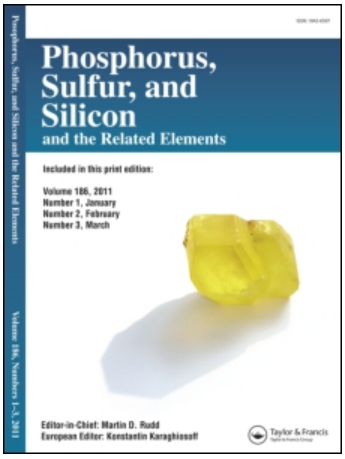

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Mechanisms of Nucleophilic Substitution at Sulfur

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To cite this Article Okuyama, Tadashi(1994) 'Mechanisms of Nucleophilic Substitution at Sulfur', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 113 — 125
To link to this Article: DOI: 10.1080/10426509408034205
URL: http://dx.doi.org/10.1080/10426509408034205

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95–96, pp. 113–125
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MECHANISMS OF NUCLEOPHILIC SUBSTITUTION AT SULFUR

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Kinetic and tracer experiments were carried out for nucleophilic substitutions at di- and tricoordinate sulfur. The breaks in pH-rate profiles were observed for hydrolysis of sulfenate and sulfinamides. The significant oxygen exchange was detected during the acid-catalyzed hydrolysis of some sulfinanilides. These are taken as evidence for the reaction intermediate. Unique reaction modes found for methoxymethyl sulfenate and sulfoxide are accounted for also by mechanisms involving sulfurane intermediates.

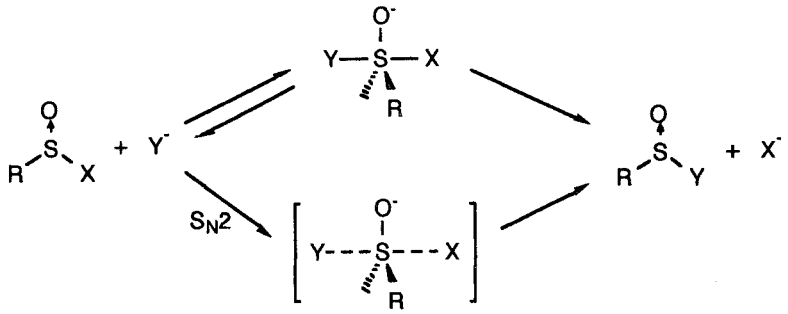
Key Words nucleophilic substitution, sulfenate ester, sulfinate ester, sulfinanilide, sulfurane, hypervalent intermediate

INTRODUCTION

Nucleophilic reactions at sulfur may proceed with or without a hypervalent intermediate (sulfurane) via the two-step addition-elimination (AE) mechanism or the concerted SN2 mechanism. The substitution reactions of sulfinic acid derivatives usually occur with predominant inversion of configuration at the sulfur, and has often been interpreted by the AE mechanism involving sulfurane intermediates.[1] However, the results are also consistent with a concerted SN2 displacement reaction that avoids formation of such an intermediate.[2] The isolation of stabilized bicyclic sulfuranes suggests that these species may form as intermediates of nucleophilic substitution at sulfur.[3] Despite continuing efforts, there are still no definitive experiments to demonstrate the formation of these species as reaction intermediates.

One of the best criteria for the existence of an intermediate along the reaction coordinate is the detection of a change in the rate-determining step. The observed break in pH-rate profiles of acid-catalyzed reactions can be taken as such evidence. The ^{18}O exchange occurring during hydrolysis of sulfinyl derivatives is also accommodated by a

Scheme 1.



mechanism involving an addition intermediate, as is considered as definitive evidence for the tetrahedral intermediate of hydrolysis of carboxylic acid derivatives.[4] These criteria were applied to the hydrolyses of sulfenate and sulfinate esters as well as sulfinamides. Examinations of unusual modes of acid-catalyzed reactions of methoxymethyl sulfenate and sulfoxide lead to the suggestion that these reactions also involve sulfuranes as reaction intermediates.

ETHYL SULFENATE ESTER[5]

Pseudo-first-order rate constants for acid-catalyzed hydrolysis of ethyl benzenesulfenate (Eq. 1) were determined spectrophotometrically in aqueous perchloric acid at 25 °C.

$$\underset{\mathbf{1}}{\text{PhSOEt}} + H_2O \xrightarrow{H^+} \text{PhSOH} + \text{EtOH} \qquad (1)$$

The pH-rate profile clearly shows a break around pH 2 (Figure 1) with two different acid-catalyzed processes. The break is accommodated by a change in the rate-determining step with changing pH in a mechanism involving an intermediate. The most plausible intermediate for this reaction is a hypervalent sulfuranide (Scheme 2). The changeover of the rate-determining step implies a change in the relative magnitudes of rate constants for the return (k_{-1}) and the breakdown (k_2) of the intermediate occurring with changing pH. This must take place because the extent of protonation

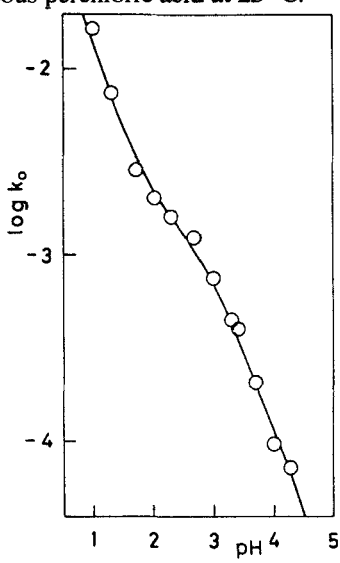
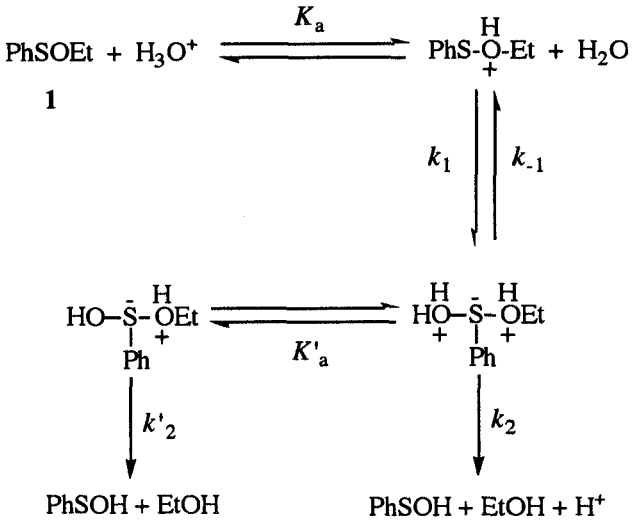


FIGURE 1 The pH-rate profile for the hydrolysis of **1**.

of the intermediate changes with pH. At lower pH, the main reaction may take place through the diprotonated hypervalent intermediate, and the breakdown of the intermediate must be rate determining ($k_{-1} > k_2$). With increasing pH, deprotonation would occur mainly at the more acidic H_2O^+ group to give the alkoxy-protonated intermediate. This would make decay of the intermediate faster than the return ($k_{-1} < k_2 + K'_a k'_2/[H^+]$), and the formation of the intermediate becomes rate determining at higher pH.

Scheme 2.



The acid-catalyzed hydrolysis is strongly accelerated by added nucleophiles. Catalytic constants for various nucleophiles (Table I) represent nucleophilicities in reaction (2). The unique feature of the reactivity is that a neutral dialkyl sulfide and thiocyanate ion are more reactive than iodide ion. These results differ from other typical nucleophilic reactivities such as those in an SN2 reaction of methyl iodide (3)[6] and in a nucleophilic reaction at the divalent sulfur of the thiolsulfinate (4).[7]

$$PhS\text{-}O^+(H)Et + Nu^- \longrightarrow PhSNu + EtOH \quad (2)$$

$$CH_3I + Nu^- \longrightarrow CH_3Nu + I^- \quad (3)$$

$$PhS\text{-}S^+(OH)Ph + Nu^- \longrightarrow PhSNu + PhSOH \quad (4)$$

The reactivity pattern of nucleophiles ($R_2S > SCN^- > I^-$) observed in the present reaction (2) at the divalent sulfur may imply that the rate-determining step is not a simple

TABLE I Nucleophilic reactivities in various reactions

nucleophile	$k_{Nu}^{H}/M^{-2}s^{-1}$ a		relative nucleophilicity in reaction		
	1	**2**	(2)	(3)[b]	(4)[c]
H_2O	0.0024	0.0044	10^{-4}		
Cl^-	17.9	9.0	1.0	1.0	1.0
Br^-	95.9	54	5.4	26	35
I^-	1160	950	65	1120	14000
SCN^-	2950	3500	165	214	5400
$(HOCH_2CH_2)_2S$	3600	5900	200	9.3[d]	829[e]
PhSOR	1900	780	100		
$ClCH_2CO_2^-$		11.1			
$CH_3CO_2^-$		104			

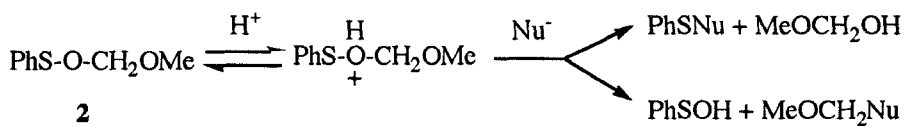
a Acid-catalyzed nucleophilic catalytic constants for the hydrolysis of **1** and **2** measured at 25 °C and an ionic strength of 0.50. [b] In methanol at 25 °C. [c] In 60 vol % aqueous dioxane at 39.1 °C. [d] A value for Et_2S. [e] A value for Bu_2S.

nucleophilic reaction. The reactivities may be accounted for by a reaction involving a sulfuranide intermediate with its decay being rate determining.

METHOXYMETHYL SULFENATE ESTER[8]

Methoxymethyl benzenesulfenate **2** is obtained easily from thermal rearrangement of methoxymethyl phenyl sulfoxide **3**.[9] The methoxymethyl sulfenate **2** shows essentially the same third-order rate constants (k_{Nu}^{H}) toward nucleophiles under acidic conditions as the simple sulfenate **1** (Table I). So, the reaction of nucleophiles must occur at the sulfur of the protonated **2** despite the possibility of reaction at the acetal carbon; **2** can be regarded as an acetal of formaldehyde (Scheme 3).

Scheme 3.

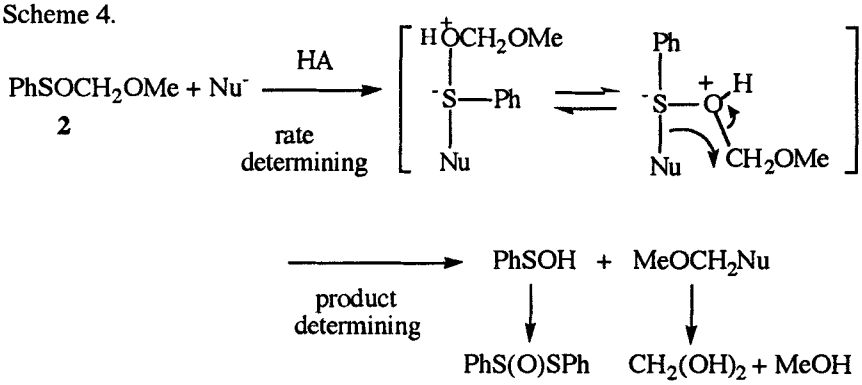


However, examination of the products from the ^{18}O-labeled substrate showed that the reaction usually takes place with cleavage between the sulfenic oxygen and the acetal

carbon, but not at the sulfur. This was confirmed by the finding that most of the label was retained in the the thiolsulfinate product from the ^{18}O-labeled **2**.

These results imply that the product-determining step (C-O cleavage) is different from the rate-determining step (S attack by a nucleophile). That is, the mechanism for this reaction involves at least two different steps, and one of probable mechanisms is that involves a sulfurane intermediate (Scheme 4). The rearrangement of the nucleophile may occur within the sulfuranide intermediate formed by nucleophilic attack at the sulfur.

Scheme 4.



SULFINATE ESTERS[10]

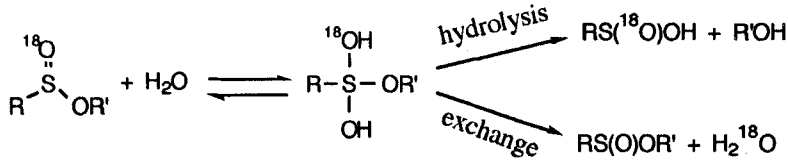
Acid hydrolysis of alkyl benzenesulfinates occurs only in strong acid. Hydrolysis rates decrease slightly in the order methyl > ethyl > isopropyl in 2 M perchloric acid while *t*-butyl benzenesulfinate is an order of magnitude more reactive. Acid hydrolysis of primary alkyl sulfinates must occur with nucleophilic attack at the sulfur, whereas the tertiary alkyl ester must undergo SN1 reaction at the carbon.

$$PhS(O)OR + H_2O \longrightarrow PhSO_2H + ROH \qquad (5)$$

Acid hydrolysis: R = *t*-Bu > Me > Et > *i*-Pr

Alkaline hydrolysis: R = Me > Et > *i*-Pr > *t*-Bu

Scheme 5.



Hydrolysis of sulfinate esters can be described formally in the same way as that of carboxylate esters (Scheme 5) without regard to the configuration of the addition intermediates. As the tetrahedral intermediate in carboxylate hydrolysis was demonstrated by the detection of ^{18}O isotope exchange during the course of hydrolysis reaction,[4] the addition intermediate of sulfinate hydrolysis would be deduced from the potential isotope exchange during the reaction. However, previous efforts along this line in alkaline hydrlysis of cyclic sulfinates[11] as well as a sulfinamide[12] are unsuccessful. We have undertaken more detailed and precise examinations on both acid and alkaline hydrolyses of a simple sulfinate ester and sulfinanilides.

The ^{18}O-labeled methyl benzenesulfinate **4**-^{18}O (45.5 % ^{18}O excess) can easily be obtained by isotope exchange in acidic methanol containing $H_2{}^{18}O$. The labelled substrate was subjected to hydrolysis both in aqueous alkaline and acid solutions. After one to three half-lives of hydrolysis, unreacted substrate was recovered by extraction and analyzed by mass spectrometry. Results are summarized in Table II. In alkaline hydrolysis any exchange seems to be detected. By contrast, a very small but definite amount of the label is lost during acid-catalyzed hydrolysis. The amount of exchange (about 1 % exchange in 3 half-lives) corresponds to the relative rates of hydrolysis and exchange of about 200.

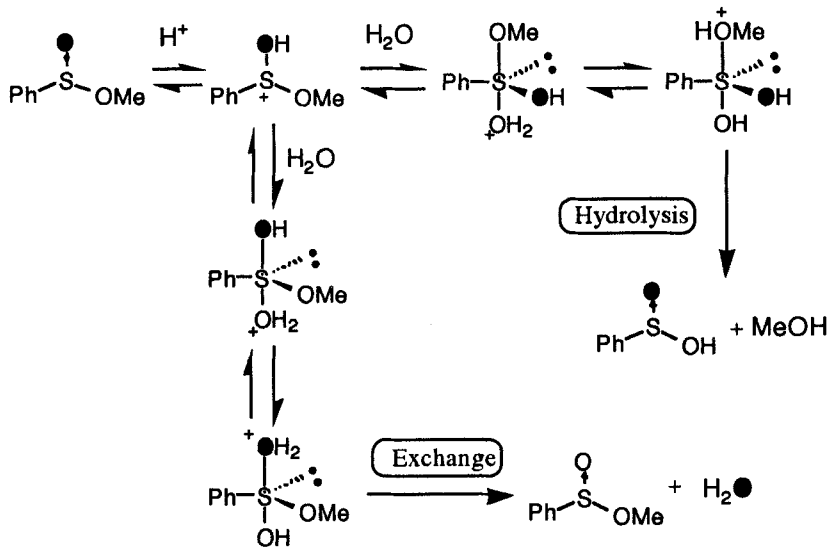
This large difference in rates is imcompatible with the reaction of water with the conjugate acid of the substrate protonated at the sulfinyl oxygen. A possible mechanism involving the sulfinyl-oxygen protonation and sulfurane intermediates is depicted in Scheme 6 with accompanying exchange. In the protonated substrate regarded as a hydroxymethoxysulfonium ion, the hydroxyl and the methoxyl groups are similar in nature, and both can equally be directed at one of the apical positions of a trigonal-

TABLE II Remaining ^{18}O in the recovered substrate during hydrolysis of **4**-^{18}O[a]

conditions (pH)	half-life	reaction time	% excess ^{18}O
unreacted		0	45.50
NaOH (10.6)		15 min	45.51
borate (9.25)	43 min	60 min	45.40
carbonate (10.08)	5.5 min	15 min	45.48
$HClO_4$ (2 M)	2 h	4 h	45.22
		6 h	45.06
		8 h	44.73

[a] Reactions were carried out at 25 °C and the recovered substrate was analyzed by mass spectrometry for the ^{18}O content.

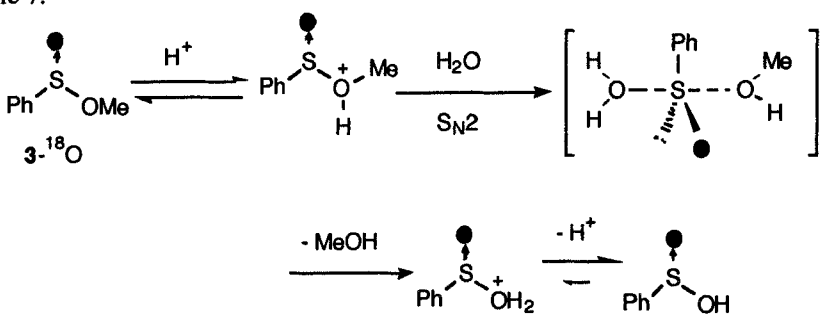
Scheme 6.



bipyramidal structure. Thus, the rates of hydrolysis and exchange could not be so much different as observed.

An alternative mechanism of acid-catalyzed hydrolysis may involve protonation at the alkoxyl oxygen as illustrated in Scheme 7. With this protonated substrate, the reaction must proceed through a concerted SN2-like process. Although the basicity of the alkoxyl oxygen is weaker than the sulfinyl oxygen, the former protonation would lead to much facile hydrolysis. A small amount of contaminated isotope exchange may come from some other competitive reactions.

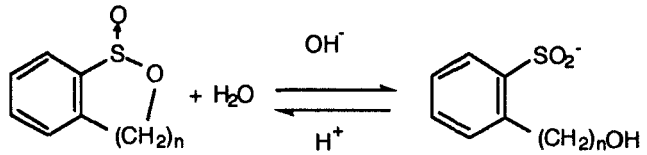
Scheme 7.



The lack of ^{18}O exchange during alkaline hydrolysis may also be due to the SN2-like mechanism. If there existed a sulfurane intermediate, rapid protonation and pseudo-rotation would have led to the isotope exchange.

CYCLIC SULFINATE ESTERS[13]

Ring opening and closure as well as oxygen isotope exchange of five- and six-membered cyclic sulfinates, **5** and **6**, were examined. Ring opening occurs readily in aqueous alkaline solution while the reverse ring closure takes place slowly in strong acid (Eq. 6).



(6)

5, n = 1; **6**, n = 2

So, the cyclic sulfinate is seemingly stable in aqueous acid. However, loss of the ^{18}O label was observed from the labeled substrates under these conditions. That is, the exchange of oxygen isotope at the sulfinyl position occurs in acid. Rates of these reactions are summarized in Table III. It is interesting to note that both ring opening and closure are more facile with the five-membered sulfinate **5** while the ^{18}O exchange of the six-membered sulfinate **6** is faster than that of **5**. Higher reactivity of five-membered ring containing sulfur is generally observed as compared with the six-membered analog.

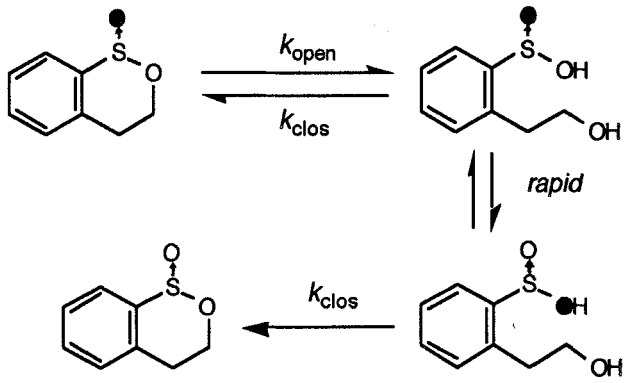
During the course of alkaline hydrolysis (ring opening) of **5** or **6**, no ^{18}O exchange was detected as was found with another cyclic sulfinate[11] and the acyclic sulfinate **4**. The exchange observed in acidic media at first glance seemed to us to suggest that the exchange

TABLE III Rate Constants for reactios of cyclic sulfinate esters at 25 ° C

reaction conditions	**5**	**6**	relative rate **5**/**6**
Ring Opening ($k_{OH}/M^{-1}s^{-1}$)			
pH 9-12	79.5	0.516	150
Ring Closure ($10^4 k_{obsd}/s^{-1}$)			
$HClO_4$, 1.82-1.86 M	0.897	0.560	1.6
HCl, 1.82-1.86 M	6.07	3.77	1.5
HBr, 1.82-1.86 M	23.9	17.0	1.3
^{18}O Exchange ($10^6 k_{obsd}/s^{-1}$)			
$HClO_4$, 1.95 M	0.308	1.57	1/5.1
HCl, 1.95 M	3.28	17.9	1/5.5
HBr, 1.95 M	8.90	53.1	1/6.0

occurred without ring opening through sulfurane intermediates because of the contrasting results, higher rate of exchange of the six-membered sulfinate. However, careful examinations showed that the exchange actually takes place through reversible acid-catalyzed ring opening and closure (Scheme 8) with the rate-determining ring opening.

Scheme 8.



The UV spectra of **6** in acid show that the ring closure is not complete and a small amount of the ring-open acid is involved at equilibrium. We can determine approximate equilibrium constants K_C for the ring closure from the UV spectra. These values are compared with those calculated from the rate constants determined independently by assuming the ^{18}O exchange occurring via ring opening, $K_C = k_{clos}/2k_{ex}$ (Table IV). Reasonable agreements of these values indicate that the exchange does occur via ring opening and closure. So, we could not find any evidence for a reaction intermediate in ring opening or closure of the cyclic sulfinates. Variation of the equilibrium constants with acidity (ionic strength) was observed probably owing to the change in acitivity of the sulfinate.[14]

TABLE IV Equilibrium constants for the ring closure to form **6** in acid solutions at 25 °C

acid	[acid]/M	K_C (UV)[a]	[acid]/M	K_C (calcd)[b]
$HClO_4$	1.714	18, 20	1.95	19.7
$HClO_4$	1.714[c]	53		
$HClO_4$	3.429	66, 52		
$HClO_4$	4.286	100, 118	4.67	70.3
HCl	1.714	16, 14	1.95	12.1

[a] Evaluated from UV spectra. [b] Calculated from kinetic data. [c] With added $NaClO_4$ of 2.571 M.

SULFINAMIDES[15]

Sulfinamides were found to be very reactive in acid. Hydrolysis of some *N*-arylbenzenesulfinamides **7** (Eq. 7) has been kinetically studied in the pH range 1-4 at 25 °C. Linear pH-rate profiles with a slope of -1 are obtained for the reactions of unsubstituted *N*-phenyl- (**7b**) and *N*-(*p*-chlorophenyl)benzenesulfinamide (**7a**), while the plots for the reactions of *N*-(*p*-methylphenyl)- (**7c**) and *N*-(*p*-methoxyphenyl)benzenesulfinamide (**7d**) show a break around pH 3 (Figure 2).

$$\underset{\mathbf{7}}{\text{PhS(O)NHAr}} + H_2O \longrightarrow PhSO_2H + ArNH_2 \qquad (7)$$

These pH-rate profiles can be accommodated by a two-step mechanism through sulfurane intermediates (Scheme 9); and a change in rate-determining step at pH ca. 3 for the reactions of **7c** and **7d**, but not for **7a** and **7b**. For simplicity, Scheme 9 represents only the different states of protonation and ignores the configurations of the individual species. The pool of intermediates shown in Scheme 9 partition between return to substrate by loss of water from the *O*-protonated and neutral intermediates (k_{-1} and k'_{-1}) and formation of product by expulsion of aniline from the *N*-protonated species (k_2). The rate-determining step for hydrolysis will be determined by the relative rates of these steps, and this depends on the energy of the respective transition states. There is net development of positive charge at the aniline nitrogen in the transition state for product formation (k_2). The positive charge will be stabilized by electron-donating substituents at the aniline ring, and this will make the second step progressively less rate determining on moving from **7a** to **7d**. We suggest that the pH-rate profiles in Figure 2 are consistent with rate-determining breakdown of the intermediate for the reactions of **7a** and **7b** in the entire pH region examined, and rate-determining formation of the intermediate for the reactions of **7c** and **7d** at low pH that switches to the rate-determining breakdown with increasing pH.

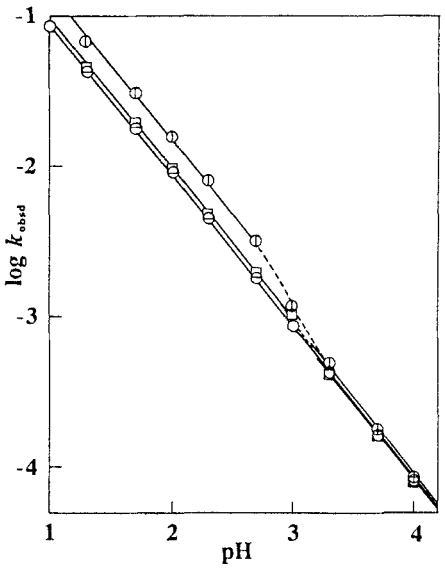
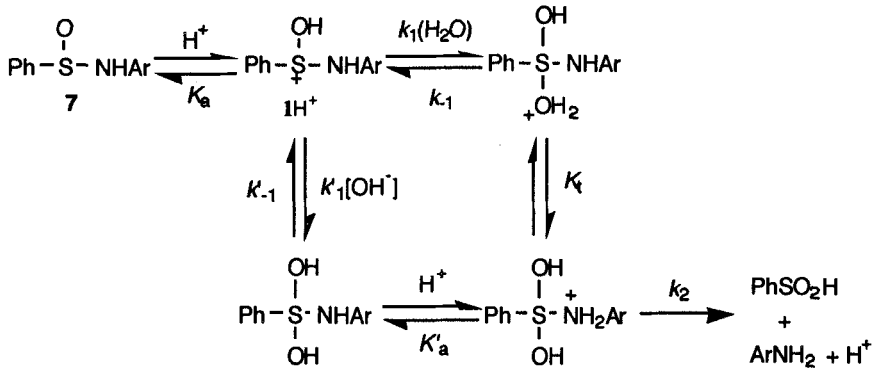


FIGURE 2 pH-Rate profiles for hydrolysis of **7b** (○), **7c** (□), and **7d** (◫).

Scheme 9.



The accumulation of the neutral sulfurane intermediate at increasing reaction pH that favors return to substrate is reflected by breaks in the pH-rate profiles for the reaction of **7c** and **7d**.

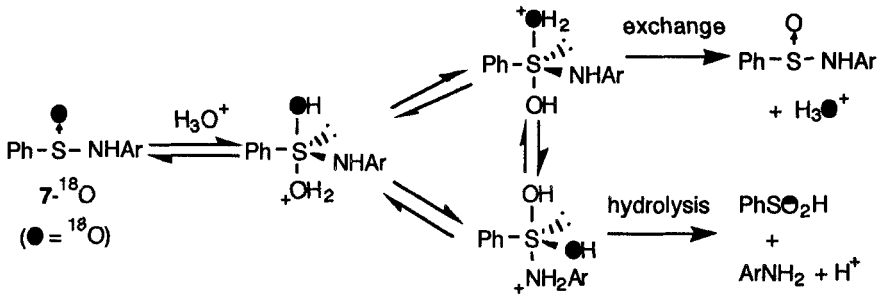
If the rate-determining step for hydrolysis of **7** is breakdown of the sulfurane intermediate, then this species should be formed in a peequilibrium step. This would lead to exchange of ^{18}O label from substrate to solvent during the course of hydrolysis reaction. This prediction was confirmed by the observation of significant loss of the label from the ^{18}O-labeled substrates during hydrolysis (Table V). These results may best be

TABLE V The ^{18}O exchange during acid hydrolysis of the labeled sulfinamides[a]

substrate	$[HClO_4]$/M	vol% CH_3CN	react. time[b]/min	excess% ^{18}O[c]
7b-^{18}O (H)			0	37.5[d]
	0.01	< 1	1.25	36.1
	0.001	< 1	13	36.1
	0.001	20	26	34.9
	0.001	50	57	31.8
7c-^{18}O (*p*-CH_3)			0	34.6[d]
	0.001	< 1	11	30.5
	0.001	< 1	22[e]	26.2
	0.001	50	42	26.2

[a] Reactions were carried out in perchloric acid containing some acetonitrile at 25 °C. The ionic strength was kept at 0.10 ($NaClO_4$) when the acetonitrile content is < 1 %, while it was not adjusted in other acetonitrile solutions. [b] One half-life of the hydrolysis unless otherwise noted. [c] Accurate to < ± 0.5 %. [d] The excess ^{18}O content before hydrolysis. [e] Two half-lives.

Scheme 10.

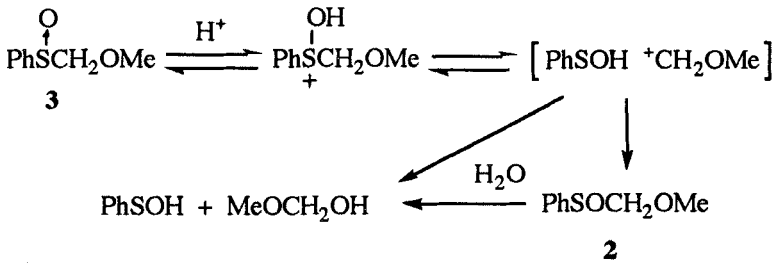


accommodated by a mechanism involving a sulfurane intermediate, which may undergo rearrangement by pseudorotation as illustrated in Scheme 10.

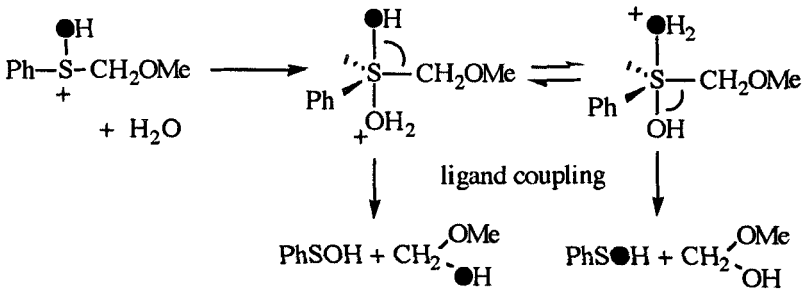
METHOXYMETHYL SULFOXIDE[16,17]

Methoxymethyl phenyl sulfoxide **3** undergoes acid-catalyzed cleavage in aqueous solution. Rates of the cleavage determined by formation of the products are equal to those of racemization of an enantiomeric sulfoxide **3**. Since acid-catalyzed cleavage of the *t*-butyl sulfoxide was formulated with accompanying racemization due to the internal return,[18] we first considered a possibility of the return to the sulfenate **2** (Scheme 11).

Scheme 11.



Scheme 12.



However, this possibility was later excluded.[17] Products from the ^{18}O-labeled substrate show that the thiolsulfinate product contains only about 50 % of the original label. These results are best accommodated by a mechanism involving a sulfurane intermediate and ligand coupling between the apical and equatorial groups of the intermediate (Scheme 12).

CONCLUDING REMARKS

Good evidence was found for the reaction intermediate in acid-catalyzed hydrolysis of alkyl sulfenate (pH-rate profile and nucleophile reactivity) and sulfinamide (pH-rate profile and ^{18}O exchange), but such evidence could not be detected for sulfinate esters. More basic substrates seem to tend to form a hypervalent intermediate in their nucleophilic reactions. Acid-catalyzed reactions of methoxymethyl sulfenate and sulfoxide are also accommodated by a mechanism involving sulfurane intermediates.

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