and that of water exchange. Table VIII summarizes the available ΔV^* data for ligand and solvent exchange on Ni(II).

For the nonlabile +III transition metal ions,[7] the small negative volumes of water exchange, as obtained using isotopic labeling, on Cr(III), Rh(III) and Ir(III) strongly suggest an associative interchange, I_a, mechanism, whereas the data for Co(III) suggest an I_d mechanism. To obtain further insight into the solvent exchange process, further high pressure NMR work is in progress with other labile +II and +III ions in a variety of nonaqueous solvents and water.

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References and Notes

(1) (a) M. Eigen, *Z. Elektrochem.*, **64,** 115 (1960); (b) M. Eigen, *Pure Appl. Chem.*, **6,** 97 (1963); (c) M. Eigen and R. G. Wilkins, *Adv. Chem. Ser.*, **No. 49,** 55 (1965).
(2) See, e.g., J. F. Coetzee, "Solute–Solvent Interactions", Vol. 2, J. F. Coetzee and C. D. Ritchie, Eds., Marcel Dekker, New York, 1976, Chapter 14.
(3) E. F. Caldin and H. P. Bennetto, *J. Solution Chem.*, **2,** 217 (1973).
(4) T. W. Swaddle, *Coord. Chem. Rev.*, **14,** 217 (1974).
(5) T. J. Swift and R. E. Connick, *J. Chem. Phys.*, **37,** 307 (1962).
(6) I. R. Lantzke, "Physical Chemistry of Organic Solvent Systems", A. K. Covington and T. Dickinson, Eds., Plenum Press, London, 1973, p 497.
(7) D. R. Stranks, *Pure Appl. Chem.*, **38,** 303 (1974).
(8) (a) H. Vanni, W. L. Earl, and A. E. Merbach, *J. Magn. Reson.*, **29,** 11 (1978); (b) W. L. Earl, H. Vanni, and A. E. Merbach, *ibid.*, **30,** 571 (1978).
(9) (a) A. E. Merbach and H. Vanni, *Helv. Chim. Acta*, **60,** 1124 (1977); (b) W. L. Earl, F. K. Meyer, and A. E. Merbach, *Inorg. Chim. Acta*, **25,** L91 (1977). To be considered as parts 1 and 2 of this series on high pressure NMR kinetics.
(10) Throughout this work a chemical shift given the symbol ω implies the units are rad s^{-1} whereas a shift δ implies the unit Hz ($\omega = 2\pi\delta$).
(11) Z. Luz and S. Meiboom, *J. Chem. Phys.*, **40,** 2686 (1964).
(12) A. Carrington and A. D. McLachlan, "Introduction to Magnetic Resonance", Harper, New York, 1967, Chapter 11.
(13) N. Bloembergen, *J. Chem. Phys.*, **27,** 595 (1957).
(14) As discussed by Kurland and McGarvey,[15] the Bloembergen formulation, which gives rise to the $1/T$ dependence, assumes that, in the absence of the magnetic field, there is only one thermally populated energy level. That such simple behavior is not observed (see below), leads us to assume that there must be several thermally populated states. The most frequently cited cause of such behavior is that of zero field splittings and/or spin orbit coupling and studies of the anomalous frequency dependence of proton NMR relaxation for $Ni(DMSO)_6^{2+}$ [16] and $Ni(CH_3CN)_6^{2+}$ [17] have been quantitatively interpreted in terms of this effect. However, the UV–visible absorption spectra of such solutions are in accord with an undistorted octahedral complex[18] and Wertz and Bolton[19] have shown that, if there is no distortion, there can be no zero field splitting. Not withstanding this problem, Kurland and McGarvey[15] have concluded that, for Ni^{2+}, zero field splitting should have a negligible effect on the Bloembergen equation. A referee has suggested that this effect may be caused by molecular collisions or, possibly, asymmetric vibrations, giving an instantaneously asymmetric nonoctahedral structure with an instantaneously nonvanishing zero-field splitting tensor which could cause non-Curie dependence. Clearly, the details of the paramagnetic shift for Ni^{2+} are still little understood, but, regardless of the shift mechanism operating, the quantum mechanical formulation involves a Boltzmann distribution summation over all the thermally accessible states.[15] Such a solution can then generally be expanded in a power series in $1/T$ and, for many cases of interest, only the first two terms predominate. Also, in the limit $1/T \rightarrow 0$, the shift should tend to zero. It should also be noted that the empirical representation of the paramagnetic shifts, where the shift is equated to the Bloembergen expression plus a constant, may have theoretical shortcomings as well as yielding erroneous coupling constants.[20]
(15) R. J. Kurland and B. R. McGarvey, *J. Magn. Reson.*, **2,** 286 (1970).
(16) J. C. Boubel and J.-J. Delpuech, *Mol. Phys.*, **27,** 113 (1974).
(17) I. D. Campbell, J. P. Carber, R. A. Dwek, A. J. Nummelin, and R. E. Richards, *Mol. Phys.*, **20,** 913 (1971).
(18) A. E. Wickenden and R. A. Krause, *Inorg. Chem.*, **4,** 4 (1965).
(19) J. E. Wertz and J. R. Bolton, "Electron Spin Resonance: Elementary Theory and Applications". McGraw-Hill, New York, 1972, p 295.
(20) W. D. Perry and R. S. Drago, *J. Am. Chem. Soc.*, **93,** 2183 (1971).
(21) Although high pressure X-ray measurements on liquids are not currently feasible, variable-temperature measurements show only very small changes in intramolecular distances. Pressure effects must be considerably smaller.
(22) J. Jonas, *Annu. Rev. Phys. Chem.*, **26,** 167 (1975).
(23) Wilmad Glass Co. Inc., Buena, N.J.
(24) Throughout the data analysis, a conventional nonlinear least-squares FORTRAN program was used. The program curve fits to any user supplied function and calculates any required derivatives numerically. A listing may be obtained from the author (K. E. Newman).
(25) See, e.g., ref 26 or 27.
(26) D. K. Ravage, T. R. Stengle, and C. H. Langford, *Inorg. Chem.*, **6,** 1252 (1967).
(27) N. A. Matwiyoff and S. V. Hooker, *Inorg. Chem.*, **6,** 1127 (1967).
(28) J. F. O'Brien and W. L. Reynolds, *Inorg. Chem.*, **6,** 2110 (1967).
(29) I. D. Campbell, R. A. Dwek, R. E. Richards, and M. N. Wiseman, *Mol. Phys.*, **20,** 933 (1971).
(30) S. F. Lincoln and R. J. West, *Aust. J. Chem.*, **26,** 255 (1973).
(31) V. K. Kapur and B. B. Wayland, *J. Phys. Chem.*, **77,** 634 (1973).
(32) E. F. Caldin, M. W. Grant, and B. B. Hasinoff, *J. Chem. Soc., Faraday Trans. 1*, **68,** 2247 (1972).

Hydrolysis of Benzaldehyde *O,S*-Acetals[1]

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Abstract: The acid-catalyzed breakdown of benzaldehyde *O*-ethyl *S*-ethyl acetal proceeds with initial C–O bond cleavage, whereas the *S*-phenyl acetal gives C–S cleavage in 90% methanol/water. Electron-withdrawing substituents on the thiol increase the amount of C–S cleavage and electron-donating substituents on the benzaldehyde increase C–O cleavage. The directions of cleavage are analyzed in terms of the *pull* exerted by the leaving group and the *push* exerted by the remaining groups. Increased electron donation by substituents on the benzaldehyde leads to decreased electron donation by substituents on the thiol for C–O cleavage. A limiting Brønsted coefficient of $\alpha_{min} = 0.84$ was determined for benzaldehyde *O*-ethyl *S*-phenyl acetal. The absence of detectable general acid catalysis is attributed to the poor hydrogen-bonding ability of thiols. The ratio of the rate constants for the acid-catalyzed and "water" reactions of this compound gives a ratio of $k_{RS^-}/k_{RSH} = 40$ for the attack of PhS^- and PhSH on an intermediate oxocarbonium ion in the reverse direction. This ratio and the large effects of polar substituents on the thiol and the benzaldehyde suggest that the rate-determining step of the "water" reaction is the diffusional separation of RS^- from the oxocarbonium ion.

The experiments described here were carried out in order to characterize further the position of bond cleavage, transition-state structures, and mechanisms of catalysis for the hydrolysis of *O,S*-acetals. Previous studies of the position of initial bond cleavage have given different conclusions for different compounds and the available data do not permit generalizations on this question.[2-5] The interpretation of transition-state structures from the available kinetic data has been hampered by the absence of definitive evidence for the position of bond cleavage, except for the reactions of benzaldehyde *O*-methyl *S*-aryl acetals.[3,6-10] An interesting and incompletely explained property of these reactions is that they do not exhibit general acid catalysis, although general acid catalysis is easily detected in the hydrolysis of the analogous oxygen acetals with OAr

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expulsion.[3,11-14] We have chosen to examine the hydrolysis of acyclic *O,S*-acetals in order to avoid the difficulties of interpretation that arise from the possibility of intramolecular ring closure to regenerate reactants after the initial bond cleavage in cyclic acetals.

Experimental Section

Materials. Commercially available organic reagents were purified before use to remove trace amounts of oxidants and water. Acetonitrile was stirred for 5 h over P_2O_5 or refluxed over CaH_2 and then distilled. Methanol, 2-chloroethanol, and propargyl alcohol were stirred three times over $NaBH_4$ for 10 min and distilled. 2,2,2-Trifluoroethanol was distilled from $NaHCO_3$ and $CaSO_4$. Benzenethiol, ethanethiol, methyl mercaptoacetate, and dioxane (which was first refluxed for 5 h over $LiAlH_4$) were distilled and stored under nitrogen in brown bottles at −15 °C until use.

O-Ethyl *S*-phenyl and *O*-ethyl *S*-ethyl acetals of benzaldehyde were synthesized by the procedure of Fife and Anderson.[3] Alternatively, benzaldehyde *O*-methyl *S*-phenyl acetal (bp 125–130 °C, 0.2 mm) and *p*-chlorobenzaldehyde *O*-ethyl *S*-phenyl acetal (bp 135–140 °C, 0.1 mm) were prepared from 0.1 mol of aldehyde and 0.1 mol of benzenethiol in 100 mL of 90% $MeOH/H_2O$ or 90% $EtOH/H_2O$ containing 0.01–0.1 M hydrochloric acid. The product separated as an oil after several hours and 20 mL of 1 M sodium hydroxide was added. After standing overnight the oil was separated and distilled.

Most *O,S*-acetals were prepared by an exchange procedure that was followed by observing changes in the NMR spectrum. A 1 M solution of *O,O*-acetal and thiol in carbon tetrachloride or acetonitrile ~10^{-3} N in HCl was prepared. Within a few minutes at 35 °C (probe temperature) the yield of *O,S*-acetal was maximal and the exchange was stopped by diluting 1/100 in CH_3CN. This diluted solution was used as a source of *O,S*-acetal within 2 days after preparation. Benzaldehyde diethyl mercaptal was prepared in the same manner from 0.1 M benzaldehyde diethyl acetal, 0.2 M ethanethiol, and 0.01 M hydrochloric acid in 30 min at room temperature. *O*-Alkyl *S*-ethyl acetals were conveniently prepared by alcohol exchange. A 0.01 M solution of benzaldehyde *O*-ethyl *S*-ethyl acetal and 10^{-3}–10^{-4} M HCl in the appropriate alcohol gave the desired *O*-alkyl *S*-ethyl acetal of benzaldehyde within 5 min. Aliquots were used immediately for kinetic experiments; on long standing the solutions gave *O,O*-dialkyl acetals and diethyl mercaptal, which were identified by their rates of hydrolysis by comparison with known compounds. Solutions of *O,S*-acetals prepared by the exchange procedures were shown to give the same rates of hydrolysis as compounds prepared by standard methods.

O,O-Dimethyl and -diethyl acetals were prepared from aldehydes and the appropriate orthoformate using a trace of *p*-toluenesulfonic acid as catalyst.[15] The higher boiling 2-chloroethanol and propargyl alcohol were dissolved in a benzene solution of aldehyde containing a catalytic amount of *p*-toluenesulfonic acid;[16] equilibrium was driven toward product by collection of the water formed using a Dean-Stark trap.

Kinetics. Reactions were initiated by the addition of a small aliquot of a stock solution of the acetal in acetonitrile to a solution of buffer or dilute acid. The final concentration of acetonitrile was <3% in all cases. Fast reactions were followed using a spring-loaded rapid-injection syringe[17] fitted in a cuvette inserted into the thermostated cell compartment of a Gilford Model 2000 recording spectrophotometer. Slower reactions were followed using a Zeiss PMQ II spectrophotometer connected to a Beckman 10-in. linear-log recorder. The temperature was maintained at 25 °C with a thermostated cell compartment. Reactions were usually followed at 244 nm for benzaldehyde, 280 nm for *p*-methoxybenzaldehyde, and 340 nm for *p*-dimethylaminobenzaldehyde acetals. Slow reactions were followed, usually at 306 nm, by trapping the benzaldehyde product with thiosemicarbazide.[18] Thiosemicarbazide concentrations were used that were shown to give thiosemicarbazone from the aldehyde product with rate constants at least ten times larger than k_{obsd} for acetal hydrolysis under the conditions of kinetic experiments. Reactions typically were monitored for 3 half-lives of reaction time and k_{obsd} values were calculated from plots of log $(A_\infty - A)$ against time, where A_∞ is the absorbance after 8–10 half-lives of reaction. Second-order rate constants, k_H, were calculated from the measured pseudo-first-order rate constants, k_{obsd}, by dividing k_{obsd} by antilog (−pH); k_{obsd} was determined at several different pH values spanning 1–2 pH units. For example, k_{obsd} = 0.106, 1.17×10^{-2}, and 1.20×10^{-3} s^{-1} at pH 1.040, 2.023, and 3.050, respectively, for the hydrolysis of benzaldehyde *O*-ethyl *S*-ethyl acetal in dilute HCl solutions at μ = 1.0 (KCl) and 25 °C, giving $k_H = 1.25 \pm 0.05$ M^{-1} s^{-1}. Rate constants for acid-catalyzed reactions are based on observed pH values, measured with a glass electrode that was standardized against standard aqueous buffers. No correction was made for the shift of the pH scale in 20% dioxane; this shift is +0.18 units for 50% dioxane.[19]

Analysis of the Position of Initial Bond Cleavage. A typical procedure is described. Benzaldehyde *O*-ethyl *S*-phenyl acetal (1 g) was allowed to react in 100 mL of 90% $MeOH/H_2O$ (10 mL of H_2O made up to 100 mL with MeOH) containing 0.1 M hydrochloric acid and 0.1 M thiosemicarbazide hydrochloride. The first-order rate constant for formation of benzaldehyde is 4.5×10^{-4} s^{-1} and that for thiosemicarbazone formation from benzaldehyde is 2.5×10^{-2} s^{-1} under these conditions. The same rate constant for acetal cleavage was obtained in the absence of thiosemicarbazide. The reaction was quenched after 1 half-life by addition of 30 mL of 1 M sodium hydroxide and 500 mL of water and the mixture was extracted twice with 50 mL of carbon tetrachloride. The combined extracts were washed with 0.1 M sodium hydroxide and with water and were dried by filtering through anhydrous sodium sulfate. The NMR spectrum was examined after concentration by rotary evaporation to 1–2 mL, giving a 1–2 M solution of *O,S*-acetal, and was found to be free of extraneous peaks. It was shown that the OCH_3 singlet would have been detected at ≤5% by adding a known amount of methanol or benzaldehyde dimethyl acetal and reexamining the spectrum: the diastereotopic methylene protons give major peaks at 232, 225, 215, and 208 Hz downfield from Me_4Si and the OCH_3 sharp singlet occurs at 205 Hz. A 5% quantity of OCH_3 generates a major sharp peak in the upfield portion of the 16-line methylene multiplet. A mixture of 0.01 M benzaldehyde and benzenethiol gave no *O,S*-acetal or other NMR signals under the same conditions, demonstrating that the trapping is effective, the reaction is irreversible, and other materials are removed from the analyzed sample during the workup. In the absence of the thiosemicarbazide trap 10–20% of benzaldehyde *O*-methyl *S*-phenyl acetal was formed from benzaldehyde and benzenethiol. In the case of *O,S*-acetals in which initial C–O cleavage occurs, formation of the *O*-methyl thioacetal was demonstrated by the following observations. The thioacetal methine proton is shifted upfield 0.1 ppm, the characteristic diastereotopic OCH_2CH_3 methylene proton multiplet is absent, and a sharp OCH_3 singlet is present at 3.1 ppm. In cases where partial exchange occurred, both methine singlets were observed and the OCH_3 singlet was present in the upfield portion of the complex methylene multiplet/quartet. In the case of benzaldehyde *O*-ethyl *S*-ethyl acetal, additional controls were run in 90% methanol: the rate constant for benzaldehyde formation is independent of the substrate concentration over the range 10^{-2}–10^{-4} M, is independent of ethanethiol concentration over the range 10^{-2}–10^{-4} M, is independent of the method used to follow benzaldehyde formation (direct or via thiosemicarbazide trap), and exhibits first-order kinetics over 90% of reaction. These results show that ethanethiol does not react directly with a carbonium ion intermediate and that ethanethiol does not compete with semicarbazide for reaction with benzaldehyde under these conditions. The change in the NMR spectrum of 1 M benzaldehyde *O*-ethyl *S*-ethyl acetal in 90% CH_3OD/D_2O containing 0.01 M DCl showed that the *O*-ethyl exchanges for the *O*-methyl group faster than detectable amounts of benzaldehyde dimethyl acetal are formed. Exchange is evidenced by the appearance of a peak 5 Hz upfield from the benzaldehyde *O*-ethyl *S*-ethyl methine (due to the methine of benzaldehyde *O*-methyl *S*-ethyl acetal) and the absence of a change in the diastereotopic SCH_2CH_3 methylene proton multiplet at 2.4 ppm. At equilibrium the predominant species are diethyl mercaptal and dimethyl acetal and at this time the SCH_2CH_3 methylene protons appear as a quartet at 2.3 ppm.

Results

Position of Bond Cleavage. The initial products that are formed upon cleavage of benzaldehyde *O,S*-acetals were determined by NMR analysis of the remaining *O,S*-acetal after allowing hydrolysis of 0.04 M *O*-ethyl monothioacetals to proceed halfway to completion in acidic 90% MeOH/HOH in the presence of thiosemicarbazide hydrochloride. Cleavage of the C–O bond under these conditions gives the *O*-methyl monothioacetal as the principal initial product, which was

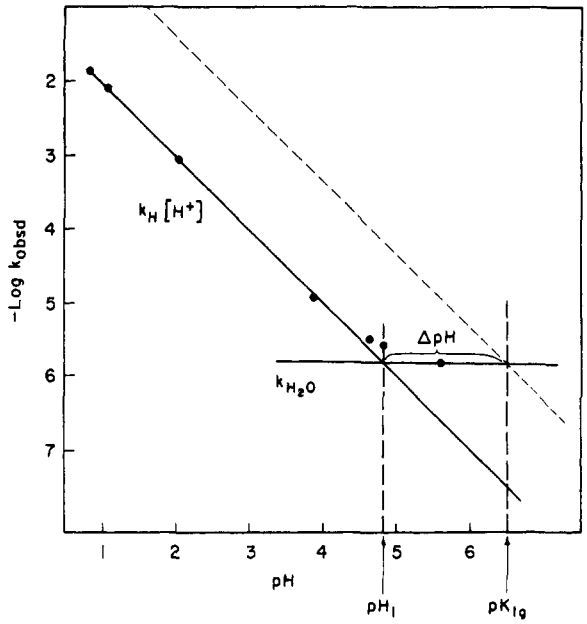
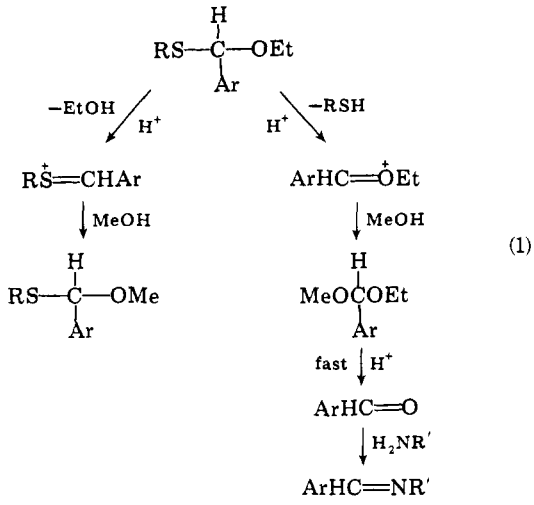


Figure 1. Dependence on pH of the rate of hydrolysis of benzaldehyde *O*-ethyl *S*-phenyl acetal at 25 °C, ionic strength 1.0. The light dashed line shows the values of k_{obsd} for acid catalysis of a reaction with ΔpH = log $(k_{RS^-}/k_{RSH}) = 0$.

extracted into carbon tetrachloride and analyzed (eq 1, left). Cleavage of the C–S bond gives the *O*-methyl *O*-ethyl acetal, which is rapidly hydrolyzed to the aldehyde and trapped as the thiosemicarbazone (eq 1, right) so that the only *O,S*-acetal that



(1)

is present when analyzed is the unreacted *O*-ethyl compound. This and subsequent equations are written with a carbonium ion intermediate, although the existence of such an intermediate has not been proved and the possibility exists that there is no such free intermediate.

The results (Table I) show only C–S cleavage for benzaldehyde *O*-ethyl *S*-phenyl acetal, confirming the result obtained by Fife and Anderson for the position of bond cleavage in 2-propanol,[3] and only C–O cleavage for benzaldehyde *O*-ethyl *S*-ethyl acetal and *p*-methoxybenzaldehyde *O*-ethyl *S*-(methyl mercaptoacetate) acetal. There are roughly equal amounts of C–S and C–O cleavage for benzaldehyde *O*-ethyl *S*-(methylmercaptoacetate) acetal and *p*-methoxybenzaldehyde *O*-ethyl *S*-phenyl acetal. Thus, C–O cleavage is favored by increasing basicity of the leaving thiol and by electron-donating substituents on the benzaldehyde.

The observed rate constants for hydrolysis in 90% MeOH/HOH are consistent with these conclusions. In the presence of 0.5 M hydrochloric acid the observed rate constant for benzaldehyde *O*-ethyl *S*-phenyl acetal is 2.5 times that for the corresponding *O*-methyl compound (5.0×10^{-3} and 2.0×10^{-3} s^{-1}, respectively), whereas the observed rate constants for benzaldehyde *O*-ethyl *S*-ethyl acetal and the corresponding *O*-methyl acetal are identical (4.6×10^{-3} s^{-1}). In water the respective values of k_H are 0.11, 0.060, 1.3, and 1.1 M^{-1} s^{-1}. Thus, the *S*-phenyl acetals maintain their identity and undergo C–S cleavage at different rates in 90% MeOH/HOH, whereas the *S*-ethyl acetals undergo rapid C–O cleavage to give the same *O*-methyl *S*-ethyl acetal (eq 1), which then slowly undergoes hydrolysis with a rate constant of 4.6×10^{-3} s^{-1}. Furthermore, the 120-fold inhibition of the hydrolysis rate for the *S*-ethyl acetals in 90% methanol is larger than the 10–15-fold inhibition for the *S*-phenyl compounds because most of the cleavage events of the *S*-ethyl acetal regenerate the *O,S*-acetal by reaction with methanol; only a small fraction give hydrolysis by reaction with water. Finally, the hydrolysis of *O*-ethyl *S*-ethyl benzaldehyde acetal in 30–70% MeOH/H_2O was found to proceed with nonlinear first-order kinetics because of competitive hydrolysis and exchange to give the *O*-methyl *S*-ethyl acetal. *O*-Ethyl-*S*-phenylbenzaldehyde was found to undergo hydrolysis with first-order kinetics for at least 3 half-lives in 50 and 40% MeOH/H_2O; i.e., this compound undergoes no detectable C–O cleavage in a predominantly aqueous medium as well as in methanol.

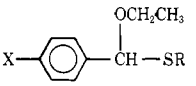
Table I. Position of Initial Bond Cleavage of Benzaldehyde *O,S*-Acetals in 90% MeOH/HOH[a]

substrate	initial bond cleavage
PhCH(OEt)SPh	C–S cleavage[b]
PhCH(OEt)SEt	C–O cleavage[b]
CH_3O–C$_6$H$_4$–CH(OEt)$SCH_2CO_2CH_3$	C–O cleavage[b]
PhCH(OEt)$SCH_2CO_2CH_3$	C–O and C–S cleavage compete[c]
CH_3O–C$_6$H$_4$–CH(OEt)SPh	C–O and C–S cleavage compete[c]

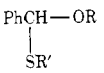
[a] Determined by examining the exchange of OEt for OMe occurring in the substrate prior to hydrolysis in 90% MeOH/H_2O catalyzed by HCl. [b] ≤5% of the other mode of cleavage occurs. [c] After 1 half-life of hydrolysis in 90% MeOH/H_2O containing HCl, $\frac{1}{3}$–$\frac{1}{2}$ of the unhydrolyzed substrate had exchanged OEt for OMe.

Rate Constants for the Hydrolysis of Benzaldehyde *O,S*-Acetals. Benzaldehyde *O*-ethyl *S*-phenyl acetal undergoes cleavage through a proton-catalyzed reaction below pH 4 and a pH-independent "water" reaction above pH 5 (Figure 1). Rate constants for the cleavage of a series of substituted benzaldehyde *O,S*-acetals were determined similarly and are summarized in Table II. The pH-independent reaction is more significant and becomes predominant at pH values below 4 for the *O*-ethyl *S*-phenyl acetals of *p*-methoxybenzaldehyde and *p*-dimethylaminobenzaldehyde (Table II) and for compounds with more acidic leaving groups, such as benzaldehyde *O*-methyl *S*-2,4-dinitrophenyl acetal.[3] Rate constants for cleavage of the less soluble acetals were determined in 20% dioxane/water. Benzaldehyde *O*-ethyl *S*-phenyl acetal cleaves 3.8 times more slowly in 20% dioxane than in water and the rate constants for cleavage of the *O,S*-acetals of *p*-methoxybenzaldehyde in 20% dioxane were found to fit structure-reactivity correlations based on rate constants for the cleavage of other acetals in water after correction by this factor.

Table II. Rate Constants for the Hydrolysis of Benzaldehyde *O,S*-Acetals[a]



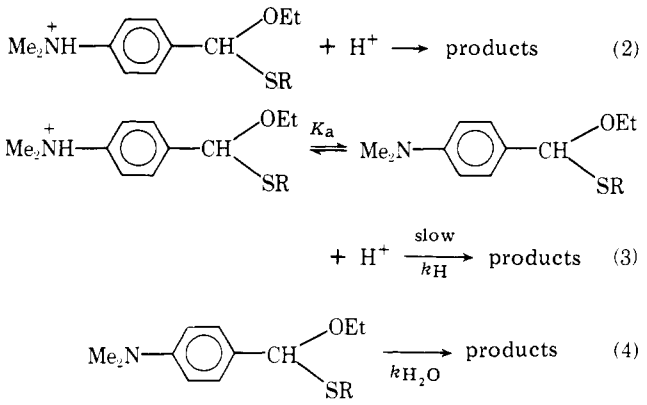
X	k_H, M^{-1} s^{-1}, for SR = SCH_2CH_3	SCH_2CH_2OH	$SCH_2CO_2CH_3$	SCH_2CF_3	SPh	k_{H_2O}, s^{-1}, for SR = SCH_2CH_3	$SCH_2CO_2CH_3$	SPh
$Me_2\overset{+}{N}H$	0.03[b]		0.0006[b]		0.012[b]			
Cl					0.011[c]			
H	1.3	0.36[d]	0.012	0.0018	0.11			1.6×10^{-6}
					0.029[c]			
CH_3O	3.0[c]		0.075[c]		0.20[c]			6×10^{-5} [c]
Me_2N	170		8.6		150	0.003	0.45	42
pK'_{RSH}[e]	10.3	9.6	7.9	7.3	6.4	10.3	7.9	6.1



SR′	k_H, M^{-1} s^{-1}, for OR = OCH_2CH_3	OCH_3	$OCH_2CH_2OCH_3$	OCH_2CH_2Cl	$OCH_2C{\equiv}CH$	OCH_2CF_3
SCH_2CH_3	1.3	1.1	0.77	0.45	0.23	0.13
SPh	0.029[c]	0.016[c]		0.0026[c]		
		0.060[a]				
pK_{ROH}[f]	16.0	15.5	14.8	14.3	13.5	12.4

[a] At 25 °C, ionic strength maintained at 1.0 with potassium chloride. [b] Calculated from the dependence of k_{obsd} on H_0 in 1–2.4 M HCl. [c] Solvent contains 20% dioxane. [d] k_H for the cyclic compound, 2-phenyl-1,3-oxathiolane, was found to be 2.6×10^{-3} M^{-1} s^{-1}. [e] W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, **93**, 4433 (1971). [f] Reference 22.

The hydrolysis of *O,S*-acetals of *p*-dimethylaminobenzaldehyde (Figure 2) proceeds through the acid-catalyzed cleavage of the N-protonated substrate below pH 0 (eq 2), an acid-catalyzed reaction of the unprotonated substrate (which appears as a kinetically equivalent pH-independent reaction of the protonated substrate) between pH 0 and 1 (eq 3), and



a reaction of the unprotonated substrate above pH 1 (eq 4). These pathways are conveniently designated as the two-proton, one-proton, and water reactions, respectively. The observed rate constant for the water reaction increases with increasing pH in the region in which the substrate is protonated and levels off to a pH-independent reaction at the pK_a of the protonated substrate, as shown for the *O*-ethyl *S*-(methyl mercaptoacetate) compound in the lower curve of Figure 2. The value of K_a for this compound is 3.5×10^{-5} M (ionic strength 1.0; K_a for *N,N*-dimethylaniline-H^+ is 8×10^{-6} M at ionic strength 0.1),[20] based on a limiting value of $k_{H_2O} = 0.45$ s^{-1} above pH 5.6, $k_{obsd} = 1.5 \times 10^{-5}$ $[H^+]^{-1}$ s^{-1} at pH 2–4, and the relationship $k_{obsd} = K_a k_{H_2O}/[H^+]$ for this pH region. The same value of K_a was assumed for the *S*-phenyl compound. The observed rate constants for the two-proton reactions were assumed to follow $-H_0$ (Figure 2)[21] and slightly different rate constants are obtained for the two- and one-proton processes if the data are plotted against other acidity functions.

In 90% CH_3CN/HOH the rates of hydrolysis of the *O*-ethyl

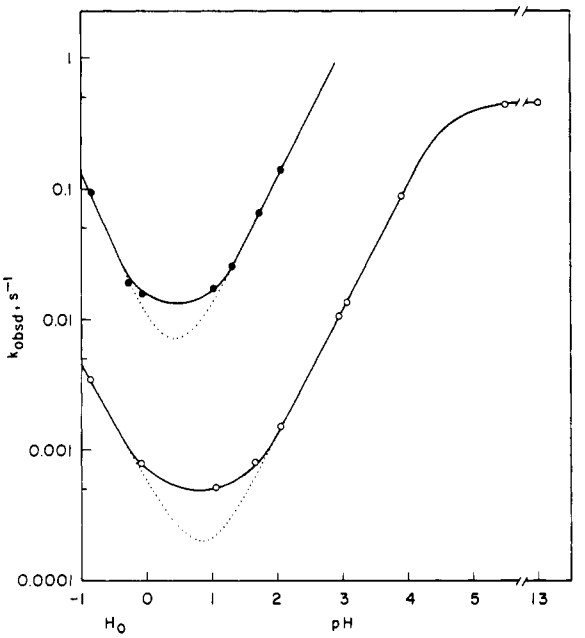


Figure 2. Plot of log k_{obsd} against pH for the hydrolysis of *p*-dimethylaminobenzaldehyde *O*-ethyl *S*-phenyl acetal (●) and *p*-dimethylaminobenzaldehyde *O*-ethyl *S*-(methyl mercaptoacetate) acetal (○). The dotted lines are the sum of the rate constants of the acid-catalyzed and acid-inhibited reactions (the two-proton and water reactions).

S-phenyl and *O*-ethyl *S*-(methyl mercaptoacetate) acetals of (protonated) *p*-dimethylaminobenzaldehyde were found to be independent of acidity in the range 10^{-3}–10^{-1} M [HCl] (k_{obsd} = 1.5–4.2 $\times$ 10^{-3} s^{-1}); the two-proton process causes an increased rate at [HCl] ~ 1 M. This shows that in the presence of an added organic solvent the water reaction is inhibited and the one-proton pathway becomes predominant. However, in 90% MeOH/HOH k_{obsd} is inversely proportional to $[H^+]$ in the range [HCl] = 10^{-3}–10^{-1} M ($k_{obsd} = 2 \times 10^{-4}$ $[H^+]^{-1}$ s^{-1}); i.e., the one-proton process is inhibited and the reaction proceeds entirely through the water reaction of the free acetal.

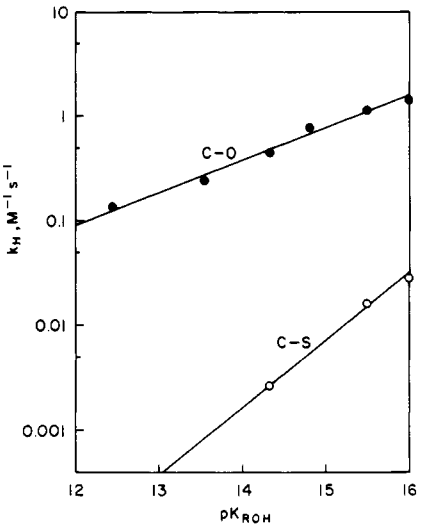


Figure 3. The dependence on the pK of the alcohol of the rate constants for cleavage of benzaldehyde O-alkyl S-ethyl acetals with alcohol leaving, in aqueous solution, (●) and benzaldehyde O-alkyl S-phenyl acetals with thiophenol leaving, in 20% dioxane (○).

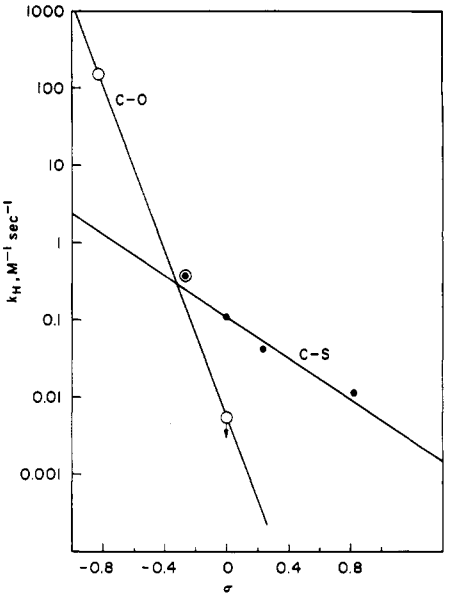


Figure 4. Hammett plot for the acid-catalyzed cleavage of substituted benzaldehyde O-ethyl S-phenyl acetals at 25 °C. C-O cleavage, (○); a limiting value is indicated by the arrow. C-S cleavage, (●); the rate constant for the p-methoxy compound is corrected by 0.5, assuming equal amounts of C-O and C-S cleavage (Table I), and by 3.8 for the solvent effect of 20% dioxane.

This is the behavior that is expected from the directions of bond cleavage described in Table I. With a strong electron-donating substituent on the benzaldehyde moiety the O,S-acetal undergoes C-O cleavage by the one-proton pathway to give a carbosulfonium ion which, in the presence of 90% methanol, usually reacts with methanol to regenerate an O,S-acetal so that hydrolysis is inhibited (eq 1). However, the water reaction involves the expulsion of thiolate anion from the O,S-acetal to give an oxocarbonium ion, which then reacts with methanol to give an O,O-acetal that undergoes rapid hydrolysis. Consequently, the water reaction becomes the predominant pathway for hydrolysis in 90% methanol.

No general acid catalysis of the hydrolysis of O-ethyl S-phenyl benzaldehyde acetal was observed in acetate buffers, 50% acid, in the range 0.2–2.0 M (μ = 1.0, KCl). A 20% decrease in the observed rate constants was accounted for by a small decrease in pH with increasing buffer concentration. The observed rate constants in 0.2, 1.0, and 2.0 M buffers of 4.0×10^{-6}, 3.7×10^{-6}, and 3.2×10^{-6} s^{-1} may be compared with 4.2×10^{-6}, 3.7×10^{-6}, and 3.1×10^{-6} s^{-1}, respectively, that were calculated from $k_H[H^+] + k_{H_2O}$ (Table II).

A rate constant of $k_H = 3.5 \times 10^{-4}$ M^{-1} s^{-1} for the hydrolysis of benzaldehyde diethyl mercaptal was obtained from measured rate constants of 2.8×10^{-5} s^{-1} in 0.1 M HCl and 0.9 M KCl and 2.5×10^{-4} s^{-1} in 1.0 M HCl, based on observed pH values.

Effects of Polar Substituents. The data are insufficient to provide accurate structure-reactivity parameters, but do indicate certain trends, especially for the reactions in which a change in structure gives a change in the position of bond cleavage. A plot of log k against the pK of the leaving alcohol[22] for the cleavage of benzaldehyde O-alkyl S-ethyl acetals has a slope of $\beta_{lg} = 0.3$ and the corresponding plot against the pK of the remaining group for the cleavage of benzaldehyde O-alkyl S-phenyl acetals, in which the thiol leaves and the alcohol remains, has a larger slope of $\beta_{rg} \sim 0.62$ (Figure 3). Such plots provide a measure of the charge development in the transition state that is "seen" by a polar substituent, using the ionization constants of the alcohols as a reference (the numerical values of the slopes will be the same for positive and negative charge development to the extent that the absolute magnitude of the electrostatic effect is independent of the sign of the charge). The more favorable effect of electron-donating substituents in the benzaldehyde on C-O than on C-S cleavage that was manifested in the observed directions of bond cleavage (Table I) appears as a steeper slope of the rate constants for C-O cleavage (open circles, Figure 4) in a Hammett plot for the hydrolysis of benzaldehyde O-ethyl S-phenyl acetals. The line drawn through the points for C-S cleavage (solid circles, Figure 4) has a slope of $\rho = -1.4$. The point for the p-methoxybenzaldehyde acetal is uncertain in this and other correlations because this compound undergoes C-O and C-S cleavage at similar rates in 90% methanol (Table I); the point in Figure 4 is based on the assumption that the rate constants for the two types of cleavage in water are equal.

Hammett correlations for cleavage of substituted benzaldehyde O-ethyl S-ethyl acetals with C-O cleavage give $\rho = -2.3$ against σ, with positive deviations for electron-donating substituents, $\rho^+ = -1.7$ against σ^+, with negative deviations for electron-donating substituents, and a good fit to $\rho = -2.0$, $\rho^r = -1.1$ ($r^+ = 0.55$, correlation coefficient = 0.999), based on the Yukawa-Tsuno treatment with an adjustable resonance contribution[23,24] (Figure 5). The structure-reactivity coefficients are summarized in Table III.

The rate of alcohol expulsion from benzaldehyde O-ethyl S-alkyl acetals shows a large dependence on the pK of the remaining thiol that becomes smaller with electron-donating substituents on the benzaldehyde. Thus, the ratio of the rate constants for the S-ethyl and S-(methyl mercaptoacetate) compounds (Table II) increases from 20 for p-dimethylamino- to 40 for methoxy- to 108 for benzaldehyde acetal; the ratio for the unsubstituted benzaldehyde compound is 216 assuming equal amounts of C-O and C-S cleavage for the S-(methyl mercaptoacetate) compound (Table I). These ratios correspond to Brønsted-type slopes of $\beta_{rg} = 0.54$, 0.65, and 1.0, respectively. The large dependence on the pK of the thiol is confirmed by the fact that the rate constant for cleavage of O-ethyl S-trifluoroethyl benzaldehyde acetal falls on the line of slope 1.0, even though this compound may undergo hydrolysis largely by C-S cleavage.

The rate of hydrolysis of benzaldehyde O-ethyl S-phenyl acetal, with C-S cleavage, is 400 times faster than predicted by the Brønsted-type correlation for the hydrolysis of the corresponding S-alkyl acetals, with C-O cleavage. This reflects

Table III. Approximate Structure-Reactivity Parameters for the Cleavage of Benzaldehyde *O,S*-Acetals[a]

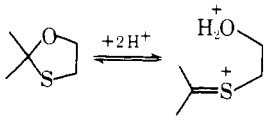
series	C–O cleavage
SEt | ArCH—OEt	$\rho = -2.0$, $\rho^r = 1.1$ ($r^+ = 0.55$ (0.999);[b] $\rho = -2.3$ (0.996)[c])
SEt | PhCH—OR	$\beta_{lg} = 0.30$ (0.99), $\rho^* = -1.1$ (0.99)[d]
SR | ArCH—OEt	$\beta_{rg} = 0.5$–1.0[e] ($\rho^* = -1.5$ to -2.8)
series	**C–S cleavage**
OEt | ArCH—SPh	$\rho \simeq -1.4$ (0.985)
OMe | PhCH—SAr	$\beta_{lg} = 0.57$, $\rho = -1.0$[f,g]
OR | PhCH—SPh	$\beta_{rg} \simeq 0.62$ (0.999) ($\rho^* = -2.2$)[g]
OEt | *p*-Me$_2$NPhCH—SR	$\beta_{lg} \simeq -1.0$ (0.999) (water reaction)

[a] Correlation coefficients are in parentheses. Data from this work are at 25 °C, ionic strength 1.0 (KCl). [b] Based on the Yukawa-Tsuno treatment.[23,24] [c] Based on σ values from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [d] Values of pK and σ^* are from ref 22 and R. W. Taft in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13. [e] Based on the pK_a values in Table II. The values of β_{rg} are 0.54 (Ar = *p*-Me$_2$NPh), 0.65 (Ar = *p*-MeOPh), and 1.0 (Ar = Ph). [f] Reference 3; at 30 °C. [g] In 20% dioxane.

an anomalously large rate of expulsion of aromatic leaving groups that is also evident in *O,O*-acetals: benzaldehyde methyl phenyl acetal undergoes acid-catalyzed hydrolysis 1.4 times faster than benzaldehyde dimethyl acetal in spite of the high pK of methanol.[14] The reason for this difference is not known. Part, but not all, of the difference may be explained by resonance stabilization of the aromatic leaving groups that decreases their pK relatively more than it stabilizes the transition state; expulsion of the bulky aromatic groups may also be accelerated by a steric effect.

Discussion

Position of Initial Bond Cleavage. In order to understand the mechanism of hydrolysis of mixed acetals it is first necessary to know which bond is cleaved in the rate-determining step. Earlier work by Clayton et al. has shown that anomerization and contraction from a six- to a five-membered ring occur concurrently with the hydrolysis of 1-methyl thioglycosides, so that C–O cleavage with ring opening and reclosure must be competitive or faster relative to C–S cleavage,[2] but Fife and Anderson have shown that the acid-catalyzed solvolysis of benzaldehyde *O*-methyl *S*-phenyl acetal in 2-propanol occurs with C–S cleavage.[3] The direction of the *equilibrium* ring opening of 2,2-dimethyl-1,3-oxathiolane in FSO_3H·SbF_5 according to eq 5 shows that the combination of leaving group



(5)

basicity and carbonium ion stability favors ROH leaving and protonation in this reaction, but does not establish the initial site of bond cleavage.[4] From the difference between the secondary isotope effects of $k_H/k_D = 1.1$ and 1.3 for hydrolysis of the two isomers of the mercaptoethanol *O,S*-ketal of $\alpha,\alpha,\alpha',\alpha'$-tetradeuterio-4-*tert*-butylcyclohexanone it has been concluded that C–O bond cleavage occurs in the rate-determining step.[5] It has also been suggested that the large inverse solvent deuterium isotope effect of $k_D/k_H = 3.0$ supports C–O cleavage for 2-methyl-1,3-oxathiolane[8] and that the smaller isotope effects of $k_D/k_H = 1.9$–2.2 and 1.3 support C–S cleavage for 2-phenyl-1,3-oxathiolane[7] and tetrahydro-2-(*p*-tolylthio)pyran,[9] respectively. An isotope effect of $k_D/k_H = 1.5$ has been observed for C–S cleavage of benzaldehyde *O*-methyl *S*-phenyl acetal.[3] However, the observed range of $k_D/k_H = 1.0$–3.1 for the hydrolysis of *O,O*-acetals[25] means that a small solvent isotope effect is not definitive evidence for C–S cleavage.

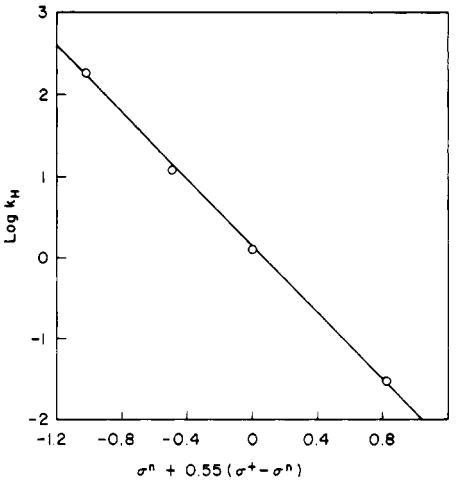


Figure 5. Hammett correlation for the acid-catalyzed hydrolysis of substituted benzaldehyde *O*-ethyl *S*-ethyl acetals based on the Yukawa treatment with $\rho = -2.0$, $\rho^r = -1.1$, and $r^+ = 0.55$. The σ^n value[23] of 0.82 for Me_3N^+ has been used for the Me_2NH^+ substituent.

The results summarized in Table I show that benzaldehyde *O,S*-acetals react preferentially with C–O bond cleavage. However, the relative ease of the two modes of cleavage is closely balanced and partial or complete C–S cleavage is observed with the relatively acidic *S*-phenyl and *S*-(methyl mercaptoacetate) leaving groups. Cleavage of the C–O bond is favored by electron-donating substituents on the benzaldehyde moiety and on the thiol. These results are consistent with the earlier demonstrations of C–O cleavage for *S*-alkyl thioglycosides and C–S cleavage for benzaldehyde *O*-methyl *S*-phenyl acetal.[2,3]

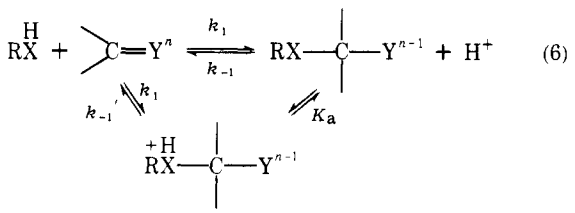
The direction of cleavage of mixed acetals is determined by the *pull* exerted by the leaving group for bond breaking and the *push* provided by the remaining group and by other substituents on the central carbon atom. The *pull* exerted by the leaving group is larger for alcohols than for thiols of comparable structure in acid-catalyzed reactions. This is shown by the 700-fold faster expulsion of phenol[14] than of thiophenol from the corresponding benzaldehyde *O*-methyl acetal and the faster expulsion of ethanol than of ethanethiol from the corresponding benzaldehyde *S*-ethyl acetal by a factor of 4000 (Table IV). There must also be a factor of >150 favoring ethanol over thiol expulsion from the corresponding benzaldehyde *O*-ethyl acetals (Table IV), since only ethanol expulsion is observed from the *O*-ethyl *S*-ethyl acetal. These trends are consistent with the relative rate constants for the cleavage of cyclic *S,S*-, *S,O*-, and *O,O*-acetals.[7,8,10,26]

The rate constants for the addition of EtSH and HOH to the carbonyl group of acetaldehyde are about the same (k_1, eq 6) in spite of the low basicity of RSH.[27] Since the equilibrium constants for the addition of RSH are some 10^3 larger than those for the addition of ROH or HOH,[27,28] the rate constants for protonation and expulsion of RSH must be approximately 10^3 smaller than those for ROH, in agreement

Table IV. Relative Rates of the Acid-Catalyzed Hydrolysis of *O,O*-, *O,S*-, and *S,S*-Acetals of Benzaldehyde

acetal	rel rate	rate-controlling bond dissociation
$PhCH(OEt)_2$	150[a]	C–O
PhCH(OEt)(SEt)	1[a]	C–O
$PhCH(SEt)_2$	2.3×10^{-4} [a]	C–S
PhCH(OCH$_3$)(OPh)	700[b]	C–O
PhCH(OCH$_3$)(SPh)	1[a]	C–S

[a] This work. [b] Reference 14.



(6)

with the data for acetals. Since protonation on oxygen is more favorable by a factor of approximately 10^4 (the values of pK_a are ~ -6.9 for simple thioethers[29,30] and ~ -2.6 for oxygen ethers[31]), the entire rate difference can be accounted for by the low basicity of sulfur. Thus, the rate constants for the reactions of protonated sulfur and oxygen are approximately the same in both the attack (k_1) and breakdown (k_{-1}') directions. In this system the relatively high carbon basicity of sulfur is manifested in the transition state for attack, as well as in the product. If it is already manifested in the transition state for attack, it is not lost in the transition state for C–S cleavage and the slow rate of the acid-catalyzed expulsion of thiols is simply a consequence of the relatively low proton basicity of sulfur.

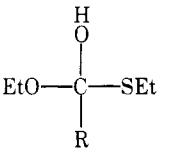
The rate of the pH-independent expulsion of *m*-nitrophenolate anion[14] is faster than that of thiophenolate anion from the corresponding benzaldehyde acetals by a factor of 10^3, in spite of the greater basicity of the oxy anion. If the rate constants are corrected to the same pK, using the value of $\beta_{lg} = -1.0$ in Table III, oxygen expulsion is favored by 10^5. Rate constants for the expulsion of thiol and oxygen anions in reactions with a constant driving force for leaving group expulsion, including eliminations from the anions of acetoacetate esters,[32] hemiacetals,[33,34] and Meisenheimer complexes,[35] support the generalization that thiol anion is favored over oxygen anion expulsion with a constant *substituent* on the leaving group and that oxygen anion is favored over thiol anion expulsion with a constant pK of the leaving group. The only exceptions to this generalization of which we are aware are the 17-fold faster expulsion of PhO^- than of PhS^- in an ElcB elimination reaction and the $>10^5$ faster expulsion of picrate than of thiopicrate from the corresponding *tert*-butyl ether in glacial acetic acid.[36]

The *push* provided by the remaining EtS group is 150 times smaller than that provided by the remaining EtO group for the acid-catalyzed expulsion of ethanol from the corresponding benzaldehyde acetal (Table IV), showing that oxygen is more effective than sulfur in stabilizing the developing positive charge on the central carbon atom in the transition states of these reactions. This factor is comparable to the rate constant ratios for the solvolysis of methyl α-chloromethyl ether and the corresponding sulfide of 139, 82, and 70 in methanol, 90% dioxane/water, and 80% dioxane/water, respectively.[37] Similar ratios have been reported for the protonation of vinyl ethers and sulfides, and the rate constants for the *Z*–*E* isomerization of *O*-alkyl and *S*-alkyl imidate cations suggest stronger electron donation from oxygen than from sulfur.[38]

However, there is only a twofold difference favoring the oxygen compound in the acid-catalyzed expulsion of acetic acid from $MeOCH_2OAc$ and $MeSCH_2OAc$ and in the corresponding ArO and ArS series the sulfur compound reacts 45 times more rapidly.[39] Calculations have also suggested that $H_2C{=}SR^+$ is more stable than $H_2C{=}OR^+$ in the gas phase.[40] Evidently the relative electron-donating ability of sulfur and oxygen varies depending on the structure of the transition state and on the solvent in a manner that is not yet understood.

The balance between the greater *pull* provided by EtO and the smaller *push* provided by EtS in aqueous solution gives a small advantage to oxygen expulsion in the acid-catalyzed cleavage of benzaldehyde *O*-ethyl *S*-ethyl acetal, in agreement with the experimental result, but the difference is not large and changes in polar substituents can change the balance to favor sulfur expulsion. A similar compensation is seen in the reactions of thiol anions with oxygen esters, in which the greater *push* provided by oxygen is balanced by the smaller *pull* of the thiol anion leaving group so that the rates of sulfur and oxygen expulsion from the tetrahedral addition intermediate are the same when the pK values of the nucleophile and leaving group are approximately the same; i.e., a change in rate-determining step occurs near $\Delta pK = 0$.[41]

The relative leaving ability of OR and SR is not determined entirely by the *push* and the *pull* provided by these two groups, but also depends on the additional push provided by electron donation at the central carbon atom from substituents on the benzaldehyde. This electron donation, by *p*-methoxy and *p*-dimethylamino substituents, is more important in aiding the weakly electron-donating sulfur atom to expel oxygen than in aiding the more strongly electron-donating oxygen atom to expel sulfur (Table I). The same tendency has been observed for substituents on R in the acid-catalyzed breakdown of the tetrahedral intermediate **1**.[42] However, the fact that these



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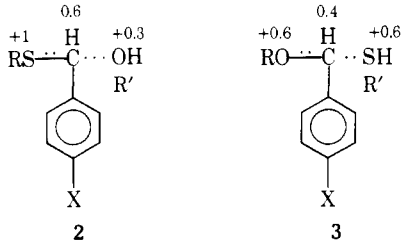
intermediates break down with both C–S and C–O cleavage, in spite of the presence of the electron-donating HO group, means that the preference for C–O cleavage in benzaldehyde acetals does not necessarily hold for other classes of compounds.

Transition-State Structures. The effects of substituents on the position of bond cleavage (Table I) and the approximate structure-reactivity parameters in Table III permit a preliminary description of the structures of the transition states



2 **3**

for oxygen and sulfur expulsion, **2** and **3**. The transition state **2** for oxygen expulsion is later, with more positive charge on the remaining group, more bond cleavage of the leaving group, and a central atom with more carbonium ion character. The effect of polar substituents in the remaining thiol group on the rate of ethanol expulsion from benzaldehyde *O,S*-acetals (β_{rg}

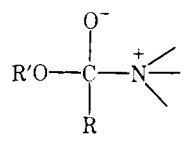
~ 1.0, $\rho^* = -2.8$) is larger than the effect of substituents in the remaining alcohol on the expulsion of thiophenol ($\beta_{rg} \sim 0.6$, $\rho^* = -2.2$). The effect of substituents in the leaving thiophenol ($\beta_{lg} = 0.6$)[3] is larger than in the leaving alcohol ($\beta_{lg} = 0.3$). There is also a large development of charge in the remaining group in the acid-catalyzed cleavage of $ArSCH_2OAc$[39] ($\rho = -2.6$; since ρ for ArSH ionization[43] is 1.9, the value of β_{rg} is >1.0).

Thus, the reason that there is a shift from C–O to C–S cleavage with electron-withdrawing substituents on the thiol is that these substituents decrease the *push* provided by the thiol for oxygen expulsion, not that they increase the leaving ability of sulfur. In fact, electron-withdrawing substituents decrease the leaving ability of sulfur ($\beta_{lg} = +0.6$), but decrease the stabilization of the transition state by the remaining sulfur atom even more ($\beta_{rg} \sim 1.0$). The values of $\beta_{lg} = 0.3$ and $\beta_{rg} \sim 0.6$ for substituted alcohols lead to the prediction that, starting with a reaction that gives comparable amounts of C–O and C–S cleavage, electron-withdrawing substituents on oxygen will increase the amount of C–O cleavage.

The conclusion that the central carbon atom has more carbonium ion character in the transition state for oxygen expulsion is based on the shift from predominant C–S to C–O cleavage with electron-donating substituents on the benzene ring and the ρ values of -2.0 to -2.3 for alcohol expulsion and ~ -1.4 for thiol expulsion. If the equilibrium constants for carbonium ion formation follow a value of ρ close to that of -3.6 for the formation of oxocarbonium ions from acetophenone ketals,[24] the values of ρ for the rate constants correspond to roughly 60 and 40% carbonium ion character in the transition states for oxygen and sulfur expulsion, respectively.

The values of $\rho = -2.0$ and $\rho^r = -1.1$ for C–O cleavage are similar to the values of $\rho = -1.95$ and $\rho^r = -1.0$ for the hydrolysis of benzaldehyde methyl phenyl acetals.[14,24] The value of $\beta_{lg} = 0.3$ is also similar to the value of $\beta_{lg} = \sim 0.2$ for benzaldehyde methyl substituted-phenyl acetals,[14] suggesting that the structures of the transition states are similar for the two reactions. A value of $\rho = -3.3$ has been reported for the hydrolysis of benzaldehyde diethyl acetals,[44] but the possibility has been raised that this more negative value is a consequence of rate-determining diffusional separation of the leaving group from the oxocarbonium ion with electron-withdrawing substituents.[24]

Structure–Reactivity Interactions and Changes in Transition State Structure. The shift from C–S to C–O cleavage, to give the relatively unstable $>C{=}SR^+$ ion, with electron-donating substituents on the benzaldehyde is an example of "giving help where it is most needed". This is manifested quantitatively in the larger negative value of ρ for C–O than for C–S cleavage, but also gives rise to a change in the structure of the transition state. A somewhat similar situation is found in the breakdown of the addition compounds **4**, in which electron-donating



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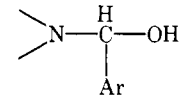
substituents on R favor oxygen expulsion, which cannot be aided by electron donation from the cationic nitrogen atom, more than nitrogen expulsion, which is aided by electron donation from R'O.[45]

The change in transition-state structure in the benzaldehyde acetal series is manifested by an interaction of substituent effects such that electron-donating substituents on the benzene ring decrease the amount of electron donation from the thiol and electron-donating substituents on the thiol decrease the amount of electron donation from the benzene ring. The former effect is evident in the five- to ten-fold decrease in the ratio of the rate constants for the *S*-ethyl and *S*-(methyl mercaptoacetate) compounds caused by electron-donating substituents on the benzene ring, corresponding to values of $\beta_{rg} \sim 1.0$, 0.65, and 0.54 for the unsubstituted, *p*-MeO, and *p*-Me_2N compounds, respectively. There is a correspondingly larger dependence on substituents in the benzaldehyde for cleavage of the SCH_2COOMe than for the SEt compound: the rate constant ratios for the Me_2N, MeO, and H acetals are 1430:13:1 for the SCH_2COOMe and 130:2.3:1 for the SEt compounds.

The same trend is observed in the acid-catalyzed dehydration of **5**, in which electron donation from nitrogen reduces



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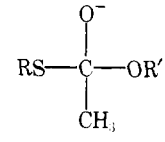
electron donation from the benzene ring to such an extent that the observed rate constants follow σ^n rather than σ or σ^+.[46] Electron-donating groups decrease the amount of electron donation from a benzene ring in solvolysis[47] and the values of r and $-\rho$ become smaller in the hydration of styrenes; this result has been analyzed by extended Hückel theory.[48] The effect of additional electron-donating substituents reducing electron donation from sulfur is continued almost to the limit in **6**, which exhibits a very small value of $\beta_{rg} = 0.16$ for the



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expulsion of oxygen.[41] The strong electron-donating effect of the oxy anion in **4** causes a smaller reduction to $\beta_{rg} = 0.37$ for oxygen assistance to thiol expulsion, so that the relative size of the substituent effects on oxygen and sulfur is reversed compared with those for benzaldehyde *O,S*-acetals.

This kind of change in transition-state structure corresponds to an "anti-Hammond" effect with movement of the transition state perpendicular to the reaction coordinate[49,50] such that stabilization of the product, by resonance, for example, leads to a transition state that more closely resembles the stabilized product. It may be regarded as a type of "resonance saturation" (although some of the stabilization provided by the sulfur atom may arise from its high polarizability). The changes in the benzaldehyde acetal series may be conveniently visualized with a three-dimensional reaction coordinate–energy diagram (Figure 6), in which electron donation from sulfur, as measured by β_{lg}, is shown on the horizontal axis and electron donation from the benzene ring, as measured by $-\rho$, is on the vertical axis. A given transition state or product represents a resonance hybrid with some combination of these two types of stabilization, as shown by the double-headed arrows and crosses. An electron-donating substituent on the benzene ring will stabilize the species and lower the energy in the lower right hand corner, so that the transition state will tend to slide downhill toward this perturbation with a decrease in the amount of electron donation from sulfur, as shown by the dotted arrow. Similarly, electron donation on sulfur will stabilize the $>C{=}SR^+$ species and shift the transition state toward the upper left corner with a decrease in electron donation from the benzene ring, as observed.

Stability of Intermediates. Although the existence of a protonated intermediate has not been demonstrated, such an intermediate could probably exist at a concentration sufficient to account for the rate of at least some of the observed reactions and with a lifetime longer than a vibration frequency. The rate

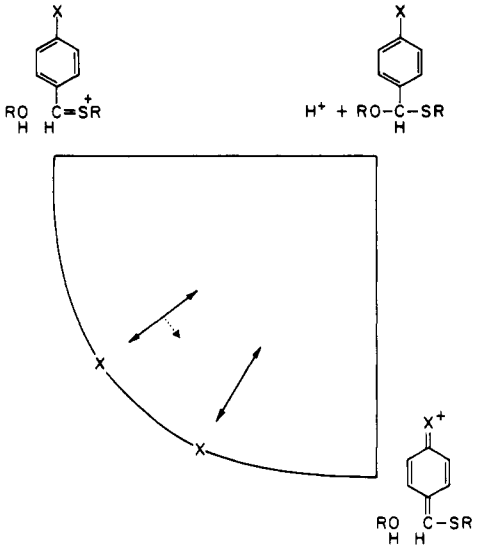
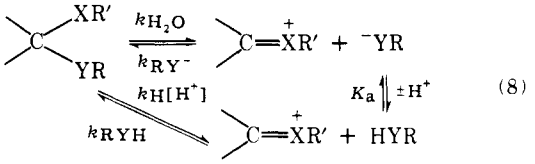


Figure 6. Reaction coordinate-energy diagram to illustrate the relative contributions of stabilization by electron donation from the sulfur atom and from the benzene ring of the transition state and product for the hydrolysis of benzaldehyde *O,S*-acetals with C-O cleavage. The energy contour lines are omitted.

constant for rate-determining breakdown of the protonated intermediate, k_{SH^+}, is given by $k_{SH^+} = k_H K_a$. For *p*-methoxybenzaldehyde *O*-ethyl *S*-(methyl mercaptoacetate) acetal, which breaks down with both C-S and C-O cleavage, the value of k_{SH^+} is on the order of 10^{10} s^{-1}. This value is calculated from $pK_a = -12.4$, based on $pK_a = -6.9$ for protonated dimethyl sulfide[29] and correcting for the effects of the OR, Ar, and COOR substituents with the appropriate σ_I values and $\rho_I = 8.4$.[51] Although this rate constant is large, it is unlikely to be as large as k_{-a}, because the barrier for cleavage of the C-S bond should be larger than for the cleavage of the >S-H$^+$ bond in the ultrafast transfer of a proton from this extremely strong acid to water, so that the protonation step itself (k_a) is unlikely to be rate determining. For less basic leaving groups the required values of k_{SH^+} and k_{-a} will be larger and may be so large as to be incompatible with a stepwise mechanism; a mechanism involving concerted proton transfer and C-S bond cleavage, with a large Brønsted α value, would then be required. Since the oxygen atom is more basic than the sulfur atom[52] and k_H is comparable for C-O and C-S cleavage (Table I), the rate constant k'_{SH^+} for expulsion of the protonated alcohol will be smaller than k_{SH^+} for C-S cleavage and a stepwise mechanism will be feasible.

(7)

For a reaction that proceeds through an oxocarbonium ion or similar intermediate according to the mechanism of eq 8,



(8)

the ratio of the rate constants for the reaction of this intermediate with the anion of the leaving group, k_{RY^-}, and with the protonated leaving group, k_{RYH}, is given by log (k_{RY^-}/k_{RYH}) = ΔpH, where ΔpH (Figure 1) is the difference between the pK of the leaving group and the pH at which the rates of the pH-independent and acid-catalyzed breakdown of the starting material are equal; i.e., $k_{H_2O} = k_H[H^+]$. When ΔpH = 0 and $k_{RY^-} = k_{RYH}$, the reactions of RY$^-$ and RYH with >C=XR′$^+$ are presumably diffusion controlled. This is shown by the diagonal dashed line in Figure 1. The rate-determining steps of the reverse, breakdown reactions, k_{H_2O} and k_H, then represent the diffusion-controlled separation of RY$^-$ and RYH, respectively, from >C=XR′$^+$. Since diffusion is not catalyzed by buffers such reactions will not be subject to general acid catalysis. Proton transfer is complete before the rate-determining step and they will exhibit only specific acid catalysis.

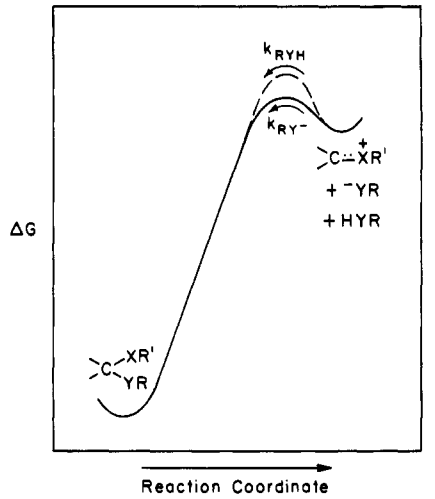


Figure 7. Gibbs free energy diagram based on pseudo-first-order rate constants at pH = pK_{RXH} for the acid-catalyzed and pH-independent cleavage of an acetal to form an intermediate carbonium ion. The solid line is for equal rate constants in both directions, with ΔpH = 0 (Figure 1). The dashed line is for the acid-catalyzed breakdown when ΔpH = log (k_{RX^-}/k_{RXH}) > 0.

The basis for this relationship may be seen qualitatively in the Gibbs free energy-reaction coordinate diagram of Figure 7, which is based on pseudo-first-order rate constants for the reaction at pH = pK_{lg}. At this pH, [RYH] = [RY$^-$] and, if the pseudo-first-order rate constants for the reaction through the two pathways are equal in both directions, the reactions may be described by the same solid line in the figure. If $k_{RHY} < k_{RY^-}$ (i.e., the reverse reaction is not diffusion controlled), the free energy of activation for the addition and expulsion of RYH will be higher in both directions, as shown by the upper, dashed line in Figure 7. The amount of this difference corresponds to the amount of acid that must be added to make the two rates equal, i.e., to ΔpH.

The relationship is shown quantitatively as follows. From eq 8

$$K_a = (k_{RYH}/k_H)(k_{H_2O}/k_{RY^-})$$

$$pK_a = \log (k_{RY^-}/k_{RYH}) + \log (k_H/k_{H_2O}) \quad (9)$$

When $\log (k_H[H^+]) = \log k_{H_2O}$ at pH_1

$$\log (k_H/k_{H_2O}) = pH_1 \quad (10)$$

Subtracting eq 10 from eq 9

$$pK_a - pH_1 = \log (k_{RY^-}/k_{RYH}) \quad (11)$$

Since the rate of attack of RY$^-$ will always be at least as large as that for RYH, so that $\log (k_{RY^-}/k_{RYH}) = \Delta pH \geq 0$, the line for the proton-catalyzed reaction must always intersect the line for the water reaction at or below the pK of the leaving group (Figure 1) for any reaction that proceeds according to the mechanism of eq 8. Any such reaction *must*, therefore,

proceed through a pH-independent pathway to a significant extent at or below the pK of the leaving group.

The rate constants for the hydrolysis of benzaldehyde O-ethyl S-phenyl acetal, shown by the solid lines in Figure 1, give $\Delta pH = 1.6 = \log (k_{RS^-}/k_{RSH})$ so that $k_{RS^-}/k_{RSH} = 40$. This very low selectivity suggests that, if the reaction proceeds through an oxocarbonium ion intermediate according to eq 8, the back-reaction of PhS^- with this intermediate is diffusion controlled. If this back-reaction is diffusion controlled, microscopic reversibility requires that the rate-determining step of the cleavage reaction is the diffusional separation of PhS^- from the ion pair intermediate with the rate constant k_d in eq 12.

$$\mathrm{ArCH(OEt)SR} \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} [\mathrm{ArCH{=}\overset{+}{O}Et}\ \ {}^-\mathrm{SR}] \xrightarrow{k_d} \mathrm{ArCH{=}\overset{+}{O}Et} + {}^-\mathrm{SR} \quad (12)$$

$$\downarrow \text{fast}$$

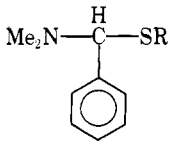
products

The following evidence is also consistent with the hypothesis that the rate-determining step of the pH-independent hydrolysis reaction is the diffusion-controlled separation of the ion pair.

(1) The values of $\Delta pH = \log (k_{RS^-}/k_{RSH})$ are ≥ 2.9 and ≥ 5.9 for the p-methoxybenzaldehyde and p-dimethylaminobenzaldehyde O-ethyl S-phenyl acetals, respectively.[53] These large rate ratios are consistent with values of k_{RSH} that decrease sharply for attack on the resonance-stabilized oxocarbonium ions and values of k_{RS^-} that are diffusion controlled, so that they are the same for all compounds. If the rate-determining step of both reactions involved C–S bond formation, the ratio k_{RS^-}/k_{RSH} would be expected to remain constant or show a relatively small change, as has been observed for the reactions of water and amines with the oxocarbonium ions formed from a series of ortho esters.[54] The large changes in the rate-constant ratio show that the reaction with RSH is highly selective and are inconsistent with the hypothesis that the low value of $k_{RS^-}/k_{RSH} = 40$ for the benzaldehyde acetal reaction is simply a consequence of a low selectivity toward nucleophiles.

A high selectivity is also required by the large value of $\Delta pH = \log (k_{RS^-}/k_{RSH}) = 3.0$ for the hydrolysis of benzaldehyde O-methyl S-p-nitrophenyl acetal,[3] compared with $\Delta pH = 1.6$ for the O-ethyl S-phenyl acetal. This difference means that the value of k_{RSH} is some 25 times larger for PhSH than for p-NO_2PhSH if k_{RS^-} is diffusion controlled for both reactions (if k_{RS^-} is not diffusion controlled the difference is larger). The large dependence of k_{RSH} on the basicity of the nucleophile ($\beta_{nuc} = 0.7$ based on these two compounds) is approximately what is expected for the transition state **3** and the observed β_{lg} value of 0.6 for the acid-catalyzed hydrolysis reaction (Table III).

(2) The rate constants k_{H_2O} for the pH-independent hydrolysis of three p-dimethylaminobenzaldehyde O,S-acetals (Table II) are directly proportional to the acid dissociation constants of the leaving thiols, corresponding to a value of $\beta_{lg} = -1.0$. This is consistent with complete cleavage of the C–S bond in the transition state and is the result that is expected if the rate-determining step is the diffusion-controlled separation of the thiol anion from the oxocarbonium ion; i.e. $k_{-b} > k_d$ (eq 12). It has also been suggested that the large negative values of $\beta_{lg} = -1.1$ and -1.2 for the pH-independent hydrolysis of 2-aryloxytetrahydrofurans and 2-aryloxytetrahydropyrans, respectively, may represent rate-determining separation of an ion pair.[24,55] In contrast, the value of β_{lg} for the rate-determining expulsion of thiol anions from **7**, to give a much more stable iminium ion intermediate,[56] is -0.57.



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(3) The large increases in rate constant with electron-donating substituents in the benzaldehyde ring are consistent with the formation of the oxocarbonium ion in a rapid equilibrium step followed by rate-determining diffusional separation of PhS^-. The rate increase for the p-methoxybenzaldehyde compound (in 20% dioxane) compared to the unsubstituted compound (in water) is 38-fold, which is close to the ratio of 77 for the equilibrium constants for formation of the corresponding oxocarbonium ions from acetophenone ketals in water;[24] if a correction of 8.4-fold is made for the effect of dioxane on the rate (based on the rate constants of the benzaldehyde compound in water and 20% dioxane[57]), the rate-constant ratio is larger than this equilibrium-constant ratio. The rate-constant ratio for the p-dimethylaminobenzaldehyde compound of 10^7 (Table II) is also larger than the estimated equilibrium-constant ratio of $10^{4.5}$ for the formation of the corresponding acetophenone oxocarbonium ions, based on the Hammett–Yukawa correlation for this equilibrium.[24]

(4) There is evidence that the reactions of sulfite anion and hydroxylamine with oxocarbonium ions derived from acetophenone ketals are diffusion controlled.[24] Since oxocarbonium ions derived from benzaldehyde acetals are expected to be less stable than those derived from acetophenone ketals and thiol anions are strong nucleophiles, it would be expected that k_{RS^-} is diffusion controlled and, therefore, that k_d represents diffusion-controlled separation in the opposite direction.

The value of the equilibrium constant for the formation of the ion pair intermediate of eq 12, $K_b = k_b/k_{-b}$, is given by $K_b = k_{HOH}/k_d$ if k_d is rate determining. If k_d is on the order of 10^{10} s^{-1}, the values of K_b are then on the order of 2×10^{-16}, 6×10^{-15}, and 4×10^{-9} for the unsubstituted, p-methoxy-, and p-dimethylaminobenzaldehyde O-ethyl S-phenyl acetals, respectively.

(5) The secondary isotope effect for deuterium substitution at the carbonyl carbon atom is $k_H/k_D = 1.12 \pm 0.01$ for the pH-independent hydrolysis of benzaldehyde O-ethyl S-phenyl acetal.[57] This isotope effect is consistent with complete C–S cleavage and formation of an oxocarbonium ion in the transition state. In contrast, the isotope effect of $k_H/k_D = 1.038 \pm 0.008$ for the acid-catalyzed reaction indicates that the C–S bond is only partly cleaved in the transition state.[57]

If the reaction does not proceed through a free oxocarbonium ion according to the mechanism of eq 8 and 12, the data require a transition state for the pH-independent reaction in which bond breaking to the leaving thiol anion is essentially complete. The data are not inconsistent with a mechanism that involves rate-determining attack of water on the $>C{=}OR^+ \cdot RS^-$ ion pair through a "preassociation" mechanism.[24]

The small ratio k_{RS^-}/k_{RSH} for PhSH suggests that the reactions of the more basic aliphatic RSH and ROH with the benzaldehyde oxocarbonium ion are diffusion controlled. If this is the case the reverse, cleavage reactions will represent diffusion-controlled separation of these leaving groups from the oxocarbonium ion or a preassociation mechanism.[24] The value of $\beta_{lg} \sim 0$ for RSH that is expected for this situation provides another possible reason for the preferential expulsion of ROH over RSH from benzaldehyde O,S-acetals.

The smallest value of ΔpH of which we are aware is ~ 0.8 for the hydrolysis of **8**,[58] which corresponds to a ratio $k_{RY^-}/k_{RYH} \sim 6$. This is consistent with a mechanism involving

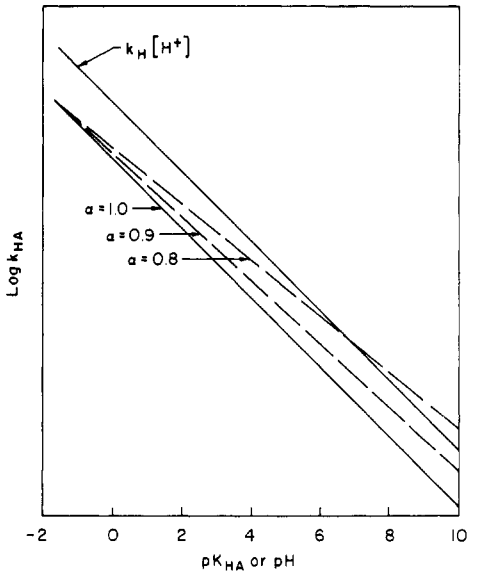
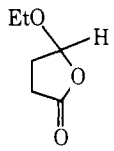


Figure 8. Plot of log ($k_H[H^+]$) against pH (upper line) superimposed on a generalized Brønsted plot (lower lines).



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rate-determining rotation of the leaving group away from the oxocarbonium ion or rate-determining attack of water on the oxocarbonium ion for both the pH-independent and acid-catalyzed hydrolysis reactions, if it is assumed that the electrostatic interaction of the carboxylate group with the oxocarbonium ion can account for a factor of 6. An oxocarbonium ion that was generated from an enol ether is known to be trapped by reaction with an adjacent carboxylate ion or carboxylic acid group faster than it reacts with water.[59]

Acid Catalysis. We have confirmed the observation of Fife and Anderson[3] that the hydrolysis of benzaldehyde *O*-ethyl *S*-phenyl acetal is not subject to detectable general acid catalysis. This result is of interest because there is a tendency for acid-catalyzed reactions to exhibit significant general acid catalysis with progressively lower values of α as the leaving group becomes less basic. For example, 2-(4-nitrophenoxy)-tetrahydropyran[13] and benzaldehyde methyl *m*-nitrophenyl acetal[14] exhibit readily detectable general acid catalysis with $\alpha = 0.5$. We would like to know why general acid catalysis at the sulfur atom is not significant for the expulsion of the weakly basic SPh group and has not been observed for other reactions involving the attack or expulsion of thiols, to the best of our knowledge.

The failure to observe general acid catalysis does not, of course, prove that the reaction is specific acid catalyzed or A1, but only serves to set a limit on possible values of α for the reaction. For this reason it is desirable to report limits for α, α_{min}, for reactions in which general acid catalysis is not detected. The value of α_{min} is given by

$$\alpha_{min} = \frac{-\log L + pH + \log [HA]}{1.74 + pK_{HA}} \qquad (13)$$

in which L is the limit for the fractional rate increase from general acid catalysis by HA above the background proton-catalyzed reaction that could definitely be detected; i.e., $k_{HA}[HA] \leqslant Lk_H[H^+]$. The relationship between the background proton-catalyzed rate and Brønsted plots for general acid catalysis with $\alpha = 0.8$ and 0.9 is shown in Figure 8. It follows from eq 13 and Figure 8 that in order to set the largest upper limit on α_{min} it is desirable to search for general acid catalysis at the highest pH that is above the pK of the weakest acid that is practicable to examine. In order to obtain a doubling of the observed rate with 1 M acid at pH = pK_{HA} it is necessary to examine an acid of $pK_{HA} = 6.8$ if $\alpha = 0.8$; for $\alpha = 0.9$ an acid of $pK_{HA} = 15.5$ would be required and only a water reaction could be observed.[60] Limits to the choice of pH and pK_{HA} are set by the incursion of a pH-independent "water" reaction, which will swamp out catalysis by a weak acid when it is the predominant background reaction, and by the slow rate of the reaction at high pH. Larger values of α or α_{min} may be determined experimentally if the rate constant for the proton falls below the Brønsted line that is followed by other acids.

The absence of a detectable increase in the rate of hydrolysis of benzaldehyde *O*-ethyl *S*-phenyl acetal in 2 M acetic acid buffers, 50% ionized, gives a value of $\alpha_{min} = 0.84$ if it is assumed that a 30% rate increase would have been detected ($L = 0.3$); α_{min} is 0.92 for $L = 0.1$. Acetic acid is a relatively weak acid that can still provide a significant concentration of free acid at the optimal pH for the experiment, close to the point of intersection of the lines for the proton-catalyzed and water reactions of the pH–rate profile (Figure 1). Fife and Anderson's data with formic acid buffers at pH 3.4 in 20% dioxane[3] give a value of $\alpha_{min} = 0.70$ for $L = 0.3$; however, there is some uncertainty in the determination of values or limits for catalytic constants in mixed aqueous–organic solvents.[61]

The absence of detectable general acid catalysis and the large value of α_{min} for this reaction are surprising for two reasons, in addition to the experimental precedent of $\alpha = 0.5$ for general acid catalysis of the expulsion of weakly basic oxygen leaving groups. First, the large positive value of $\beta_{lg} = 0.57$ ($\rho = -1.0$) for the proton-catalyzed expulsion of SAr,[3] compared with $\beta_{lg} \sim 0.2$ ($\rho = -0.60$) for expulsion of OAr from benzaldehyde acetals,[14] suggests that there is a large positive charge on the protonated, weakly basic SAr leaving group. It might be expected that hydrogen bonding of a buffer base to this proton would stabilize the transition state and thereby give rise to significant general acid catalysis. Second, it has been argued that general acid catalysis should become significant when the attack of the conjugate base of the leaving group on an oxocarbonium ion in the reverse reaction is diffusion controlled, because hydrogen bonding to a buffer acid will increase the total concentration of this base at equilibrium.[24,62] Evidence is described above that the attack of PhS^- on benzaldehyde oxocarbonium ions is diffusion controlled.

The following explanations may be considered to account for the absence of detectable general acid catalysis.

(1) The rapid rate of the "water" reaction and the small value of ΔpH mean that there is only a small range of pH and pK over which buffer catalysis can be examined;[62] i.e., weak acid catalysts, with which general acid catalysis is most likely to be detectable, cannot be studied. Nevertheless, the large value of $\alpha_{min} = 0.84$ means that catalysis would easily have been detected if it occurred to a comparable extent as with oxygen acetals.

(2) General acid catalysis could not be detected if the reaction of RSH with the oxocarbonium ion were diffusion controlled, as noted above. The value of $k_1/k_2 = 40$ shows that there is a low selectivity in the back-reaction for the benzaldehyde acetal and that k_2 is probably close to diffusion controlled, but the structure–reactivity parameters, $\rho = -1.4$, $\beta_{lg} = 0.57$, and $\beta_{rg} = 0.62$, and the secondary deuterium isotope effect[57] of $k_H/k_D = 1.038 \pm 0.008$ show that the reaction of PhSH is not diffusion controlled.

(3) The structure of the transition state might be such that significant stabilization by general acid catalysis would not be

expected. However the small value of $\rho = -1.4$ and the large β_{lg} of 0.57 suggest that there is relatively little C-S bond cleavage (ρ for expulsion of the OPh group is -2.26)[14] and a strongly acidic protonated leaving group in the transition state, as noted above, so that the opportunity for stabilization by hydrogen bonding to a buffer base or by partial proton transfer should be even larger than for oxygen acetals. General acid catalysis would also serve to avoid the formation of the highly unstable S-protonated *O,S*-acetal as a reaction intermediate.

(4) Fife and Anderson have suggested that general acid catalysis does not occur because cleavage of a C-S bond is more difficult than cleavage of a C-O bond and general acid catalysis occurs when bond cleavage to form a relatively stable carbonium ion is facile.[3] An increased stability of the bond to the leaving group will lower the energy of the top relative to the bottom of the reaction coordinate-energy diagram for a reaction of this kind, such as that shown in Figure 9, and thereby tend to shift the transition state to the left by motions perpendicular and parallel to a diagonal reaction coordinate.[50] The value of α for general acid catalysis will therefore increase and eventually reach 1.0. However, the low basicity of sulfur means that the energy of the protonated intermediate in the upper left corner is raised relative to that of the anionic intermediate in the lower right corner of the diagram, which will tend to shift the transition state downhill toward the lower right corner (perpendicular to the reaction coordinate) with a decrease in α. Since the decrease in basicity toward the proton of 10^4 is larger than the increase in basicity toward carbon of 10^3, it is unlikely that there will be an increase in α from the latter effect that is large enough to make general acid catalysis undetectable. Furthermore, it has been noted above that the rate constants for the expulsion of *protonated* thiols and alcohols are similar, so that cleavage of the C-S bond does not appear to be significantly more difficult than cleavage of the C-O bond once protonation has occurred (in the absence of protonation RS^- is generally expelled faster than RO^- for constant R, as noted above).

(5) It remains possible that the reaction is general acid catalyzed but that α is larger than 0.84, too large for experimental detection. The solvent deuterium isotope effect[3] of $k_D/k_H = 1.51$ is smaller than the value close to 3.0 that is ordinarily expected for specific acid catalysis of oxygen expulsion.[25,63] The low isotope effect could represent general acid catalysis but is also consistent with complete protonation of sulfur in the transition state if protonation of the substrate has the same low isotope effect that is observed for reactions of RSH, which is attributed to low stretching and bending frequencies of the S-H bond.[27,64] It is probable, but not proved, that the S-protonated acetal also has such low frequencies.

(6) The most probable explanation is that hydrogen bonding involving the sulfur atom in the transition state is weak, so that there is little catalytic advantage from general acid catalysis. The transition state for general acid catalysis is stabilized by hydrogen bonding if the proton is at either a potential maximum or minimum, and if this hydrogen bonding is unfavorable the transition state will be of correspondingly higher energy. Relatively unfavorable hydrogen bonding in the transition state is the probable explanation for the slow rates of proton transfer involving thiols.[65] Since proton transfer to or from sulfur is required for general acid-base catalysis, this slow rate of proton transfer provides direct experimental evidence that such catalysis is likely to be unfavorable. The general-acid-catalyzed reaction represents general base catalysis of PhSH attack in the reverse direction and hydrogen bonding to thiols is known to be weak.[66] The small difference between the pK of the thiol and the acetate catalyst provides still another reason that a strong hydrogen bond in the transition state is not expected.

In summary, the data support the transition states for

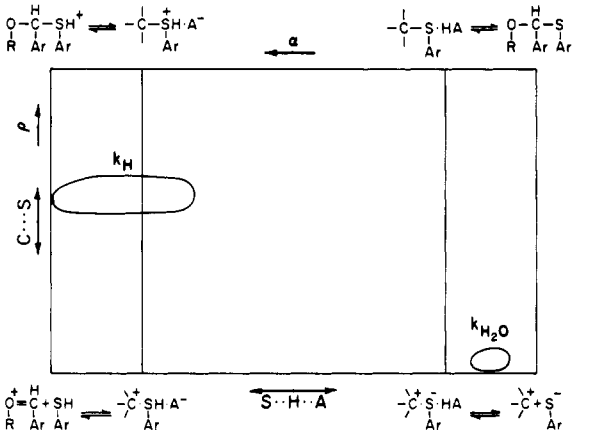

Figure 9. Reaction coordinate-energy diagram for the cleavage of benzaldehyde *O,S*-acetals with proton transfer on the horizontal axis and C-S bond cleavage on the vertical axis. The positions of the transition states for the acid-catalyzed and water reactions are indicated by circles. The energy contour lines are not shown.

cleavage of benzaldehyde *O*-alkyl *S*-aryl acetals that are shown in the reaction coordinate-energy diagram of Figure 9. The transition state for the acid-catalyzed expulsion of SAr with the rate constant k_H is in the upper left region of the diagram, with more proton transfer and less breaking of the bond to the leaving group compared with that for the expulsion of OAr. If there is any general acid-base catalysis it must involve weak hydrogen bonding by the buffer base to a protonated transition state ($\alpha_{min} = 0.84$). The transition state for the pH-independent, water reaction is in the lower right corner, and probably represents a transport step, the separation of ArS^- from the oxocarbonium ion (HA = HOH). In the reverse direction this reaction involves diffusion-controlled combination of ArS^- with the oxocarbonium ion, followed by rapid C-S bond formation in an uncatalyzed step. The transition state for the acid-catalyzed hydrolysis of benzaldehyde *O,S*-acetals with C-O cleavage does not appear to differ greatly from that for the corresponding *O,O*-acetals.

References and Notes

(1) Supported by grants from the National Science Foundation (BG-31740) and the National Institutes of Health (GM20888). J. L. J.: Department of Chemistry, California State University, Long Beach, Calif. 90840.
(2) Clayton, C. J.; Hughes, N. A.; Saeed, S. A. *J. Chem. Soc. C* **1967,** 644.
(3) Fife, T. H.; Anderson, E. *J. Am. Chem. Soc.* **1970,** *92,* 5464.
(4) Guinot, F.; Lamaty, G.; Munsch, H. *Bull. Soc. Chim. Fr.* **1971,** 541.
(5) Guinot, F.; Lamaty, G. *Tetrahedron Lett.* **1972,** 2569.
(6) De, N. C.; Fedor, L. R. *J. Am. Chem. Soc.* **1968,** *90,* 7266.
(7) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1969,** *91,* 4217.
(8) Pihlaja, K. *J. Am. Chem. Soc.* **1972,** *94,* 3330. It has also been suggested that the sharp curvature in the plots against mole fraction deuterium in D_2O-H_2O mixtures is caused by the cleavage of both the C-S and C-O bonds, with different solvent isotope effects (Albery, W. J. In "Proton Transfer Reactions", Caldin, E. F.; Gold, V., Ed.; Wiley: New York, N.Y., 1975; p 293).
(9) Fedor, L. R.; Murty, B. S. R. *J. Am. Chem. Soc.* **1973,** *95,* 8407.
(10) Pihlaja, K.; Jokila, J.; Heinonen, U. *Finn. Chem. Lett.* **1974,** 275.
(11) Fife, T. H., *Acc. Chem. Res.* **1972,** *5,* 264.
(12) Anderson, E.; Capon, B. *J. Chem. Soc. B* **1969,** 1033.
(13) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970,** *92,* 1681.
(14) Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* **1975,** 1113.
(15) Rabjohn, N., Ed. "Organic Syntheses", Collect. Vol. IV; Wiley: New York, N.Y., 1963; p 21.
(16) Horning, E. C., Ed. "Organic Syntheses," Collect. Vol. III; Wiley: New York, N.Y., 1955; p 644.
(17) Perlmutter-Hayman, B.; Wolff, M. A. *Isr. J. Chem.* **1965,** *3,* 155.
(18) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969,** *91,* 6353.
(19) Pollack, R. M.; Kayser, R. H.; Damewood, J. R., Jr. *J. Am. Chem. Soc.* **1977,** *99,* 8232.
(20) Jensen, J. L.; Gardner, M. P. *J. Phys. Chem.* **1973,** *77,* 1557.
(21) Arnett, E. M.; Mach, G. W. *J. Am. Chem. Soc.* **1966,** *88,* 1177.
(22) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960,** *82,* 795.
(23) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1966,** *39,* 2274. Hine, J. "Structural Effects on Equilibria in Organic Chemistry", Wiley: New York, N.Y., 1975; pp 72-78.
(24) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 8238.

(25) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974,** *74,* 581.
(26) However, 1-thioglycosides, 5-thioxylopyranosides, and 5-thioribopyranosides undergo hydrolysis at similar or faster rates compared with the corresponding oxygen compounds (Capon, B. *Chem. Rev.* **1969,** *69,* 407). It is not known to what extent these differences reflect effects of ring conformation, reversal of ring opening prior to hydrolysis, or other factors.
(27) Lienhard, G. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966,** *88,* 3982.
(28) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968,** *90,* 6154.
(29) Bonvicini, P.; Levi, A.; Lucchini, V.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2* **1972,** 2267.
(30) This difference in basicity is also reflected in the faster rates of acid-catalyzed proton transfer and exchange of alcohols than of thiols in nonaqueous media by factors of 10^4–10^6 (Delpuech, J. J.; Nicole, D. *J. Chem. Soc., Perkin Trans. 2* **1974,** 1025.
(31) Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973,** *95,* 5960.
(32) Yaggi, N. F.; Douglas, K. T. *J. Am. Chem. Soc.* **1977,** *99,* 4844.
(33) The rate constants for expulsion of EtS^- and EtO^- from $^-OCH(CH_3)XEt$ favor EtS^- expulsion by a factor of 150. This is based on $k = 5.8 \times 10^6$ s^{-1} for EtS^- (Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 7931) and $k = 3.8 \times 10^4$ s^{-1} for EtO^- expulsion. The latter value was obtained from the rate constant of 3.2×10^4 s^{-1} for the breakdown of acetaldehyde hydrate anion, from $k_{OH^-} = 8 \times 10^4$ M^{-1} s^{-1} (Bell, R. P.; Rand, M. H.; Wynne-Jones, K. M. A. *Trans. Faraday Soc.* **1956,** *52,* 1093) and an estimated pK of 13.6, and from a factor of 1.2 favoring EtO^- over HO^- expulsion from the corresponding formaldehyde compounds.[34] Based on a value of $\beta_{lg} = -1.1$ for the hydroxide ion catalyzed breakdown of formaldehyde hemiacetals and a fall-off factor of 0.2 for the pK_a values of $ROCH_2OH$ with changing pK_{ROH},[34] the rate constant for the expulsion of an alcohol of p$K = 10.35$ from $^-OCH(CH_3)OR$ is expected to be 4.7×10^9 s^{-1}. Thus, for equal pK of the leaving groups of RO^- expulsion is favored over RS^- expulsion by a factor of ~800.
(34) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978,** *100,* 5444.
(35) Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2* **1976,** 901.
(36) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1975,** 940. Sinnott, M. L.; Whiting, M. C. *J. Chem. Soc. B* **1971,** 965.
(37) McClelland, R. A. Private communication.
(38) McClelland, R. A. *Can. J. Chem.* **1977,** *55,* 548. Washtien, W.; Abeles, R. H. *Biochemistry* **1977,** *16,* 2485. Walter, W.; Meese, C. D. *Chem. Ber.* **1977,** 2463–2479.
(39) McClelland, R. A. *Can. J. Chem.* **1975,** *53,* 2772.
(40) Bernardi, F.; Csizmadia, I. G.; Schlegel, H. B.; Wolfe, S. *Can. J. Chem.* **1975,** *53,* 1144. Bernardi, F.; Csizmadia, I. G.; Epiotis, N. D. *Tetrahedron* **1975,** *31,* 3085.
(41) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 451.
(42) Hershfield, R.; Yeager, M. J.; Schmir, G. L. *J. Org. Chem.* **1975,** *40,* 2940. Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1973,** *95,* 3994.
(43) De Maria, P.; Fini, A.; Hall, F. M. *J. Chem. Soc., Perkin Trans. 2* **1975,** 1540.
(44) Dunlap, R. B.; Ghanim, G. A.; Cordes, E. H. *J. Phys. Chem.* **1969,** *73,* 1898.
(45) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 6970.
(46) Funderburk, L. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1978,** *100,* 6708.
(47) Winstein, S.; Morse, B. K ; Grunwald, E.; Schreiber, K. C.; Corse, J. *J. Am. Chem. Soc.* **1952,** *74,* 1113.
(48) Louden, G. M.; Berke, C. *J. Am. Chem. Soc.* **1974,** *96,* 4508.
(49) Thornton, E. R. *J. Am. Chem. Soc.* **1967,** *89,* 2915.
(50) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977,** *99,* 7948.
(51) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964,** *2,* 323. Fox. J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974,** *96,* 1436.
(52) Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973,** *95,* 5960.
(53) These rate constant ratios are lower limits because the acid-catalyzed reactions of these compounds in water probably occur with C–O as well as C–S cleavage (Table I), so that the rate constants k_H for C–S cleavage are smaller than the observed values of k_H.
(54) Koehler, K.; Cordes, E. H. *J. Am. Chem. Soc.* **1970,** *92,* 1576.
(55) Lönnberg, H.; Pohjola, V. *Acta Chem. Scand., Ser. A* **1976,** *30,* 669. Craze, G-A; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978,** 354.
(56) Schubert, W. M.; Motoyama, Y. *J. Am. Chem. Soc.* **1965,** *87,* 5507.
(57) Ferraz, J. P.; Cordes, E. H. *J. Am. Chem. Soc.,* following paper in this issue.
(58) Fife, T. H. *J. Am. Chem. Soc.* **1965,** *87,* 271. The value of ΔpH was calculated assuming that the pK_a of the carboxylic acid group of the oxocarbonium ion is 4.23, the same as that of $^+H_3NCH_2CH_2CH_2COOH$ (Jencks, W. P.; Regenstein, J. "Handbook of Biochemistry", Vol. 1; 3rd ed.; Fasman, G. D., Ed.; Chemical Rubber Publishing Co.: Cleveland, Ohio, 1976; p 305); a lower pK from the strong electron-withdrawing effect of the oxocarbonium ion would give a smaller value of ΔpH and k_{RY^-}/k_{RYH}.
(59) Louden, G. M.; Smith, C. K.; Zimmerman, S. E. *J. Am. Chem. Soc.* **1974,** *96,* 465.
(60) The reason that the line for $k_H[H^+]$ falls 1.7 units above the Brønsted line for $\alpha = 1.0$ in Figure 8 is essentially that the total concentration of an H_3O^+–H_2O "buffer" is 55 times larger than that of an ordinary buffer at a standard state of 1 M.
(61) Salomaa, P.; Kankaanperä, A.; Lahti, M. *J. Am. Chem. Soc.* **1971,** *93,* 2084.
(62) Jencks, W. P. *Acc. Chem. Res.* **1976,** *9,* 425.
(63) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972,** *9,* 275.
(64) Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971,** *93,* 4433.
(65) Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968,** *7,* 818.
(66) Vinogradov, S. N.; Linnell, R. H. "Hydrogen Bonding", Van Nostrand-Reinhold: Princeton, N.J., 1971; p 122. Kollman, P.; McKelvey, J.; Johansson A.; Rothenberg, S. *J. Am. Chem. Soc.* **1975,** *97,* 955.

Kinetic α Secondary Deuterium Isotope Effects for *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal Hydrolysis[1]

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Abstract: The rate of hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal at 25 °C in 20% dioxane–80% water is independent of pH over the range pH 6–12; $k_{obsd} = 1.9 \times 10^{-7}$ s^{-1}. Under more acidic conditions, the rate increases linearly with the activity of the hydrated proton; $k_2 = 2.95 \times 10^{-2}$ M^{-1} s^{-1}. The kinetic α secondary deuterium isotope effect for acid-catalyzed hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal, measured at 25 °C in 20% aqueous dioxane containing 0.05 M HCl, is $k_H/k_D = 1.038 \pm 0.008$, a value consistent with a transition state in which the C–S bond is stretched rather little. In contrast, the corresponding isotope effect for the pH-independent hydrolysis of this substrate, measured at 42.5 °C in 20% dioxane, is 1.13 ± 0.02, a value consistent with complete C–S bond cleavage in the transition state and rate-determining diffusion apart of the ion-pair formed as the initial intermediate, in accord with the suggestion of Jensen and Jencks.

The hydrolysis of *O*-alkyl *S*-phenyl benzaldehyde acetals occurs with acid catalysis[3,4] as does that for the structurally related 2-phenyl-1,3-oxathiolanes.[5,6] For the former compounds at least, acidic hydrolysis is known to involve initial C–S bond cleavage followed by C–O bond cleavage in a subsequent step.[3,4] Structure–reactivity correlations, the entropy of activation, and a solvent deuterium isotope effect are all consistent with an A-1 mechanism. In addition, the hydrolysis of *O*-methyl-*S*-2,4-dinitrophenylbenzaldehyde acetal occurs with a pH-independent reaction, thought to reflect an unimolecular decomposition of this substrate to form the thiophenoxide anion and the oxocarbonium ion.[3]

Both to better understand the mechanism of hydrolysis of *O*-alkyl *S*-phenyl acetals and its relationship to those determined in some detail for hydrolysis of simple acetals,[7] it is desirable to examine these reactions more thoroughly. Herein, we report kinetic α deuterium isotope effects for hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal, both for the acid-cat-

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