

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

For the nonlabile +III transition metal ions,<sup>7</sup> 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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## Hydrolysis of Benzaldehyde *O,S*-Acetals<sup>1</sup>

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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  $\alpha_{\text{min}} = 0.84$  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  $k_{\text{RS}}/k_{\text{RSH}} = 40$  for the attack of  $\text{PhS}^-$  and  $\text{PhSH}$  on an intermediate oxocarbenium 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  $\text{RS}^-$  from the oxocarbenium 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.<sup>2-5</sup> 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.<sup>3,6-10</sup> 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

expulsion.<sup>3,11-14</sup> 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<sub>2</sub>O<sub>5</sub> or refluxed over CaH<sub>2</sub> and then distilled. Methanol, 2-chloroethanol, and propargyl alcohol were stirred three times over NaBH<sub>4</sub> for 10 min and distilled. 2,2,2-Trifluoroethanol was distilled from NaHCO<sub>3</sub> and CaSO<sub>4</sub>. Benzenethiol, ethanethiol, methyl mercaptoacetate, and dioxane (which was first refluxed for 5 h over LiAlH<sub>4</sub>) 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.<sup>3</sup> 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<sub>2</sub>O or 90% EtOH/H<sub>2</sub>O 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<sup>-3</sup> 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<sub>3</sub>CN. 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<sup>-3</sup>–10<sup>-4</sup> 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.<sup>15</sup> The higher boiling 2-chloroethanol and propargyl alcohol were dissolved in a benzene solution of aldehyde containing a catalytic amount of *p*-toluenesulfonic acid;<sup>16</sup> 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<sup>17</sup> 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.<sup>18</sup> Thiosemicarbazide concentrations were used that were shown to give thiosemicarbazone from the aldehyde product with rate constants at least ten times larger than  $k_{\text{obsd}}$  for acetal hydrolysis under the conditions of kinetic experiments. Reactions typically were monitored for 3 half-lives of reaction time and  $k_{\text{obsd}}$  values were calculated from plots of  $\log(A_{\infty} - A)$  against time, where  $A_{\infty}$  is the absorbance after 8–10 half-lives of reaction. Second-order rate constants,  $k_{\text{H}}$ , were calculated from the measured pseudo-first-order rate constants,  $k_{\text{obsd}}$ , by dividing  $k_{\text{obsd}}$  by  $\text{antilog}(-\text{pH})$ ;  $k_{\text{obsd}}$  was determined at several different pH values spanning 1–2 pH units. For

example,  $k_{\text{obsd}} = 0.106, 1.17 \times 10^{-2},$  and  $1.20 \times 10^{-3} \text{ s}^{-1}$  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  $\mu = 1.0$  (KCl) and 25 °C, giving  $k_{\text{H}} = 1.25 \pm 0.05 \text{ M}^{-1} \text{ s}^{-1}$ . 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.<sup>19</sup>

**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<sub>2</sub>O (10 mL of H<sub>2</sub>O 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  $4.5 \times 10^{-4} \text{ s}^{-1}$  and that for thiosemicarbazone formation from benzaldehyde is  $2.5 \times 10^{-2} \text{ s}^{-1}$  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<sub>3</sub> singlet would have been detected at  $\leq 5\%$  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<sub>4</sub>Si and the OCH<sub>3</sub> sharp singlet occurs at 205 Hz. A 5% quantity of OCH<sub>3</sub> 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<sub>2</sub>CH<sub>3</sub> methylene proton multiplet is absent, and a sharp OCH<sub>3</sub> singlet is present at 3.1 ppm. In cases where partial exchange occurred, both methine singlets were observed and the OCH<sub>3</sub> 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<sup>-2</sup>–10<sup>-4</sup> M, is independent of ethanethiol concentration over the range 10<sup>-2</sup>–10<sup>-4</sup> 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<sub>3</sub>OD/D<sub>2</sub>O 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<sub>2</sub>CH<sub>3</sub> methylene proton multiplet at 2.4 ppm. At equilibrium the predominant species are diethyl mercaptal and dimethyl acetal and at this time the SCH<sub>2</sub>CH<sub>3</sub> 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

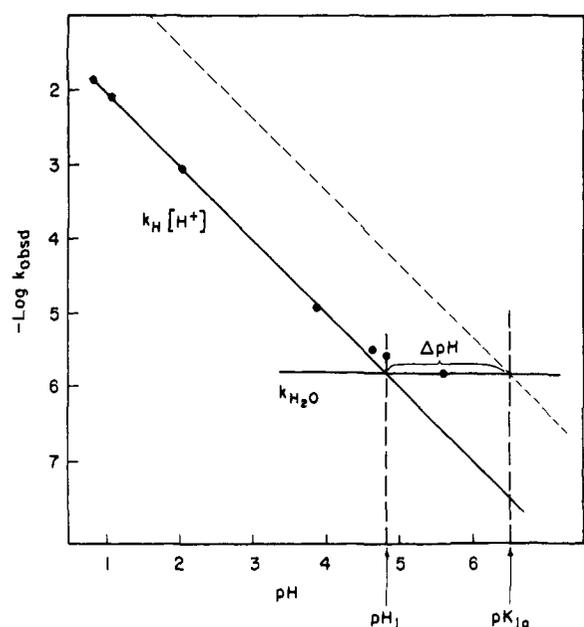
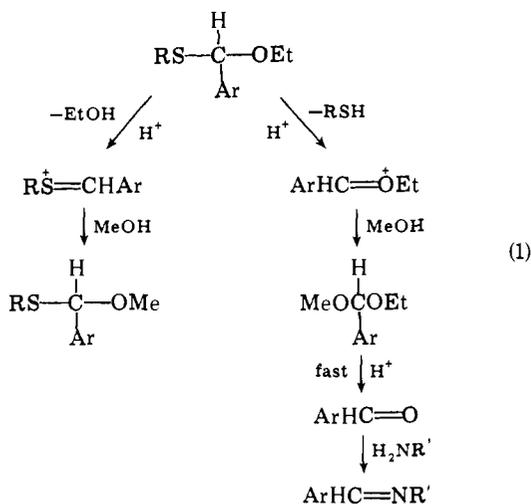


Figure 1. Dependence on pH of the rate of hydrolysis of benzaldehyde *O*-ethyl *S*-phenyl acetal at 25 °C, ionic strength 1.0. The light dashed line shows the values of  $k_{\text{obsd}}$  for acid catalysis of a reaction with  $\Delta\text{pH} = \log(k_{\text{RS}^-}/k_{\text{RSH}}) = 0$ .

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



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,<sup>3</sup> 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

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

substrate	initial bond cleavage
$\text{PhCH} \begin{array}{l} \text{OEt} \\   \\ \text{SPh} \end{array}$	C-S cleavage <sup>b</sup>
$\text{PhCH} \begin{array}{l} \text{OEt} \\   \\ \text{SEt} \end{array}$	C-O cleavage <sup>b</sup>
$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH} \begin{array}{l} \text{OEt} \\   \\ \text{SCH}_2\text{CO}_2\text{CH}_3 \end{array}$	C-O cleavage <sup>b</sup>
$\text{PhCH} \begin{array}{l} \text{OEt} \\   \\ \text{SCH}_2\text{CO}_2\text{CH}_3 \end{array}$	C-O and C-S cleavage compete <sup>c</sup>
$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH} \begin{array}{l} \text{OEt} \\   \\ \text{SPh} \end{array}$	C-O and C-S cleavage compete <sup>c</sup>

<sup>a</sup> Determined by examining the exchange of OEt for OMe occurring in the substrate prior to hydrolysis in 90% MeOH/H<sub>2</sub>O catalyzed by HCl. <sup>b</sup> ≤5% of the other mode of cleavage occurs. <sup>c</sup> After 1 half-life of hydrolysis in 90% MeOH/H<sub>2</sub>O containing HCl, 1/3-1/2 of the unhydrolyzed substrate had exchanged OEt for OMe.

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 ( $5.0 \times 10^{-3}$  and  $2.0 \times 10^{-3} \text{ s}^{-1}$ , respectively), whereas the observed rate constants for benzaldehyde *O*-ethyl *S*-ethyl acetal and the corresponding *O*-methyl acetal are identical ( $4.6 \times 10^{-3} \text{ s}^{-1}$ ). In water the respective values of  $k_{\text{H}}$  are 0.11, 0.060, 1.3, and  $1.1 \text{ M}^{-1} \text{ s}^{-1}$ . 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  $4.6 \times 10^{-3} \text{ s}^{-1}$ . 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<sub>2</sub>O 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<sub>2</sub>O; i.e., this compound undergoes no detectable C-O cleavage in a predominantly aqueous medium as well as in methanol.

**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.<sup>3</sup> 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<sup>a</sup>

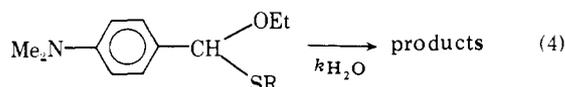
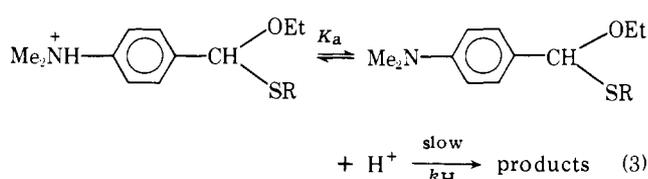
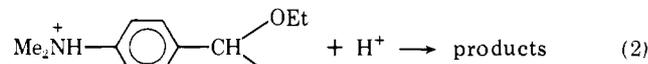
X	$k_H, M^{-1} s^{-1}$ , for SR =					$k_{H_2O}, s^{-1}$ , for SR =		
	SCH <sub>2</sub> CH <sub>3</sub>	SCH <sub>2</sub> CH <sub>2</sub> OH	SCH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	SCH <sub>2</sub> CF <sub>3</sub>	SPh	SCH <sub>2</sub> CH <sub>3</sub>	SCH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	SPh
Me <sub>2</sub> N <sup>+</sup> H	0.03 <sup>b</sup>		0.0006 <sup>b</sup>		0.012 <sup>b</sup>			
Cl					0.011 <sup>c</sup>			
H	1.3	0.36 <sup>d</sup>	0.012	0.0018	0.11			1.6 × 10 <sup>-6</sup>
CH <sub>3</sub> O	3.0 <sup>c</sup>		0.075 <sup>c</sup>		0.20 <sup>c</sup>			6 × 10 <sup>-5</sup> <sup>c</sup>
Me <sub>2</sub> N	170		8.6		150	0.003	0.45	42
pK' <sub>RSH</sub> <sup>e</sup>	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 <sub>2</sub> CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	OCH <sub>2</sub> CH <sub>2</sub> Cl	OCH <sub>2</sub> C≡CH	OCH <sub>2</sub> CF <sub>3</sub>
SCH <sub>2</sub> CH <sub>3</sub>	1.3	1.1	0.77	0.45	0.23	0.13
SPh	0.029 <sup>c</sup>	0.016 <sup>c</sup>		0.0026 <sup>c</sup>		
		0.060 <sup>a</sup>				
pK <sub>ROH</sub> <sup>f</sup>	16.0	15.5	14.8	14.3	13.5	12.4

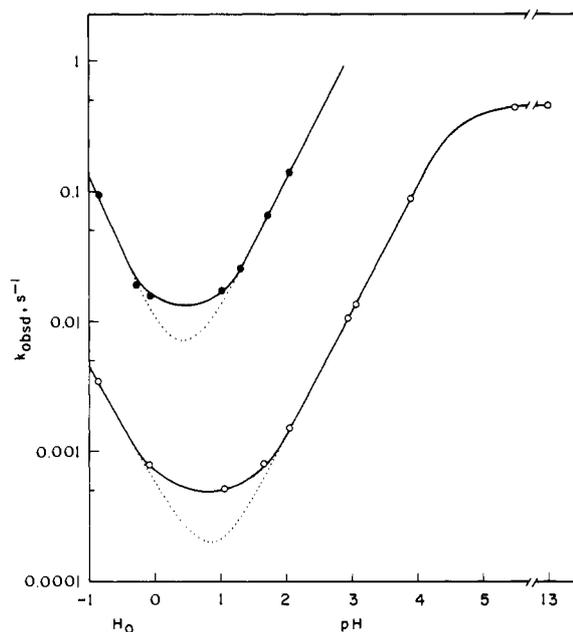
<sup>a</sup> At 25 °C, ionic strength maintained at 1.0 with potassium chloride. <sup>b</sup> Calculated from the dependence of  $k_{\text{obsd}}$  on  $H_0$  in 1–2.4 M HCl. <sup>c</sup> Solvent contains 20% dioxane. <sup>d</sup>  $k_H$  for the cyclic compound, 2-phenyl-1,3-oxathiolane, was found to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



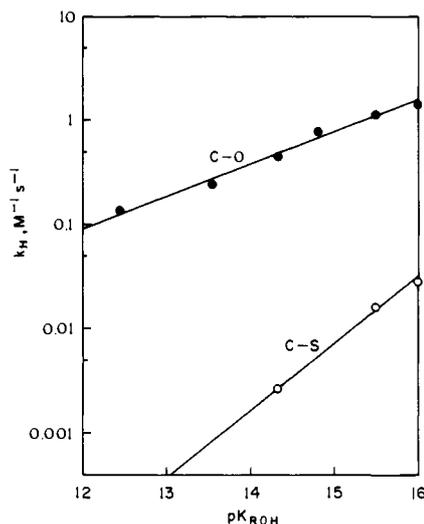
a reaction of the unprotonated substrate above pH 1 (eq 4). These pathways are conveniently designated as the two-proton, one-proton, and water reactions, respectively. The observed rate constant for the water reaction increases with increasing pH in the region in which the substrate is protonated and levels off to a pH-independent reaction at the pK<sub>a</sub> 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  $3.5 \times 10^{-5} M$  (ionic strength 1.0;  $K_a$  for *N,N*-dimethylaniline- $H^+$  is  $8 \times 10^{-6} M$  at ionic strength 0.1),<sup>20</sup> based on a limiting value of  $k_{H_2O} = 0.45 s^{-1}$  above pH 5.6,  $k_{\text{obsd}} = 1.5 \times 10^{-5} [H^+]^{-1} s^{-1}$  at pH 2–4, and the relationship  $k_{\text{obsd}} = K_a k_{H_2O} / [H^+]$  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)<sup>21</sup> 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<sub>3</sub>CN/HOH the rates of hydrolysis of the *O*-ethyl



**Figure 2.** Plot of  $\log k_{\text{obsd}}$  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] ( $k_{\text{obsd}} = 1.5$ – $4.2 \times 10^{-3} s^{-1}$ ); the two-proton process causes an increased rate at [HCl]  $\sim 1 M$ . 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  $k_{\text{obsd}}$  is inversely proportional to  $[H^+]$  in the range [HCl] =  $10^{-3}$ – $10^{-1} M$  ( $k_{\text{obsd}} = 2 \times 10^{-4} [H^+]^{-1} s^{-1}$ ); i.e., the one-proton process is inhibited and the reaction proceeds entirely through the water reaction of the free acetal.



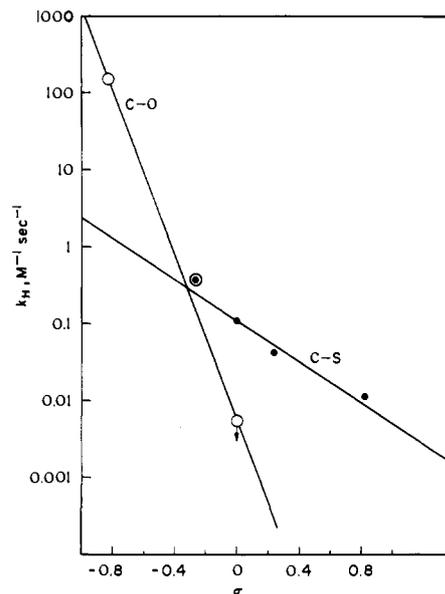
**Figure 3.** The dependence on the  $pK$  of the alcohol of the rate constants for cleavage of benzaldehyde *O*-alkyl *S*-ethyl acetals with alcohol leaving, in aqueous solution, (●) and benzaldehyde *O*-alkyl *S*-phenyl acetals with thiophenol leaving, in 20% dioxane (○).

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 oxocarbenium 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 ( $\mu = 1.0$ , 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  $4.0 \times 10^{-6}$ ,  $3.7 \times 10^{-6}$ , and  $3.2 \times 10^{-6} \text{ s}^{-1}$  may be compared with  $4.2 \times 10^{-6}$ ,  $3.7 \times 10^{-6}$ , and  $3.1 \times 10^{-6} \text{ s}^{-1}$ , respectively, that were calculated from  $k_H[H^+] + k_{H_2O}$  (Table II).

A rate constant of  $k_H = 3.5 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  for the hydrolysis of benzaldehyde diethyl mercaptal was obtained from measured rate constants of  $2.8 \times 10^{-5} \text{ s}^{-1}$  in 0.1 M HCl and 0.9 M KCl and  $2.5 \times 10^{-4} \text{ s}^{-1}$  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<sup>22</sup> 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



**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.

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  $\sigma$ , with positive deviations for electron-donating substituents,  $\rho^+ = -1.7$  against  $\sigma^+$ , 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<sup>23,24</sup> (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<sup>a</sup>

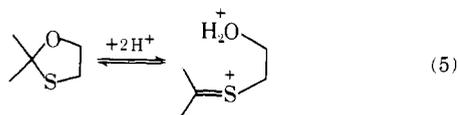
series	C-O cleavage
SEt	$\rho = -2.0, \rho^r = 1.1$
ArCH—OEt	$(r^+ = 0.55 (0.999));^b \rho =$
SEt	$-2.3 (0.996)^c$
PhCH—OR	$\beta_{lg} = 0.30 (0.99), \rho^* = -1.1$
SR	$(0.99)^d$
ArCH—OEt	$\beta_{rg} = 0.5-1.0^e (\rho^* = -1.5 \text{ to}$
	$-2.8)$
series	C-S cleavage
OEt	$\rho \approx -1.4 (0.985)$
ArCH—SPh	
OMe	$\beta_{lg} = 0.57, \rho = -1.0^f, g$
PhCH—SAr	
OR	$\beta_{rg} \approx 0.62 (0.999) (\rho^* =$
PhCH—SPh	$-2.2)^g$
OEt	$\beta_{lg} \approx -1.0 (0.999) (\text{water}$
<i>p</i> -Me <sub>2</sub> NPhCH—SR	reaction)

<sup>a</sup> Correlation coefficients are in parentheses. Data from this work are at 25 °C, ionic strength 1.0 (KCl). <sup>b</sup> Based on the Yukawa-Tsuno treatment.<sup>23,24</sup> <sup>c</sup> Based on  $\sigma$  values from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). <sup>d</sup> Values of  $pK$  and  $\sigma^*$  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. <sup>e</sup> Based on the  $pK_a$  values in Table II. The values of  $\beta_{rg}$  are 0.54 (Ar = *p*-Me<sub>2</sub>NPh), 0.65 (Ar = *p*-MeOPh), and 1.0 (Ar = Ph). <sup>f</sup> Reference 3; at 30 °C. <sup>g</sup> In 20% dioxane.

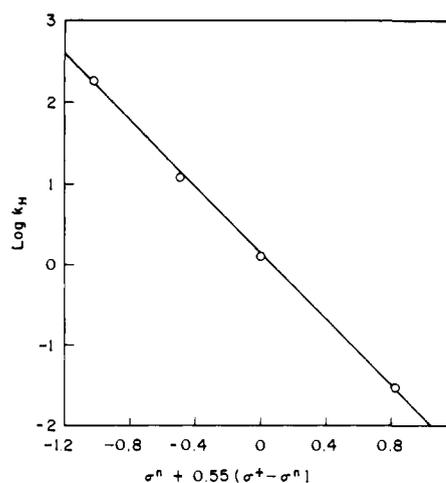
an anomalously large rate of expulsion of aromatic leaving groups that is also evident in *O,O*-acetals: benzaldehyde methyl phenyl acetal undergoes acid-catalyzed hydrolysis 1.4 times faster than benzaldehyde dimethyl acetal in spite of the high  $pK$  of methanol.<sup>14</sup> The reason for this difference 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 anomization 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,<sup>2</sup> 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.<sup>3</sup> The direction of the *equilibrium* ring opening of 2,2-dimethyl-1,3-oxathiolane in FSO<sub>3</sub>H·SbF<sub>5</sub> according to eq 5 shows that the combination of leaving group



basicity and carbonium ion stability favors ROH leaving and protonation in this reaction, but does not establish the initial site of bond cleavage.<sup>4</sup> 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



**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  $\sigma^n$  value<sup>23</sup> of 0.82 for Me<sub>3</sub>N<sup>+</sup> has been used for the Me<sub>2</sub>NH<sup>+</sup> substituent.

concluded that C-O bond cleavage occurs in the rate-determining step.<sup>5</sup> 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<sup>8</sup> 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<sup>7</sup> and tetrahydro-2-(*p*-tolylthio)pyran,<sup>9</sup> 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.<sup>3</sup> However, the observed range of  $k_D/k_H = 1.0-3.1$  for the hydrolysis of *O,O*-acetals<sup>25</sup> means that a small solvent isotope effect is not definitive evidence for C-S cleavage.

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.<sup>2,3</sup>

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<sup>14</sup> 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.<sup>7,8,10,26</sup>

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.<sup>27</sup> Since the equilibrium constants for the addition of RSH are some 10<sup>3</sup> larger than those for the addition of ROH or HOH,<sup>27,28</sup> the rate constants for protonation and expulsion of RSH must be approximately 10<sup>3</sup> smaller than those for ROH, in agreement



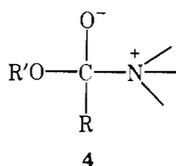
$\sim 1.0$ ,  $\rho^* = -2.8$ ) is larger than the effect of substituents in the remaining alcohol on the expulsion of thiophenol ( $\beta_{rg} \sim 0.6$ ,  $\rho^* = -2.2$ ). The effect of substituents in the leaving thiophenol ( $\beta_{lg} = 0.6$ )<sup>3</sup> is larger than in the leaving alcohol ( $\beta_{lg} = 0.3$ ). There is also a large development of charge in the remaining group in the acid-catalyzed cleavage of  $\text{ArSCH}_2\text{OAc}$ <sup>39</sup> ( $\rho = -2.6$ ; since  $\rho$  for  $\text{ArSH}$  ionization<sup>43</sup> is 1.9, the value of  $\beta_{rg}$  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  $\rho$  values of  $-2.0$  to  $-2.3$  for alcohol expulsion and  $\sim -1.4$  for thiol expulsion. If the equilibrium constants for carbonium ion formation follow a value of  $\rho$  close to that of  $-3.6$  for the formation of oxocarbenium ions from acetophenone ketals,<sup>24</sup> the values of  $\rho$  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.<sup>14,24</sup> 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,<sup>14</sup> 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,<sup>44</sup> 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 oxocarbenium ion with electron-withdrawing substituents.<sup>24</sup>

**Structure-Reactivity Interactions and Changes in Transition State Structure.** The shift from C–S to C–O cleavage, to give the relatively unstable  $>\text{C}=\text{SR}^+$  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  $\rho$  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

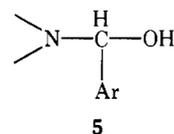


substituents on R favor oxygen expulsion, which cannot be aided by electron donation from the cationic nitrogen atom, more than nitrogen expulsion, which is aided by electron donation from  $\text{R}'\text{O}$ .<sup>45</sup>

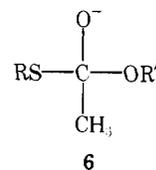
The change in transition-state structure in the benzaldehyde acetal series is manifested by an interaction of substituent effects such that electron-donating substituents on the benzene ring decrease the amount of electron donation from the thiol and electron-donating substituents on the thiol decrease 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<sub>2</sub>N compounds, respectively. There is a correspondingly larger dependence on substituents in the benzaldehyde for cleavage of the  $\text{SCH}_2\text{COOMe}$  than for the  $\text{SEt}$  compound: the rate constant ratios for the Me<sub>2</sub>N, MeO, and H acetals are 1430:13:1 for the  $\text{SCH}_2\text{COOMe}$  and 130:2.3:1 for the  $\text{SEt}$  compounds.

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



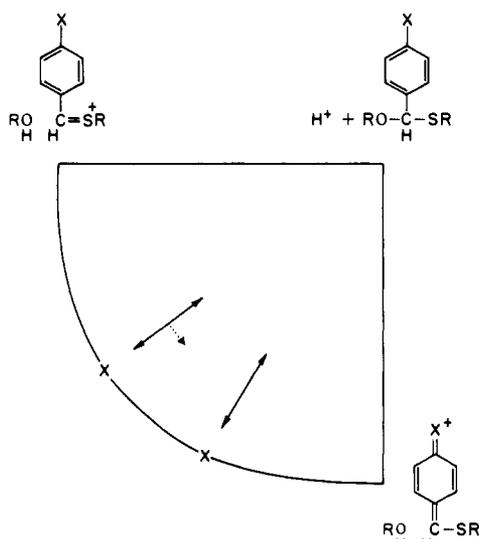
electron donation from the benzene ring to such an extent that the observed rate constants follow  $\sigma^n$  rather than  $\sigma$  or  $\sigma^+$ .<sup>46</sup> Electron-donating groups decrease the amount of electron donation from a benzene ring in solvolysis<sup>47</sup> and the values of  $r$  and  $-\rho$  become smaller in the hydration of styrenes; this result has been analyzed by extended Hückel theory.<sup>48</sup> 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



expulsion of oxygen.<sup>41</sup> 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.

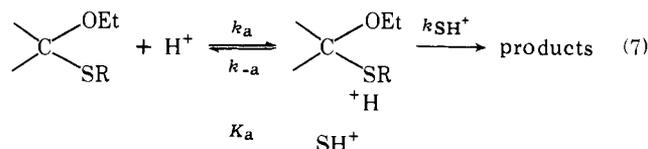
This kind of change in transition-state structure corresponds to an “anti-Hammond” effect with movement of the transition state perpendicular to the reaction coordinate<sup>49,50</sup> such that stabilization of the product, by resonance, for example, leads to a transition state that more closely resembles 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  $\beta_{lg}$ , 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  $>\text{C}=\text{SR}^+$  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



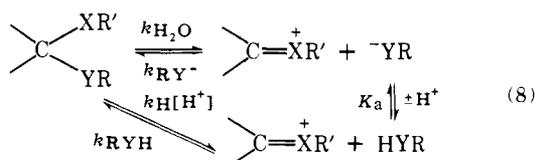
**Figure 6.** Reaction coordinate-energy diagram to illustrate the relative contributions of stabilization by electron donation from the sulfur atom and from the benzene ring of the transition state and product for the hydrolysis of benzaldehyde *O,S*-acetals with C-O cleavage. The energy contour lines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

constant for rate-determining breakdown of the protonated intermediate,  $k_{SH^+}$ , is given by  $k_{SH^+} = k_H K_a$ . For *p*-me-

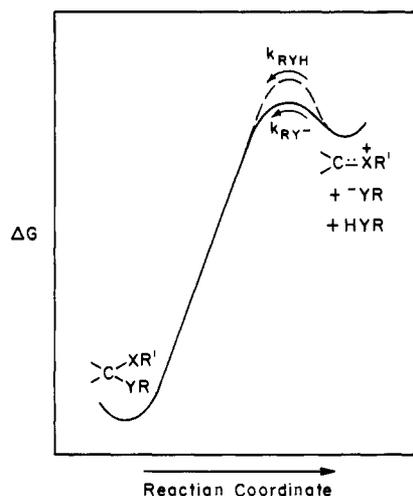


thoxybenzaldehyde *O*-ethyl *S*-(methyl mercaptoacetate) acetal, which breaks down with both C-S and C-O cleavage, the value of  $k_{SH^+}$  is on the order of  $10^{10} \text{ s}^{-1}$ . This value is calculated from  $\text{p}K_a = -12.4$ , based on  $\text{p}K_a = -6.9$  for protonated dimethyl sulfide<sup>29</sup> and correcting for the effects of the OR, Ar, and COOR substituents with the appropriate  $\sigma_1$  values and  $\rho_1 = 8.4$ .<sup>51</sup> 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  $>\text{S}-\text{H}^+$  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  $\alpha$  value, would then be required. Since the oxygen atom is more basic than the sulfur atom<sup>52</sup> 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.

For a reaction that proceeds through an oxocarbenium ion or similar intermediate according to the mechanism of eq 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  $\log(k_{RY^-}/k_{RYH}) = \Delta\text{pH}$ , where  $\Delta\text{pH}$  (Figure 1) is the difference be-



**Figure 7.** Gibbs free energy diagram based on pseudo-first-order rate constants at  $\text{pH} = \text{p}K_{RXH}$  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  $\Delta\text{pH} = 0$  (Figure 1). The dashed line is for the acid-catalyzed breakdown when  $\Delta\text{pH} = \log(k_{RY^-}/k_{RYH}) > 0$ .

tween the  $\text{p}K$  of the leaving group and the  $\text{pH}$  at which the rates of the pH-independent and acid-catalyzed breakdown of the starting material are equal; i.e.,  $k_{H_2O} = k_H[\text{H}^+]$ . When  $\Delta\text{pH} = 0$  and  $k_{RY^-} = k_{RYH}$ , the reactions of  $\text{RY}^-$  and  $\text{RYH}$  with  $>\text{C}=\text{XR}'^+$  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  $\text{RY}^-$  and  $\text{RYH}$ , respectively, from  $>\text{C}=\text{XR}'^+$ . 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.

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  $\text{pH} = \text{p}K_{lg}$ . At this  $\text{pH}$ ,  $[\text{RYH}] = [\text{RY}^-]$  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  $k_{RYH} < k_{RY^-}$  (i.e., the reverse reaction is not diffusion controlled), the free energy of activation for the addition and expulsion of  $\text{RYH}$  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  $\Delta\text{pH}$ .

The relationship is shown quantitatively as follows. From eq 8

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

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

When  $\log(k_H[\text{H}^+]) = \log k_{H_2O}$  at  $\text{pH}_1$

$$\log(k_H/k_{H_2O}) = \text{pH}_1 \quad (10)$$

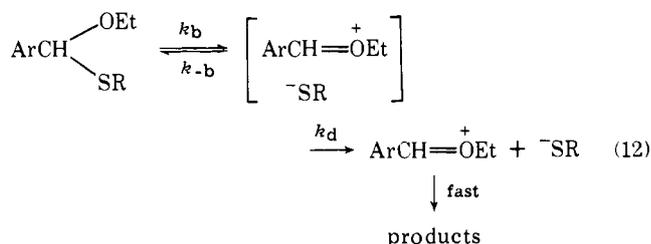
Subtracting eq 10 from eq 9

$$\text{p}K_a - \text{pH}_1 = \log(k_{RY^-}/k_{RYH}) \quad (11)$$

Since the rate of attack of  $\text{RY}^-$  will always be at least as large as that for  $\text{RYH}$ , so that  $\log(k_{RY^-}/k_{RYH}) = \Delta\text{pH} \geq 0$ , the line for the proton-catalyzed reaction must always intersect the line for the water reaction at or below the  $\text{p}K$  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 oxocarbenium 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.



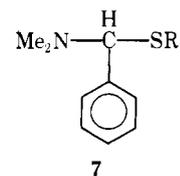
The following evidence is also consistent with the hypothesis that the rate-determining step of the pH-independent hydrolysis reaction is the diffusion-controlled separation of the ion pair.

(1) The values of  $\Delta pH = \log(k_{RS^-}/k_{RSH})$  are  $\geq 2.9$  and  $\geq 5.9$  for the *p*-methoxybenzaldehyde and *p*-dimethylaminobenzaldehyde *O*-ethyl *S*-phenyl acetals, respectively.<sup>53</sup> These large rate ratios are consistent with values of  $k_{RSH}$  that decrease sharply for attack on the resonance-stabilized oxocarbenium 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 oxocarbenium ions formed from a series of ortho esters.<sup>54</sup> 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,<sup>3</sup> 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  $\beta_{lg}$  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 oxocarbenium 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.<sup>24,55</sup> In contrast, the value of  $\beta_{lg}$  for the

rate-determining expulsion of thiol anions from 7, to give a much more stable iminium ion intermediate,<sup>56</sup> is  $-0.57$ .



(3) The large increases in rate constant with electron-donating substituents in the benzaldehyde ring are consistent with the formation of the oxocarbenium 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 oxocarbenium ions from acetophenone ketals in water;<sup>24</sup> 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<sup>57</sup>), 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 oxocarbenium ions, based on the Hammett-Yukawa correlation for this equilibrium.<sup>24</sup>

(4) There is evidence that the reactions of sulfite anion and hydroxylamine with oxocarbenium ions derived from acetophenone ketals are diffusion controlled.<sup>24</sup> Since oxocarbenium 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  $10^{10} \text{ s}^{-1}$ , the values of  $K_b$  are then on the order of  $2 \times 10^{-16}$ ,  $6 \times 10^{-15}$ , and  $4 \times 10^{-9}$  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.<sup>57</sup> This isotope effect is consistent with complete C-S cleavage and formation of an oxocarbenium 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.<sup>57</sup>

If the reaction does not proceed through a free oxocarbenium 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  $>C=OR^+$   $RS^-$  ion pair through a "preassociation" mechanism.<sup>24</sup>

The small ratio  $k_{RS^-}/k_{RSH}$  for  $PhSH$  suggests that the reactions of the more basic aliphatic  $RSH$  and  $ROH$  with the benzaldehyde oxocarbenium ion are diffusion controlled. If this is the case the reverse, cleavage reactions will represent diffusion-controlled separation of these leaving groups from the oxocarbenium ion or a preassociation mechanism.<sup>24</sup> 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  $\Delta pH$  of which we are aware is  $\sim 0.8$  for the hydrolysis of 8,<sup>58</sup> which corresponds to a ratio  $k_{RY^-}/k_{RYH} \sim 6$ . This is consistent with a mechanism involving

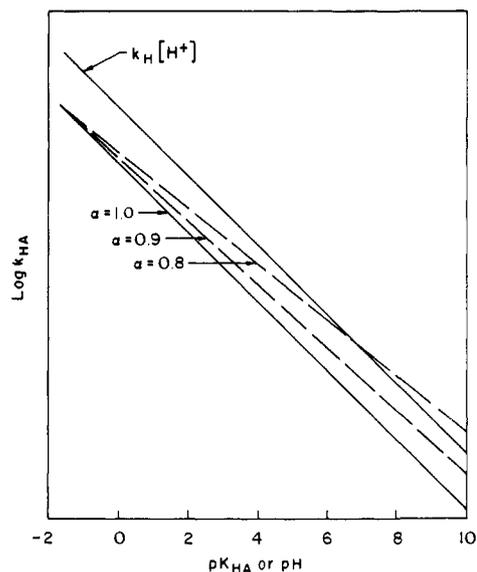
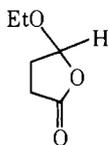


Figure 8. Plot of  $\log(k_H[H^+])$  against pH (upper line) superimposed on a generalized Brønsted plot (lower lines).



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rate-determining rotation of the leaving group away from the oxocarbenium ion or rate-determining attack of water on the oxocarbenium 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 oxocarbenium ion can account for a factor of 6. An oxocarbenium 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.<sup>59</sup>

**Acid Catalysis.** We have confirmed the observation of Fife and Anderson<sup>3</sup> 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  $\alpha$  as the leaving group becomes less basic. For example, 2-(4-nitrophenoxy)-tetrahydropyran<sup>13</sup> and benzaldehyde methyl *m*-nitrophenyl acetal<sup>14</sup> 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  $\alpha$  for the reaction. For this reason it is desirable to report limits for  $\alpha$ ,  $\alpha_{\min}$ , for reactions in which general acid catalysis is not detected. The value of  $\alpha_{\min}$  is given by

$$\alpha_{\min} = \frac{-\log L + \text{pH} + \log [\text{HA}]}{1.74 + \text{p}K_{\text{HA}}} \quad (13)$$

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.,  $k_{\text{HA}}[\text{HA}] \leq Lk_H[\text{H}^+]$ . 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  $\alpha_{\min}$  it is desirable to search for general acid catalysis at the highest pH that is above the  $\text{p}K_{\text{HA}}$  of the weakest acid that is practicable to examine. In order to obtain a doubling of the observed rate with 1 M acid at  $\text{pH} = \text{p}K_{\text{HA}}$  it is necessary to examine an acid of  $\text{p}K_{\text{HA}} = 6.8$  if  $\alpha = 0.8$ ; for  $\alpha = 0.9$  an acid of  $\text{p}K_{\text{HA}} = 15.5$  would be required and only a water reaction could be observed.<sup>60</sup> Limits to the choice of pH and  $\text{p}K_{\text{HA}}$  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  $\alpha$  or  $\alpha_{\min}$  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 ( $L = 0.3$ );  $\alpha_{\min}$  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<sup>3</sup> 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.<sup>61</sup>

The absence of detectable general acid catalysis and the large value of  $\alpha_{\min}$  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  $\beta_{\text{lg}} = 0.57$  ( $\rho = -1.0$ ) for the proton-catalyzed expulsion of SAR,<sup>3</sup> compared with  $\beta_{\text{lg}} \sim 0.2$  ( $\rho = -0.60$ ) for expulsion of OAr from benzaldehyde acetals,<sup>14</sup> 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 oxocarbenium 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.<sup>24,62</sup> Evidence is described above that the attack of PhS<sup>-</sup> on benzaldehyde oxocarbenium 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  $\Delta\text{pH}$  mean that there is only a small range of pH and  $\text{p}K$  over which buffer catalysis can be examined;<sup>62</sup> 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 oxocarbenium 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,  $\rho = -1.4$ ,  $\beta_{\text{lg}} = 0.57$ , and  $\beta_{\text{rg}} = 0.62$ , and the secondary deuterium isotope effect<sup>57</sup> 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  $\beta_{\text{lg}}$  of 0.57 suggest that there is relatively little C-S bond cleavage ( $\rho$  for expulsion of the OPh group is  $-2.26$ )<sup>14</sup> 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.<sup>3</sup> 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.<sup>50</sup> The value of  $\alpha$  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  $\alpha$ . 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  $\alpha$  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  $\text{RS}^-$  is generally expelled faster than  $\text{RO}^-$  for constant R, as noted above).

(5) It remains possible that the reaction is general acid catalyzed but that  $\alpha$  is larger than 0.84, too large for experimental detection. The solvent deuterium isotope effect<sup>3</sup> of  $k_{\text{D}}/k_{\text{H}} = 1.51$  is smaller than the value close to 3.0 that is ordinarily expected for specific acid catalysis of oxygen expulsion.<sup>25,63</sup> 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.<sup>27,64</sup> 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.<sup>65</sup> 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.<sup>66</sup> The small difference between the  $\text{pK}$  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

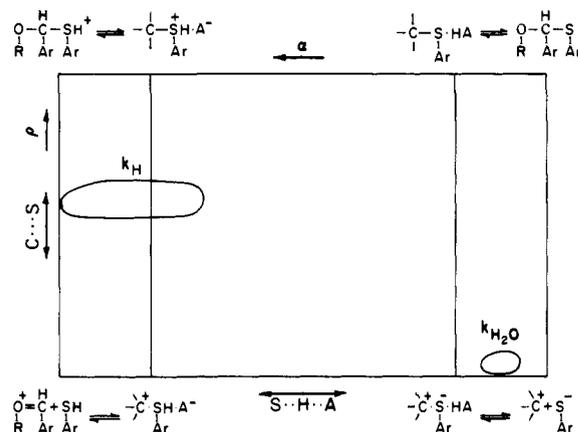


Figure 9. Reaction coordinate-energy diagram for the cleavage of benzaldehyde *O,S*-acetals with proton transfer on the horizontal axis and C-S bond cleavage on the vertical axis. The positions of the transition states for the acid-catalyzed and water reactions are indicated by circles. The energy contour 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  $k_{\text{H}}$  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 ( $\alpha_{\text{min}} = 0.84$ ). The transition state for the pH-independent, water reaction is in the lower right corner, and probably represents a transport step, the separation of  $\text{ArS}^-$  from the oxocarbenium ion ( $\text{HA} = \text{HOH}$ ). In the reverse direction this reaction involves diffusion-controlled combination of  $\text{ArS}^-$  with the oxocarbenium 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.

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## Kinetic $\alpha$ Secondary Deuterium Isotope Effects for *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal Hydrolysis<sup>1</sup>

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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;  $k_{\text{obsd}} = 1.9 \times 10^{-7} \text{ s}^{-1}$ . Under more acidic conditions, the rate increases linearly with the activity of the hydrated proton;  $k_2 = 2.95 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ . The kinetic  $\alpha$  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  $k_{\text{H}}/k_{\text{D}} = 1.038 \pm 0.008$ , 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  $1.13 \pm 0.02$ , 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<sup>3,4</sup> as does that for the structurally related 2-phenyl-1,3-oxathiolanes.<sup>5,6</sup> 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.<sup>3,4</sup> 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 oxocarbenium ion.<sup>3</sup>

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,<sup>7</sup> it is desirable to examine these reactions more thoroughly. Herein, we report kinetic  $\alpha$  deuterium isotope effects for hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal, both for the acid-cat-