General Acid Catalysis in Benzophenone Ketal Hydrolysis

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Received August 26, 1968

Benzophenone diethyl ketal, 2,2-diphenyl-1,3-dioxolane, 2,2-di(*p*-methoxyphenyl)-1,3-dioxolane, 2,2-di(*p*-tolyl)-1,3-dioxolane and 2,2-di(*p*-chlorophenyl)-1,3-dioxolane were prepared and their kinetics of hydrolysis studied in aqueous dioxane formate, chloroacetate and dichloroacetate buffers. General acid catalysis was observed for hydrolysis of ketals of benzophenone, 4,4′-dimethoxybenzophenone and 4,4′-dimethylbenzophenone in chloroacetate and dichloroacetate buffers. Catalytic coefficients for the buffer acids and for hydrogen ion were derived from the kinetic data. Hydrogen ion catalytic coefficients correlate closely with Hammett's substituent constants for the *para* substituents. The entropy of activation for hydrogen ion catalyzed hydrolysis is near zero for benzophenone diethyl ketal and slightly negative for the 2,2-diaryl-1,3-dioxolanes. The relationship between acetal and ketal structures and the mechanisms (A1 or SE2) by which they hydrolyze are discussed.

An overwhelming body of experimental evidence supports an A1 mechanism for acid-catalyzed hydrolysis of typical acetals and ketals. This mechanism involves preequilibrium protonation of the acetal or ketal, followed by rate-limiting dissociation of the conjugate acid to a mesomeric alkoxycarbonium ion and alcohol (eq 1).[2]

$$RR^1C(OR^2)_2 + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RR^1C(OR^2)\overset{+}{O}HR^2 \xrightarrow[-R^2OH]{k_2} RR^1\overset{+}{C}{=}OR^2 \xrightarrow[+H_2O]{\text{fast}} RR^1C{=}O + R^2OH + H^+ \qquad (1)$$

The A1 mechanism requires that the reaction be catalyzed only by hydronium ion. Other possible mechanisms of acetal and ketal hydrolysis are the A2 mechanism, which involves rate-limiting reaction of the conjugate acid of the substrate with water or other nucleophiles, and the SE2 mechanism, which involves rate-limiting proton transfer from the acid catalyst to the substrate. Both of these mechanisms require general acid catalysis rather than specific hydronium ion catalysis. Until recently, when Fife showed that the hydrolysis of 2-*p*-methoxyphenyl-4,4,5,5-tetramethyl-1,3-dioxolane is catalyzed by formic acid as well as by hydronium ion,[3] all attempts to detect catalysis of acetal and ketal hydrolysis by acids other than the solvated proton were unsuccessful. Fife attributed the general acid catalysis for this reaction to the operation of an A2 mechanism.

Our interest in the demonstration of general acid catalysis in hydrolysis of acetals and ketals stems from the fact that hydrolysis reactions of a closely related group of compounds, the carboxylic and carbonic ortho esters, typically are general acid catalyzed,[4–8] even though these reactions almost certainly involve formation of dialkoxy- and trialkoxycarbonium ion intermediates.[8,9] A considerable body of kinetic and other data supports the hypothesis that general acid catalysis of ortho ester hydrolysis occurs by an SE2 mechanism involving rate-limiting proton transfer to alkoxy oxygen.[10]

In ortho ester hydrolysis, essentially every proton transfer from catalyst to substrate results in carbonium ion formation, whereas proton transfer in acetal and ketal hydrolysis is usually reversible. It is not possible to decide whether formation of dialkoxycarbonium ions from ortho esters and acids is a concerted electrophilic displacement reaction, or whether a conjugate acid whose conversion into products is more rapid than its dissociation to starting materials is a discrete intermediate. A concerted mechanism seems more likely.[2,10] The experimental evidence requires that the proton be largely transferred to alkoxy oxygen in the rate-limiting step, and that the transition state for this rate-limiting step has little carbonium ion character.[10]

Replacing the acyl hydrogen of an acetal by an alkoxy group has two mechanistically significant effects on the hydrolysis reaction: the activation energy for proton transfer from the catalyst to an alkoxy oxygen is increased because of the inductive effect of the third alkoxy group, and the activation energy for carbonium ion formation is reduced because of resonance interaction of the extra alkoxy group with the carbonium carbon atom. Both of these effects act to shift the rate-limiting step of the reaction from carbonium ion formation (A1) to proton transfer from the acid catalyst (SE2).

These considerations suggested a rational approach to the search for acetals and ketals whose hydrolyses would involve rate-limiting proton transfer and therefore would resemble those of ortho esters in exhibiting general acid catalysis. Structural features in acetals and ketals which diminish their basicity or increase the stability of the alkoxycarbonium ions derived from them should shift the mechanism of their hydrolysis reactions closer to that typical of ortho esters. Substitutents on the carbonyl carbon of an acetal or ketal which both withdraw electrons from oxygen and stabilize the alkoxycarbonium ion intermediate should be particularly effective in shifting the hydrolysis mechanism toward the SE2 end of the spectrum.

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[1] National Science Foundation Summer Research Participant, 1966.

[2] For a recent comprehensive review of acetal and ketal hydrolysis, see E. H. Cordes, *Progr. Phys. Org. Chem.*, 1 (1967).

[3] T. H. Fife, *J. Amer. Chem. Soc.*, **89**, 3228 (1967).

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

[5] R. H. De Wolfe and R. M. Roberts, *J. Amer. Chem. Soc.*, **76**, 4379 (1954).

[6] R. H. De Wolfe and J. L. Jensen, *ibid.*, **85**, 3264 (1963).

[7] H. Kwart and M. B. Price, *ibid.*, **82**, 5123 (1960).

[8] A. J. Kresge and R. J. Preto, *ibid.*, **87**, 4593 (1965).

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

[10] C. A. Bunton and R. H. DeWolfe, *ibid.*, **30**, 1371 (1965).

Since aryl groups have substantial negative inductive effects, and also are very effective in stabilizing arylcarbonium ions, benzophenone ketals were selected as the most promising candidates for detection of general acid catalyzed hydrolysis. The reasonableness of this choice is supported by the fact that benzophenone diethyl ketal is only $\frac{1}{20}$ as reactive as benzaldehyde diethyl acetal toward hydronium ion catalyzed hydrolysis in 50% dioxane at 25°,[11,12] which clearly indicates that carbonium ion stability is not the principal factor determining benzophenone ketal reactivity. This suggested that benzophenone ketals, like ortho esters, may hydrolyze by the SE2 mechanism. Accordingly, benzophenone diethyl ketal and a series of benzophenone ethylene ketals were synthesized and their hydrolysis in aqueous dioxane buffers was studied in the hope of demonstrating catalysis by buffer acids.

We found that hydrolysis of some of these ketals is catalyzed by chloroacetic and dichloroacetic acids. This observation confirms the principle that the A1 and SE2 mechanisms are extremes of a mechanistic continuum. Some of the implications of this principle are discussed in detail following a presentation of the experimental results.

Experimental Section

Reagents.—All commercially obtained materials were purified as indicated. 1,4-Dioxane, obtained from J. T. Baker and Co., was refluxed over sodium metal for several days and distilled shortly before use. Monochloroacetic acid (Matheson Coleman and Bell) was recrystallized from benzene. Dichloroacetic acid, prepared by the method of Cope, Clark and Connor,[13] was purified by reduced pressure distillation. Formic acid (98%) from Allied Chemical Co. was used as obtained. Reagent grade sodium chloride, sodium perchlorate and sodium nitrate were dried at 100° and stored in desiccators prior to use. Benzophenone, 4,4′-dichlorobenzophenone, 4,4′-dimethylbenzophenone and 4,4′-dimethoxybenzophenone were obtained from Matheson Coleman and Bell, Eastman Kodak Co., and City Chemical Corp. of New York. Benzophenone diethyl ketal was prepared according to the method of Mackenzie.[14]

2,2-Diaryl-1,3-dioxolanes.—The benzophenone ethylene ketals were prepared by the general method of Schulzenbacher, Bergmann and Panises.[15] The appropriate benzophenone derivative was refluxed with a mixture of an excess of ethylene glycol, benzene or xylene and a trace of ethanesulfonic acid. The water which formed during ketalization was azeotropically removed by use of a Barrett trap. Yields were improved by filling the trap with Linde Molecular Sieves, Type A4. 2,2-Diphenyl-1,3-dioxolane, prepared in this manner, was purified by reduced pressure distillation, bp 145–147.5° (3.5 torr) [lit.[16] bp 125–128° (0.9 torr)]. 2,2-Di(*p*-tolyl)-1,3-dioxolane was recrystallized from absolute methanol, mp 41.2–42.5°. This product exhibited no carbonyl absorption at 1650–1670 cm^{-1}, lacked the absorption maximum of the parent ketone at 265 mμ (ethanol), and exhibited nmr absorptions having chemical shifts (relative to tetramethylsilane in carbon tetrachloride) of 2.3 (singlet), 7.15 (doublet) and 4.0 ppm (singlet) (relative areas 3.0, 2.0, and 2.0, respectively). 2,2-Di(*p*-chlorophenyl)-1,3-dioxolane was recrystallized from ligroin–ethyl acetate, mp 86.7–87.2°. It showed no carbonyl absorption at 1650–1670 cm^{-1}, showed negligible absorption at 265 mμ in ethanol solution (where the ketone has an absorption maximum), and exhibited nmr absorptions having chemical shifts of 4.0 (singlet) and 7.5 ppm (overlapping doublets) (relative areas 1.0 and 1.0). 2,2-Di(*p*-methoxyphenyl)-1,3-dioxolane was recrystallized from petroleum ether (bp 30–60°)–ethyl acetate, mp 142.8–143.2°. It showed negligible carbonyl absorption in the infrared region at 1670 cm^{-1}, negligible absorption at the ketone maximum of 295 mμ, and exhibited nmr absorptions having chemical shifts of 3.8 (singlet), 4.0 (singlet), 6.9 (doublet) and 7.5 ppm (doublet). Acid hydrolysis (aqueous ethanol) of all of these dioxolanes yielded products whose ultraviolet spectra were identical with those of the benzophenones from which they were prepared.

Buffer solutions were prepared by partly neutralizing weighed amounts of the appropriate carboxylic acid with standard sodium hydroxide. Except where otherwise noted, the ionic strengths of the buffers used in a series of runs was maintained constant by addition of sodium chloride to the more dilute buffers. The pH values of the buffers used in kinetic runs were measured at the temperatures of the rate determinations, using a Corning Model 10 or a Leeds and Northrup pH meter. The measurement of pH in aqueous dioxane solutions has been reported to yield valid results up to 70% dioxane.[17] Reaction solutions were prepared by mixing carefully measured volumes of the stock buffer, the sodium chloride solution, and 1,4-dioxane.

Kinetic Measurements.—The first-order hydrolysis reactions were followed spectrophotometrically, using a Gilford 2000 single beam spectrophotometer set at the wavelength of the uv absorption maximum of the benzophenone product. The temperature of the cell compartment was maintained constant to within ±0.1°. For each run, 3.0 ml of the aqueous dioxane buffer solution was allowed to come to thermal equilibrium with the cell compartment, 50 μl of a solution of the ketal in dioxane was added, the contents of the cell were rapidly mixed, and the increase in absorbance was measured as a function of time for at least four half-lives. First-order rate constants were calculated by the Guggenheim method,[18] or by a computer program which assumes first-order kinetics and calculates rate constants using an adjusted infinity value.[19] The two procedures yielded rate constants identical within experimental error when applied to the same set of data. At least three replicate rate determinations were made for each set of reaction conditions. Replicate rate constants varied by ±3% or less.

Results

General Acid Catalysis.—Preliminary experiments failed to detect general acid catalysis of benzophenone ketal hydrolysis in formate buffers. The stronger acids chloroacetic and dichloroacetic acid accordingly were chosen for use in a more detailed search for general acid catalysis. Kinetic data for hydrolysis of the various ketals at 30° in chloroacetate and dichloroacetate buffers containing 20 and 50% dioxane by volume are listed in Table I. Compositions and properties of the buffers used are summarized in Table II.

Salt effects were minimized by maintaining the ionic strength of each series of buffer solutions constant with sodium chloride. If it is assumed that the p*K* of dichloroacetic acid, like that of acetic acid,[20] is about 0.45 p*K* unit larger in 20% dioxane than in water, straightforward calculations show that the dichloroacetic acid and dichloroacetate ion concentrations of the 20% dioxane dichloroacetate buffers are not significantly influenced by dissociation of the buffer acid.

The simplest procedure for evaluating catalytic coefficients of buffer acids is to plot observed reaction rates *vs.* buffer concentration for experiments done at the same temperature, solvent composition, ionic strength and buffer ratio in buffers of different buffer acid concentration. The slope of the (theoretically)

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[11] M. M. Kreevoy and R. W. Taft, *J. Amer. Chem. Soc.*, **77**, 5590 (1955).

[12] M. M. Kreevoy and R. W. Taft, *ibid.*, **79**, 4016 (1957).

[13] A. C. Cope, J. R. Clark, and R. Connor in "Organic Syntheses," Coll. Vol. IV, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, p 181.

[14] J. E. Mackenzie, *J. Chem. Soc.*, **69**, 985 (1887).

[15] M. Schulzenbacher, E. Bergmann, and E. R. Panises, *J. Amer. Chem. Soc.*, **70**, 2827 (1948).

[16] T. H. Fife and L. Hagopian, *J. Org. Chem.*, **31**, 1772 (1965).

[17] H. P. Marshall and E. Grunwald, *J. Chem. Phys.*, **21**, 2143 (1953).

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

[19] R. C. Newcomb, personal communication.

[20] E. J. King, "Acid-Base Equilibria," The Macmillan Co., New York, N. Y., 1965, p 258.

Table I

Summary of Kinetic Data for Hydrolysis of Benzophenone Ketals

Buffer	% dioxane	k_{obsd}, sec^{-1}
	2,2-Diphenyl-1,3-dioxolane	
DCA-1	20	5.39×10^{-4}
DCA-2	20	5.42×10^{-4}
DCA-3	20	4.96×10^{-4}
	2,2-Di(*p*-methoxyphenyl)-1,3-dioxolane	
DCA-1	20	1.43×10^{-2}
DCA-2	20	1.41×10^{-2}
DCA-3	20	1.34×10^{-2}
DCA-4	20	1.07×10^{-2}
DCA-5	50	2.18×10^{-4}
DCA-6	50	2.15×10^{-4}
DCA-7	50	2.04×10^{-4}
DCA-8	50	2.00×10^{-4}
FA-1	20	1.14×10^{-4} (35°)
FA-2	20	1.22×10^{-4} (35°)
FA-3	20	1.23×10^{-4} (35°)
	2,2-Di(*p*-tolyl)-1,3-dioxolane	
DCA-1	20	3.38×10^{-3}
DCA-2	20	3.26×10^{-3}
DCA-3	20	3.00×10^{-3}
	2,2-Di(*p*-chlorophenyl)-1,3-dioxolane	
DCA-1	20	4.58×10^{-5}
DCA-2	20	4.61×10^{-5}
DCA-3	20	4.63×10^{-5}
DCA-4	20	3.99×10^{-5}
	Benzophenone diethyl ketal	
DCA-5	50	9.33×10^{-4}
DCA-6	50	9.12×10^{-4}
DCA-7	50	8.89×10^{-4}
DCA-8	50	8.58×10^{-4}
MCA-1	50	6.29×10^{-5}
MCA-2	50	6.12×10^{-5}
MCA-3	50	5.85×10^{-5}

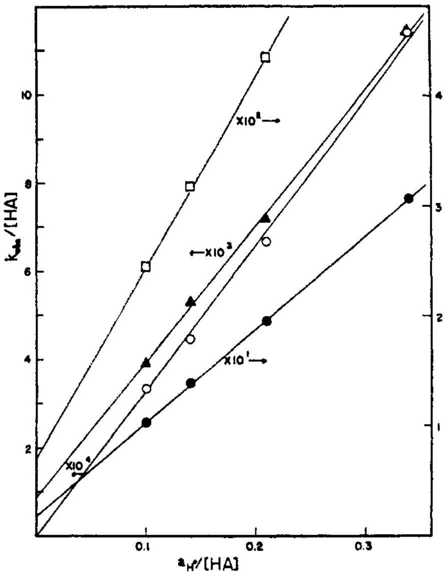


Figure 1.—Plot of k_{obsd}/[HA] *vs.* a_{H^+}/[HA] for hydrolysis of 2,2-diaryl-1,3-dioxolanes in 20% dioxane dichloroacetate buffers at 30°: ▲, 2,2-diphenyl-1,3-dioxolane; ●, 2,2-di(*p*-methoxyphenyl)-1,3-dioxolane; □, 2,2-di(*p*-tolyl)-1,3-dioxolane; ○, 2,2-di(*p*-chlorophenyl)-1,3-dioxolane.

straight line thus obtained is equal to the catalytic coefficient of the buffer acid. We found that pH values (presumably a valid measure of hydrogen ion activity in aqueous dioxane solutions[18]) varied somewhat for aqueous dioxane buffers of a given series, owing to secondary salt effects or small variations in dioxane concentration. For these solutions the reaction rate due to hydronium ion catalysis would not be constant, and slopes of plots of k_{obsd} *vs.* [HA] would not be accurate measures of buffer acid catalytic coefficients. Since the rate law for acetal hydrolysis in buffer solutions is $k_{obsd} = k_{HA}[HA] + k_{H^+}a_{H^+}$, the intercept of a plot of k_{obsd}/[HA] *vs.* a_{H^+}/[HA] is equal to k_{HA}, and the slope is equal to k_{H^+}. Values of k_{HA} determined from such plots should not be influenced by small variations of hydrogen ion activity of the buffer solutions. Representative plots of this kind are given in Figures 1 and 2, and catalytic coefficients derived from them are summarized in Table III.

Table II

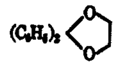
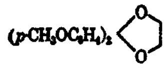
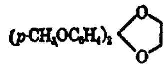
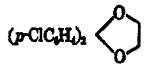
Compositions and Properties of Buffer Solutions

Buffer	Buffer acid	[HA]	[HA]/[A⁻]	% dioxane[a]	Ionic strength	a_{H^+}[b]
DCA-1	Cl_2CHCO_2H	0.138	0.525	20	0.131	1.41×10^{-2}
DCA-2	Cl_2CHCO_2H	0.103	0.525	20	0.131	1.45×10^{-2}
DCA-3	Cl_2CHCO_2H	0.064	0.525	20	0.131	1.45×10^{-2}
DCA-4	Cl_2CHCO_2H	0.034	0.525	20	0.131	1.19×10^{-2}
DCA-5	Cl_2CHCO_2H	0.042	0.500	50	0.082	1.44×10^{-3}
DCA-6	Cl_2CHCO_2H	0.031	0.500	50	0.082	1.51×10^{-3}
DCA-7	Cl_2CHCO_2H	0.020	0.500	50	0.082	1.58×10^{-3}
DCA-8	Cl_2CHCO_2H	0.010	0.500	50	0.082	1.68×10^{-3}
MCA-1	$ClCH_2CO_2H$	0.131	1.43	50	0.125	1.38×10^{-4}
MCA-2	$ClCH_2CO_2H$	0.088	1.43	50	0.125	1.41×10^{-4}
MCA-3	$ClCH_2CO_2H$	0.044	1.43	50	0.125	1.42×10^{-4}
FA-1	HCO_2H	0.207	0.675	20	0.148	9.55×10^{-5}
FA-2	HCO_2H	0.155	0.675	20	0.148	8.31×10^{-5}
FA-3	HCO_2H	0.103	0.675	20	0.148	9.35×10^{-5}
FA-4	HCO_2H	0.052	0.675	20	0.148	8.31×10^{-5}

[a] % dioxane = (volume of dioxane/(volume of dioxane + volume of aqueous solution) × 100. [b] a_{H^+} = antilog (−pH). pH measurements at 30°, except for formate buffers, for which pH was measured at 35°.

TABLE III

CATALYTIC COEFFICIENTS FOR BENZOPHENONE KETAL HYDROLYSIS AT 30°

Buffer acid	Ketal	k_{HA}	k_{H^+}	% dioxane	Ionic strength
Cl_2CHCO_2H		9×10^{-4}	3.6×10^{-2}	20	0.131
Cl_2CHCO_2H		1.7×10^{-2}	8.5×10^{-1}	20	0.131
Cl_2CHCO_2H		1.5×10^{-3}	1.2×10^{-1}	50	0.082
Cl_2CHCO_2H		7×10^{-3}	1.7×10^{-1}	20	0.131
Cl_2CHCO_2H		0	3.3×10^{-3}	20	0.131
Cl_2CHCO_2H	$(C_6H_5)_2C(OC_2H_5)_2$	8×10^{-3}	4.3×10^{-1}	50	0.082
$ClCH_2CO_2H$	$(C_6H_5)_2C(OC_2H_5)_2$	7×10^{-5}	3.9×10^{-1}	50	0.125

Figures 1 and 2, and Table III, show that hydrolyses of all of the ketals studied except that of 2,2-di(*p*-chlorophenyl)-1,3-dioxolane are measurably catalyzed by dichloroacetic acid in 20 and/or 50% dioxane at 30°, and that benzophenone diethyl ketal hydrolysis is catalyzed by monochloroacetic acid in 50% dioxane. The general acid catalysis in most instances is small, but is well beyond the range of experimental error in the rate determinations.

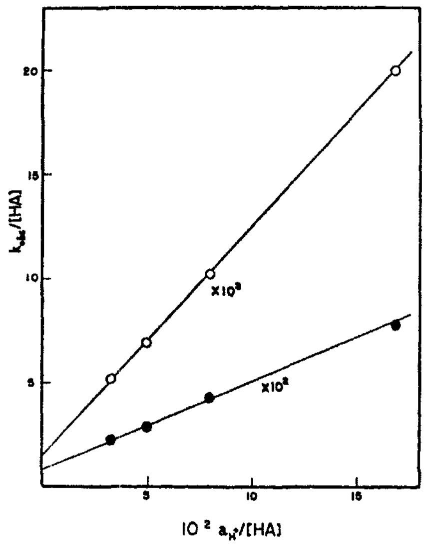


Figure 2.—Plot of $k_{obsd}/[HA]$ *vs.* $a_{H^+}/[HA]$ for hydrolysis of benzophenone ketals in 50% dioxane dichloroacetate buffers at 30°: ○, 2,2-di(*p*-methoxyphenyl)-1,3-dioxolane; ●, benzophenone diethyl ketal.

We considered the possibility that the buffer catalysis might be an artifact produced by salt effects. The buffers of a given series differ not only in the concentration of the weak acid, but also in the relative amounts of sodium chloride and sodium carboxylate present in solution. Specific salt effects on dissociation constants of the buffer acids are allowed for in the method of analyzing the rate data. Specific salt effects on the hydrolysis reaction itself are more difficult to evaluate, but we believe that they cannot be responsible for the observed buffer catalysis. We would expect reactions as similar to those discussed here to exhibit similar responses to specific anions. However, buffer catalysis was not observed for all of the hydrolysis reactions. 2,2-Di(*p*-chlorophenyl)-1,3-dioxolane hydrolysis did not exhibit buffer catalysis in dichloroacetate buffers, and 2,2-di(*p*-methoxyphenyl)1,3-dioxolane hydrolysis did not exhibit buffer catalysis in formate buffers. For this reaction, k_{obsd}/a_{H^+} actually increases as the concentration of formic acid decreases, so that the specific salt effect appears to be in the opposite direction to that required to produce a spurious catalysis. (Koehler and Cordes observed a similar slight decrease in rates of hydrolysis of acetone dimethyl ketal and acetophenone diethyl ketal with increasing carboxylate buffer concentration.[21]) Since buffer catalysis is exhibited by some, but not all, of the hydrolysis reactions and since the magnitude of this catalysis varies with ketal structure in the manner expected for true general acid catalysis, we conclude that the buffer catalysis is due to the carboxylic acid rather than to a salt effect on the hydronium ion catalyzed reaction.

Substituent Effects.—Figure 3 shows a plot of log k_{H^+} *vs.* Hammett's σ substitutent constants for hydrolysis of 2,2-diaryl-1,3-dioxolanes in 20% dioxane dichloroacetate buffers at 30°.[22a] The experimental points fall fairly close to a straight line of slope $\rho = -4.6$. The

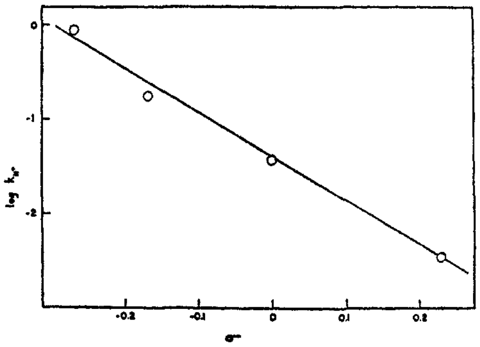


Figure 3.—Plot of log k_{H^+} *vs.* Hammett's σ constants for hydrolysis of 2,2-diaryl-1,3-dioxolanes in 20% dioxane dichloroacetate buffers at 30°.

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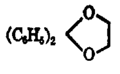
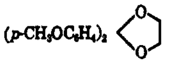
[21] See ref 2, p 32.

[22] (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); (b) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **79**, 1913 (1957).

Table IV

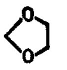
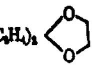
Hydrolysis of Benzophenone Ketals in 30% Dioxane Dichloroacetate Buffers at Different Temperatures

Ketal	T, °C	a_{H^+}	k_{ext}[a]	k_{H^+}[b]	Log k_{H^+}
	298	1.20×10^{-3}	9.85×10^{-3}	8.21	0.914
$(C_6H_5)_2C(OC_2H_5)_2$	303	1.12×10^{-3}	1.37×10^{-3}	12.2	1.086
	308	1.10×10^{-3}	2.00×10^{-3}	18.2	1.260
	303	1.12×10^{-3}	3.60×10^{-5}	3.21×10^{-2}	−1.494
	308	1.10×10^{-3}	4.93×10^{-5}	4.48×10^{-2}	−1.349
	318	1.08×10^{-3}	1.10×10^{-4}	1.04×10^{-1}	−0.983
	303	1.12×10^{-3}	8.15×10^{-4}	0.728	−0.138
	308	1.10×10^{-3}	1.18×10^{-3}	1.07	0.029
	313	1.08×10^{-3}	1.65×10^{-3}	1.53	0.185
	318	1.06×10^{-3}	2.31×10^{-3}	2.18	0.338

[a] Rate extrapolated to zero buffer concentration. [b] $k_{H^+} = k_{ext}/a_{H^+}$.

Table V

Activation Parameters for Benzophenone Ketal Hydrolysis in 30% Dioxane

Ketal	$\Delta H^{\ddagger}$,[a]	$\Delta S^{\ddagger}$,[a] eu	Correlation coefficient[b]
$(C_6H_5)_2C(OC_2H_5)_2$	13.9	1.4	1.00
	14.6	−8.3	0.998
	14.0	−6.0	1.00

[a] At 25°, using rate constants of units l. sec^{-1} mol^{-1}. [b] For log k_{H^+} *vs.* $1/T$.

correlation of log k_{H^+} with Brown's σ^+ substituent constants[22b] is poor. These facts taken together indicate that there is little carbonium ion character in the rate-limiting transition state for hydronium ion catalyzed hydrolysis of 2,2-diaryl-1,3-dioxolanes, but that reactivity parallels substrate basicity. The experimental points in a Hammett plot of log k_{HA} *vs.* σ also fall near a straight line whose slope is somewhat less than that for the hydrogen ion catalyzed reaction. However, the low precision of the k_{HA} values makes it inadvisable to attach any significance to difference in ρ values for the two reactions.

Other acid-catalyzed reactions which probably proceed through mesomeric carbonium ion intermediates having aryl groups conjugated with the carbonium center, yet which give approximately linear Hammett plots include hydrolysis of trimethyl orthobenzoates in 70% methanol,[8] hydrolysis of 2-aryl-4,4,5,5-tetramethyl-1,3-dioxolanes,[3] and hydrolysis of benzaldehyde diethyl acetals and ethylene acetals.[23] Buffer catalysis (probably general acid catalysis) was demonstrated for the first two of these reactions. Buffer catalysis was not observed for hydrolysis of the benzaldehyde acetals, and for these compounds σ^+ substituent constants correlated the data almost as well as σ constants.

Solvent Deuterium Isotope Effects.—2,2-Diphenyl-1,3-dioxolane was hydrolyzed at 30° in 1.3% dioxane–98.7% water (or deuterium oxide) solutions which were 0.0197 *N* in HCl. For these solutions, $k_{D^+} = 1.97 \times 10^{-1}$ l./mol sec and $k_{H^+} = 7.50 \times 10^{-2}$ l./mol sec, $k_{D^+}/k_{H^+} = 2.63$.

Activation Parameters.—Catalytic coefficients for hydronium ion catalyzed hydrolysis of benzophenone diethyl ketal, 2,2-diphenyl-1,3-dioxolane and 2,2-di(*p*-methoxyphenyl)-1,3-dioxolane were determined at several temperatures in 30% dioxane dichloroacetate buffers. The kinetic data appear in Table IV, and enthalpies and entropies of activation calculated from them appear in Table V. As is typical for acid-catalyzed acetal, ketal and ortho ester hydrolysis, entropies of activation have values near zero, with the ethylene ketal hydrolyses having entropies of activation several entropy units more negative than that for hydrolysis of the diethyl ketal.

Discussion

Acid-catalyzed reactions which involve formation of carbonium ion intermediates can in principle have a continuous spectrum of mechanisms ranging from the A1 mechanism typical of aliphatic acetal and ketal hydrolysis to the SE2 mechanism typical of ortho ester hydrolysis.

The A1 mechanism is characterized by specific hydronium ion catalysis, entropies and volumes of activation near zero, deuterium solvent isotope effects leading to k_{D^+}/k_{H^+} values near 3, and high sensitivity of substrate reactivity to carbonium ion stabilizing structural alterations. The SE2 mechanism, on the other hand, is characterized by true general acid catalysis (rather than nucleophilic catalysis), by volumes and entropies of activation near zero, by k_{D^+}/k_{H^+} values somewhat smaller (2.0–2.7) than those for reactions occurring by the A1 mechanism, and by reactivities (for a series of structurally related compounds) which correlate with substrate basicity rather than with stability of carbonium ion intermediates.

What structural features determine whether a particular substrate hydrolyzes by the A1 mechanism, the SE2 mechanism, or by a mechanism intermediate between the two? Reactions which occur by both of these mechanisms are characterized by formation of resonance-stabilized carbonium ion intermediates. The two mechanisms differ in that for the A1 mechanism carbonium ion formation is the rate-limiting step, while for the SE2 mechanism substrate protonation (perhaps concentrated with carbonium ion formation) is the rate-limiting step.

The reaction coordinate–free energy diagrams of Figure 4 clarify the different responses of substrate reactivity to substrate structure for the A1 and the SE2 mechanisms, and provide a point of departure for discussing the relationships between substrate structure and the mechanism of hydrolysis.

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[23] T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).

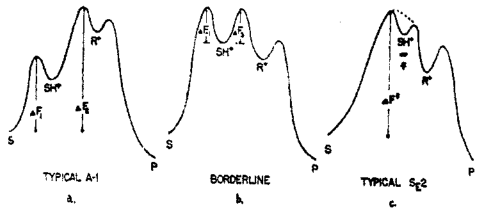

Figure 4.—Reaction coordinate–free energy diagrams for A1, SE2, and borderline mechanisms of acid-catalyzed hydrolysis of acetals, ketals, and ortho esters.

The free energy of activation for an A1 reaction is the sum of the free energy change accompanying substrate protonation and the free energy of activation for dissociation of the substrate conjugate acid to the carbonium ion intermediate. Substituents at the reaction site which stabilize the carbonium ion intermediate will lower the activation energy for its formation from the conjugate acid, and hence will lower the activation energy for the over-all reaction. This is the reason why there is a close correlation between substrate reactivity and stability of the carbonium ion intermediate for reactions occurring by the A1 mechanism.

For an SE2 reaction the energy of activation for dissociation of the protonated substrate to the carbonium ion does not enter into the energy of activation for the over-all reaction, regardless of whether the protonated substrate is an intermediate or a transition state. The free energy of activation for this mechanism is simply the free energy of activation for the proton transfer from the acid catalyst to the substrate. The influence of substrate structure on the activation energy for substrate protonation will therefore closely parallel the influence of structure on substrate basicity. This explains why, for a structurally related series of compounds, SE2 reactivity parallels substrate basicity.

Structural changes in an acetal or ketal which hydrolyzes by the A1 mechanism (Figure 4a) will shift the reaction toward the SE2 mechanism (Figure 4c) if they act to increase the value of the ratio $\Delta F_1/\Delta F_2$ of Figure 4a. A particularly effective way of increasing the value of this ratio is to introduce substituents at the carbonyl carbon which simultaneously withdraw electrons from acetal or ketal oxygen (thus increasing ΔF_1) and stabilize the carbonium ion intermediate (thus decreasing ΔF_2). If such structural changes cause the value of $\Delta F_1/\Delta F_2$ to equal or exceed unity (Figure 4b and c), the mechanism of the reaction changes from A1 to SE2. Adding an additional alkoxy group or two aryl groups to a carbon already bonded to two alkoxy groups is sufficient to cause $\Delta F_1/\Delta F_2$ to exceed unity, since ortho esters and benzophenone ketals hydrolyze by the SE2 mechanism. A substituent on oxygen which sufficiently reduces its basicity may also suffice to shift the mechanism of hydrolysis from A1 to SE2. For example, Fife and Jao found that 2-ethoxytetrahydropyran hydrolyzes by an A1 mechanism in 50% dioxane, while 2-aryloxytetrahydropyrans hydrolyze by the SE2 mechanism.[24]

For a series of structurally related compounds whose hydrolyses are near the borderline between the A1 and the SE2 mechanisms, reactivity should be more strongly influenced by substrate basicity than by carbonium ion stability (Figure 4b). Whether borderline reactions are general acid catalyzed or not will depend on the ratio of ΔF_{-1} to ΔF_3. If $\Delta F_{-1} < \Delta F_3$, the reaction will be specific acid catalyzed, while if $\Delta F_{-1} \gtrsim \Delta F_3$, the reaction will be general acid catalyzed.

Structural changes in groups bonded to the reaction site will usually produce opposing changes in ΔF_{-1} and ΔF_3. For example, inductive electron release to oxygen by a carbonyl substituent will make the protonated substrate less acidic and increase ΔF_{-1}, while simultaneously reducing ΔF_3 by stabilizing the transition state for carbonium ion formation. Therefore (for a series of closely related substrates) base strengthening, carbonium ion stabilizing substituents will increase the value of $\Delta F_{-1}/\Delta F_3$ and shift the mechanism of hydrolysis toward the SE2 side of the borderline. When ΔF_{-1} is larger than ΔF_3, formation of the conjugate acid is the rate-limiting step and the detection of general acid catalysis is possible in principle. Once this borderline has been crossed, the ease with which general acid catalysis can be detected experimentally will depend on the Brønsted catalysis law α value for the reaction. For a series of structurally related substrates, with different acyl or carbonyl substituents, ΔF_{-1} will be largest, and the potential energy surface leading from the transition state for protonation to the protonated substrate will be steepest, for the most basic substrate. It follows that the Brønsted catalysis law constant α will be smallest for the most basic substrate of the series.[25] Lowering the value of α has the effect of increasing the relative importance of catalysis by weak acids, and thus makes general acid catalysis more easily detected experimentally. It is not surprising, therefore, that for a series of closely related acetals, ketals, or ortho esters which hydrolyze by the SE2 mechanism, the relative contribution of general acid catalysis to the total reaction tends to increase as the basicity of the substrate increases.

The preceding discussion of structural effects on mechanisms of acetal hydrolysis suggests that SE2 hydrolysis with general acid catalysis may be demonstrable whenever it is observed that substrate basicity rather than carbonium ion stability is the dominant factor in determining acetal or ketal hydrolytic reactivity. Thus we have shown that the unexpected observation that benzaldehyde diethyl acetal hydrolyzes more rapidly than benzophenone diethyl ketal is due to the fact that the latter compound reacts by the SE2 rather than the A1 mechanism. The observation that crotonaldehyde diethyl acetal is more reactive than cinnamaldehyde diethyl acetal[26] suggests that cinnamaldehyde acetals may also undergo general acid catalyzed hydrolysis. It is likely that the SE2 mechanism will be operable in hydrolyses of other acetals and ketals which form unusually stable alkoxycarbonium ion intermediates.

Implicit in the preceding discussion are the assumptions that all acetal, ketal and ortho ester hydrolyses involve carbonium ion intermediates, and that for a given general acid catalyzed reaction the mechanism of catalysis by hydronium ion and by weak acids is es-

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[24] T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).

[25] R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 169.

[26] L. A. Yanovskaya and V. M. Belikova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1363 (1965).

sentially the same. In effect, these assumptions preclude the A2 mechanism. For hydrolysis reactions of aliphatic acetals and ketals,[2] and ortho esters,[10] an overwhelming body of evidence excludes the A2 mechanism. It seems reasonable to conclude that acid-catalyzed hydrolysis reactions of acetals, ketals, and ortho esters rarely if ever occur by the A2 mechanism.

A possible exception to this generalization is the hydrolysis of 2-aryl-4,4,5,5-tetramethyl-1,3-dioxolanes.[3] Fife observed buffer catalysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane hydrolysis in formate buffers at 40°, and concluded on the basis of this and other data on hydrolyses of 2-aryl-4,4,5,5-tetramethyl-1,3-dioxolanes that these compounds hydrolyze by an A2 mechanism. We believe that the experimental evidence is too ambiguous to justify this conclusion.

First, the value of k_{D^+}/k_{H^+} for this reaction is 2.4, which is typical of SE2 reactions but considerably larger than the values of 1.3–1.7 characteristic of A2 reactions. Second, the slope of a plot of log k_{obsd} *vs.* log $C_{H_3O^+}$ for one of these 2-aryl-1,3-dioxolanes is 2.0, rather than approximately 1.0 as expected for an A2 reaction. A Bunnett plot of $(\log k_{obsd} + H_0)$ *vs.* log a_{H_2O} is strongly curved, with an average slope of +2. The curvature, together with the lack of knowledge of *w* values for established SE2 reactions, makes it inadvisable to interpret the average *w* value for this reaction. The entropy of activation for hydrolysis of 2-phenyl-4,4,5,-5-tetramethyl-1,3-dioxolane is −14 eu, which, although more negative than entropies of activation for 2-aryl-1,3-dioxolane hydrolyses[23] (which probably occur by an A1 mechanism), is substantially more positive than entropies of activation observed for authentic A2 reactions.[27] The surprisingly small reactivity of the 2-aryl-4,4,5,5-tetramethyl-1,3-dioxolanes relative to benzaldehyde ethylene ketals may be due either to diminished basicity of the conjugate acid (due to steric hindrance to hydration), or to steric hindrance to concerted attack by hydrated protons ($H_9O_4^+$) on dioxolane oxygen, or possibly even to reversible carbonium ion formation.[28] In summary, none of the evidence clearly requires an A2 mechanism for hydrolysis of these hindered dioxolanes, and much of it is more compatible with an SE2 mechanism.

Kinetic solvent isotope effects on SE2 reactions involving rate-limiting proton transfers from acids to oxygen may at first seem surprising, since they frequently lead to k_{D^+}/k_{H^+} values characteristic of secondary rather than primary solvent isotope effects.[29] It was noted above that orthocarboxylate hydrolysis typically has k_{D^+}/k_{H^+} values ranging from 2 to 2.7, and we observed $k_{D^+}/k_{H^+} = 2.6$ for hydrolysis of 2,2-diphenyl-1,3-dioxolane at 30°. If these reactions involve rate-limiting proton transfer from hydronium ion to the reactant, one might expect an important primary isotope effect.

The observed isotope effect arises, of course, from the effect of replacing protium oxide by deuterium oxide on the free energy difference between the reactants and the rate-limiting transition state. The observed large Brønsted catalysis law α values ($\alpha \simeq 0.7$) for ortho ester hydrolysis and the fact that water is much more basic than ortho esters or ketals both suggest that the proton is nearly completely transferred from hydronium ion to substrate oxygen in the transition state. The transition state structurally resembles the conjugate acid, and therefore has a large zero point vibrational energy due to strong hydrogen bonding to water. Since the rate-limiting transition state for the SE2 mechanism has the same composition as the rate-limiting transition state for the A1 mechanism, and differs from it only slightly in charge distribution, bond lengths, and hydrogen-bonded interactions with solvent, it is natural that the two mechanisms should exhibit similar kinetic solvent isotope effects. The fact that k_{D^+}/k_{H^+} is somewhat smaller for the SE2 reactions than for the A1 reactions is understandable, since the proton is completely transferred to substrate oxygen in the A1 transition state, and only mostly transferred in the SE2 transition state.

Registry No.—2,2-Diphenyl-1,3-dioxolane, 4359-34-6; 2,2-di(*p*-methoxyphenyl)-1,3-dioxolane, 19018-64-5; 2,2-di(*p*-tolyl)-1,3-dioxolane, 19018-65-6; 2,2-di(*p*-chlorophenyl)-1,3-dioxolane, 19018-66-7; benzophenone diethyl ketol, 6397-77-9.

Acknowledgment.—The authors are indebted to the Committee on Research, University of California at Santa Barbara, and to Biomedical Sciences Support Grant USPHS-FR-07099, for generous support of this research.

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[28] B. Capon and D. Thacker, *J. Chem. Soc., B*, 185 (1967).

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Substituent Effects in the Polarography of Aromatic Diazonium Salts

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Contribution No. 434 from the Research Council of Alberta, Edmonton, Canada

Received June 28, 1968

Polarographic reduction of a number of substituted benzenediazonium tetrafluoroborates in the aprotic solvent, sulfolane, has been carried out. The most positive wave is a reversible one-electron step. The half-wave potential of this wave correlates well with Hammett σ values and is defined by the equation $E_{1/2} = 0.229\sigma + 0.314 \pm 0.024$ V.

The polarographic activity of diazotized aromatic amines was first reported by Elofson and Mecherly,[1] who used the facile reduction of diazonium salts at the dropping mercury electrode in a series of amperometric titrations of diazonium salts with coupling agents. In

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[1] R. M. Elofson and P. A. Mecherly, *Anal. Chem.*, **21**, 565 (1949).