A Search for Carboxyl-Group Catalysis in Ketal Hydrolysis

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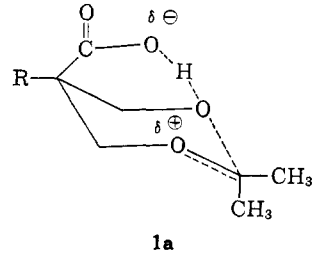
Abstract: The pH–rate profiles for the hydrolysis of 19 1,3-dioxanes and 1,3-dioxolanes, seven of which were carboxyl substituted, have been determined. The rates of hydrolysis were found not to be sensitive to the concentration of formate and acetate buffers at constant pH showing the compounds not to be susceptible to intermolecular general acid catalyzed hydrolysis. The log of the pseudo-first-order rate constants (k_{obsd}) for the hydrolysis of all dioxolanes and dioxanes not substituted by carboxyl groups when plotted *vs.* pH provided linear plots of slope *ca.* −1.0, indicating the mechanism of hydrolysis is specific acid catalysis. For the carboxyl-substituted dioxolanes and dioxanes, the pH–log k_{obsd} profiles are characterized by the superimposition of a plateau rate upon the specific acid catalyzed region, followed in the low acid region by a descending leg of approximate slope of −1.0. The plateau and second descending leg are found to have kinetically equivalent interpretations as participation by the undissociated carboxyl group in the hydrolysis or the specific acid catalyzed hydrolysis of the carboxylate anion form of the ketals. The latter mechanism has been shown to be correct on the basis that the log k_{rate} values for the calculated constants for specific acid catalyzed hydrolysis of the undissociated ketals (K–COOH) and dissociated ketals (K–COO^-) exhibit no positive deviations from Hammett plots (σ^*) constructed from the rate constants for specific acid catalysis of the hydrolysis of ketals not containing carboxyl groups. Literature reports of the participation of neighboring carboxyl groups in the hydrolysis of acetals are discussed.

Lysozyme is the first enzyme whose tertiary structure has been determined.[2] From chemical studies[3] and X-ray diffraction studies of a lysozyme–polysaccharide complex[4] it is possible to infer that carboxyl groups are the only functional groups which are both present at the active site and likely to be involved in the bond-breaking steps. Carboxyl groups have previously been implicated in the action of α-amylase[5] and β-glucosidase.[6] It is, therefore, of interest to determine the mechanistic significance of neighboring carboxyl groups in glycoside hydrolysis and in acetal and ketal hydrolysis in general.

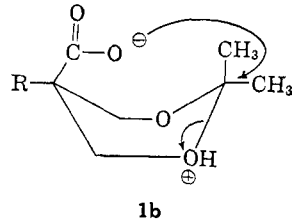
Intermolecular general acid catalysis by carboxylic acids of acetal or ketal hydrolysis has not been established, though Kreevoy and Taft[7] suggested that they may have noted a trace of formic acid catalysis in the hydrolysis of acetal and chloroacetal in 50% aqueous dioxane.[8] For the analogous ortho esters, general acid catalyzed hydrolysis is easily detectable, even in water.[9,10]

Intramolecular catalysis of the hydrolysis of *o*-carboxyphenyl β-D-glucoside[11] and more recently that of another simple phenolic acetal[12] by undissociated carboxyl groups has been claimed. Intramolecular general acid catalysis has also been claimed recently in the hydrolysis of poly- and oligouronides.[13] For these intramolecular models differentiation of mechanisms could not be made on the basis of the structure of the compound undergoing hydrolysis.

Our purpose in conducting the study described here was to examine the hydrolyses of several compounds which would allow differentiation between two possible intramolecular mechanisms, if they did indeed take place, on the basis of steric considerations. In intramolecular carboxyl group catalysis, two kinetically indistinguishable mechanisms are possible: intramolecular general acid catalysis and specific acid nucleophilic attack. The first compounds (Table I) studied, 5-carboxy-2,2,5-trimethyl-1,3-dioxane (I) and 5-carboxy-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane (II), allow the possibility of intramolecular general acid catalysis (**1a**); however, specific acid nucleophilic catalysis (**1b**) is sterically impossible (in **1–4** the transi-

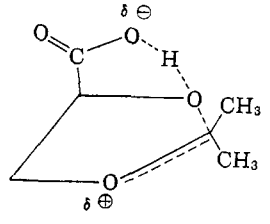


1a

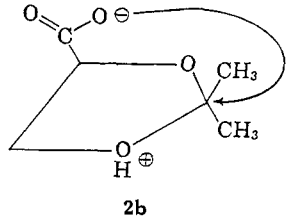


1b

R = $-CH_3$, $-CH_2OH$



2a



2b

(1) Predoctoral Fellow, National Institutes of Health. A portion of the material to be submitted by D. P. for the Ph.D. in Chemistry, University of California at Santa Barbara, Santa Barbara, Calif.

(2) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature*, **206**, 757 (1965).

(3) J. A. Rupley, *Proc. Roy. Soc.* (London), **167**, 416 (1967).

(4) (a) L. N. Johnson and D. C. Phillips, *Nature*, **206**, 761 (1965); (b) C. C. F. Blake, L. N. Johnson, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Proc. Roy. Soc.* (London), **167**, 378 (1967).

(5) S. Ono, K. Hiromi, and Y. Yoshikawa, *Bull. Chem. Soc. Japan*, **31**, 957 (1958).

(6) B. H. J. Hofstee, *J. Am. Chem. Soc.*, **80**, 3966 (1958).

(7) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **77**, 3146 (1955).

(8) It is highly unlikely that any intermolecular catalysis was observed here since an acetal which would be more susceptible to general acid catalysis (the dioxolane of mesityl oxide) exhibited no general acid catalysis when hydrolyzed (in formate or cacodylate buffers, in water or aqueous dioxane): C. A. Bunton, R. W. DeWolfe, and J. Valentine, unpublished data.

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

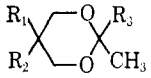
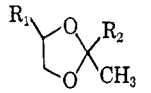
(10) J. N. Bronsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

(11) B. Capon, *Tetrahedron Letters*, 911 (1963).

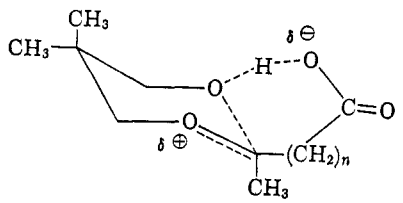
(12) B. Capon and M. C. Smith, *Chem. Commun.*, **1**, 523 (1965).

(13) O. Smidsrød, A. Haug, and B. Larsen, *Acta Chem. Scand.*, **20** 1026 (1966).

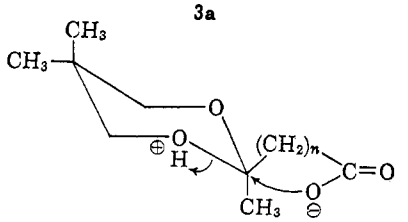
Table I. Structures of 1,3-Dioxolanes and 1,3-Dioxanes

		R_1	R_2	R_3
	I	COOH	CH_3	CH_3
	II	COOH	CH_2OH	CH_3
	III	CH_2OH	CH_3	CH_3
	IV	CH_2OH	CH_2OH	CH_3
	V	CH_3	CH_3	CH_3
	X	CH_3	CH_3	CH_2COOH
	XI	CH_3	CH_3	CH_2CH_2COOH
	XII	CH_3	CH_3	$CH_2COOC_2H_5$
	XIII	CH_3	CH_3	$CH_2CH_2COOC_2H_5$
	XIV	CH_3	CH_3	CH_2Cl
	VI	COOH	CH_3	
	VII	CH_2OH	CH_3	
	VIII	CH_3	CH_3	
	IX	H	CH_3	
	XV	H	CH_2COOH	
	XVI	H	CH_2CH_2COOH	
	XVII	H	$CH_2COOC_2H_5$	
	XVIII	H	$CH_2CH_2COOC_2H_5$	
	XIX	H	CH_2Cl	

tion states for general acid catalysis are pictured arbitrarily in analogy to an A1 mechanism). Similarly, 4-carboxy-2,2-dimethyl-1,3-dioxolane (VI) allows the possibility of intramolecular general acid catalysis (**2a**) but not specific acid nucleophilic catalysis (**2b**). The third set of compounds, 2-carbomethyl- and 2-carboxyethyl-2,5,5-trimethyl-1,3-dioxane (X and XI), allows both intramolecular general acid catalysis (**3a**) and nucleophilic attack (**3b**). The fourth set, 2-carboxymethyl- and 2-carboxyethyl-2-methyl-1,3-dioxolane (XV and XVI), also allows both possible intramolecular mechanisms. In this paper we describe the kinetics and elucidate the mechanisms for the hydrolysis of 19 ketals including those of structures **1–4**.

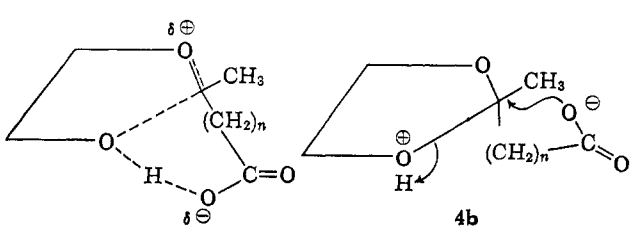


3a



3b

$n = 1$ or 2



4a **4b**

$n = 1$ or 2

Experimental Section

Materials. All of the compounds used in the kinetic studies were synthesized using one of the five general procedures described below. In Table II there is summarized for each ketal the procedure employed in the synthesis, the analysis,[14] and the determined physical properties. The pK_a's were determined by half-neutralization at $\mu = 1.0$ with KCl.

Procedure A. In general, the substituted 1,3-dioxanes and 1,3-dioxolanes were synthesized by the acid-catalyzed condensation of the appropriate diol and ketone according to the method of Conrad, *et al.*[15] For example, 2,2,5,5-tetramethyl-1,3-dioxane (V) was prepared by refluxing equimolar quantities of 2,2-dimethyl-1,3-propanediol and acetone in benzene with a trace of *p*-toluenesulfonic acid as catalyst. Water was continuously removed from the reaction by use of a Dean–Stark trap. The product was separated by distillation and further purified by redistillation on a Nester–Faust spinning-band column.

Procedure B. Several substituted 1,3-dioxolanes were prepared according to the method of Renoll.[16] This procedure is similar to procedure A, but substitutes low-boiling petroleum ether (bp 30–60°) as the reaction solvent.

Procedure C. 2,2-Dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (IV) was synthesized by condensing pentaerythritol with acetone (12-fold excess) in aqueous solvent.[17] HCl was used as catalyst, and the reaction was allowed to proceed at ambient temperature for 10 hr. Water and excess acetone were removed by flash evaporation, and the product was recrystallized from absolute ethanol.

Procedure D. The potassium salts of I, II, and VI were synthesized by the permanganate oxidation of the corresponding hydroxy compounds. Thus, III was treated with aqueous permanganate at 70–80° for 3 hr, according to the oxidation procedure of Shriner, *et al.*,[18] to yield I. IV was treated with permanganate at room temperature according to the detailed method of Fournier[19] to yield II. VII was treated with basic permanganate at room temperature according to the procedure of Reichstein[20] to yield VI. The filtrate from each reaction mixture was evaporated to dryness, then extracted with absolute ethanol. After concentration of the ethanol solution, anhydrous ether was added, precipitating the

(14) Analysis performed by A. Bernhardt, Max Plack Institut, Mulheim, Germany, and Elek Microanalytical Laboratories, Torrance, Calif.

(15) W. E. Conrad, B. D. Gesner, L. A. Levasseur, R. F. Murphy, and H. M. Conrad, *J. Org. Chem.*, **26**, 3571 (1961).

(16) M. Renoll and M. S. Newman, *Org. Syn.*, **28**, 73 (1948).

(17) L. Othner, *Chem. Ber.*, **61**, 116 (1928).

(18) R. L. Shriner and E. C. Kleiderer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 538.

(19) H. Fournier, *Bull. Soc. Chim. France*, **5**, 920 (1909), as translated in W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green, and Co., London, 1957, p 135.

(20) T. Reichstein, A. Pedolin, and A. Grüssner, *Helv. Chim. Acta*, **18**, 598 (1935).

Table II. Synthetic Procedures, Physical Properties, and Analyses of Ketals

Ketal	Syn proc	Yield, %	Bp (mm) or mp, °C	Lit. mp or bp (mm), °C	$n^{20}D$	Lit. n_D (°C)	pK_a'[d]	Calcd, % C	Calcd, % H	Found, % C	Found, % H
I[a,c]	D	74	304–306				4.49	41.70	6.56	41.63	6.39
II[a,c]	D	25	274–276				4.18	38.60	6.12	38.92	5.70
III	A	73	74–75 (0.40)	135 (30)[e]	1.4527						
IV	C	15	125–126	128–129[f]							
V	A	40	143–144 (760)	144–145 (760)[g]	1.4194	1.4178[g]					
VI[a]	D	51	244–246				3.20	39.11	4.94	39.59	5.16
VII	B	74	51–52 (0.10)	80–81 (11)[h]	1.4338						
VIII	B	38	99–100 (760)	99–100 (760)[i]	1.3940	1.4019 (18.5)[i]					
IX	B	37	89 (760)	91.5–93 (760)[j]	1.3992	1.3995 (20)[j]					
X[b]	E	33	304–306				4.37	51.40	7.19	50.97	6.80
XI[b]	E	81	239–240				4.63	53.55	7.63	53.05	7.55
XII	A	47	67–68 (0.55)		1.4402			61.05	9.34	61.00	9.09
XIII	A	56	102–103 (0.35)		1.4444			62.55	9.64	62.77	9.45
XIV	A	48	39–40 (0.70)		1.4526			53.75[m]	8.45	53.87	8.51
XV[b]	E	33	216–217				4.15	42.83	5.41	42.89	5.65
XVI[b]	E	44	230–232				4.80	46.13	6.10	45.69	6.45
XVII	A	48	43–44 (0.10)	99.5–101 (17)[k]	1.4318	1.43262 (20)[k]					
XVIII	A	11	52–53 (0.25)		1.4341			57.42	8.56	57.22	8.59
XIX	A	47	30 (1.0)	56(13)[l]	1.4451	1.4456 (18)[l]					

[a] Potassium salt. [b] Sodium salt. [c] Analyzing as the monohydrate. [d] pK_a''s determined by half-neutralization at $\mu = 1.0$ with KCl. [e] W. E. Conrad, *et al.*, *J. Org. Chem.*, **26**, 3571 (1961). [f] L. Othner, *Chem. Ber.*, **61**, 116 (1928). [g] C. R. Rondestvedt, Jr., *J. Org. Chem.*, **26**, 2247 (1961). [h] M. Renoll and M. S. Newman, *Org. Syn.*, **28**, 73 (1948). [i] A. A. Petrov, *J. Gen. Chem. USSR*, **16**, 61 (1946). [j] H. Dauben, Jr., B. Loken, and H. Ringold, *J. Am. Chem. Soc.*, **76**, 1395 (1954). [k] E. J. Salmi, *Chem. Ber.*, **71**, 1803 (1938). [l] C. Feugeas, *Bull. Soc. Chim. France*, 2568 (1963). [m] *Anal.* Calcd for Cl: 19.87. Found: 20.15.

Table III. Kinetic Data for the Hydrolyses of Ketals [H_2O; 30 ± 0.1°; $\mu = 1.0$ with KCl]

Ketal	X_1	X_2	$\Sigma\sigma^*$[c]	k_H, l. mole^{-1} min^{-1}	k_b, l. mole^{-1} min^{-1}	pK_{app}	Slope of log k_{obsd}–pH profile
			5,5-Disubstituted 2,2-Dimethyl-1,3-dioxanes				
Ia	COOH	CH_3	2.08[a,b]	2.5×10^1			
Ib	COO^-	CH_3	0.37[a,b]		1.9×10^2	4.0	
IIa	COOH	CH_2OH	2.64[a,b]	1.38×10^1			
IIb	COO^-	CH_2OH	0.93[a,b]		1.17×10^2	4.0	
III	CH_2OH	CH_3	0.56[a]	1.5×10^2			−0.96
IV	CH_2OH	CH_2OH	1.12[a]	9.24×10^1			−0.96
V	CH_3	CH_3	0.0[a]	3.3×10^2			−1.00
			4-Substituted 2,2-Dimethyl-1,3-dioxolanes				
VIa	COOH		2.08[b]	7.08×10^{-1}			
VIb	COO^-		0.37[b]		4.57	2.6	
VII	CH_2OH		0.56[a]	5.13			−1.19
VIII	CH_3		0.0[a]	2.34×10^1			−0.80
IX	H		0.49[a]	2.39×10^1			−0.95
			2-(X-Methyl)-2,5,5-trimethyl-1,3-dioxanes				
Xa	COOH		2.08[b]	1.05			
Xb	COO^-		0.37[b]		2.09×10^2	4.4	
XIa	CH_2COOH		0.75[b]	4.99×10^1			
XIb	CH_2COO^-		0.13[b]		3.63×10^2	4.6	
XII	$COOC_2H_5$		1.99[a]	1.05			−0.86
XIII	$CH_2COOC_2H_5$		0.72[a]	4.47×10^1			−1.14
V	H		0.49[a]	3.3×10^2			−1.00
XIV	Cl		2.94[a]	6.61×10^{-2}			−1.00
			2-(X-Methyl)-2-methyl-1,3-dioxolanes				
XVa	COOH		2.08[b]	8.71×10^{-2}			
XVb	COO^-		0.37[b]		1.48×10^1	4.5	
XVIa	CH_2COOH		0.75[b]	2.82			
XVIb	CH_2COO^-		0.13[b]		3.09×10^1	4.75	
XVII	$COOC_2H_5$		1.99[a]	4.47×10^{-2}			−1.00
XVIII	$CH_2COOC_2H_5$		0.72[a]	2.57			−0.88
IX	H		0.49[a]	2.39×10^1			−0.95
XIX	Cl		2.94[a]	2.40×10^{-3}			−1.00

[a] R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 556. [b] M. Charton, *J. Org. Chem.*, **29**, 1222 (1964). [c] A σ^* value of 2.94 for COOH has been listed,[a] but consistently places points above the line in our plots. Similarly a value of −0.38 for COO^- has been listed[b] which consistently places points below the line in our plots. Values of 2.08 for COOH[b] and 0.37[b] for COO^- which gave consistent results were, therefore, used. Use of either of these σ^* values for COOH and COO^- would not have changed the conclusions of this study.

potassium salt as a gum which solidified upon standing. The potassium salts were purified by dissolving them in a minimum volume of hot absolute ethanol and reprecipitating them by the addition of anhydrous ether.

Procedure E. The sodium salts of the remaining carboxyl-substituted ketals were prepared by the basic hydrolysis of their ethyl esters by a method described by Fife.[21] For example, ethyl

(21) T. H. Fife, *J. Am. Chem. Soc.*, **87**, 271 (1965).

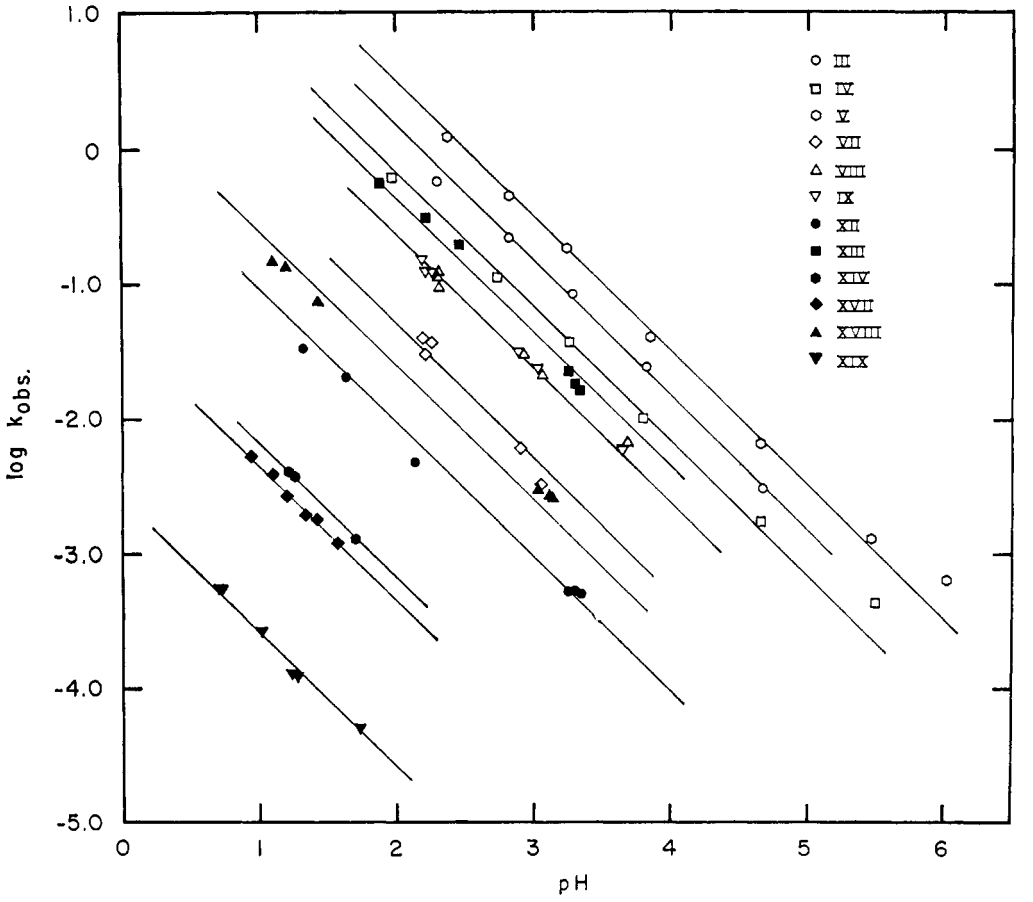


Figure 1. pH–log K_{obsd} profiles (k_{obsd} in min^{-1}) for the hydrolyses of 1,3-dioxanes and 1,3-dioxolanes not possessing carboxyl groups. Points are experimental and all lines have been drawn with the theoretical slope of −1.0. The Roman numerals pertain to the compounds in Table I.

2-methyl-2-carboxymethyl-1,3-dioxolane (XVII) was added to an equimolar quantity of sodium hydroxide in a minimum volume of hot 95% ethanol. The reaction mixture was cooled to room temperature and allowed to stand for 10 hr. Chilling and adding anhydrous ether precipitated sodium 2-methyl-2-carboxymethyl-1,3-dioxolane (XV). All sodium salts were recrystallized from absolute ethanol.

Kinetics. All kinetic measurements were done at 30 ± 0.1° in aqueous buffers at μ = 1.0 with KCl. Substrate concentrations averaged 0.02 *M*. Buffers employed were potassium acetate (pH 3.4–6.0), potassium formate (pH 2.2–3.8), and hydrochloric acid (pH 0.6–2.3). With the exception of compounds XII, XIV, and XIX, where the rates of hydrolysis were very slow, at least one buffer dilution experiment using three formate buffer concentrations at constant μ was performed for each ketal studied. In no instance was a buffer catalytic term detected. The hydrolyses were followed spectrophotometrically at 280 mμ, the approximate λ_{max} of the ketone products. The pseudo-first-order rate constants (k_{obsd}) were obtained by multiplying the slope of plots of log $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ *vs.* time (t) by 2.303.

Apparatus. A Radiometer 22 pH meter equipped with a PHA 630 Pa scale expander and a Type GK 2021 C combined electrode was used to determine pH. The electrode was stored at the temperature of the kinetic measurements. All kinetic measurements were made using a Gilford 2000 recording spectrophotometer, a Zeiss M4QIII monochromator equipped with a Gilford multiple-sample absorbance recorder, or a Zeiss M4QIII monochromator equipped with a Zieler multiple-sample absorbance recorder.

Results

Since the ketals are not subject to buffer catalysis and all reactions were carried out at constant pH, the rate constants obtained experimentally (k_{obsd}) were pseudo first order. For those ketals not possessing carboxyl groups, log k_{obsd} was found to be a linear function of pH (slope = −1.0 ± 0.2 for 12 ketals; see Figure 1), indicating that the mechanism of hydrolysis is specific acid catalysis. The pH–log k_{obsd} profiles of all carboxyl-substituted ketals studied may be derived from the kinetically equivalent eq 1 and 2, where $k_c = k_b K_{app}$.

$$k_{obsd} = [k_H a_H^2 + k_c a_H]/(K_{app} + a_H) \quad (1)$$

$$k_{obsd} = [k_H a_H^2 + k_b a_H K_{app}]/(K_{app} + a_H) \quad (2)$$

In (1) and (2) the constant K_{app} is the kinetically apparent acid dissociation constant of the carboxyl groups obtained from the best fit of the equations to the pH–log k_{obsd} profile; a_H is the hydrogen ion activity as measured by the glass electrode. The rate constants of (1) and (2) may be interpreted in the following manner: (a) k_H is the second-order rate constant for specific acid catalyzed hydrolysis of the undissociated form of ketal

$$\text{K–COOH} \xrightarrow{k_H[H^+]} \text{product} \quad (3)$$

(b) k_c is the first-order rate constant for the spontaneous hydrolysis of ketal with an undissociated carboxyl group

$$\text{K–COOH} \xrightarrow{k_c} \text{product} \quad (4)$$

and (c) k_b is the second-order rate constant for specific acid catalyzed hydrolysis of ketal with a dissociated carboxyl group.

$$\text{K–COO}^- \xrightarrow{k_b[H^+]} \text{product} \quad (5)$$

The immediate problem of the investigation is to ascertain whether k_c or k_b more correctly describes the

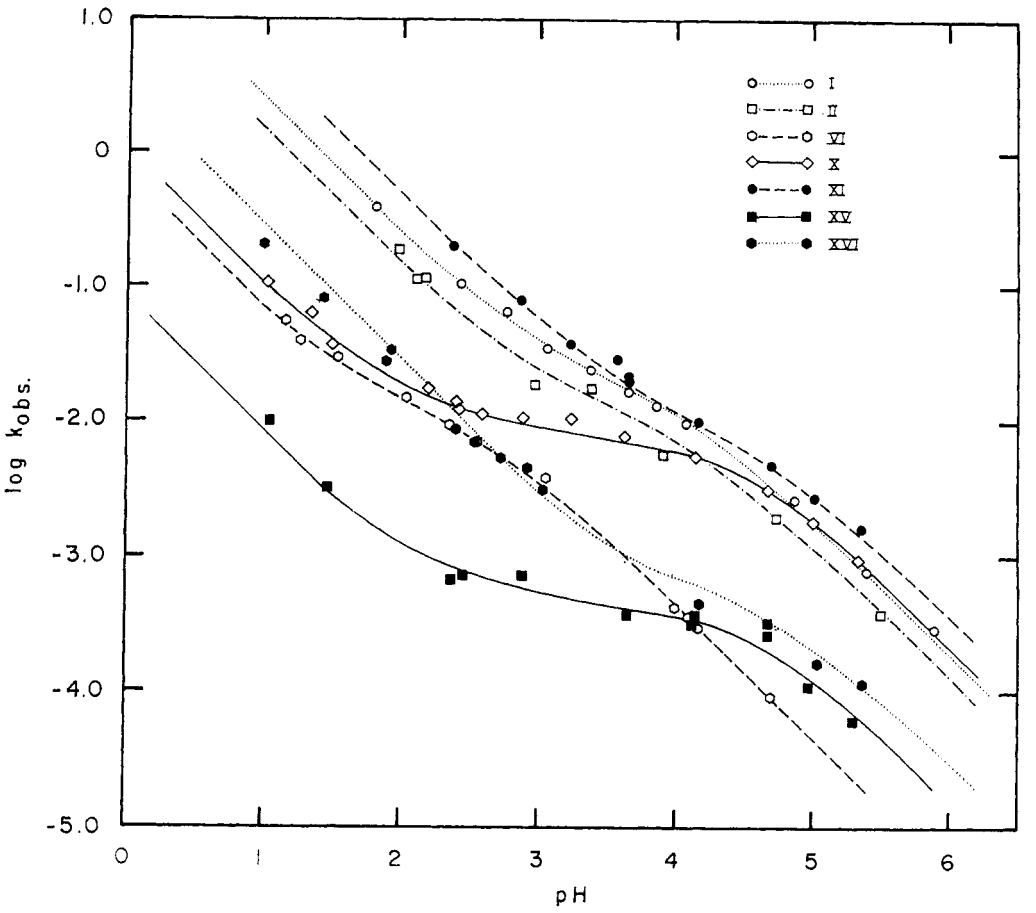


Figure 2. pH–log k_{obsd} profiles (k_{obsd} in min^{-1}) for the hydrolyses of 1,3-dioxanes and 1,3-dioxolanes possessing carboxyl substituents. Points are experimental and the curves calculated from eq 6 and the values of k_H, k_b, and K_{app} provided in Table III. The Roman numerals pertain to the compounds of Table I.

mechanism of hydrolysis at low a_H. Thus, if (4) were correct, intramolecular participation by the undissociated carboxyl group as a general acid catalyst would be indicated, whereas if (5) were correct, only specific acid catalysis of the hydrolysis of the ketal anion would be apparent. The pH–log k_{obsd} profiles for the hydrolyses of the ketals possessing carboxyl substituents are provided in Figure 2. In Figure 2 the points are experimental and the curves constructed from the most satisfactory solution of eq 1 or 2. A tabulation of the determined values of K_{app}, K_H, and k_b is provided in Table III.

To evaluate the significance of changes in electronic effects with ionization of the carboxyl groups on the hydrolysis of the carboxyl-substituted ketals, Hammett plots were constructed according to the equation log k_H or log $k_b = \rho\sigma^* + C$.[22] The values of σ^* for substituents of the 5,5-disubstituted 2,2-dimethyl-1,3-dioxanes were considered to be additive. The σ^* and $\Sigma\sigma^*$ values employed are included in Table III.

The Hammett plot for the hydrolyses of the 5,5-disubstituted 2,2-dimethyl-1,3-dioxanes (compounds I–V of Table I; Figure 3) is linear with no significant deviations and $\rho = -0.52$. The plot for the 4-substituted 2,2-dimethyl-1,3-dioxolanes (compounds VI–IX of Table I; Figure 4) shows a scattering of points of similar σ^* value. The 2-(X-methyl)-2,5,5-trimethyl-1,3-dioxanes (compounds X–XIV and V of Table I; Figure 5) and the 2-(X-methyl)-2-methyl-1,3-dioxolanes (compounds XV–XIX and IX of Table I; Figure 6) give linear plots having ρ values of -1.33 and -1.48, respectively, and with no significant deviations.

Inspection of (3) and (5) reveals that the constants k_b and k_H pertain to the same mechanism. Therefore, if (5) rather than (4) is mechanistically correct it would be anticipated that the difference in the values of k_H and k_b for any carboxy ketal would be provided by the Hammett equation when the difference in σ^* for the –COOH and $-COO^-$ groups is taken into account. If intramolecular carboxyl group catalysis were of any significance, the points corresponding to ionized carboxyl-substituted ketals would be expected to show a positive deviation from the Hammett plot, indicating the presence of an additional mechanism of kinetic significance for hydrolysis. Since the points for the carboxyl-substituted ketals exhibit no significant positive deviations from the Hammett plots, no justification for (4) exists and (5) more correctly describes the mechanism.

The rates of hydrolysis of I were determined at pH = pD[23] = 4.39 and 5.85, acidities at which hydrolysis would be accounted for by the k_c or k_b terms of eq 1 and 2. The pK_a' values of I were determined by half-neutralization to be 4.49 and 5.05 in H_2O and D_2O,

(22) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 556.

(23) The pH meter reading in D_2O solutions was converted to pD by employing the formula of T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

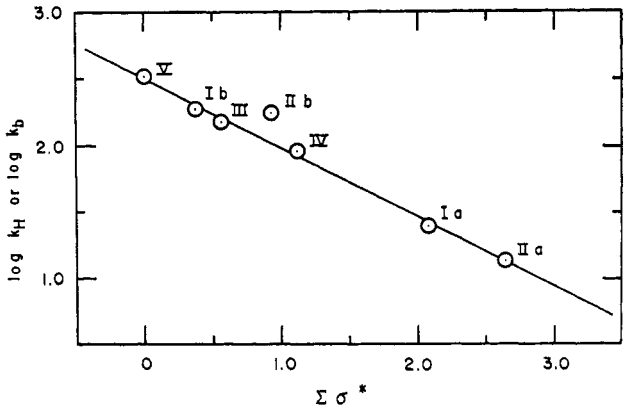


Figure 3. Hammett plot (σ^*) for the specific acid catalyzed hydrolyses of 5,5-disubstituted 2,2-dimethyl-1,3-dioxanes. Values of constants employed are provided in Table III; k_H and k_b are in l. mole^{-1} min^{-1}.

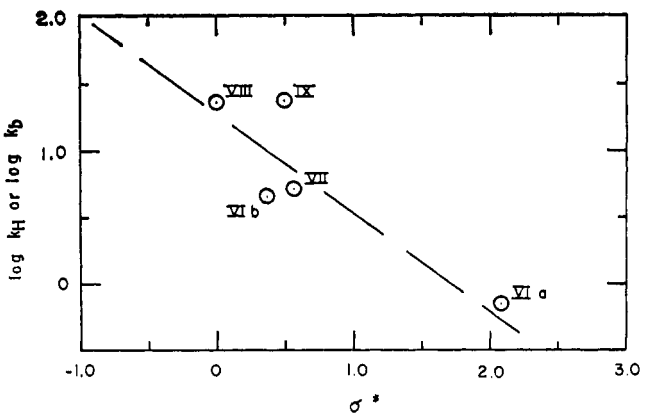


Figure 4. Hammett plot (σ^*) for the specific acid catalyzed hydrolyses of 4-substituted 2,2-dimethyl-1,3-dioxolanes. Values of constants employed are provided in Table III; k_H and k_b are in l. mole^{-1} min^{-1}.

respectively. The ratio $K_a^{H_2O}/K_a^{D_2O} = 3.65$ is in accord with the value of 3.33 determined previously for acetic acid.[24] The values of the calculated deuterium solvent kinetic isotope effects for k_c and k_b, obtained from (1) and (2) using the determined values of k_{obsd} and K_a' in H_2O and D_2O, are: $k_c^{H_2O}/k_c^{D_2O} = 0.75 \pm 0.01$ and $k_b^{H_2O}/k_b^{D_2O} = 0.21 \pm 0.01$, calculated from one experiment at each of the two pH = pD values employed. In previous studies the ratio of k^{H_2O}/k^{D_2O} for the specific acid catalyzed hydrolysis of dioxolanes and dioxanes has been found to vary from 0.31 to 0.42,[25,26] whereas for general acid catalyzed reactions the value of k^{H_2O}/k^{D_2O} is found to lie between 0.7 and 1.4, with values greater than unity being more probable.[27] The determined deuterium solvent isotope effects are in equal accord with the mechanism of either (4) or (5), as anticipated from the fact that the position of the proton in the transition state cannot be stipulated by the value of the deuterium isotope effect.[28] This point has not been fully appreciated (see Discussion).

(24) S. Korman and V. K. LaMer, *J. Am. Chem. Soc.*, **58**, 1396 (1936); V. K. LaMer and J. P. Chittum, *ibid.*, **58**, 1642 (1936).
(25) T. H. Fife and L. Hagopian, *J. Org. Chem.*, **31**, 1772 (1966).
(26) M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **85**, 3006 (1963).
(27) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).
(28) M. L. Bender, F. J. Kézdy, and B. Zerner, *J. Am. Chem. Soc.*, **85**, 3017 (1963); see also T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 157.

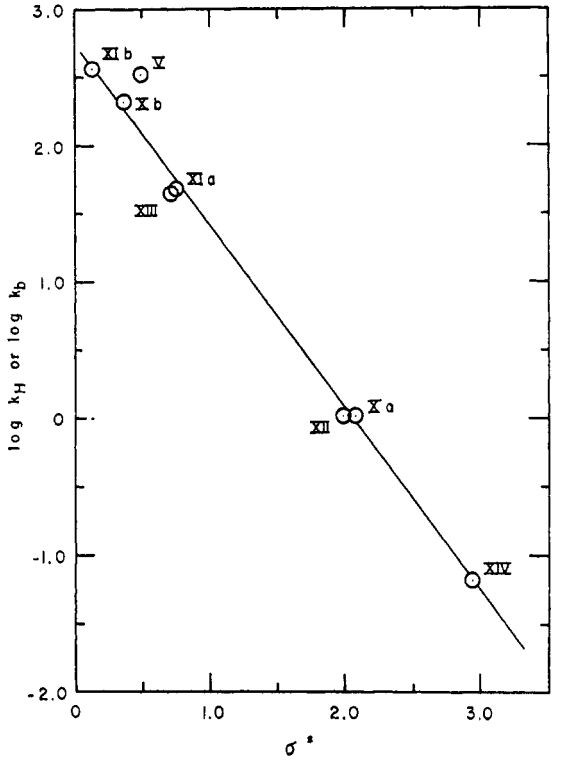


Figure 5. Hammett plot (σ^*) for the specific acid catalyzed hydrolyses of 2-(X-methyl)-2,5,5-trimethyl-1,3-dioxanes. Values of constants employed are provided in Table III; k_H and k_b are in l. mole^{-1} min^{-1}.

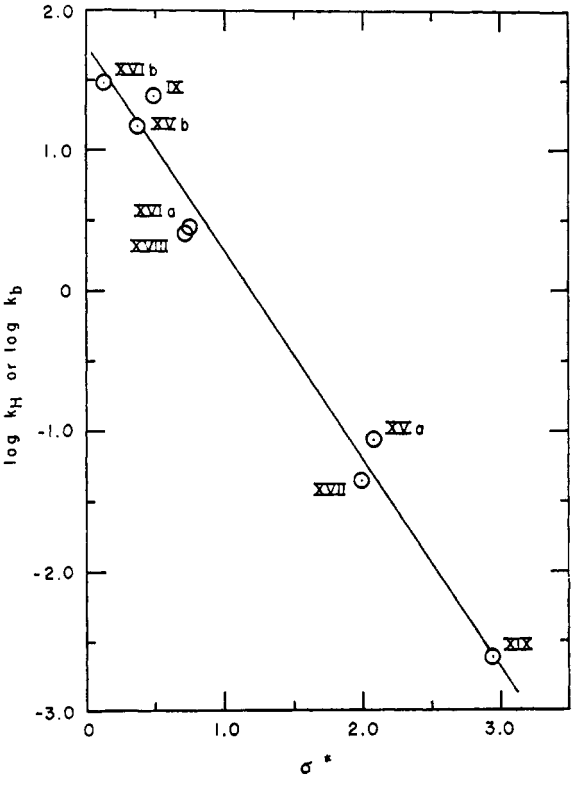
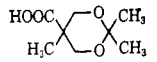
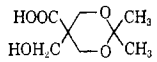
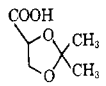
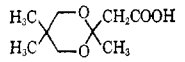
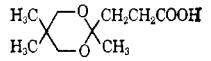
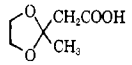
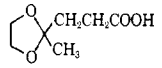
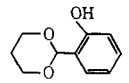
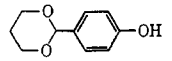
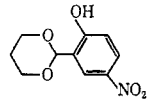
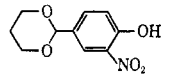
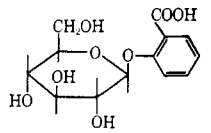
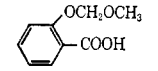
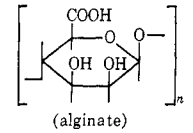
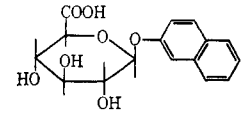


Figure 6. Hammett plot (σ^*) for the specific acid catalyzed hydrolyses of 2-(X-methyl)-2-methyl-1,3-dioxolanes. Values of constants employed are provided in Table III; k_H and k_b are in l. mole^{-1} min^{-1}.

Table IV. Kinetic Data and Conditions for the Hydrolyses of Acetals and Ketals

	Compound	k_H, l. mole^{-1} min^{-1}	$k_b = k_c/K_a$, l. mole^{-1} min^{-1}	$k_b/k_H = k_c/K_aK_H$	Temp, °C, solvent	Ref
I		2.5×10^1	1.9×10^2	7.6	30 H_2O	*a*
II		1.38×10^1	1.17×10^2	8.5	30 H_2O	*a*
VI		7.08×10^{-1}	4.57	6.0	30 H_2O	*a*
X		1.05	2.09×10^2	200	30 H_2O	*a*
XI		4.99×10^1	3.63×10^2	7.3	30 H_2O	*a*
XV		8.71×10^{-2}	1.48×10^1	180	30 H_2O	*a*
XVI		2.82	3.09×10^1	11	30 H_2O	*a*
XX		3.3×10^2	1.86×10^5	564	25 10% acetonitrile–H_2O	26
XXI		9.17×10^2	1.98×10^5	216	25 10% acetonitrile–H_2O	26
XXII		4.5	4.5×10^3	1000	25 10% acetonitrile–H_2O	26
XXIII		9.0	7.8×10^3	867	25 10% acetonitrile–H_2O	26
XXIV		*b*	*b*	est. $10^{4\,c}$	91.35 *d*	11
XXV		*b*	*b*	est. 300 to 650[c]	45 *d*	12
XXVI	 (alginate)	5.83×10^{-4}	4.67×10^{-1}	800	50.1 H_2O	13
XXVII		7.2×10^{-4}	1.14	1580	90.1 *d*	31

[a] Results presented in this paper. [b] Rate constants not given by the authors(s). [c] These values are estimates of the author(s) of the papers referred to. See Discussion for details. [d] Solvent system not specified by the author(s).

Discussion

For simple acetals and ketals, catalysis of hydrolysis by the lyate species is specific acid. The influence of a carboxyl group on the hydrolysis of an acetal or ketal may be due to the inductive effect of the –COOH or $-COO^-$ group on the specific acid rate constant or, alternatively, to the actual participation of the –COOH group as an intramolecular general acid (**1a**) or nucleophilic specific acid catalyst (**1b**). Since kinetic equations do not stipulate the position of the proton in the transition state, it is obvious that specific acid catalysis of the hydrolysis of $K–COO^-$ (5) and intramolecular participation of the carboxyl group in the hydrolysis of K–COOH (4) are kinetically indistinguishable (*i.e.*, $[K–COOH]$ is kinetically equivalent to $[K–COO^-]\cdot[H^+]$).

$$k_c\left[\frac{a_H}{K_a + a_H}\right] = k_b a_H\left[\frac{K_a}{K_a + a_H}\right] \qquad (6)$$

We have shown in this study that for the carboxyl-substituted 1,3-dioxanes and 1,3-dioxolanes (Table I; compounds I, II, VI, X, XI, XV, and XVI) the correct interpretation of the role of the carboxyl group is provided by the inductive and electrostatic effects for which σ^* serves as an index. In the design of these compounds care was taken that the various possible mech-

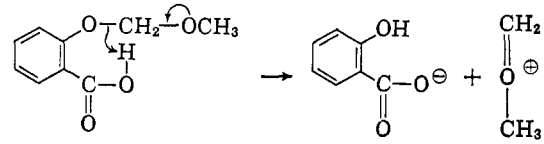
anisms for direct carboxyl participation were possible (see **1**, **2**, **3**, and **4**).[29]

The question arises as to whether the influence of ionizable substituents on the hydrolysis of other ketals and acetals may also be explained through electronic effects. The hydrolyses of a number of appropriately substituted acetals have been reported to follow the same kinetic rule as the carboxyl-substituted ketals of this study. A compilation of the pertinent literature is presented with our own data in Table IV.

Rather thoroughly studied are the 2-(hydroxyphenyl)-1,3-dioxanes (compounds XX–XXIII of Table IV). Comparable rate constants and pH–log k_{obsd} profiles for the *o*- and *p*-hydroxy-substituted compounds led Bender and Silver[26] to the *inescapable conclusion* that the mechanisms were specific acid catalyzed hydrolysis of the undissociated and dissociated phenolic acetals. Additional support for these mechanisms was thought to arise from the determined values of the deuterium solvent kinetic isotope effect. However, as shown by the deuterium solvent kinetic isotope effects for compound I of the present study and by theoretical computation,[28] this type of isotope effect can no more tell the position of the proton in the transition state than can the kinetic expression.

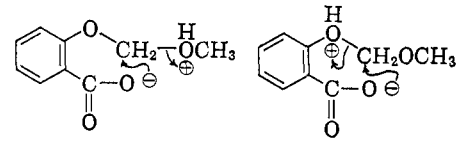
The next entry in Table IV is the *o*-carboxyphenyl β-D-glucoside (compound XXIV). The hydrolysis of XXIV is also quantitatively accounted for by the expression (6) between pH *ca.* 1.0 and 6.0. For this case Capon[11] favored intramolecular participation of the carboxyl group as a nucleophile on the O-1 protonated glucoside, participation of the carboxyl as an intramolecular general acid catalyst, or a concerted combination of the two. When the rate constant was calculated in the form of k_c [*i.e.*, the right-hand side of (6)] and compared to k_H for the *p*-carboxyl isomer determined at higher acidity (structures **5** and **6**), it was found that $k_b/k_H = k_c/K_a k_H = 10^4$. No mention of the shape of the log k_{obsd}–pH profile for the *para* isomer of XXIV in the pH range 1.0 to 2.6 was given. From other data on the hydrolyses of *ortho*-, *para*-, and *meta*-substituted phenyl β-D glucosides, the rate constant for specific acid catalyzed hydrolysis is seen to be sensitive to electronic effects ($\rho = -0.7$ at 60° in water)[30] so that the ionization of either the *o*- or *p*-carboxyl group, with the resultant change in the Hammett σ value from 0.0 to 0.45,[31] must influence the value of k_H. Furthermore, it should be noted that *ortho* substituents in general, as compared to the same *para* substituent, accelerate the rate of specific acid catalyzed hydrolysis of phenyl β-D-glucosides.[30] In addition the rate ratio calculated by Capon is rather comparable to that calculated in the same manner for the phenolic acetal XXII (column four of Table IV). Selection of the most plausible mechanism for the hydrolysis of XXIV must await publication of more detailed investigations.

The hydrolysis of the simple acetal XXV is characterized by the same type log k_{obsd}–pH profile as the hydrolysis of the preceding compounds of Table IV. The hydrolysis of XXV at pH 4.11 was stated to be 650 times greater than that for the corresponding methyl ester, and at pH 4.08 to be 300 times greater than for the *para* isomer of XXV. The mechanism favored by Capon



(7)

was that of (7). The alternative nucleophilic specific



5a **5b**

acid mechanism of **5a** was considered unlikely on the basis that the resulting lactone intermediate in (**5a**) is stable under conditions in which XXV is hydrolyzed rapidly. The second nucleophilic specific acid mechanism considered, **5b**, was also discarded on the basis that even though the intermediate ester hydrolyzed at a rate greater than that of XXV, the determined rate data could not be explained with any reasonably assumed value for the rate constant of **5b** and the known rate constant for hydrolysis of intermediate. Alternate mechanisms not considered are those involving general acid catalysis by protonation of the terminal methoxyl group and intramolecular nucleophilic attack on the terminal methyl group preceded by a preequilibrium protonation of the terminal methoxyl group. Again, the value of a deuterium solvent kinetic isotope effect was offered as substantiating evidence for (7), and again we must point out that an isotope effect of this nature has no bearing on the choice between kinetically equivalent mechanisms. One might note that at an acid concentration of 4×10^{-3} *M* (pH 2.4), the acidity at which the isotope effect data was obtained, only specific acid catalyzed hydrolysis of the undissociated form of XXV should have been observed since the plateau rate was quoted as occurring in the pH range of 3.1 to 5.5. It is interesting, therefore, that the value of $k^{H_2O}/k^{D_2O} = 1.43$ is in accord with either general acid or nucleophilic specific acid catalysis but much greater than that anticipated for simple specific acid catalysis (see Results).

Finally, Smidsrød, Haug, and Larsen[13] observed apparent intramolecular carboxyl group catalysis in the pH–log k_{obsd} profile for the hydrolysis of oligouronides (XXVI). On the basis of the interpretation of the mechanism afforded the hydrolysis of XXIV, the authors favor intramolecular general acid catalysis. Capon and Ghosh[32] observed the log k_{obsd}–pH profile characteristic of apparent intramolecular carboxyl group catalysis for XXVII. On the assumption of only specific acid catalyzed hydrolysis they stated, "the relative rates of the specific hydrogen ion catalyzed hydrolysis of the ionized glucuronide, glucoside, and deionized glucuronide are 1580:78:1 which correlate

(29) It has been pointed out by Professor T. H. Fife that while the two mechanisms involving a neighboring carboxyl group, general acid catalysis and specific acid nucleophilic catalysis, might be possible for X, XI, XV, and XVI, the situation is unfavorable in comparison to similarly substituted acetals for the mechanism involving nucleophilic attack. This is true because the methyl group at C_1 would sterically hinder nucleophilic attack more than hydrogen and also greatly stabilize an intermediate carbonium ion, so that by the Hammond principle [G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955)] the A1 transition state would more closely resemble the conjugate acid and as a result make any nucleophilic attack less effective.

(30) R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).

(31) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(32) B. Capon and B. Ch. Ghosh, *Chem. Commun.*, **1**, 586 (1965).

well with the inductive substituent constants." They concluded that 2-naphthyl β-D-glucuronide (XXVII), as well as other glucuronides, hydrolyze by specific acid catalyzed mechanisms only.

In conclusion it may be stated that of the 15 compounds in Table IV, all of the ketals (from this study) and most acetals hydrolyze by specific acid catalysis. Only the acetals XXV and XXVI may hydrolyze in the low-acid region by carboxyl group participation.

Acknowledgments. This work was supported by a grant from the National Institutes of Health. We wish to thank Professor T. H. Fife for his helpful discussions.

Stable Carbonium Ions. XLI.[1a] Protonated Aliphatic Alcohols and Their Cleavage to Carbonium Ions

George A. Olah, Jean Sommer,[1b] and Eli Namanworth[1c]

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. *Received February 21, 1967*

Abstract: A series of aliphatic alcohols have been studied in HSO_3F–SbF_5–SO_2 solution. O-Protonation was observed by nmr spectroscopy with negligible exchange rates at temperatures ranging from −60 to +60°. The protonated alcohols cleave at higher temperatures to carbonium ions. The kinetics of cleavage of protonated 1-propanol, 1-butanol, 1-pentanol, and 1-hexanol have been measured by nmr spectroscopy, and the mechanism of the reaction is discussed.

We reported in a previous short preliminary communication[2] that normal and secondary aliphatic alcohols can be protonated in the strong acid system FSO_3H–SbF_5–SO_2 and can be observed at −60° with slow exchange rates. We wish now to report in detail the observation of protonated aliphatic alcohols at temperatures up to +60° and their cleavage to carbonium ions.

Results and Discussion

The following aliphatic alcohols were protonated in FSO_3H–SbF_5–SO_2 solution at −60°: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *n*-amyl, isoamyl, neopentyl, *n*-hexyl, and neohexyl alcohol.

The protonated aliphatic alcohols give well-resolved nmr spectra at −60°.

$$ROH \xrightarrow[-60°]{FSO_3H\text{–}SbF_5\text{–}SO_2} R\overset{+}{O}H_2$$

The protons on oxygen are shifted downfield approximately to −9.3 ppm from external TMS capillary. Figures 1–12 show the nmr spectra at −60°. Assignments of chemical shifts and coupling constants are summarized in Table I.

Protonated Methyl Alcohol. $CH_3OH_2^+$ (Figure 1) shows the methyl triplet at 4.7 ppm and the OH_2^+ quadruplet at −9.4 ppm, J_{H-H} = 3.6 cps.

Protonated Ethyl Alcohol. $CH_3CH_2OH_2^+$ (Figure 2) shows the methyl triplet at −1.9 ppm (J_{H-H} = 7.1 cps) and the OH_2^+ triplet at −9.3 ppm (J_{H-H} = 3.6 cps). The methylene signal is the expected nine-line pattern at −4.9 ppm as the coupling with the CH_3 group is about twice that with OH_2^+.

Protonated *n*-Propyl Alcohol. $CH_3CH_2CH_2OH_2^+$ (Figure 3) shows the methyl triplet at −0.8 ppm (J_{H-H} = 7.2 cps), the C_2 methylene multiplet (six lines) at −1.8 ppm, the C_1 methylene multiplet (seven lines) at −4.7 ppm, and the OH_2^+ triplet at −9.4 ppm (J_{HH} = 3.5 cps).

Protonated Isopropyl Alcohol. $(CH_3)_2CHOH_2^+$ (Figure 4) shows the methyl doublet at −1.7 ppm (J_{HH} = 7.0 cps), the OH_2^+ doublet at −9.1 ppm (J_{HH} = 3.0 cps), and the methine proton multiplet at −5.5 ppm.

Protonated *n*-Butyl Alcohol. $CH_3CH_2CH_2CH_2OH_2^+$ (Figure 5) shows the methyl triplet at −1.1 ppm (J_{HH} = 7.0 cps), methylene multiplets (C_2, C_3) between −1.2 and −2.1 ppm, the C_1 multiplet (seven lines) at −5.0 ppm, and the OH_2^+ triplet at −9.4 ppm (J_{HH} = 3.5 cps).

Protonated Isobutyl Alcohol. $(CH_3)_2CHCH_2OH_2^+$ (Figure 6) shows the methyl doublet at −1.1 ppm (J_{HH} = 7.0 cps), the methine proton multiplet at −2.3 ppm, the methylene multiplet (five lines) at −4.7 ppm, and the OH_2^+ triplet at −9.4 ppm (J_{HH} = 3.6 cps).

Protonated *sec*-Butyl Alcohol. $CH_3C(OH_2^+)HCH_2CH_3$ (Figure 7) shows one methyl triplet at −0.9 ppm (J_{HH} = 7.5 cps), the methyl group nearest to the oxygen as a doublet at −2.6 ppm (J_{HH} = 6.4 cps), the methylene multiplet at −1.9 ppm, the methine proton multiplet at −5.4 ppm, and the OH_2^+ doublet at −9.1 ppm (J_{HH} = 3.0 cps).

Protonated *n*-Amyl Alcohol. $CH_3(CH_2)_4OH_2^+$ (Figure 8) shows the methyl triplet at −0.9 ppm, the methylene (C_2 to C_4) multiplets between −1.1 and −2.3 ppm, the C_1 methylene multiplet (seven lines) at −4.9 ppm, and the OH_2^+ triplet at −9.3 ppm (J_{HH} = 3.4 cps).

(1) (a) Part XL: G. A. Olah, D. H. O'Brien, and C. U. Pittman Jr., *J. Am. Chem. Soc.*, **89**, 2996 (1967); (b) NATO Postdoctoral Research Investigator, 1966–1967; (c) National Science Foundation Postdoctoral Investigator, 1965–1966.

(2) G. A. Olah and E. Namanworth, *J. Am. Chem. Soc.*, **88**, 5327 (1966).