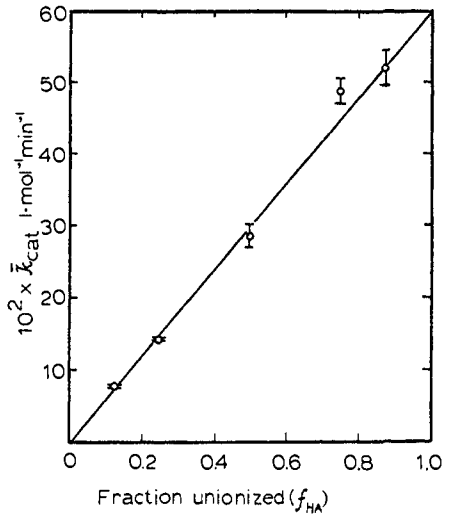


Figure 2. A replot of the slopes of the lines, $\tilde{k}_{cat}$, in Figure 1, against fraction of the buffer in the conjugate acid form. The points are experimental, the error bars are standard deviations, and the line is calculated from a weighted, linear least-squares analysis of the data. The left- and right-hand intercepts are respectively -0.002 ± 0.033 and 0.599 ± 0.036 M^{-1} min^{-1}.

strongly buffer catalyzed. Figure 1 illustrates this behavior for **1g**, which is exemplary of the behavior of **1c–k**. The lines in this figure are the least-squares lines calculated according to

$$k_\psi = \tilde{k}_{cat}[B_T] + k_0 \quad (5)$$

in which k_ψ is the observed pseudo-first-order rate constant, and $[B_T]$ is the total, stoichiometric concentration of buffer at constant pH. That only the acidic component of the buffer catalyzed the reaction (*i.e.*, apparent general acid catalysis) was shown by a weighted, linear least-squares fit of the $\tilde{k}_{cat}$ values ("apparent catalytic constants") to the equation

$$\tilde{k}_{cat} = (k_{HA} - k_A)f_{HA} + k_A \quad (6)$$

in which f_{HA} = fraction of the buffer in the acidic form, k_{HA} = the second-order rate constant ("catalytic constant") for catalysis by the acidic buffer component HA, and k_A = the catalytic constant for catalysis by the basic buffer component A. As Figure 2 illustrates, k_A is zero within experimental error. This behavior is typical of all compounds studied which showed buffer catalysis, *i.e.*, only apparent general acid catalysis was observed. For the hydrolytic reaction of **2**, buffer catalysis was not observed.

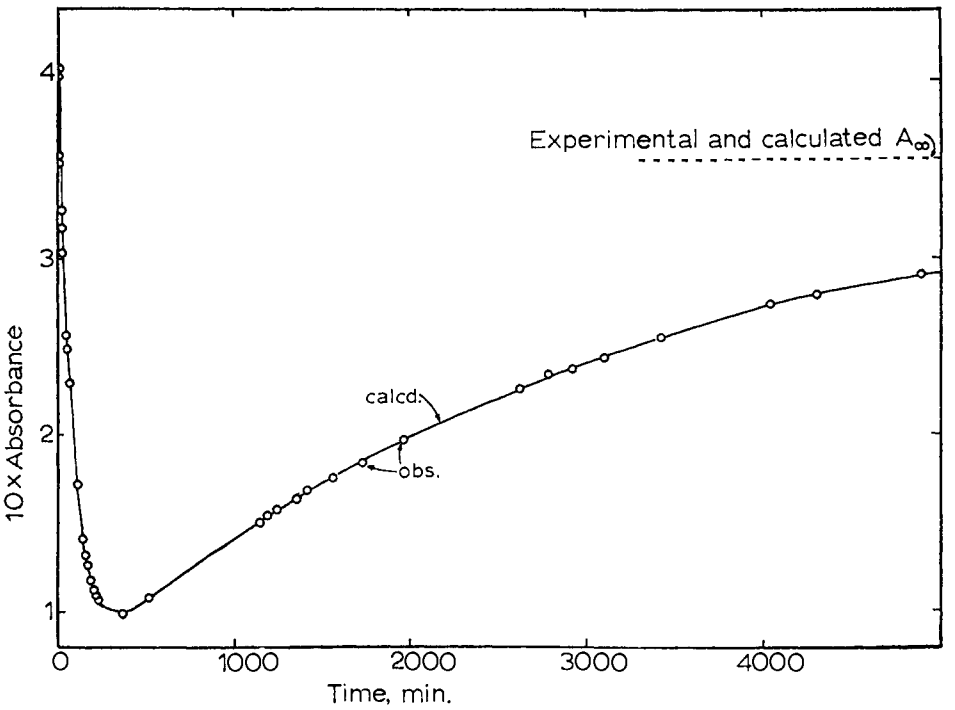


Figure 3. The absorbance *vs.* time curve for the **1a,b** → **2** → **4**, **1a,b** → **4** conversion. The points are experimental, and the line was calculated by a nonlinear least-squares fit of the data to eq 7. The conditions of the experiment are described in the text.

The reaction of **1a** did not display clean, first-order behavior, especially at the higher pH values used. The progress curve of absorbance *vs.* time for this compound at pH 6.60 (shown in Figure 3) was fitted to the five-parameter equation in which A_t is the observed

$$A_t = A_\infty + A_1 e^{-k_{\psi 1} t} + A_2 e^{-k_{\psi 2} t} \quad (7)$$

absorbance at time t, A_∞ is the absorbance at the completion of the entire reaction, and the A_i and $k_{\psi i}$ are arbitrary amplitude and pseudo-first-order rate

was carried out on programmed desk calculators. Weighted linear and all nonlinear least-squares calculations were carried out according to the methods described by Wentworth[28] on the Cornell University IBM 360/65 Computer System.

Results

The hydrolysis of compounds **1c–k** and **2** to the corresponding acetophenones showed excellent pseudo-first-order kinetic behavior. The hydrolyses of **1c–k** were

(28) W. E. Wentworth, *J. Chem. Educ.*, **42**, 96 (1965). We used a program written by Professor C. F. Wilcox, Jr., which effects a weighted least-squares fit to any function of up to ten observables and seven parameters. We are indebted to Professor Wilcox for assistance with our computations and for helpful discussion.

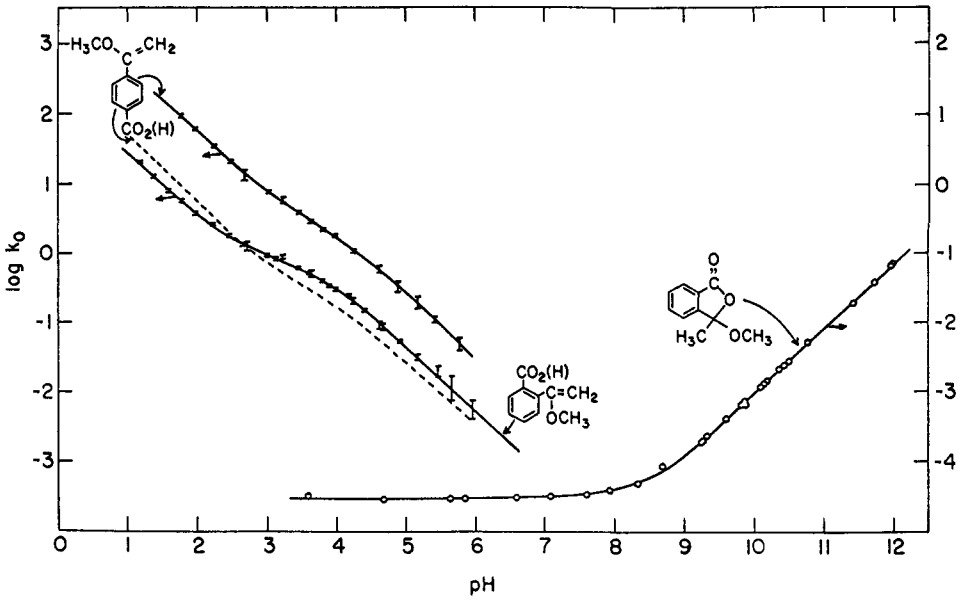


Figure 4. The dependence of log k_0 *vs.* pH for the hydrolysis of **1a,b** and **1c,d** (left axis) and **2** (right axis). The experimental points for **1c,d** are drawn one log unit higher for clarity; the actual values are described by the dotted line. The points are experimental, and the error bars (for **1a,b,c,d**) represent standard deviations. The lines are calculated from a weighted, nonlinear least-squares fit of the data to eq 11 (in the case of **1a,b,c,d**), or from a nonlinear least-squares fit of the data to eq 12 (in the case of **2**). For the right axis, log k_0 corresponds to log k_{24} in the text.

constants, respectively. This equation is valid for the pseudo-first-order interconversion of three species.[29] The value of $k_{\psi 2}$ was identical with that found independently, under identical conditions, for the **2** → 2-acetylbenzoic acid (**4**) interconversion; for example, $k_{\psi 2}$ at pH 6.60, 0.500 *M* total phosphate, was (3.14 ± 0.04) × 10^{-4} min^{-1}, in excellent agreement with the observed rate constant for the **2** → **4** conversion, (3.16 ± 0.03) × 10^{-4} min^{-1}. This fact, the isolation of **2** in high yield at the minimum in the progress curve, the irreversibility of the overall reaction as well the **2** → **4** conversion, the lack of more than one deuterium per molecule incorporated into **4** when the reaction was run in deuterated solvent, and the lack of incorporation deuterium into unreacted **1a** (see below) indicated that the maximally complex scheme consistent with eq 7 for the reaction of **1a** is

$$\begin{array}{ccc} \mathbf{1a} & \xrightarrow{k_{12}} & \mathbf{2} \\ & {\scriptstyle k_{14}}\searrow \quad \swarrow{\scriptstyle k_{24}} & \\ & \mathbf{4} & \end{array} \qquad (8)$$

Equation 8 allows the interpretation of the empirical parameters of eq 7 as in eq 9a–e, in which ϵ_i is the molar

$$k_{\psi 1} = k_{14} + k_{12} \qquad (9a)$$

$$k_{\psi 2} = k_{24} \qquad (9b)$$

$$A_\infty = \epsilon_4[S_0] \qquad (9c)$$

$$A_1 = \left(\epsilon_1 + \frac{k_{12}\epsilon_2 - (k_{24} - k_{14})\epsilon_4}{k_{24} - k_{14} - k_{12}}\right)[S_0] \qquad (9d)$$

$$A_2 = \left(\frac{k_{12}(\epsilon_4 - \epsilon_2)}{k_{24} - k_{14} - k_{12}}\right)[S_0] \qquad (9e)$$

extinction coefficient of species *i*, and $[S_0]$ is the stoichiometric substrate concentration [**1a** + **2** + **4**]. $k_{\psi 1}$ was found to be dependent on the concentration of the acidic component of the buffer, following eq 5 and 6 with $k_A = 0$ within experimental error. The derived parameters for k_{cat} and k_0 (based on eq 5 and 6) are tabulated in Table I. Table II, in the microfilm edition, is a complete account of all our kinetic data; see Supplementary Material Available.

When values of log k_0 (eq 5) were plotted against pH, linear plots were obtained for compounds **1e–k** which had slopes of about −1; no spontaneous water catalysis was observed for any of these compounds. This fact, coupled with the observations above associated with buffer catalysis, indicates that the rate law for hydrolysis of compounds **1e–k** is

$$k_\psi = k_{H_3O^+}[H^+] + k_{HA}[HA] \qquad (10)$$

where $[H^+]$ = antilog[−pH], and HA is the conjugate acid of the buffer used in the kinetic solution; $k_{H_3O^+}[H^+] = k_0$ of eq 5. It should be noticed that k_0 is rather small compared to $k_{HA}[HA]$, especially at the higher pH values; since k_0 is an extrapolated value based on considerably larger numbers, the uncertainty in k_0 is rather large, typically 10–20%. Values of log $k_{H_3O^+}$ for all compounds are tabulated in Table III. These values were computed from the values of log k_0 calculated from the linear log k_0 *vs.* pH dependence at pH 5.5, where most of the data for all compounds overlap, by adding 5.5 to the observed value of log k_0 at this pH. Extrapolations of log k_0 *vs.* pH plots to pH 0 were not used to determine $k_{H_3O^+}$ because of the lengthy extrapolations that would be required and the rather large errors in k_0.

Plots of log k_0 *vs.* pH for **1a,b** and **1c,d**, however, were clearly nonlinear (Figure 4) and obeyed[30] eq 11, in

(29) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, pp 173–177.

(30) The actual form of this equation which was fitted to the data replaced the exponent 2 in the numerator of the first term with (1 + *m*), and the first-power dependence in the numerator of the second term with *m*. The best-fit values of *m* for both **1a,b** and **1c,d** was found to be 0.96 ± 0.02. This empirical parameter *m* was used to take into account routinely observed deviations of log k_0 *vs.* pH plots from a theoretical slope of −1.0. See, for example, the discussion in ref 28 of the use of such parameters to take into account systematic deviations. The value of *m* is sufficiently close to unity that it will be taken as such in the subsequent discussion.

Table I. pH and Buffer Dependence for Vinyl Ether Hydrolysis

Entry	Buffer[a]	pH(pD) (±0.02)	$\bar{k}_{cat}$,[b] M^{-1} min^{-1}	k_0,[b] min^{-1}
		Hydrolysis of **1a,b**, 29.9 ± 0.05° ($k_\psi = k_{\psi 1}$, eq 7)		
1	KH_2PO_4	5.96	$(2.85 \pm 0.40) \times 10^{-1}$	$(5.55 \pm 1.90) \times 10^{-3}$
2	KH_2PO_4	5.66	$(4.31 \pm 0.80) \times 10^{-1}$	$(1.15 \pm 0.45) \times 10^{-2}$
3	CH_3CO_2H	5.46	$(2.78 \pm 0.21) \times 10^{-1}$	$(1.93 \pm 0.32) \times 10^{-2}$
4	CH_3CO_2H	5.17	$(5.14 \pm 0.15) \times 10^{-1}$	$(3.17 \pm 0.23) \times 10^{-2}$
5	CH_3CO_2H	5.19	$(5.14 \pm 0.06) \times 10^{-1}$	$(2.54 \pm 0.08) \times 10^{-2}$
6	CH_3CO_2H[c]	5.19	$(5.29 \pm 0.06) \times 10^{-1}$[c]	$(2.89 \pm 0.08) \times 10^{-2}$[c]
7	CH_3CO_2H	4.91	$(7.00 \pm 0.03) \times 10^{-1}$	$(5.48 \pm 0.04) \times 10^{-2}$
8	CH_3CO_2H	4.67	$(9.49 \pm 0.50) \times 10^{-1}$	$(8.85 \pm 0.80) \times 10^{-2}$
9	CH_3CO_2H	4.40	$(1.09 \pm 0.01) \times 10^{0}$	$(1.53 \pm 0.02) \times 10^{-1}$
10	CH_3CO_2H	4.18	$(1.10 \pm 0.03) \times 10^{0}$	$(2.38 \pm 0.05) \times 10^{-1}$
11	CH_3CO_2H	3.89	$(1.16 \pm 0.01) \times 10^{0}$	$(3.45 \pm 0.02) \times 10^{-1}$
12	HCO_2H	4.62	$(8.81 \pm 0.80) \times 10^{-1}$	$(9.19 \pm 1.00) \times 10^{-2}$
13	HCO_2H	4.24	$(1.54 \pm 0.02) \times 10^{0}$	$(2.10 \pm 0.17) \times 10^{-1}$
14	HCO_2H	4.00	$(2.04 \pm 0.01) \times 10^{0}$	$(3.07 \pm 0.01) \times 10^{-1}$
15	HCO_2H	3.80	$(2.59 \pm 0.02) \times 10^{0}$	$(3.95 \pm 0.02) \times 10^{-1}$
16	HCO_2H	3.62	$(2.48 \pm 0.19) \times 10^{0}$	$(5.25 \pm 0.30) \times 10^{-1}$
17	HCO_2H	3.63	$(2.47 \pm 0.30) \times 10^{0}$	$(5.07 \pm 0.50) \times 10^{-1}$
18	HCO_2H	3.44	$(2.59 \pm 0.05) \times 10^{0}$	$(6.10 \pm 0.06) \times 10^{-1}$
19	HCO_2H	3.24	$(2.17 \pm 0.30) \times 10^{0}$	$(8.86 \pm 0.50) \times 10^{-1}$
20	HCO_2H	3.13	$(2.50 \pm 0.06) \times 10^{0}$	$(8.22 \pm 0.09) \times 10^{-1}$
21	HCO_2H	3.01	$(2.25 \pm 0.22) \times 10^{0}$	$(9.40 \pm 0.30) \times 10^{-1}$
22	HCO_2H	2.68	$(2.00 \pm 0.01) \times 10^{0}$	$(1.34 \pm 0.01) \times 10^{0}$
23	HCl	2.48		$(1.79 \pm 0.02) \times 10^{0}$
24	HCl	2.25		$(2.55 \pm 0.03) \times 10^{0}$
25	HCl	1.98		$(3.83 \pm 0.04) \times 10^{0}$
26	HCl	1.78		$(5.81 \pm 0.07) \times 10^{0}$
27	HCl	1.58		$(8.16 \pm 0.09) \times 10^{0}$
28	HCl	1.38		$(12.8 \pm 0.2) \times 10^{0}$
29	HCl	1.18		$(20.3 \pm 0.3) \times 10^{0}$
30	CH_3CO_2D	5.81	$(6.71 \pm 0.05) \times 10^{-2}$	$(3.70 \pm 0.07) \times 10^{-3}$
31	CH_3CO_2D	5.49	$(1.11 \pm 0.02) \times 10^{-1}$	$(6.15 \pm 0.30) \times 10^{-3}$
32	CH_3CO_2D	5.17	$(1.66 \pm 0.01) \times 10^{-1}$	$(1.05 \pm 0.02) \times 10^{-2}$
33	$DCl(D_2O)$	2.01		$(1.12 \pm 0.02) \times 10^{0}$
		Hydrolysis of **1a,b**, 53.0 ± 0.05°		
34	CH_3CO_2H	5.67	$(1.70 \pm 0.14) \times 10^{0}$	$(1.44 \pm 0.18) \times 10^{-1}$
35	CH_3CO_2H	5.35	$(2.74 \pm 0.19) \times 10^{0}$	$(2.82 \pm 0.26) \times 10^{-1}$
36	CH_3CO_2H	5.02	$(3.77 \pm 0.24) \times 10^{0}$	$(4.81 \pm 0.32) \times 10^{-1}$
		Hydrolysis of **1c,d**, 29.9° ($k_\psi = k_{\psi 1}$, eq 7)		
37	KH_2PO_4	5.77	$(4.46 \pm 0.15) \times 10^{-1}$	$(4.69 \pm 0.80) \times 10^{-3}$
38	CH_3CO_2H	5.42	$(4.16 \pm 0.08) \times 10^{-1}$	$(1.10 \pm 0.10) \times 10^{-2}$
39	CH_3CO_2H	5.17	$(6.44 \pm 0.23) \times 10^{-1}$	$(1.92 \pm 0.31) \times 10^{-2}$
40	CH_3CO_2H	5.19	$(6.47 \pm 0.03) \times 10^{-1}$	$(1.95 \pm 0.03) \times 10^{-2}$
41	CH_3CO_2H[c]	5.19[c]	$(7.56 \pm 0.34) \times 10^{-1}$[c]	$(1.21 \pm 0.46) \times 10^{-2}$[c]
42	CH_3CO_2H	4.88	$(9.87 \pm 0.36) \times 10^{-1}$	$(3.32 \pm 0.50) \times 10^{-2}$
43	HCO_2H	4.62	$(1.00 \pm 0.05) \times 10^{0}$	$(5.72 \pm 0.60) \times 10^{-2}$
44	HCO_2H	4.24	$(1.70 \pm 0.04) \times 10^{0}$	$(1.10 \pm 0.05) \times 10^{-1}$
45	HCO_2H	4.00	$(2.04 \pm 0.03) \times 10^{0}$	$(1.79 \pm 0.03) \times 10^{-1}$
46	HCO_2H	3.80	$(2.61 \pm 0.01) \times 10^{0}$	$(2.17 \pm 0.01) \times 10^{-1}$
47	HCO_2H	3.62	$(2.84 \pm 0.09) \times 10^{0}$	$(2.96 \pm 0.01) \times 10^{-1}$
48	HCO_2H	3.44	$(2.93 \pm 0.09) \times 10^{0}$	$(3.88 \pm 0.12) \times 10^{-1}$
49	HCO_2H	3.24	$(2.65 \pm 0.46) \times 10^{0}$	$(5.99 \pm 0.60) \times 10^{-1}$
50	HCO_2H	3.01	$(3.21 \pm 0.05) \times 10^{0}$	$(7.50 \pm 0.07) \times 10^{-1}$
51	HCO_2H	2.68	$(3.50 \pm 0.14) \times 10^{0}$	$(1.36 \pm 0.20) \times 10^{0}$
52	HCl	2.49		$(2.15 \pm 0.03) \times 10^{0}$
53	HCl	2.25		$(3.59 \pm 0.04) \times 10^{0}$
54	HCl	1.98		$(6.06 \pm 0.07) \times 10^{0}$
55	HCl	1.78		$(9.27 \pm 0.09) \times 10^{0}$
56	CH_3CO_2D	5.81	$(8.99 \pm 0.30) \times 10^{-2}$	$(1.09 \pm 0.40) \times 10^{-3}$
57	CH_3CO_2D	5.49	$(1.48 \pm 0.02) \times 10^{-1}$	$(1.99 \pm 0.20) \times 10^{-3}$
58	CH_3CO_2D	5.17	$(1.97 \pm 0.06) \times 10^{-1}$	$(4.94 \pm 0.80) \times 10^{-3}$
59	$DCl(D_2O)$	2.01		$(1.79 \pm 0.02) \times 10^{0}$
60	$DCl(D_2O)$	1.51		$(5.59 \pm 0.06) \times 10^{0}$
61	$DCl(D_2O)$	1.01		$(15.5 \pm 0.2) \times 10^{0}$
		Hydrolysis of **1c,d**, 53.0 ± 0.05°		
62	CH_3CO_2H	5.67	$(1.94 \pm 0.17) \times 10^{0}$	$(5.92 \pm 0.23) \times 10^{-2}$
63	CH_3CO_2H	5.35	$(3.45 \pm 0.18) \times 10^{0}$	$(1.18 \pm 0.21) \times 10^{-1}$
64	CH_3CO_2H	5.03	$(4.59 \pm 0.18) \times 10^{0}$	$(2.00 \pm 0.24) \times 10^{-1}$
		Hydrolysis of **1e**, 29.9 ± 0.05°		
65	KH_2PO_4	6.99	$(3.28 \pm 0.15) \times 10^{-1}$	$(1.74 \pm 0.46) \times 10^{-3}$
66	KH_2PO_4	6.42	$(7.64 \pm 0.33) \times 10^{-1}$	$(3.48 \pm 0.12) \times 10^{-3}$
67	KH_2PO_4	5.86	$(1.08 \pm 0.62) \times 10^{0}$	$(1.74 \pm 0.50) \times 10^{-2}$
68	KH_2PO_4	5.34	$(1.89 \pm 0.70) \times 10^{0}$	$(3.09 \pm 0.42) \times 10^{-2}$

Table I. (*Continued*)

Entry	Buffer[a]	pH(pD) (±0.02)	k_{cat},[b] M^{-1} min^{-1}	k_0,[b] min^{-1}
69	CH_3CO_2H	4.77	(3.42 ± 0.14)	(1.35 ± 0.12) × 10^{-1}
70	KH_2PO_4	7.61	(6.38 ± 1.67) × 10^{-2}	(1.94 ± 0.45) × 10^{-4}
71	KD_2PO_4	6.93	(1.42 ± 0.70) × 10^{-1}	(4.12 ± 0.25) × 10^{-4}
72	KD_2PO_4	6.37	(2.20 ± 0.22) × 10^{-1}	(9.94 ± 1.20) × 10^{-4}
		Hydrolysis of **1e**, 53.0 ± 0.05°		
73	KH_2PO_4	7.04	(1.10 ± 0.07) × 10^{-1}	(9.78 ± 1.94) × 10^{-3}
74	KH_2PO_4	6.54	(2.94 ± 0.06) × 10^{-1}	(1.44 ± 0.02) × 10^{-2}
75	KH_2PO_4	5.85	(3.97 ± 0.68) × 10^{-1}	(1.11 ± 0.33) × 10^{-1}
		Hydrolysis of **1f**, 29.9 ± 0.05°		
76	CH_3CO_2H	5.11	(4.04 ± 0.16) × 10^{-2}	(2.77 ± 0.30) × 10^{-3}
77	CH_3CO_2H	4.66	(7.20 ± 0.23) × 10^{-2}	(6.83 ± 0.40) × 10^{-3}
78	CH_3CO_2H	4.14	(1.03 ± 0.07) × 10^{-1}	(2.18 ± 0.10) × 10^{-2}
79	CH_3CO_2H	3.76	(1.22 ± 0.16) × 10^{-1}	(4.68 ± 0.25) × 10^{-2}
80	HCO_2H	3.29	(5.20 ± 0.12) × 10^{-1}	(1.47 ± 0.02) × 10^{-1}
		Hydrolysis of **1g**, 29.9 ± 0.05°		
81	CH_3CO_2H	5.56	(7.71 ± 0.05) × 10^{-2}	(1.49 ± 0.07) × 10^{-3}
82	CH_3CO_2H	5.20	(1.41 ± 0.02) × 10^{-1}	(4.69 ± 0.25) × 10^{-3}
83	CH_3CO_2H	4.70	(2.85 ± 0.16) × 10^{-1}	(1.48 ± 0.22) × 10^{-2}
84	CH_3CO_2H	4.19	(4.88 ± 0.18) × 10^{-1}	(3.62 ± 0.25) × 10^{-2}
85	CH_3CO_2H	3.80	(5.19 ± 0.25) × 10^{-1}	(9.30 ± 0.30) × 10^{-2}
		Hydrolysis of **1h**, 29.9 ± 0.05°		
86	KH_2PO_4	7.41	(1.76 ± 0.02)	(5.78 ± 0.51) × 10^{-3}
87	KH_2PO_4	7.06	(4.90 ± 0.70)	(8.70 ± 2.4) × 10^{-3}
88	KH_2PO_4	6.99	(4.39 ± 0.02)	(1.16 ± 0.05) × 10^{-2}
89	KH_2PO_4	6.42	(9.38 ± 0.03)	(1.69 ± 0.11) × 10^{-2}
90	KH_2PO_4	5.88	(14.1 ± 0.1)	(6.11 ± 0.02) × 10^{-2}
91	KH_2PO_4	5.36	(24.1 ± 7.8)	(2.75 ± 0.46) × 10^{-1}
		Hydrolysis of **1i**, 29.9 ± 0.05°		
92	KH_2PO_4	7.46	(4.26 ± 0.76) × 10^{-1}	(2.15 ± 1.82) × 10^{-3}
93	KH_2PO_4	6.99	(1.26 ± 0.04)	(4.16 ± 0.11) × 10^{-3}
94	KH_2PO_4	6.43	(2.39 ± 0.67)	(1.73 ± 0.24) × 10^{-2}
95	KH_2PO_4	5.90	(4.47 ± 0.18)	(2.29 ± 0.85) × 10^{-2}
96	KH_2PO_4	5.35	(6.58 ± 0.45)	(8.40 ± 3.06) × 10^{-2}
		Hydrolysis of **1j**, 29.9 ± 0.05°		
97	CH_3CO_2H	5.48	(4.29 ± 0.01) × 10^{-1}	(1.82 ± 0.02) × 10^{-2}
98	CH_3CO_2H	5.19	(7.39 ± 0.30) × 10^{-1}	(2.77 ± 0.53) × 10^{-2}
99	CH_3CO_2H	4.68	(1.49 ± 0.04)	(7.50 ± 0.67) × 10^{-2}
100	CH_3CO_2H	4.20	(2.30 ± 0.27)	(2.03 ± 0.42) × 10^{-1}
101	CH_3CO_2H	3.88	(2.33 ± 0.47)	(4.30 ± 0.73) × 10^{-1}
		Hydrolysis of **1k**, 29.9 ± 0.05°		
102	CH_3CO_2H	3.87	(6.40 ± 0.02) × 10^{-1}	(1.63 ± 0.02) × 10^{-2}
103	HCO_2H	3.62	(2.00 ± 0.37)	(2.60 ± 0.59) × 10^{-2}
104	HCO_2H	3.14	(3.07 ± 0.51)	(7.48 ± 0.81) × 10^{-2}
105	$ClCH_2CO_2H$	2.66	(1.69 ± 0.03)	(2.40 ± 0.05) × 10^{-1}
106	$ClCH_2CO_2H$	2.30	(1.99 ± 0.07)	(4.48 ± 0.10) × 10^{-1}

[a] Buffer identified by the conjugate acid of the acid-base pair. [b] Equation 5; all errors are standard deviations. [c] 0.5 *M* KBr present as part of inert electrolyte; the balance of 1 *M* ionic strength contributed by buffer and KCl.

$$k_0 = k_{0,SH}\left(\frac{[H^+]^2}{K_{SH} + [H^+]}\right) + k_{0,S}\left(\frac{K_{SH}[H^+]}{K_{SH} + [H^+]}\right) \quad (11)$$

which the constants of the system have been arbitrarily interpreted as $k_{0,SH}$, the second-order rate constant for a proton-catalyzed reaction of the un-ionized substrate **1b** or **1d**; $k_{0,S}$, the second-order rate constant for a proton-catalyzed reaction of the ionized substrate **1a** or **1c**; and K_{SH}, the apparent ionization constant of the substrate carboxyl group. Kinetically indistinguishable interpretations of this dependence will be dealt with below. The values of log $k_{0,SH}$, log $k_{0,S}$, and pK_{SH} are also given in Table III.

Because of the obvious involvement of **2** in the reaction scheme, the hydrolysis of **2** to **4** was studied independently. The reaction was not buffer catalyzed. The pH dependence for the hydrolysis of **2** is given in Table IV in the microfilm edition of this journal, and shown also in Figure 4. This followed the equation[31]

$$k_{24} = k_{2\psi} = k_{H_2O} + k_{OH}'/[H^+] \quad (12)$$

Table III. Rate Coefficients for Catalysis of Enol Ether Hydrolysis by Hydronium Ion at 29.9°

Compd	log $k_{H_3O^+}$, M^{-1} min^{-1}	Compd	log $k_{H_3O^+}$, M^{-1} min^{-1}
1a[a,c]	3.48 ± 0.08	**1g**	2.80 ± 0.37
1b[b,c]	2.41 ± 0.03	**1h**	4.56 ± 0.50
1c[a,d]	3.27 ± 0.11	**1i**	4.35 ± 1.42
1d[b,d]	2.68 ± 0.04	**1j**	3.76 ± 0.22
1e	3.97 ± 0.55	**1k**	2.19 ± 0.13
1f	2.55 ± 0.05		

[a] The value of log $k_{H_3O^+}$ given is the value of $k_{0,S}$ of eq 11. [b] The value of log $k_{H_3O^+}$ given is the value of $k_{0,SH}$ of eq 11. [c] pK_{SH} (eq 11) = 3.69 ± 0.03. [d] pK_{SH} (eq 11) = 3.96 ± 0.06.

(31) An arbitrary exponent *m* for the hydrogen ion dependence was also used here, and found to be 0.95 ± 0.02; see ref 30.

with $k_{H_2O} = (2.99 \pm 0.05) \times 10^{-4}$ min^{-1}, $k_{OH}' = (3.09 \pm 0.42) \times 10^{-12}$ M min^{-1}. This behavior is consistent with that observed for other acylals.[32] Because the spectra of **2** and **4** are essentially identical at pH values well below the pK_a of **4**, it was not possible to follow the **2** → **4** conversion at pH values much lower than **4**. There is, undoubtedly, a specific acid catalyzed component[32b] to the reaction, the upper limit of the rate of which, at any pH, may be estimated by projecting a line of slope[31] −0.95 from the observed log k_0 *vs.* pH profile at the experimental point measured at lowest pH. Thus, if there is such an acid-catalyzed reaction, its second-order rate constant can be no larger than about 0.87 M^{-1} min^{-1}.

Use of the extinction coefficients of the detectable species in the reaction of **1a** at 260 nm (the wavelength maximum change for the two reactions **1a** → **2** and **2** → **4**) as determined by methods described in the Experimental Section allowed us to determine k_{12}, k_{14}, and k_{24} (eq 8 and 9) separately for the complete reaction at pH 6.60, potassium phosphate buffer, total phosphate = 0.500 M. This determination gave $k_{24} = (3.15 \pm 0.02) \times 10^{-4}$ min^{-1} (compare with the value of k_{24} determined independently), $k_{12} = (1.04 \pm 0.07) \times 10^{-2}$ min^{-1}, and $k_{14} = (0.80 \pm 0.05) \times 10^{-2}$ min^{-1}; this means that k_{14} is 8 ± 5% of $k_{\psi 1}$. Although the uncertainty in k_{14} is high, this rate constant is not zero. An attempt to fit eq 7, using the interpretations of the parameters given by eq 9, with k_{14} set at zero, resulted in a considerably inferior fit of the data; likewise, the "F-test"[33] attested to the statistical significance of k_{14} to a 99.99% confidence level. Because the second phase of the complete reaction of **1a**, the **2** → **4** conversion, is so slow, this detailed analysis was not carried out at every pH. However, the uv spectrum measured at the minimum in the progress curve in the reaction of **1a** corresponded closely at all pH values to that of **2**, so that, in the region of pH in which the spectrum of **2** is quite distinct from that of **4**, *i.e.*, pH >4, the conclusion that k_{14} is a minor component of $k_{\psi 1}$ is reasonable. At pH values ≪4, the spectra of **2** and **4** are virtually identical, undoubtedly because of the predominance of the "pseudo acid" form of **4** (the pK_a of **4** measured in our solvent system by titration is 4.00 ± 0.02). Thus, at low pH, kinetic information on the direct path from **1a** to **4** is not available. However, product studies at lower pH, detailed in the Experimental Section, enabled us to quantitate the relative amounts of **2** and **4** at the end of the first phase of the reaction. It was found that **4** comprised 2.6 ± 0.2% of the total material (**2** + **4**) isolated; control experiments detailed in the Experimental Section attested to our ability to estimate this number accurately. Thus, $k_{14} \approx 0.03 k_{\psi 1}$ at the lower pH values. This amount of **4** could not have arisen from the **2** → **4** conversion, for which the maximum possible rate (see above) is only 0.12% of $k_{\psi 1}$ at the pH of this product identification experiment. Thus, at all pH values, the $k_{\psi 1}$ determined from the first phase of the reaction is the composite rate constant given by eq 9a, although the k_{12} term highly dominates $k_{\psi 1}$ to the extent of about 92–97%.

Deuterium incorporation into **1a,b** to yield **2-*d*** gave 0.9 ± 0.1 deuterium incorporated per molecule of **2** in both the acidic and basic regions of pH. This fact suggests that the **1a,b** → **2** conversion is essentially irreversible; significant reversibility in this reaction should exchange protons for deuterium, if normal isotope effects for the exchange are assumed. A study of the exchange of deuterium into unreacted **1a** showed that, though about 2 half-lives, the ratio of protons in the methoxy group to those in the vinyl region was 1.5 ± 0.1; 10% exchange could have been detected; evidently, none was observed. This confirms the conclusion of the previous deuterium incorporation experiment, and suggests that all reactions of **1a** are essentially irreversible.

Discussion

Vinyl Ether Hydrolysis Mechanism. The hydrolyses of vinyl ethers and related compounds have been studied by a number of groups.[17] This reaction has been thought to proceed generally *via* an initial, rate-limiting proton transfer to the enol ether double bond. For enol ethers **1c–k**, pseudo-first-order hydrolyses to the corresponding acetophenones are general acid catalyzed as expected for the above mechanism. Solvent isotope effects, $k_{H_3O^+}/k_{D_3O^+}$, are greater than unity and of the magnitude expected for an initial, rate-limiting proton transfer. These effects are tabulated in Table V. Kresge's[17g] group found that the hydrolysis of β-methoxy-*trans*-β-methylstyrene showed $k_{H_3O^+}/k_{D_3O^+}$ of 2.99; likewise, the hydrolysis of α-phenylvinyl diethyl phosphate[34] was characterized by an isotope effect of 2.5; similarly, the hydrolysis of α-acetoxystyrene *via* a rate-limiting proton transfer[35] was 3.1. Our values are in agreement with these.[36]

Table V. Solvent Isotope Effects and Brønsted α Values for Vinyl Ether Hydrolysis

Compd	$k_{H_3O^+}/k_{D_3O^+}$[a]	k_{HA}/k_{DA}[b]	α
1e	3.46 ± 1.17	5.13 ± 0.55[c]	0.55 ± 0.14
1a	2.63 ± 0.24	5.77 ± 0.39[d]	0.49 ± 0.05
1b	2.69 ± 0.19		
1c	4.89 ± 1.57	7.13 ± 0.59[d]	0.48 ± 0.01
1d	3.16 ± 0.36		

[a] Solvent isotope effect on k_0 (eq 5 or 11). [b] Solvent isotope effect on the catalytic rate constant for buffer catalysis. [c] Phosphate buffer. [d] Acetate buffer.

A correlation of log k_0 (values from Table III) with σ^+ for compounds **1d–k** is shown in Figure 5. Again, it must be remembered that the values of log k_0 are somewhat imprecise because of the determination of k_0 by extrapolation, and the fact that k_0 is a relatively small per cent of the k_ψ values on which its determination is based, particularly for the compounds studied at low pH (the compounds with electron-donating substituents). It was clear, however, from a plot of the data, that log k_0 for the *p*-methoxy analog **1h** fell well below the line defined by the other points. A weighted,

(32) (a) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Amer. Chem. Soc.*, 87, 4545 (1965); (b) T. H. Fife, *ibid.*, 87, 271 (1965); (c) K. Bowden and A. M. Last, *J. Chem. Soc., Perkin Trans. 2*, 358 (1973).

(33) P. R. Bevington, "Data Reduction and Error Analysis for the Physical Sciences," McGraw-Hill, New York, N. Y., 1969, p 200.

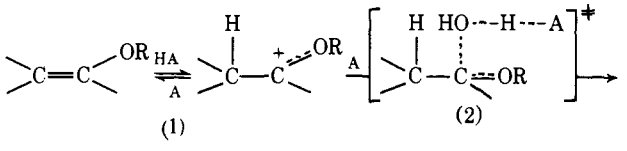
(34) C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 91, 6072 (1969).

(35) D. S. Noyce and R. M. Pollack, *J. Amer. Chem. Soc.*, 91, 119 (1969).

(36) See also A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Amer. Chem. Soc.*, 90, 4174 (1968).

linear least-squares correlation gave, for all points except that for **1h**, $\rho = -2.25 \pm 0.15$. This compares with the value found for the hydrolysis of α-arylvinyl diethyl phosphates,[37] -2.1, and that for α-acetoxystyrenes, -1.9. Brønsted α values were computed for carboxylic acid and phosphate buffers for the hydrolysis of **1a**, **1c**, and **1e**, and are also shown in Table V. They are all equal within experimental error, and have a value of about 0.5. Kresge and Chen[7g] observed a Brønsted exponent of 0.7 for the hydrolysis of β-methoxy-*trans*-β-methylstyrene.

Kresge and Chen noted the possibility that, for hydrolysis leading to a suitably stable α-oxycarbonium ion, a change in rate-determining step might occur so that protonation of the vinyl ether double bond becomes a pre-rate-determining process, and hydration of the resulting α-oxycarbonium ion becomes rate limiting. They noted that a deuterium isotope effect of *ca.* 3 was "compatible only with a rate-limiting transfer of a proton from catalyst to substrate." This statement is, however, not strictly correct. The mechanism shown in eq 13 is one which should lead to "specific acid–general base" catalysis, a phenomenon which is kinetically indistinguishable from general acid catalysis. If the primary isotope effect on step (2) in this mechanism is ~6.3, the secondary effect on step (2) is 1.2, and the



(1) (2)

products (13)

equilibrium effect on step (1) is ~0.4, all values which are theoretically reasonable,[38] an isotope effect $k_{H_3O^+}/k_{D_3O^+}$ of about 3 may be calculated. Furthermore, general base catalysis of step (2) is reasonable in theory,[12] and it has been observed in practice.[39] Step (2) in the direction given, however, is very closely related to the microscopic reverse of the general acid catalyzed hydrolysis of ketals. Fife[10e] has shown that general acid catalysis of ketal hydrolysis is observed when the oxycarbonium ion produced is exceptionally stable; indeed, Ritchie's[39] observations have been on such exceptionally stable carbonium ions, those of certain triaryl dyes. The ions produced in the vinyl ether hydrolyses studied herein and cited above,[17] according to Fife's empirical findings,[10e,40] would not be those expected to show general base catalysis in step (2) of mechanism 13. Furthermore, observed solvent isotope effects for step (2) are in fact quite low[41] (*ca.* 1.2 for the stable ions studied), so that one might indeed expect a substantial reduction in isotope effect for a mechanistic change in vinyl ether hydrolysis to that shown in eq 13. However, isotope effects in processes related to acetal hydrolysis are quite variable,[42] and the isotope effect of 3 *per se* cannot rule out the mechanism of eq 13. Equation 13 predicts deuterium exchange into

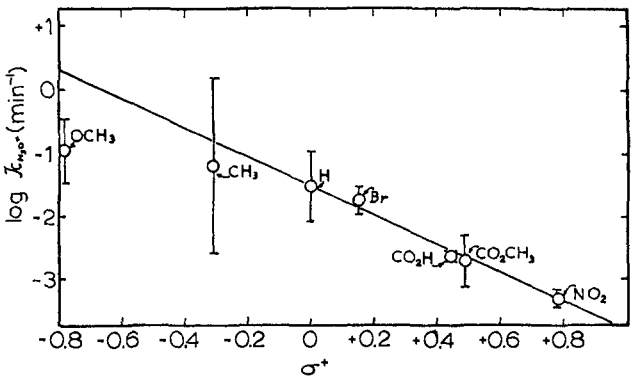


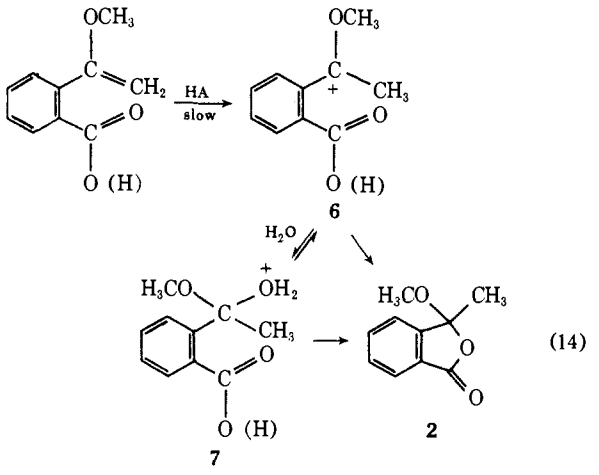
Figure 5. A correlation of the logarithms of the rate constants for hydronium ion catalysis of vinyl ether hydrolysis with σ^+. The error bars are standard deviations, and the line is calculated from a weighted, linear least-squares analysis of the data. Note that the point for the *p*-methoxy analog **1h** is omitted from the correlation, as discussed in the text. The value of ρ is -2.25 ± 0.15.

unreacted vinyl ether; incorporation of one deuterium per molecule into the product carbonyl compound has been observed in vinyl ether hydrolysis, a fact which suggests that such exchange into unreacted starting material does not occur.[17a] The previous discussion shows that the observation of general acid catalysis is a necessary but not sufficient condition to rule out mechanisms which are reasonable alternatives to the rate-determining proton transfer mechanism; nevertheless, the similarity of mechanistic parameters in our study to those of many closely related reactions, isotope incorporation work in these related reactions, and the empirical observations of Fife concerning the likelihood of general acid catalysis in processes related to ketal hydrolysis, suggest that the best mechanistic description for the hydrolysis of the para-substituted enol ethers studied herein is that involving an initial, rate-determining proton transfer to substrate.

The deviation of **1h** from the σ^+ correlation may, in fact, indicate a change of rate-determining step to general base catalyzed carbonium ion hydration. k_{ψ} *vs.* [total buffer] plots for this compound were linear with nonzero slopes (see in particular entry 87 in Table II of the microfilm edition), but no Brønsted α or isotope effect was determined. It is interesting to note that, in this case, the intermediate immediately following carbonium ion hydration might be considered to be that derived from hydrolysis of a "vinylogous ortho ester." The hydrolyses of a number of ortho esters proceed with general acid catalysis.[43] It is also interesting that the data from Tidwell's laboratory[37] for hydrolysis of α-arylvinyl phosphates at 25° show similar curvature when plotted *vs.* σ^+. These data are also extrapolated data, and the probable errors are unspecified. The possibility that the observed deviations from the σ^+ correlation are due to experimental error cannot be rigorously excluded at this time. This reaction is under further investigation.

Hydrolysis of *o*-Carboxyl Substituted Vinyl Ethers. The reaction of **1a,b** at high pH shows isotope effects and buffer catalysis much like the other enol ethers studied, and therefore appears to be proceeding by essentially the same mechanism, which is shown in eq 14. We cannot rigorously distinguish between the

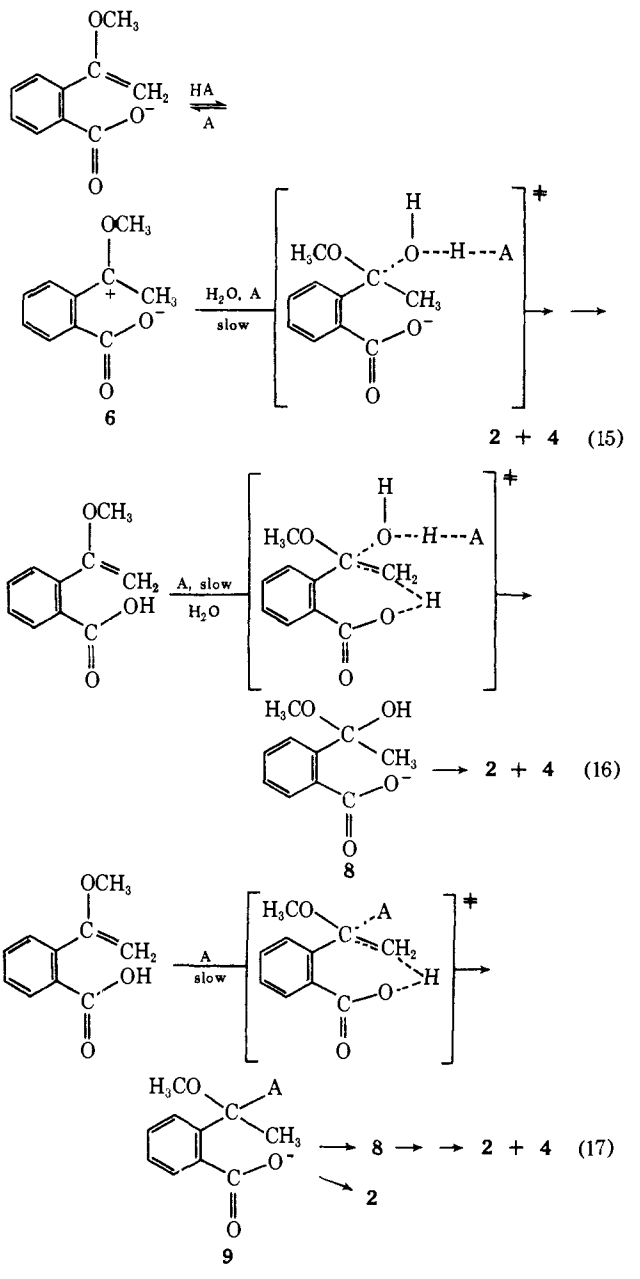
(37) R. D. Frampton, T. T. Tidwell, and V. A. Young, *J. Amer. Chem. Soc.*, **94**, 1271 (1972).
(38) See, for example, C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 3207 (1961).
(39) C. D. Ritchie, *J. Amer. Chem. Soc.*, **94**, 3275 (1972).
(40) T. H. Fife and E. Anderson, *J. Org. Chem.*, **36**, 2357 (1971).
(41) E. A. Hill and W. J. Mueller, *Tetrahedron Lett.*, 2565 (1968).
(42) T. H. Fife and L. H. Brod, *J. Amer. Chem. Soc.*, **92**, 1681 (1970).
(43) T. H. Fife, *Accounts Chem. Res.*, **5**, 268 (1972).



(14)

alternatives of an open carbonium ion intermediate, **6**, for **1a**, and a concerted nucleophilic attack by the carboxylate concurrent with protonation by HA. However, we showed that a small percentage of the reaction of **1a** proceeded to **4** directly; **4** cannot arise from hydrolysis of **2**, which is too slow. This means that attack of water on **6** competes observably with the **6** → **2** closure. If the attack of water to give **7** is not concerted with protonation of **1a**,[44] then the intermediacy of **6** appears reasonable.

The mechanisms of eq 15–17 are all kinetically indistinguishable from that of eq 14 in that they all predict behavior like that observed for a general acid catalyzed reaction of substrate anion, as observed at high pH. The mechanism of eq 15 is ruled out by the absence of exchange of the vinyl hydrogens of substrate in deuterated solvent, by the lack of more than one deuterium incorporated into **2**, and by the theoretical considerations associated with the discussion of the mechanism of eq 13. The mechanism of eq 16 seems unlikely on the same theoretical grounds to the extent that this process resembles a carbonium ion hydration. In addition, the mechanism depicted in this equation is of formally higher molecularity than that of eq 14; this fact might lead one to expect a more negative activation entropy and perhaps a more positive activation enthalpy for this mechanism compared to the same parameters of mechanism 14. The calculated activation parameters are, for acetate buffer catalysis of hydrolysis of **1a**, $\Delta H^{\pm} = 12.3 \pm 0.8$ kcal/mol, $\Delta S^{\pm} = -24.8 \pm 2.6$ eu. The corresponding parameters for hydrolysis of **1c**, for which this mechanisn is impossible, and for which mechanism 14 is presumably operative, are $\Delta H^{\pm} = 12.0 \pm 0.1$ kcal/mol, $\Delta S^{\pm} = -25.5 \pm 0.1$ eu (all values at 302.9°K). The essential identity of activation parameters for **1a** and **1c** could, of course, be the result of a fortuitous correspondence for two different mechanisms, but the simplest interpretation is that both compounds react *via* the same mechanism, that of eq 14. The mechanism of eq 17 cannot be differentiated by activation parameters or isotope effects.



Furthermore, acylals (*e.g.*, **9**) hydrolyze much more rapidly than the corresponding vinyl ethers[46] so that **9** is a viable intermediate. The mechanism of eq 17 implies a nucleophilic contribution to the catalysis; interpretation of the **1a** → **2** conversion in terms of this mechanism leads to

$$k_{\psi 1} = \left(\frac{[H^+]}{K_{SH} + [H^+]}\right) \sum_i k_{N,i}[N_i] \qquad (18)$$

in which K_{SH} is the ionization constant of **1a,b**, $[N_i]$ is the concentration of the ith nucleophilic species in solution, and the summation indicates kinetic contributions from all nucleophiles in solution. If this equation is valid, then the data for catalysis of the reaction by various buffers permit the calculation of a Swain–Scott susceptibility parameter,[47] s; the value of s calculated

(44) The dehydration of alcohols $R_1R_2C(OH)CHR_3R_4$[45] proceeds with either loss of optical activity or exchange of ^{18}O from solvent which is considerably faster than dehydration. Thus, in the microscopic reverse reaction, attack of water cannot be concerted with protonation of the olefin.

(45) (a) D. S. Noyce, D. R. Hartter, and R. M. Pollack, *J. Amer. Chem. Soc.*, 90, 3791 (1968); (b) I. Dostrovsky and F. S. Klein, *J. Chem. Soc.*, 791 (1955); (c) E. Grunwald, A. Heller, and F. S. Klein, *ibid.*, 2604 (1957); (d) R. H. Boyd, R. W. Taft, Jr., A. P. Wolf, and D. R. Christman, *J. Amer. Chem. Soc.*, 82, 4729 (1960).

(46) P. Salomäa, *Acta Chem. Scand.*, **19**, 1263 (1965); **20**, 1802 (1966), and references cited therein.

(47) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, 75, 141 (1953). The Swain–Scott n value for formate was estimated by assuming that the n values for structurally related nucleophiles are linearly related to the pK_a values of their conjugate acids, a procedure that has been used

for this reaction is 0.8, a value in good agreement with that for other reactions involving nucleophilic attack at carbon in aqueous solution.[49] Applying eq 18 for all nucleophiles present in solution for entry 5, Table I, gives $k_{N,acetate}/k_{N,chloride} = 32$. By many known criteria of nucleophilicity,[49] chloride is somewhat more nucleophilic toward carbon than acetate; the observed inverse dependence of k_N on nucleophile is not in accord with this finding. Furthermore, the substitution of 0.5 *M* KBr as the inert electrolyte has a negligible effect on the value of k_0 (Table I, entries 5 and 6). Using the susceptibility parameter of 0.8 in the Swain–Scott equation, it is estimated that k_0 would increase by a factor of 3–4 in the presence of KBr. Expressed another way, calculation of $k_{N,acetate}/k_{N,bromide}$ from eq 18 and the data gives a value of 24 for this ratio, again in the wrong direction and differing by more than two orders of magnitude from the known relative nucleophilicities of acetate and bromide to carbon in aqueous solution.[46,50] It is, of course, possible that the salt effects predicted by eq 18 and other unspecified salt effects conspire to give no net effect. Furthermore, the strict applicability of the Swain–Scott equation assumed here may not hold for this particular mechanism, particularly for nucleophiles of differing type. The weight of available evidence, however, is against the mechanism of eq 17, and the most reasonable mechanism for the reaction of **1a,b** in the high pH region appears to be that of eq 14, in which the carboxyl group is un-ionized.

The intramolecular transfer of a proton is therefore apparently not observed in this reaction; eq 16 and 17 have been excluded above, and a mechanism involving intramolecular proton transfer without participation of the buffer conjugate base would not show catalysis by external buffers. Such intramolecular transfers would proceed through a seven-center transition state (including the proton, and excluding for the moment water chains),[51] and such a transfer would require rotation of the incipient carbonium ion out of coplanarity with the benzene ring. The kinetic consequences of the seven-center proton transfer have not been systematically examined to our knowledge,[52] but the effects of elimination of conjugative overlap are classical results of organic chemistry.

The reaction of **1a,b** at low pH is slower than the corresponding reaction of **1c,d** by a factor of about 2; an almost identical difference is observed for the hydrolysis of **1f** *vs.* **1g**. Although the effects of *o*-carboxyl and -carbomethoxy groups in reactions which develop benzylic carbonium ions have not been estimated, the rate retardations observed herein are of the same order as those encountered when comparing the ortho and para effects of other substituents of similar steric and electronic properties.[53] There is no evidence for participation of the carboxyl group of **1a,b** at low pH, and the reaction is evidently best described by the mechanism of eq 14, with the carboxyl group un-ionized.

The Effect of Carboxyl Group Ionization on Vinyl Ether Protonation Rates. The effect of the carboxyl group ionization on the rates of the hydrogen ion catalyzed reaction of **1a,b** and **1c,d** can be obtained by comparing $k_{0,S}$ and $k_{0,SH}$ (eq 11, Table III) for each compound; this is equivalent to taking the antilog of the vertical distance between the high and low pH arms of the profiles in Figure 4. For **1a,b**, the ionization of the carboxyl group accelerates the double bond protonation reaction by a factor of only 11.6 ± 2.8; for **1c,d**, the corresponding factor is 3.9 ± 0.5.

The effect of carboxyl group ionization on the rates of the buffer-catalyzed reaction can also be determined. If the substrates can ionize, as is the case with **1a,b** and **1c,d**, and if the conjugate base of the buffer acid makes no catalytic contribution (*i.e.*, $k_A = 0$ in eq 6), then the slope of the k_ψ *vs.* [total buffer] plot, $\tilde{k}_{cat}$, will be given by

$$\tilde{k}_{cat} = (k_{HA,SH} - k_{HA,S})f_{SH}f_{HA} + k_{HA,S}f_{HA} \quad (19)$$

in which f_{HA} was defined for eq 6, $k_{HA,S}$ is the second-order catalytic constant for catalysis of the reaction of ionized substrate by the buffer acid HA, $k_{HA,SH}$ is the corresponding rate constant for the HA catalyzed reaction of un-ionized substrate, and f_{SH} is the fraction of substrate in the un-ionized form. For a given buffer, a plot of $\tilde{k}_{cat}/f_{HA}$ *vs.* f_{SH} should be linear, allowing the determination of $k_{HA,S}$ and $k_{HA,SH}$ (Figure 6). Formic acid buffers were used, since the apparent pK_a of formic acid in this solvent system, 3.62, is close to that of both **1a,b** and **1c,d**, and the same buffer could therefore be used over a wide range of f_{SH}. For calculating f_{SH}, the kinetically determined pK_{SH} values (eq 11, Table III) were used. A weighted, linear least-squares analysis based on the data of entries 12–22 and 43–51 of Table I gave (k values in M^{-1} min^{-1}) for **1a,b**, $k_{HA,S}$ = 9.85 ± 0.23, $k_{HA,SH}$ = 1.24 ± 0.45, $k_{HA,S}/k_{HA,SH}$ = 7.9 ± 2.7; and for **1c,d**, $k_{HA,S}$ = 10.80 ± 0.33, $k_{HA,SH}$ = 3.28 ± 0.57, $k_{HA,S}/k_{HA,SH}$ = 3.30 ± 0.49. Thus, the effect of ionization of the carboxyl group of the substrate on the protonation of **1a,b** by formic acid is perhaps somewhat less than the corresponding effect on the H_3O^+ catalyzed reaction. This observation accords with the expectation that there is perhaps some electrostatic repulsion between the developing anion in the catalyzing buffer acid and the ionized carboxyl of the substrate that would not be present in the hydronium ion catalyzed reaction; this effect is relatively minor, however. The important observation is that the ionized carboxyl group does not preferentially assist the carboxylic acid catalyzed reaction.

The sources of the modest accelerations observed upon the ionization of the substrate carboxyl group are twofold. First, electrostatic interaction of the developing carbonium ion and the ionized carboxylate, which

before.[48] The specific rate constant for formate catalysis was calculated by an extrapolation procedure (see below), and that for acetate was estimated by a similar procedure; application of the Swain–Scott equation to the data for formate and acetate yields the susceptibility parameter.

(48) A. J. Kresge and R. J. Preto, *J. Amer. Chem. Soc.*, 87, 4593 (1965).

(49) K. M. Ibne-Rasa, *J. Chem. Educ.*, **44**, 89 (1967).

(50) We attempted a similar experiment in the presence of KI as the inert electrolyte; iodide is considerably more nucleophilic than bromide. Unfortunately, small amounts of oxidation of I^- to I_2 gave variable and irreproducible absorption in the region of interest, which was further aggravated by the radiation from the deuterium lamp.

(51) C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 3214 (1961).

(52) There is evidence in the gas phase that hydrogen bonding (as a model for proton transfer) is not especially unfavorable when incorporated in larger rings compared to incorporation in a six-membered ring: R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, **95**, 3504 (1973).

(53) For example, compare the effects of the *o*- and *p*-chloro substituents in the following cases: (a) R. W. Bott, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.*, 384 (1965); (b) D. S. Noyce and M. J. Jorgenson, *J. Amer. Chem. Soc.*, **84**, 4312 (1962).

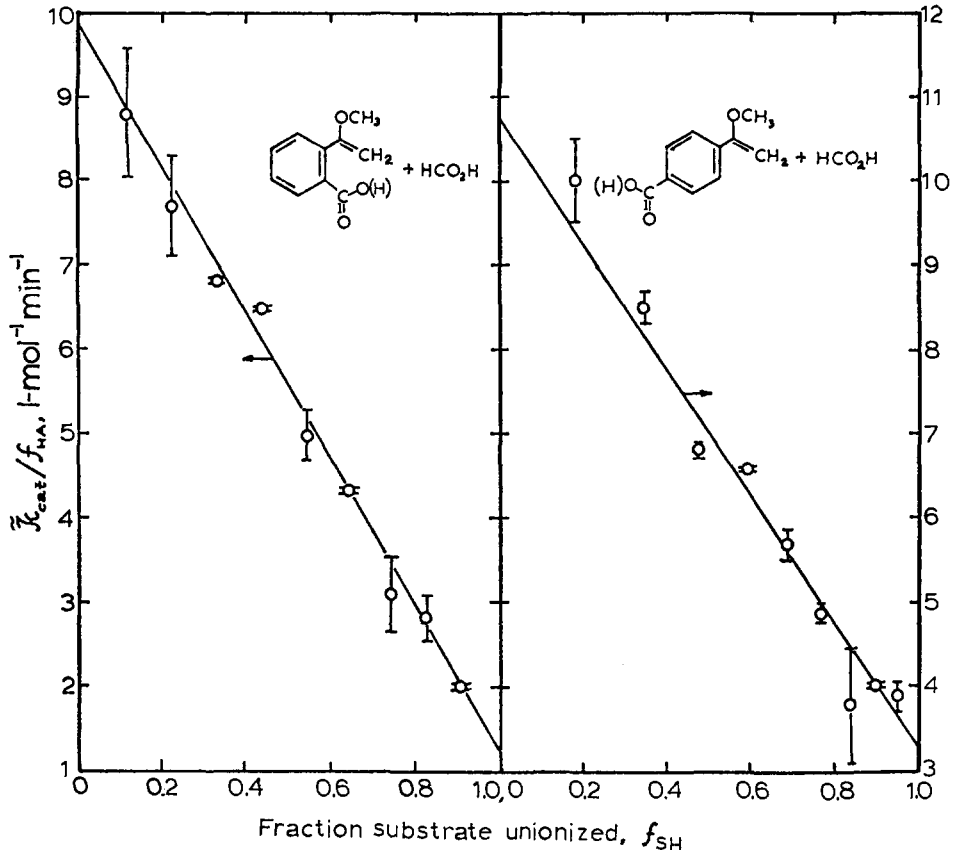


Figure 6. Plots of the hydrolysis data for formate buffer catalysis of the reaction of **1a,b** (left plot) and **1c,d** (right plot). The points are experimental, the error bars represent standard deviations, and the line was calculated from a weighted, linear least-squares fit of the data according to eq 19.

we have abbreviated with the term "electrostatic catalysis,"[8] is the type of catalytic effect attributed to Asp$_{52}$ in lysozyme-catalyzed hydrolyses. Second, there can be a resonance interaction of the enol ether vinyl group with the carboxyl group leading to ground-state stabilization; such an interaction should be less important when the carboxyl group is ionized. The resonance effect should be more pronounced when an aromatic system is not interposed between the electronically interacting vinyl and carboxyl groups. Fife observed[54] for 2-ethoxy-1-cyclopentenecarboxylic acid a ratio of 220 for the hydrolysis reaction when the hydrogen ion catalyzed rates for the carboxyl-ionized *vs.* un-ionized species were compared. Our factors of *ca.* 12 (for H_3O^+ catalysis) and 7 (for buffer catalysis) may thus be regarded as upper limits for electrostatic catalysis in aqueous solution for this type of reaction. Thus, the electrostatic component in aqueous solution for general acid catalyzed α-oxocarbonium ion formation from vinyl ethers is quite small.

Reaction Products in the Hydrolysis of 1a,b. The product of the reaction of both **1a** and **1b** was shown to be initially the pseudoester **2** to the extent of about 92–97%, the remaining material being the direct hydrolysis product, 2-acetylbenzoic acid (**4**). The efficient competition of the intramolecular ionized carboxylate of the substrate **1a** with water in the trapping of the carbonium ion intermediate was expected, but the nearly exclusive formation of **2** from **1b** was not expected. Participation of the un-ionized carboxyl group in the hydrolysis of **1b** was ruled out above. Assuming that the mechanism for formation of **2** from **1b** is stepwise (proceeds through the carbonium ion intermediate) rather than concerted, the preferential trapping of the carbonium ion derived from the protonation of the carbon–carbon double bond of **1b** may be understood as follows. Using the formalism discussed by Kurz,[55] it is easily shown that the pK_a of the substrate carboxylic acid group in the transition state for the hydrolysis of **1b**, p$K_{SH}^{\pm}$, is related to the corresponding pK_a of the ground state, pK_{SH}, by the relation

$$pK_{SH} - pK_{SH}^{\pm} = \log k_{0,S} - \log k_{0,SH} \qquad (20)$$

where $k_{0,S}$ and $k_{0,SH}$ were defined in eq 11. This analysis gives p$K_{SH}^{\pm}$ = 2.59; the pK_a of the carboxyl group in the fully developed carbonium ion should be considerably lower. This pK_a value implies[56] that the rate of ionization of this group in the carbonium ion, expressed as a second-order rate constant for reaction with water, is in excess of 10^8 M^{-1} sec^{-1}. The nucleophilic attack of water on the resonance-stabilized carbonium ion may occur at a considerably lower rate.[57] Thus, the immediate result of the confrontation of the carbonium ion derived from **1b** with water is ionization of the carboxyl group. The resulting carboxylate ion will then be an efficient competitor with water for the positive carbon. *Thus, efficient nucleophilic attack on an α-oxycarbonium ion by a suitably situated carboxyl*

(54) T. H. Fife, *J. Amer. Chem. Soc.*, 87, 1084 (1965).

(55) J. L. Kurz, *Accounts Chem. Res.*, 5, 1 (1972).
(56) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).
(57) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 11 (1964), point 4, and entry *m*, Table IV.

group does not require that the carboxyl group be ionized in the ground state.

Relevance of This Work to Lysozyme Catalysis. It is obvious that vinyl ethers are not ketals and for this reason the applicability of this work to lysozyme catalysis might be questioned. Lysozyme has not been shown to hydrolyze vinyl ethers, but it also probably does not hydrolyze many of the ketals or even glycosides which have been valuable as simple model compounds for the understanding of lysozyme catalysis. The reaction studied here is a general acid catalyzed α-oxycarbonium ion formation; the lysozyme-catalyzed reaction is believed to be a "general acid catalyzed" α-oxycarbonium ion formation. In this model, protonation is on carbon, and a carbon–carbon π bond is broken in the process; in lysozyme catalysis, protonation is on oxygen, and a carbon–oxygen σ bond is broken in the process. Despite differences in the vinyl ether and chitin oligosaccharide systems, very similar intermediates are formed by very closely related mechanisms; indeed, examples in model systems of general acid catalyzed ketal hydrolysis are the exception rather than the rule.[10e] Most important, the energetics of ketal and vinyl ether hydrolysis (*i.e.*, the difference in energy in ground and transition states) for corresponding ketals and enol ethers derived from a given carbonyl compound and alkoxy fragment are virtually identical,[58] and the molar free energy difference between the corresponding vinyl ethers and ketals themselves is small, on the order of 3 kcal.[58a] The advantage of the study of vinyl ethers is the ability to characterize definitively the proton catalysis mechanism and therefore to isolate the effect of a carboxyl group acting as an "electrostatic catalyst" in general acid catalyzed α-oxycarbonium ion formation, relatively free of kinetic ambiguities. In short, we believe that the differences between lysozyme-like ketal hydrolysis and vinyl ether hydrolysis are sufficiently minor that the utility of the vinyl ether system in providing the lysozyme-like mechanism of oxycarbonium ion formation outweighs the relatively minor differences that will result in the effects observed.

Only recently has a possible case of general acid–electrostatic catalysis been advanced for ketal hydrolysis,[14] in which intramolecular acid catalysis in water of the hydrolysis of benzaldehyde disalicyl acetal was accelerated by only a factor of 31 by ionization of the second carboxyl group. The evidence presented for the role of the second carboxyl group was limited to a pH–rate profile, but, assuming the correctness of the authors' contention that the factor of 31 represents electrostatic catalysis, this example and the case studied here are in agreement: such catalysis in aqueous solution is weak.

Indeed, Fife has suggested[10e,14b] that it may be possible to account for lysozyme-like rate accelerations without invoking electrostatic catalysis by Asp_{52}. Alternative roles for Asp_{52} may be considered. This residue may be playing a structural role.[10e] It may perhaps be relevant that the low-molecular weight protein of lactose synthetase, α-lactalbumin,[59] a protein which has been shown to be highly homologous in sequence to lysozyme, retains the residue (Asp_{49}) equivalent to Asp_{52} in lysozyme, but has replaced Glu_{35} of lysozyme with a histidine (His_{32}). This protein does not hydrolyze chitin oligosaccharides, and, indeed, has no known catalytic role of its own. Asp_{52} in lysozyme may act to preserve stereochemistry *via* a covalent or electrostatic interaction with the α face of the intermediate, substrate-derived carbonium ion; in our demonstration that **2** was formed from **1b** at low pH, we illustrated that an abnormally low pK_a of the carboxyl group is not required for such an interaction. In fact, the elegant difference titration work of Parsons and Raftery[60a] (which, however, has not gone unchallenged[60b]) showed that the pK_a of Asp_{52} is in fact not abnormally low, as it was once postulated. Finally, it must be considered that the lysozyme hydrolytic site may provide an environment particularly suitable to the transmission of electrostatic effects. In fact, Asp_{52} is in a rather hydrophobic environment, and the rather selective esterification of this carboxyl group by triethyloxonium fluoroborate[15b] may have been due to site direction of this large trialkyloxonium ion by forces generally associated with hydrophobic bonding. Initial efforts in the probe of the effect of microenvironment in aqueous solution on electrostatic catalysis have been made in the many studies of the effect of carboxylate-containing micelles in the hydrolysis of ketals;[10c,61] the complexity of micellar systems makes it difficult to interpret the results of these studies on a detailed molecular basis. We are currently approaching the question of microenvironmental effects in some model compounds.

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Supplementary Material Available. Tables II and IV will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-465.

(58) (a) P. Salomäa, *Acta Chem. Scand.*, 20, 1802 (1966); (b) cases where this generalization is less reliable have been developed: A. Kankaanpera, P. Salomäa, P. Juhala, R. Saltonen, and M. Mattsen, *J. Amer. Chem. Soc.*, **95**, 3618 (1973).

(59) K. Brew, F. J. Castellino, T. C. Vanaman, and R. L. Hill, *J. Biol. Chem.*, **245**, 4570 (1970).

(60) (a) S. M. Parsons and M. A. Raftery, *Biochemistry*, **11**, 1623 (1972); (b) S. Banerjee, I. Kregar, V. Turk, and J. A. Rupley, *J. Biol. Chem.*, **248**, 4786 (1973).

(61) R. B. Dunlap, G. A. Ghanim, and E. H. Cordes, *J. Phys. Chem.*, **73**, 1898 (1969).