Effects of α-Deuterium Substitution, Polar Substituents, Temperature, and Salts on the Kinetics of Hydrolysis of Acetals and Ortho Esters[1]

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Abstract: Kinetic secondary deuterium isotope effects for the hydrolysis of ethyl orthoformate, 1.05, and propionaldehyde diethyl acetal, 1.17, reveal that the transition state for ortho ester hydrolysis resembles the substrate although that for hydrolysis of acetals derived from aliphatic aldehydes resembles the intermediate carbonium ion. Secondary deuterium isotope effects for hydrolysis of substituted benzaldehyde diethyl acetals increase from 1.04 to 1.09 to 1.15 as the nature of the polar substituent changes from methoxy to hydrogen to nitro. Thus, the transition state structure for hydrolysis of these substrates increasingly resembles the carbonium ion intermediates as the electron-withdrawing power of the substituent in the aldehyde moiety increases and the substrate reactivity, hence, decreases. Corresponding isotope effects for hydrolysis of (2-para-substituted phenoxy)tetrahydropyrans decrease from 1.10 to 1.06 as the polar substituent is changed from methoxy to nitro. Thus, the transition state for these reactions increasingly resembles the carbonium ion intermediates as the electron-donating power of the polar substituent in the leaving group (and the substrate reactivity) increases. Second-order rate constants for the hydrolysis of para-substituted methyl orthobenzoates in aqueous solution are well correlated by the Hammett substituent constants, $\rho = -1.16$. This value accords with the conclusion that little carbon–oxygen bond cleavage has occurred at the transition state for ortho ester hydrolysis. General acid catalysis for orthobenzoate hydrolysis in water is not detectable. Activation parameters have been determined for the hydrolysis of substituted methyl orthobenzoates. Values of entropy of activation for hydrolysis are near zero and show no systematic trend as the nature of the polar substituent is varied. Rate constants for hydrolysis of *p*-nitrobenzaldehyde diethyl acetal increase severalfold as the concentration of alkali and alkaline earth halides is increased from zero to 1–3 *M*. The rate changes principally reflect the increased activity of the hydrated proton with increasing salt concentration.

Despite a series of investigations extending over four decades including substantial effort in the past few years, there remain two poorly illuminated points central to the understanding of the mechanism of hydrolysis of acetals, ketals, and ortho esters.[4] First, there is the matter of the change in reactivity of these substrates upon replacement of methyl groups with methoxy groups in the series $RC(CH_3)_2OCH_3$, $RC(CH_3)(OCH_3)_2$, $RC(OCH_3)_3$, $C(OCH_3)_4$. The transition from ether to ketal is accompanied by an enormous increase in reactivity; in contrast, those from ketal to ortho ester and ortho ester to orthocarbonate are accompanied by decreases in reactivity.[4,5] Second, there is the matter of timing of proton transfer relative to cleavage of the carbon–oxygen bond of substrate. Generally, the hydrolysis of the very weakly basic ortho esters and orthocarbonates is considered to occur with general acid catalysis[6–9] while the hydrolysis of the more basic acetals and ketals is not. It has been established that very weakly basic ketals and those yielding particularly stable carbonium ion intermediates may hydrolyze with participation of proton transfer in the transition state.[10–15]

It seems likely that more detailed understanding of both the matter of structure–reactivity correlations and of involvement of proton transfer in the transition state for these reactions depends on establishment of the degree of carbon–oxygen bond cleavage in the transition state. In the investigations reported herein, attention is directed principally to this point through a reinvestigation of structure–reactivity correlations for the hydrolysis of para-substituted methyl orthobenzoates and study of kinetic secondary deuterium isotope effects for hydrolysis of orthoformates and acetals. Temperature and salt effects for these reactions have also been probed. A preliminary account of a portion of this work has been published.[16]

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Glass-distilled water was used throughout. Commercially obtained organic acids and amines, except formic and acetic acids, were either recrystallized or redistilled prior to use. Dioxane and methanol were purified according to the procedure of Wiberg and the dioxane was stored frozen under nitrogen until

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used.[17] *p*-Chlorobenzotrichloride was obtained from Chemical Procurements, Inc., and used without further purification. Methyl ortho-*p*-fluorobenzoate was a gift of Dr. R. W. Taft. 2,2-Dimethoxypropane was obtained commercially and redistilled before use.

Methyl orthobenzoate and methyl ortho-*p*-chlorobenzoate were prepared *via* the Williamson synthesis as previously described.[18,19] Methyl orthobenzoate was obtained as an oily liquid and was vacuum distilled on a Nester/Faust spinning band column, bp 78° (0.5 mm). Methyl ortho-*p*-chlorobenzoate was vacuum distilled, bp 74.8° (0.5 mm). A 60-MHz nmr spectrum of a neat sample of this ortho ester with a tetramethylsilane internal lock showed the ring multiplet at 7.1 ppm downfield and a singlet at 2.7 ppm downfield (approximate integrated intensities are in the ratio 1:2.25, respectively).

Methyl ortho-*p*-hydroxybenzoate, methyl ortho-*p*-methoxybenzoate, and methyl ortho-*p*-methylbenzoate were prepared from the corresponding nitriles *via* imido ester hydrochlorides.[18,20,21] The progress of the alcoholysis of the imido esters was followed by infrared spectroscopy. Methyl ortho-*p*-methoxybenzoate and methyl ortho-*p*-methylbenzoate, bp 98° (6.5 mm), were vacuum distilled on a Nester/Faust spinning band apparatus. The ester content of the fractions was monitored by observing the ester carbonyl band in the infrared. This distillation served to separate methyl ortho-*p*-methylbenzoate from its ester but did not yield ester-free methyl ortho-*p*-methoxybenzoate. Consequently, methyl ortho-*p*-methoxybenzoate was treated with 1 *N* sodium hydroxide overnight at room temperature with vigorous stirring and then extracted into ether. This treatment effected complete removal of the ester and the infrared spectrum was that expected for methyl ortho-*p*-methoxybenzoate.

Methyl ortho-*p*-nitrobenzoate was prepared in low yield by the nitration of α,α,α-trichlorotoluene followed by treatment of the *p*-nitro-α,α,α-trichlorotoluene with sodium methoxide.[22]

Methyl ortho-*p*-hydroxybenzoate and methyl ortho-*p*-nitrobenzoate were purified by chromatography on a 100-cm Sephadex LH20 column using methanol as solvent. Complete separation of ester from ortho ester was not achieved even though some of the methyl ortho-*p*-nitrobenzoate fractions were passed through the column twice. The ultraviolet properties of the esters resulting from the hydrolysis of the ortho esters were identical with those described by Kwart and Price.[8] In addition, methyl ortho-*p*-hydroxybenzoate was found to have λ_{max} 225 and λ_{max} 295 mμ in acidic and basic solutions, respectively. The stock solution of methyl ortho-*p*-hydroxybenzoate used in the kinetic runs contained 92% ortho ester and that of methyl ortho-*p*-nitrobenzoate contained at least 75% ortho ester as judged from ultraviolet spectra of these solutions in the absence of appreciable ortho ester hydrolysis.

Ethyl orthoformate-α-d_1, bp 145° (760 mm) (lit.[23] bp 145–146° (760 mm)), was prepared by the ethanolysis of the α-deuterated formimino ester hydrochloride according to the procedure of McElvain and Nelson.[24] An equimolar mixture of deuterium cyanide, deuterium chloride, and ethanol-d_1 gave the α-deuterated formimino ester hydrochloride in a 75% yield. The deuterium cyanide and deuterium chloride were prepared according to the methods of Oae, Tagaki, and Ohno.[23] Ethanol-d_1 was prepared from ethyl orthoformate and deuterium oxide as described by Shiner and Smith.[25]

Propionaldehyde diethyl acetal-α-d_1, bp 121° (760 mm) (lit.[20] bp 121–123° (760 mm)), was prepared by the Grignard reaction of ethyl orthoformate-α-d_1 with ethylmagnesium bromide in anhydrous ether.[26]

Ethyl orthoformate, propionaldehyde diethyl acetal, and deuterium oxide were commercial products and were purified by distillation before use.

Benzaldehyde-α-d_1 was prepared by a published procedure.[27] *p*-Methoxybenzaldehyde-α-d_1 was prepared by the reduction of 4,4′-dimethoxybenzil to 4,4′-dimethoxydihydrobenzoin-d_2 with 0.5 equiv of lithium aluminum deuteride[28] followed by cleavage with lead tetraacetate[29] to yield 2 equiv of the deuterated aldehyde. The overall yield of *p*-methoxybenzaldehyde-α-d_1 from 4,4′-dimethoxybenzil was 73%. 4,4′-Dimethoxybenzil was prepared by oxidation of 4,4′-dimethoxybenzoin with cupric sulfate.[30]

p-Nitrobenzaldehyde-α-d_1 was synthesized in the following way. 2-(*p*-Nitrophenyl)-1,3-dithiane was prepared from *p*-nitrobenzaldehyde and 1,3-propanedithiol by a procedure for the preparation of 2-phenyl-1,3-dithiane.[27] It was recrystallized from ethanol as yellow needles, mp 141–142°; 77% yield.

The proton in the 2 position was exchanged by dissolving 10.4 g (0.0232 mol) of dithiane in 195 ml of dioxane, and adding a solution of 0.187 g (0.00214 mol) of NaOH in 17.0 ml (0.850 mol) of D_2O. The resulting deep red solution was allowed to stand in the dark 24 hr at 25°, and following which 0.003 equiv of DCl was added, the solvent removed on a rotary evaporator, and the residue recrystallized from ethanol to give 10.3 g of 2-(*p*-nitrophenyl)-1,3-dithiane-*2-d*, mp 141–141.5°, 97.1% yield.

The dithiol was removed by oxidation with bromine. A 10.3-g (0.0231 mol) sample of dithiane was dissolved in a solution consisting of 77.0 ml of H_2O, 97.5 ml of acetic acid, and 425 ml of dioxane. A 28.7-g (0.170 mol) sample of Br_2 was added slowly with stirring, at which point the bromine color persisted in the solution. The solution was then combined with an equal volume of water and lead diacetate added until no further precipitation occurred. The solution was then decanted and evaporated on a rotary evaporator, and the residue recrystallized from aqueous ethanol. Sublimation at 100° (1.0 mm) gave 3.02 g of *p*-nitrobenzaldehyde α-d_1, mp 104.5–105.5°, 87.1% yield.

2,3-Dihydropyran-*5-d* was prepared through metalation of the corresponding protio compound with *n*-pentylsodium.[31] To ensure complete metalation, 2.13 g-atoms of sodium, 0.67 mol of *n*-pentyl chloride, and 0.154 mol of 2,3-dihydropyran were employed.[32] The metalated substrate was destroyed with deuterium oxide and the organic phase was decanted and distilled to yield the desired 2,3-dihydropyran-*5-d*. The overall yield was 40%.

2-(Para-substituted phenoxy)tetrahydropyrans were prepared from 2,3-dihydropyran and the appropriate phenol by a modification of the method of Fife and Jao.[11] The reactions were conducted in dilute ether solution, *p*-toluenesulfonic acid was employed as catalyst, and the catalyst was neutralized with sodium carbonate. Evaporation of the ether and several recrystallizations from ether–petroleum ether yielded 2-(*p*-methoxyphenoxy)tetrahydropyran, mp 28.5–28.8°, and the deuterated derivative, mp 28.5–28.8°; 2-(*p*-chlorophenoxy)tetrahydropyran, mp 48.7–49.0°, and the corresponding deuterated derivative, mp 48.3–49.0°; 2-(*p*-nitrophenoxy)tetrahydropyran, mp 61.0–61.1°, and the corresponding deuterated derivative, mp 62.2–62.8°.

Benzaldehyde diethyl acetals were prepared from ethyl orthoformate and ethanol by the method of Fife and Jao.[33]

Kinetics. All reactions were monitored spectrophotometrically employing a Zeiss PMQ II spectrophotometer. Hydrolysis of the substituted benzaldehyde diethyl acetals was followed by observing the appearance of the benzaldehyde products: *p*-nitro, 267 mμ; *p*-methoxy, 287 mμ; and unsubstituted, 243 mμ. Aqueous solutions were employed for these substrates and pH was maintained constant with the use of 0.05 *M* formate, acetate, and phosphate buffers, as appropriate. Hydrolysis of 2-(para-substituted phenoxy)tetrahydropyrans was followed by observing the appearance of the product phenols: *p*-methoxy, 302 mμ; *p*-chloro, 292 mμ; *p*-nitro, 347 mμ. These reactions were studied in 50% (v/v) aqueous dioxane solutions, ionic strength 0.50 (maintained with lithium chloride), with the pH maintained constant through use of 0.02

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M trichloro- and dichloroacetate buffers. Hydrolysis of propionaldehyde diethyl acetal was followed by observing the appearance of propionaldehyde at 280 mμ. The reactions were studied in 50% aqueous dioxane in the presence of dilute hydrochloric acid. Ethyl orthoformate hydrolysis was monitored by observing the appearance of ethyl acetate at 220 mμ. Aqueous dioxane (50%) was employed as solvent, and the ionic strength was maintained at 0.05 with lithium chloride. Dilute acetate buffers were employed to maintain constant pH. Hydrolysis of methyl orthobenzoates was followed by observing the formation of benzoic acid products as described by Kwart and Price.[8] Except where noted otherwise, aqueous solutions were employed. Ionic strength was maintained at 0.50 through the use of lithium chloride.

For those kinetic runs employed in the determination of deuterium isotope effects, systematic errors in the rate ratio were reduced by either following protio and deuterio reactions simultaneously or one immediately following the other. In all cases, at least six runs were done together: three with the protio and three with the deuterio substrates. All such measurements were accomplished at 25.0 ± 0.5°; the temperature change in the reaction cell change during each run averaged 0.015°. Temperature measurements were made in the reaction cells by means of a Leeds-Northrup K-3 Universal potentiometer and a constantan-copper thermocouple with the reference junction maintained at 0°. Each first-order rate constant was determined by recording approximately 145 absorbance observations taken over the first 2.3 half-lives. The experimental data were then fitted to a first-order rate equation utilizing a computer program, KINPROG,[34] and a CDC 3400-3600 computer facility.

For those reactions not involving determination of isotope effects, first-order rate constants were evaluated from the slopes of plots of log $(A_\infty - A_t)$ *vs.* time in the usual manner or by the Guggenheim method. Infinite time values were obtained by checking the reactions at an estimated 10 half-times and at appropriate intervals thereafter until the optical density remained constant. There was negligible interference with these measurements due to ester hydrolysis. Second-order rate constants were evaluated from plots of log k_{obsd} *vs.* pH. In all cases such plots were linear with a slope of unity.

Values of pH were recorded with a Radiometer PHM 4c pH meter equipped with a glass electrode. Values of pH were recorded at the temperature of the kinetic runs.

Thermodynamic Parameters. E_a, the Arrhenius energy of activation, was evaluated from a plot of ln k_{obsd} *vs.* $1/T$. The slope, $-E_a/R$, was obtained by a least squares treatment of the data employing a CDC 3600/3400 computer system. At a given temperature, $\Delta H^{\ddagger} = E_a - RT$. $\Delta G^{\ddagger}$ is obtained by use of the equation[35]

$$-\Delta G^{\ddagger} = \log\left(\frac{k_2 h}{kT}\right)(2.303RT)$$

Finally, $\Delta S^{\ddagger}$ is evaluated from the relationship: $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$. Second-order rate constants are considered to be accurate to ±5%; consequently, values of $\Delta S^{\ddagger}$ are accurate to ±2 eu.[36]

Deuterium Content. Deuterium analyses were accomplished with a Varian A-60 magnetic resonance spectrophotometer. The proton magnetic resonance spectra of neat samples of all deuterated compounds indicated that each had an isotopic purity of at least 98%.

Results

The ratios of rate constants for the acid-catalyzed hydrolysis of the diethyl acetals of propionaldehyde, *p*-nitro-, *p*-methoxy-, and unsubstituted benzaldehydes, and ethyl orthoformate and the corresponding α-deuterio compounds in aqueous solution at 25° were determined as described in the Experimental Section. The results are collected in Table I. The secondary deuterium isotope effect for the hydrolysis of *p*-methoxybenzaldehyde diethyl acetal was also determined in 98% ethanol and in aqueous solution containing 0.02 *M* sodium dodecyl sulfate (Table I). The individual rate constants were reproducible to within ±1% and the rate ratios are considered to be accurate to within ±0.01. In each case, the protio species reacts more rapidly than the deuterio one; however, the observed isotope effects vary widely. Note particularly the trend toward increasing isotope effect with increasing electron withdrawal in the benzaldehyde moiety and the striking difference in isotope effect between propionaldehyde diethyl acetal and ethyl orthoformate. Neither change of solvent from water to 98% ethanol nor addition of sodium dodecyl sulfate has an appreciable effect on the isotope effect.

Table I. Secondary Deuterium Isotope Effects for the Rates of Hydrolysis of Benzaldehyde Diethyl Acetals, Propionaldehyde Diethyl Acetal, and Ethyl Orthoformate

Substrate	$k_H/k_{\alpha D}$
p-Nitrobenzaldehyde diethyl acetal[a]	1.15 ± 0.01
Benzaldehyde diethyl acetal[a]	1.09 ± 0.01
p-Methoxybenzaldehyde diethyl acetal[a]	1.04 (1.02),[c] (1.03)[d] ± 0.01
Propionaldehyde diethyl acetal[b]	1.17 ± 0.01
Ethyl orthoformate[a]	1.05 ± 0.01

[a] Reaction conducted in aqueous solution at 25°. Values of pH maintained constant by use of dilute acetate or phosphate buffers. [b] Reaction conducted in 50% aqueous dioxane containing dilute hydrochloric acid at 25°. [c] Reaction conducted in 98% ethanol containing dilute hydrochloric acid at 25°. [d] Reaction conducted in aqueous solution containing 0.02 *M* sodium dodecyl sulfate.

α-Deuterium isotope effects were also determined for the acid-catalyzed hydrolysis of 2-(substituted phenoxy)-tetrahydropyrans. The *p*-methoxy, *p*-nitro, and *p*-chloro derivatives were chosen as substrates for study. The isotope effects were measured in 50.0% aqueous dioxane at 25°, ionic strength 0.50 maintained with lithium chloride, and are collected in Table II. Constant pH was maintained through the use of 0.02 *M* dichloroacetate and trichloroacetate buffers as appropriate. The indicated ratios are the mean of five separate determinations and the uncertainties are three standard deviations of the mean. In each case, the protio substrate reacts more rapidly than the deuterio one. Note that the isotope effect decreases with increasing electron-withdrawing power of the polar substituent in the leaving group.

Table II. Secondary Deuterium Isotope Effects for the Rate of Hydrolysis of 2-(Substituted phenoxy)tetrahydropyrans in 50% Aqueous Dioxane at 25° [a]

Substrate	$k_H/k_{\alpha D}$
2-(*p*-Methoxyphenoxy)tetrahydropyran	1.106 ± 0.008
2-(*p*-Chlorophenoxy)tetrahydropyran	1.095 ± 0.007
2-(*p*-Nitrophenoxy)tetrahydropyran	1.063 ± 0.005

[a] Ionic strength 0.50 (lithium chloride); pH maintained with 0.02 *M* dichloro- and trichloroacetate buffers.

First-order rate constants for hydrolysis of para-substituted methyl orthobenzoates in aqueous solution at 25° at several values of pH are collected in Table III. Logarithms of these constants are plotted against pH in Figure 1. In each case, excellent straight lines with slopes of unity are obtained from which second-order

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Table III. Values of First-Order Rate Constants for the Specific Acid-Catalyzed Hydrolysis of Substituted Methyl Orthobenzoates at Ionic Strength 0.50 M at 25°

Substituent	pH[a]	k_{obsd}, min^{-1}
p-OH	2.89	15.5
	3.44	5.37
	3.83	1.94
	3.99	1.35
	4.98	0.143
	5.02	0.126
	7.26	0.00078
p-OCH$_3$	2.84	18.7
	3.08	7.87
	3.78	1.39
	3.86	1.43
	3.87	1.38
	3.98	0.992
	4.01	0.92
	4.38	0.21
	4.63	0.204
	4.82	0.147
	5.02	0.090
	5.21	0.050
	5.24	0.045
	5.28	0.475
p-CH$_3$	3.08	6.0
	3.86	1.02
	3.87	1.01
	4.01	0.76
	4.38	0.192
	4.63	0.190
	4.82	0.119
	4.82	0.116
	5.21	0.450
	5.24	0.0405
	5.28	0.0408
p-H	2.85	5.63
	3.08	3.33
	3.42	1.70
	3.80	0.654
	3.88	0.612
	4.48	0.157
	4.92	0.0182
	5.02	0.0190
	5.08	0.178
p-F	2.55	9.44
	2.87	4.47
	3.36	1.41
	3.82	0.522
	3.96	0.365
	4.94	0.0407
	5.00	0.0554
p-Cl	2.62	6.50
	2.84	3.08
	3.23	1.63
	3.50	0.672
	3.68	0.485
	3.96	0.266
p-NO$_2$	2.06	6.03
	1.91	8.01
	2.12	5.21, 4.95
	2.63	1.43
	2.67	1.41
	2.91	0.756
	3.42	0.220
	4.00	0.0563

[a] pH maintained with 0.01–0.05 M chloroacetate, formate, acetate, propionate, and N-ethylmorpholine buffers or with dilute solutions of hydrochloric acid in the appropriate ranges of pH.

rate constants have been calculated. These are collected in Table IV.

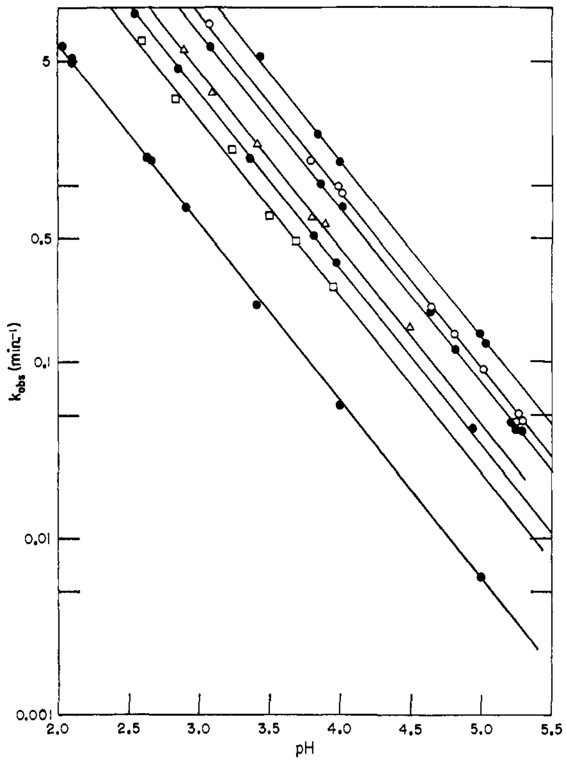

Figure 1. Logarithms of first-order rate constants for the hydrolysis of a series of para-substituted methyl orthobenzoates at 25° and ionic strength 0.50 M as a function of pH. From top to bottom the substituents are: hydroxy, methoxy, methyl, unsubstituted, fluoro, chloro, and nitro.

The second-order rate constant for hydrolysis of methyl orthobenzoate is in reasonably good agreement with a previous determination made in this laboratory under similar conditions[37] but is fivefold smaller than the value reported by DeWolfe and Jensen for hydrolysis of the corresponding ethyl ortho ester in water at 20°.[38] The value is substantially greater than those reported for the same reaction in aqueous methanol solutions, as expected.[8]

Table IV. Values of Second-Order Rate Constants for the Specific Acid Catalyzed Hydrolysis of Substituted Methyl Orthobenzoates at 25° and Ionic Strength 0.50 M in Aqueous Solution

Substituent	$k_2 \times 10^{-3}$, M^{-1} min^{-1}
o-Hydroxy	13.6[a]
p-Methoxy	9.63
p-Methyl	7.45
Unsubstituted	4.45
p-Fluoro	3.52
p-Chloro	2.41
p-Nitro	0.64

[a] For the pH range 2.8–5.02.

A plot of the logarithms of second-order rate constants for hydrolysis of the substituted methyl orthobenzoates against the Hammett substituent constants is provided in Figure 2. The data are correlated by a straight line with a value of $\rho = -1.16$. This value is substantially smaller than that previously reported by Kwart and Price for the same reactions in 70% aqueous methanol solutions.[8]

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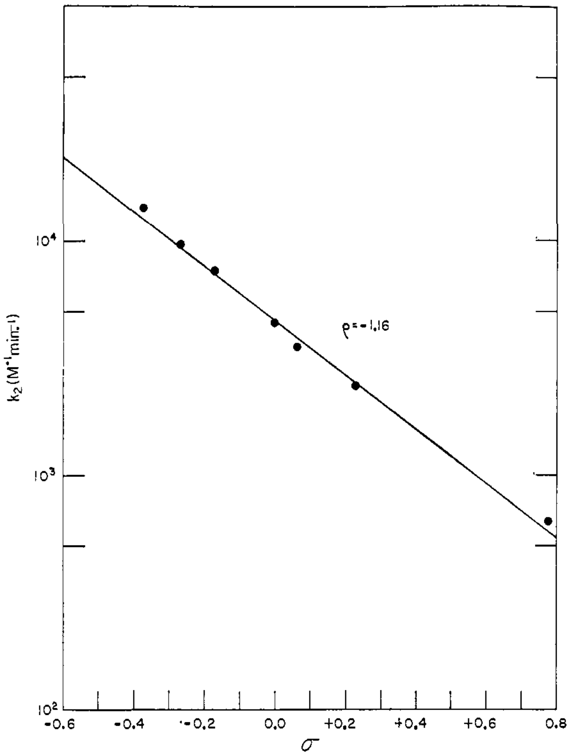


Figure 2. Hammett plot for the acid-catalyzed hydrolysis of a series of para-substituted methyl orthobenzoates in aqueous solution at 25°. Ionic strength 0.50 *M*, maintained with LiCl.

First-order rate constants were also measured for the hydrolysis of para-substituted methyl orthobenzoates in 98% aqueous methanol containing 0.005 *M* HCl; values are collected in Table V. These constants, too, are well-correlated by a single straight line in a Hammett plot. The derived value of ρ is -2.3, compared with a value of -2.0, for the same reactions in 70% aqueous methanol.[8]

Table V. Values of First-Order Rate Constants for the Specific Acid Catalyzed Hydrolysis of Substituted Methyl Orthobenzoates in Aqueous Methanol Solutions Containing 0.05 *M* Hydrochloric Acid at 25°

Substituent	k_{obsd}, min^{-1}
p-Cl	0.578
p-H	2.24
p-CH_3	4.62
p-OCH_3	7.53
p-OH	15.1

General acid catalysis for the hydrolysis of methyl orthobenzoates was sought in aqueous solution and in 70% aqueous dioxane. The hydrolysis of methyl orthobenzoate in the presence of acetate (0.0002–0.10 *M*) buffers in aqueous solution and trichloroacetate (0.0025–0.5 *M*) and acetate (0.002–0.2 *M*) buffers in 70% aqueous dioxane showed no consistent evidence for general acid catalysis under conditions in which a 10% rate increase as a function of buffer concentration would have been detected. Methyl ortho-*p*-methylbenzoate and methyl ortho-*p*-methoxybenzoate in the presence of acetate (0.02–0.50 *M*), propionate (0.02–0.50 *M*), and formate (0.005–0.05 *M*) buffers in aqueous solution and dichloroacetate (*p*-methoxy substrate only) (0.02–0.10 *M*) and trichloroacetate (0.05–0.5 *M*) buffers in 70% aqueous dioxane also showed no evidence for general acid catalysis nor did the hydrolysis of methyl ortho-*p*-chlorobenzoate in the presence of chloroacetate (0.0005–0.5 *M*) and acetate (0.0002–0.5 *M*) buffers in aqueous solutions. Hydrolysis of methyl ortho-*p*-nitrobenzoate in the presence of formate (0.004–0.05 *M*), β-bromopropionate (0.002–0.05 *M*), and acetate (0.002–0.1 *M*) buffers in aqueous solution showed no evidence for general acid catalysis.

Rate constants for acid-catalyzed hydrolysis of a series of para-substituted methyl orthobenzoates in aqueous solution as a function of temperature are collected in Table VI. In each case, second-order rate constants generate excellent straight lines in Arrhenius plots from which activation energies, and other acti-

Table VI. Rate Constants for the Hydrolysis of a Series of Substituted Methyl Orthobenzoates at Several Temperatures

Substituent	pH[a]	Temp, °K	k_{obsd}, min^{-1}	$k_2 \times 10^{-3}$, M^{-1} min^{-1}
p-OH	4.92	298.01	0.165	13.6
	4.92	298.01	0.165	13.6
	4.92	298.01	0.165	13.6
	4.92	306.85	0.352	29.4
	4.71	310.81	0.804	41.2
	4.71	318.11	1.36	69.5
p-OCH_3	4.92	298.01	0.112	9.26
	4.92	298.01	0.116	9.60
	4.92	298.01	0.118	9.71
	4.92	306.85	0.272	2.24
	4.71	310.88	0.624	32.0
	4.71	318.01	1.038	53.2
p-CH_3	4.92	298.01	0.0965	7.98
	4.92	298.01	0.090	8.18
	4.92	306.85	0.0214	1.76
	4.71	310.98	0.488	25.2
	4.71	310.88	0.517	26.5
	4.71	317.94	0.855	43.8
p-H	3.92	298.01	0.600	4.96
	3.92	298.01	0.613	5.07
	3.92	298.01	0.613	5.07
	3.63	306.85	2.60	11.1
	3.63	306.85	2.48	10.6
	3.63	306.85	2.57	11.0
	3.63	311.21	3.64	15.5
	3.63	311.09	3.61	15.4
	3.64	318.09	5.63	24.6
	3.64	318.04	6.19	27.1
p-Cl	3.92	298.01	0.248	2.32
	3.92	298.01	0.253	2.09
	3.92	298.01	0.255	2.11
	3.63	306.85	1.11	4.72
	3.63	306.85	1.13	4.83
	3.63	306.85	1.12	4.80
	3.63	311.16	1.60	6.84
	3.63	311.08	1.59	6.78
	3.64	318.04	2.44	10.7
	3.64	318.01	2.73	11.9
p-NO_2	3.92	298.01	0.0683	0.565
	3.92	298.01	0.0679	0.562
	3.92	298.01	0.0666	0.551
	3.63	306.85	0.321	1.37
	3.63	306.85	0.324	1.38
	3.63	306.85	0.330	1.41
	3.63	311.04	0.452	1.93
	3.63	311.01	0.450	1.92
	3.64	317.92	0.807	3.52
	3.64	317.98	0.802	3.50

[a] pH determined at the temperature of the run.

Table VII. Activation Parameters for the Hydrolysis of a Series of Substituted Methyl Orthobenzoates[a]

Substituent	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
p-OH	15.4	14.8	14.3	−1.8
p-OCH$_3$	16.5	15.9	14.5	−4.8
p-CH$_3$	16.2	15.6	14.6	−3.3
p-H	15.5	14.9	14.9	0.1
p-Cl	15.7	15.1	15.4	1.1
p-NO$_2$	17.4	16.8	16.2	−2.2

[a] Temperature-dependent activation parameters have been calculated for 25°.

vation parameters, were calculated. These are collected in Table VII. Generally, values for entropy of activation near zero or slightly negative are obtained. The entropy of activation for hydrolysis of methyl orthobenzoate, 0.1 eu, is substantially less positive than a value reported earlier[37] but agrees well with that previously determined for hydrolysis of ethyl orthobenzoate, −0.3 eu.[38] Enthalpies and entropies of activation for hydrolysis of the methyl orthobenzoates show no discernible trend as the nature of the polar substituent is varied.

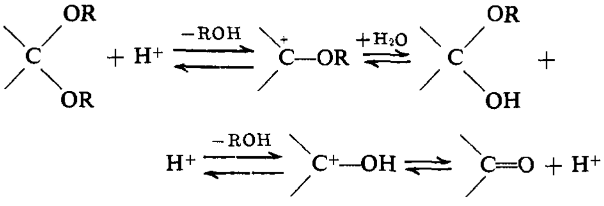
First-order rate constants for the hydrolysis of *p*-nitrobenzaldehyde diethyl acetal in aqueous solution at 30° are collected in Table VIII as a function of the concentration of several alkali and alkaline earth halides. In each run, the total acid concentration was maintained at 0.005 *M* through the addition of hydrochloric acid. Each of the salts studied elicits increasing hydrolysis rates with increasing concentration although modest differences between results obtained with different salts do occur.

Table VIII. First-Order Rate Constants for the Hydrolysis of *p*-Nitrobenzaldehyde Diethyl Acetal in 0.005 *M* Hydrochloric Acid at 30° as a Function of the Concentration of Several Salts

Salt	Concn, *M*	k_{obsd}, min^{-1}	Salt	Concn, *M*	k_{obsd}, min^{-1}
NaCl	0.000	0.14	MgCl$_2$	0.00	0.13
	0.30	0.18		0.18	0.15
	0.90	0.32		0.52	0.25
	1.50	0.40		0.88	0.47
	2.10	0.59		1.23	0.65
	2.85	0.69		1.67	1.34
LiCl	0.00	0.14	CaCl$_2$	0.00	0.13
	0.32	0.18		0.13	0.20
	0.97	0.26		0.40	0.28
	1.62	0.45		0.68	0.36
	2.27	0.66		0.95	0.44
	3.08	0.99		1.28	0.86
KCl	0.00	0.15	SrCl$_2$	0.00	0.14
	0.30	0.17		0.13	0.18
	0.90	0.27		0.39	0.22
	1.50	0.33		0.66	0.33
	2.10	0.41		0.92	0.49
	2.85	0.58		1.25	0.89
KBr	0.00	0.14	BaCl$_2$	0.00	0.14
	0.30	0.15		0.13	0.15
	0.90	0.30		0.40	0.27
	1.50	0.39		0.69	0.40
	2.10	0.63		0.94	0.52
	2.85	1.04		1.27	0.80

Discussion

The hydrolysis of acetals, ketals, and ortho esters proceeds by a well-established pathway involving rate-determining carbonium ion formation preceded by or concerted with substrate protonation (eq 1).[4] Resolution of difficulties surrounding structure–reactivity correlations and susceptibility to general acid catalysis for these reactions (*vide infra*) requires a more detailed understanding of the pertinent transition state structures.



(1)

Secondary Deuterium Isotope Effects. Isotope effects on reaction rates have proved useful in many instances as indicators of changes of mechanism or transition state geometry as a function of substrate structure, solvent, and the like. For example, α-deuterium isotope effects, which depend principally on changes in force constants between the ground and transition states at the point of isotopic substitution, have provided a powerful tool for distinguishing between nucleophilic (S$_N$2) and limiting (S$_N$1) mechanisms in several solvolytic reactions.[39−44] The α-deuterium isotope effects for hydrolysis of ethyl orthoformate and diethyl acetals have proved equally useful in understanding transition state structures for these reactions. The observed isotope effects reveal a striking change in transition state structure as a function of the stability of the derived carbonium ion.

The secondary deuterium isotope effect for the hydrolysis of substituted benzaldehyde diethyl acetals increases with increasing electron withdrawing power of the polar substituent (Table I). These data indicate that the extent of C–O bond cleavage in the transition state increases markedly as the stability of the intermediate carbonium ion diminishes. A transition state with little or no C–O bond stretching should yield an isotope effect near unity while one in which this bond is fully cleaved should yield an isotope effect near 1.23.[40,42] Thus, the transition state for hydrolysis of the *p*-methoxy derivative has little carbonium ion character while that for hydrolysis of the *p*-nitro derivative has a good deal of such character. The observed changes cannot be accounted for in terms of increasing nucleophilic participation by solvent since just such a case has been previously identified and the changes, as expected, are in the opposite direction.[41] The change in transition state structure as a function of substrate reactivity for hydrolysis of the benzaldehyde acetals is perhaps the largest yet observed among carbonium ion processes; the tendency of the transition state to increasingly resemble the product carbonium ion as substrate reactivity decreases (corresponding to a decrease in car-

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[39] V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, **90**, 418 (1968).

[40] V. J. Shiner, Jr., M. W. Rapp, M. Wolfsberg, and E. A. Halevi, *ibid.*, **90**, 7171 (1968).

[41] V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, Jr., *ibid.*, **92**, 232 (1970).

[42] A. Streitwieser, Jr., and G. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969).

[43] J. A. Llewellyn, R. E. Robertson, and J. M. W. Scott, *Can. J. Chem.*, **38**, 222 (1960).

[44] K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *ibid.*, **38**, 1505 (1960).

bonium ion stability) is in qualitative agreement with the predictions of Leffler,[45] Hammond,[46] and Thornton.[47]

Note that the α-deuterium isotope effects for the hydrolysis of α-phenethyl chlorides are, in contrast to the results reported here, independent of the nature of the polar substituent.[39] This is consistent with and evidence for distinct rate-determining steps in the two sets of reactions: ion-pair dissociation for the phenethyl chlorides and carbonium ion formation for the acetals.[4,39]

Comparison of the isotope effects for the hydrolysis of ethyl orthoformate and propionaldehyde diethyl acetal with those for hydrolysis of the benzaldehyde acetals reveals, in light of the above discussion, that the transition state for the former substrate has little, and that for the latter substrate has much, carbonium ion character. These conclusions accord with our expectations in light of the transition state structure–carbonium ion stability correlation developed above.

Generalizing, it seems fair to conclude that hydrolysis of orthocarbonates and ortho esters is characterized by reactantlike transition states while hydrolysis of acetals and ketals derived from aliphatic substrates is characterized by carbonium ion-like transition states. Acetals and ketals derived from aromatic substrates may be expected, as is the case directly studied here, to occupy either of the above categories, or an intermediate one, depending on the nature of polar substituents (one may note that, for example, *p*-methoxybenzaldehyde diethyl acetal is a "phenyligous" orthoformate).

The generalization suffices to account for relative reactivities of acetals, ketals, ortho esters, and orthocarbonates.[5] In this series of substrates, hydrogen atoms or alkyl groups are successively replaced by alkoxy groups. The latter are both more electron withdrawing inductively and more electron donating through resonance than the former. Hence, the net effect of replacement of an alkyl group by an alkoxy one on the stability of a transition state will depend on the degree of carbonium ion formation in that transition state: alkoxy groups will stabilize a transition state possessing marked carbonium ion character but destabilize one possessing little such character relative to alkyl groups.[38] It follows that ketals are generally more reactive than ortho esters derived from them by replacement of an alkyl group by an alkoxy one since this replacement is accompanied by a transformation from a carboniumlike transition state to a reactantlike one. Thus, the relative energies of the transition states for ketal and ortho ester hydrolysis cannot be rationalized on the basis of comparative ground state and intermediate state energies. It also follows, then, that orthocarbonates should be even less reactive than ortho esters, which accords with experimental observation. This is a particularly complicated example in which rate constants and equilibrium constants exhibit divergent behavior with a simple structural change in the substrate.

Secondary deuterium isotope effects for the hydrolysis of 2-(substituted phenoxy)tetrahydropyrans reveal a change in transition state structure as a function of the nature of the leaving group (Table II). The difference in isotope effect between the *p*-chloro and *p*-methoxy derivatives is not significant but that between these two species and the *p*-nitro one certainly is. In all cases, the isotope effects indicate that the transition states have only modest carbonium ion character. The extent of carbonium ion formation increases with increasing substrate reactivity, *i.e.*, with increasing electron-donating power of the polar substituent, but *decreases* with increasing reactivity of the *protonated* substrate. This finding is in accord with the Hammond postulate,[46] the rule of Thornton,[47] and with previous experimental observations including (i) the susceptibility of the *p*-nitro substrate, but not the others, to general acid catalysis and (ii) the existence of a marked pH-independent reaction for hydrolysis of the *p*-nitro substrate only. On the basis of these observations, Fife and coworkers have concluded that the transition state is reached sooner along the reaction coordinate with increasing electron withdrawal in the polar substituent,[11,13] a conclusion fully corroborated in the present studies.

Dilute aqueous solutions of sodium dodecyl sulfate and other anionic surfactants markedly catalyze the hydrolysis of benzaldehyde diethyl acetals.[48] The observation that this reaction is more sensitive to the nature of polar substituents in the presence of sodium dodecyl sulfate than in purely aqueous solution has been suggested to result from differences in degree of C–O bonding stretching in the transition state in the two solvents.[48] Failure to observe a distinct change in the secondary deuterium isotope effect for hydrolysis of *p*-methoxybenzaldehyde upon addition of sodium dodecyl sulfate (Table I) renders this suggestion unlikely, though not impossible. The data can be nicely accounted for in terms of the change in transition state structure as a function of polar substituent: the charge is most localized in the *p*-methoxy substrate which is most sensitive to the electrostatic catalysis and is least localized in the *p*-nitro substrate, the least sensitive to the catalysis. It is also possible that the difference reflects a medium effect (see below).

Structure–Reactivity Correlations. One important observation made in this study is that second-order rate constants for hydrolysis of substituted methyl orthobenzoates are correlated by the Hammett σ constants and a value of ρ of only -1.16 (Figure 2). This value is substantially smaller than that of -2.0 obtained by Kwart and Price for hydrolysis of the same substrates in 70% aqueous methanol and of that of -2.3 obtained in this study for hydrolysis in 95% aqueous methanol.[8] As had been pointed out earlier, use of solvents containing such high percentages of alcohol can elicit a change in rate-determining step from carbonium ion formation to reaction of the carbonium ion with solvent water molecules.[38,49] The nature of the rate-determining step is determined by the relative rates at which the carbonium ion reacts with alcohol to regenerate substrate and with water to generate products. Clearly, increasing concentrations of alcohol favor the former process with respect to the latter. Note that these two reactions are quite similar in nature as is

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(45) J. E. Leffler, *Science*, 117, 340 (1953).

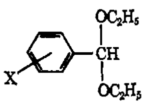
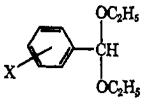
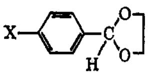
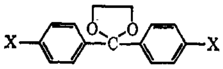
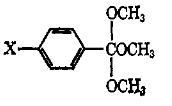
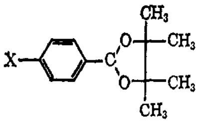
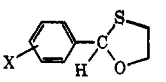
(46) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).

(47) E. R. Thornton, *ibid.*, **89**, 2915 (1967).

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

(49) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, 77, 5590 (1955).

Table IX. A Summary of Linear Free Energy Relationship and General Acid Catalysis Data for Some Acid-Catalyzed Hydrolysis Reactions

	Substrates	Solvent	Correlation obeyed	$\rho(r)$	General acid catalysis	Ref
1.		50% aqueous dioxane	$\text{Log}(k/k_0) = \sigma\rho$	-3.35	No	11
2.		50% aqueous dioxane Water	$\text{Log}(k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)]$ $\text{Log}(k/k_0) = \sigma\rho$	-3.35 (0.5) -3.3	No No	11, 4 48
3.		50% aqueous dioxane	$\text{Log}(k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)]$	-3.25 (0.5)	No	11, 4
4.		20% aqueous dioxane	$\text{Log}(k/k_0) = \sigma\rho$	-4.6	Probable	14
5.		Water	$\text{Log}(k/k_0) = \sigma\rho$	-1.16	Probable[a]	This study
6.		Water	$\text{Log}(k/k_0) = \sigma\rho$	-2.0	Yes	10
7.		50% dioxane	$\text{Log}(k/k_0) = \sigma^+\rho^+$	-2.11[b]	No	50

[a] General acid catalysis for these reactions could not be detected in this study but has been reported for hydrolysis of the same substrates in 70% methanol.[8] [b] ρ^+.

emphasized by the similarity of secondary deuterium isotope effects in the two solvents (Table I). It follows that the difference in values of ρ reflects a solvent effect, not a difference in extent of C-O bond cleavage or formation in the transition states.

The value of ρ for hydrolysis of substituted methyl orthobenzoates in aqueous solution is the smallest value yet measured for reactions in this general class. For the sake of comparison, a collection of related data is provided in Table IX. Also included there is information relevant to the existence of general acid catalysis for these reactions

These structure-reactivity correlations are consistent with and provide support for the conclusions drawn above on the basis of secondary deuterium isotope effects. Compare, for example, the large negative values of ρ for those reactions considered to involve substantial carbonium ion character in the transition state (entries 1, 2, 3, and 4 in Table IX) with that for hydrolysis of the methyl orthobenzoates which proceeds *via* reactantlike transition states (entry 5, Table IX). (Note that the value of ρ for hydrolysis of the benzophenone ketals was calculated on the usual substituent constants even though the substrates are disubstituted.[14] Therefore, the value should be substantially reduced, perhaps halved, for direct comparison with others in Table IX.) Thus, the extent of C-O bond cleavage deduced on the basis of isotope effects parallels the susceptibility of these reactions to effects of polar substituents. Moreover, rate constants for those substrates considered to hydrolyze by reactantlike transition states are correlated by the σ, not the σ^+, substituent constants. In other cases, such as that of the substituted benzaldehyde acetal hydrolysis in water, for which the transition state structure changes as a function of the nature of the polar substituent (see above), the correlation of rate constants with σ also receives a natural explanation: for those substituents capable of strong electron donation by resonance, the transition states possess little carbonium ion character so that such electron donation is not particularly important. Those substrates hydrolyzing through carbonium ion-like transition states do not possess substituents capable of strong electron donation through resonance.

General Acid Catalysis. Data concerning the susceptibility of acetal, ketal, and ortho ester hydrolysis to general acid catalysis are included in Table IX. Conclusions for two sets of reactions are in question. Kwart and Price have reported general acid catalysis for hydrolysis of methyl orthobenzoates in 70% aqueous methanol.[8] Despite a thorough search for such catalysis in both aqueous and 70% aqueous dioxane solutions in this study, no evidence for such catalysis could be detected (Results). The catalysis detected by Kwart and Price was not marked; it seems reasonable to conclude that the catalysis probably does exist but is marginally detectable. DeWolfe, *et al.*, have reported general acid catalysis for hydrolysis of benzophenone ketals.[14] However, the magnitude of the catalysis observed is very small and is not actually reflected in increasing rates as a function of increasing buffer concentration but as constant rates coupled with small rises in pH with increasing buffer concentration. Conclusions based on such data must be considered tentative.

On the whole, data concerning susceptibility to general acid catalysis accord well with the conclusions

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(50) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, 91, 4217 (1969).

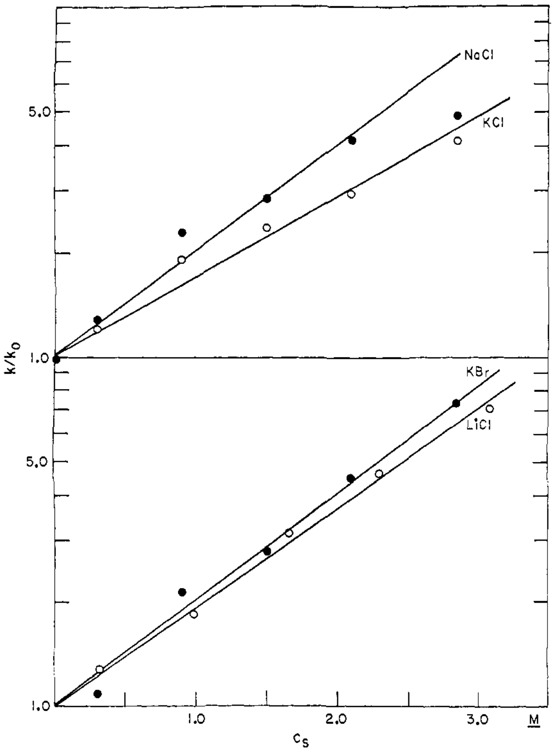

Figure 3. Semilogarithmic plot of rate constants for hydrolysis of *p*-nitrobenzaldehyde diethyl acetal against the concentration of several salts.

drawn above. Detection of such catalysis requires that the value of the Brønsted exponent, α, be less than unity, that is, that proton transfer not be complete in the transition state. If the degree of proton transfer parallels the degree of C–O bond cleavage in the transition state, it follows that those substrates generating particularly stable carbonium ion intermediates should be most susceptible to general acid catalysis. Orthocarbonate hydrolysis is certainly subject to general acid catalysis[51] and, as noted above, methyl orthobenzoate hydrolysis probably is. If benzophenone ketal hydrolysis is subject to general acid catalysis, this must reflect the stability of the intermediate carbonium ions. The hydrolysis of simple acetals is not subject to general acid catalysis (Table IX). Tropone diethyl ketal hydrolysis, in which a particularly stable carbonium ion is formed, is subject to general acid catalysis.[12] Thus, it appears that extent of proton transfer and extent of C–O bond cleavage in the transition state for these reactions do change in a parallel way, although there exists no compelling reason for correlation of C–O bond cleavage with H–O bond formation. Note particularly that the degree of proton transfer and C–O bond cleavage in the transition state are far from equal. All measured values of α are large, indicating that proton transfer is essentially complete although the isotope effects indicate that C–O bond cleavage is far from complete. This observation indicates the dangers in drawing detailed inferences about transition state structures from values of Brønsted exponents.

Activation Parameters. Values of entropy of activation for hydrolysis of the methyl orthobenzoates studied fall in the range characteristic of A1 reactions and, therefore, are consistent with a substantial body of evidence suggesting that hydrolysis of acetals, ketals, and ortho esters generally proceeds without participation of solvent as nucleophilic reagent in the transition state. The only substrates which are suggested to violate this statement are 2-aryl-4,4,5,5-tetramethyl-1,3-dioxolanes which Fife has suggested may hydrolyze by an A2 pathway.[10] Available data do not rigorously justify such a conclusion. An apparently unconsidered possibility is quite capable of rationalizing the available data, including the large negative value for the entropy of activation. Specifically, it is possible that an A1 process leads to the generation of a carbonium ion in the usual manner but that this carbonium ion reacts intramolecularly with the displaced alcohol more rapidly than intermolecularly with solvent, causing attack of solvent on the carbonium ion to become rate determining.

Salt Effects. One of the early indications that acetal hydrolysis proceeds through a carbonium ion route was the observation that the hydrolysis of methylal follows the Hammett H_0 acidity function fairly closely.[51] This study was followed up by one in which the rate of this reaction was studied as a function of the concentration of several salts but at constant acid concentration.[52] It was observed that the salts increased both the acidity of the solution as measured by H_0[53] and the hydrolysis rate but that the salt effects on the reaction rate did not correlate well with those on the acidity function. To a first approximation, the condition that a linear relationship between log K and H_0 exists may be formulated as[51]

$$\log k/k_0 = -\Delta H_0 + \log f_S/f_B \qquad (2)$$

in which f_S is the activity coefficient for the substrate and f_B is that for the Hammett base employed to establish the acidity function. It follows that the salt effects on the rate of methylal hydrolysis reflect, in part, variations in the ratio f_S/f_B.

It seems reasonable that use of an acetal whose structure is more nearly related to that of typical Hammett bases, *p*-nitroaniline for example, than methylal might generate more nearly parallel effects of salts on rate and the acidity function. To examine this supposition, the salt effects on hydrolysis of *p*-nitrobenzaldehyde diethyl acetal were investigated (Table VIII). Generally, the salt effects on hydrolysis of methylal and *p*-nitrobenzaldehyde diethyl acetal are similar though less marked in the latter case. In Figure 3, the logarithms of k/k_0, in which k_0 is the rate constant in the absence of added salt, have been plotted against the concentration of some alkali halides. With some minor deviations, sensibly straight lines are obtained. Since the change in H_0 is also linear in salt concentration, the slopes (slope$_{\text{rate}}$ = a, slope$_{H_0}$ = b) of the respective lines can be compared directly as a measure of the difference between rate changes and acidity changes elicited by salts. For those cases in which the information is available, the data are the following: LiCl: $a = 0.28$, $b = 0.245$; NaCl: $a = 0.30$, $b = 0.205$; KCl: $a = 0.22$, $b = 0.145$. On the whole, the changes in H_0 more nearly account for the

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(51) D. McIntyre and F. A. Long, *J. Amer. Chem. Soc.*, 76, 3240 (1954).

(52) F. A. Long and D. McIntyre, *ibid.*, 76, 3243 (1954).

(53) M. A. Paul, *ibid.*, 76, 3236 (1954).

changes in rate in this case than in that of methylal hydrolysis[52] but salt-specific effects on activity coefficients of the substrate and Hammett base are clearly still present. This is not unexpected since it has been established that salt effects on activity coefficients of anilines reflect, in part, the solvation of the basic function.[54]

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(54) W. Proudlock and D. Rosenthal, *J. Phys. Chem.*, 73, 1695 (1969).

Secondary β-Deuterium Effects on the Rates of Solvolyses of Benzonorbornen-2(*exo*)- and -2(*endo*)-yl *p*-Bromobenzenesulfonates

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Abstract: C$_3$-Deuterated benzonorbornen-2(*exo*)- and -2(*endo*)-yl brosylates and their aromatic nitrated derivatives were synthesized and solvolyzed in acetic and formic acids to measure the β-deuterium effects on the rates of solvolysis. Benzonorbornen-2(*exo*)-yl-*3*(*exo*)-*d* and -*3,3*-d_2 brosylates (**1-d$_1$e-OBs** and **1-d$_2$e-OBs**) showed markedly small deuterium effects in both acetolysis (1.03 for **1-d$_1$e-OBs** and 1.05 for **1-d$_2$e-OBs**) and formolysis (1.04 for **1-d$_2$e-OBs**) compared to the values for the corresponding endo epimers, which were, in acetolysis, 1.16 for the *3*(*exo*)-*d* and 1.28 for the *3,3*-d_2 and, in formolysis, 1.15 for the *3*(*exo*)-*d* and 1.24 for the *3,3*-d_2 compound. When two nitro groups were introduced into the C$_6$ and C$_7$ positions of the benzene ring, the magnitudes of the deuterium effects were raised with the *exo*-brosylates (in acetolysis, 1.10 for the dinitro-*3*(*exo*)-*d* and 1.12 for the dinitro-*3,3*-d_2), but decreased with the *endo*-brosylates (in acetolysis, 1.13 for the dinitro-*3*(*exo*)-*d* and 1.22 for the dinitro-*3,3*-d_2). A geometric dependence of the β-deuterium effects was observed in the solvolyses of the dinitro *exo*-brosylates; the increment of the effects on conversion of the dinitro-*3*(*exo*)-*d* into the dinitro-*3,3*-d_2 compound was very small, from 1.10 to 1.12 (in acetolysis). In the case of the dinitro *endo*-brosylates, such conversion raised the effects substantially, from 1.13 to 1.22. Results with the exo system are discussed in terms of competing aryl participation and hyperconjugative electron release mainly due to the exo proton at C$_3$, and release of steric compression at the reaction site; those with the endo system are discussed in terms of competing solvent participation and hyperconjugation due to both the exo and endo protons at C$_3$, as well as the release of steric compression.

Since the original findings by Lewis and Boozer[1] and by Shiner[2] that deuteration β to the leaving group could affect the reaction rate, secondary β-isotope effects have provided a subtle but powerful tool for the investigation of mechanistic details of solvolysis reactions.[3] Such a study relevant to neighboring group participation was first reported by Saunders,[4] who found that in formic acid 2-phenylethyl and 2-phenylethyl-*2,2*-d_2 *p*-toluenesulfonates (tosylates) both solvolyze at the same rate, but in acetic acid the parent tosylate reacts 4% faster than the deuterated tosylate. The absence of a β-isotope effect in formic acid was interpreted as being a result of predominant phenyl participation. However, kinetic effects due to the presence of β-phenyl groups are often extremely modest, in spite of the fact that such groups significantly affect product formation.[5,6] The group has been considered by Winstein as a "marginal" neighboring group.[6] Some controversy still exists concerning the clear description of neighboring aryl participation in solvolysis.[7-9]

A number of contrasting results of theoretical importance have been found between the solvolytic behavior of *exo*-2-norbornyl arenesulfonate (or halide) and that of its endo epimer.[10] Studies of secondary β-deuterium effects have yielded good examples of such contrasts. The effect caused by C$_3$ dideuteration of *exo*-2-norbornyl bromide was small, k_H/k_D = 1.09 (polarimetric) and 1.02 (titrimetric), while that in the case of *endo*-2-norbornyl bromide was large, k_H/k_D = 1.16 (conductometric).[11] A low effect (k_H/k_D = 1.014) was also reported for *exo*-2-norbornyl-*3,3*-d_2 brosylate and the value of k_H/k_D for *endo*-2-norbornyl-*3,3*-d_2 brosylate was 1.26.[12a] However, the nature of the norbornyl cation and the role of

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