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Acid-Catalyzed Cleavage of Methoxymethyl Phenyl Sulfoxide. Solvent Effects and Mode of Bond Cleavage

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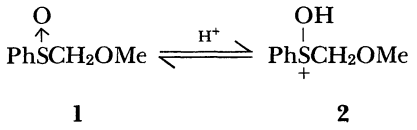
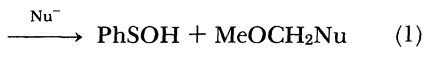
Rate constants for the acid-catalyzed hydrolysis of methoxymethyl phenyl sulfoxide increase with increasing composition of dioxane in aqueous dioxane solution in contrast to the isomeric sulfenate which is strongly decelerated by added dioxane fraction (up to 90 vol%). The isotope distribution in the products obtained from the [^{18}O]-sulfoxide was examined in 95 vol% aqueous dioxane. About 90% of the ^{18}O was retained in the product *S*-phenyl benzenethiosulfinate from the reaction with hydrochloric and hydrobromic acid while only 50—60% of the ^{18}O was found in the thiosulfinate from the reaction with perchloric acid. A plausible reaction mechanism involving ligand coupling within a hypervalent intermediate is proposed for the partial loss of the ^{18}O label in the latter reaction.

We have recently reported kinetic results for acid-catalyzed cleavage of methoxymethyl phenyl sulfoxide (**1**) in aqueous solution, and two possible pathways (Eqs. 2 and 3) are suggested in addition to an S_N2-like cleavage of the S–C bond of the protonated substrate **2** (Eq. 1).[1] That is, in order to accommodate the mechanistic A-1 nature of the reaction and the lack of racemization of **1**, intermediate formation of the isomeric sulfenate **6** via the ion pair **5** (Eq. 2) was considered. However, a mechanism involving a nucleophilic attack at the sulfur to form the hypervalent intermediate (sulfurane) **7** leading to the products by ligand coupling[2] (Eq. 3) could not be excluded. The final product was the thiosulfinate **4** which results from rapid condensation of **3** (Eq. 4).

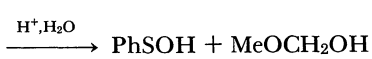


1 **2**



3 (1)

5 **6**



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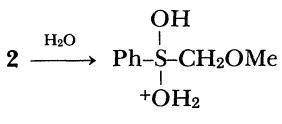
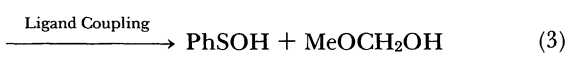
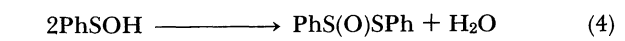


7

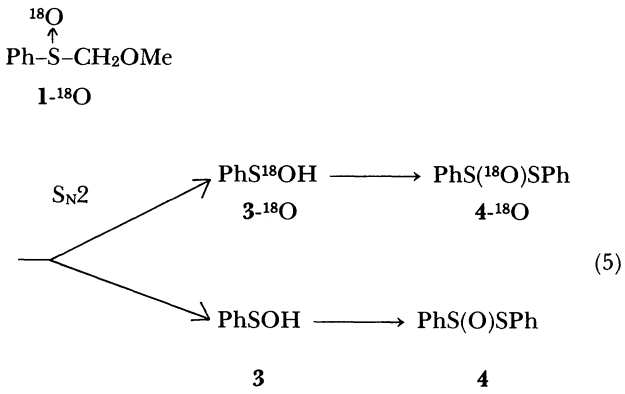


(3)



3 **4** (4)

In order to determine which pathway is more plausible for the acid-catalyzed hydrolysis of **1**, the reaction of the ^{18}O-labeled substrate **1**-^{18}O has been examined. In the S_N2-like reaction, the ^{18}O label should be retained in the product **4** (Eq. 1), while some of the ^{18}O may be lost in the hydrolysis of the sulfenate ester **6** (Eq. 2).[3]



1-^{18}O **3**-^{18}O **4**-^{18}O **3** **4** (5)

In the pathway involving ligand coupling of the sulfurane intermediate **7** (Eq. 3), the extent of retention of ^{18}O depends on the relative ease of coupling of the original and incoming OH groups with the methoxymethyl group.

The correlation of the bond cleavage in the above mechanisms with the extent of ^{18}O retention in the product **4** can hold only if no loss of ^{18}O takes place in the intermediate **3** as well as in the substrate or the product during the reaction. Although the oxygen exchange of the sulfoxide in aqueous solution does not seem to be faster than the hydrolysis,[4–6] the oxygen exchange of **4** may be as rapid as the hydrolysis of **1** in aqueous acid.[7] The O exchange of **3** may be even much faster than the hydrolysis of **1** in aqueous

solution. The acid-catalyzed OH exchange of **3** with water (Eq. 6) should be mechanistically similar to the acid-catalyzed hydrolysis of a sulfenate ester PhSOR (Eq. 7) and the latter reaction is 10^3 times as fast as the hydrolysis of **1** in wholly aqueous solution.[8] Under these circumstances, the isotope distribution experiments in hydrolysis of the labeled substrate are meaningless.

$$\underset{\textbf{3}\text{-}^{18}O}{PhS\text{-}^{18}OH} + H_3O^+ \rightleftharpoons PhS\text{-}^{18}O^+H_2 + H_2O \longrightarrow \underset{\textbf{3}}{PhS\text{-}OH} + H_2{}^{18}O \quad (6)$$

$$PhS\text{-}OR + H_3O^+ \rightleftharpoons PhS\text{-}{}^+OHR + H_2O \longrightarrow PhS\text{-}OH + ROH \quad (7)$$

However, we have fortunately found that solvent effects on the rates for hydrolyses of **1** and **6** (or another simple sulfenate[8]) are quite different: the hydrolysis of **6** is greatly decelerated with the increase of organic fraction of mixed aqueous solutions while that of **1** is accelerated with increasing composition of organic solvent, and in 95% aqueous dioxane **1** is hydrolyzed more rapidly than **6**. So, we could examine the ^{18}O distribution in the product from hydrolysis of the labeled **1**-^{18}O with little influence from the exchange reactions in predominantly organic aqueous solution. The ^{18}O exchange of the labeled **4** seems also to be retarded in organic aqueous solution. The present paper describes results of such examinations and presents a more plausible mechanism for the acid-catalyzed bond cleavage of **1**.

Results and Discussion

Rates for the acid-catalyzed hydrolysis of the sulfoxide **1** and the sulfenate **6** were determined in aqueous dioxane of varying composition. The observed rate constants are summarized in Table 1, and the corrected rate constants at $[HClO_4]$=0.1 M[9] (1 M= 1 mol dm^{-3}) are plotted logarithmically against vol % of dioxane in the reaction media (Fig. 1).

Solvent-dependent changes in rates for the hydrolyses of **1** and **6** are quite contrasting. The rate for **6** very rapidly decreases with increasing fraction of dioxane showing a minimum value at above 90% dioxane and then increases in solutions of still higher content of dioxane. This type of solvent effects on the rate can be seen for other acid-catalyzed reactions in aqueous solution probably owing to the ionic nature of the transition state.[10] By contrast, the rate for the reaction of **1** increases slowly (up to about 80%) and then rapidly with increasing composition of dioxane.

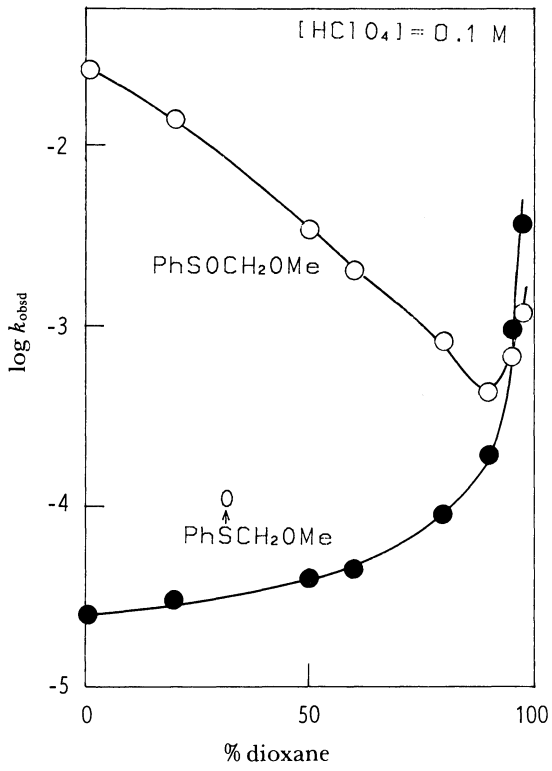


Fig. 1. Rate constants for the hydrolyses of the sulfoxide **1** (●) and the sulfenate **6** (○) in aqueous dioxane at $[HClO_4]$=0.1 M and 25 °C. The ordinate shows vol% content of dioxane.

Table 1. Solvent Effects on the Hydrolysis Rates of **1** and **6**[a]

Dioxane	**1**		**6**	
vol%	$[HClO_4]$/M	$10^3 k_{obsd}/s^{-1}$	$[HClO_4]$/M	$10^3 k_{obsd}/s^{-1}$
1	0.40	0.0999	0.02	5.4
20	0.40	0.118	0.10	13.8
50	0.40	0.158	0.10	3.3
60	0.40	0.179	0.10	2.0
80	0.40	0.521	0.10	0.81
90	0.10	0.178	0.10	0.40
95	0.10	0.92	0.10	0.75
97.5	0.10	3.6	0.10	1.20

a) Measured in aqueous dioxane at 25 °C without added salt.

Although **6** is about 10^3 times more reactive than **1** in wholly aqueous solution, crossover of the relative reactivity occurs at 95% of dioxane and **1** becomes more reactive in predominantly organic aqueous solution.

If the sulfenate **6** had been an intermediate for the reaction of **1** as postulated in Eq. 2,[1] an apparent curvature of the first-order plot should have been observed for the reaction of **1** (owing to the accumulation of the intermediate) in predominantly organic aqueous solution (>90% dioxane) where **6** is similarly or less reactive. Furthermore, formation of **6** should have been detected if the reaction had been quenched in the intermediate stage of the reaction. In reality, we could observe neither anomalous kinetic behavior nor formation of **6**. Pseudo-first-order plots for the formation of **4** in the reaction of **1** in 90—97.5 vol% aqueous dioxane were nicely linear to give k_{obsd} recorded in Table 1. The reactions of **1** were quenched at about the half-life time of the reaction by neutralization with alkali and the reaction mixture was directly (or after extraction with dichloromethane and concentration) analyzed by HPLC. Only the substrate **1** and the product **4** were detected and no sign of formation of **6** was found. In consequence, a possibility of intermediate formation of the sulfenate **6** and hence a mechanism shown in Eq. 2 can clearly be excluded. Our previous suggestion[1] that **6** be a possible intermediate has to be withdrawn.

In predominantly organic media, the oxygen exchange of the sulfenic acid should be strongly retarded and the isotope distribution in the hydrolysis products may reflect satisfactorily the bond cleavage due to the hydrolysis reaction of the present concern. So, we undertook such determination in aqueous dioxane solution.

The ^{18}O-labeled sulfoxide **1**-^{18}O of 93.2 atom % isotopic purity was obtained by bromine oxidation of methyl phenyl sulfide in the presence of ^{18}O-enriched water (97%)[11] followed by α-bromination[12] and nucleophilic substitution[13] (Eq. 8).

$$\mathrm{PhSCH_3} \xrightarrow{\mathrm{Br_2,\ H_2{}^{18}O}} \mathrm{PhS{}^{18}OCH_3} \xrightarrow{\mathrm{NBS/Br_2}} \mathrm{PhS{}^{18}OCH_2Br} \xrightarrow{\mathrm{MeONa}} \mathbf{1}\text{-}{}^{18}\mathrm{O} \qquad (8)$$

The last step of the synthesis was carried out in a smaller scale immediately before each use since the sulfoxide **1** is known to rearrange to the sulfenate **6** slowly even at room temperature.[14]

The reaction products from **1**-^{18}O in aqueous dioxane were extracted with dichloromethane and **4** was immediately separated from the unreacted **1**-^{18}O since a (wet) solution of **1**-^{18}O gives easily the labeled **4** without any loss of the label on standing at room temperature. The solution of the isolated **4** was subjected to mass spectral analysis. From the relative intensities of the peaks at *m/z* 234 and 236 the ^{18}O content of the product **4** and then % retention of the ^{18}O were calculated. The results are summarized in Tables 2 and 3.

A definitive tendency seen in these results is that the % retention of the label is greater for the reactions in the presence of chloride or bromide ion than in their absence. The distinct difference observed for the reactions in 95% aq dioxane suggests that the reactions in perchloric acid and in halide acids proceed through different mechanisms. The latter reactions in hydrochloric and hydrobromic acids result in about 90% retention in contrast to about 50% retention observed for the former. This implies that the halide-catalyzed reaction takes place essentially in 100% retention of the label, since the halide-independent reaction which leads to some loss of the label should competitively occur in the dilute halide acid solutions. The halide

Table 2. Bond Cleavage of the ^{18}O-Labeled Substrate **1**-^{18}O[a]

HX (concn/M)	$t_{1/2}$ / min	$10^3[\mathbf{1}]_0$ / M	Reaction time / min	%^{18}O[b]	%^{18}O Retention[c]
		95 vol% Aqueous dioxane			
$HClO_4$ (0.05)	20	0.5	20	46.2	49.6
		1.0	20	50.2	53.8
		2.0	20	58.0	62.2
$HClO_4$ (0.10)	11	1.0	10	48.2	51.7
		1.0	30	43.8	47.0
HCl (0.05)	6.2	1.0	7	86.2	92.5
		1.0	15	83.9	90.0
HBr (0.05)	1.2	1.0	2	81.1	87.0
		90 vol% Aqueous dioxane			
$HClO_4$ (0.10)	70	1.0	70	32.5	34.8
		1.0	150	28.8	30.9
HCl (0.10)	12	1.0	20	68.3	73.2

a) Reaction was carried out with the substrate of 93.2% ^{18}O isotopic purity at 25 °C. b) Observed atom% of ^{18}O found in the product **4**. c) % Retention of the ^{18}O in the product **4**.

Table 3. Bond Cleavage of **1**-^{18}O in 60 vol% Aqueous Dioxane[a]

Nu^- (concn/M)	$t_{1/2}$	$10^3[\mathbf{1}]_0$	Reaction time	%^{18}O[b]	%^{18}O Retention[c]
	min	M	min		
None	65	0.33	65	10.6	11.4
		0.33	260	7.4	7.9
		1.0	65	13.7	14.7
		1.0	195	11.9	12.8
		2.0	195	17.5	18.8
Cl^- (0.10)	37	0.33	37	33.6	36.1
		0.33	147	26.1	28.0
		1.0	40	49.3	52.9
Cl^- (0.40)	18	0.33	18	29.5	31.7
		0.33	55	21.8	23.4
		2.0	54	37.4	40.1
Br^- (0.20)	9.4	1.0	9	30.3	32.5
		1.0	28	12.9	13.8

a) Determined at $[H^+]$=0.40 M and 25 °C. b) Observed atom% of ^{18}O found in the product **4**. c) % Retention of the ^{18}O in the product **4**.

reaction must take place through an S_N2-type mechanism (Eq. 1).

Other general features of the data given in Tables 2 and 3 are: (1) The retention increases with a dioxane fraction of the media, and (2) with an initial concentration of the substrate $[\mathbf{1}]_0$, while (3) the retention decreases with reaction time. The large solvent effects observed on the % retention are no doubt largely due to the OH exchange of the intermediate sulfenic acid **3** with water and partly due to the exchange of the product **4** as pointed out above. The effects of $[\mathbf{1}]_0$ result from the competition which **3** undergoes between the condensation to afford **4** (Eq. 4) and the exchange (Eq. 6). The smaller the initial concentration $[\mathbf{1}]_0$, the smaller will the stationary-state concentration of the intermediate **3** be and hence the more important will the first-order reaction of **3**, OH exchange with water, become as compared with the second-order condensation, resulting in the greater loss of the label. Since the substrate concentration becomes smaller with progress of the reaction, the % retention becomes smaller with reaction time. The oxygen exchange in **4**, if any, tends also to lead to loss of the label with reaction time.

The % retention of the label in **4** from the reaction in 95% aq dioxane ranges roughly 50—60% in the absence of halide ion. These values of retention very likely reflect the hydrolysis reaction. Since 90% retention was observed in halide acids in the same medium, the OH exchange of **3** should hardly affect the results. Although halide ions accelerate the hydrolysis of **1**,[1] they sould also strongly catalyze the OH exchange of **3** as was observed for the hydrolysis of sulfenate esters.[8] It is not reasonable to assume that the exchange is more rapid than the hydrolysis of **1** in perchloric acid, and hence it may be concluded that the acid-catalyzed hydrolysis of **1**-^{18}O in the absence of nucleophilic assistance occurs with 50—60% retention of ^{18}O in the sulfenic acid product **3**. Strictly, the conclusion applies only to the reaction in 95% aq dioxane. Nonetheless, the distinct tendency that the % retention is always smaller in the absence of halide ion than in its presence (Table 3) may suggest that the above ratio of the retention is also occurring in other aqueous media.

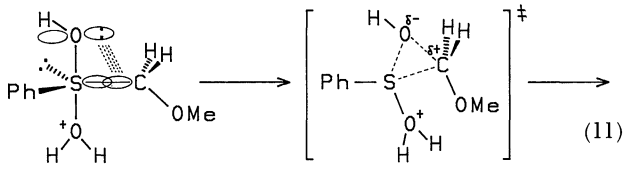
One question may arise here why the effects of $[\mathbf{1}]_0$ which tends to increase the % retention occurs if the OH exchange of **3** does not take place in the medium. Because of an extremely high nucleophilicity of the sulfenic acid,[15] **3** could react with **1** in a similar way to halide ions even in its stationary-state concentration (Eq. 9). This increases the % retention of the label.

$$\mathrm{Ph{-}\overset{+}{S}(^{18}OH){-}CH_2OMe} + \mathrm{PhSOH} \longrightarrow \mathrm{PhS^{18}OH} + \mathrm{Ph\overset{+}{S}(OH)CH_2OMe} \qquad (9)$$

Thus, the net retention in the unassisted acid-catalyzed hydrolysis of **1**-^{18}O may well be about 50% of the label. This conclusion is best accommodated by the mechanism involving ligand coupling within the sulfurane intermediate (Eq. 3). Since the proton transfer equilibrium is very rapid (Eq. 10) and since both of the OH groups are very likely located in the apical positions, the coupling of the methoxymethyl group with one of the two OH should occur in an equal probability.

$$\mathrm{Ph\overset{+}{S}(^{18}OH)(^{+}OH_2){-}CH_2OMe} \rightleftharpoons \mathrm{Ph\overset{+}{S}(^{18}OH_2)(OH){-}CH_2OMe} \qquad (10)$$

The ligand coupling mechanism[2] involving a sulfurane intermediate has been proposed by Oae and co-workers[16] for the reaction of 1-phenylethyl 2-pyridyl sulfoxide with a Grignard reagent to give 2-(1-phenylethyl)pyridine with complete retention of configuration at the benzylic carbon. A similar process is well-known under the name of reductive elimination in the field of organometallic chemistry. A progress of bonding in this process may be visualized in Eq. 11 for the present reaction.



(11)

$PhS\overset{+}{O}H_2 + HOCH_2OMe$

The unusual solvent effects observed may arise from the homolytic and concerted nature of the bond cleavage and formation in this process. The reaction of halides may take a different pathway (S_N2, Eq. 1) because of their higher nucleophilicity. If it proceeded through ligand coupling of the sulfurane intermediate, the considerable loss of the label sould have been observed also for the halide reaction.

Experimental

Experiments were carried out in the same way as described previously.[1]

Methoxymethyl Phenyl [^{18}O]Sulfoxide (1-^{18}O). To a magnetically stirred mixture of methyl phenyl sulfide (Aldrich, 2 g, 16 mmol), pyridine (4 cm^3, ca. 50 mmol), ^{18}O-enriched water (97%, Sigma, 1 g), and dichloromethane (30 cm^3) was added dropwise a solution of bromine (2.8 g, 17.5 mmol) in CH_2Cl_2 (35 cm^3) on an ice bath. After stirring for 10 h, the excess of bromine was destroyed by addition of anhydrous Na_2SO_3, and then water was added. The mixture was washed with aqueous sodium chloride, dried over $MgSO_4$ and the solvent was removed by evaporation. The residues were chromatograghed with a silica-gel column (Merck Kieselgel 60) using 1:2 (v/v) hexane–ethyl acetate as an eluent to give the pure sulfoxide (1.9 g, 83% yield).[11]

The methyl phenyl [^{18}O] sulfoxide (1.9 g, 13.4 mmol) was brominated in the presence of pyridine (1.2 cm^3, 15 mmol) in a CH_2Cl_2 solution (40 cm^3) by addition of a mixture of *N*-bromosuccinimide (2.4 g, 13.5 mmol), bromine (1.1 g, 6.8 mmol), and CH_2Cl_2 (30 cm^3) under stirring at room temperature. After 6 h stirring, the mixture was washed with aq Na_2SO_3 and then aq NaCl and dried over $MgSO_4$. The solvent was removed under vacuum. The ^1H NMR spectrum and HPLC of the residue showed that the conversion was quantitative and the product was practically pure bromomethyl phenyl sulfoxide.[12] The bromomethyl sulfoxide was used for the next step without purification.

Methoxylation of the bromomethyl sulfoxide was carried out in methanol containing ca. 4 M of sodium methoxide.[13] About 0.1 g of the bromomethyl sulfoxide was dissolved in 2 cm^3 of the sodium methoxide solution and left standing at room temperature for a few h. The product was extracted with CH_2Cl_2, washed with aq NaCl, and dried over $MgSO_4$. The solvent was removed under vacuum. The ^1H NMR spectrum and HPLC showed that the product was practically pure **1**-^{18}O. ^1H NMR ($CDCl_3$), δ=3.68 (s, 3H), 4.34 (s, 2H), 7.4—7.7 (m, 5H). The mass spectrum showed that the ^{18}O isotopic purity is 93.2 atom % from the relative intensity of the peaks at *m/z* 170 and 172. The product was stored as an acetonitrile solution in a refrigerator and used within a few days.

Determination of ^{18}O Content in the Product. Aqueous dioxane solutions (>60% dioxane) were prepared in a volumetric flask by placing required amounts of acid, salt, and water and then filling the flask with dioxane. A necessary amount of acid solution was equilibrated at 25 °C in a flask immersed in a constant temperature bath and an acetonitrile solution containing **1**-^{18}O (3—5 mg) was introduced from a syringe. After brief shaking, the mixture was left standing for an appropriate reaction time and quenched by neutralization with a calculated amount of alkali. The products were extracted with CH_2Cl_2 and concentrated by evaporation. The thiosulfinate product **4** was isolated by preparative HPLC (Finepak SIL $C_{18}S$, 1:1 (v/v) CH_3CN–H_2O). The eluted solution was extracted with CH_2Cl_2. The resulting extract was concentrated and subjected to mass spectral analysis on a spectrometer JEOL DX 303. From the relative intensities of the peaks at *m/z* 234 and 236, content of ^{18}O was calculated.

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