208, respectively). A completely independent route to the synthesis of this class of compounds was recently reported: D. N. Harpp and A. Granata, *Tetrahedron Lett.*, 3001 (1976). The cyclic trisulfide (n = 6) originally reported as monomeric has been shown by vapor pressure osmometric molecular weight determination to be a dimer.

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(20) Triazole is a smaller molecule than benzimidazole; thus solvation of the charged species by a nonpolar solvent is preferable to that of a larger one.^{21a} In addition, 1,2,4-triazole is more soluble in the common organic solvents^{22} making it more available to participate as a base or catalyst in the reaction. Finally, it has been pointed out^{19,21} that pK_as observed in aqueous media are unlikely to be the same in other solvents, especially those with a much lower dielectric constant. The trend, however, should remain approximately the same.

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General Acid Catalyzed Breakdown of Ketone Bisulfites[1]
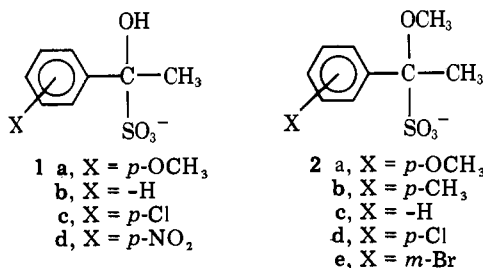
P. R. Young and W. P. Jencks*

Contribution No. 1181 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. Received August 29, 1977

Abstract: The cleavage of 1-methoxy-1-arylethanesulfonic acids, $MeOC(Me)(Ar)SO_3^-$, at 25 °C is catalyzed by the proton and by general acids with α = 0.6 (Ar = $MeOC_6H_4$), k_{H^+}/k_{D^+} = 0.56, k_{H_2O}/k_{D_2O} = 2.2 for catalysis by citric acid buffers, and ρ = −2.0 (ρ^r = −1.0) for catalysis by the proton. The acid catalyzed cleavage of acetophenone bisulfites, $HOC(Me)(Ar)SO_3^-$, shows similar properties with α = 0.54 (Ar = $MeOC_6H_4$) k_{H^+}/k_{D^+} = 0.81, and ρ = −1.6 (ρ^r = −1.0). These similarities and the fact that the absolute rate constants for the two reaction series generally differ by less than an order of magnitude indicate that part, and probably all, of the observed reaction with the acetophenone series occurs by the same mechanism as with the O-methyl series, which is kinetically unambiguous. This class n mechanism involves proton donation to the leaving sulfite ion and, in the reverse direction, proton removal from bisulfite as it attacks the oxocarbonium ion >C=OR$^+$ (R = Me or H). It is argued that buffer catalysis is enforced in the O-methyl series by the diffusion-controlled reaction of SO_3^{2-}, but not water or HSO_3^-, with the oxocarbonium ion. An observed decrease in α with electron-withdrawing substituents on the acetophenone (α = 0.31 for p-nitroacetophenone bisulfite) can be explained if the proton is in a potential well and motion along the reaction coordinate involves only C–S cleavage in the transition state.

The predominant mechanism (eq 1) for the breakdown of bisulfite addition compounds of carbonyl compounds in-

$$HO-\underset{|}{\overset{|}{C}}-SO_3^- \;\rightleftharpoons\; O=C\diagup\diagdown + HSO_3^- \qquad (1)$$
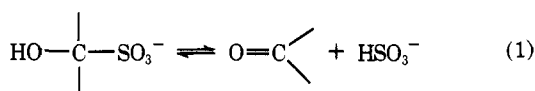
volves base catalysis with a large Brønsted β value; in the reverse direction this corresponds to the addition of sulfite dianion with modest general acid catalysis.[2] However, at low pH values this reaction pathway is slow and the breakdown of the bisulfite addition compounds of benzaldehyde[3] and p-methoxyacetophenone[2] has been reported to proceed through an acid catalyzed pathway. In the reverse direction this corresponds to acid catalysis of the addition of bisulfite ion to the carbonyl compound. Bisulfite ion is a very weak base and, to the best of our knowledge, there is no example of a reaction in aqueous solution involving bisulfite ion as a nucleophile. We were interested, therefore, in investigating the mechanism of acid catalysis of the addition of this weak nucleophile and of the breakdown of the addition compound. To resolve kinetically ambiguous mechanisms for general acid–base catalysis it is useful to use compounds containing a CH$_3$O– group as models for reactions of compounds containing an HO– group in which there is no removal of the proton from the oxygen atom in the transition state. To this end, we have studied the general acid catalyzed breakdown of substituted acetophenone bisulfites, **1**, and of the analogous 1-methoxy-1-arylethanesulfonic acids, **2**, in aqueous solution.

1 a, X = p-OCH$_3$
  b, X = –H
  c, X = p-Cl
  d, X = p-NO$_2$

2 a, X = p-OCH$_3$
  b, X = p-CH$_3$
  c, X = –H
  d, X = p-Cl
  e, X = m-Br

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Organic acids (with the exception of reagent grade formic and acetic acids) were purified by recrystallization or distillation. Substituted acetophenones and acetophenone dimethyl ketals[4] were purified by distillation under reduced pressure or by recrystallization.

Stock solutions of the carbonyl bisulfites were prepared by dissolving a sufficient amount of the carbonyl compound in 1–4 M potassium bisulfite solution to give a final concentration of ~0.01 M and were stored at 4 °C under a nitrogen or argon atmosphere.[2] Aliquots (10–20 μL) were diluted into thermostated spectrophotometer cells containing 3.0 mL of the desired buffer solution and sufficient hydrogen peroxide (10 μL of a 31% solution) to oxidize the excess sulfite to sulfate, thereby driving the reaction to completion. Addition of excess hydrogen peroxide (or its total elimination in the case of p-methoxyacetophenone) gave no detectable change in the observed rate constant. The oxidation of sulfite under the conditions used was much faster than the breakdown of the ketone bisulfites, being complete in
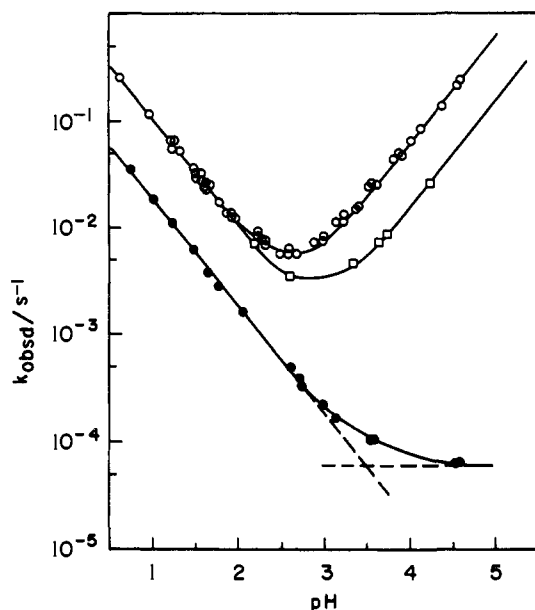
Figure 1. Dependence on pH of the observed first-order rate constants for the breakdown of p-methoxyacetophenone bisulfite at 25 °C, ionic strength 1.0 with KCl (O), and Me_4NCl (□), and of 1-(4-methoxyphenyl)-1-methoxyethanesulfonic acid, 25 °C, ionic strength 1.0 with KCl (●). All data are extrapolated to zero buffer concentration and the solid lines are calculated from the rate constants given in the text.

Table I. Hydronium Ion Catalysis of the Breakdown of Acetophenone Bisulfites and the Corresponding α-Methoxysulfonic Acids[a]

Substit- uent	Substituted acetophenone bisulfites 1, $k_{H^+}/M^{-1}s^{-1}$	Substituted α-methoxysulfonic acids 2, $k_{H^+}/M^{-1}s^{-1}$
p-OCH₃	1.1	0.19
p-CH₃		5.7×10^{-2}
-H	0.15	1.7×10^{-2}
p-Cl	7.8×10^{-2}	6.7×10^{-3}
m-Br		2.3×10^{-3}
p-NO₂	7.8×10^{-3}	

[a] Ionic strength maintained at 1.0 with KCl; $T = 25$ °C. The second-order rate constants are based on 10^{-pH}.

the mixing time. The same rate constants were obtained with stock solutions that had stood for several weeks as with fresh solutions.

Stock solutions of the α-methoxysulfonic acids **2a–e** were prepared by hydrolysis of the corresponding acetophenone dimethyl ketal in the presence of 1.0 M potassium bisulfite buffer, 50% ionized, pH 6.6.[4] After sufficient time was allowed for the hydrolysis to go to completion, 10–20-μL aliquots were withdrawn and diluted into spectrophotometer cells as described above. Fresh solutions of the α-methoxysulfonic acids were prepared daily.

Kinetic Measurements. The rates of dissociation of the carbonyl bisulfites and α-methoxysulfonic acids were followed by measuring the increase in carbonyl absorbance as previously described.[4] Reaction rates were followed using a Zeiss PM6KS spectrophotometer equipped with an automatic cell changer and a digital printout. Constant temperature was maintained at 25 °C by the use of a thermostated cell compartment; the ionic strength was maintained at 1.0 with KCl or Me_4NCl. First-order rate constants were determined from semilogarithmic plots of $(A_\infty - A_t)$ against time. Such plots were typically linear for over 3–4 half-times. The pH of each solution was determined at the completion of the experiment using a Radiometer PHM-26 pH meter equipped with a combined glass electrode. Minor variations in pH accompanying buffer dilution at constant buffer ratio were compensated for using the relationship

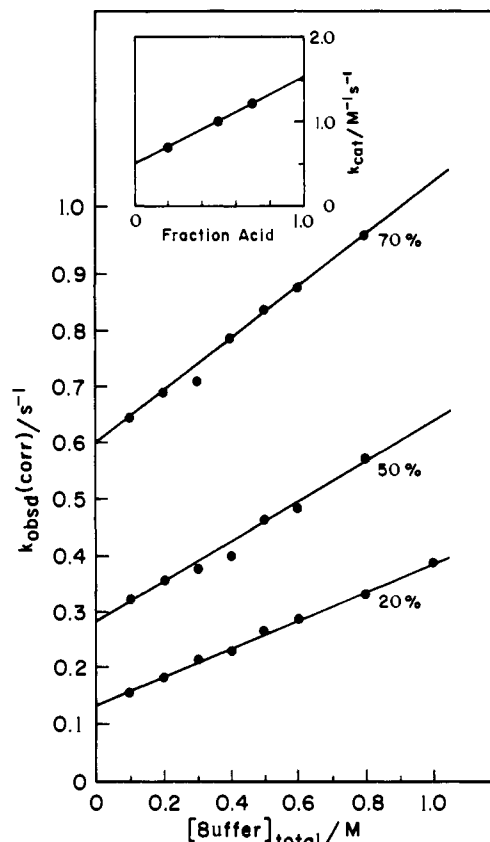$$k_{obsd}(corr) = k_{obsd} + \Delta(a_{H^+})k_{H^+} \qquad (2)$$

Figure 2. Dependence of the corrected first-order rate constants for the breakdown of p-methoxyacetophenone bisulfite on the concentration of phosphoric acid buffers at three buffer ratios at the indicated percent acid, ionic strength 1.0 with Me_4NCl, 25 °C.

where k_{H^+} is the apparent catalytic constant for hydronium ion catalysis. Catalytic constants for buffer catalysis ($k_{cat.}$) were determined by the least-squares slope of plots of $k_{obsd}(corr)$ against buffer concentration and typically were based on six to eight buffer concentrations. Where required, hydrochloric acid was added to buffer solutions to compensate for ionization of the buffer conjugate acid.[5]

Results

Hydronium Ion Catalysis. The dependence on pH of the first-order rate constants for the breakdown of p-methoxyacetophenone bisulfite, **1a,** and of 1-(4-methoxyphenyl)-1-methoxyethanesulfonic acid, **2a,** in the absence of general acids and bases (k_0) is shown in Figure 1. The data for the ketone bisulfites are consistent with the rate laws of the following equations:

$$k_0 = k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{H_2O}[H_2O] \qquad (3)$$

$$k_{obsd} = k_0 + k_{BH}[BH] + k_B[B] \qquad (4)$$

Values of k_0 were obtained from experiments in dilute hydrochloric acid or from the ordinate intercepts of plots of k_{obsd} against total buffer concentration (Figure 2). The pH-rate profile shows that the reaction is both acid and base catalyzed and gives second-order rate constants, based on hydrogen ion activities, of $k_{H^+} = 1.1$ M^{-1} s^{-1}, $k_{OH^-} = 5.8 \times 10^8$ M^{-1} s^{-1}, and k_{H_2O} (55 M) $= 1.2 \times 10^{-3}$ s^{-1} (ionic strength 1.0, KCl, 25 °C).[2] The breakdown of the α-methoxysulfonic acid **2a** is not subject to hydroxide ion or general base catalysis and gives rate constants of $k_{H^+} = 0.19$ M^{-1} s^{-1} and k_{H_2O} (55 M) $= 6 \times 10^{-5}$ s^{-1}. The results for the p-methoxy compounds are representative of the other compounds investigated and second-order rate constants for hydronium ion catalysis are listed in Table I.

Table II. General Acid Catalysis of the Breakdown of Acetophenone Bisulfites and of 1-(4-Methoxyphenyl)-1-methoxyethanesulfonic Acid[a]

Buffer	pK_a	Fraction of Acid	Concn range, M^b	$10^4 k_{cat}/M^{-1} s^{-1}$ [c]	$10^4 k_{BH}/M^{-1} s^{-1}$ [d]	$10^4 k_{BH'}/M^{-1} s^{-1}$ [e]
			p-Methoxyacetophenone			
H_3O^+	-1.74			10800	10800	
				13300[f]	13300[f]	
$F_2CHCOOH$ (DF)	1.13[g]	0.15	0.1-1.0	57	280	200
		0.30	0.1-1.0	110		
		0.45	0.1-0.8	140		
$CNCH_2COOH$ (CN)	2.33[g]	0.30	0.1-0.8	17	70	50
		0.50	0.1-0.8	35		
		0.70	0.1-0.8	48		
H_3PO_4 (P)	2.08[h,i]	0.20	0.1-1.0	70	160	
		0.50	0.1-0.8	100		
		0.70	0.1-0.8	130		
Citric acid (C_1)	2.60	0.50	0.1-1.0	73	40	
		0.70	0.1-1.0	61		
$HCOOH^j$ (F)	3.56[g]	0.10	0.1-0.7	33	27	17
		0.20	0.1-0.75	42		
		0.40	0.1-0.8	53		
		0.50	0.1-0.8	60		
$ClCH_2COOH$ (CA)	2.70[g]	0.50	0.1-0.8	38	67	48
		0.60	0.1-0.8	41		
		0.70	0.1-0.8	49		
		0.85	0.1-0.7	57		
			p-Chloroacetophenone			
H_3O^+	-1.74			780	780	
H_3PO_4	2.08[h,i]	0.40	0.1-0.8	16	31	
		0.70	0.1-0.8	20		
		0.90	0.1-0.8	28		
			p-Nitroacetophenone			
H_3O^+	-1.74			77	77	
$ClCH_2PO_3H_2$ (CP)	0.95[i]	0.20	0.1-0.8	3.5	13	
		0.25	0.1-0.8	4.3		
		0.50	0.1-0.8	7.3		
		0.65	0.1-1.0	8.8		
$Me_2AsO_2H_2^+$ (Cac)	1.77[i]	0.50	0.1-0.8	8.2	7.8	
		0.75	0.1-0.8	8.0		
H_3PO_4 (P)	2.08[h,i]	0.10	0.1-0.8	10.5	6.5	6.1
		0.50	0.1-0.9	7.8		
		0.80	0.1-0.8	7.1		
		0.95	0.1-0.8	5.2		
$CNCH_2COOH$ (CN)	2.33[h,i]	0.85	0.1-0.8	2.0	1.2	2.0
		0.90	0.1-0.8	1.7		
HCOOH (F)	3.56[g]	0.99	0.1-0.8	1.2	1.2	
			1-(4-Methoxyphenyl)-1-methoxyethanesulfonic Acid			
H_3O^+	-1.74			1900	1900	
				3400[f]	3400[f]	
H_3PO_4 (P)	1.72[k]	0.15	0.1-0.8	0.88	15	
		0.50	0.1-0.8	7.5		
$CNCH_2COOH$ (CN)	2.33[g]	0.30	0.1-0.8	1.2	4	
Citric acid (C_1)	2.60[i]	0.30	0.1-1.0	2.1	5.4	
		0.50	0.1-0.9	3.3		
		0.50[f]	0.1-1.0[f]	1.5[f]		
HCOOH (F)	3.56[g]	0.50	0.1-0.9	0.57	1.2	
		0.70	0.1-1.0	0.83		
Citric acid Anion (C_2)	4.28[i]	1.0		0.7	0.7	

[a] Ionic strength 1.0 with KCl unless otherwise stated; $T = 25$ °C. [b] Total buffer concentration. [c] Observed second-order rate constant for buffer catalysis. [d] Determined from the ordinate intercept of a plot of k_{cat} vs. fraction base. [e] Second-order rate constant for buffer catalysis corrected for salt and solvent effects. [f] In 99% D_2O. [g] Reference 5. [h] Ionic strength 1.0 with Me_4NCl. [i] Determined by potentiometric titration. [j] Reference 2. [k] E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 4377 (1968).

General Acid Catalysis. Table II summarizes the second-order rate constants for general acid catalysis of the breakdown of *p*-methoxy-, *p*-chloro-, and *p*-nitroacetophenone bisulfites and of 1-methoxy-1-(4-methoxyphenyl)ethanesulfonic acid. Observed catalytic constants, k_{cat}, were obtained from the slopes of plots of observed first-order rate constants against total buffer concentration (Figures 2 and 3). The second-order rate constants for the acidic and basic components of the buffer

(k_{BH} and k_B, respectively) were obtained from the ordinate intercepts of plots of k_{cat} against the fraction of the acidic component of the buffer (inset, Figure 2). General base catalysis of the breakdown of carbonyl bisulfites has been previously described.[2]

Since relatively small rate enhancements were observed with some buffer acids, it is important to determine the effects of added salts and organic solvents on k_{H^+} as this represents a
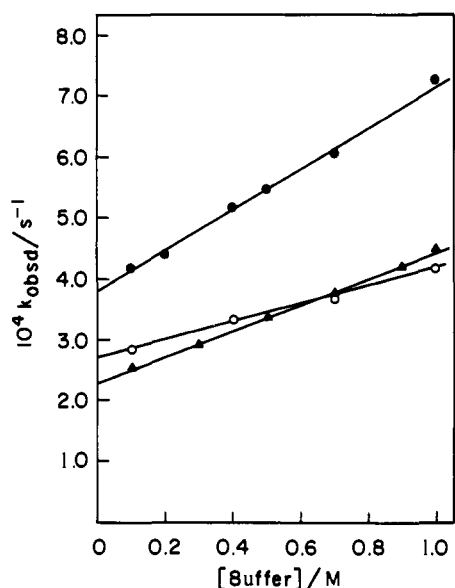
Figure 3. Dependence of the observed first-order rate constants for the breakdown of 1-(4-methoxyphenyl)-1-methoxyethanesulfonic acid on the concentration of citric acid buffers. Buffer ratios are 50% (●) and 30% (▲) acid in H_2O and 50% acid in D_2O (○); ionic strength 1.0 with KCl, 25 °C.

Figure 4. Brønsted plot for the general acid catalyzed breakdown of 1-(4-methoxyphenyl)-1-methoxyethanesulfonic acid at 25 °C, ionic strength 1.0 with KCl. The catalysts used are listed in Table II. Superimposed on the Brønsted plot are dashed lines representing observed first-order rate constants for the proton and water catalyzed reactions.

Table III. Salt and Solvent Effects on the Breakdown of Acetophenone Bisulfites and α-Methoxysulfonic Acids[a]

Additions	Concn, M	pH	$k_{H^+}/M^{-1} s^{-1}$ [b]
p-Methoxyacetophenone			
KCl	1.0	1.60	1.07
Me$_4$NCl	1.0	1.60	1.03
HOAc[c]	1.0	1.53	1.14
EtOH[c]	1.0	1.59	1.22
CH$_3$CONH$_2$[c]	1.0	1.56	1.27
KNO$_3$	1.0	1.59	1.16
CF$_3$COOK	1.0	1.57	1.17[d]
p-Nitroacetophenone			
KCl	1.0	0.52	7.8×10^{-3}
Me$_4$NCl	1.0	0.55	8.3×10^{-3}
H$_3$PO$_4$[c]	1.0	0.05	7.3×10^{-3} [d]
Dioxane[c]	1.0	1.48	e
CF$_3$COOK	1.0	1.45	e
1-(4-methoxyphenyl)-1-methoxyethanesulfonic acid			
KCl	1.0	0.55	0.19
Citric acid[c]	1.0	0.52	0.19
Formic acid[c]	1.0	0.71	0.18
Dioxane[c]	1.0	3.61	f
CF$_3$COOK	1.0	3.55	f

[a] At 25 °C. [b] Observed second-order rate constant for hydronium ion catalysis. [c] Ionic strength 1.0 with KCl. [d] $(k_{obsd} - k_{BH}[BH])/a_H$; the value of k_{BH} was determined from buffer dilution experiments at higher pH or was estimated from the Brønsted plot (Figure 4). In all cases $k_{BH}[BH]$ was less than 10% of k_{obsd}. [e] At pH-rate minimum, 9% decrease in rate observed. [f] In pH-independent region; no change in rate observed.

large fraction of k_{obsd}. The results for the compounds investigated are shown in Table III. For *p*-methoxyacetophenone bisulfite, organic solvents and anions other than chloride ion cause small increases in k_{H^+}. For *p*-chloroacetophenone bisulfite there is no significant effect and for *p*-nitroacetophenone bisulfite the salt and solvent effects result in a small decrease in the observed value of k_{H^+}. No significant salt or solvent effects were observed for the α-methoxysulfonic acid **2a**. General acids have little or no effect on the rate at low pH
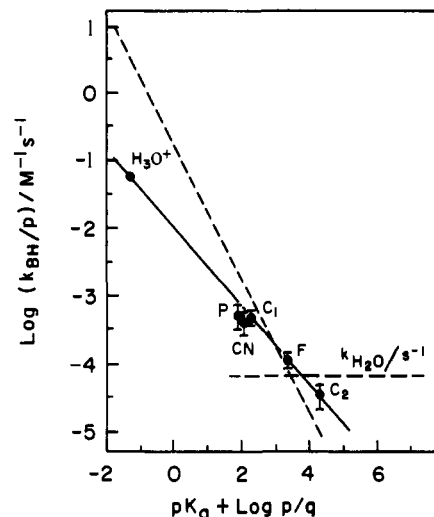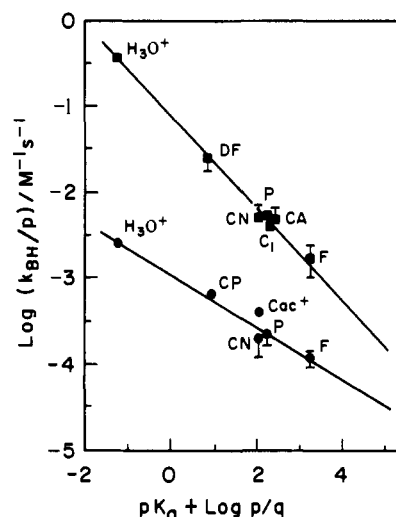

Figure 5. Brønsted plots for the general acid catalyzed breakdown of *p*-methoxy-(■) and *p*-nitroacetophenone bisulfites (●). The catalysts used are listed in Table II; the slopes of the lines are 0.54 ± 0.05 and 0.31 ± 0.03 for the *p*-methoxy and *p*-nitro compounds, respectively. Ionic strength was maintained at 1.0 with KCl or Me$_4$NCl, T = 25 °C.

values, at which the contribution of the k_{H^+} term to the observed rate becomes large. Approximate corrections for these salt and solvent effects on $k_{cat.}$ were calculated[2] from

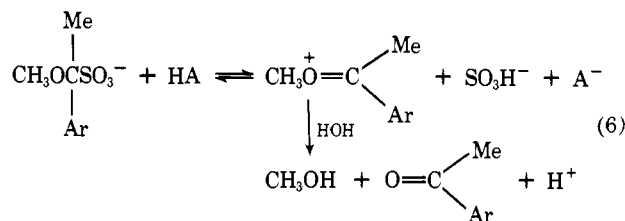$$k_{cat.}' = k_{cat.} + [P(\text{fraction acid}) + Q(\text{fraction base})]k_0 \quad (5)$$

and $P = Q = -0.1$ for average salt and solvent effects of +10% M^{-1} for *p*-methoxyacetophenone bisulfite, and $P = Q = 0.1$ for average salt and solvent effects of −10% M^{-1} for *p*-nitroacetophenone bisulfite. The values of k_{BH}' listed in Table II were determined from plots of $k_{cat.}'$ against the fraction of the buffer in the acidic form. In the Brønsted plots of Figures 4 and 5, the corrected values of the catalytic constants are plotted as the symbols and in all cases the uncorrected values fall within the error limits indicated. Statistical factors of p = 1 and q = 2 were used for citric acid (Figure 4), assuming that the acidic central carboxyl group is primarily responsible for the observed catalysis.

The solvent isotope effects in 99% deuterium oxide are k_{H^+}/k_{D^+} = 0.81 and 0.56 for *p*-methoxyacetophenone bisulfite

and for 1-(4-methoxyphenyl)-1-methoxyethanesulfonic acid (**2a**), respectively. For the latter compound, $k_{cat.}^{H_2O}/k_{cat.}^{D_2O}$ = 2.2 for citric acid, 50% monoanion (Figure 3). Under these conditions catalysis by citric acid accounts for 90% of the observed catalysis in water.

Discussion

Cleavage of the α-Methoxysulfonic Acids, 2. Catalysis of the substituted phenyl-α-methoxyethanesulfonic acid reactions is described by eq 6. In the breakdown direction, the catalyzing

$$
\begin{array}{c}
\text{Me} \\
| \\
\text{CH}_3\text{OCSO}_3^- \;+\; \text{HA} \;\rightleftharpoons\; \text{CH}_3\overset{+}{\text{O}}{=}\text{C}\overset{\text{Me}}{\underset{\text{Ar}}{\diagup\backslash}} \;+\; \text{SO}_3\text{H}^- \;+\; \text{A}^- \\
| \\
\text{Ar}
\end{array}
$$

$$
\downarrow \text{HOH} \qquad\qquad (6)
$$

$$
\text{CH}_3\text{OH} \;+\; \text{O}{=}\text{C}\overset{\text{Me}}{\underset{\text{Ar}}{\diagup\backslash}} \;+\; \text{H}^+
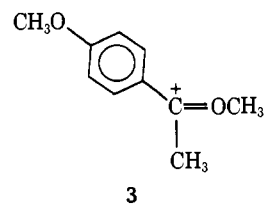$$

acid increases the leaving ability of the sulfite group by partial proton donation; general acid catalysis avoids the formation of the unstable fully protonated sulfonic acid, which would be an intermediate in a specific acid catalyzed reaction. In the reverse, synthesis direction, the catalyzing base removes a proton from the weakly nucleophilic bisulfite ion to facilitate S–C bond formation and, again, avoids the formation of a protonated sulfonic acid intermediate. This mechanism is analogous to the mechanism of general acid catalysis of the hydrolysis of acetals,[6] except that the catalysis presumably involves proton donation to a sulfite oxygen atom[7] rather than to the atom that is directly bonded to carbon.

The Brønsted α value for general acid catalysis of the breakdown reaction is ~0.6 (Figure 4). Competition from proton catalysis and the water reaction (dashed lines, Figure 4) make catalysis of the breakdown of the α-methoxysulfonic acids difficult to detect.[8] However, several considerations suggest that the observed general acid catalysis is real and does not represent a solvent or specific salt effect on the rate.

The strongest evidence that the observed catalysis does not represent a nonspecific solvent effect on the background proton catalyzed reaction comes from an examination of the effects of citric and formic acids on the rate at two widely different pH values. If citric acid, for example, increased k_{H^+} by a solvent effect, the same percent rate increase in k_{H^+} should be observed at any pH value, whereas, if citric acid increases the rate by general acid catalysis, this rate increase will disappear at low pH values because it will be swamped out by the much faster proton catalyzed reaction. In fact, 1 M citrate and formate buffers give rate increases of 90 and 50% at pH 3.0–3.1 but no rate increase at pH 0.5–0.7 (Table III), showing that the observed acid catalysis does not represent an effect on k_{H^+}. The facts that the catalysis is dependent on the buffer acid concentration at different buffer ratios (Figure 3 and Table II) and that the rate constant at pH 3.5 is unchanged when potassium trifluoroacetate is substituted for potassium chloride suggest that the observed catalysis is not a result of specific salt effects. The solvent isotope effect of k_{H_2O}/k_{D_2O} = 2.2 for catalysis by citric acid buffers provides further evidence that the rate increase involves true catalysis, with a significant loss of zero-point energy for the proton in the buffer catalyzed reaction.

It can be argued that buffer catalysis in this and related reactions *must* exist.[9] There is evidence that the reaction of sulfite dianion with the oxocarbonium ion **3** is diffusion controlled and that the attack of HSO_3^- is not.[4] When this is the case, there must exist a pathway for concerted or hydrogen bond catalysis of the addition of sulfite to the oxocarbonium ion and, therefore, for catalysis of the breakdown of the α-methoxysulfonic acid in the reverse direction. The reason for
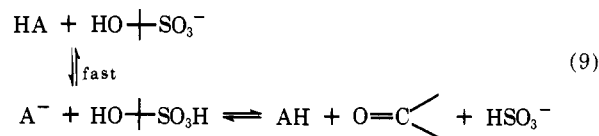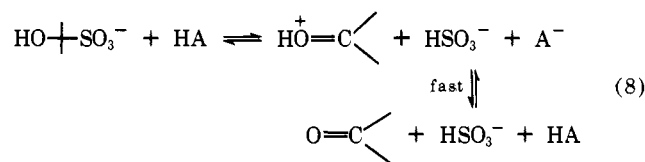
$$
\begin{array}{c}
\text{CH}_3\text{O}\text{-}\langle\text{C}_6\text{H}_4\rangle\text{-}\overset{+}{\text{C}}{=}\text{OCH}_3 \\
| \\
\text{CH}_3
\end{array}
$$

3

this is simply that, if the reaction of SO_3^{2-} is diffusion controlled, anything that increases the concentration of SO_3^{2-} will increase the observed rate. In the presence of buffer acids at pH values below the pK_a of HSO_3^-, the concentration of SO_3^{2-} will be increased by hydrogen bonding to the acid, as described by the equilibrium constant K_{AB} of

$$
SO_3^{2-} + HA \overset{K_{AB}}{\rightleftharpoons} SO_3^{2-} \cdot HA \qquad (7)
$$
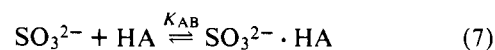
A rough estimation of $K_{AB} \approx 6.5\ \text{M}^{-1}$ for an acid of $pK_a = 3$, according to an equation proposed by Hine,[10] suggests that this increase should be sufficient to give a detectable increase in total SO_3^{2-} concentration and, therefore, in the observed rate. A rate increase caused by hydrogen bonding of HA to SO_3^{2-} will appear experimentally as a kinetically equivalent term involving A^- and HSO_3^- in the addition direction and as general acid catalysis in the breakdown direction (eq 6). Although this argument indicates that catalysis must exist in a system of this kind, a still lower energy concerted mechanism is likely to be preferred if the energy barriers for bond formation or cleavage in the stepwise processes are small or absent. This appears to be the case in the reaction described here, as will be discussed shortly.

Cleavage of Acetophenone Bisulfites (1). General acid catalysis of the breakdown of acetophenone bisulfites could occur through either of two kinetically ambiguous mechanisms, as shown in eq 8 and 9. It is apparent that these two mechanisms

$$
\text{HO}\text{-}\text{SO}_3^- + \text{HA} \rightleftharpoons \overset{+}{\text{HO}}{=}\text{C}\diagdown + \text{HSO}_3^- + \text{A}^-
$$
$$
\text{fast} \downarrow\uparrow \qquad\qquad (8)
$$
$$
\text{O}{=}\text{C}\diagdown + \text{HSO}_3^- + \text{HA}
$$

$$
\text{HA} + \text{HO}\text{-}\text{SO}_3^-
$$
$$
\downarrow\uparrow \text{fast} \qquad\qquad (9)
$$
$$
\text{A}^- + \text{HO}\text{-}\text{SO}_3\text{H} \rightleftharpoons \text{AH} + \text{O}{=}\text{C}\diagdown + \text{HSO}_3^-
$$

are kinetically ambiguous because the initial reactants and the stoichiometric composition and charge of the transition state of the rate-determining step are the same for the two mechanisms. This ambiguity does not exist for the α-methoxysulfonates, **2**, because substitution of a methyl group for the hydroxyl proton makes the mechanism of eq 9 impossible so that these compounds must react according to eq 6, which is analogous to the mechanism of eq 8. Equation 8 represents a class n mechanism,[9] with catalysis of the entering and leaving of the nucleophile as described for eq 6. Equation 9 represents a class e mechanism with proton donation from the buffer acid to the carbonyl group, the electrophilic reagent, in the addition direction and proton removal from the hydroxyl group of an uncharged α-hydroxysulfonic acid in the breakdown direction (the sulfonic acid is formed by protonation of the sulfonate anion in an initial fast equilibrium step).

The following evidence shows that catalysis of the breakdown of acetophenone bisulfites is similar to that of the kinetically unambiguous breakdown of α-methoxysulfonates according to eq 6 and that at least some, and probably all, of the catalysis of the acetophenone bisulfite reactions occurs according to the equivalent mechanism of eq 8.

(1) The methyl group of the α-methoxysulfonates, **2**, is a model for the proton that remains fixed on the carbonyl oxygen atom in the rate-determining step of the mechanism of eq 8. The fact that the rate constant for the acid catalyzed breakdown of p-methoxyphenyl-α-methoxyethanesulfonate, **2a**, is only sixfold smaller than that for p-methoxyacetophenone bisulfite, **1a**, means that at least part of the latter reaction must occur by the same mechanism as the former reaction (eq 6 and 8). It is likely that the protonated carbonyl group and the transition state leading to its formation according to the mechanism of eq 8 are stabilized by hydrogen bonding to the solvent, which is not possible for the oxocarbonium ion forming reaction of eq 6, so that stabilization by this hydrogen bonding may well account for the factor of 6 and all of the p-methoxyacetophenone reaction may reasonably be explained by the mechanism of eq 8. Substitution of a proton for a methyl group in **4** causes a larger increase in the proton catalyzed rate of

$$
\begin{array}{c}
\text{OH} \quad \text{OR} \\
| \quad / \\
\text{Et}_2\text{CCH} \\
\quad \backslash \\
\quad \text{OMe}
\end{array}
$$

4, R = Me, H
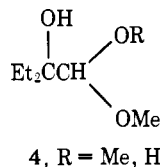
cleavage, by an estimated factor of 500-fold.[11]

(2) Structure–reactivity correlations show similar behavior for the breakdown of the α-hydroxy and α-methoxy compounds with respect to both polar and resonance effects of substituents on the benzene ring (Figure 6). Hammett plots based on σ and σ^+ are nonlinear but a satisfactory correlation is obtained according to eq 10[4,12,13] with $\rho = -1.6$, $\rho^r = -1.0$,

$$
\log (k/k_0) = \rho\sigma^n + (\rho^r/\rho)(\sigma^+ - \sigma^n) \tag{10}
$$

and $r^+ = 0.6$ for the acetophenone bisulfites (upper line) and $\rho = -2.0$, $\rho^r = -1.0$, and $r^+ = 0.5$ for the phenyl-α-methoxyethanesulfonic acids (lower line). The parameters ρ and ρ^r are measures of polar and resonance effects, respectively, and $\rho^r/\rho = r^+$. The absolute difference in rate between the two series of compounds is approximately an order of magnitude.

(3) The Brønsted slope, α, for general acid catalysis of the breakdown of p-methoxyacetophenone bisulfite is 0.54 ± 0.05 (Figure 5, upper line). This is similar to the value of $\alpha = 0.6$ for breakdown of the p-methoxyphenyl-α-methoxyethanesulfonate and is consistent with the same mechanism of acid catalysis for both reactions. The value of α for p-nitroacetophenone bisulfite is 0.31 ± 0.03 (Figure 5, lower line) and a two-point Brønsted plot for p-chloroacetophenone bisulfite based on the rate constants in Table II gives a value of $\alpha = 0.4$. Although these Brønsted slopes are not of high accuracy because of the relatively small catalytic constants and the different classes of acids examined, the *change* in the slope with electron-withdrawing substituents appears to be well beyond experimental error. This change can be described by an interaction coefficient[14-16] $\partial\alpha/\partial\sigma = 1/c_1 = p_{xy} = -0.18$; however, the data are not of sufficient accuracy to demonstrate more than the existence and sign of this coefficient.

(4) The solvent isotope effects for the proton catalyzed breakdown of p-methoxyacetophenone bisulfite and p-methoxyphenyl-α-methoxyethanesulfonic acid are both inverse, with similar, but not identical, values of $k_{H^+}/k_{D^+} = 0.81$ and 0.56, respectively.

(5) The observed Hammett ρ values are difficult to explain according to the mechanism of eq 9 but are consistent with eq 8. The overall equilibrium of eq 9 is correlated by a value of $\rho = -1.2$ ($\rho^r = -0.8$).[4] The observed rate constants are correlated by $\rho = -1.6$ ($\rho^r = -1.0$), so that the transition state is stabilized more than the product by electron-donating sub-
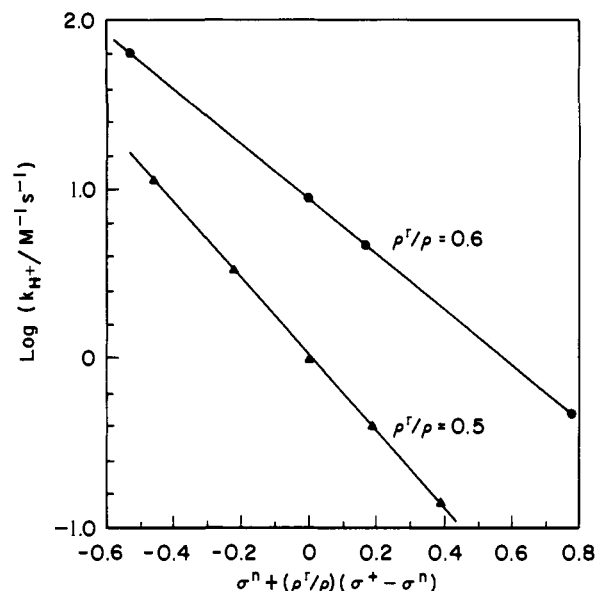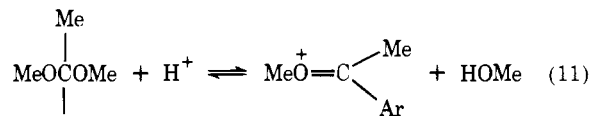
Figure 6. Dependence upon $[\sigma^n + (\rho^r/\rho)(\sigma^+ - \sigma^n)]$ of the acid catalyzed breakdown of acetophenone bisulfites ($\bullet$), $\rho^r/\rho = 0.6$, and of 1-methoxy-1-arylethanesulfonic acids ($\blacktriangle$), $\rho^r/\rho = 0.5$, at ionic strength 1.0 with KCl and 25 °C.

stituents according to this mechanism. The value of ρ for general acid catalyzed attack of bisulfite on the carbonyl group is given by $\rho_{attack} = \rho_{breakdown} - \rho_{eq} = -0.4$, ($\rho^r_{attack} = -0.2$), requiring that the transition state for addition to the carbonyl group is stabilized by electron-donating substituents. This is a surprising result for a reaction in which protonation of the carbonyl group is far from complete ($\alpha = 0.54$) and we are not aware of a precedent for general acid catalyzed addition to the carbonyl group in which the rate is increased by electron-donating substituents. On the other hand, the equilibrium formation of an oxocarbonium ion from substituted acetophenone dimethyl ketals (eq 11) proceeds with an estimated

$$
\begin{array}{c}
\text{Me} \\
| \\
\text{MeOCOMe} + \text{H}^+ \rightleftharpoons \text{MeO}\overset{+}{=}\text{C}\overset{\text{Me}}{\underset{\text{Ar}}{\diagdown}} + \text{HOMe} \tag{11} \\
| \\
\text{Ar}
\end{array}
$$

value of $\rho = -3.6$ ($\rho^r = -2.2$).[4] If it is assumed that the same ρ values describe the equilibrium formation of oxocarbonium ions from acetophenone bisulfites and their O-methyl analogues, as described in eq 6 and the first step of eq 8, then the observed values of $\rho = -1.6$ and -2.0, respectively ($\rho^r = -1.0$), for the rate constants for acid catalyzed breakdown of these compounds indicate that the transition state is roughly halfway between reactants and the oxocarbonium ion product, as measured by both polar and resonance substituent effects. This is a reasonable result and is consistent with the mechanism of eq 8. The acid catalyzed hydrolysis of acetophenone ketals[4] is also accelerated by electron-donating substituents with similar values of $\rho = -2.0$ and $\rho^r = -0.7$.

We conclude that the acid catalyzed addition–elimination reaction of bisulfite and carbonyl compounds proceeds through a class n mechanism that is similar in several respects to the mechanism of acid catalyzed cleavage of acetals and ketals. The major experimental difference between the two series of reactions is that electron-withdrawing substituents decrease the Brønsted α coefficient for the bisulfite reaction but increase α for the acid catalyzed cleavage of methyl phenyl acetals of substituted benzaldehydes.[17] An increase in α with electron-withdrawing substituents on the benzene ring is expected for a class n reaction mechanism in which there is motion of the proton that is concerted or coupled with heavy atom rear-
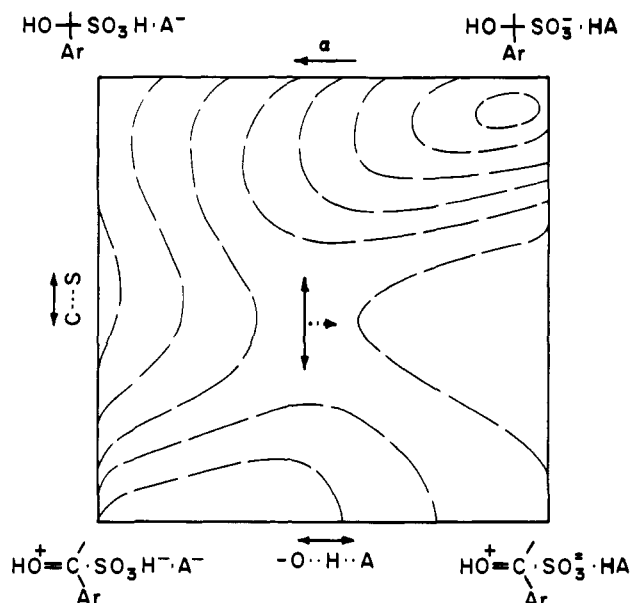
Figure 7. Three-dimensional reaction coordinate diagram for the general acid catalyzed cleavage of carbonyl bisulfites according to the mechanism of eq 8.

rangements in the transition state and which may be described by a more-or-less diagonal reaction coordinate on a three-dimensional energy diagram with separate axes for proton transfer and heavy atom rearrangements.[15-17] A decrease in α with electron-withdrawing substituents is consistent with a diagonal reaction coordinate for a class e reaction mechanism such as that of eq 9 (this corresponds to a positive p_{xy} coefficient and a negative curvature c' on the energy surface; however, an increase in α with electron-withdrawing substituents with negative p_{xy}, and positive c' is also consistent with a class e mechanism).[16]

The observed change in α in the bisulfite reaction is consistent with a class n reaction mechanism if the proton is in the potential well of a hydrogen bond, with a vertical reaction coordinate that corresponds to C–S bond cleavage in the transition state (Figure 7). A set of contour lines has been drawn on the diagram of Figure 7, with no barrier for proton transfer and a small barrier for C–S bond formation from sulfite dianion. These contour lines are speculative and indicate one conceivable geometry of the surface; we do not mean to suggest that we prefer this to other possible geometries with a vertical reaction coordinate.

A transition state of this kind is consistent with the following.

(1) A decrease in α with electron-withdrawing substituents on the benzene ring is expected for this mechanism because a less basic sulfonate moiety will bring about a smaller shift of the proton away from HA in the potential well for proton motion in the transition state. There is direct evidence for such a shift in the position of the proton in the potential well of the hydrogen bond formed between pyridine 1-oxide and a series of acids of varying strength.[18] This may be regarded as an "anti-Hammond" effect with motion of the proton perpendicular to the reaction coordinate.[16,19] In the diagram of Figure 7 it corresponds to a motion of the transition state to the right, as shown by the dotted arrow, when the energy of the bottom and the left side of the diagram is increased by electron-withdrawing substituents on the benzene ring. The data also require that there is a decreased (more negative) ρ with increasing strength of the catalyzing acid; this relationship is described by $\partial\alpha/\partial\sigma = \partial\rho/-\partial pK_{HA} = p_{xy}$.[16] This change reflects the decrease in the negative charge on the sulfonate as the proton moves closer to the sulfonate in the hydrogen bond formed with

stronger acids. If this interpretation is correct, it means that a negative value of $\partial\alpha/\partial\sigma$ is not necessarily diagnostic of a class e reaction mechanism. The change in α in this particular case arises because electron-withdrawing substituents on the benzene ring not only lower the energy of the top relative to the bottom edge of the diagram, but also cause a (smaller) decrease in the energy of the upper right relative to the upper left corner. The value of ρ for the ionization of benzylsulfonic acids, which is a measure of this change in energy, is probably similar to the value of $\rho = 0.5$ for the ionization of phenylacetic acids.[20]
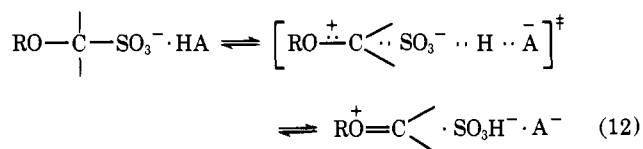
(2) In the cleavage of an acetal the proton is added directly to the oxygen atom that is undergoing bond cleavage to carbon with a resultant large increase in basicity, whereas in the cleavage of a bisulfite addition compound the proton is added to an oxygen atom that is separated from the bond undergoing cleavage to carbon by an intervening sulfur atom. It appears reasonable that there should be more coupling, manifested by a diagonal component in the reaction coordinate, between bond formation to the proton and bond cleavage to carbon when the same atom is involved in both processes than when two atoms are involved and the overall reaction involves at least five atoms. Catalysis of bisulfite addition and expulsion probably represents a *concerted* reaction mechanism, in the sense that it does not proceed through steps or intermediates, which is enforced by the absence of a significant barrier for proton transfer and, probably, for the formation of the C–S bond in the lower right corner of the diagram of Figure 7. However, the structure–reactivity data provide no indication of *coupling*, in the sense of simultaneous motion of the proton and C–S bond cleavage.

(3) The solvent deuterium isotope effect of $k_{H_2O}/k_{D_2O} = 2.2$ for the bisulfite reaction catalyzed by citric acid buffers is larger than might be expected for an ordinary hydrogen bond but smaller than the maximum that could be expected if there were complete loss of the zero point energy of the transferred proton in the transition state. It is consistent with a transition state in which there has been considerable *transfer* of the proton to a position roughly midway between the donor and acceptor atoms, as indicated by α values in the range of 0.3 to 0.6, but in which most of the zero point energy of the proton is retained. It is also within the range of values that have been observed for stable hydrogen bonds, with no intervening water molecule, that lie in a broad, single potential well or in a double well with a small barrier and very rapid exchange of the proton between the two wells.[21]

(4) Hydrogen bonds to proton acceptors that have opposite charges on adjacent atoms (5) have an enhanced stability, for a given basicity,[22] and are likely to be strong hydrogen bonds with large deuterium isotope effects.[18,21] Sulfite ion (6) is an acceptor of this kind.

5

6
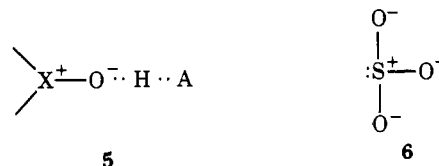
(5) It has been pointed out above that the evidence for a diffusion-controlled reaction of sulfite dianion with the oxocarbonium ions formed from acetophenone ketals means that there should be significant buffer catalysis of sulfite addition and expulsion at low pH values by a hydrogen bonding or some lower energy mechanism. It is reasonable that, if there is little or no barrier for proton transfer and for the addition of sulfite dianion to the oxocarbonium ion in an encounter complex, the lowest energy transition state for the buffer catalyzed reaction should resemble that for the concerted mechanism shown in eq 12 (R = CH_3 or H), rather than that for the diffusion of a

$$RO-\overset{|}{\underset{|}{C}}-SO_3^- \cdot HA \rightleftharpoons \left[RO \overset{+}{=\!=} C \!\!\diagdown\!\! SO_3^- \cdots H \cdots A \right]^{\ddagger}$$

$$\rightleftharpoons RO\overset{+}{=}C\!\!\diagdown \cdot SO_3H^- \cdot A^- \quad (12)$$

hydrogen-bonded complex, $SO_3^{2-} \cdot HA$, to the oxocarbonium ion. The fact that the values of α and ρ for the rate constants are approximately half of those for the equilibrium constants for complete proton transfer and C–S cleavage, respectively, support a central transition state as shown in Figure 7.[23]

The principal driving force for catalysis of this reaction by the mechanism of eq 8 arises from the instability of the sulfonic acid intermediate in the upper left corner of the diagram of Figure 7. The reaction mechanism avoids this intermediate by following a path near the center of the diagram. The pK_a of the free sulfonic acid has been estimated to be approximately -8[2,24] and there is, therefore, a strong driving force for avoiding its formation by hydrogen bonding to a buffer base. General acid catalysis of most carbonyl addition reactions involves proton donation to the carbonyl oxygen atom through a class e mechanism (e.g., eq 9) and we are not aware of a well-established precedent for the specific acid–general base catalysis addition mechanism of eq 8 in which the carbonyl group is protonated in an initial fast step, followed by general base catalysis of nucleophile attack. There is no evidence for bifunctional acid–base catalysis involving both the carbonyl and sulfite groups because the rate constants for catalysis by bifunctional acids do not fall above the Brønsted line that passes through the catalytic constant for the proton, which is not capable of bifunctional catalysis, and because there is no large increase in rate relative to the α-methoxysulfonic acid, which is not subject to bifunctional catalysis. The class n mechanism is presumably observed in this reaction because of the very low nucleophilicity of HSO_3^-, the instability of the product formed from the addition of HSO_3^-, and the fact that catalysis of this kind is enforced by the diffusion-controlled reaction of SO_3^{2-} with the oxocarbonium ion. The fact that the observed catalysis is somewhat less than that estimated from the Hine equation[10] suggests that the value of $\tau = 0.024$ used to estimate K_{AB} from this equation may be too large.

References and Notes

(1) Supported in part by grants from the National Science Foundation (BM471-01501 A03) and the National Institute of General Medical Sciences of the National Institutes of Health (GM 20888). P.R.Y. was partially supported by a fellowship (CA 05356) from the National Cancer Institute of the National Institutes of Health.
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(23) According to the proposed mechanism there should be a change in the position of the proton and in α with changing substituents on the catalyzing acid, as well as on the acetophenone bisulfite, which should give rise to a Brønsted plot with upward curvature and a negative sign of the coefficient $\partial \alpha / \partial pK_{HA} = p_x$.[16] In fact, the data are not inconsistent with such curvature and, if the points for the "water" reaction are included in the same plot, show curvature. The change in α with changing substituent on the acetophenone bisulfite, $\partial \alpha / \partial \sigma = p_{xy}$, may then be demonstrated by plotting log (k_i / k_j) against pK_{HA}, where k_i and k_j are rate constants for catalysis of the reactions of two acetophenone bisulfites by acids of the same pK (the slope of the resulting Brønsted line is 0 for $i = j$). The coefficients p_x and p_{xy} are themselves not likely to remain constant over a large range of structural variation in a system of this kind; they must approach zero as the proton approaches limiting positions near the donor or acceptor atoms.
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Naphtho[1,8-*cd*:4,5-*c'd'*]bis[1,2,6]thiadiazine.
A Compound of Ambiguous Aromatic Character

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Abstract: The synthesis and chemical and physical properties of the title compound are reported. Naphtho[1,8-*cd*:4,5-*c'd'*]-bis[1,2,6]thiadiazine (5) is found to possess the chemical stability normally associated with an aromatic compound but its electrochemistry, electronic spectrum, and ^1H NMR chemical shift suggest that the compound is antiaromatic. On this basis it is concluded that 5 is a compound of ambiguous aromatic character. It is pointed out that many of the traditional measures of aromatic character are non-ground-state properties when applied to certain classes of compounds (including 5). The chemical stability of the molecule is explained on the basis of the chemical inertness of the –NSN– linkage (relative to other structural units).

In attempting to test the generally accepted definitions of aromaticity chemists have synthesized many new compounds with unusual chemical and physical properties.[1] It is generally held that certain of these properties, in conjunction with various structural classifications, may serve as arbiters of the aromatic character of any new material. Among these tests for aromatic character, the foremost seem to be the resonance energy and ring current criteria, although other evi-