Dual Reactivity of Methoxymethyl Benzenesulfenate in Nucleophilic Substitution[1)]

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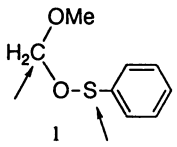
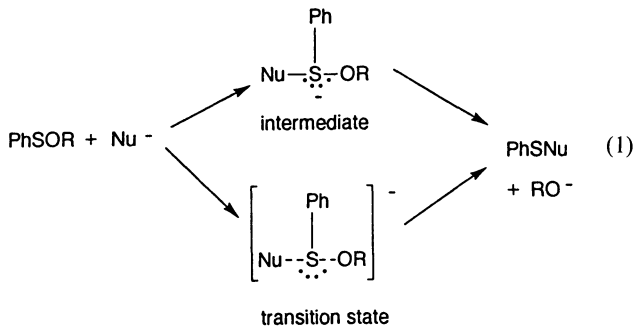
Hydrolysis of methoxymethyl benzenesulfenate is catalyzed by both acid and base. Acid-catalyzed hydrolysis is further accelerated by various nucleophiles like halide ions, thiocyanate, dialkyl sulfide, and the substrate itself. The catalytic constants coincide with those for ethyl benzenesulfenate within 2-fold in magnitude. The nucleophilic reactivity strongly suggests the reaction at the sulfenyl sulfur, but examination of the products from the ^{18}O-labeled substrate showed that the bond cleavage occurs mostly between the oxygen and the proformyl carbon except for the acid-catalyzed water reaction which undergoes the S–O cleavage. A mechanism for a nucleophilic reaction at the sulfur to form a sulfurane intermediate which breaks down with the C–O cleavage is presented. The hydrolysis rate is also strongly dependent on the second order of buffer concentrations in carboxylate and tertiary amine buffer solutions. The third-order term involves both the general acid and the conjugate base of the buffer, and the latter reacts at the sulfur as a nucleophile in the rate-determining step but leads to the C–O cleavage in the same way as the other catalytic nucleophiles.

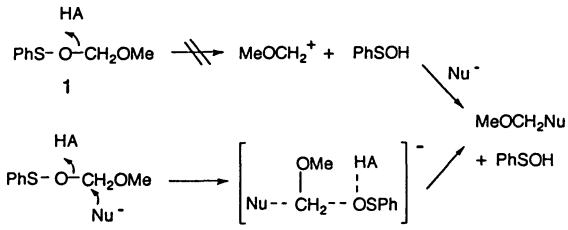
Methoxymethyl benzenesulfenate (**1**) has dual structural characteristics as an ester of benzenesulfenic acid and as an acetal of formaldehyde. Typical sulfenate esters undergo nucleophilic attack at the sulfur to lead to the S–O bond cleavage.[2)] The nucleophilic substitution at sulfur could in principle take place concertedly via an S_N2-like pathway or stepwise through a hypervalent intermediate (Eq. 1).[3,4)] The intermediacy of the hypervalent sulfur compound depends on its lifetime and definitive evidence has been reported only in few cases.[3,4)] We have recently found that the acid-catalyzed hydrolysis of ethyl benzenesulfenate occurs via a hypervalent intermediate (sulfurane) formed by a nucleophilic attack at the sulfur.[5)]





(1)

Alternatively, the methoxymethyl sulfenate **1** may react at the proformyl carbon as an acetal in acidic media to liberate sulfenic acid (Eq. 2). Methoxycarbenium ion is a possible intermediate of this reaction. However, it is considered that the lifetime of methoxcarbenium ion *in aqueous solution* is too short for this ion to be a real intermediate of the reaction.[6–8)] Cleavage of some methoxymethyl derivatives (**2a** and **2b**) was found to occur by nucleophilic assistance to avoid the methoxycarbenium intermediate[9,10)] while such assistance was weak and not easily observed for other derivatives like **2c**.[11)]



(2)

$MeOCH_2X$ **2a**, X=2,4-$(NO_2)_2C_6H_3O$
b, X=ArN^+Me_2
c, X=4-ClC_6H_4O

Simple heterolytic cleavages at the S–O (as a sulfenate) and at the C–O bond (as an acetal) respectively lead to the reactions shown in Eqs. 3 and 4.

$$PhS\text{-}OCH_2OMe \longrightarrow PhS^+ + MeOCH_2O^- \quad (3)$$

$$PhSO\text{-}CH_2OMe \longrightarrow MeOCH_2{}^+ + PhSO^- \quad (4)$$

Since the pK_a of PhSOH is evaluated to be about 10,[12)] the sulfenic acid is more acidic than the methoxy alcohol ($pK_a \approx 13.5$),[13)] and $PhSO^-$ may be a better nucleofuge than $MeOCH_2O^-$ (and in acidic media PhSOH may leave more easily than $MeOCH_2OH$). On the other hand, methoxycarbenium ion is more stable than benzenesulfenium ion in the gas phase in a sense that the reaction (5) is exothermic.[14)] Although the lifetime of methoxycarbenium ion in aqueous media is too short to

be a discrete intermediate,[6-8] both of the factors should favor the C–O cleavage over the S–O cleavage of **1**.

$$PhS^+ + MeOCH_3 \longrightarrow PhSH + MeOCH_2^+ \quad (5)$$

The methoxymethyl sulfenate **1** has shown in fact a dual character in its reactivity. The product analysis of the ^{18}O-labeled substrate showed that the nucleophilic reaction with **1** occurs mostly through bond cleavage between the sulfenic oxygen and the proformyl carbon suggesting the carbon attack (via the acetal route of Eq. 2), while the rate of reaction was found to be strongly dependent on the added nucleophiles and was close to that for the ethyl sulfenate in conformity to the reaction at the sulfenyl sulfur.[1a,5]

The hydrolysis of **1** is strongly buffer-dependent in carboxylate and tertiary amine buffer solutions, following a second order of buffer concentration.[1b] The general acid and the conjugate base (as a nucleophile) are cooperatively participating in the transition state to accelerate the reaction. Although well-established third-order terms of buffer catalysis has rarely been found in aqueous solution,[15] such a cooperative catalysis is generally presumed for enzymic reactions.[16] Detailed analyses of the cooperative catalysis may rend important implications to the enzymic mechanism as well as the mechanistic chemistry in general.

In this paper will be given details of the results on catalysis of hydrolysis of the methoxymethyl sulfenate **1**, and a possible mechanism will be proposed for the reaction involving a rate-determining nucleophilic reaction at the sulfur but leading to the C–O cleavage in the ensuing step. Driving forces for the cooperative general-acid catalyzed nucleophilic reaction of the sulfenate will also be considered.

Results

When the sulfenate **1** is dissolved in acidic or buffer solutions below pH 7, *S*-phenyl benzenethiosulfinate (**4**) is quantitatively formed as a final product (Eq. 6).[1]

$$\mathbf{1} \longrightarrow \underset{\mathbf{3}}{PhSOH} \longrightarrow \underset{\mathbf{4}}{PhS(O)SPh} \quad (6)$$

The primary hydrolysis product, benzenesulfenic acid (**3**), undergoes very readily condensation by itself or with the sulfenate **1** to give **4**. The UV spectrum of **1** smoothly changes into that of **4** (λ_{max}, 275 nm) with an isosbestic point at 246 nm, and the reaction was monitored by an increase in the absorbance at 275 nm. These reaction features are closely similar to those observed for a simple sulfenate, ethyl benzenesulfenate **5**.[5]

Kinetics in Perchloric Acid. Although pseudo-first-order plots were nicely linear to >90% conversion in buffer solutions and in the presence of nucleophiles (see below), first-order kinetics broke down in perchloric acid in the absence of any added nucleophile. The "initial" rate constants k_i were obtained from the ln ΔA – t plots in the same way as in the case of the ethyl sulfenate **5**.[5] A short induction period was seen at higher acid concentrations ($[HClO_4]$=0.02—0.1 M) (1 M=1 mol dm^{-3}), but it could not be observed at still higher concentration of acid ($[HClO_4]$>0.2 M) because of the rapidity of the reaction ($t_{1/2}$<20 s): The initial part of the reaction cannot be observed. In these cases, k_i was determined from the steepest slope just after the induction or the first observable slope (at about 5 s after mixing). Results obtained at 25 °C and the ionic strength of 0.50 maintained with $NaClO_4$ are summarized in Table 1.

The k_i inceases linearly with the initial substrate concentration $[\mathbf{1}]_0$ (Eq. 7).

$$k_i = k_0 + k_{SE}'[\mathbf{1}]_o \quad (7)$$

The substrate can be a catalyst for the hydrolysis, and the water- and substrate-catalyzed reactions (k_0 and k_{SE}') are competing with each other. This is a reason for the deviation from the first-order kinetics. The rate

Table 1. Initial Rate Constants ($10^3\ k_i/s^{-1}$) in Perchloric Acid at Various Initial Concentrations of the Substrate **1**[a]

10^3 [$HClO_4$]	10^4 [**1**]$_o$/M				$10^3\ k_0$	k_{SE}'	k_{SE}^{H}[b]
M	0.50	1.00	1.50	2.00	s^{-1}	$M^{-1}s^{-1}$	$M^{-2}s^{-1}$
0.05	0.0490	0.0664	0.0764	0.0856	0.0394	0.240	4800
0.10	0.0592	0.0728	0.0847	0.0960	0.0476	0.244	2440
0.20	0.0860	0.105	0.122	0.141	0.0680	0.364	1820
0.50	0.192	0.231	0.260	0.304	0.156	0.730	1460
1.0	0.310	0.353	0.389	0.433	0.270	0.810	810
2.0	0.607	0.703		0.875	0.521	1.78	890
5.0	1.49	1.70	1.89	2.10	1.29	4.04	808
10	2.90	3.33		4.10	2.52	7.96	796
20	5.68[c]	6.32	7.09	7.70	4.99	13.7	685
50	12.3[c]	14.5[c]	16.1	19.0	10.1	43.4	868
100	20.9[c]	24.7[c]	29.7[c]	33.2	16.7	83.8	838
200	35.4	45.7	51.0		28.4	156	780
500	63.3	83.7	99.0		46.3	357	714

a) Measured at 25 °C and an ionic strength of 0.50 ($NaClO_4$). b) $k_{SE}^{H}=k_{SE}'/[HClO_4]$. c) A short induction period was observed.

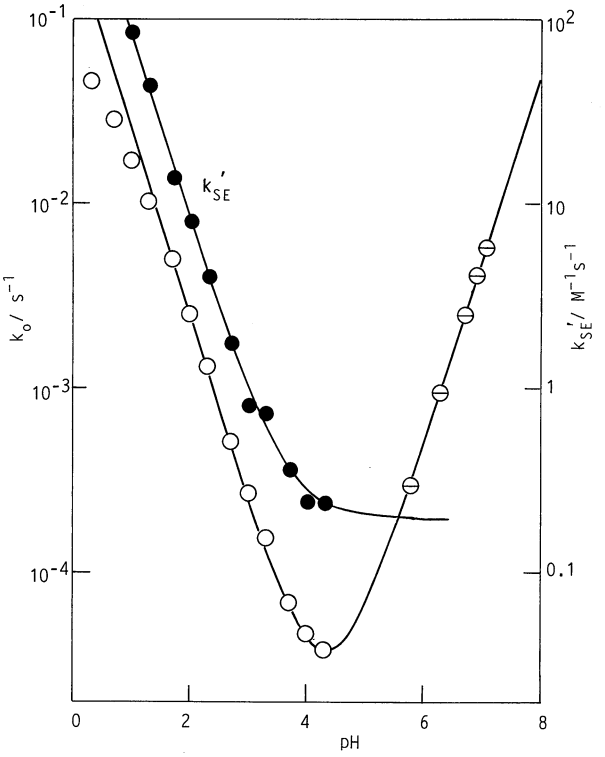


Fig. 1. pH-rate profiles for the hydrolysis of **1** at the ionic strength of 0.50 and 25 °C. k_0 obtained from k_i in perchloric acid (○) and from k_{obsd} in buffer solutions (⊖): left ordinate. k_{SE}' (●) for the substrate catalysis: right ordinate.

constants k_0 and k_{SE}' obtained both increase with acidity of the reaction medium and are logarithmically plotted against pH (−log[$HClO_4$]) in Fig. 1. The slopes for log k_0–pH and log k_{SE}'–pH are both −1 in the pH range 1—3, but the rate constants level off at higher pH.[17] Both of the reactions are catalyzed by acid but the uncatalyzed reactions become important at higher pH (Eqs. 8 and 9). The k_0 increases at still higher pH as examined in buffer solutions (see below).

$$k_0 = k_{H_2O} + k_H[H^+] + k_{OH}[OH^-] \quad (8)$$

$$k_{SE}' = k_{SE} + k_{SE}^{H}[H^+] \quad (9)$$

The catalytic constants evaluated are: k_H=0.242(±0.004) $M^{-1}s^{-1}$, k_{H_2O}=1.5(±0.4)×10^{-5} s^{-1}, k_{OH}=4.87(±0.14)×10^4 $M^{-1}s^{-1}$, k_{SE}^{H}=780(±60) $M^{-2}s^{-1}$, and k_{SE}=0.20(±0.04) $M^{-1}s^{-1}$.

Kinetic solvent isotope effects were examined by comparing k_i (2.18×10^{-3} s^{-1}) obtained at [$DClO_4$]=5.0×10^{-3} M and [**1**]$_0$=1.0×10^{-4} M with the corresponding value in $HClO_4$ (1.70×10^{-3} s^{-1}). The isotope effects are inverse: k_H/k_D=0.78.

Effects of Added Nucleophiles. The hydrolysis of **1** is strongly accelerated by added nucleophiles such as halide ions and a neutral dialkyl sulfide. In the presence of these nucleophiles, the UV spectral changes closely resemble that observed in perchloric acid and the reaction follows pseudo-first-order kinetics. The observed rate constants k_{obsd} obtained from the 275-nm absorbance in acidic solutions containing Cl^-, Br^-, I^-,

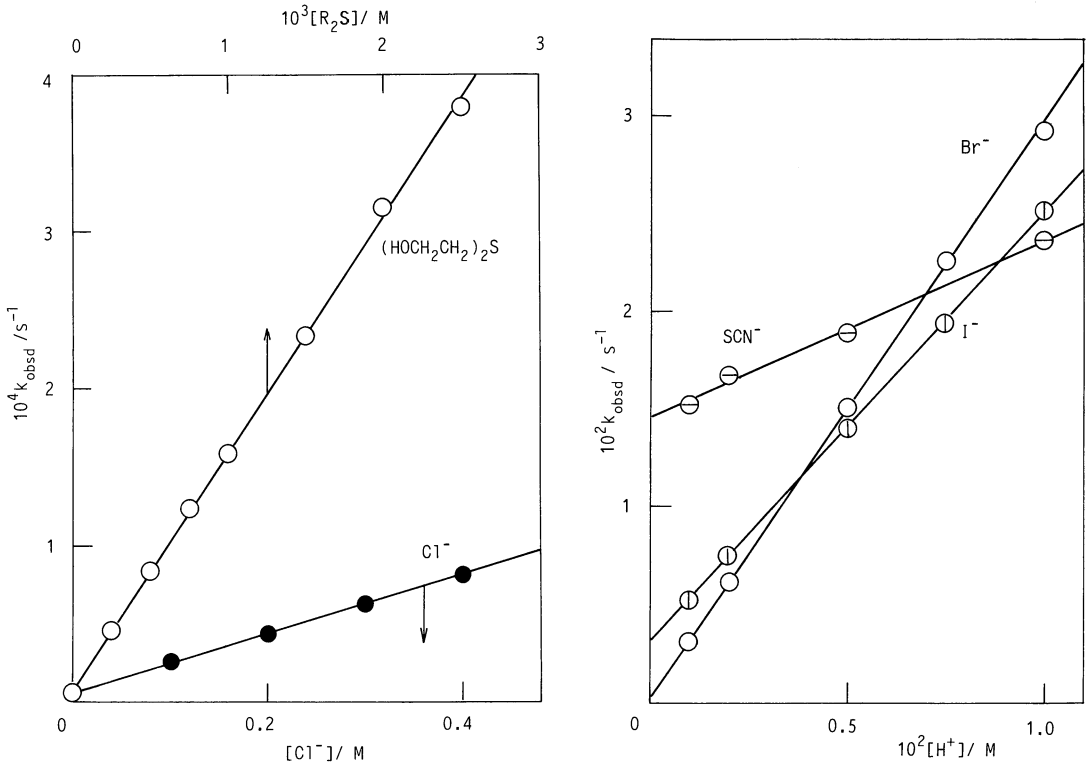


Fig. 2. (a) Effects of added nucleophiles at [H^+]=2.0×10^{-3} M for Cl^- (●) and $(HOCH_2CH_2)_2S$ (○). (b) Effects of acid concentration at [Br^-]=0.05 M (○), [I^-]=2.0×10^{-3} M (Ⓘ), and [SCN^-]=2.0×10^{-4} M (⊖).

and $(HOCH_2CH_2)_2S$ increase linearly with concentration of a nucleophile [Nu] at the constant acid concentration or with $[H^+]$ at the constant [Nu] (Fig. 2), obeying Eq. 10.

$$k_{obsd} = k_{H_2O} + k_H[H^+] + k_{Nu}[Nu] + k_{Nu}^H[H^+][Nu] \quad (10)$$

The intercept and the slope of the plots of k_{osd} vs. $[H^+]$ at the constant [Nu] are $k_{H_2O}+k_{Nu}[Nu]$ and $k_H+k_{Nu}^H[Nu]$, respectively. The values of catalytic constants k_{Nu} and k_{Nu}^H were calculated using the k_{H_2O} and k_H obtained above. On the other hand, the intercept and the slope of the plots of k_{obsd} vs. [Nu] at the constant $[H^+]$ are $k_{H_2O}+k_H[H^+]$ and $k_{Nu}+k_{Nu}^H[H^+]$, respectively, and the k_{Nu} and k_{Nu}^H were evaluated from the slopes at two different acid concentrations. The results are summarized in Tables 2 and 3. (Tables of k_{obsd} are deposited as Document No. 9030 at the Office of the Editor of Bull. Chem. Soc. Jpn.)

The catalytic effects of added nucleophiles were also observed in the hydrolysis of the ethyl sulfenate **5**.[5] The rate constants k_{Nu}^H for **5** are given in the fourth column of Table 3, which coincide remarkably well with those for **1** within 2-fold. The reaction behavior of **1** is usually very similar to that of **5**[5] but the action of iodide ion is contrastingly different toward the two sulfenates. Iodide only accelerates the hydrolysis of the methoxymethyl ester **1** while it reduces **5** to diphenyl disulfide.[5,18]

The reaction of thiocyanate ion with **1** seems to be stepwise as was observed for **5** (Eq. 11).[5] However, the UV spectral change for the second reaction of **1** is much smaller than that for **5**.

$$\mathbf{1} + SCN^- \xrightarrow{H^+} PhSSCN \xrightarrow{H_2O} PhSOH + SCN^- \quad (11)$$

It was only seen at higher concentrations of SCN^- where the first reaction is very rapid. The rate constants for the first nucleophilic reaction were measured at 261 nm, an isosbestic point for the second reaction, and those for the second reaction were determined from the absorbance increase at 275 nm in the later part of the reaction. The rate constant for the second reaction is independent of acid concentration (2.2×10^{-3} s^{-1}) and essentially equal to that obtained from the reaction of **5** (2.15×10^{-3}

Table 2. Summary of Kinetic Results in the Nucleophile-Catalyzed Hydrolysis of **1**[a]

10^2 [Nu][b]	10^2 $[H^+]$[b]	10^3 (Intercept)[c,d]	Slope[d,e]	k_{Nu}	k_{Nu}^H
M	M	s^{-1}	M^{-1} s^{-1}	M^{-1} s^{-1}	M^{-2} s^{-1}
		Nu=Cl^-			
20	0.1—1.0(5)	0.304(0.149)	2.01(0.03)	0.0015	8.8
0—40(5)	0.20	0.589(0.052)	0.0188(0.0002)		
				(0.0002)[f]	9.3
0—50(6)	1.0	2.11(0.36)	0.0932(0.0012)		
		Nu=Br^-			
5.0	0.1—1.0(5)	0.414(0.244)	2.91(0.04)	0.0083	53.2
0—10(7)	0.20	0.531(0.118)	11.6(0.2)		
				(0.5)[f]	55.5
0—10(7)	1.0	2.17(0.42)	56.0(0.8)		
		Nu=I^-			
0.08	0.1—1.0(5)	1.63(0.22)	0.933(0.036)	2.04	850
0.20	0.1—1.0(5)	3.02(0.12)	2.21(0.02)	1.51	980
0—0.50(6)	0.20	0.580(0.044)	3.48(0.02)		
				1.45	1020
0—0.50(6)	1.0	2.01(0.36)	11.61(0.12)		
		Nu=SCN^-			
0.020	0.02—5.0(9)	14.6(0.2)	0.890(0.008)	73.0	3190
0—0.10(8)	0.20	0.371(0.120)	81.8(0.3)		
				74	3900
0—0.050(6)	1.0	1.70(0.49)	113(2)		
		Nu=$(HOCH_2CH_2)_2S$			
0.050	0—1.0(5)	1.90(0.02)	3.22(0.04)	3.80	5940
0—0.25(8)	0.20	0.770(0.211)	15.1(0.2)		
				3.3	5890
0—0.10(6)	1.0	2.50(0.19)	62.2(0.4)		

a) Measured at 25 °C and an ionic strength of 0.50 ($NaClO_4$). b) Values in parentheses show the number of data points. c) The intercepts for the acidity dependency (at given [Nu]) and the [Nu] dependency (at given $[H^+]$) correspond to k_{Nu}[Nu] and k_0, respectively. d) Values in parentheses are standard deviations. e) The slopes for the acidity dependency and the [Nu] dependency correspond to k_{Nu}^H[Nu] and $k_{Nu}+k_{Nu}^H[H^+]$, respectively. f) Not reliable with large uncertainties.

Table 3. Rate Constants for Nucleophilic Catalysis in the Hydrolysis of **1**[a]

Nucleophile	$k_{Nu}/M^{-1}s^{-1}$ (rel value)	$k_{Nu}^{H}/M^{-2}s^{-1}$ (rel value)	$k_{Nu}^{H}/M^{-2}s^{-1}$ for **5**[b]	k_{Nu}/k_{Cl^-} for **2b**[c]
H_2O	2.7×10^{-7} [d] (2×10^{-4})	4.4×10^{-3} [e] (5×10^{-4})	2.4×10^{-3} [e]	0.01
OH^-	4.87×10^{4} (3×10^{7})			2.3
Cl^-	0.0015 (1)	9.0 (1)	17.9	1
Br^-	0.008 (5)	54 (6)	95.9	2.2
I^-	1.6 (10^3)	950 (110)	1160	7.0
SCN^-	73 (4.9×10^{4})	3500 (390)	2950	
$(HOCH_2CH_2)_2S$	3.6 (2.4×10^{3})	5900 (650)	3600	
1 (5)	0.2 (130)	780 (87)	1900	
$ClCH_2CO_2^-$		11.1 (1.2)		
$MeOCH_2CO_2^-$	0.0010 (0.67)	18.8 (2.1)		
$CH_3CO_2^-$	0.0012 (0.8)	104 (12)		
$Me_3CCO_2^-$	0.0017 (1.1)	199 (22)		
MES	0.050 (33)			

a) Measured at the ionic strength of 0.50 and 25 °C. b) Rate constants for the ethyl sulfenate **5**.[5] c) Relative nucleophilicity toward **2b**.[10] d) $k_{H_2O}/55$. e) $k_H/55$.

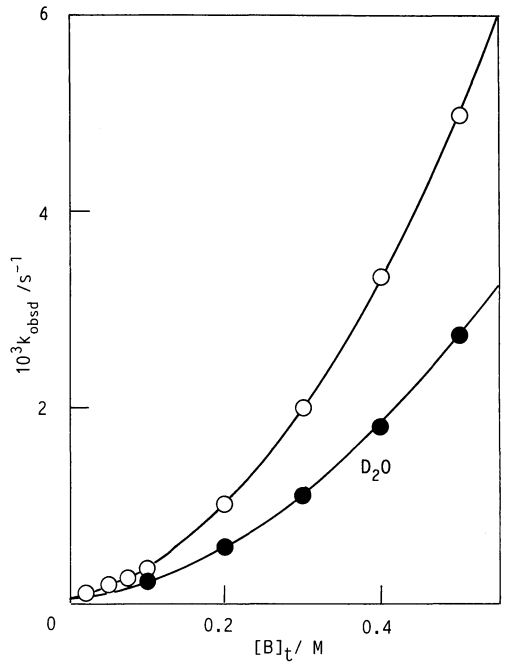


Fig. 3. Effects of concentrations of acetate buffer in H_2O (○) and D_2O (●) at the buffer ratio of 1 (ionic strength, 0.50) and 25 °C.

s^{-1});[5] the second reaction must be decay of the intermediate PhSSCN. The rate constant for the first reaction is dependent on both $[SCN^-]$ and $[H^+]$ and obeys Eq. 10. The nucleophilic rate constants obtained from the first reaction are listed in Tables 2 and 3.

Kinetics in Buffer Solutions. The hydrolysis of **1** proceeds smoothly in buffer solutions of carboxylates and tertiary amines and follows pseudo-first-order kinetics as is monitored at 275 nm. The rate constants k_{obsd} determined at the constant ionic strength of 0.50 are strongly buffer-dependent and follow Eq. 12 which involves a second-order term of total buffer concentration $[B]_t$ (Fig. 3).

$$k_{obsd} = k_0 + k_1[B]_t + k_2[B]_t^2 \quad (12)$$

Here, k_0 cannot always easily be evaluated by extrapolation of the parabolic curve. Reliable k_0 values were obtained by extrapolation from the data at lower buffer concentrations of MES (2-morpholinoethanesulfonate) and MOPSO (3-morpholino-2-hydroxypropanesulfonate) buffers at pH 5.77—7.06 and are plotted against pH in Fig. 1. The k_0 values increase with pH and the hydrolysis must be catalyzed by hydroxide ion. The theoretical curve of Fig. 1 is drawn according to Eq. 8 with the rate constants given above.

Apparent second- and third-order rate constants, k_1 and k_2, were evaluated from the linear correlation of Eq. 13 using k_0 calculated by Eq. 8 and are summarized in Table 4 for various buffer solutions.

$$(k_{obsd} - k_0)/[B]_t = k_1 + k_2[B]_t \quad (13)$$

From the results at different buffer ratios, it was found that the k_1 is dependent on both the conjugate acid and base of the buffer while the k_2 is maximum at the buffer ratio of 1. The overall rate constants can be expressed by Eq. 14. The buffer-catalytic constants are summarized in Table 5.

$$k_{obsd} = k_0 + k_A[HA] + k_B[A^-] + k_{AB}[HA][A^-] \quad (14)$$

In order to examine the solvent deuterium isotope effects, hydrolysis rates of **1** were determined in acetate ($[B]_t$=0.1—0.5 M) and MES ($[B]_t$=0.05 and 1.0 M) buffer solutions in deuterium oxide at the buffer ratio of unity. Although the second-order dependence on buffer concentration is apparent as in H_2O (Fig. 3), the decomposition of k_{obsd} into each kinetic term of Eq. 12 cannot be performed. All the k_{obsd} are smaller than those obtained in the corresponding protium buffer solutions, and k_H/k_D ranges 1.62—1.85 (average being 1.76) in the acetate buffers and k_H/k_D is about 2.0 in the MES buffers at the same buffer ratio of unity.

Buffer effects were also examined in the presence of typical nucleophiles, bromide ion and bis(2-hydroxy-

Table 4. Buffer-Dependent Rate Constants in the Hydrolysis of **1**

Buffer	pH	$[B]_t$[a]/M	$10^2 k_1$[b]/$M^{-1}s^{-1}$	$10 k_2$[b]/$M^{-2}s^{-1}$
Chloroacetate	2.46	0.1—0.5(5)	1.82 (0.03)	0.121 (0.008)
	2.78	0.1—0.5(5)	1.15 (0.02)	0.135 (0.005)
Methoxyacetate	3.11	0.1—0.5(5)	0.560 (0.013)	0.119 (0.004)
	3.40	0.1—0.5(5)	0.419 (0.005)	0.146 (0.002)
	3.71	0.1—0.5(5)	0.319 (0.039)	0.129 (0.012)
Acetate	3.95	0.05—0.5(7)	0.225 (0.011)	0.092 (0.004)
	4.58	0.02—0.5(8)	0.195 (0.019)	0.155 (0.007)
	5.18	0.05—0.5(7)	0.140 (0.015)	0.107 (0.006)
Pivalate	4.49	0.05—0.2(4)	0.226 (0.010)	0.178 (0.008)
	4.88	0.05—0.2(4)	0.213 (0.009)	0.260 (0.006)
	5.49	0.05—0.2(4)	0.180 (0.009)	0.164 (0.006)
Succinate	5.26	0.1—0.25(4)	0.101 (0.030)	0.437 (0.017)
	5.74	0.1—0.2(3)	0.055 (0.012)	0.281 (0.009)
MES[c]	5.77	0.01—0.2(7)	1.79 (0.13)	17.0 (0.2)
	6.28	0.01—0.3(9)	3.12 (0.25)	20.1 (0.2)
	6.70	0.01—0.15(7)	4.15 (0.12)	13.9 (0.2)
	7.06	0.01—0.2(7)	3.65 (0.33)	8.18 (0.31)
MOPSO[d]	6.91	0.025—0.2(8)	2.38 (0.06)	1.36 (0.05)
MOPS[e]	6.60	0.025—0.2(8)	10.9 (0.5)	24.4 (0.5)
	7.20	0.025—0.1(4)	22.5 (0.5)	39.6 (0.6)
	7.50	0.025—0.1(4)	35.4 (0.3)	26.0 (0.5)
TMEDA[f]	6.02	0.01—0.05(5)	93.1 (16.6)	1180 (60)
	6.33	0.01—0.05(5)	121 (24)	1460 (80)
	6.55	0.01—0.05(5)	152 (8)	1360 (30)
DMAPN[g]	6.68	0.01—0.04(4)	121 (15)	1150 (60)
	7.35	0.01—0.04(4)	345 (19)	1650 (80)

a) The range of total buffer concentrations employed and values in parentheses show the number of data points. b) Values given in parentheses are standard deviations. c) 2-Morpholinoethanesulfonate. d) 3-Morpholino-2-hydroxypropanesulfonate. e) 3-Morpholinopropanesulfonate. f) *N,N,N′,N′*-Tetramethylethylenediamine. g) 3-(Dimethylamino)propiononitrile.

Table 5. Buffer Catalytic Constants for the Hydrolysis of **1**[a]

HA[b] (pK_a)	$10^3 k_A$/$M^{-1}s^{-1}$	$10^3 k_B$/$M^{-1}s^{-1}$	k_{AB}/$M^{-2}s^{-1}$
H_3O^+ (−1.7)	242		
$ClCH_2CO_2H$ (2.5)	35	(ca. 0)	0.054
$MeOCH_2CO_2H$ (3.4)	7.5	(1.0)	0.058
CH_3CO_2H (4.6)	2.6	1.2	0.062
Me_3CCO_2H (4.9)	2.5	1.7	0.10
$^-O_2CCH_2CH_2CO_2H$ (5.25)	(1.8)	(0.2)	0.17
MES (6.3)	(7)	50	8.0
MOPSO (6.9)	(ca. 0)	(48)	0.54
MOPS (7.2)	(2)	450	15
$^+HMe_2NCH_2CH_2NMe_2H^+$ (6.33)	(300)	2100	580
$NCCH_2CH_2NMe_2H^+$ (7.35)	(ca. 0)	6700	660

a) Measured at 25 °C and the ionic strength of 0.50 maintained with $NaClO_4$. Rate consatants given in parentheses are less reliable. b) For abbreviations, see footnotes of Table 4. The pK_a values are given as the observed pH of the buffer solution at [HA]=[A^-].

ethyl) sulfide. The k_{obsd} obtained at [Br^-]=0.30 M and [$(HOCH_2CH_2)_2S$]=0.001 M in acetate buffer solutions are plotted against concentration of the conjugate acid [HA] in Fig. 4. The plots are essentially linear and k_{obsd} obtained at three different buffer ratios give almost the same slopes of lines against [HA]. The reaction of the nucleophile is dependent only on the conjugate acid of the buffer (Eq. 15). The apparent general acid catalytic constants k_{HA} (k_{Nu}^{HA}[Nu]) for the nucleophilic reaction of the sulfide at [$(HOCH_2CH_2)_2S$]=0.001 M are summarized in Table 6.

$$k_{obsd} = k_0 + k_{Nu}^{HA}[Nu][HA] \quad (15)$$

Bond Cleavage of the ^{18}O-Labeled Substrate. In order to determine which of the S–O and O–C bonds breaks during the reaction (Scheme 1), the ^{18}O-labeled substrate **1**-^{18}O was subjected to the hydrolysis under essentially the same conditions as those employed for kinetic measurements. To solubilize the substrate at about 10 times higher in concentration than that of kinetic measurements, 10 vol% of acetonitrile was used as a cosolvent. The labeled substrate **1**-^{18}O of 91% ^{18}O

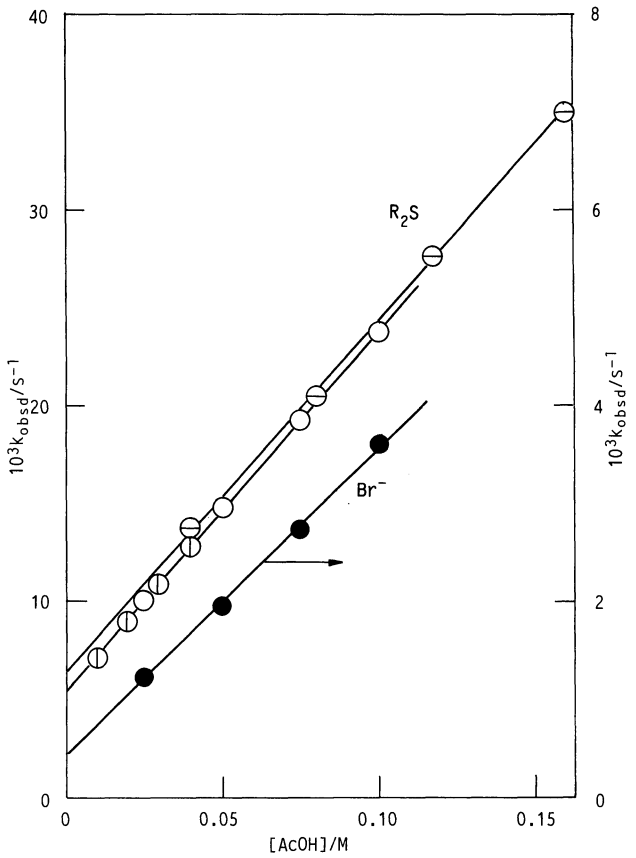


Fig. 4. Dependence of the k_{obsd} obtained in acetate buffers on concentrations of the conjugate acid in the presence of 0.30 M Br^- at pH 4.58 (●) and in the presence of 0.001 M $(HOCH_2CH_2)_2S$ at pH 3.95 (⊖), 4.58 (○), and 5.18 (⊕). Reactions were carried out at the ionic strength of 0.50 and 25 °C.

Table 6. General-Acid Catalytic Constants in the Presence of $(HOCH_2CH_2)_2S$ for the Hydrolysis of **1**[a]

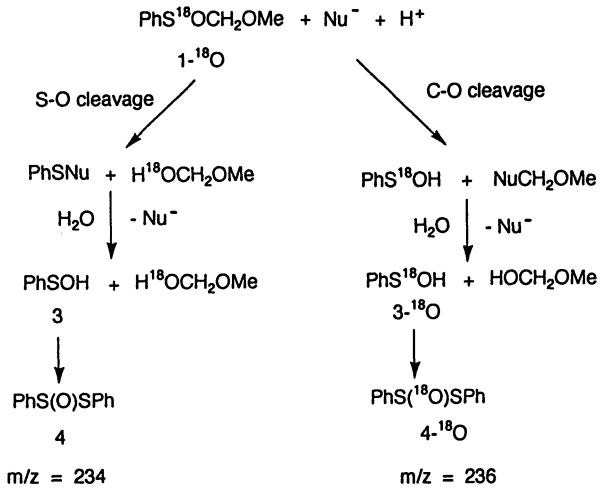
HA	$k_{HA}/M^{-1}s^{-1}$
H_3O^+	5.9
$ClCH_2CO_2H$	0.952
$MeOCH_2CO_2H$	0.418
CH_3CO_2H	0.184
Me_3CCO_2H	0.168
Succinate	0.150

a) Measured in the presence of the sulfide at $[R_2S]$= 0.001 M and at 25 °C and the ionic strength of 0.50.

content was prepared by thermal rearrangement of methoxymethyl phenyl sulfoxide-^{18}O (Eq. 16).[19]

$$PhS(^{18}O)CH_2OMe \longrightarrow PhS^{18}OCH_2OMe \quad (16)$$
$$\textbf{1}\text{-}^{18}O$$

The reaction of **1**-^{18}O was carried out under various conditions and quenched at about 50% conversion unless the reaction is too fast. The ^{18}O content of the final product **4** was determined by mass spectrometry from the intensity ratio of the peaks at m/z 234 and 236. Values of the percentage retention of ^{18}O in the product



Scheme 1.

Table 7. Bond Cleavage of **1**-^{18}O in the Hydrolysis[a]

$[H^+]/M$	Nu (concn/M)	$10^3[\mathbf{1}]_0$ / M	% ^{18}O retention[b]
2×10^{-3}	None	0.21	32.3
		0.62	53.0
		1.5	70.8
		3.0	79.4
5×10^{-4}	Cl^- (0.10)	2.0	88.6
5×10^{-4}	Br^- (0.05)	0.22	92.5
		0.54	93.7
		1.0	94.6
		1.07	94.9
2×10^{-4}	SCN^- (2×10^{-4})	1.0	97.6[c]
2×10^{-3}	SCN^- (2×10^{-4})	2.0	97.5[c]
2×10^{-4}	R_2S[d] (5×10^{-4})	1.0	90.8
		2.0	87.3
0	OH^- (4×10^{-5})	2.0	15.0[c]

a) Reactions were carried out in aqueous solutions containing 10 vol% of acetonitrile (ionic strength, 0.45) at 25 °C and quenched at about 50% conversion. b) % ^{18}O retained in the product **4**. c) Conversion was almost complete. d) $(HOCH_2CH_2)_2S$.

Table 8. Bond Cleavage of **1**-^{18}O in Buffer Solutions[a]

$[B]_t$ / M	$10^3[\mathbf{1}]_0$ / M	% ^{18}O retention	% Contribution to k_{obsd}[b]			
			k_0	k_A	k_B	k_{AB}
Acetate ([HA]/[A⁻]=3, pH=4.1)						
0.10	0.5	94.7	11.7	50.5	7.8	30.1
Acetate ([HA]/[A⁻]=1, pH=4.6)						
0.10	0.5	93.1	9.7	34.0	15.7	40.6
0.20	1.0	96.8	3.6	25.1	11.6	59.8
0.40	1.0	97.0	1.1	15.9	7.3	75.7
MES ([HA]/[A⁻]=1, pH=6.3)						
0.05	1.0	89.2	12.8	2.4	17.0	67.9

a) Reactions were carried out in aqueous solution containing 10 vol% of acetonitrile (ionic strength, 0.45) at 25 °C and quenched at about one half-life. b) Calculated from the rate constants given in Table 5.

4 calculated are given in Table 7 for the reactions in aqueous perchloric acid in the absence and presence of added nucleophiles and in Table 8 for the reactions in buffer solutions. The degree of ^{18}O retention is usually very high and this result indicates a high percentage of the C–^{18}O bond cleavage. However, in the absence of added nucleophile, a considerable loss of ^{18}O was observed and the degree of retention largely depends on the substrate concentration $[\mathbf{1}]_0$.

If the reaction occurs simply in a manner summarized in Scheme I, the nucleophilic attacks at the sulfenyl sulfur and at the proformyl carbon will lead, respectively, to the bond cleavages at the S–^{18}O and the C–^{18}O and then to the loss and retention of the label in the product **4**. The C–O bond cleavage observed seems to suggest that the nucleophiles mostly react at the carbon. However, the high nucleophilic reactivity, which is remarkably similar to that toward the ethyl sulfenate **5**, conforms to the reaction at the sulfur. This inconsistency can be accommodated by a multi-step mechanism involving a preceding rate-determining step followed by a product-determining step.

Discussion

Nucleophilic Reaction. The ^{18}O labeling experiments show that the acid nucleophilic catalyzed hydrolysis of **1** takes place mostly with the C–O bond cleavage, while the nucleophilic reactivity indicates that the catalysis arises as a result of attack by the nucleophile at the sulfur. That is, the rate-determining nucleophilic reaction step must precede the product-determining step.

As summarized in Table 3, the acid-catalyzed reactivities of various nucleophiles toward **1** are closely similar to those toward the ethyl sulfenate **5**.[5] The rate constants $k_{Nu}{}^{H}$ for **1** and **5** are identical within a factor of 2. This remarkable agreement in the rate constants strongly suggests that nucleophiles react with **1** in the same manner as with **5** in the rate-determining step. Since **5** is known to undergo nucleophilic attack at the sulfur, the nucleophiles must react also at the sulfur of **1** in the rate-determining step. So, the difference in the alkoxyl group (methoxymethyl and ethyl) has only a minor effect on the reactivity of the sulfenates.

The results summarized in Table 7 show that the reactions of added nucleophiles with the ^{18}O-labeled substrate **1**-^{18}O take place mostly (>90%) with the C–O bond cleavage. The rate of the oxygen isotope exchange of the intermediate sulfenic acid **3** with solvent water is not known but the exchange can be as rapid as the sulfenate hydrolysis because of the similarity of reaction mechanism.[20] However, the exchange in **3** cannot be appreciable under the reaction conditions (pH <7); the competitive trapping leading to **4** may be rapid enough. The isotope exchange of the product **4** is much slower.[21] The observed results in acidic media must essentially reflect the bond cleavage in the hydrolysis.

That is, the acid nucleophilic catalyzed hydrolysis of **1** takes place predominantly with the C–O bond cleavage. This seems to imply that the nucleophile should attack to the carbon in a primary product of hydrolysis (Eq. 17).

$$\mathbf{1} + Nu^- + HA \longrightarrow PhSOH + MeOCH_2Nu + A^- \quad (17)$$

Any possibilities for the nucleophile to attack directly at the proformyl carbon of **1** should be considered. In the hydrolysis of the methoxymethyl derivatives (**2**), nucleophilic assistance was usually observed in accord with the instability of a possible intermediate, methoxycarbenium ion.[6–10] However, such a nucleophilic assistance was found to be very weak as is seen in the last column of Table 3, and structure-reactivity correlations exhibited behavior intermediate between that expected for S_N2 and carbocation reactions.[10] The assistance could not be detected even in a similar reaction with **2c**.[11] In contrast, the present reaction is strongly dependent on the nucleophilicity of the catalyst. Furthermore, the nucleophilic reactivities of various nucleophiles summarized in Table 3 are much different from those observed for a typical S_N2 reaction of methyl iodide (n_{MeI});[22] e.g., a dialkyl sulfide is more reactive than iodide toward **1** while it is 10^2-fold less reactive toward CH_3I. Nucleophilic reactivity does not conform to the reaction at the proformyl carbon in spite of the C–O cleavage observed. In other words, although the kinetic results show that the nucleophilic reactions occur at the sulfur, the products arise as a result of bond cleavage at the proformyl carbon of **1**. These results can only be accommodated by a mechanism involving separate rate- and product-determining steps. Such a mechanism will be considered below.

The reaction of iodide ion with the ethyl sulfenate **5** in an aqueous solution resulted in the reduction of **5** to form diphenyl disulfide.[18] This must be characteristic of the sulfenate reaction involving a sulfenyl iodide as an intermediate which can receive a nucleophilic attack at the iodine atom to lead to reduction (Eqs. 18—20).

$$PhSOR + HI \longrightarrow PhSI + ROH \quad (18)$$

$$PhSI + HI \longrightarrow PhSH + I_2 \quad (19)$$

$$PhSH + PhSOR \longrightarrow PhSSPh + ROH \quad (20)$$

In contrast, iodide only accelerates hydrolysis of **1** under the same conditions, and no sign of reduction of **1** nor formation of iodine was found. This is consistent with the conclusion that **1** undergoes hydrolysis via the reaction at the carbon (Eq. 21).

$$\mathbf{1} + I^- \xrightarrow{HA} PhSOH + ICH_2OMe \xrightarrow{H_2O} \mathbf{4} + HOCH_2OMe + I^- \quad (21)$$

Reaction of other nucleophiles must proceed in the same way as iodide via the C–O cleavage. However, thiocyanate seems in part to react with **1** via the S–O cleavage judging from the UV spectral change which suggests occurrence of an ensuing reaction of the intermediate (Eq. 11). Since the tracer experiments show

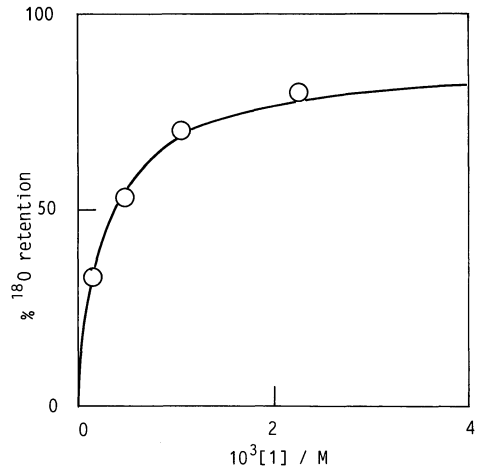


Fig. 5. Effects of the initial substrate concentration on the bond cleavage of 1-^{18}O. The ^{18}O content of **4** was determined at about 50% conversion and [**1**] is set equal to 0.75[**1**]$_0$ (see text).

that most of the reaction takes place through the C–O cleavage, the S–O cleavage reaction with an apparent two-step process (Eq. 11) may constitute only less than 10% of the total reaction.

In the absence of added nucleophile, % retention of the isotope in the product **4** increases with the initial substrate concentration [**1**]$_0$ as is seen in Fig. 5. The hydrolysis rate was also found to increase with [**1**]$_0$. The substrate itself can be a nucleophilic catalyst and the substrate-catalyzed hydrolysis (k_{SE}') must proceed mainly with the C–O cleavage while the water reaction (k_0) occur mostly with the S–O cleavage. The % retention of ^{18}O in the product **4** from 1-^{18}O may be represented by Eq. 22 as a function of the substrate concentration [**1**], if the k_{SE}' reaction occurs with x% retention of ^{18}O and the k_0 reaction with a complete loss of ^{18}O.

$$\%^{18}\text{O retention} = \frac{xk_{SE}'[\mathbf{1}]}{k_0 + k_{SE}'[\mathbf{1}]} \tag{22}$$

Since the ^{18}O content of **4** was determined at about 50% conversion, the products were formed while the substrate concentration changed from [**1**]$_0$ to 0.5[**1**]$_0$. So, we take 0.75[**1**]$_0$ for [**1**] to fit the results to Eq. 22. The best fit was obtained (by the least-squares treatment) with x=87% and k_0/k_{SE}'=2.7×10^{-4} M, and the calculated curve is drawn with these parameters in Fig. 5. The value of k_0/k_{SE}' obtained kinetically at [H$^+$]=2×10^{-3} M is 2.9×10^{-4} M (Table 1) in an excellent agreement with that obtained from the labeling experiments. Acceleration by the substrate may occur in the same way as the other nucleophiles, while water reacts differently via the S–O cleavage.

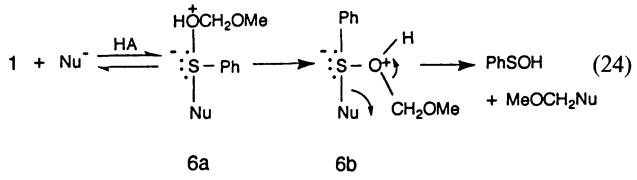
The nucleophilic reaction is catalyzed by acid (k_{Nu}^H) but the uncatalyzed process (k_{Nu}) also contributes significantly to the nucleophilic reaction of **1**. A similar nucleophilic reaction of the ethyl sulfenate **5**, which takes place at the sulfenyl sulfur, only occurs with assistance of acid and no neutral term (k_{Nu}) was observed.[5] This difference seems to suggest that the nucleophiles in part attack directly at the proformyl carbon of the neutral **1**. The methoxymethyl derivative is much more amenable to nucleophilic attack than the ethyl analog. Benzenesulfenate ion can also be a satisfactory nucleofuge to depart from the carbon on nucleophilic attack.

The pH-rate profile (Fig. 1) is of an inverse bell shape and the hydrolysis is catalyzed by hydroxide ion as well as acid. Some contribution from the uncatalyzed reaction is also apparent. Such contributions from water and hydroxide reactions are much less important in the hydrolysis of a simple sulfenate **5**[5] and this must reflect ease in the nucleophilic reaction at the methoxymethyl group of **1**. The product analysis in alkaline solution is difficult because of the lability of the product **4** under the reaction conditions. Analysis of **4** obtained from 1-^{18}O in a very weakly alkaline solution shows an extensive loss of the label (Table 7) contrary to the expectation. This could be due to the hydroxide reaction via the S–O cleavage, but it is more likely that the loss occurs via the hydroxide exchange of the intermediate sulfenic acid **3** with the solvent water (Eq. 23).

$$\underset{\mathbf{3}}{\text{PhS}^{18}\text{OH}} + \text{OH}^- \longrightarrow \text{PhSOH} + {}^{18}\text{OH}^- \tag{23}$$

The latter reaction can be more rapid than the trapping of **3** (by **1**) leading to **4**; nucleophilicity of OH$^-$ being greater than that of **1**.

Reaction Mechanism. The composite acid nucleophilic catalyzed hydrolysis of **1** involving a separate rate- and product-determining steps may take place with a sulfurane intermediate **6**. As a possible reaction course leading to the C–O cleavage from **6**, we propose one depicted in Eq. 24. Details of the first step will be given below in the buffer catalysis section.



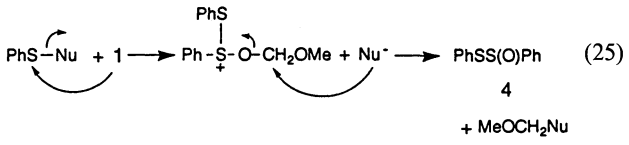
(24)

The initially formed sulfurane intermediate **6a** in the rate-determining step may change into the structure **6b** by pseudorotation,[23] and the weakly bonded nucleophile in an apical position switches bonding to the proformyl carbon to lead to the C–O cleavage.

A role of the catalyzing acid played in solvolysis reactions is in general to assist the departure of the leaving group. However, in the present mechanism the acid may promote the reaction by enhancing the electronegativity of the apical oxygen and thus stabilizing the hypervalent bonding[23] of the intermediate **6a**. The driving force for the switching of the nucleophile from

the sulfur to the proformyl carbon in the product-determining step may be a better leaving ability of PhSOH compared with $MeOCH_2OH$. In the case of the water reaction H_2O is too weak a nucleophile to undergo the internal nucleophilic bond switching and the reaction leads to the S–O cleavage.

An alternative pathway could be possible, which involves an initial (rate-determining) sulfur attack of the nucleophile followed by a second reaction, displacement of Nu of the intermediate by **1** and, in the final step, the nucleophilic reaction occurs at the carbon leaving the label in the product **4** (Eq. 25). If this were the case, the water reaction would have competed with the nucleophilic reaction of the substrate **1** in the second step as in the case of competing first- and second-order reactions in the absence of added nucleophiles. The water reaction must lead to loss of the labels ^{18}O in the product **4**. This tendency was not found in the reaction with bromide ion with varying concentration of the substrate (Table 7). Therefore, this alternative pathway can be excluded.[24]

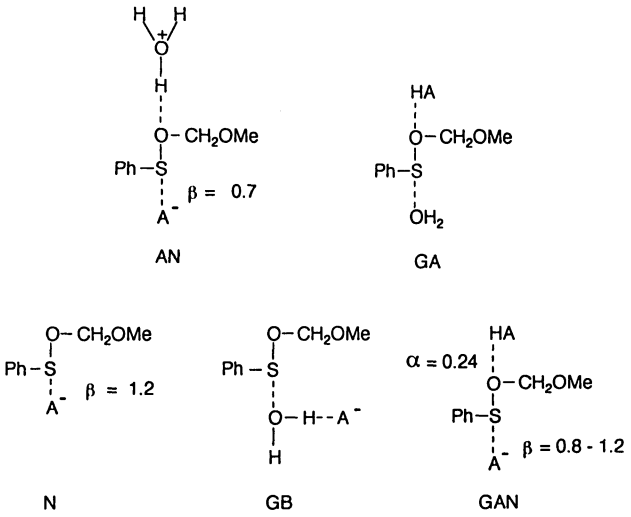


(25)

Mechanism of Buffer Catalysis. An additional remarkable feature of the present reaction is the second-order acceleration by buffer: both acid and base components participate simultaneously in the rate-determining transition state of the hydrolysis (k_{AB}). Acid and base components of the buffer also catalyze the reaction separately (k_A and k_B).

All the three kinetic processes involving buffer catalysis were found to proceed mostly with the C–O bond cleavage. The product **4** obtained from hydrolysis of **1**-^{18}O in acetate and MES buffer solutions contains more than 90% of the original label as summarized in Table 8. In order to examine if a different type of buffer-catalytic process occurs through a different mode of bond breaking, the % fraction of the total reaction pursued by each buffer-catalytic course is calculated from the catalytic constants and given in Table 8. The loss of ^{18}O can be ascribed to the uncatalyzed reaction (k_0) and all the three types of catalytic processes (k_A, k_B, and k_{AB}) seem to take place via the C–O cleavage. Carboxylate and amine both operate as nucleophiles leading to the C–O cleavage rather than the S–O cleavage of **1**. So, the conjugate base component of the buffer must react in the same way as the other nucleophiles at the sulfur to form a sulfurane intermediate in the rate-determining step but to lead to the C–O cleavage in the ensuing step (Eq. 24).

The apparent general acid-catalyzed reaction (k_A) is probably occurring via the (kinetically equivalent) nucleophilic attack of the base with the aid of the hydroxonium ion catalysis (AN) rather than via the general acid-catalyzed water attack (GA). The latter pathway involving the water reaction should have resulted in the S–O bond cleavage. In the same way, the k_B process may involve a nucleophilic reaction of the conjugate base at the sulfur (N) leading to the C–O cleavage rather than a general base-catalyzed attack of water at the sulfur (GB).



The third-order process involving both general acid and base components (k_{AB}) must take place through the general acid-catalyzed nucleophilic attack of the conjugate base at the sulfur as depicted by GAN in the rate-determining step. Again, the C–O cleavage takes place in the product-determining step. These conclusions are also compatible with the observation that the buffer catalysis in the presence of a strong nucleophile involves only the general acid term. The electrophilic center of the substrate is preferentially attacked by the added nucleophile and only the acid component of the buffer can play a role in the catalytic process. That is, in the transition state GAN, A^- is replaced by Nu^-.

Buffer catalytic constants given in Tables 5 and 6 are logarithmically plotted against pK_a of the conjugate acid in Fig. 6. The catalytic constants are not always very precise and points scatter considerably. The mechanistically simplest term k_{HA} in the presence of the sulfide gives a Brønsted slope $\alpha_{HA}=0.24$ for the general acid catalysis. The slope β_B for the k_B term seems to be about unity or greater. The plot of k_{AB} shows a large scatter but the overall slope β_{AB} can also be nearly unity. Since the slope for the $\log k_{AB}$–pK_a plot should be a composite of those for k_{HA} and k_B ($\beta_{AB}=\beta_B-\alpha_{HA}$), the observations are not incompatible with the expectation. The slope α_A for k_A is about 0.31 including carboxylic acids and hydroxonium ion. Since the k_A term arises from the hydroxonium-ion catalyzed nucleophilic reaction by the conjugate base (k_B^H), $k_A[HA]=k_B^H[H^+][A^-]$

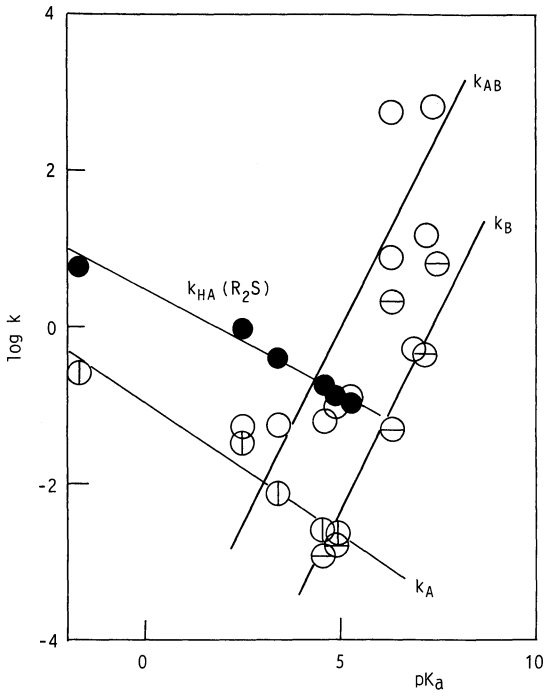


Fig. 6. Brønsted plots for the buffer-catalytic constants in the hydrolysis of **1**. (○) k_{AB}, (⊖) k_B, (⊕) k_A, (●), k_{HA} in the presence of 0.001 M $(HOCH_2CH_2)_2S$. Data were obtained at the ionic strength of 0.50 and 25 °C.

and thus $k_A=K_ak_B^H$. The Brønsted β_B^H for k_B^H is evaluated to be $\beta_B^H=1-\alpha_A\approx0.7$. The Brønsted β values for the nucleophilic reactions are shown in the schematical transition state structures, N, GAN, and AN, approximately as 1.2, 0.8—1.2, and 0.7 for the uncatalyzed, general-acid, and hydroxonium-ion catalyzed reactions, respectively. The magnitude of β becomes smaller with strength of the catalyzing acid in accord with the reactivity-selectivity rule.

Deuterium solvent isotope effects on the overall buffer-catalyzed reactions were found to be small but normal, $k_H/k_D=1.7$—2, while those found in dilute perchloric acid are slightly inverse, $k_H/k_D=0.78$. These values are consistent with general acid-catalyzed reactions involving proton-transfer to a heteroatom and a concomitant bonding change between the two heavy atoms.[25] Many of general acid-catalyzed hydrolyses of acetals and ortho esters show k_H/k_D values of 0.5—3, while for typical reactions involving specific acid catalysis $k_H/k_D=0.25$—0.5.[25,26]

The third-order term involving the acid and base components of the buffer catalysis is important as bifunctional catalysis similar to that operating at the active site of enzymes, but well-established examples of this kind are rarely found for chemical reactions in aqueous solution. The only reported example is the enolization of carbonyl compounds and has been examined repeatedly in these four decades.[15] The third-order term is only a minor contributor to the whole rate of the enolization and has been a subject of much controversy, but the concerted general acid-base catalysis has recently been established.[15] By contrast, the present reaction is mainly due to the third-order term in usual buffer solutions (Table 8) and the *nucleophilic reaction of the conjugate base at the sulfur* is promoted by general acid. The large electrophilic tendency to receive nucleophilic attack seems to be characteristic of the divalent sulfur atom and a driving force of the nucleophilic catalysis.

Although general acid-catalyzed nucleophilic reactions are not uncommon for carbonyl and related compounds, the nucleophiles involved in such reactions are usually one component of reactants (or solvent) instead of the catalyst. In this sense, the buffer catalysis is simply second order. The driving force for general acid catalysis of these reactions has been discussed in terms of the stability of intermediates by Jencks.[27] The catalysis is enforced to avoid unstable intermediates and transition states. The unprotonated sulfurane (deprotonated form of **6a**) must be unstable and the pK_a of the protonated sulfurane must be pretty high.

Since the k_{AB} process is important in this reaction, bifunctional buffers like *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and succinate may have a chance to operate as a bifunctional catalyst. If this were the case, the second-order k_{AB} term should have been less important and the k_A or k_B term would have been greater than that expected for the pK_a. However, these potential bifunctional catalysts showed strong second-order dependence and had little enhancement in the k_A or k_B term. The bifunctional catalysis was not observed with either succinate or TMEDA. This result may arise from the unfavorable stereochemical arrangement of the electrophilic (sulfur) and basic centers (oxygen) of the sulfenate in the transition state. The oxygen and the incoming nucleophile are both favorably situated in the apical positions of the trigonal bipyramidal arrangement around the central sulfur. The acid should consequently be placed far apart from the nucleophile as in the structure GAN.

In conclusion, the present reaction takes place through the concerted general acid-catalyzed nucleophilic reaction at the sulfenyl sulfur in the initial rate-determining step followed by the rearrangement of the nucleophile to bonding to the proformyl carbon to give the C–O bond cleaved product. The nucleophile is regenerated by rapid reaction of the intermediate with water to be a catalyst. The base component of the buffer can be a nucleophilic catalyst to constitute the third-order term of the buffer catalysis. Such strongly nucleophilic nature of this reaction is a reflection of the strongly electrophilic nature of the divalent sulfur of the sulfenate.

Experimental

Materials. Methoxymethyl benzenesulfenate (**1**) was

obtained by thermal rearrangement[19] of methoxymethyl phenyl sulfoxide which was prepared in the same way as described previously.[28] Vacuum distillation of the sulfoxide at ca. 100 °C resulted in a quantitative conversion to **1**. ^{1}H NMR ($CDCl_3$) δ=3.75 (s, 3H), 4.82 (s, 2H), 7.0—7.5 (m, 5H). Since **1** is not stable, a small amount (0.1—0.2 g) of the sulfoxide was each time subjected to a Kugelrohr distillation at ca. 0.7 mmHg (1 mmHg ≈133.322 Pa) and 100 °C, and the fraction obtained was stored as a solution in acetonitrile in a refrigerator and used within a week.

The ^{18}O-labelled substrate **1**-^{18}O was also obtained in the same way from the labelled sulfoxide.[20] The ^{18}O content was determined by mass spectrometry to be 91%.

Methoxyacetic, acetic, and pivalic acids, 3-(dimethylamino)propionitrile, *N,N,N',N'*-tetramethylethylenediamine, and bis(2-hydroxyethyl) sulfide are distilled before use. MES, MOPS, and MOPSO buffers were obtained from Sigma Chemical Co. and used without purification. Inorganic salts of best commercial grade were dried at 110—130 °C. Glass-distilled water was used.

Kinetic Measurements. Rates were determined spectrophotometrically at 25 °C. Details of the procedure are the same as those described previously for the simple sulfenate.[5] The ionic strength was maintained at 0.50 with $NaClO_4$.

Determination of ^{18}O Content in the Product. The reaction of **1**-^{18}O was carried out in aqueous solutions containing 10 vol% of acetonitrile at an ionic strength of 0.45. An appropriate amount of the aqueous solution (10—100 mL) was equilibrated at 25 °C in a constant temperature bath and the stock solution containing a necessary amount of **1**-^{18}O (ca. 5 mg) was added with a syringe to the solution. After an appropriate time of reaction, products were extracted with CH_2Cl_2, and **4** was isolated by HPLC and analyzed with a mass specrometer JEOL DX 303 in the same way as before.[20]

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References

1) Preliminary accounts of this work are reported in: a) T. Okuyama and T. Fueno, *Chem. Lett.*, **1989**, 2193; b) T. Okuyama, R. D. Gandour and T. Fueno, *ibid.*, **1990**, 273.

2) D. R. Hogg and J. Stewart, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 43; S. Braverman and D. Reisman, *Tetrahedron*, **30**, 3891 (1974).

3) J. L. Kice, *Adv. Phys. Org. Chem.*, **17**, 115 (1980).

4) T. Okuyama, "The Chemistry of Sulphenic Acids and Their Derivatives," ed by S. Patai, Wiley, Chichester (1990), Chap. 18.

5) T. Okuyama, T. Nakamura, and T. Fueno, *J. Am. Chem. Soc.*, **112**, 9345 (1990).

6) W. P. Jencks, *Acc. Chem. Res.*, **13**, 161 (1980).

7) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 8238 (1977).

8) T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, **111**, 7888 (1989).

9) G.-A. Craze, A. J. Kirby, and R. Osborne, *J. Chem. Soc., Perkin Trans. 2*, **1978**, 357.

10) B. L. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, **102**, 6789 (1980).

11) B. M. Dunn and T. C. Bruice, *J. Am. Chem. Soc.*, **93**, 5725 (1971).

12) The pK_a of $(CH_3)_3CSOH$ was found to be 10.5 (T. Okuyama and K. Miyake, unpublished results).

13) L. H. Funderburk, L. Aldwin, and W. P. Jencks, *J. Am. Chem. Soc.*, **100**, 5444 (1978).

14) S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin, and W. G. Mallard, *J. Phys. Chem. Ref. Data*, **17** (S1), 1-872 (1988).

15) R. P. Bell and P. Jones, *J. Chem. Soc.*, **1953**, 88; A. F. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **97**, 6221 (1975); A. F. Hegarty and W. P. Jencks, *ibid.*, **97**, 7188 (1975); W. J. Albery and J. S. Gelles, *J. Chem. Soc., Faraday Trans. 1*, **78**, 1569 (1982); W. J. Albery, *ibid.*, **78**, 1579 (1982); R. P. Bell, "The Proton in Chemistry," 2nd ed, Chapman & Hall, London (1978), Chap. 8; A. F. Hegarty and J. Dowling, *J. Chem. Soc., Chem. Commun.*, **1991**, 996.

16) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw Hill, New York (1969), pp. 217—229.

17) The pH-k_0 profile in Fig. 1 shows negative deviations at higher acidity, and this might be due to a change in the rate-determining step as was observed for **5**.[5]

18) T. Okuyama, T. Nakamura, and T. Fueno, *Tetrahedron Lett.*, **31**, 1017 (1990).

19) T. J. Maricich and C. K. Harrington, *J. Am. Chem. Soc.*, **94**, 5115 (1972).

20) T. Okuyama and T. Fueno, *Bull. Chem. Soc. Jpn.*, **63**, 3111 (1990).

21) J. L. Kice and J. P. Cleveland, *J. Am. Chem. Soc.*, **95**, 104 (1973).

22) R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968).

23) R. A. Hayes and J. C. Martin, in "Organic Sulfur Chemistry," ed by F. Bernardi, I. G. Csizmadia, and A. Mangini, Elsevier, Amsterdam (1985), Chap. 8.

24) This pathway can be excluded because the high ^{18}O retention was observed at the low [**1**-^{18}O]$_0$ in the presence of bromide ion. Another possibility can also be considered, where **6** undergoes the C–O cleavage to give $MeOCH_2^+$ (or $MeOCH_2Nu$ with nucleophilic assistance). However, the leaving ability of a possible nucleofuge Nu-S$^-$(Ph)-OH (a hypervalent species) cannot be better than that of PhSOH and this is hardly rationalizable.

25) R. Eliason and M. M. Kreevoy, *J. Am. Chem. Soc.*, **100**, 7037 (1978).

26) R. P. Bell, "The Proton in Chemistry," 2nd ed, Chapman & Hall, London (1978), p. 291; E. H. Cordes and H. G. Bull, *Chem. Rev.*, **74**, 581 (1974).

27) W. P. Jencks, *Acc, Chem. Res.*, **9**, 425 (1976).

28) T. Okuyama, M. Toyoda, and T. Fueno, *Bull. Chem. Soc. Jpn.*, **63**, 1316 (1990).