

it must be measured against a background of the fully tritiated 2- and 3-methyl groups.

Effect of Alkyl Group Size on Rate.—A question that has received little attention in carbanion reactions is the relative inductive effects of different alkyl substituents. For instance, what is the rate of exchange of a methyl group when it is effected by a methyl, ethyl, isopropyl, or *t*-butyl group? The most reliable data will be obtained with these substituents in the *meta* or *para* positions where steric effects are not significant. Relative rate constants for several compounds are summarized in column 1 of Table VII.

TABLE VII
RELATIVE INDUCTIVE EFFECTS OF ALKYL GROUPS

Hydrocarbon	—Rate constant rel. to toluene—	
	Exptl.	Calcd. for CH ₃ group
<i>p</i> -Xylene	0.033	0.033
<i>p</i> -Ethyltoluene	.026	.041
<i>p</i> -Cymene	.023	.03
<i>p</i> - <i>t</i> -Butyltoluene	.033	.033
<i>m</i> -Xylene	.51	.51
<i>m</i> -Ethyltoluene	.24	.33

For those compounds containing nonequivalent hydrogens, *p*-ethyltoluene and *p*-cymene, the experimental rate constant is, as before, an average value. The rate constant for the methyl group of each hydrocarbon can be calculated if the rate of exchange of all other hydrogens is backed out. This was accomplished by assuming that a methyl substituent has the same effect on all other alkyl groups as it does on another methyl group. These data are presented in column 2. Within a given series there appears to be little or no difference in the inductive effect as the size of the alkyl group is varied. The largest deviation occurs with the *meta* isomers. Data on other *meta* alkyl substituents are not yet available, so it is impossible to tell if this is a general phenomenon.

The preceding data have demonstrated the usefulness of dimethyl sulfoxide as a solvent for determining relative acidities. It is clear that over a small range of acidities, any relative order of acidity will be solvent dependent. We hope to extend the present work to include the effect of solvent polarity on relative acidities, particularly with the xylenes, ethylbenzene, and cumene. Finally, it has been shown that substituents

behave in an additive manner, from a free-energy standpoint, and that cumulative effects can be predicted from simple models.

Experimental

Procedures employed during this study were essentially identical with those described in the previous paper.² Approximately 50–50 mole % blends were prepared for each hydrocarbon with toluene. These mixtures were then injected into prethermally stated base-solvent solutions as described previously. Each hydrocarbon was used as received from the source given below.

Toluene	Baker (Analyzed Reagent)
<i>o</i> -Xylene	Matheson Coleman and Bell (Reagent)
<i>m</i> -Xylene	Matheson Coleman and Bell (Reagent)
<i>p</i> -Xylene	Matheson Coleman and Bell (Reagent)
1,2,4,5-Tetramethylbenzene	Matheson Coleman and Bell (Reagent)
Cumene	Matheson Coleman and Bell (Reagent)
<i>p</i> -Cymene	Matheson Coleman and Bell (Reagent)
1,2,3-Trimethylbenzene	Aldrich (Puriss.)
1,2,4-Trimethylbenzene	Aldrich (Puriss.)
1,3,5-Trimethylbenzene	Aldrich (Puriss.)
1,2,3,4-Tetramethylbenzene	K & K Laboratories
1,2,3,5-Tetramethylbenzene	K & K Laboratories
<i>o</i> -Ethyltoluene	K & K Laboratories
<i>m</i> -Ethyltoluene	K & K Laboratories
<i>p</i> -Ethyltoluene	K & K Laboratories
<i>p</i> - <i>t</i> -Butyltoluene	Fisher
Pentamethylbenzene	Eastman
Hexamethylbenzene	Eastman

Radio-assaying gas chromatographic analyses were carried out on a 10-ft. Dow Corning silicone oil column (DC-200) at 100–135° for all compounds except the tetra-, penta- and hexamethylbenzenes. For these compounds, a 2-ft. silicone rubber column was used at 125°. Mole response factors given by Messner¹⁵ were employed in the calculation of chemical peak areas when available. Other mole response factors were extrapolated from the data of Messner and are given below.

Tetramethylbenzenes	1.66
Pentamethylbenzenes	1.82
Hexamethylbenzene	1.99
1,2,3-Trimethylbenzene	1.50
<i>o</i> -Ethyltoluene	1.50
<i>m</i> -Ethyltoluene	1.50
<i>p</i> -Cumene	1.6
<i>p</i> - <i>t</i> -Butyltoluene	1.8

After sampling for the kinetic portion of each experiment was complete, the samples were allowed to remain in the temperature bath for a time equivalent to at least ten half-lives of the slower of the two reactions. At this time final samples were withdrawn and equilibrium specific activities were determined.

(15) A. E. Messner, E. M. Rosie, and P. A. Argabright, *Anal. Chem.*, **31**, 230 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

The Hydrolysis of Substituted 2-Phenyl-1,3-dioxanes^{1a}

BY MYRON L. BENDER^{1b} AND MARC S. SILVER^{1c}

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A series of 2-(substituted phenyl)-1,3-dioxanes have been prepared and the pH-rate profiles of their hydrolyses determined. All the acetals show the usual hydronium ion-catalyzed hydrolyses. In addition, those acetals containing an *o*- or *p*-phenolic substituent exhibit a hydrolytic reaction which is independent of external hydronium ion but which is dependent on the un-ionized form of the acetal. The hydrolyses of those acetals containing *o*-phenolic substituents could formally be attributed to intramolecular general acid catalysis. However, the comparable hydrolysis of acetals containing *p*-phenolic substituents and the effect of deuterium oxide on the kinetics indicates that the best interpretation of the spontaneous hydrolysis of the phenolic acetals is the hydronium ion-catalyzed hydrolysis of the phenolate ion form of the substrates.

The cleavage of the acetal linkages of polysaccharides is catalyzed by enzymes which appear to contain no prosthetic groups² and which therefore presumably

(1) (a) Supported by the National Science Foundation and the U. S. Atomic Energy Commission; (b) Alfred P. Sloan Foundation Research Fellow; (c) National Science Foundation Postdoctoral Fellow on leave of absence from Amherst College.

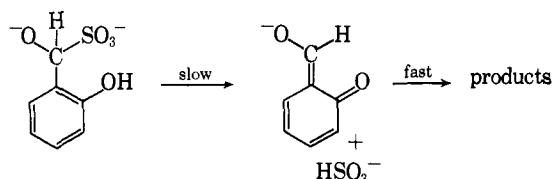
(2) E. H. Fischer and E. A. Stein in "The Enzymes," 2nd Ed., Vol. 4, Academic Press, Inc., New York, N. Y., 1960, Chapter 18.

utilize acidic and/or basic sites of the constituent amino acids as the catalytic functions. On the other hand, the hydrolysis of acetals has been cited as an example of a hydrolytic reaction that is subject to specific hydronium ion catalysis.^{3,4} The failure⁴⁻⁶ to detect general

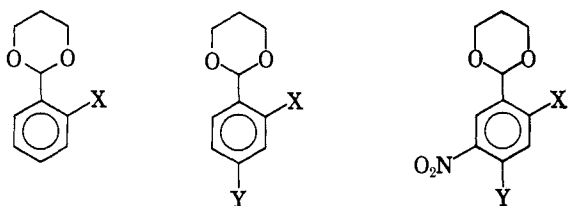
(3) P. D. Bartlett in H. Gilman "Organic Chemistry, an Advanced Treatise," Vol. 11I, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 115-116.

acid catalysis of acetal hydrolysis may merely stem from a poor choice of experimental conditions or model compounds. Thus DeWolfe and Roberts⁷ showed that general acid catalysis of ethyl orthoformate hydrolysis was detectable in dioxane-water mixtures but not in water itself.

Much evidence has recently accrued to testify to the efficacy of suitably positioned functional groups in providing intramolecular catalysis of chemical reactions. For example, Blackadder and Hinshelwood⁸ have suggested the enhanced rate of decomposition of the bisulfite addition complex of salicylaldehyde may arise from the action of the *o*-phenolic group as a general acid.

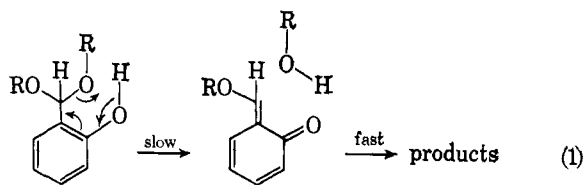


We have attempted a similar approach for detecting intramolecular general acid catalysis of acetal hydrolysis by studying the hydrolysis of a series of substituted 2-phenyl-1,3-dioxanes (I-VI). Models suggested that the *o*-phenolic group in III and V is suitably located to act as a general acid catalyst for the hydroly-



I, X = H III, X = OH, Y = H V, X = OH, Y = H
II, X = OMe IV, X = H, Y = OH VI, X = H, Y = OH

sis of the acetal bonds. An extreme model for this hypothetical interaction is shown in eq. 1. Such an effect would manifest itself, kinetically, as an apparent water reaction of the pertinent acetals. We have therefore determined the pH-rate profiles of the hydrolysis of acetals I-VI.



Experimental

Materials.—Compounds I-VI were synthesized from commercial starting materials by the procedure of Ceder.⁹ Table I records the properties of I-VI. Reagent grade inorganic chemicals were used without further purification. Acetonitrile was purified by four or five distillations from phosphorus pentoxide. Aqueous buffers of ionic strength 0.1 were prepared from HCl-KCl, HOAc-NaOAc, and $\text{KH}_2\text{PO}_4\text{-Na}_2\text{HPO}_4$. The 10% acetonitrile-water buffers used for kinetics studies were prepared by pipetting a known volume of acetonitrile into a volumetric flask and diluting to the mark with the appropriate 0.1 μ aqueous buffer. All volumes were measured and all dilutions performed at 25° and the procedure was highly reproducible. Buffers in D_2O

(4) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77**, 3146 (1955), suggested they might have observed a trace of catalysis by molecular formic acid in the hydrolysis of acetal and chloroacetal in 50% aqueous dioxane.

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

(6) J. N. Brønsted and C. Grove, *J. Am. Chem. Soc.*, **52**, 1394 (1930).

(7) R. H. DeWolfe and R. M. Roberts, *ibid.*, **76**, 4379 (1954). Note that Kreevoy and Taft⁴ also utilized dioxane-water solvents.

(8) D. A. Blackadder and C. Hinshelwood, *J. Chem. Soc.*, 2720 (1958).

(9) O. Ceder, *Arkiv Kemi*, **6**, 523 (1954).

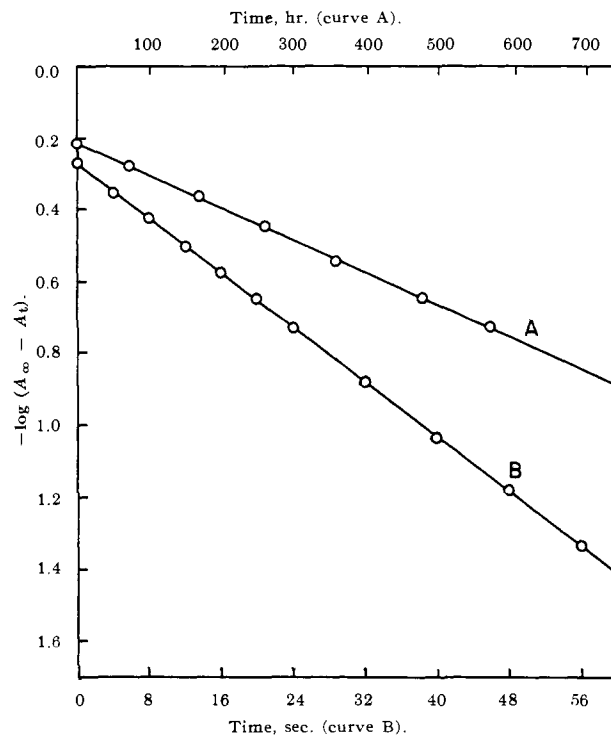


Fig. 1.—Kinetics of the hydrolysis of 2-(2-hydroxyphenyl)-1,3-dioxane (III) in 10% acetonitrile at 25.0°: A, pH 8.76; B, pH 2.11.

were prepared in the same manner; the DCl in D_2O was obtained from Dr. B. Zerner.¹⁰

Kinetic Measurements.—Rates were measured at 25.0°, using conventional spectrophotometric technique.⁹ The very fast runs were followed in a thermostated Cary Model 14 PM recording spectrophotometer, the others in a thermostated Beckman DU spectrophotometer. The appearance of product was followed at the wave lengths indicated (in $\text{m}\mu$): I and V, 249.5; II and III, 255.5; IV, 280; VI, 260 (pH 1-5) and 310 (pH 5-8). The apparent pH of each run was determined using a Radiometer Model 4b pH meter standardized against 0.05 M potassium acid phthalate (pH 4.01)¹¹ except that for runs at pH or pD 1 and 2 the meter was standardized against 0.01 M potassium tetroxalate (pH 2.15).¹¹ To determine pD, 0.40 was added to the pH meter reading.¹²

TABLE I
PROPERTIES OF SUBSTITUTED 2-PHENYL-1,3-DIOXANES

Compd.	M.p., °C. ^a	Formula	Carbon, % ^b		Hydrogen, % ^b	
			Calcd.	Found	Calcd.	Found
I	48, 2-48, 9°					
II	69, 80-80.3	$\text{C}_{11}\text{H}_{14}\text{O}_3$	68.02	68.31	7.27	7.50
III	60-61	$\text{C}_{10}\text{H}_{12}\text{O}_3$	66.65	66.62	6.71	6.70
IV	115, 126-129	$\text{C}_{10}\text{H}_{12}\text{O}_3$	66.65	66.60	6.71	6.57
V	97.5, 100-101	$\text{C}_{10}\text{H}_{11}\text{O}_3\text{N}$	53.33	53.26	4.92	4.77
VI	70, 73-75	$\text{C}_{10}\text{H}_{11}\text{O}_3\text{N}$	53.33	53.34	4.92	5.05

^a The first value for II, IV, V, and VI indicates softening. ^b Analyses by Micro-Tech Laboratories, Skokie, Ill. ^c Lit.⁹ m.p. 49.5-50°.

Infinity values for slow runs were obtained by sealing samples in ampoules and heating at 100° an appropriate length of time. No difficulties from sample decomposition were encountered in this heat treatment. Good first-order plots were obtained for all compounds except III, which showed erratic behavior in the region pH 7-9. Salicylaldehyde, the reaction product of III, was proved to be unstable under these conditions by following the change in absorption with time of a solution of the aldehyde in pH 8 buffer. In three weeks, the absorption of the solution at 255.5 $\text{m}\mu$ had diminished by 15%. Over the same period of time and under the same conditions, *p*-hydroxybenzaldehyde and 2-hydroxy-4-nitrobenzaldehyde appeared to be completely stable. The pH 8 solutions of all three aldehydes could be heated at 100° for several hours without a detectable change in their absorption maxima. It was assumed that the change in absorption of

(10) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, **83**, 2267 (1961).

(11) R. G. Bates, G. D. Pinching, and E. R. Smith, *J. Res. Natl. Bur. Standards*, **45**, 418 (1950).

(12) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

TABLE II
 RATES OF HYDROLYSIS AND pK_a DATA FOR 2-(SUBSTITUTED PHENYL)-1,3-DIOXANES^{a,c}

2-(X-Phenyl)-1,3-dioxane, X =	pK_a		$k_1 = k_2 K_A \times 10^3,$ sec. ⁻¹		$-k_3, M^{-1} \text{ sec.}^{-1}$		$\frac{k_2(\text{H}_2\text{O})}{k_2(\text{D}_2\text{O})}$	$-k_2, M^{-1} \text{ sec.}^{-1}$		$\frac{k_2(\text{H}_2\text{O})}{k_2(\text{D}_2\text{O})}$
	H ₂ O	D ₂ O	H ₂ O	D ₂ O	H ₂ O	D ₂ O		H ₂ O	D ₂ O	
H (I)								0.39	1.22	0.32
2-MeO (II)								3.6	10.6	.34
2-HO (III)	9.71		0.06		3100			5.5	13.9	.40
4-HO (IV)	9.75	10.36 ^b	0.058	0.046	3300	10500	0.31	15.3	39.6	.39
2-HO-5-NO ₂ (V)	6.56	7.10	2.0	1.5	75	190	.38	0.075	0.18	.42
4-HO-5-NO ₂ (VI)	6.63	7.18 ^b	3.1	2.4	130	360	.36	0.15		

^a 10% acetonitrile-water at 25°. ^b Calcd.; see Experimental. ^c For definition of rate constants, see eq. 7.

solutions of III at pH 7-9, arising from the decomposition of the product salicylaldehyde, was a zero-order process. Infinity values for runs in this pH range were determined at the beginning and end of the reaction period. Application of the assumption of zero-order change in infinity absorption with time gave reasonably good corrected first-order plots, which will, nevertheless be regarded with suitable skepticism. Figure 1 shows two typical rate runs.

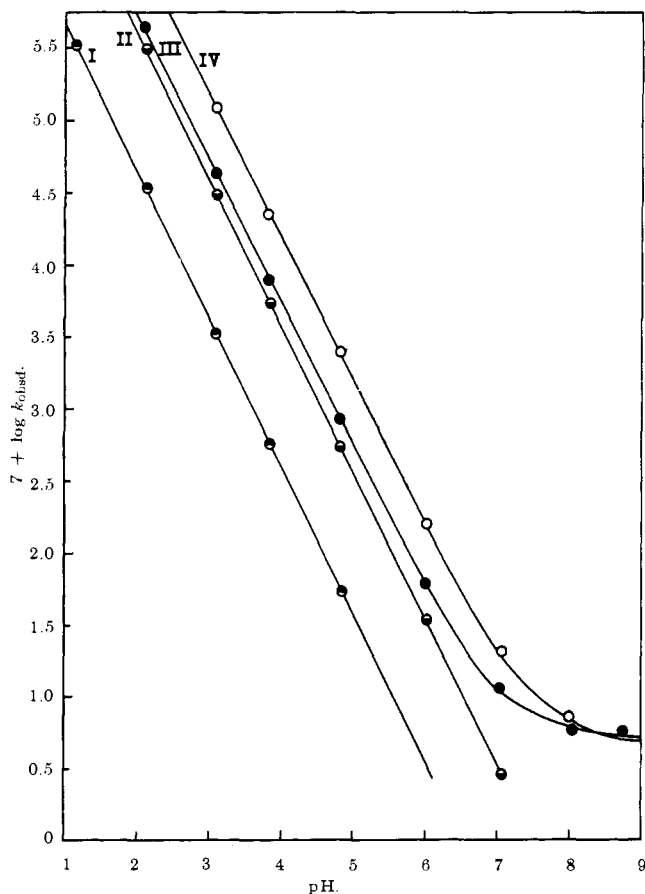


Fig. 2.—pH-rate profiles in 10% acetonitrile at 25°: I, 2-phenyl-1,3-dioxane; II, 2-(2-methoxyphenyl)-1,3-dioxane; III, 2-(2-hydroxyphenyl)-1,3-dioxane; IV, 2-(4-hydroxyphenyl)-1,3-dioxane. Curves III and IV are the theoretical curves calculated from eq. 5 and the data of Table II.

Proof that hydrolysis of the acetals did in fact yield the corresponding aldehydes was obtained in two cases (IV at pH 6.01 and V at pH 7.05) by demonstrating that the ultraviolet spectrum of the hydrolysis products was identical with that of a synthetic mixture prepared from the appropriate aldehyde and propylene glycol.

pK_a Determinations.—The pK_a 's of III-VI were determined spectrophotometrically in 10% acetonitrile-water at the same ionic strength as that used in the kinetics. The results are included in Table II. The last traces of *p*-hydroxybenzaldehyde could not be removed from IV and the pK_a of this compound may consequently be in slight error. The pK_a of V was measured in 10% acetonitrile-D₂O and found to be 7.10 ($\Delta pK_a = 0.54$). The ΔpK_a predicted from the equation below is 0.54.¹³ The

(13) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 195.

pK_a of VI was measured at $\mu = 0.1$ in H₂O (pK_a 6.46) and in

$$\log K_H/K_D = 0.02 pK_a + 0.41$$

D₂O (pK_a 7.01, ΔpK_a 0.55; calcd. from the above equation, 0.54). It was assumed that the change in pK_a for VI would be the same in 10% acetonitrile-water. Compound V is closely analogous to *p*-nitrophenol, for which a ΔpK_a of 0.56¹⁴ and 0.48¹⁵ has been reported. Compound VI is closely analogous to *o*-nitrophenol, for which a ΔpK_a of 0.57¹⁴ and 0.75¹⁵ has been reported. The pK_a of IV in 10% acetonitrile-D₂O was estimated from the measured value in 10% acetonitrile-H₂O and from the above equation.

Results

The rates of hydrolysis of acetals I-VI were measured as a function of pH at 25° in 10% acetonitrile-water. The unsubstituted and *o*-methoxy compound (I and II) showed the usual hydronium ion-catalyzed hydrolysis of acetals, which can be represented by eq. 2. Plots of $\log k_{\text{obsd}}$ vs. pH for I and II are shown in Fig. 2. The slopes of the lines (least squares calculations) are -1.02 and -1.01 , respectively, as compared to the theoretical slope of -1.00 . The preferred values for the pH-independent, second-order rate constants k_2 were chosen so as to minimize the average deviation between the observed and calculated rate constants for the individual runs. These results are presented in Table II. A value of k_2 (defined in eq. 2 and 3) equal to $0.41 M^{-1} \text{ sec.}^{-1}$ can be calculated for I in pure water at 25° from the data of Ceder,³ in good agreement with our measured value.

$$\text{rate} = k_{\text{obsd}}[\text{S}] = k_2[\text{S}][\text{H}^+] \quad (2)$$

$$k_{\text{obsd}} = k_2[\text{H}^+] \quad (3)$$

[S] = concn. of acetal
 k_{obsd} = obsd. pseudo-first-order constant
 k_2 = apparent pH-independent second-order rate constant

Plots of $\log k_{\text{obsd}}$ vs. pH for the acetals containing a phenolic hydroxyl group (III-VI) are shown in Fig. 2 and 3. The pH dependence of the hydrolysis of the acetals containing phenolic hydroxyl groups is significantly different from those of the acetals I and II. This difference is particularly evident in a comparison of the pH dependencies of acetals II and V. The former compound contains an *o*-methoxy group and exhibits in its hydrolytic reaction a linear dependence on acidity up to pH 7. The latter compound, however, which contains an *o*-hydroxyl group (of pK_a 6.56 because of the presence of a 5-nitro substituent), exhibits in its hydrolytic reaction a linear dependence on acidity only to pH 3; at pH's between 3 and 6 the rate constant of hydrolysis is quite insensitive to the hydrogen ion concentration, whereas at pH's above 6 the reaction is again sensitive to the hydrogen ion concentration. The pH dependence of the hydrolysis of acetals III-VI are readily explained if: (1) in addition to the second-order (hydronium ion-catalyzed) decomposition of the acetal, a term for a first-order decomposition of the un-ionized acetal is included in the kinetic expression;

(14) D. C. Martin and J. A. V. Butler, *J. Chem. Soc.*, 1366 (1939); H₂O at 18°.

(15) A. O. McDougall and F. A. Long, *J. Phys. Chem.*, **66**, 429 (1962); H₂O at 25°.

and (2) allowance is made for the ionization of the phenol to the phenolate anion as the pH is raised. Equation 4 is the rate law for this situation and eq. 5 is the derived expression for k_{obsd} in terms of measured quantities and the first- and second-order rate constants, k_1 and k_2 . Values were again assigned to k_1 and k_2 so as to minimize the average deviations between the calculated and observed rate constants for the individual runs; these values are also listed in Table II.

$$\text{rate} = k_{\text{obsd}}[S] = k_1[\text{SH}] + k_2[\text{H}^+][\text{SH}] \quad (4)$$

$$k_{\text{obsd}} = \frac{1}{1 + K_A/[\text{H}^+]} (k_1 + k_2[\text{H}^+]) \quad (5)$$

[S] = concn. of acetal in all forms
 [SH] = concn. of acetal in undissociated form
 [S⁻] = [S] - [SH] = concn. of acetal as phenolate anion
 $K_A = [\text{H}^+][\text{S}^-]/[\text{HS}] = \text{ionization constant of acetal}$

Figures 2 and 3 show that the agreement between the calculated curves and observed values for the rate constants was satisfactory.

A further check on the validity of the interpretation of the kinetics of the hydrolysis of V and VI is available. In the higher region of the pH range studied, the apparent unimolecular reaction is essentially the sole reaction path, since the condition $k_2[\text{H}^+] \ll k_1$ is fulfilled. Equation 5 is now transformed into eq. 6, which predicts that a plot of $1/k_{\text{obsd}}$ vs. $1/[\text{H}^+]$ should be linear, with slope K_A/k_1 and intercept $1/k_1$. Such plots were made and found to be linear. Least squares

$$1/k_{\text{obsd}} = 1/k_1 + (K_A/k_1)(1/[\text{H}^+]) \quad (6)$$

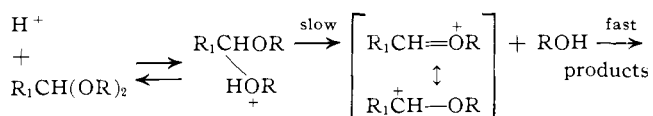
calculations gave, for V, $\text{p}K_a = 6.59$, $k_1 = 1.87 \times 10^{-5}$ sec.⁻¹, and, for VI, $\text{p}K_a = 6.65$, $k_1 = 2.92 \times 10^{-5}$ sec.⁻¹. These results are in good agreement with the values obtained by the other procedure and confirm the general validity of our interpretation of the kinetics of the hydrolysis of I–VI in the pH range studied.

The hydrolyses in D₂O were treated in precisely the same fashion as those in H₂O. However, many fewer runs were performed in D₂O and consequently the values in Table II for reaction in this solvent are less reliable.

Discussion

Observation of an apparent unimolecular reaction (k_1) in the hydrolysis of the phenolic acetals III–VI leads to consideration of possible mechanistic interpretations. On the basis of their apparent unimolecular reaction the *o*-isomers III and V apparently exhibit intramolecular general acid catalysis as depicted in eq. 1. However, acetals IV and VI, with a *p*-phenolic group, show a k_1 term which is as large as that of the corresponding *o*-isomers. Therefore assignment of a unique role to the *ortho* function as an intramolecular general acid catalyst in these hydrolyses is untenable, and an explanation for the apparent unimolecular reactions must be sought elsewhere.

The accepted mechanism⁵ for acetal hydrolysis is a rapid, reversible protonation of an acetal oxygen followed by a rate-controlling heterolysis to a resonance-stabilized carbonium ion and an alcohol molecule.



Both the pre-equilibrium and the rate-determining steps should be greatly aided by electron-releasing groups in the R₁ portion of the acetal. In the present investigations, R₁ is a phenyl or substituted phenyl group. Electron release from an *o*- or *p*-phenolic oxyanion is among the strongest possible on a benzene ring. Therefore, the acid-catalyzed hydrolysis of the *phenolate form* of III–IV should be extremely rapid. A

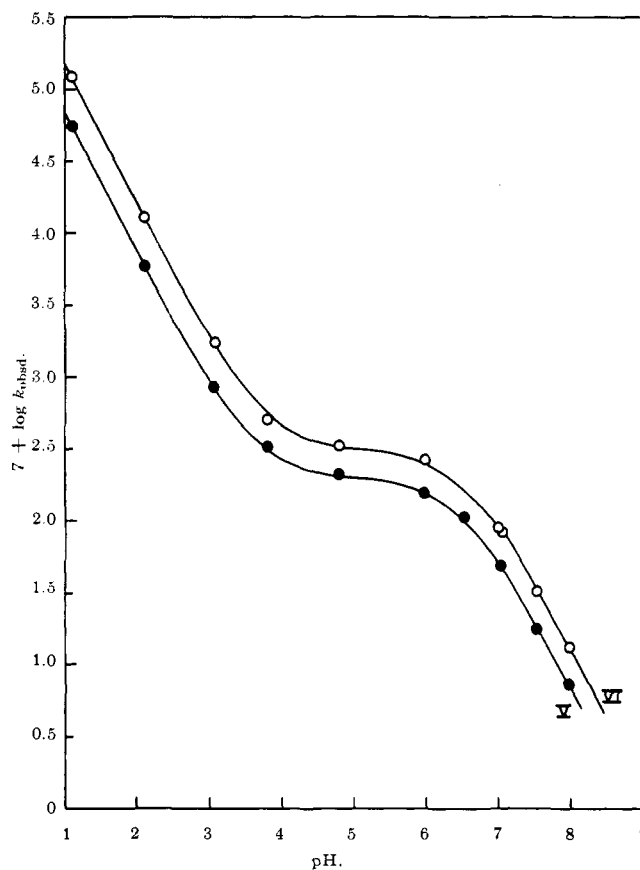
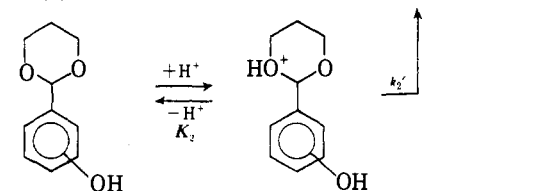
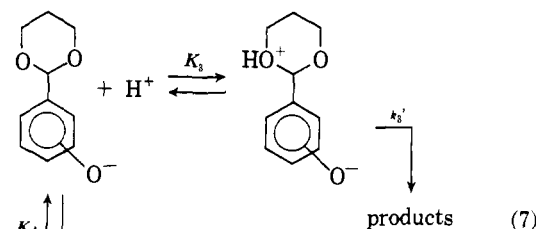


Fig. 3.—pH-rate profiles in 10% acetonitrile at 25°C: VI, 2-(4-hydroxy-5-nitrophenyl)-1,3-dioxane; V, 2-(2-hydroxy-5-nitrophenyl)-1,3-dioxane. The curves are the theoretical ones calculated from eq. 5 and the data of Table II.

simple and consistent explanation for the first-order, pH-independent, kinetic term in the hydrolysis of III–VI can be derived if we assume that this term represents the specific hydronium ion-catalyzed hydrolysis of the phenolate anion form of the acetal.



$$k_1 = K_A K_3 k_3' \quad (8)$$

$$k_3 = K_3 k_3' \quad (9)$$

$$k_2 = K_2 k_2' \quad (10)$$

Scheme 7 illustrates the reactions under consideration. Equations 8–10 follow from eq. 4, 5, and 7. Rate constant k_2 (see eq. 10) involves the equilibrium protonation of an acetal oxygen of the undissociated phenolic form of acetals III–VI or of I or II, followed by a slow ionization to a carbonium ion and alcohol molecule; the two steps are not presently separable. Rate constant k_3 , as defined by eq. 9, involves precisely the same two processes operating on the *phenolate ion*

form of acetals III-VI. Values for k_3 are calculated from the directly determined values of k_1 and K_a with the use of eq. 8 and 9. Comparison of k_3 to k_2 reveals that the former is considerably larger (Table II). The large magnitude of the k_3 's reflects the very great electron-donating ability of the *o*- or *p*-phenolic oxyanions relative to other phenyl substituents (even -OH is much poorer). A quantitative estimate of this electron-donating ability is not possible here, for the data are too limited and the reaction too complex. Both the equilibrium protonation, which should correlate with σ , and the heterolysis, which would probably correlate with σ^+ , are presumably significantly affected by the substituents in the aromatic ring.¹⁶

Deuterium oxide solvent isotope effects can serve as a useful test of the postulated mechanism. The value for $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$ in the hydrolysis of acetal at 15° in dilute HCl is 0.38.¹⁷ We have found that the specific acid-catalyzed hydrolysis of the neutral acetals I-V has a similar isotope effect: $k_2(\text{H}_2\text{O})/k_2(\text{D}_2\text{O}) = 0.32-0.42$ (Table II).

Determination of the D_2O effect on k_1 (using eq. 5) indicates that the ratio $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$ is greater than unity. However, it is not proper to compare this isotope effect with that calculated for k_2 above. The proper comparison involves k_3 and k_2 since both these processes represent a pre-equilibrium followed by a slow ionization step (eq. 7). It would therefore be predicted that the D_2O effect on k_3 should be similar to that on k_2 . Using eq. 6 and the $\text{p}K_a$ of the phenols in D_2O it is found that $k_3(\text{H}_2\text{O})/k_3(\text{D}_2\text{O}) = 0.31-0.38$ (Table II). The deuterium oxide solvent isotope effects are therefore completely in accord with the interpretations placed upon the kinetic data.

The net effects of the *o*- and *p*-phenolate anions on the hydrolysis of the acetal linkage are the same. However, it does not follow that the effect of these substituents on the component steps must be the same. The closer proximity of the *o*-phenolate anion to the site of protonation on the acetal oxygen might, by electro-

(16) Treatment of a more extensive set of data by the method of H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **78**, 815 (1959), might prove of interest.

(17) W. J. C. Orr and J. A. V. Butler, *J. Chem. Soc.*, 330 (1937).

static field effects, increase the basicity (K_3) of the *o*-phenolate acetals relative to their *p*-isomers. If k_3' were larger for the *p*-isomers, the over-all rate, as reflected in k_3 , could still be the same for the isomeric pairs.¹⁸ At present, there is no justification for differentiating between the roles of the *o*- and *p*-phenolate substituents in the present acetal hydrolyses. However, a *m*-phenolate substituent could not provide the direct resonance stabilization of the intermediate and would be expected to show a much smaller unimolecular reaction.

The unimolecular reaction we have observed is formally an intramolecular general acid-catalyzed reaction, having the same kinetic expression as eq. 1. Mechanistically, however, it represents the specific hydronium ion-catalyzed hydrolysis of the phenolate anion form of the acetal as shown in eq. 7. The rate of the phenolate anion reaction in eq. 7 is so great that the reaction of eq. 1 would have to be extremely facile if it were to be detected in the presence of the former reaction. However, it is conceivable that a reaction analogous to eq. 1 could occur and be detected with an acidic *o*-substituent whose anion could not engage in a direct resonance stabilization of the carbonium ion formed in the reaction.¹⁹

Mechanisms 1 and 7 differ essentially only in the position of the proton in the transition state. Mechanism 1 indicates that the proton is partially transferred in the transition state while mechanism 7 indicates that it is fully transferred. A number of other apparent intramolecular acidic catalyses appear to conform to the results found in this paper, namely, that the proton transfer is essentially complete in the transition state of the reaction.²⁰

(18) A crude test of the proposition regarding protonations was made by determining the ionization constants of analogs of the phenolic acetals, 2- and 4-hydroxy-5-nitrobenzylamines, which appear to exist as the zwitterions. The first $\text{p}K_a$'s and the second $\text{p}K_a$'s are essentially identical for the two isomers. In these aromatic systems, the effect of charge is relayed with equal effectiveness, whatever the means, to the *ortho* and *para* positions.

(19) NOTE ADDED IN PROOF.—This prediction is borne out in the recent demonstration (B. Capon, *Tetrahedron Letters*, **14**, 911 (1963)) that in the hydrolysis of σ -carboxyphenyl- β -D-glucoside, the σ -carboxy group acts as an intramolecular general acid catalyst and increases the rate of hydrolysis substantially as compared to the corresponding *p*-carboxy derivative.

(20) M. L. Bender and J. M. Lawlor, *J. Am. Chem. Soc.*, **85**, 3010 (1963).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Isotopic and Kinetic Studies of the Mechanism of Hydrolysis of Salicyl Phosphate. Intramolecular General Acid Catalysis¹

BY MYRON L. BENDER² AND JOHN M. LAWLOR³

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Several experiments indicate that no salicyloyl phosphate intermediate is formed in the hydrolysis of salicyl phosphate: (1) no hydroxamic acid is formed when salicyl phosphate hydrolyzes in the presence of hydroxylamine; (2) when salicyl phosphate is hydrolyzed in H_2^{18}O , no oxygen-18 is introduced into the salicylic acid produced, unlike the corresponding experiment in aspirin hydrolysis. Salicyloyl cyclic phosphate hydrolyzes *via* salicyl phosphate as an intermediate; thus the former compound cannot be an intermediate in the hydrolysis of the latter. The shape of the pH-rate profile of salicyl phosphate hydrolysis in deuterium oxide is identical with that in water, although the curve is shifted to higher pH. The deuterium oxide solvent isotope effect for the hydrolysis of salicyl phosphate dianion has been determined: $k^{\text{H}_2\text{O}}/k^{\text{D}_2\text{O}} = 0.96$. The dianion of 8-hydroxy-1-naphthyl dihydrogen phosphate hydrolyzes 10 times faster than the dianion of the 8-methoxy ester. The experimental data given above are not consistent with mechanisms of salicyl phosphate hydrolysis involving intramolecular nucleophilic attack by either *o*-carboxylate ion or by phosphate dianion. The data are, however, consistent with a mechanism for the facile hydrolysis of salicyl phosphate in which the *o*-carboxylic acid group donates a proton to the leaving oxygen atom in the hydrolysis.

Introduction

The facile hydrolyses of *o*-carboxyaryl phosphates have been extensively studied.⁴⁻⁷ The hydrolyses of

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(2) Alfred P. Sloan Foundation Research Fellow.

(3) University of Melbourne, Victoria, Australia.

these compounds are kinetically first order with respect to the ester, the dianion hydrolyzes faster than the

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