

AN ABSTRACT OF THE THESIS OF

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Title: MECHANISTIC STUDIES OF THE RACEMIZATION OF
OPTICALLY ACTIVE PHENYL BENZENETHIOLSULFINATE
AND RELATED REACTIONS

Abstract approved: _____

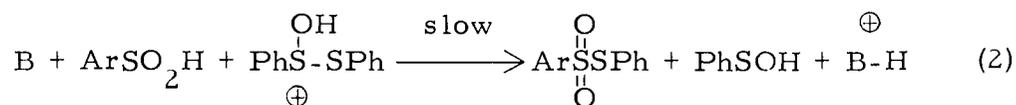
John L. Kice

A. The Thiolsulfinate-Mercaptan Reaction

Phenyl benzenethiolsulfinate reacts rapidly with alkyl mercaptans (equation 1) to yield phenyl alkyl disulfides in moist acetic acid. Kinetic studies show that the reaction is first-order in both

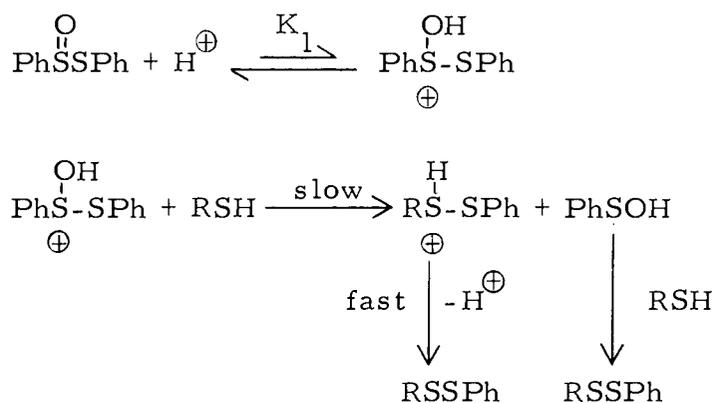


thiolsulfinate and mercaptan and subject to specific- H^+ catalysis. These results can best be accommodated by the mechanism shown in Chart 1. The rate-determining step of this mechanism involves a nucleophilic attack by the mercaptan at the sulfenyl sulfur atom of the sulfinyl-protonated thiolsulfinate. This step differs from the rate-determining step (equation 2) proposed for the thiolsulfinate-sulfonic acid reaction in that proton transfer from the mercaptan to



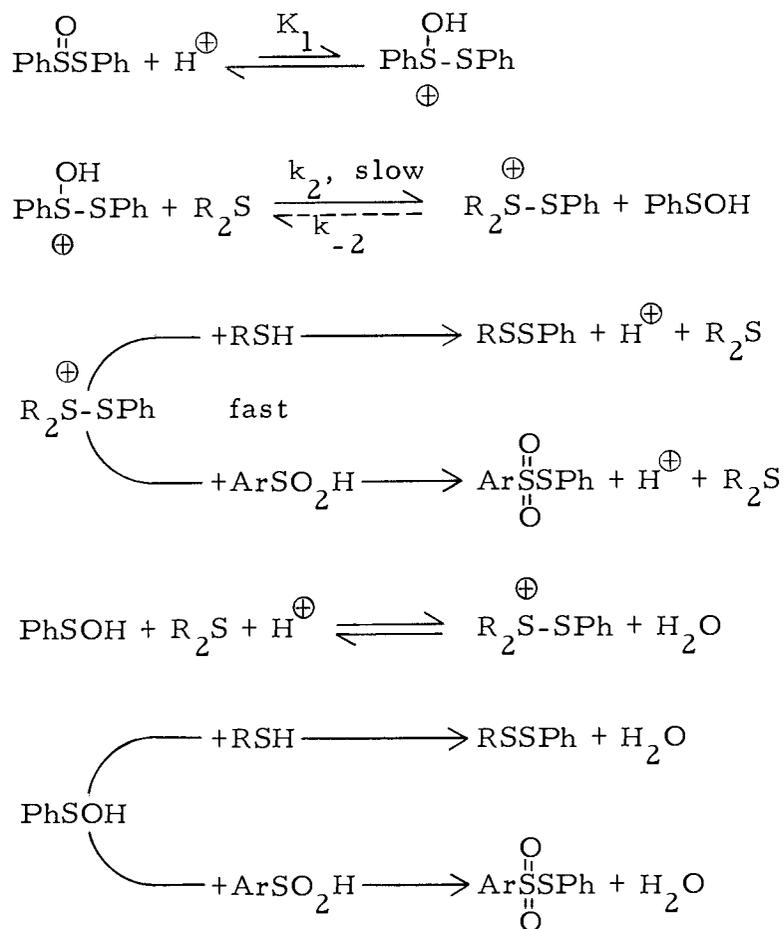
a general base is not concerted with the formation of the new S-S bond. Thus the correctness of the explanation given earlier (31) for the requirement of a general base in the sulfinic acid-thiolsulfinate reaction is substantiated by this observation.

Chart 1



The mercaptan-thiolsulfinate reaction can be accelerated by the addition of organic sulfides. This sulfide-catalyzed reaction exhibits the same formal kinetics, the same dependence on sulfide structure and the same rate as is found in the sulfide-catalyzed sulfinic acid-thiolsulfinate reaction (31). These results confirm Chart 2 as the mechanism for the sulfide-catalyzed reactions of thiolsulfinate with either mercaptan or sulfinic acid.

Chart 2



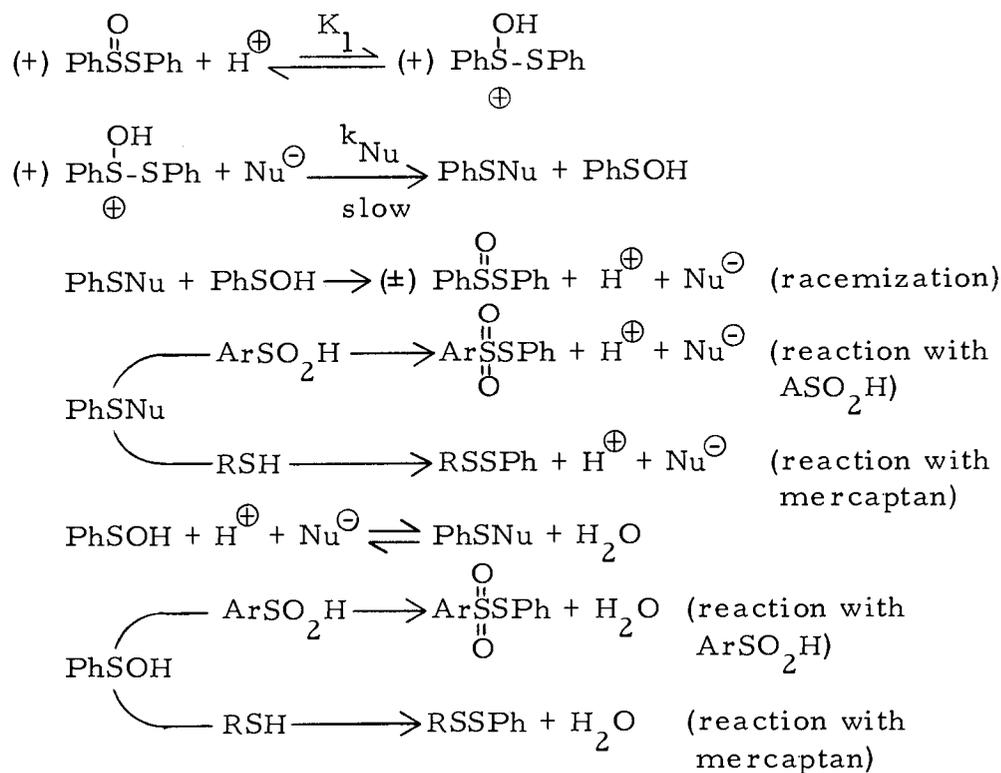
B. Racemization of Optically Active Phenyl Benzenethiolsulfinate

Optically active phenyl benzenethiolsulfinate has been prepared by the asymmetric oxidation of phenyl disulfide using (+) percamphoric acid.

In acidic aqueous dioxane in the absence of added nucleophiles (+) phenyl benzenethiolsulfinate racemizes only very slowly, but in the presence of alkyl sulfides, halide ions, or thiocyanate ion racemization is quite rapid. The racemization reaction is first-order

in both nucleophile and hydrogen ion. Its solvent kinetic isotope effect suggests it is specific hydrogen ion catalyzed. Although only racemization of (+) phenyl benzenethiolsulfinate occurs in their absence, the addition of small amounts of sulfinic acid or mercaptan leads to disappearance of the thiolsulfinate via nucleophile and acid catalyzed reactions with these reagents. The formal kinetics and rate constants for these latter reactions are exactly the same under a given set of conditions as those for racemization, indicating that all three reactions have the same rate-determining step. Chart 3 illustrates the mechanism proposed for these results.

Chart 3



The rate-determining step (k_{Nu}) of this mechanism involves a nucleophilic attack at the sulfenyl sulfur atom of the sulfinyl-protonated thioisulfinate. The values of k_{Nu} provide a quantitative measure of the relative reactivity of nucleophiles in a substitution at sulfenyl sulfur: Nucleophile, $k_{\text{Nu}}/k_{\text{Cl}}$: I^- , 1.4×10^4 ; SCN^- , 5.4×10^3 ; $n\text{-Bu}_2\text{S}$, 8.2×10^2 ; Br^- , 35; Cl^- , (1.0). Comparison with data for the reactivity of the same nucleophiles in substitutions at sulfinyl sulfur, sulfonyl sulfur, and peroxide oxygen reveals that in terms of Hard and Soft Acid and Base Theory (HSAB), sulfenyl sulfur is much softer electrophilic center than either sulfinyl or sulfonyl sulfur, and actually appears to be about as soft as peroxide oxygen.

In acetic acid-1% water the rate of loss of optical activity of (+) phenyl benzenethioisulfinate is also catalyzed by organic sulfides. The rate of loss of optical activity is sensitive to sulfide structure in a way that is comparable to what is found in the sulfide-catalyzed thioisulfinate-sulfinic acid reaction and the formal kinetics are the same as those found in the latter reaction. These results confirm the reversibility of the k_2 step in the mechanism proposed for the sulfide-catalyzed disproportionation of thioisulfates, Chart 4.

Mechanistic Studies of the Racemization of Optically
Active Phenyl Benzenethiolsulfinate
and Related Reactions

by

George Blackmore Large

A THESIS

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degree of

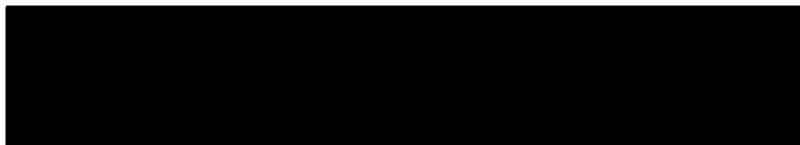
Doctor of Philosophy

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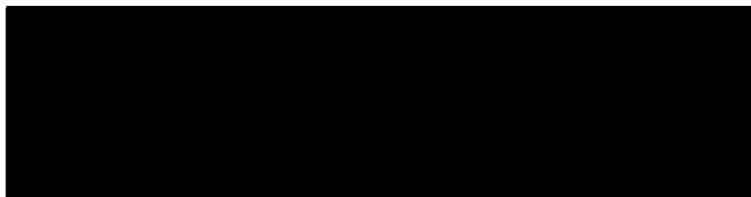
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To Jeri

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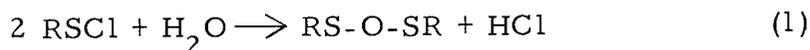
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MECHANISTIC STUDIES OF THE RACEMIZATION OF OPTICALLY
ACTIVE PHENYL BENZENETHIOLSULFINATE
AND RELATED REACTIONS

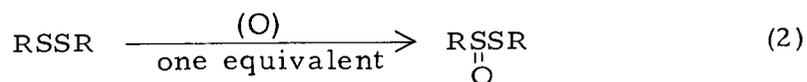
I. INTRODUCTION

Organosulfur compounds having the general structure $R(S_2O)R$ appear in the earlier literature both as anhydrides of sulfenic acids ($RS-O-SR$) and as thiolsulfinates, esters of the hypothetical thiol-sulfenic acid.

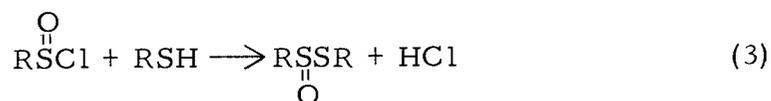
Zincke and coworkers were the first to report the preparation of sulfenic anhydrides, which they claimed to have isolated from the hydrolysis of sulfenyl chlorides, equation 1 (67-71).



Thiolsulfinates were reported to be synthesized by the mono oxidation of disulfides, equation 2 (23, 35, 54), and by the

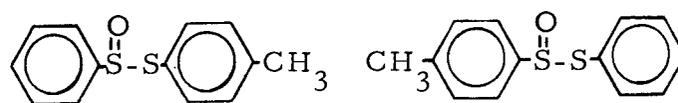


coupling of a sulfinyl chloride and a mercaptan, equation 3 (4, 8).



For many years sulfenic anhydrides and thiolsulfinates were considered two distinct types of compounds. However, a few years ago Vinkler and Klivényi established that they were, in fact, one and

the same (64). They showed this by demonstrating that the same product was obtained from each of the three reactions just described. From several considerations they also were able to show that the correct structure for this product is that of a thiolsulfinate. First, there is its infrared spectrum. Thiolsulfinites exhibit an intense band at 1100 cm^{-1} , of the same sort as Ghersetti and Modena have observed for all organosulfur compounds known to contain the sulfinyl sulfur group (17, 18). Second, as Vinkler and Klivényi pointed out, it is most unlikely that the oxidation of the disulfide at room temperature (equation 2) would result in cleavage of the sulfur-sulfur bond and rearrangement to produce the sulfenic anhydride structure. A third proof of the thiolsulfinate structure was provided by Backer and Kloosterziel (4). They recognized that if the two groups attached to the sulfur atoms are structurally different two isomeric thiolsulfinites, $\text{RS(O)SR}'$ and $\text{RSS(O)R}'$ are possible, but only one sulfenic anhydride, $\text{RS-O-SR}'$. Since they found that reaction of benzenesulfinyl chloride with p-toluenethiol gave a thiolsulfinate (I) isomeric with the one (II) from the reaction of p-toluenesulfinyl chloride with thiophenol, it is clear that the thiolsulfinate structure must be the correct one.



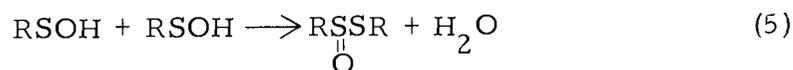
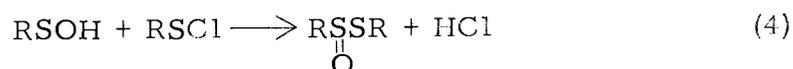
I

II

In this introduction we shall give some indication of the chemical importance of thiolsulfinates and a sufficient discussion of their chemistry to enable one to understand the thesis topic. A more extensive review of the chemistry of thiolsulfinates can be found in the Introduction of the Ph. D. thesis of Clifford G. Venier (62) and the Introduction of the M. S. thesis of Wayne H. Stanley (55).

A number of investigators have found thiolsulfinates to be biologically active (20, 38, 47, 48, 57-61). Cavillito, Small and their coworkers observed that the very great bacteriostatic effect of garlic oil was due to allyl 2-propenylthiolsulfinate (11-13, 54). They also observed this bacteriostatic action with other thiolsulfinates prepared by the oxidation of the corresponding disulfides. They conjectured that this property of thiolsulfinates was due to their reaction with the thiol groups of the essential cell protein.

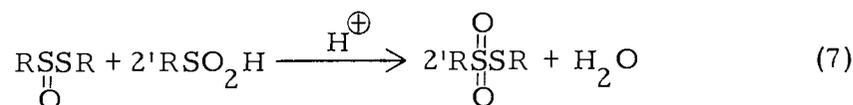
The importance of thiolsulfinates was enhanced when Vinkler and Klivényi found that they were invariably the first isolable product of the hydrolysis of sulfenyl chlorides. Presumably the formation of thiolsulfinate in this reaction proceeds through initial hydrolysis of a sulfenyl halide molecule to a sulfenic acid, which then reacts either with sulfenyl halide or another molecule of sulfenic acid (equations 4 and 5) to form thiolsulfinate (63).



Thiolsulfinates are quite reactive chemically. Under acidic conditions they disproportionate fairly readily into disulfides and thioisulfonates, equation 6 (7, 62).



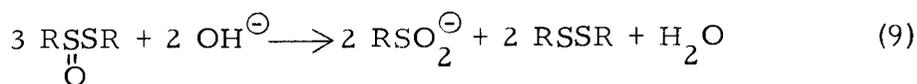
This reaction, as well as their reaction with sulfinic acids (equation 7), has been studied by Kice and coworkers (31).



Another acid catalyzed reaction of thiolsulfinates is their reaction with mercaptans, equation 8 (53). It was mentioned earlier that the reaction of thiolsulfinates with mercaptans has been suggested to be responsible for the bacteriostatic effects of thiolsulfinates.



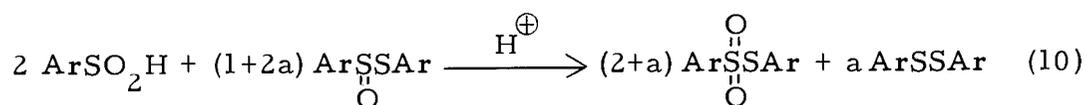
Under basic conditions thiolsulfinates hydrolyze very readily, giving disulfides and sulfinic acids, equation 9 (55, 67-71).



Reactions of thiolsulfinates which are particularly pertinent to this thesis are the thiolsulfinate-sulfinic acid reaction, the thiolsulfinate-mercaptan reaction, and the sulfide-catalyzed disproportionation reaction. Let us first discuss what is known about the thiolsulfinate-sulfinic acid reaction in some detail.

Thiolsulfinate-Sulfinic Acid Reaction

Aryl sulfinic acids react quite rapidly with aromatic thiolsulfinates in moist acetic acid containing some sulfuric acid. As was mentioned earlier a thiolsulfonate is the principal product. However, a precise product study reveals that a little disulfide is also formed, equation 10 (31). The amount of disulfide formed depends on the



initial concentrations of sulfinic acid and thiolsulfinate and other reaction conditions, but a in equation 10 is usually about 0.1 to 0.2. The reaction can be studied kinetically by following the disappearance of thiolsulfinate spectrophotometrically. Such a study reveals that the reaction is: (1) first-order in both thiolsulfinate and sulfinic acid; (2) accelerated by electron withdrawing substituents in the aromatic

ring of the sulfinic acid; and (3) catalyzed by added sulfuric acid.

Measurement of the solvent kinetic isotope effect ($k_{\text{HOAc}}/k_{\text{DOAc}} = 1.3$) suggests that the acid catalysis is of the general acid rather than specific lyonium ion variety.

Alkyl sulfides in very low concentrations (10^{-4} to 10^{-5} M) dramatically accelerate the thiolsulfinate-sulfinic acid reaction. Kinetic study of this sulfide-catalyzed reaction discloses that it is first-order in both thiolsulfinate and alkyl sulfide, but that even though the sulfinic acid is involved in the stoichiometry of the reaction, its rate is independent of sulfinic acid concentration. This result shows that the sulfinic acid is not involved in the rate-determining step of the sulfide-catalyzed process.

The sulfide-catalyzed reaction is also strongly acid catalyzed. However, measurement of the solvent kinetic isotope effect ($k_{\text{HOAc}}/k_{\text{DOAc}} = 0.75$) indicates that in this instance the acid catalysis is now of the specific lyonium ion variety.

The sulfide-catalyzed reaction shows a marked dependence of the rate on sulfide structure. A plot of $\log k$ for a series of alkyl sulfides (R_2S) versus $\Sigma\sigma^*$ for R gives a straight line with slope, ρ^* , equal to -2.0. This means that electron-withdrawing substituents in the R groups markedly reduce the reactivity of a sulfide in the reaction and strongly suggests that in the rate-determining step the sulfide is converted to a sulfonium species $\text{R}_2\text{S}^{\oplus}$.

A mechanism for the sulfide-catalyzed reaction which is consistent with all these results is shown in Chart I.

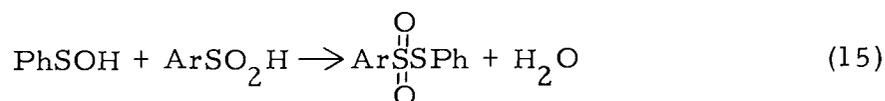
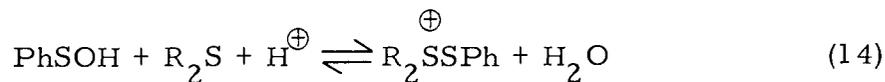
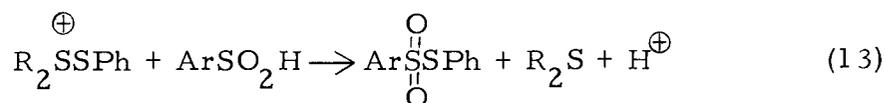
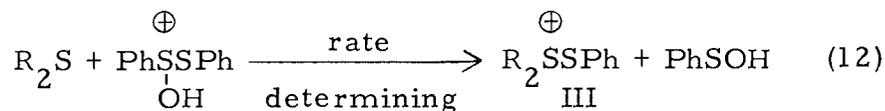
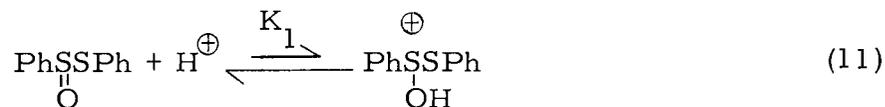


Chart I

In the rate-determining step the sulfinyl-protonated thiosulfinate undergoes nucleophilic attack by the sulfide; this produces the thiosulfonium species (III) and sulfenic acid. Sulfenic acid then reacts very rapidly with III to form thiosulfonate. The sulfenic acid has two possible routes by which it can be converted to thiosulfonate. First, it can be converted by equation 14 to III, which then reacts rapidly with sulfenic acid, or it can react directly with sulfenic acid, equation 15.

The mechanism of the non-sulfide catalyzed, or "normal", thiosulfinate-sulfenic acid reaction will now be considered. One will

recall that this reaction is first-order in both thiolsulfinate and sulfinic acid and that it shows a different dependence of rate on the acidity of the medium than the sulfide-catalyzed reaction, being general acid catalyzed rather than specific- H^{\oplus} catalyzed. Since one way one can get general acid catalysis is to have an initial equilibrium involving protonation of the substrate which is followed by some rate-determining step involving both the protonated substrate and a general base, the mechanism shown in Chart II has been suggested for the normal reaction. In this mechanism the rate-determining step (equation 16) involves a general base catalyzed attack of sulfinic acid on the protonated thiolsulfinate. The function of the general base is to remove the proton of the sulfinic acid, and the structure of the transition state for the rate-determining step is assumed to be as shown in IV.

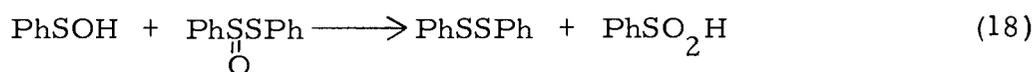
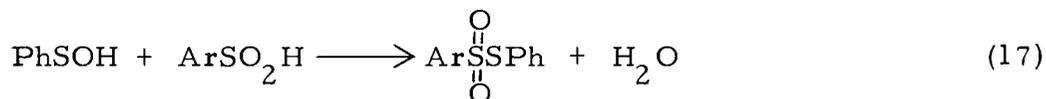
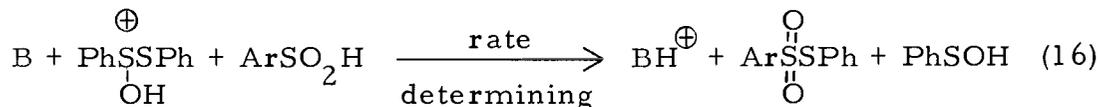
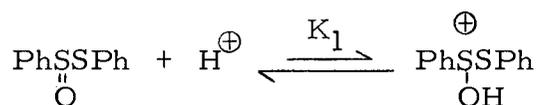
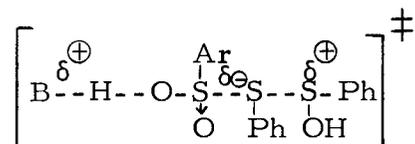
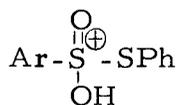


Chart II



IV

One can reasonably ask why the involvement of a general base is necessary in this reaction. The most reasonable explanation would seem to be the following. If the removal of the sulfinic acid proton were not concerted with the formation of the new S-S bond reaction of the sulfinic acid would lead to the initial formation of V, the sulfonyl-protonated thioisulfinate. Sulfone groups are extremely weak basic

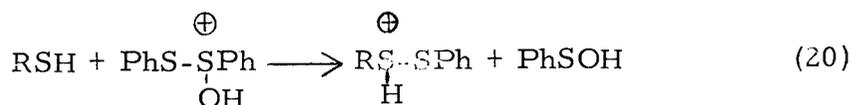


V

sites; the pKa of the conjugate acid of dimethyl sulfone, for example, is -12.3 (21). This means that an intermediate with a protonated sulfonyl group like V will be a very unstable species and would be formed only with difficulty. Formation of V can be avoided in the reaction by having the removal of the sulfinic acid proton by a general base concerted with formation of the new S-S bond.

Of course, because the involvement of a general base in the rate-determining step involves an increase in the molecularity of the reaction, one would expect to observe it only in cases similar to the present one where the intermediate that would be formed in the absence of the proton transfer is particularly unstable. In the case of acid-catalyzed reactions of thiolsulfinates with species NuH where the intermediate $\text{HNu}^{\oplus}\text{-SPh}$ is not so energetically unfavorable as V one might therefore expect to find that such a proton transfer is not required in the rate-determining step. Such reactions would not require the presence of the general base in the rate-determining step and would therefore exhibit specific hydrogen ion rather than general acid catalysis.

Study of the thiolsulfinate-mercaptan reaction (equation 8) would seem to represent a system where one could test the validity of these ideas. In this reaction the intermediate which would result from the direct attack of RSH on the protonated thiolsulfinate (equation 20) would



VI

be VI, a protonated disulfide. Since sulfides are much more basic than sulfones ($\text{Me}-\overset{\oplus}{\underset{\text{H}}{\text{S}}}-\text{Me}$ has a pK_a of -6) (3, p. 388), VI should be considerably more favorable energetically than V. Therefore, it seems reasonable that, if the previous explanation of the origin of general acid catalysis for the thiolsulfinate-sulfinic acid reaction is the correct one, the thiolsulfinate-mercaptan reaction in acetic acid solvent should exhibit specific hydrogen ion rather than general acid catalysis. One of the goals of the present research was to study the thiolsulfinate-mercaptan reaction kinetically and determine whether or not this was so.

Study of the thiolsulfinate-mercaptan reaction can also be used to test the validity of a very important aspect of the mechanism of the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction. The mechanism for the sulfide-catalyzed reaction shown in Chart I predicts that alkyl sulfides should also catalyze the reaction of

thiolsulfinates with other reagents NuH via mechanisms analogous to those in Chart I and having in each case the same rate-determining step (equation 12). Because the rate-determining step for all these sulfide-catalyzed reactions should be the same, they should all have the same rate under a given set of conditions. Therefore another aim of the present study of the thiolsulfinate-mercaptan reaction was to see if the reaction was subject to catalysis in acetic acid by added alkyl sulfides and, if it was, to determine if the formal kinetics and rates of these sulfide-catalyzed reactions were the same as those of the corresponding sulfide-catalyzed thiolsulfinate-sulfinic acid reactions.

Sulfide-Catalyzed Disproportionation of Aryl Thiolsulfinates

The acid-catalyzed disproportionation of aromatic thiolsulfinates (equation 6) in moist acetic acid has also been found to be catalyzed by small amounts (10^{-4} to 10^{-5} M) of alkyl sulfides (62). The sulfide-catalyzed disproportionation exhibits the same formal rate law as the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction. Thus, both reactions are first-order in catalyzing sulfide, first-order in thiolsulfinate, and strongly acid catalyzed, their rates changing with added strong acid concentration in the same way as the Hammett acidity function, H_0 . The solvent kinetic isotope effect for the sulfide-catalyzed disproportionation ($k_{\text{HOAc}}/k_{\text{DOAc}} = 0.78$) indicates that this reaction is specific hydrogen ion catalyzed, as is the

sulfide-catalyzed sulfinic acid-thiolsulfinate reaction. Although thus very similar in many aspects, the reactions do show one important difference in behavior. Each exhibits a different dependence of rate on sulfide structure. Thus, while ethyl sulfide is 2.7×10^4 more reactive than phenyl sulfide as a catalyst for the thiolsulfinate-sulfinic acid reaction, it is only 47 times more reactive than the phenyl compound as a catalyst for the disproportionation reaction.

One way to explain how the two reactions can have identical formal kinetics and yet exhibit a quite different dependence of rate on sulfide structure is if the mechanism of the sulfide catalyzed disproportionation is as shown in Chart III. In this mechanism, III and sulfenic acid, once they have been formed by step k_2 , can either (1) revert back to protonated thiolsulfinate and sulfide (step k_{-2}) or (2) react together in a different fashion (step k_3) to give new intermediates which then react further with additional thiolsulfinate to give the final products. In this type of mechanism, if $k_3 > k_{-2}$, step k_2 will be rate-determining and the overall reaction rate will be closely similar to that of the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction, which also has the same process as its rate-determining step (see Chart I). This situation seems to come fairly close to being obtained with the less reactive sulfide catalysts such as phenyl sulfide or thiodiglycolic acid. On the other hand, when $k_3 \ll k_{-2}$ in this type of mechanism, then most of III and sulfenic acid formed by step k_2 will revert back

to protonated thiolsulfinate and R_2S via step k_{-2} before they have a chance to react via step k_3 . In this situation k_3 will be rate-determining, and, more important, the overall rate will be considerably less than the rate of the corresponding thiolsulfinate-sulfinic acid reaction where k_2 is rate-determining. This seems to be the situation that obtains with the more reactive sulfide catalysts, such as n-butyl or ethyl sulfide. Such an explanation, of course, requires that k_3/k_{-2} vary in a pronounced fashion with sulfide structure in just the opposite of the way that k_2 does. Since there are fairly good reasons¹ for thinking that k_{-2} probably shows rather little dependence of rate on sulfide structure, what this really means is that k_3 has to be strongly dependent on sulfide structure and that electron-withdrawing groups in R of R_2S must accelerate k_3 quite markedly. Any suggestion for the mechanism of the k_3 step must be in accord with this.

¹Mr. Nicolai A. Favstritsky, unpublished results.

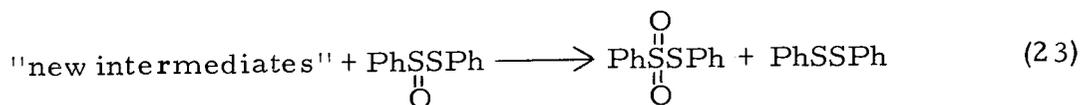
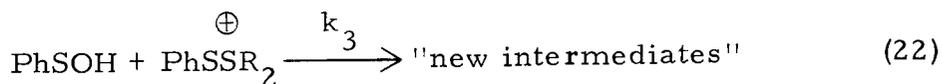
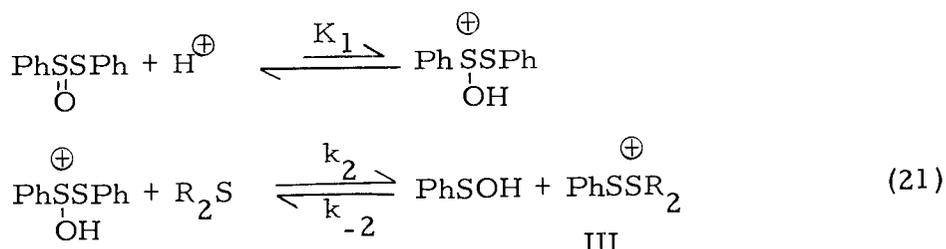
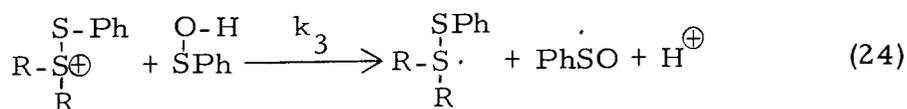


Chart III

Two possibilities have been suggested for the k_3 and subsequent product forming steps (Chart III equations 22 and 23). The first is a radical process initiated by an electron transfer from sulfenic acid to III (equation 24 in Chart IV). The second is an ionic



III

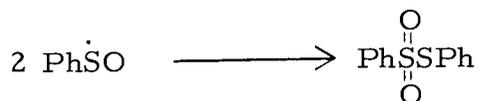
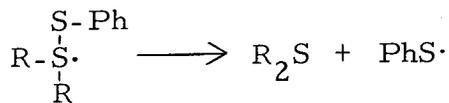


Chart IV

process and is shown in Chart V. Both of these are consistent with

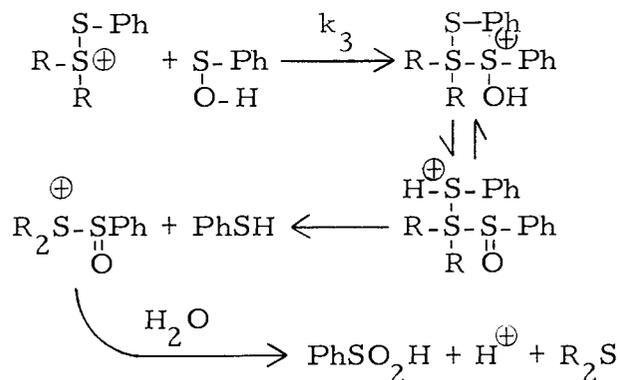


Chart V

the requirement that k_3 should be accelerated by the presence of electron-withdrawing R groups in R_2S . Presumably experiments designed to see if radical intermediates are actually produced in the sulfide-catalyzed disproportionation would allow one to decide whether the mechanism in Chart IV is correct or not. This was one of the other points which we wished to investigate in the present research.

If optically active phenyl benzenethiolsulfinate were available one could test the correctness of certain other aspects of the mechanism suggested for the sulfide-catalyzed disproportionation reaction in Chart III. We have postulated for sulfides such as benzyl or n-butyl that $k_3 \ll k_{-2}$ so that the occurrence of step k_2 forming PhSOH and III is followed in such cases almost all the time by the return of these species to R_2S and protonated thiolsulfinate (step k_{-2}) rather than by their reaction via step k_3 . This leads to the rate of

such sulfide-catalyzed disproportionations being much slower than the rate of the corresponding sulfide-catalyzed thioisulfinate sulfinic acid reaction, where k_2 is rate determining. Since return of III and PhSOH via the k_{-2} step must yield racemic thioisulfinate, one would expect that optically active phenyl benzenethioisulfinate would undergo a ready sulfide and acid catalyzed racemization under such conditions much more rapidly than it undergoes sulfide-catalyzed disproportionation. Furthermore since k_2 will be the rate-determining for this racemization its rate should be the same as the rate of the sulfide-catalyzed thioisulfinate-sulfinic acid reaction under the same conditions. Such a result would confirm the reversibility of the k_2 step in the mechanism suggested for the sulfide-catalyzed disproportionation reaction. However, optically active aromatic thioisulfinate, in which the sole source of asymmetry is the sulfinyl sulfur, were not known prior to this research. Consequently, the preparation of an optically active aromatic thioisulfinate and the subsequent use of this compound in experiments designed to test the reversibility of the k_2 step became two more goals of the present research.

Optically active aromatic thioisulfinate, as we shall see shortly, can be easily prepared by the asymmetric oxidation of the corresponding disulfide with (+)percamphoric acid. Aside from the use of this compound to determine the correctness of certain aspects of the proposed sulfide-catalyzed disproportionation mechanism, it soon became

apparent that the acid and nucleophile catalyzed racemization of (+) phenyl benzenethiolsulfinate under related conditions could be used to provide quantitative information about the reactivity of various nucleophiles in displacements at the sulfenyl sulfur atom of thiol-sulfinate. Such quantitative data for the substitution at sulfenyl sulfur are of great general interest, since previously only qualitative information has been available for reactions involving sulfenyl compounds (16). In reference to the Theory of Hard and Soft Acids and Bases (43-45), which is receiving much current interest, such information can be used to precisely classify sulfenyl sulfur on a scale of hard and soft electrophilic centers.

To summarize, the aims of the present research are: (1) to investigate the mechanisms of the normal and sulfide-catalyzed thiol-sulfinate-mercaptan reactions in order to test the correctness of certain aspects of the mechanisms proposed for the corresponding thiol-sulfinate-sulfinic acid reactions; (2) to prepare an optically active aromatic thiolsulfinate and to utilize this compound both to test the correctness of certain aspects of the proposed sulfide-catalyzed disproportionation mechanism and also to provide quantitative data on nucleophilic reactivity in substitutions at sulfenyl sulfur; and (3) to carry out experiments designed to determine if radical intermediates are produced in the sulfide-catalyzed disproportionation reaction.

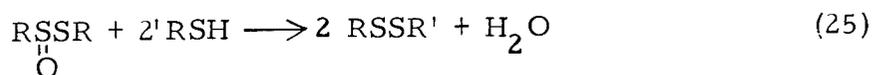
THIOLSULFINATE-MERCAPTAN REACTION

Results

The reaction between alkyl mercaptans and aromatic thiol-sulfinates, while being recognized as a general method for the preparation of unsymmetrical disulfides (53), had not been studied mechanistically prior to this investigation.

As noted in the Introduction, mechanistic and kinetic details of the thiolsulfinate-mercaptan reaction in acetic acid were of particular interest because, hopefully, the results could be used to test the correctness of the mechanism proposed for the "normal" thiolsulfinate-sulfinic acid reaction. Moreover, if the reaction could be catalyzed by small amounts of alkyl sulfides in this medium the generality of the sulfide catalyzed process as predicted by the mechanism proposed for the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction could be validated.

Venier (62) found that mercaptans do react readily with thiol-sulfinates in moist acetic acid containing some sulfuric acid and that the stoichiometry of the reaction under these conditions is as shown in equation 25.



Kinetics of the Thiolsulfinate-Mercaptan Reaction

The kinetic studies were carried in acetic acid 1-2% water as solvent. Varying amounts of sulfuric acid were added as a strong acid catalyst. The kinetic runs were performed in a special reaction cell designed for in-situ operation (see Experimental, page 119). The reaction was conveniently followed by the change in the ultraviolet absorption at a single wavelength. It was also convenient to operate under conditions where the mercaptan was always present in considerable stoichiometric excess over the thiolsulfinate. The reaction between n-butyl mercaptan and phenyl benzenethiolsulfinate was the specific reaction chosen for the kinetic study. As Figure 1 shows the disappearance of the thiolsulfinate followed good first-order kinetics under such conditions.

The kinetic order in mercaptan can be assessed by determining the influence of mercaptan concentration on k_1 , the experimental first-order rate constant for the disappearance of thiolsulfinate. Table 1 contains the results of runs designed to establish this kinetic order. Figure 2 graphically illustrates these results by a plot of the observed rate constants versus the average mercaptan concentration. The linearity of this plot and the constancy of $k_{\text{RSH}} (k_1 / (\text{RSH})_{\text{av.}})$ in Table 1 clearly indicate that the reaction is first-order in mercaptan. The second-order rate constant, k_{RSH} , for a run is calculated by

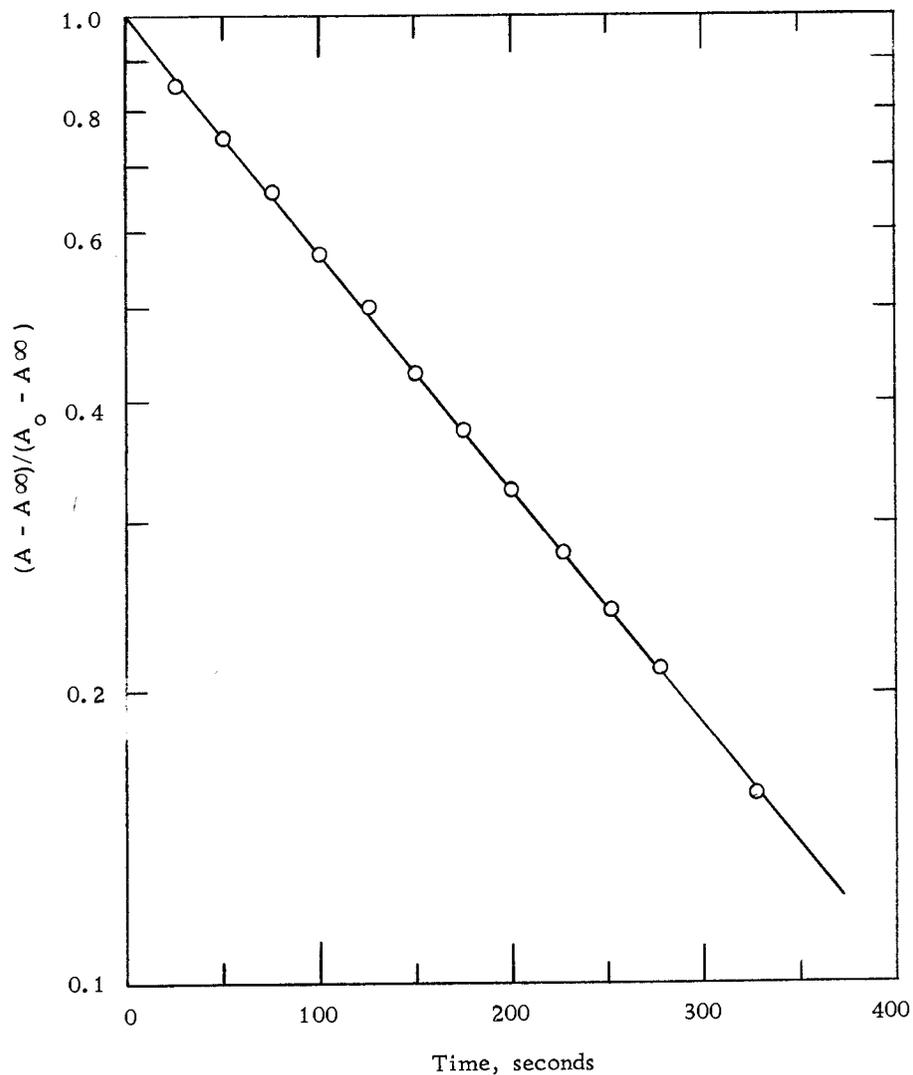


Figure 1. Rate of Disappearance of Phenyl Benzenethiolsulfinate in Acetic Acid-0.1 M Sulfuric Acid-0.56 M Water at 39.6°. Initial Concentrations of PhS(O)SPh = 0.31×10^{-3} and n-ButylSH = 3.1×10^{-3} M.

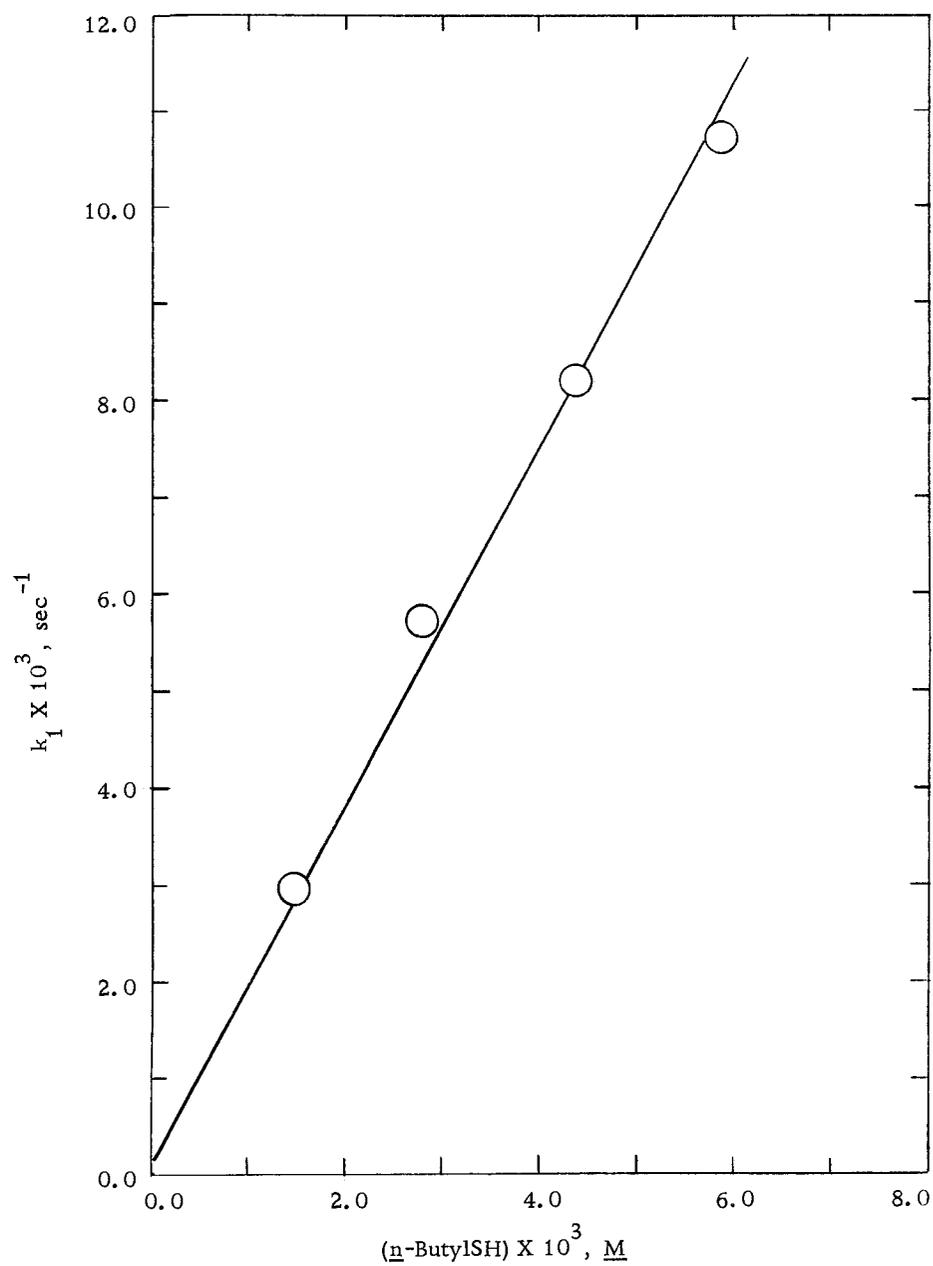


Figure 2. Dependence of k_1 on Average Mercaptan Concentration.

dividing the average mercaptan concentration into the experimental first-order rate constant k_1 . The average is used because the kinetic runs were generally carried with only a ten to one ratio of initial concentrations of mercaptan to thiolsulfinate. This is not a sufficient mercaptan excess to assume a constant concentration throughout the run. The average concentration is taken to be the initial mercaptan concentration minus half the stoichiometric quantity of mercaptan consumed in the course of the reaction. This is conveniently calculated by $(\text{RSH})_{\text{av.}} = (\text{RSH})_{\text{initial}} - \frac{1}{2}(\text{PhSSPh})_{\text{initial}}$.

Table 1. Dependence of Rate on Mercaptan Concentration.^a

$(\text{PhSSPh})_{\text{O}} \times 10^3$, <u>M</u>	$(\text{n-ButylSH})_{\text{O}} \times 10^3$, <u>M</u>	$k_1 \times 10^3$, sec^{-1}	$k_{\text{RSH}}^{\text{b}}$, $\text{M}^{-1} \text{sec}^{-1}$
0.16	1.6	2.95	2.0
0.31	3.1	5.7	2.0
	4.7	8.2	1.9
	6.2	10.7	1.8

^a All runs at 39.6° in 0.10 M sulfuric acid-0.56 M water-acetic acid.

^b k_{RSH} equals $(k_1 / (\text{RSH})_{\text{av.}})$.

That the reaction is also first-order in thiolsulfinate is shown both by the clear first-order kinetics obtained for the disappearance of thiolsulfinate (see for example Figure 1) and the results shown in Table 2. The constancy of k_1 , the observed first-order rate constant,

for different initial thiolsulfinate concentrations conclusively demonstrates that the thiolsulfinate-mercaptan reaction is first-order in thiolsulfinate.

Table 2. Independence of k_1 on Thiolsulfinate Concentration.^a

$(\text{PhSSPh})_o \times 10^3,$ <u>M</u>	$(\text{n-ButylSH})_o \times 10^3,$ <u>M</u>	$k_1 \times 10^3,$ sec^{-1}
0.28	2.8	4.3
0.21		4.5
0.14		4.6

^a All runs at 39.6° in acetic acid-0.09 M sulfuric acid-0.56 M water.

The thiolsulfinate-mercaptan reaction was found to be strongly acid catalyzed. The exact dependence of its reaction rate on the acidity of the medium was determined by two series of experiments. One series was run in acetic acid-0.56 M water with varying amounts of added sulfuric acid. In the other series, the stoichiometric concentration of water in the solvent was varied at a constant sulfuric acid concentration of 0.10 M. The results of these runs are shown in Table 3. A plot of $\log k_{\text{RSH}}$ against the Hammett acidity function, $-H_o$, for these solutions (49) yields a straight line of slope 1.1, Figure 3. This result is comparable to the acid dependence exhibited by the sulfide-catalyzed reaction of thiolsulfinate with sulfinic acid.

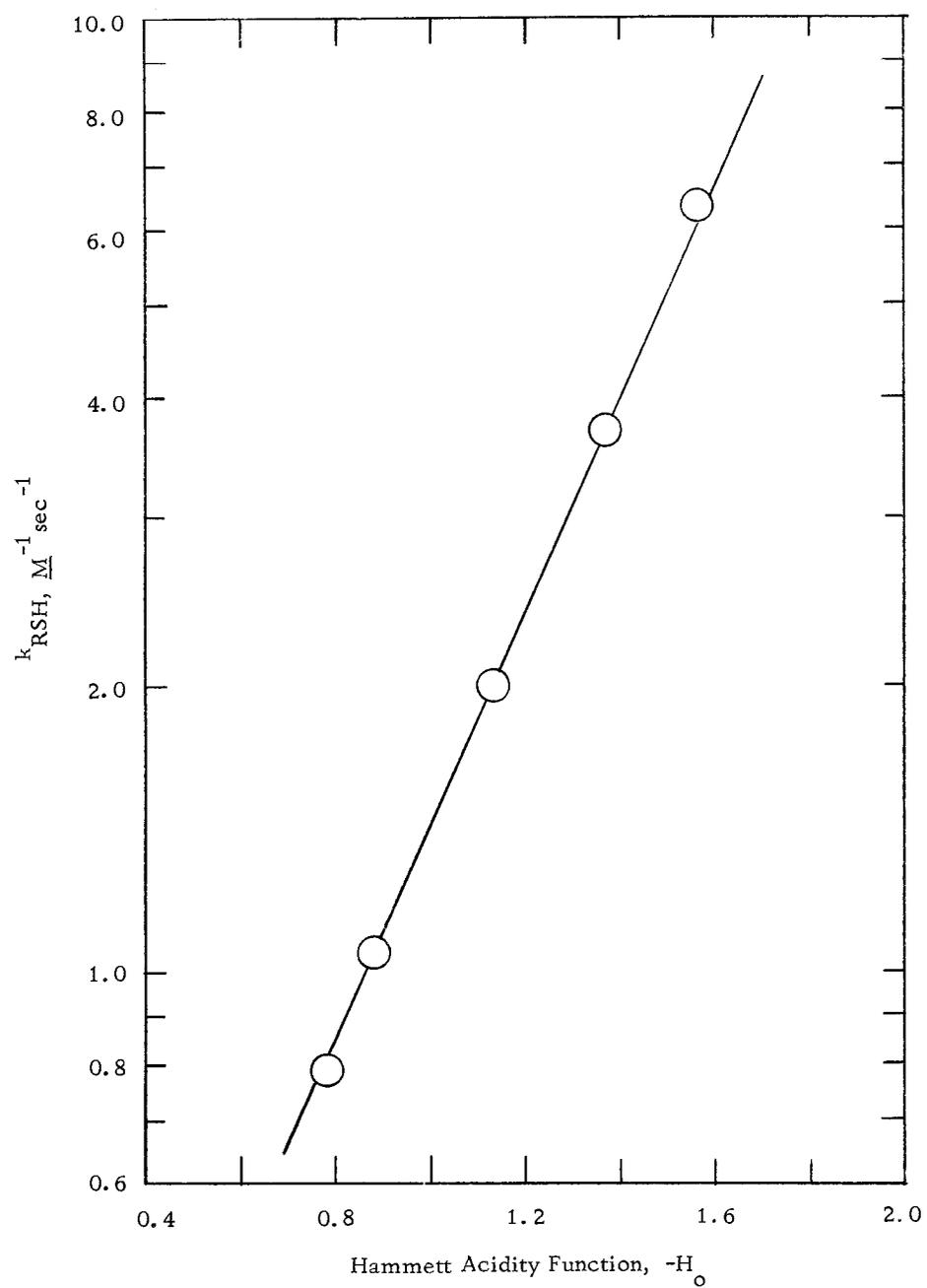


Figure 3. Acidity Dependence of the Thiolsulfinate-Mercaptan Reaction.

However, this type of acid catalysis is quite different from that exhibited in the "normal" thiosulfinate-sulfinic acid reaction where the reaction rate changes linearly with the stoichiometric concentration of strong acid.

Table 3. Effects of Sulfuric Acid and Water Concentration on Reaction Rate. ^a

(H_2SO_4) , <u>M</u>	(H_2O) , <u>M</u>	k_{RSH} , $\frac{\text{M}^{-1}}{\text{sec}^{-1}}$
0.05	0.56	0.79
0.10	1.12	1.04
0.10	0.56	2.0
0.15	0.56	3.7
0.20	0.56	6.4

^a All runs at 39.6° in acetic acid with initial $(\text{PhS(O)SPH}) = 0.00031$ M and initial (n-butylSH) = 0.0031 M.

Kinetics of the Sulfide-Catalyzed Thiosulfinate-Mercaptan Reaction

The addition of small amounts of alkyl sulfides to the thiosulfinate-mercaptan reaction mixture resulted in a large acceleration of the reaction rate. The catalytic effect of 0.20×10^{-4} M n-butyl sulfide on this reaction is demonstrated in Figure 4.

The sulfide-catalyzed reaction was studied with three different sulfides. The results are summarized in Table 4. Again k_1 is the

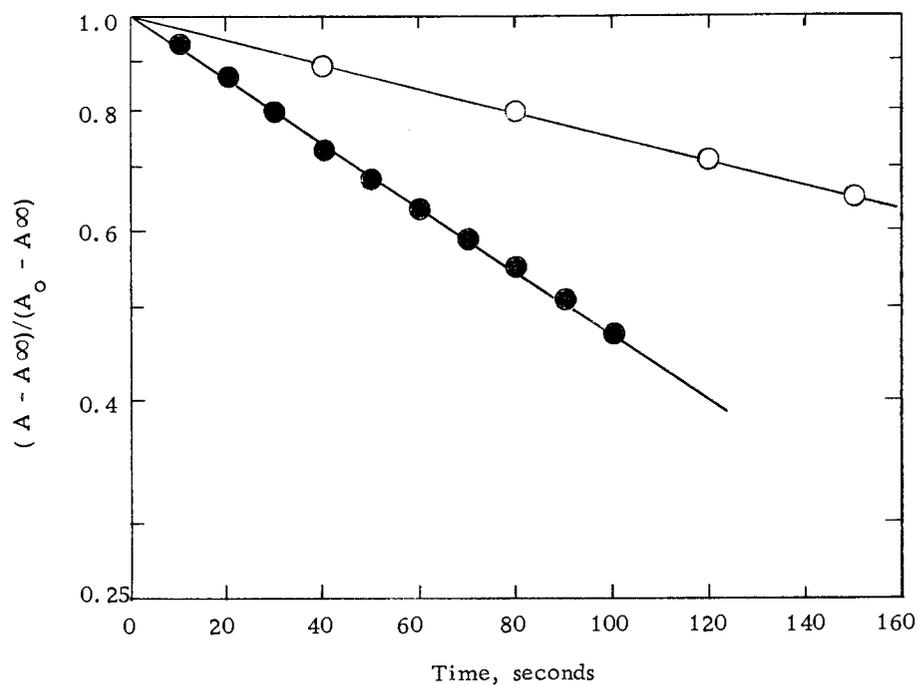


Figure 4. Rate of Disappearance of Phenyl Benzenethiolsulfinate in Acetic Acid-0.10 M Sulfuric Acid-0.56 M Water at 39.6°. Initial Concentration of PhS(O)SPh = 0.00016 M and n-ButylSH = 0.0016 M.

○ - Uncatalyzed.

● - 0.2×10^{-4} M n-Butyl₂S Catalyzed.

Table 4. Kinetics of the Sulfide-Catalyzed Reaction of Phenyl Benzenethiolsulfinate with n-Butyl Mercaptan. ^a

$(\text{PhS(O)SPh})_0 \times 10^3$, <u>M</u>	$(\text{n-ButylSH})_0 \times 10^3$, <u>M</u>	$(\text{R}_2\text{S}) \times 10^4$, <u>M</u>	(H_2SO_4) , <u>M</u>	$k_1 \times 10^3$, sec ⁻¹	$\left[\frac{k_1 - k_1^0}{(\text{R}_2\text{S})} \right]^b$
<u>n</u> -Butyl Sulfide					
0.31	3.1	0.75	0.1	21.4	2.1×10^2
		0.38	0.1	13.3	2.0×10^2
0.16	1.6	0.20	0.1	7.4	2.2×10^2
Benzyl Sulfide					
0.31	3.1	0.60	0.1	7.1	23
		1.20	0.1	8.6	24
		3.00	0.1	14.2	28
	4.7	3.00	0.1	16.7	28
	6.2	3.00	0.1	17.5	23
	3.1	3.00	0.05	5.1	9.7
Benzyl Phenyl Sulfide					
0.16	1.6	18.8	0.1	3.9	0.52
		37.5	0.1	4.8	0.49

^a All runs at 39.6° in acetic acid-0.56 M water.

^b k_1^0 equals rate of disappearance of PhS(O)SPh under identical conditions but in the absence of added sulfide as given in Table 1.

observed experimental first-order rate constant for the disappearance of thiolsulfinate, and, therefore, is the sum of the "normal" and sulfide-catalyzed thiolsulfinate-mercaptan reactions. That is k_1 can be expressed as

$$k_1 = k_{\text{RSH}}(\text{RSH}) + k_{\text{cat.}}$$

The rate obtained in the absence of sulfide, k_1° , is given by

$$k_1^{\circ} = k_{\text{RSH}}(\text{RSH})$$

so that

$$k_{\text{cat.}} = k_1 - k_1^{\circ}$$

where $k_{\text{cat.}}$ is the observed first-order rate constant for the sulfide-catalyzed reaction.

The kinetic order in sulfide of this sulfide-catalyzed reaction can be determined by runs in which only the sulfide concentration is varied. For each of the sulfides listed in Table 4 one finds $k_{\text{cat.}} / (\text{R}_2\text{S})$ to be independent of sulfide concentration. This indicates that the sulfide-catalyzed reaction is first-order in sulfide.

The influence of mercaptan concentration on the rate of the sulfide-catalyzed reaction was determined in a series of runs using benzyl sulfide as a catalyst. The results, shown in Table 4, show that there is no significant variation in $k_{\text{cat.}} / (\text{R}_2\text{S})$ with mercaptan concentration. Such a result demonstrates that the rate of the

sulfide-catalyzed thioisulfinate-mercaptan reaction is independent of mercaptan concentration and means that the mercaptan plays no role in the sulfide-catalyzed reaction until after the rate-determining step.

The catalyzing constant, $k_{\text{cat.}}$, can now be defined more explicitly since the sulfide-catalyzed reaction has been established to be first-order in both thioisulfinate and sulfide and independent in mercaptan concentration, i. e.

$$k_{\text{cat.}} = k_S(R_2S)$$

where k_S is the actual second-order rate constant for the sulfide-catalyzed thioisulfinate-mercaptan reaction.

The dependence of the rate of the sulfide-catalyzed reaction on the acidity of the medium was determined in runs using benzyl sulfide as the catalyst at two different sulfuric acid concentrations in acetic acid-0.56 M water. The results, shown in Table 4, indicate the same dependence on acid concentration as for the "normal" thioisulfinate-mercaptan reaction.

Discussion

A major aim of the present study of the thioisulfinate-mercaptan reaction was to produce information which would allow one to test the correctness of certain aspects of the mechanisms previously proposed for the "normal" and sulfide-catalyzed reactions of thioisulfinites with

sulfinic acids. The results will now be discussed, beginning with that part of the data which is relevant to the question of the mechanism of the "normal" thiosulfinate-mercaptan reaction.

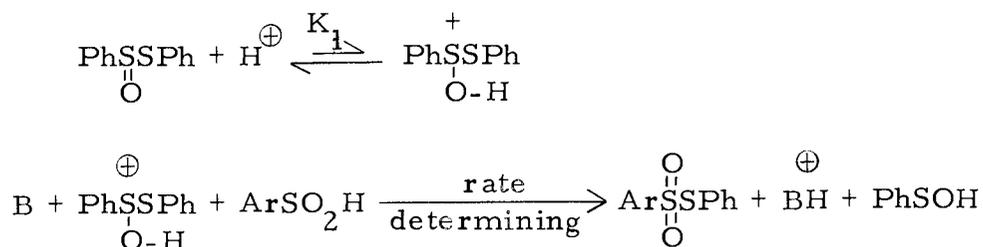
Thiosulfinate-Mercaptan Reaction

The kinetic study of the reaction between phenyl benzene-thiosulfinate and n-butylmercaptan in acetic acid-water solvent revealed that the reaction is first-order in both thiosulfinate and mercaptan and that it is strongly acid catalyzed. The rate of the reaction changes with strong acid concentration in the same way as the Hammett acidity function, $-H_0$.

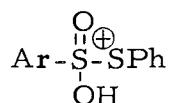
This type of dependence of rate on strong acid concentration is quite different from the one observed for the "normal" thiosulfinate-sulfinic acid reaction. In the latter case the rate of the reaction changes linearly with the stoichiometric concentration of strong acid rather than showing a dependence on H_0 . On the other hand the dependence of rate on acid concentration found for the thiosulfinate-mercaptan reaction is identical to that observed for the sulfide-catalyzed reaction of sulfinic acids with thiosulfates. Since the sulfide catalyzed thiosulfinate-sulfinic acid reaction is known to exhibit specific hydrogen ion catalysis, it seems clear that the thiosulfinate-mercaptan reaction is also specific hydrogen ion catalyzed. The "normal" thiosulfinate-sulfinic acid reaction, on

the other hand, is general acid catalyzed.

The key steps of the mechanism previously suggested for the "normal" thiosulfinate-sulfinic acid reaction are shown below.



One will recall that the function of the general base B in the rate-determining step is to remove the sulfinic acid proton while the new sulfur-sulfur bond is being formed. This, presumably, avoids the formation of a very unstable intermediate, the protonated thiosulfonate (V). The prediction was that in reactions similar to the



V

thiosulfinate-sulfinic acid reaction one would expect to observe general acid catalysis where the intermediate that would be formed in the absence of the proton transfer is particularly unstable. However, in acid catalyzed reactions of thiosulfonates with species NuH where the intermediate $\text{H}-\text{Nu}-\text{SPh}^{\oplus}$ is not so energetically unfavorable as V one might expect to observe that such a proton transfer is not

required in the rate-determining step. Consequently the presence of the general base would no longer be required in the rate-determining step and the reaction would exhibit specific hydrogen ion rather than general acid catalysis. Accordingly, the mechanism shown in Chart VI is suggested for the thiosulfinate-mercaptan reaction.

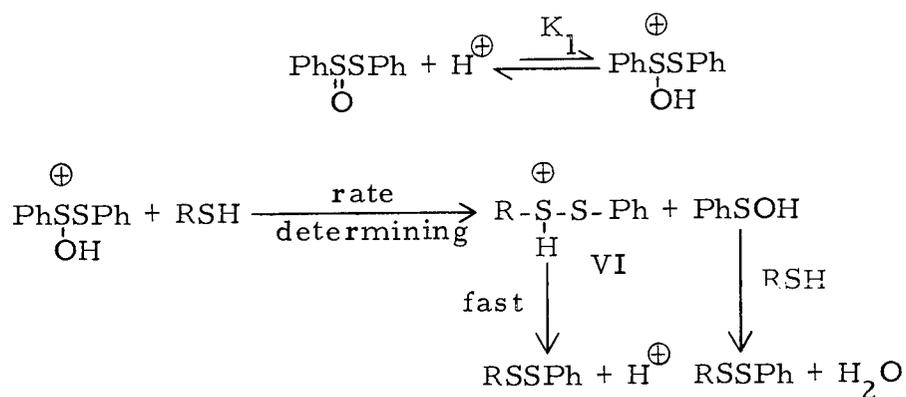


Chart VI

This mechanism involves a nucleophilic attack by mercaptan on the protonated thiosulfinate in the rate-determining step forming the protonated disulfide (VI) and sulfenic acid. Sulfenic acid reacts rapidly with mercaptan to form the disulfide while VI simply loses its proton. The mechanism shown in Chart VI would of course exhibit specific hydrogen ion catalysis.

The study of the thiosulfinate-mercaptan reaction has thus presented strong evidence in favor of the mechanism proposed earlier for the sulfinic acid-thiosulfinate reaction. In particular it suggests that the hypothesis which had been advanced to explain the

need for a general base in the rate-determining step of the sulfinic acid reaction is indeed the correct one.

Sulfide-Catalyzed Thiolsulfinate-Mercaptan Reaction

Just as they did in the case of the thiolsulfinate-sulfinic acid reaction, alkyl sulfides exert a marked catalytic effect on the rate of the thiolsulfinate-mercaptan reaction. Kinetic studies of the sulfide-catalyzed process show that the reaction is first-order in both sulfide and thiolsulfinate and catalyzed by added sulfuric acid. The rate of the reaction changes directly with the proton donating power of the media as measured by the Hammett acidity function, H_0 . However, the rate of the reaction is independent of mercaptan concentration, indicating that mercaptan is not involved until after the rate-determining step of the reaction.

The results given above are completely consistent with the following mechanism (Chart VII) for the sulfide-catalyzed reaction:

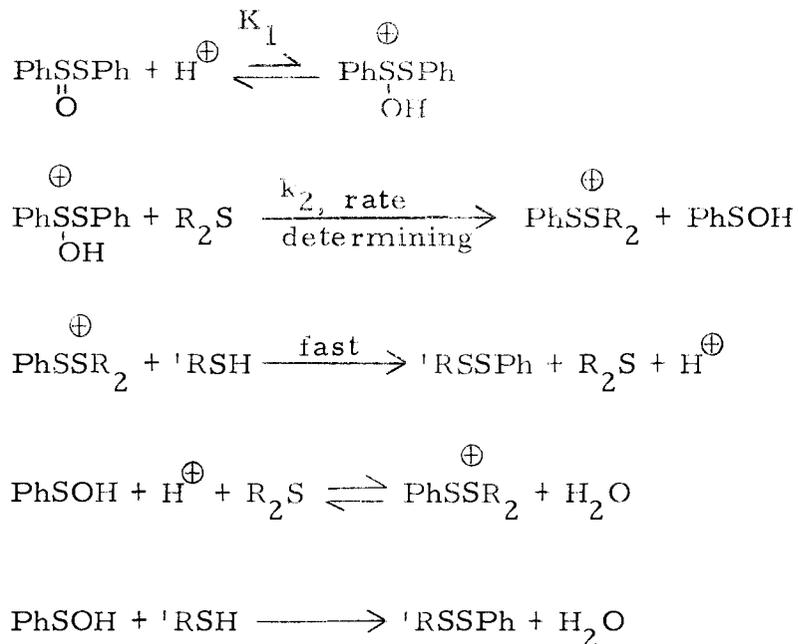


Chart VII

One should note that this mechanism involves exactly the same rate-determining step as that proposed for the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction (Chart I, page 7). Accordingly, the second-order rate constants, k_S , for the two processes should be the same under a given set of conditions. A comparison of k_S for the two sulfide-catalyzed reactions with the three sulfides studied is given in Table 5. For a given sulfide k_S is in each case closely similar for the two reactions, even though the overall spread of reactivities of the three sulfides spans a factor of about 400.

Table 5. Rate Constants for the Sulfide-Catalyzed Reactions of Phenyl Benzenethiolsulfinate. ^a

Sulfide	$k_S, \underline{M}^{-1} \text{sec}^{-1}$	
	Thiolsulfinate-Mercaptan Reaction	Thiolsulfinate-Sulfinic Acid Reaction (31)
n-Bu ₂ S	2.1×10^2	1.7×10^2
(C ₆ H ₅ CH ₂) ₂ S	25	21
C ₆ H ₅ CH ₂ SC ₆ H ₅	0.50	0.42

^a All data are for acetic acid-0.56 M water-0.10 M sulfuric acid as solvent. The data for the sulfinic acid reaction were obtained at 39.4° and those for the mercaptan reaction at 39.6°.

The k_S values for the two reactions given in Table 5 are similar enough to suggest that the two sulfide-catalyzed reactions do indeed have the same rate-determining step. However, the rate constants for the various sulfide-catalyzed thiolsulfinate-mercaptan reactions seem in each case to be a few percent larger than the k_S for the analogous sulfide-catalyzed sulfinic acid-thiolsulfinate reaction. Because the accuracy of measurement of k_S is probably no better than $\pm 10\%$ in any case, this difference ($\sim 20\%$) is not actually much larger than the experimental uncertainty in k_S itself. We suspect, however, that the difference is probably real. Undoubtedly part of the difference is due to the fact that the k_S values for the sulfide-catalyzed thiolsulfinate-mercaptan reaction were obtained at 0.2°

higher temperature than those for the corresponding thiolsulfinate-sulfonic acid reaction. This would account for some, although not all, of the apparent difference. The rest of the difference, if it is real, is probably due to the following: n-butyl mercaptan is almost certainly more reactive than p-toluenesulfonic acid toward the intermediate $R_2\overset{\oplus}{S}SPh$. As support for this assertion consider the reactivity of these reagents in their "normal" reactions with thiolsulfinate under similar conditions [$k_{\text{n-butyl mercaptan}} = 1.9 \text{ M}^{-1} \text{ sec}^{-1}$ and $k_{\text{p-toluenesulfonic acid}} = 0.009 \text{ M}^{-1} \text{ sec}^{-1}$ (31, Table II, p. 3558)]. The mercaptan is more reactive than the sulfonic acid by a factor of 500. Therefore, it is not unreasonable to assume that the mercaptan should also react faster than the sulfonic acid does with the intermediate $R_2\overset{\oplus}{S}SPh$. If this is true, the lower rate observed in the sulfide-catalyzed sulfonic acid-thiolsulfinate reaction could result from the fact that in the sulfide-catalyzed sulfonic acid reaction a small fraction of the $R_2\overset{\oplus}{S}SPh$ formed in step k_2 does not react with sulfonic acid but rather is captured by $PhSOH$ and returns via the reverse of the k_2 step to sulfide and thiolsulfinate. In the sulfide-catalyzed mercaptan reaction, on the other hand, every $R_2\overset{\oplus}{S}SPh$ produced by step k_2 is captured by mercaptan before it has a chance to react with $PhSOH$ and return to thiolsulfinate and sulfide. Of course the fraction of $R_2\overset{\oplus}{S}SPh$ returning in this way must be small enough so that the rate of the overall reaction does not exhibit any significant

rate dependence on sulfinic acid concentration. However, all that would be required to explain the difference in the k_S values is to have about 5-15% of the $R_2S^{\oplus}SPh$ not be captured by sulfinic acid, and this fraction is small enough so that one would not expect to see any significant dependence of k_S on sulfinic acid concentration. As a matter of fact, when one reexamines the data for the sulfide-catalyzed sulfinic acid-thiolsulfinate reaction one sees some evidence that k_S for that reaction may indeed show a very slight dependence on sulfinic acid concentration just as would be predicted by the above consideration. Table 6 contains the relevant data.

Inspection of Table 6 shows that k_S does show a slight tendency to increase with sulfinic acid concentration. The increase is small ($\sim 5-10\%$) and therefore within the experimental uncertainty of k_S . Therefore, one cannot say definitely if the tendency observed here is real.

In view of the preceding discussion it would appear that we should make a few minor modifications in the mechanisms we have previously suggested (Charts I and VII) for the sulfide-catalyzed reactions of thiolsulfonates with mercaptans and sulfinic acids. Chart VIII summarizes the present view of the mechanistic picture for the two sulfide-catalyzed reactions.

Table 6. Kinetics of the Sulfide-Catalyzed Reaction of Phenyl Benzenethiolsulfinate with *p*-Toluenesulfonic Acid.^a

$(\text{ArSO}_2\text{H})_o \times 10^2,$ <u>M</u>	$(\text{R}_2\text{S}) \times 10^4,$ <u>M</u>	$k_1 \times 10^4,$ sec ⁻¹	$k_S = \left[\frac{k_1 - k_1^o}{(\text{R}_2\text{S})} \right]^b$
Benzyl Sulfide			
3.0	0.10	4.5	21
	0.18	6.1	21
	0.20	6.4	20
5.0	0.20	8.9	23
6.0	0.20	9.7	23
Benzyl Phenyl Sulfide			
3.0	15	8.3	0.39
	10	6.5	0.41
	5.0	4.5	0.42
4.5	5.0	5.9	0.44
6.0	5.0	7.1	0.40
7.5	5.0	8.8	0.46
9.0	5.0	10.0	0.44
<u>n</u> -Butyl Sulfide			
3.0	0.099	18.2	1.6×10^2
	0.020	5.8	1.7×10^2
6.0	0.020	8.4	1.7×10^2

^a Reference 31, Table V, p. 3560. All runs in acetic acid-0.10 M sulfuric acid-0.56 M water at 39.4° with initial $(\text{PhS(O)SPh}) = 3.8 \times 10^{-3}$ M.

^b k_1^o equals $k_{\text{ArSO}_2\text{H}}(\text{ArSO}_2\text{H})_{\text{av}}$ for the particular reaction conditions.

two sulfide-catalyzed reactions, the results nevertheless demonstrate the fundamental correctness of the mechanism which was originally proposed for the sulfide-catalyzed sulfinic acid-thiolsulfinate reaction.

OPTICALLY ACTIVE PHENYL BENZENETHIOLSULFINATE

Results

The original purpose in preparing an optically active aromatic thiolsulfinate was to allow one to test experimentally some of the aspects of the mechanism that had been proposed for the sulfide-catalyzed disproportionation of thiolsulfinites in acetic acid-water. However, once such an optically active thiolsulfinate had been prepared, investigation of the racemization of this compound by sulfides and common anionic nucleophiles in acidic aqueous dioxane showed that such a compound could also be used advantageously to provide quantitative data on nucleophilic reactivity in substitutions at sulfenyl sulfur. This section deals first with the preparation of optically active phenyl benzenethiolsulfinate, second with the subsequent study of its nucleophile and acid catalyzed racemization in aqueous dioxane, and finally with the sulfide-catalyzed racemization of the thiolsulfinate in acetic acid-water-sulfuric acid under the same conditions under which the sulfide-catalyzed disproportionation has already been studied.

Preparation of Optically Active Phenyl Benzenethiolsulfinate

Optically active phenyl benzenethiolsulfinate was prepared by the asymmetric oxidation of phenyl disulfide using (+) percamphoric

acid. This method of asymmetric oxidation has been successful in preparing optically active sulfoxides from unsymmetrical sulfides (5, 6, 34, 36). The method used was similar to that described by Montanari and coworkers (36) for the sulfide to sulfoxide oxidation. A solution of known titer of (+) percamphoric acid in chloroform (250 ml. of 0.1 M) was slowly added during a period of one hour to a solution of phenyl disulfide in chloroform (5.45 grams, 0.025 moles in 200 ml.) at -5° . The mixture was stirred for an additional one hour period and allowed to come to room temperature. The mixture was then filtered to remove the precipitated (+) camphoric acid. The filtrate was washed several times with 5% aqueous bicarbonate solution, washed twice with water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the product was recrystallized by dissolving in a minimum amount of chloroform and adding n-hexane. The yellow needles were washed with cold n-hexane and recrystallized again. The yield was approximately 60%. The melting point was found to be 69° . The literature value (4) is $69-70^{\circ}$. The specific rotation was found to range from $+14$ to $+8^{\circ}$ in aqueous dioxane ($c = 5$, at $436 \text{ m}\mu$). The compound exhibits a positive plain dispersion curve (Figure 5) in the region $700-400 \text{ m}\mu$.

The optical purity and absolute configuration of (+) phenyl benzene-thiolsulfinate has been determined by Fava and coworkers (50). The reaction of thiolsulfinate with a Grignard was used to

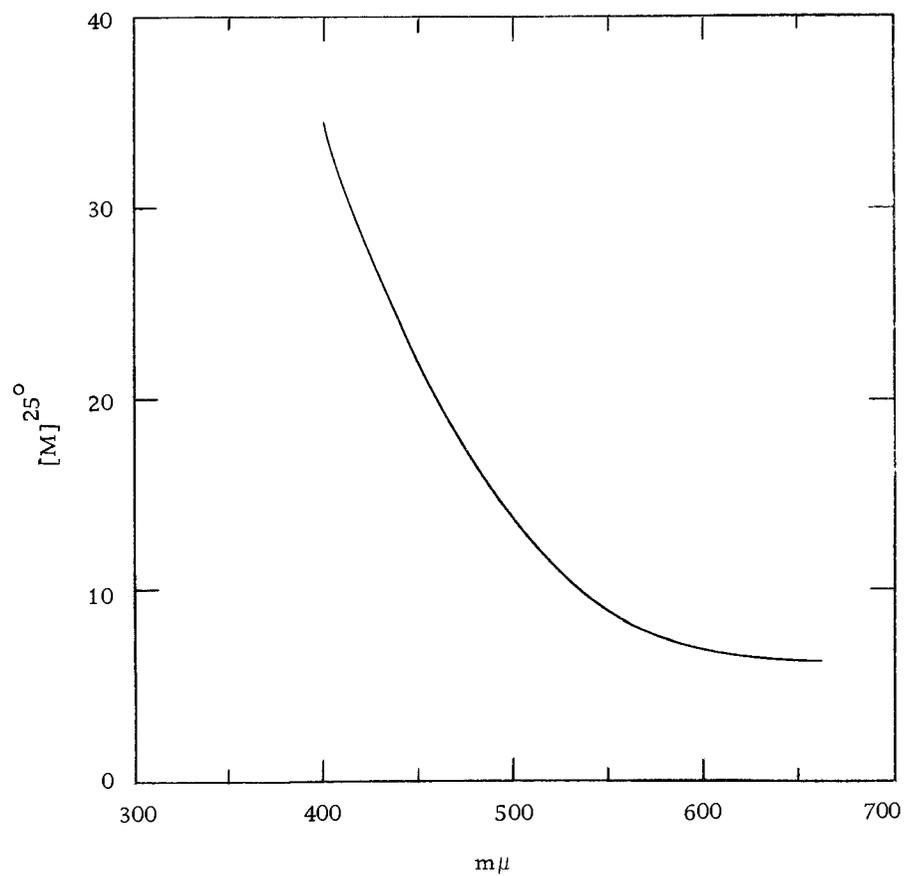
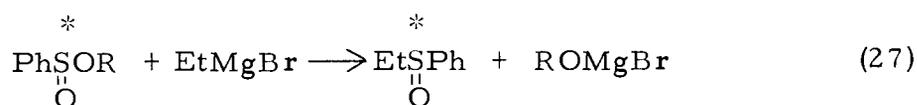


Figure 5. Plain Dispersion Curve of (+) Phenyl Benzene-thiolsulfinate.

produce an optically active sulfoxide, equation 26.



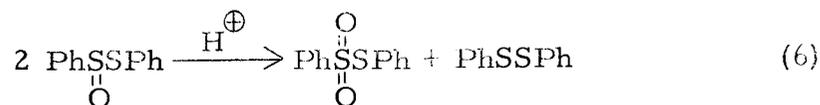
This reaction is similar to the preparation of optically active sulfoxides by treating sulfinic acid esters with Grignard reagents, equation 27 (1,2). The latter reaction is known to proceed with complete inversion of configuration. The optical purity of the



sulfoxide can then be used to gauge the optical purity of the initial thiolsulfinic acid and to establish the absolute configuration of the original optically active thiolsulfinic acid. Results from this type of experiment indicate that the optical purity of thiolsulfinic acid is from 1 to 2% and that (+) phenyl benzenethiolsulfinic acid has R configuration.

Although, the physical properties and absorption spectra of optically active phenyl benzenethiolsulfinic acid were identical to the inactive material, it was important to establish that the observed rotation was in fact due to the thiolsulfinic acid and not to traces of some strongly dextrorotatory impurity which might have become incorporated in the thiolsulfinic acid. That all the rotation was due to the thiolsulfinic acid was shown in the following manner. Disproportionation of thiolsulfinic acid under acidic conditions, equation 6, gives

thiolsulfonate and disulfide.



Neither of these compounds is capable of optical activity. Accordingly, if all the optical activity of the thiolsulfinate is in fact due to optically active thiolsulfinate, subjecting a sample to conditions that will disproportionate the thiolsulfinate should lead to complete loss of optical activity in the sample. On the other hand, if the activity is due to an impurity, the sample recovered after disproportionation will still be optically active. A sample of optically active phenyl benzenethiolsulfinate, $(\alpha)_{\text{D}} = +5.11 \pm 0.13^{\circ}$ ($c = 5$, chloroform) was subjected to disproportionation under very mild conditions. In acetic acid-0.56 M water-0.2 M sulfuric acid in the presence of small amounts of alkyl sulfides ($(\text{PhCH}_2)_2\text{S}$ equal to 3×10^{-4} M) phenyl benzenethiolsulfinate undergoes particularly rapid disproportionation ($t_{1/2}$ equal to 15 minutes at 40°)(62, Appendix 2, p. 134). A sample of optically active thiolsulfinate was subjected to these conditions for a period of four hours. The specific rotation of the sample recovered was found to be $(\alpha)_{\text{D}} = -0.05 \pm 0.26^{\circ}$ ($c = 5$, chloroform). This result clearly demonstrates that all the optical activity of the thiolsulfinate samples is due to optically active phenyl benzenethiolsulfinate.

Utilization of Optically Active Phenyl Benzenethiolsulfinate to Provide Quantitative Data on Nucleophilic Reactivity in Substitution Reactions at Sulfenyl Sulfur

In aqueous dioxane containing acid and suitable nucleophilic catalysts, optically active phenyl benzenethiolsulfinate was found to undergo rapid racemization. As will be seen shortly, this acid and nucleophile catalyzed racemization of the thiolsulfinate can provide quantitative data on the relative reactivity of various common nucleophiles toward sulfenyl sulfur in a nucleophilic substitution reaction.

Racemization of (+) Phenyl Benzenethiolsulfinate in 60% Dioxane

Optically active phenyl benzenethiolsulfinate racemizes only very slowly ($k_a = 4.3 \times 10^{-6} \text{ sec}^{-1}$ at 39.1°) in 60% aqueous dioxane (v/v) which contains 0.1 to 0.5 M perchloric acid. The rate of racemization appears to be independent of the concentration of perchloric acid and seems to be of the magnitude predicted for these conditions for the purely thermal racemization of phenyl benzenethiolsulfinate from the data of Fava and Koch.² Addition of a small amount of sulfide or a common anionic nucleophile such as chloride, bromide, iodide, or thiocyanate greatly accelerates the rate of loss of optical

²Dr. A. Fava and Dr. P. Koch, private communication.

activity. Figure 6 illustrates the large rate enhancement due to the addition of 0.01 M bromide ion. That the loss of optical activity is due solely to the racemization of the thiosulfinate and not to its undergoing some reaction like disproportionation could be demonstrated as follows: Measurement of the ultraviolet spectrum of the solution after the loss of optical activity was complete showed that the loss of optical activity was not accompanied by any change in the ultraviolet spectrum of the solution. Such experiments were done for the catalysis involving iodide, thiocyanate, and n-butyl sulfide. If a disproportionation of the thiosulfinate to disulfide and thiosulfonate were responsible for the loss of optical activity the final solution should exhibit a very different ultraviolet spectrum from that at the beginning. This demonstrates that the loss of optical activity is not the result of a chemical reaction that would cause the disappearance of thiosulfinate.

Kinetics of the Nucleophile and Acid Catalyzed Racemization of (+) Phenyl Benzenethiosulfinate

Kinetic studies of the acid and nucleophile catalyzed racemization of (+) phenyl benzenethiosulfinate were carried out using two different types of nucleophiles. Common inorganic anions such as Cl^{\ominus} , Br^{\ominus} , I^{\ominus} , and SCN^{\ominus} represented one type, and alkyl sulfides the other. The results obtained with the anionic nucleophiles are shown

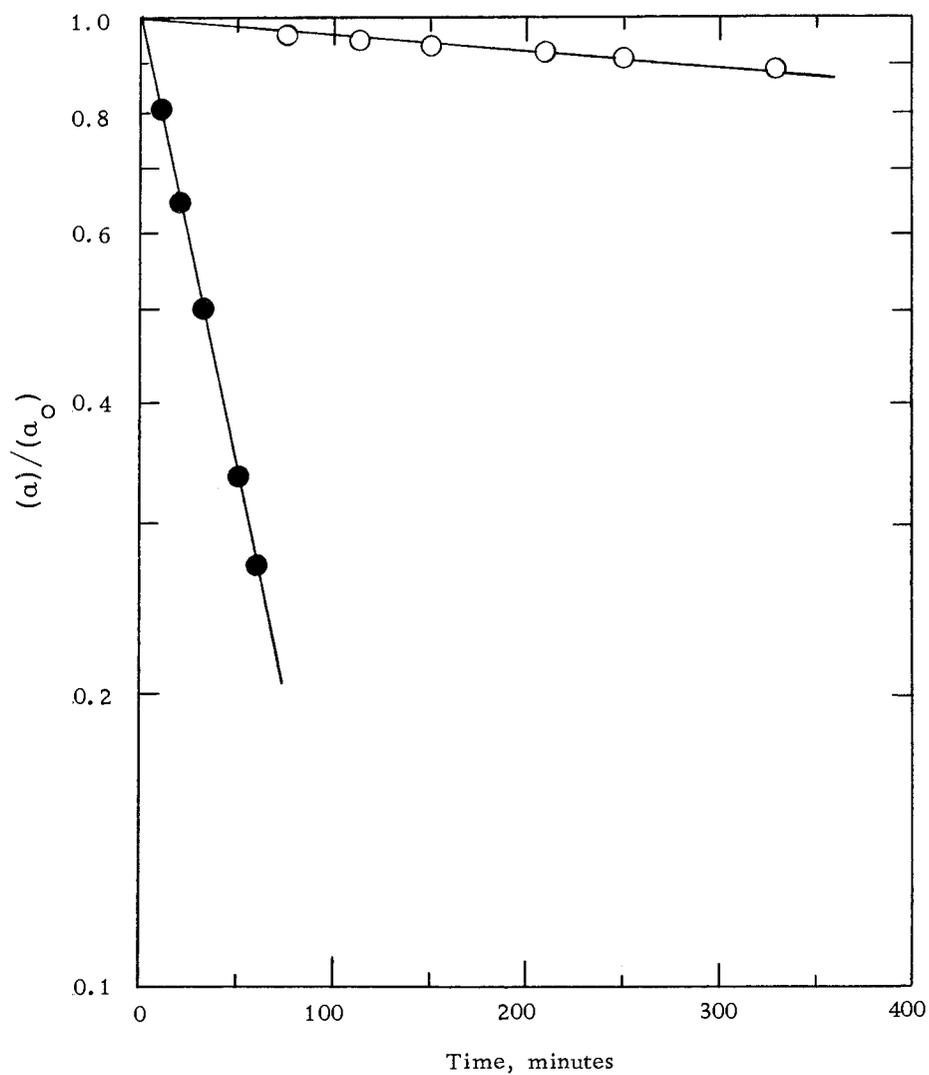


Figure 6. Racemization of 0.05 M (+) Phenyl Benzenethiolsulfinate in 60% Dioxane-0.1 M HClO_4 at 39.1°.

○ - Uncatalyzed.

● - 0.01 M Potassium Bromide Catalyzed.

in Table 7, those for the sulfides in Table 8. One important reason for studying the alkyl sulfides was to provide evidence for the exact mechanistic relationship between the racemization and the sulfide-catalyzed reactions of thiolsulfinate with sulfinic acid or mercaptan.

In each table the experimental rate of the racemization k_a is found in the next to the last column. The last column gives $k_a - k_a^0$, the corrected experimental rate for the nucleophile catalyzed racemization, divided by the nucleophile concentration. We shall call this quantity k'_{Nu} [$k'_{Nu} = (k_a - k_a^0) / (Nu)$], for reasons that will soon become apparent.

The kinetic-order with respect to nucleophile can be assessed by observing the influence of the nucleophile concentration on the value of k'_{Nu} found in Tables 7 and 8. The constancy of k'_{Nu} with each set of runs (see for example runs 1-3, 7-9, 15-19, and 31-32) demonstrates that the racemization of (+) phenyl benzenethiol-sulfinate is first-order in catalyzing nucleophile. This can also be demonstrated by plotting k_a versus the nucleophile concentration, Figure 7.

Racemization rates for both types of nucleophiles were found to be subject to large salt effects. This can be seen from experiments carried out at a fixed perchloric acid concentration but with different amounts of added lithium perchlorate. For the anionic nucleophiles an increase in ionic strength under otherwise constant

Table 7. Kinetics of Anion-Catalyzed Racemization of (+) Phenyl Benzenethiolsulfinate in Acidic 60% Dioxane.^a

Run No.	Nucleophile	(Nu ⁻) X 10 ² , <u>M</u>	(HClO ₄), <u>M</u>	(LiClO ₄), <u>M</u>	k X 10 ⁴ , sec ⁻¹	$k'_{\text{Nu}} = \left[\frac{k_a - k_a^0}{(\text{Nu}^-)} \right]^b$
1	I ⁻	0.020	0.10	0.00	26	13
2		0.015	0.10	0.00	20	13
3		0.010	0.10	0.00	13	13
4			0.10	0.40	7.8	7.8
5			0.20	0.30	16	16
6			0.05	0.45	4.0	4.0
7	SCN ⁻	0.20	0.02	0.00	28	1.4
8		0.10	0.02	0.00	14	1.4
9		0.05	0.02	0.00	7.1	1.4
10		0.10	0.02	0.48	6.3	0.63
11			0.01	0.49	3.3	0.33
12			0.005	0.495	1.7	0.17
13			0.03	0.47	9.3	0.93
14			0.05	0.45	13	1.3
15	Br ⁻	3.0	0.10	0.00	10	0.034
16		2.0	0.10	0.00	6.8	0.034
17		1.5	0.10	0.00	5.5	0.036
18		1.0	0.10	0.00	3.6	0.036
19					15 (D ₂ O)	0.13
20			0.30	0.00	7.4	0.074
21			0.10	0.40	1.9	0.019
22			0.20	0.30	3.8	0.038
23			0.30	0.20	5.7	0.057
24			0.40	0.10	7.9	0.079
25			0.50	0.00	10	0.10
26			0.00	0.00	0.04	
27	Cl ⁻	10.0	0.40	0.00	2.3	0.0023
28			0.30	0.10	1.8	0.0018
29			0.20	0.20	1.3	0.0013
30			0.10	0.30	0.60	0.00056

^a All runs at 39.1^o and initial (+) phenyl benzenethiolsulfinate concentration equal to 0.05 M.

^b k_a^0 , rate of racemization in the absence of added nucleophile is $0.04 \times 10^{-4} \text{ sec}^{-1}$ under these conditions.

Table 8. Kinetics of Sulfide-Catalyzed Racemization of (+) Phenyl Benzenethiolsulfinate in Acidic 60% Dioxane. ^a

Run no.	Sulfide	$(R_2S) \times 10^2$, <u>M</u>	$(HClO_4)$, <u>M</u>	$(LiClO_4)$, <u>M</u>	$k_a \times 10^4$, sec ⁻¹	$k'_{Nu} = \left[\frac{k_a - k_a^o}{(R_2S)} \right]^b$
31	<u>n</u> -Butyl	0.20	0.10	0.00	2.6	0.13
32		0.10	0.10	0.00	1.38	0.13
33					2.48(D ₂ O)	0.24
34		0.20	0.20	0.00	3.9	0.39
35		0.30	0.30	0.00	7.8	0.78
36		0.40	0.40	0.00	14	1.4
37		0.50	0.50	0.00	24	2.4
38		0.10	0.10	0.40	4.5	0.45
39		0.20	0.20	0.30	8.7	0.87
40	Benzyl	1.00	0.10	0.00	0.81	0.0077
41	Thiodipropionic Acid	10.0	0.10	0.00	2.7	0.0027

^a All runs at 39.1° and initial (+) phenyl benzenethiolsulfinate concentration equal to 0.05 M.

^b k_a^o , rate of racemization in the absence of added sulfide is 0.04×10^{-4} sec⁻¹ under these conditions.

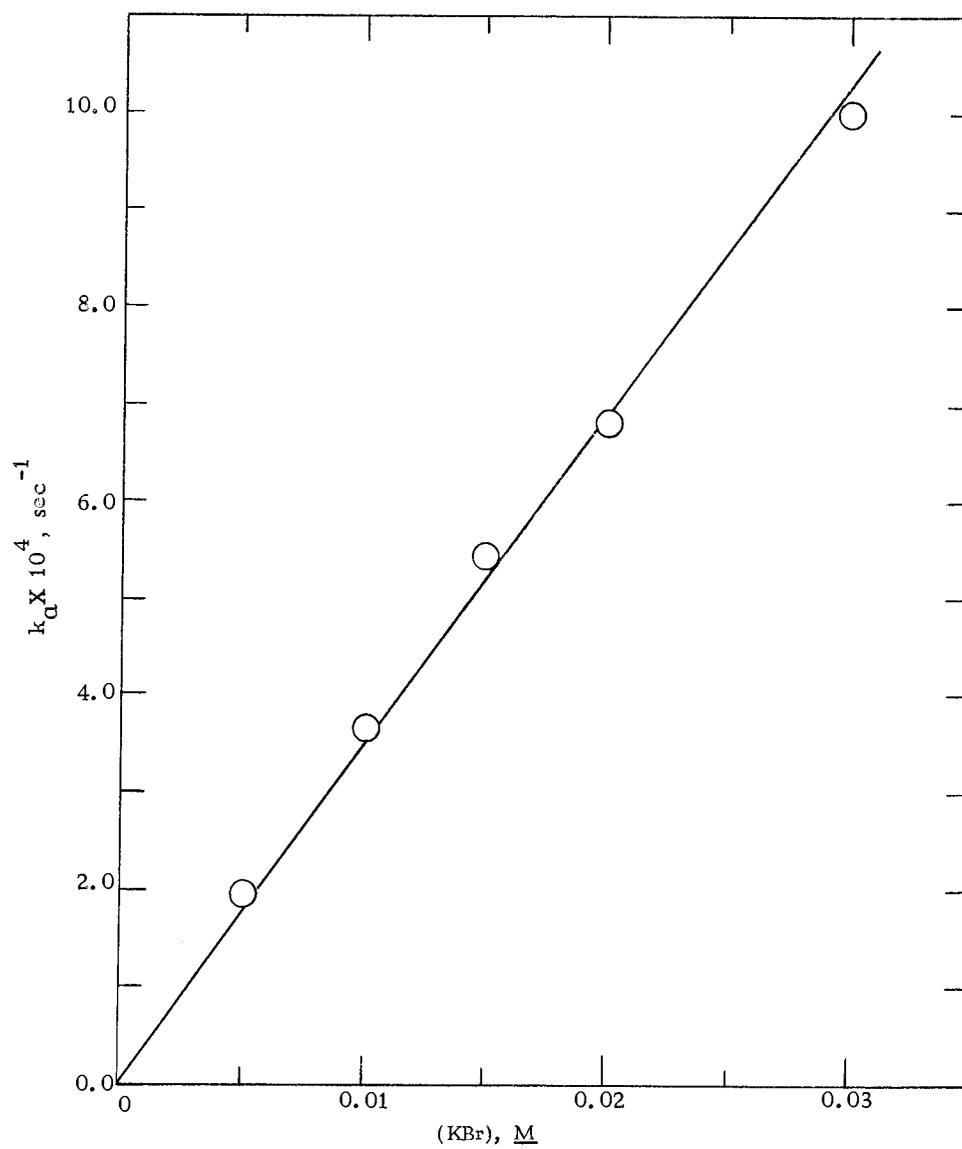


Figure 7. Variation of the Experimental Rate Constant, k_d , with Potassium Bromide Concentration.

conditions leads to a marked decrease in rate (compare runs 3 and 4, 8 and 10, and 18 and 21). On the other hand, with the sulfides an increase in ionic strength leads to an increase in k_a (compare runs 32 and 38). Because of these salt effects the dependence of k_a on (H^{\oplus}) was studied in all cases in runs carried out at a fixed ionic strength of 0.5. Under such conditions k_a increases linearly with (H^{\oplus}) as can be seen from Figure 8. This plot also shows that there is no detectable intercept at $(H^{\oplus}) = 0.00 \text{ M}$. This indicates that the only important pathway for racemization of (+) phenyl benzenethiolsulfinate is one involving both acid and nucleophile catalysis. Verification of this conclusion was provided by a run in which no perchloric acid but $0.01 \text{ M Br}^{\ominus}$ was added (run 26). From the experiments in Tables 7 and 8 one can conclude that the racemization depends on acid and nucleophile in the following way:

$$k_a - k_a^0 = k_{\text{Nu}}'' (H^{\oplus})(\text{Nu})$$

Values of k_{Nu}'' for the various nucleophiles can be derived from the slope of plots of k_{Nu}' versus (H^{\oplus}) . Figures 9-13 contain such plots for Cl^{\ominus} , Br^{\ominus} , I^{\ominus} , SCN^{\ominus} , and n-butyl₂S. Due to the basicity of SCN^{\ominus} the dependence of k_a on (H^{\oplus}) was studied with perchloric acid concentrations of 0.03 M or less in order to avoid acidities where protonation of the nucleophile would be important. Table 9 contains the values of k_{Nu}'' obtained from the plots in Figures 9-13.

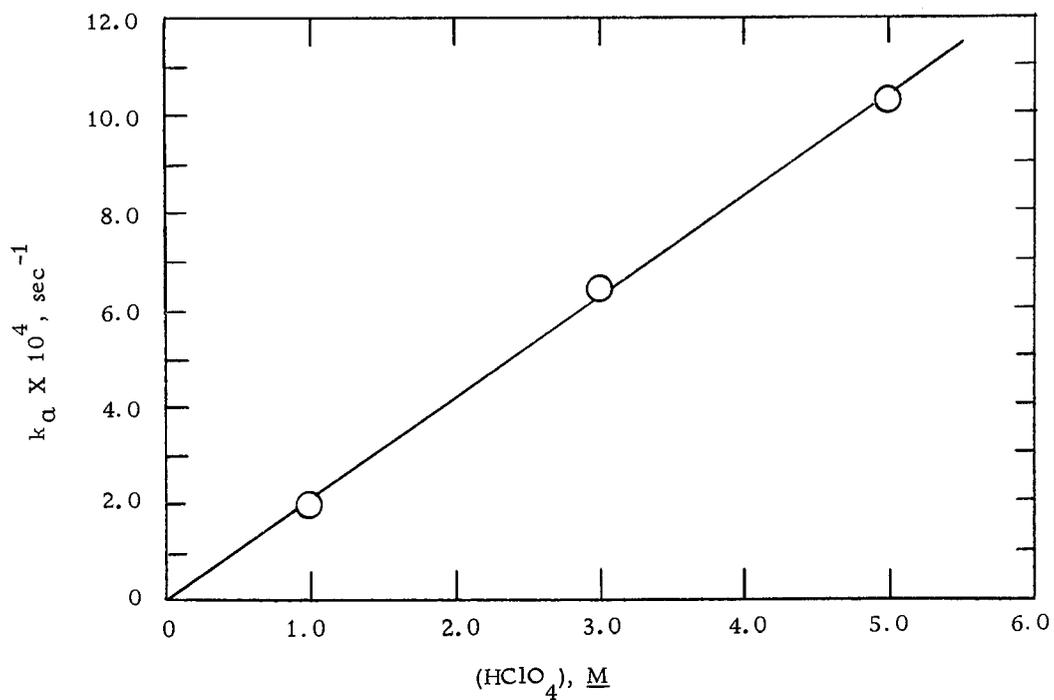


Figure 8. Racemization Dependence on Perchloric Acid Concentration at Constant Ionic Strength, 0.01 M KBr and 0.5 M ClO_4^- at 39.1° in 60% Dioxane.

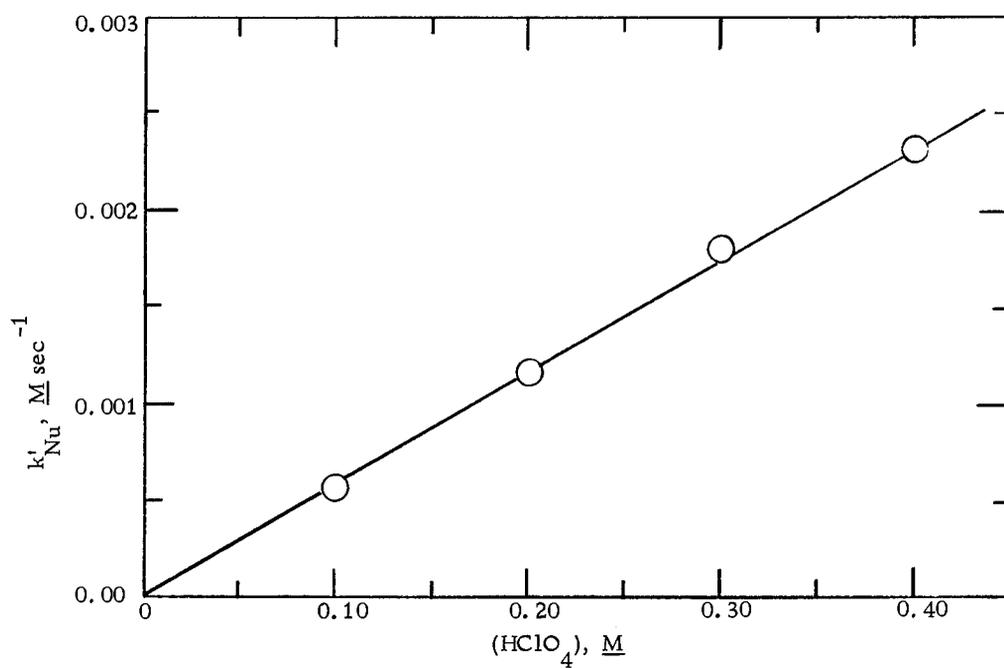


Figure 9. Plot of k'_{Nu} versus (HClO_4) for Chloride Ion.

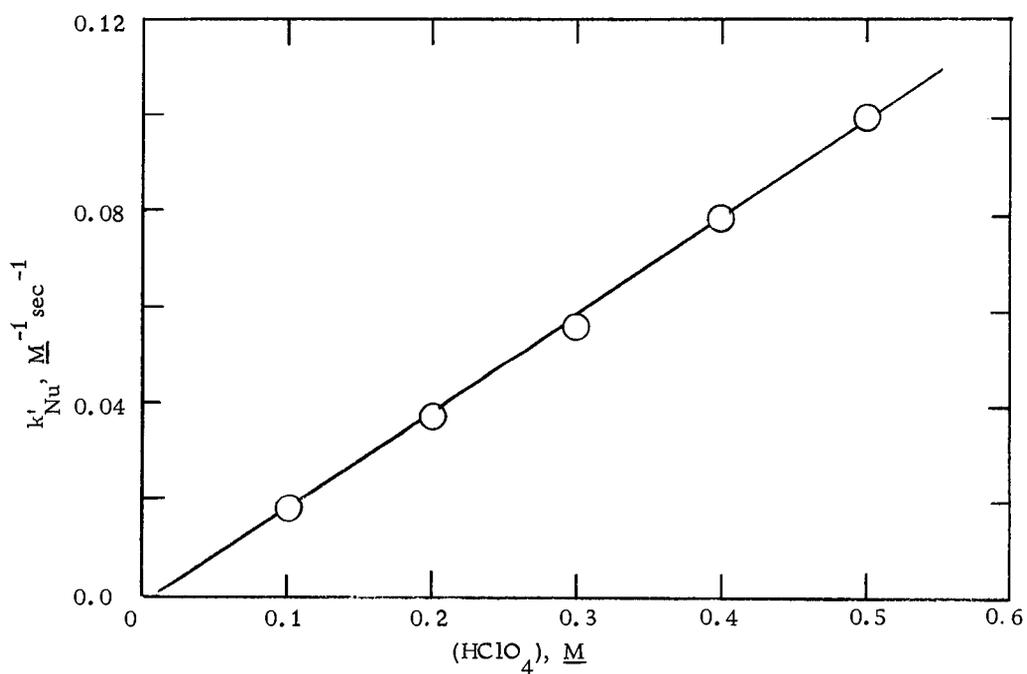


Figure 10. Plot of k'_{Nu} versus (HClO_4) for Bromide Ion.

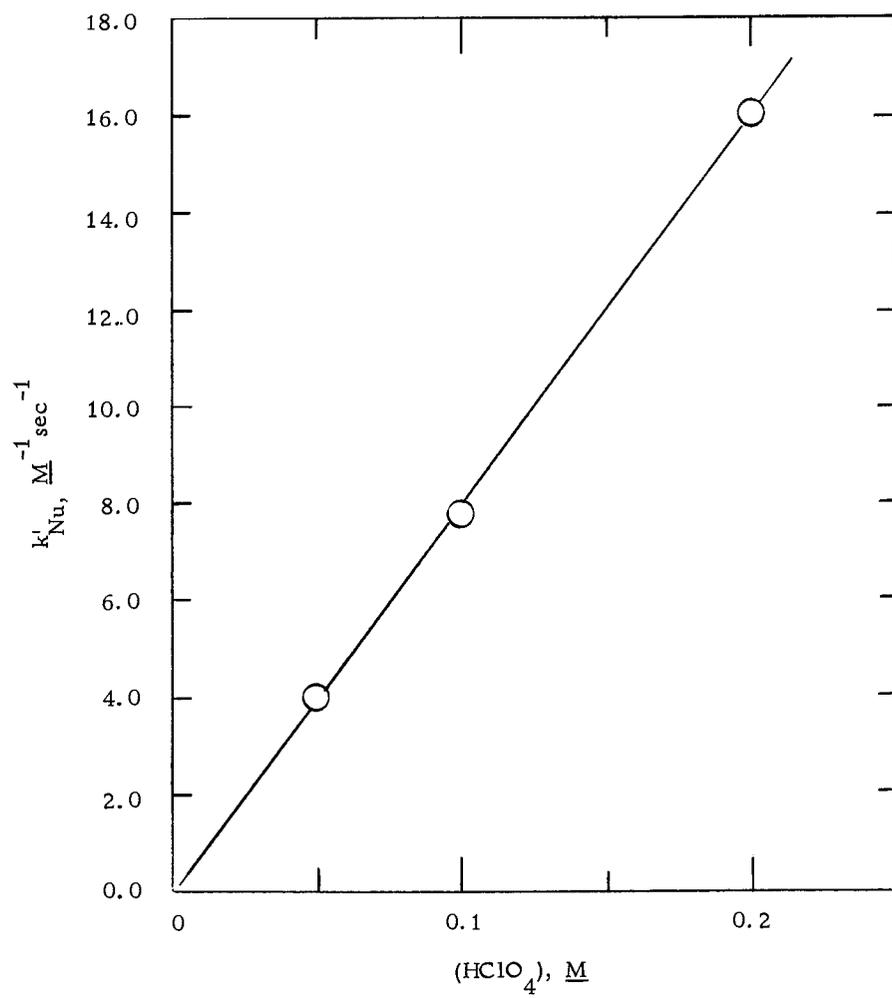


Figure 11. Plot of k'_{Nu} versus $(HClO_4)$ for Iodide Ion.

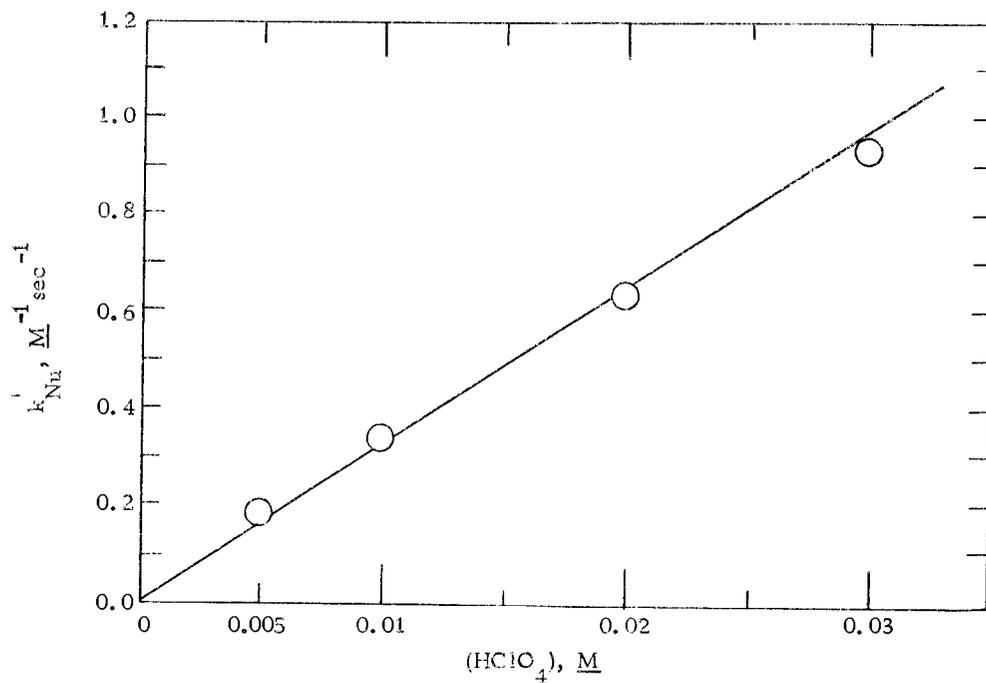


Figure 12. Plot of k'_{Nu} versus (HClO_4) for Thiocyanate Ion.

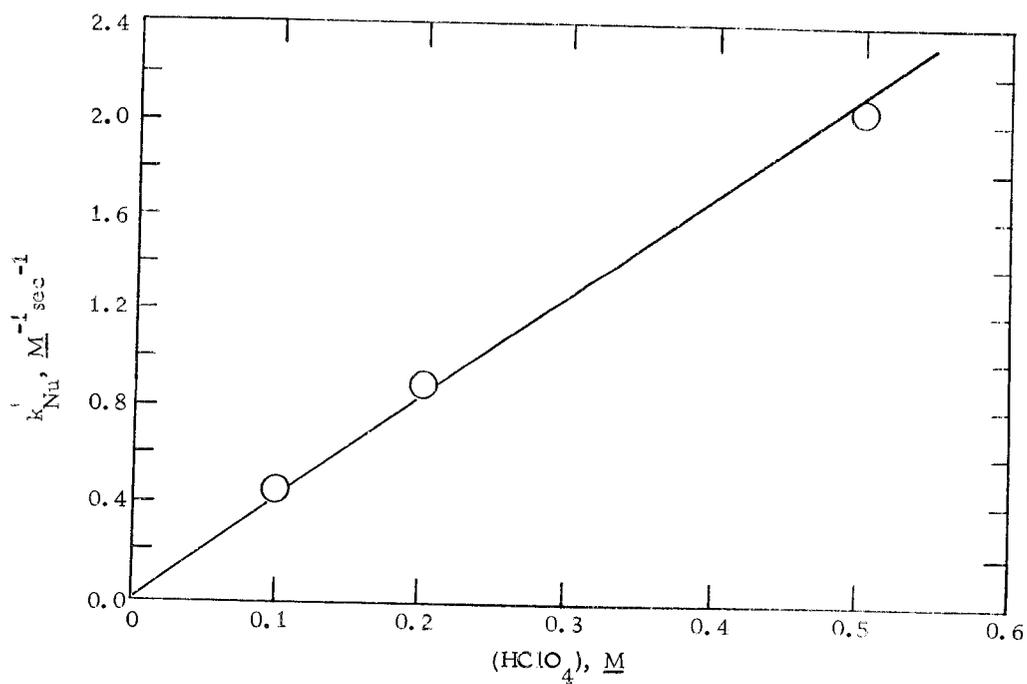


Figure 13. Plot of k'_{Nu} versus (HClO_4) for n -Butyl₂S.

Table 9. Nucleophilic Reactivity Toward Sulfenyl Sulfur in Protonated Phenyl Benzene-thiolsulfinate. ^a

Nucleophile	k'_{Nu} $\text{M}^{-2} \text{sec}^{-1}$
Cl^-	0.0057
Br^-	0.20
SCN^-	31
I^-	78
$\underline{n}\text{-Bu}_2\text{S}$	4.7

^aAll data are in 60% dioxane at a constant ionic strength of 0.50 and at 39.1°.

The solvent isotope effect for the n-butyl sulfide catalyzed racemization was measured and found to be $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.54$ (runs 32 and 33). That for the bromide ion catalyzed racemization was also measured. It was $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.28$ (runs 18 and 19). The solvent isotope effect for the n-butyl sulfide catalyzed reaction can be interpreted in a straightforward manner as being indicative of the racemization involving specific hydrogen ion rather than general acid catalysis.

Related Studies in 60% Dioxane

During our investigation into the characteristics of the nucleophile and acid catalyzed racemization of (+) phenyl benzenethiolsulfinate

in 60% dioxane some related and highly pertinent experiments were carried out involving reactions of inactive thiolsulfinate with sulfinic acid and mercaptan under similar conditions. These reactions were conveniently run in a reaction cell designed for in-situ operation (see Experimental page 119). The rate of the reaction was followed by observing the change in the ultraviolet absorption spectrum of the solution at a single wavelength.

Experiments with Added Sulfinic Acid. Just as in moist acetic acid, aryl thiolsulfinate in aqueous dioxane undergo an acid and sulfide-catalyzed reaction with aryl sulfinic acids. A limited kinetic study, shown in Table 10, reveals that this sulfide catalyzed reaction is first-order in sulfide and thiolsulfinate, but independent of sulfinic acid concentration.

Comparison of the k_S values for this sulfide-catalyzed thiolsulfinate-sulfinic acid reaction (Table 10) with k'_{Nu} for the sulfide-catalyzed racemization (Table 8) under the same reaction conditions shows that the rates of the two processes are identical, within experimental error. The two reactions therefore obviously involve the same rate-determining step.

Comparison of the various features of the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction in 60% dioxane (Table 10) with previous data (31) for the same process in acetic acid-water suggest that the reaction probably involves the same rate-determining step

Table 10. Kinetics of Alkyl Sulfide and Bromide Ion Catalyzed Thiolsulfinate-Sulfinic Acid Reaction in Acidic 60% Dioxane. ^a

Nucleophile	(Nu) × 10 ² , <u>M</u>	(HClO ₄), <u>M</u>	k ₁ × 10 ⁴ , ^b sec ⁻¹	k _S = $\left[\frac{k_1 - k_1^0}{(\text{Nu})} \right]^c$
none	0.00	0.50	3.4	
		0.30	3.3	
		0.10	3.2	
<u>n</u> -Butyl ₂ S	0.1 0.2	0.30	11.4	0.81
		0.30	18	0.74
		0.50	46	2.1
		0.10	6.1	0.14
Br ⁻	1.0	0.30	7.4	0.074

^a All runs at 39.1° and initial (PhS(O)SPh) = 1.56 × 10⁻⁴ M and (PhSO₂H) = 1.2 × 10⁻³ M.

^b k₁ equals experimental rate of disappearance of PhS(O)SPh.

^c k₁⁰ equals k₁ for runs in which no sulfide is present and otherwise similar conditions as given in the first section of table.

Table 11. Kinetics of Alkyl Sulfide-Catalyzed Thiolsulfinate-Mercaptan Reaction in Acidic 60% Dioxane.^a

Nucleophile	(Nu) × 10 ² , <u>M</u>	(HClO ₄), <u>M</u>	k ₁ × 10 ⁴ , sec ⁻¹ ^b	k _S = $\left[\frac{k_1 - k_1^0}{(\text{Nu})} \right]^c$
none	0.00	0.2	0.14	
		0.3	0.13	
<u>n</u> -Butyl ₂ S	0.10	0.30	7.6	0.75
		0.20	14.9	0.74
		0.20	7.5	0.37

^a All runs at 39.1° and initial (PhS(O)SPh) = 1.56 × 10⁻⁴ M and (n-ButylSH) = 3.12 × 10⁻³ M.

^b k₁ equals experimental rate of disappearance of (PhS(O)SPh).

^c k₁⁰ equals k₁ for runs in which no sulfide is present and otherwise similar conditions as given in the first section of table.

experimental error, as k'_{Nu} for both the sulfide-catalyzed racemization and the sulfide-catalyzed sulfinic acid-thiolsulfinate reaction. In acidic 60% dioxane three different sulfide-catalyzed processes can all be shown to involve the same rate-determining step: (1) the racemization of (+) phenyl benzenethiolsulfinate, (2) the thiolsulfinate-sulfinic acid reaction, and (3) the thiolsulfinate-mercaptan reaction.

Utilization of Optically Active Phenyl Benzenethiolsulfinate to Study Aspects of the Sulfide-Catalyzed Disproportionation Reaction

Study of the sulfide-catalyzed loss of optical activity of solutions of optically active phenyl benzenethiolsulfinate in acetic acid-water solution under the same conditions used earlier to study the sulfide-catalyzed disproportionation of phenyl benzenethiolsulfinate can provide information concerning the correctness of certain aspects of the mechanism postulated for the sulfide-catalyzed disproportionation reaction.

Kinetics of Loss of Optical Activity

Results Using the Less Reactive Sulfides. The kinetic studies were carried out in acetic acid-0.56 M water as solvent. Sulfuric acid was added in varying amounts as a strong acid catalyst, and small quantities of various alkyl and aryl sulfides were used as nucleophilic catalysts. The rate of loss of optical activity was

followed by measuring the optical rotation of the solution at 436 m μ . The marked catalytic effect of very small amounts of suitable alkyl sulfides on the rate of loss of optical activity can be seen in Figure 14. Several different sulfides were studied kinetically. The results of these studies with the less reactive sulfides are summarized in Table 12. The next to the last column in this table gives k_a , the experimental first-order rate constant for the loss in optical activity under the various reaction conditions.

The experimental rate of loss of optical activity (k_a) will be the sum of the rates of all reactions that result in loss of optical activity. To obtain an experimental rate constant for the rate of the sulfide-catalyzed loss of optical activity one must subtract from k_a the rate of loss of optical activity observed under the same conditions in the absence of the sulfide, k_a^0 . In the last column of Table 12 one finds values of $[(k_a - k_a^0)/(R_2S)]$. This quantity we term k_S^a . Suitable examination of k_S^a values will now reveal how the rate of sulfide-catalyzed loss of optical activity depends on the various reaction variables.

Let us consider first the dependence of k_S^a on the acidity of the medium. The influence of acid concentration on the rate of loss of optical activity can be determined from runs at constant sulfide concentration. The results of runs using the less reactive sulfides are shown in Table 13. The observation that $\log k_S^a + H_0$ remains

Table 12. Kinetics of the Sulfide-Catalyzed Loss of Optical Activity of Solutions of (+) Phenyl Benzenethiolsulfinate in Acetic Acid-1% Water for the Less Reactive Sulfides.^a

Sulfide	(H ₂ SO ₄), <u>M</u>	(R ₂ S) × 10 ⁴ , <u>M</u>	k _a × 10 ⁴ , sec ⁻¹	k _S ^a = $\left[\frac{k_a - k_a^o}{(R_2S)} \right]$ ^b
Benzyl	0.1	0.21	7.95	35
		0.42	14.3	33
		0.81	23.9	29
		1.00	30.1	29
		2.00	50.8	25
		4.00	86	21
		0.81	66.1	79
Thiodipro- pionic Acid	0.1	1.25	6.23	4.4
		2.50	12.0	4.5
		10.0	35.2	3.45
		20.0	68.3	3.38
		2.50	29.6	11.3
Benzyl Phenyl	0.1	12.3	9.25	0.752
		12.3	27.4	2.14
Phenyl	0.1	220	4.49	0.0172
		220	10.9	0.0436

^a All runs at 39.1° in acetic acid containing 0.56 M water and the amount of sulfuric acid indicated. The initial concentration of (+) phenyl benzenethiolsulfinate in all runs was 0.05 M.

^b k_a^o equals 0.71 × 10⁻⁴ sec⁻¹ for 0.1 M sulfuric acid and 1.27 × 10⁻⁴ sec⁻¹ for 0.2 M sulfuric acid concentration.

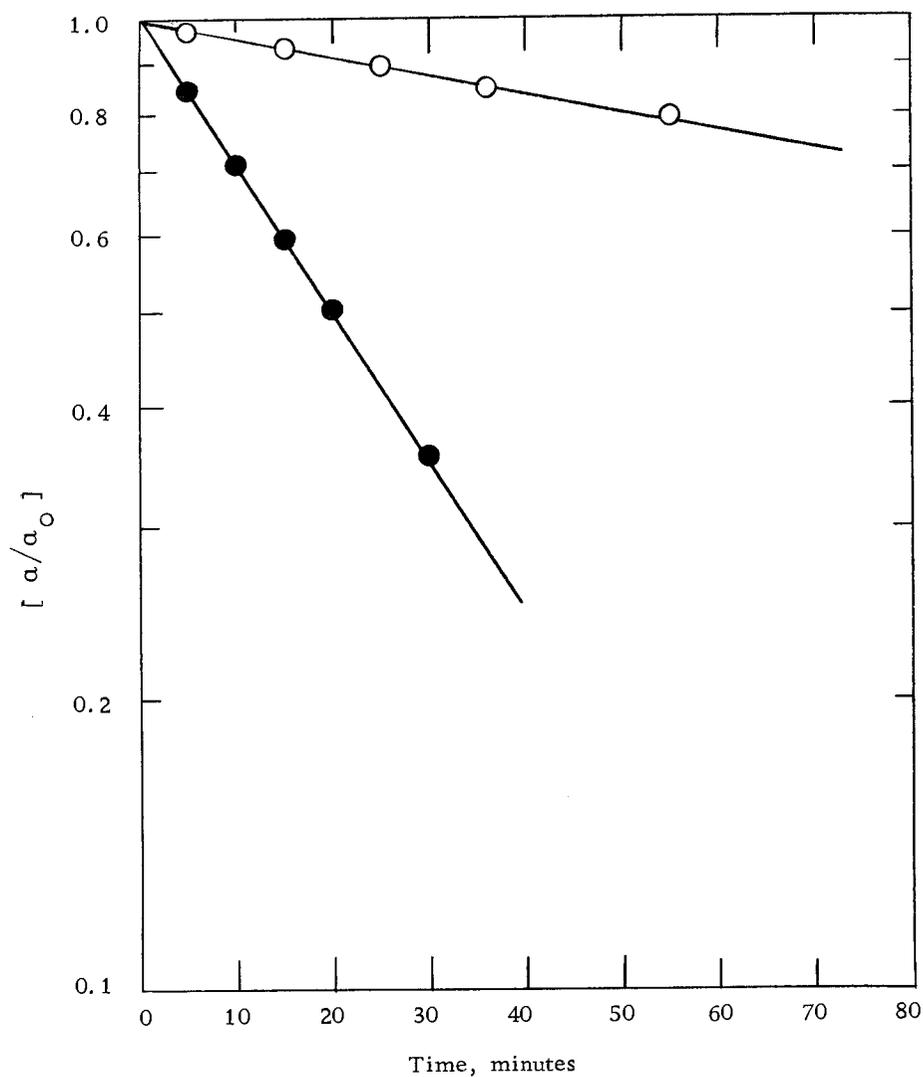


Figure 14. Rate of Loss of Optical Activity of Solutions of (+) Phenyl Benzenethiolsulfinate in Acetic Acid-0.10 M Sulfuric Acid-0.56 M Water at 39.1°. Initial Concentration of (+) PhS(O)SPh = 0.05 M.

○ - Uncatalyzed

● - 0.36×10^{-5} M n-Butyl Sulfide Catalyzed.

approximately constant for each sulfide indicates that the rate of sulfide-catalyzed loss of optical activity follows the change in H_o of the medium. The dependence of k_S^a on acidity is thus the same as the acidity dependence exhibited by the rates of the sulfide-catalyzed disproportionation and the sulfide-catalyzed reactions of thiolsulfonates with sulfinic acid or mercaptan. Since these latter reactions have been shown to be specific acid catalyzed, the sulfide catalyzed loss of optical activity of (+) phenyl benzenethiolsulfonate is inferred also to be specific acid catalyzed.

Table 13. Dependence of k_S^a on Acidity.^a

Sulfide	(H ₂ SO ₄), <u>M</u>	k_S^a , <u>M</u> ⁻¹ sec ⁻¹	log $k_S^a + H_o^b$
Benzyl	0.1	29	0.33
	0.2	79	0.34
Thiodipropionic Acid	0.1	4.5	-0.48
	0.2	11.3	-0.50
Benzyl Phenyl	0.1	0.695	-1.29
	0.2	2.14	-1.23
Phenyl	0.1	0.0172	-2.89
	0.2	0.0436	-2.92

^a All runs at 39.1° in acetic acid-0.56 M water and the amount of sulfuric acid indicated. This data is taken from Table 12 for runs at identical sulfide concentration.

^b H_o for 0.1 M sulfuric acid equals -1.13 and for 0.2 M equals -1.56 (49).

Examination of the k_S^a values for the different sulfides in Table 12 reveals that the rate is very sensitive to sulfide structure. The dependence of k_S^a on sulfide structure is very similar to the dependence of rate on structure observed for the sulfide-catalyzed reaction of thiolsulfonates with sulfinic acid (k_S), and is, therefore, very different from the dependence of rate on structure observed for the sulfide-catalyzed disproportionation (k_d). Comparison of the various rate constants for these sulfide-catalyzed reactions are given in Table 14.

Table 14. Comparison of the Second-Order Rate Constants for the Sulfide-Catalyzed Reactions of Thiolsulfonate for the Less Reactive Sulfides. ^a

Sulfide	$k_S^a, \underline{M}^{-1} \text{sec}^{-1b}$	$k_S, \underline{M}^{-1} \text{sec}^{-1c}$	$k_d, \underline{M}^{-1} \text{sec}^{-1d}$
Benzyl	35 → 21	21	0.89
Thiodipropionic Acid	5.2 → 3.4	3.1	0.48
Benzyl Phenyl	0.752	0.42	0.34
Phenyl	0.0172	0.0087	0.016

^a All runs at 40° in acetic acid-0.1 M sulfuric acid-0.56 M water.

^b See Table 12 page 66.

^c Reference 31, Table VI, p. 3561.

^d Reference 62, Appendix 2, p. 134-135.

Although the variation of k_S^a with structure is large and quite similar to the variation of k_S with structure for the sulfide-catalyzed sulfinic acid-thiolsulfinate reaction, it appears that in certain cases k_S^a shows some dependence on sulfide concentration, which, of course, it should not do if the reaction were strictly first-order in sulfide. Thus with benzyl sulfide and thiodipropionic acid as catalysts k_S^a decreases somewhat with increasing sulfide concentration. This result is illustrated in Figures 15 and 16. As sulfide concentration is increased k_S^a appears to decrease to a constant value which is very close to the rate constant for the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction (k_S) under the same reaction conditions. Runs at higher sulfide concentration were not possible due to the very fast rates of loss of optical activity. That k_S^a is significantly larger than k_S at low sulfide concentration for sulfides such as benzyl and thiodipropionic acid indicates an additional complication present in racemization of (+) phenyl benzenethiolsulfinate not found in the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction. The fact that k_S^a decreases with increasing sulfide concentration suggests an "extra" racemization reaction is present at low sulfide concentrations which is suppressed by further added sulfide.

The observations that the sulfide-catalyzed loss of optical activity is catalyzed by strong acid in the same fashion as the other sulfide-catalyzed reactions of thiolsulfinites in moist acetic acid and

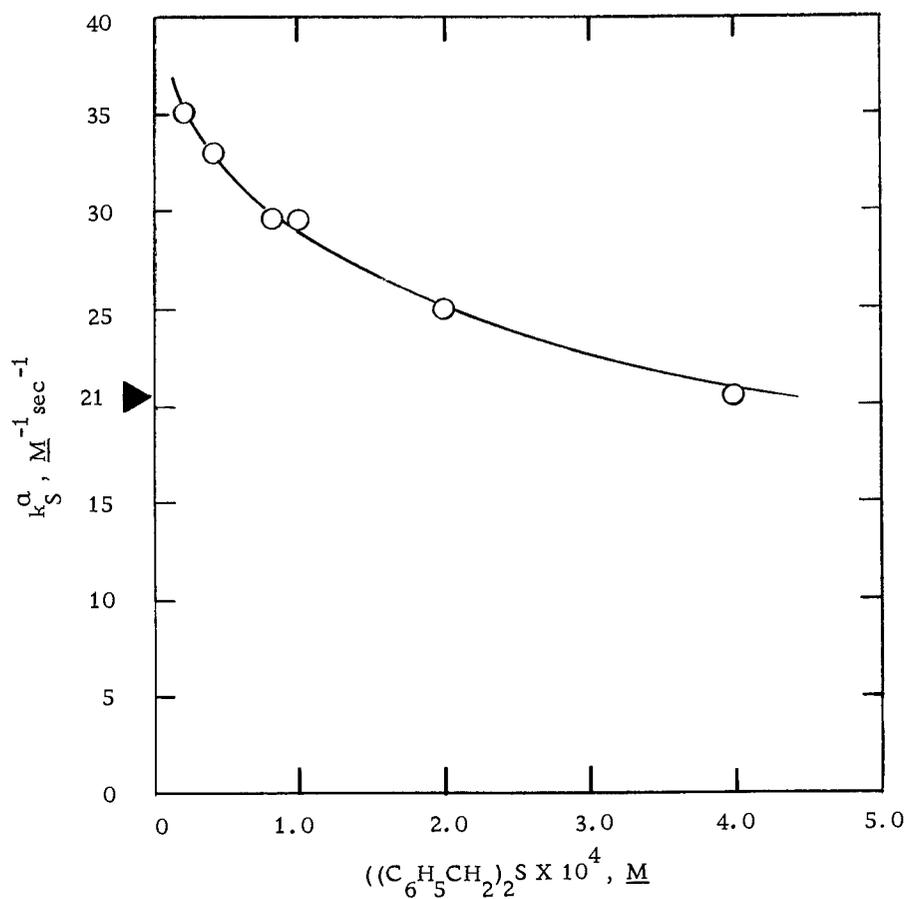


Figure 15. Dependence of k_S^a on Benzyl Sulfide Concentration in Acetic Acid-0.1 M Sulfuric Acid-0.56 M Water.

► k_S , for the Sulfide-Catalyzed Thiolsulfinate-Sulfinic Acid Reaction (31, Table VI, p. 3561).

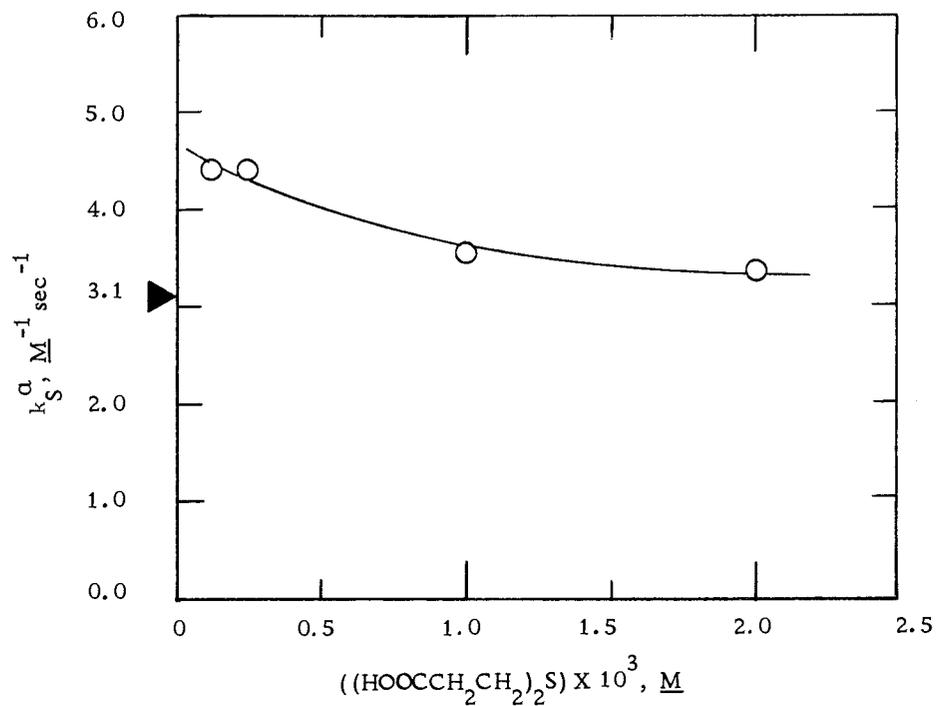


Figure 16. Dependence of k_S^a on Thiodipropionic Acid Concentration in Acetic Acid-0.1 M Sulfuric Acid-0.56 M Water.

► k_S^a , for the Sulfide-Catalyzed Thiol-sulfinate-Sulfinic Acid Reaction (31, Table VI, p. 3561).

that at high sulfide concentration there is a close relationship between k_S and k_S^a , suggest that the sulfide-catalyzed loss of optical activity and the sulfide-catalyzed thioisulfinate-sulfinic acid reaction involve the same basic series of steps up through the rate-determining step. There is apparently, however, some additional pathway for loss of optical activity beyond what would be expected from the mechanism shown in Chart III and this additional racemization can be suppressed by increasing the concentration of added sulfide. The main pathway for loss of optical activity would, however, presumably be that involving nucleophilic attack of sulfide on the sulfenyl sulfur of the sulfinyl-protonated thioisulfinate.

Results Using the Very Reactive Sulfides. Kinetic studies were also made using some much more reactive sulfides (i. e., tetrahydrothiophene, n-butyl sulfide, and ethyl sulfide) under conditions identical to those used in the last section. The results of these runs are shown in Table 15 and are quite different from those obtained using the less reactive sulfides. Instead of k_S^a being greater than or equal to k_S it is now found as is shown in Table 16 to be less than k_S for the very reactive sulfides. If the rate-determining step in the sulfide-catalyzed loss of optical activity is

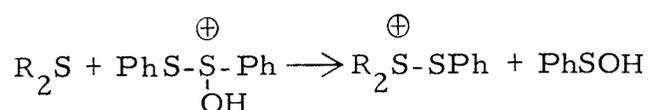


Table 15. Kinetics of the Sulfide-Catalyzed Loss of Optical Activity of Solutions of (+) Phenyl Benzenethiolsulfinate in Acetic Acid-1% Water for the More Reactive Sulfides.^a

Sulfide	(H ₂ SO ₄), <u>M</u>	(R ₂ S) × 10 ⁴ , <u>M</u>	k _a × 10 ⁴ , sec ⁻¹	k _S ^a = $\left[\frac{k_a - k_a^o}{(R_2S)} \right]^b$
Tetrahydro- thiophene	0.1	0.028	7.8	253
		0.055	14.8	254
Ethyl	0.1	0.126	17.7	135
		0.150	19.7	127
		0.631	83	130
<u>n</u> -Butyl	0.1	0.036	5.78	140
		0.050	7.86	142
		0.056	8.57	140

^a All runs at 39.1° in acetic acid containing 0.56 M water and the amount of sulfuric acid indicated. The initial concentration of (+) phenyl benzenethiolsulfinate in all runs was 0.05 M.

^b k_a^o equals 0.71 × 10⁻⁴ sec⁻¹ for 0.1 M sulfuric acid and 1.27 × 10⁻⁴ sec⁻¹ for 0.2 M sulfuric acid concentration.

then k_S^a should, of course, be equal to k_S . However, before deciding that the present results mean that the mechanism for the loss of optical activity is something different than this, one ought to realize that if, with these very reactive sulfides, conditions are such that a significant portion of the sulfide is tied up at equilibrium as $\oplus R_2S-SPh$, one could well get just this sort of result, because the actual concentration of free sulfide will be significantly lower than the stoichiometric concentration of sulfide used in calculating k_S^a . That a large fraction of the total sulfide might be tied up under these conditions is particularly likely because of the very low (10^{-5} to 10^{-6} M) concentration of sulfide and much higher (0.05 M) concentration of thiolsulfinate used in the runs with the very reactive sulfides.

Table 16. Comparison of the Second-Order Rate Constants for the Sulfide-Catalyzed Reactions of Thiolsulfinate for the More Reactive Sulfides. ^a

Sulfide	$k_S^a, \underline{M}^{-1} \text{sec}^{-1}{}^b$	$k_S, \underline{M}^{-1} \text{sec}^{-1}{}^c$	$k_d, \underline{M}^{-1} \text{sec}^{-1}{}^d$
Tetrahydrothiophene	250	370	1.2
Ethyl	130	200	0.67
<u>n</u> -Butyl	140	170	0.85

^aAll runs at 40° in acetic acid-0.1 M sulfuric acid-0.56 M water.

^bSee Table 12 page 66.

^cReference 31, Table VI, p. 3561.

^dReference 62, Appendix 2, p. 134-135.

Fortunately there is a relatively easy way to test whether the explanation just given is the correct one for the lower values of k_S^a than k_S . Sulfenic acid is a good scavenger for R_2S-SPh (see Introduction and sections on thiolsulfinate-mercaptan reaction), and therefore addition of sulfenic acid should lead to conditions where k_S^a is once again at least equal to k_S , since it should scavenge R_2S-SPh and increase the equilibrium concentration of sulfide. Therefore a series of runs was carried out using both the very reactive and the less reactive sulfides in which the rate of loss of optical activity was measured in the presence of added benzenesulfenic acid.

Experiments with Added Sulfenic Acid

The results of runs with added benzenesulfenic acid are given in Table 17. The $k_S^{a'}$ values are estimated from the experimental results in the table in the same manner as k_S^a in Tables 12 and 15. Comparing $k_S^{a'}$ with the corresponding k_S^a reveals that for catalysis by the very reactive sulfides $k_S^{a'}$ is somewhat greater than k_S^a (Table 17), whereas for sulfides such as benzyl and thiodipropionic acid $k_S^{a'}$ values are only slightly greater than the corresponding k_S^a value and thus very similar to k_S^a .

These results support the idea that the cause of the lower values of k_S^a for the runs (Table 15) catalyzed by very low concentrations of

very reactive sulfides is that a significant fraction of the total added sulfide is tied up as R_2S^{\oplus} -SPh.

Table 17. Kinetics of the Sulfide-Catalyzed Loss of Optical Activity of Solutions of (+) Phenyl Benzenethiolsulfinate and Added Benzenesulfinic Acid in Acetic Acid-1% Water. ^a

Sulfide	$(R_2S) \times 10^4,$ <u>M</u>	$k_a \times 10^4,$ sec-1	$k_S^{a'} = \left[\frac{k_a - k_a^o}{(R_2S)} \right]^b$
Ethyl	0.010	10.5	380
	0.030	18.5	390
	0.040	21.4	370
<u>n</u> -Butyl	0.056	20.3	240
	0.358	96.3	250
Benzyl	0.161	11.2	28
	0.104	9.5	27
	0.208	12.4	27
Thiodipropionic Acid	1.25	11.8	4.1
	2.25	15.8	4.0

^a All runs at 39.1° in acetic acid containing 0.1 M sulfuric acid and 0.56 M water. The initial concentration of the phenyl benzenethiolsulfinate in all runs is 0.01 M and for PhSO₂H it is 0.10 M.

^b k_a^o equals $6.7 \times 10^{-4} \text{ sec}^{-1}$.

Discussion

One of the primary goals of the present research was to prepare an optically active aromatic thioisulfinate in which the sole source of asymmetry would be the sulfinyl sulfur. The availability of such a compound would, of course, be of great assistance in the elucidation of mechanisms of thioisulfinate reactions. Our initial contemplated use for this compound was to examine certain aspects of the mechanism suggested for the sulfide-catalyzed disproportionation reaction. However, from a study of its racemization under related conditions it became apparent that study of the racemization of such an optically active thioisulfinate could also provide quantitative data on the relative reactivity of some common nucleophiles toward sulfinyl sulfur. The results of these various investigations will now be discussed beginning with the method employed to prepare (+) phenyl benzenethioisulfinate.

The Asymmetric Synthesis of (+) Phenyl Benzenethioisulfinate

Thioisulfates, as was mentioned in the Introduction, can be prepared by a number of methods. They can be obtained from the hydrolysis of sulfinyl halides, from the coupling of a sulfinyl chloride and a mercaptan, and by the mono oxidation of a disulfide. Of these reactions only the last two held promise for the preparation of an

optically active thiolsulfinate. Since an optically active sulfinyl chloride was not known and because the asymmetric oxidation of unsymmetrical sulfides was a known procedure for the preparation of optically active sulfoxides, we decided to employ the asymmetric oxidation of a disulfide as our method. As the results indicate, the procedure is successful, and optically active phenyl benzenethiolsulfinate can be obtained in good yield, albeit in low optical purity, from this synthetic route. This mildly stereoselective synthesis of aromatic thiolsulfinate was also observed quite independently by Fava and his coworkers (51) in their laboratory. This group studied the purely thermal racemization of (+) aromatic thiolsulfinate and also the racemization as catalyzed by nucleophiles alone in aprotic solvents. Their results will be examined later together with our findings on the nucleophile and acid catalyzed racemization in protic solvents.

Fava and coworkers (50) have determined the absolute configuration and the optical purity of the (+) phenyl benzenethiolsulfinate resulting from this synthetic procedure. They have also extended the asymmetric oxidation to other sulfinyl compounds, such as sulfenic esters and sulfenamides, and have prepared optically active sulfinate esters and sulfinamides.

The successful preparation of an optically active thiolsulfinate has been made available a new tool with which thiolsulfinate reactions

can be studied. The method used for the preparation appears to be a general synthetic route to optically active sulfoxides, thioisulfinates, and sulfinic esters.

The Nucleophile and Acid Catalyzed Racemization of
(+) Phenyl Benzenethiolsulfinate in 60% Dioxane

The racemization of (+) phenyl benzenethiolsulfinate by the cooperative efforts of acidic and nucleophilic catalysts in 60% dioxane has produced some very interesting results pertaining to the reactivity of various nucleophiles in displacements at the sulfenyl sulfur atom of thioisulfinates. We shall first discuss those results pertinent to the mechanism of this racemization.

Racemization Mechanism

Investigation into the mechanism of the acid and nucleophile catalyzed racemization of (+) phenyl benzenethiolsulfinate has demonstrated that the formal kinetics can be represented by the following equation:

$$k_a - k_a^0 = k_{\text{Nu}}'' (\text{Nu}) (\text{H}^{\oplus})$$

Any mechanism proposed must be compatible with this relationship and accommodate the following additional facts: (1) In the presence of acidic and nucleophilic catalysts the racemization of (+) phenyl

benzenethiolsulfinate is the only reaction observed. However, if sulfinic acid or mercaptan is also present, one observes a reaction involving the disappearance of thiolsulfinate, and the formal kinetics and rates of these reactions are exactly the same as those for the racemization of (+) phenyl benzenethiolsulfinate under the same reaction conditions; this shows that all three reactions have the same rate-determining step. (2) All three reactions exhibit a similar dependence on strong acid concentration, and the racemization reaction has been shown to be specific acid catalyzed, as evidenced by the solvent kinetic isotope effect of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.54$ for catalysis by n-butyl sulfide.

The common rate-determining step indicates that the initial stages of the racemization involve the same steps as the acid and nucleophile catalyzed thiolsulfinate-sulfinic acid reaction or the thiolsulfinate-mercaptan reaction. This suggests the mechanism for the racemization reaction is as shown in Chart IX.

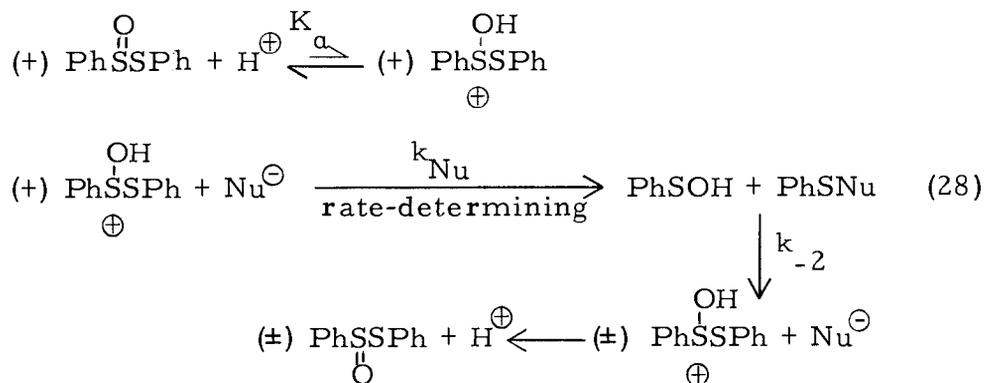


Chart IX

In this mechanism the rate-determining step involves attack by the nucleophilic catalyst on the sulfenyl sulfur of the protonated thiolsulfinate. The intermediates formed by this step, PhSOH and PhSNU, return via k_{-2} to form racemic thiolsulfinate. If sulfinic acid or mercaptan is present the intermediates are captured by these reagents and prevented from returning to thiolsulfinate. A more complete mechanistic picture of the racemization and the reactions with sulfinic acid and mercaptan is presented in Chart X.

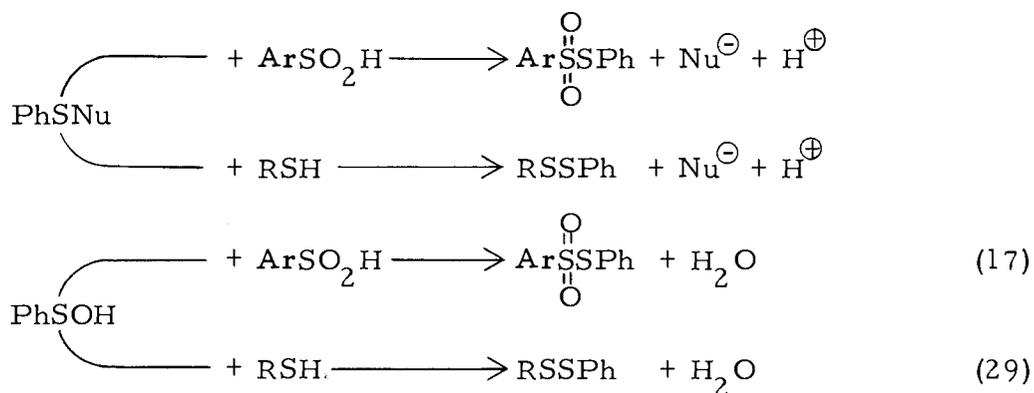
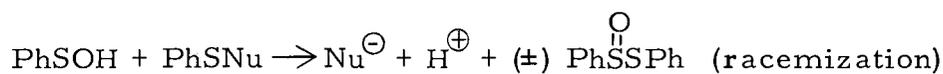
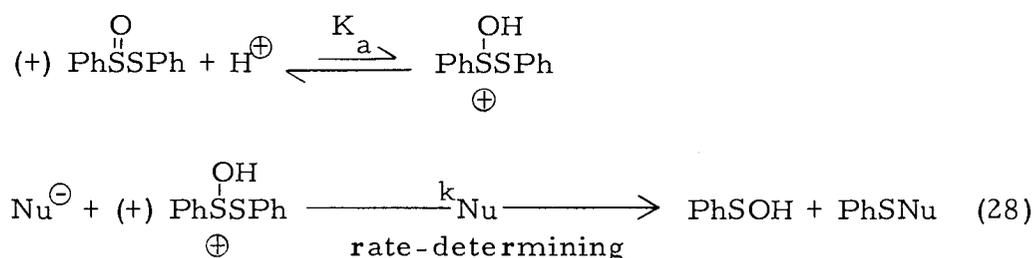


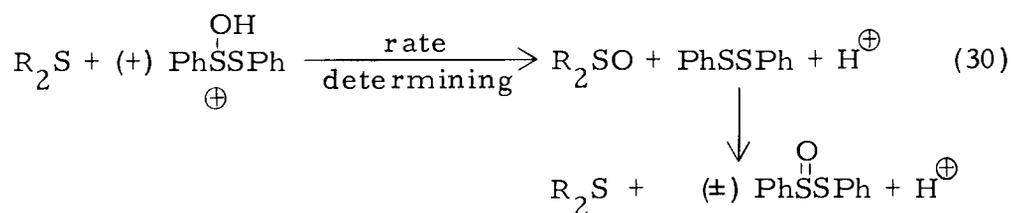
Chart X

This mechanism is completely compatible with the earlier mechanisms suggested for the sulfide-catalyzed reactions with sulfinic acid or mercaptan. Since the racemization rate and sulfinic acid (or mercaptan) reaction rates are identical for a given set of conditions, there is essentially no return (step k_{-2}) involving PhSOH and PhSNU to form protonated thiolsulfinate and nucleophile when sulfinic acid or mercaptan is present. The ability of these reagents to compete so successfully with PhSOH for the capture of PhSNU is believed to be due largely to the fact that they are always present in much greater concentration than PhSOH. It is not known for certain just how PhSOH is converted to products in the sulfinic acid or mercaptan reactions. Thus sulfenic acid may react directly with sulfinic acid or mercaptan (equations 17 and 29) or alternatively, sulfenic acid could be converted to PhSNU by the reaction given in equation 14, and PhSNU would then react rapidly with sulfinic acid or mercaptan.

While the mechanism in Chart X is completely compatible with all of the experimental data and with our previous conclusions regarding the mechanisms of the sulfide-catalyzed reactions of thiolsulfinate with mercaptan or sulfinic acid, alternative mechanisms for the racemization and the other reactions were explored. These mechanisms differed from each other in such matters as the point of nucleophilic attack and the site of protonation on the thiolsulfinate. Each of these alternative mechanisms was unacceptable for one or a

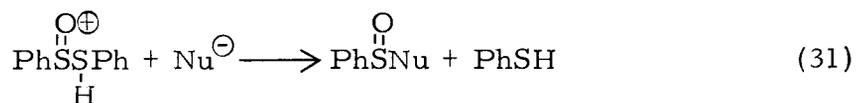
number of reasons and a brief discussion of the causes of their rejection is worthwhile.

One alternative mechanism involves nucleophilic attack at the oxygen atom of the protonated thioisulfinate, producing optically inactive sulfoxide and disulfide, equation 30.



Reoxidation of the disulfide would result in racemic thioisulfinate. The results of an independent experiment carried out in this laboratory³ eliminated this possibility by showing that an acidic solution of alkyl sulfoxide is incapable of oxidizing phenyl disulfide.

The other mechanisms considered and rejected featured nucleophilic attack on the sulfinyl sulfur. The rate-determining step of one of these mechanisms is shown in equation 31. This

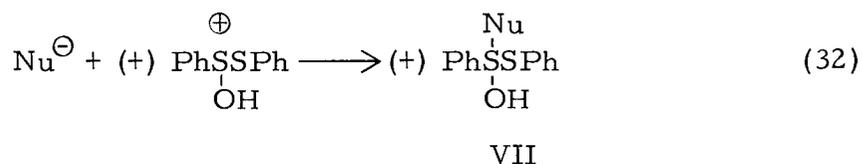


mechanism was rejected because it involves the formation of thiophenol, and if thiophenol were produced under these circumstances one would observe disulfide formation in the sulfide-catalyzed

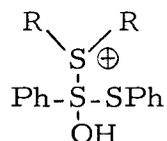
³Dr. Clifford G. Venier, unpublished results.

sulfinic acid-thiolsulfinate reaction. Such a mechanism also cannot explain the acid and nucleophile catalyzed disappearance of the thiol-sulfinate in the presence of added mercaptan, since the $\text{PhS}^{\ominus}\text{Nu}$ formed in equation 31 would be expected to react rapidly with the added mercaptan simply to regenerate thiolsulfinate.

Another mechanism involving attack at sulfinyl sulfur has as its rate-determining reaction that shown in equation 32.

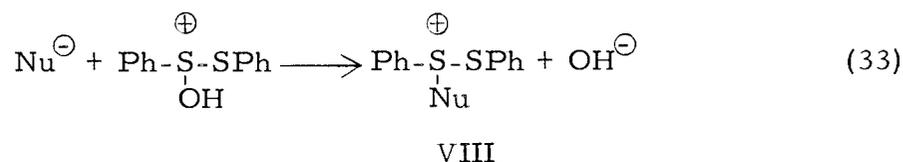


For this reaction to be rate-determining in the catalyzed reactions with sulfinic acid or mercaptan, one would have to assume: (1) that the attack of sulfinic acid (or mercaptan) at the sulfenyl sulfur atom of VII occurs more rapidly than the corresponding reaction with protonated thiolsulfinate; (2) that reaction of sulfinic acid (or mercaptan) with VII occurs more rapidly than VII returns to nucleophile and protonated thiolsulfinate. In order for the first assumption to be correct one would have to propose that $\text{Ph} \overset{\text{Nu}}{\underset{\text{OH}}{\text{S}}}$ would be a better leaving group than $\text{Ph} \overset{\oplus}{\underset{\text{OH}}{\text{S}}}$. This seems extremely unlikely. For this mechanism under sulfide catalysis the intermediate VII would be

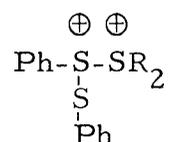


and it seems very improbable that this intermediate would react faster with sulfinic acid or mercaptan than it would revert to protonated thiolsulfinate and sulfide.

One more alternative mechanism can be proposed involving nucleophilic attack at sulfinyl sulfur. This mechanism would have for its rate-determining step the direct displacement of OH^\ominus by the nucleophile as shown in equation 33. Such a reaction is extremely



unlikely for several reasons. First, in a reaction of this kind PhS^\ominus would be expected to be displaced more readily than OH^\ominus , for the reason that PhS^\ominus is by far the better leaving group. Second, under alkyl sulfide catalysis the intermediate VIII would correspond to



an energetically very unfavorable intermediate.

Nucleophilicity of Some Common Nucleophiles Toward Sulfenyl Sulfur

Since we have now shown that the mechanism in Chart IX is almost certainly the correct one for the racemization of (+) phenyl

benzenethiolsulfinate, study of the racemization should provide quantitative information on the reactivity of various nucleophiles towards the sulfenyl sulfur atom of thiolsulfinate. One will recall that for each nucleophile studied we have plotted values of k'_{Nu} against the acid concentration (Figures 9-13); the slopes of these plots give k''_{Nu} for each nucleophile. In terms of the mechanism in Chart IX k''_{Nu} is equal to $k_{\text{Nu}} K_a$. Values of $k_{\text{Nu}} K_a$ for the acid and nucleophile catalyzed racemization of (+) phenyl benzenethiolsulfinate are shown in first column of Table 18. Since K_a refers to the equilibrium involving protonation of thiolsulfinate, it is the same for all the nucleophile catalyzed racemizations. Therefore, the ratio of k''_{Nu} values provides a direct measure of the relative reactivity of two nucleophiles towards the sulfenyl sulfur of the protonated thiolsulfinate. The second column of Table 18 shows $(k_{\text{Nu}}/k_{\text{Cl}})$ for all of the nucleophiles studied.

Recently from a study of the catalysis of the hydrolysis of aryl sulfinyl sulfones Kice and Guaraldi (27) obtained quantitative information on the relative reactivity of some common nucleophiles toward sulfinyl sulfur in 60% aqueous dioxane. The actual reaction used to measure these rates is shown in equation 34.

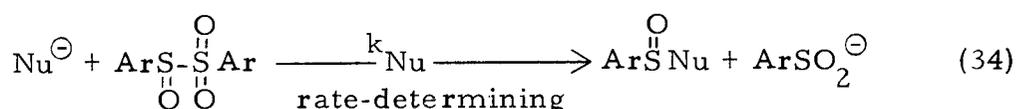


Table 19 gives $(k_{\text{Nu}}/k_{\text{Cl}})$ values derived from this study as well as those derived from the present study on the substitution at sulfenyl sulfur.

Table 18. Nucleophilic Reactivity Toward Sulfenyl Sulfur in Protonated Thiolsulfinate.^a

Nucleophile	$k_{\text{Nu}}'' = k_{\text{Nu}} K_a, \text{ M}^{-2} \text{ sec}^{-1}$	$(k_{\text{Nu}}/k_{\text{Cl}})$
Cl^-	0.0057	(1.0)
Br^-	0.20	35
SCN^-	31	5.4×10^3
I^-	78	1.4×10^4
$\underline{n}\text{-Bu}_2\text{S}$	4.7	8.2×10^2

^a All data in 60% dioxane at a constant ionic strength of 0.50.

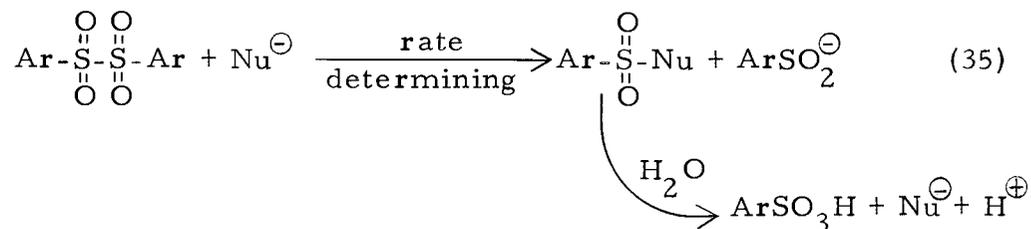
Table 19. Relative Nucleophilicity of Some Common Nucleophiles Toward Sulfenyl and Sulfinyl Sulfur.^a

Nucleophile	$(k_{\text{Nu}}/k_{\text{Cl}})$	
	Substitution at Sulfenyl Sulfur	Substitution at ^b Sulfinyl Sulfur
Cl^-	(1.0)	(1.0)
Br^-	35	5.3
SCN^-	5.4×10^3	13
I^-	1.4×10^4	90

^a All data in 60% dioxane.

^b Reference 27, Table I, p. 6137.

Substitution at sulfonyl sulfur is currently being investigated in this laboratory.⁴ Preliminary studies involving the nucleophile catalyzed hydrolysis of α -disulfones (equation 35) reveal



that in 60% dioxane only the very basic (hard) nucleophiles such as fluoride ion are effective catalysts for this reaction. This can be demonstrated by comparing the second-order rate constants obtained from the substitutions at sulfonyl and sulfinyl sulfur in 60% dioxane, see Table 20. Chloride and bromide ions are such poor catalysts for the hydrolysis of the α -disulfone that their reactivity in reaction 35 cannot be measured accurately. However, from the limited information given in Table 20 one can recognize that nucleophilic reactivity towards sulfonyl sulfur is quite different from that exhibited toward sulfinyl sulfur.

⁴Mr. George J. Kasperek, unpublished results.

Table 20. Nucleophilic Reactivity Toward Sulfinyl and Sulfonyl Sulfur in 60% Dioxane.

Nucleophile	$k_{\text{Nu}}^a, \text{ M}^{-1} \text{ sec}^{-1}$	
	Substitution at Sulfinyl Sulfur	Substitution at Sulfonyl Sulfur ^b
F^-	4.0	5.8
CH_3COO^-	9.0	0.15
Cl^-	12	-- ^c
Br^-	64	-- ^c

^a Reference 27, Table 1, p. 6137.

^b G. J. Kasperek, unpublished results.

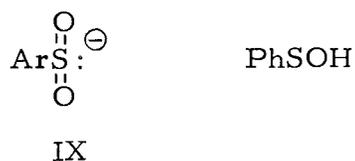
^c Too slow to measure accurately.

Comparing the data for substitutions at sulfenyl, sulfinyl, and sulfonyl sulfur one notices (1) that highly polarizable, weakly basic nucleophiles like iodide and thiocyanate, are much more reactive compound to chloride in the substitution at sulfenyl sulfur than in the one at sulfinyl sulfur (see Table 19) and (2) that the nonpolarizable nucleophiles like fluoride and acetate are much more reactive compared to chloride in the substitution at sulfonyl sulfur than they are in the one at sulfinyl sulfur (see Table 20). In the Theory of Hard and Soft Acids and Bases (HSAB) chloride ion is considered to be a borderline base, being neither very hard nor very soft. The highly polarizable nucleophiles like iodide or thiocyanate are considered much "softer" Lewis bases than chloride, and the nonpolarizable and basic

nucleophiles like fluoride or acetate are considered to be much "harder" Lewis bases than chloride. HSAB predicts that the softest Lewis base will react with particular advantage with the softest Lewis acid and similarly that the hardest Lewis base will react with advantage with the hardest Lewis acid. Sulfenyl sulfur would therefore be classified as a softer Lewis acid (or electrophile) than sulfinyl sulfur from the information given in Table 19, and sulfonyl sulfur would be classified as a harder Lewis acid (or electrophile) than sulfinyl sulfur from the information given in Table 20. Therefore, we can conclude that ArS^{\oplus} , ArS^{\oplus} , and ArS^{\oplus} represent a series of electrophiles of increasing hardness. This order of increasing hardness is in accord with what one would expect. Each covalent bond to oxygen decreases by one the number of unshared pairs of outer shell electrons on sulfur, thus decreasing the number of easily excited outer electrons. Easily excited outer shell electrons are one of the characteristics which are particularly prone to make an electrophilic center soft.

Pearson and Songstad (45) have suggested that having a soft base as a leaving group will make a given center more reactive toward soft nucleophiles. They call an effect of this kind a "symbiotic effect." In the present substitutions involving sulfenyl sulfur (equation 28) and sulfinyl sulfur (equation 34) or sulfonyl sulfur (equation 35), the leaving groups are PhSOH in the first case and

ArSO_2^\ominus in the last two cases. These should not differ very much in their softness and, if anything, ArSO_2^\ominus should be softer than PhSOH . The softness of a base, as Saville⁵ has pointed out, is determined in large measure by its possessing vacant orbitals of fairly low energy which may overlap with filled orbitals of a (soft) acid, or electrophile, to generate a π -bond, thereby contributing to over-all acid-base bonding. In a sulfinate ion acting through sulfur as the nucleophilic site (IX) the sulfur 3d orbitals should be energetically

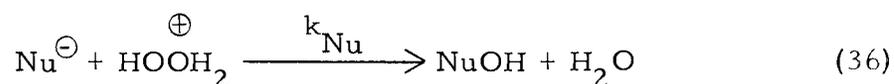


more accessible by virtue of the formally higher oxidation state than they would be in the sulfenic acid wherein sulfenyl sulfur experiences only a slight inductive effect of a σ -bonded oxygen. The significance of this conclusion with regard to the present data on substitution at sulfenyl and sulfinyl sulfur in Table 19 is that a symbiotic effect cannot be responsible for the enhanced reactivity of soft nucleophiles toward the sulfenyl sulfur of protonated thiolsulfinate. Thus sulfenyl sulfur is indeed a softer electrophilic center than sulfinyl sulfur, and, of course, very much softer than sulfonyl sulfur.

Peroxide oxygen is one electrophilic center which has been

⁵Dr. Brian Saville, private communication.

classified as being quite soft, and, according to Edward's (15) earlier prediction, should be a softer electrophilic center than sulfenyl sulfur. However, a comparison of his data (last column of Table 21) on the acid catalyzed reaction of nucleophiles with hydrogen peroxide in aqueous solution (equation 36) with the



$(k_{\text{Nu}}/k_{\text{Cl}})$ values for sulfenyl sulfur as given in the first column in Table 21 reveals that in response to changes in softness of the nucleophiles the two centers behave in essentially the same fashion.

Table 21. Relative Reactivity of Nucleophiles in Substitutions at Sulfenyl Sulfur and Peroxide Oxygen.

Nucleophile	$(k_{\text{Nu}}/k_{\text{Cl}})$	
	Substitution at ^a Sulfenyl Sulfur	Substitution at ^b Peroxide Oxygen
Cl^-	(1.0)	(1.0)
Br^-	35	2.8×10^2
SCN^-	5.4×10^3	5.0×10^2
I^-	1.4×10^4	2.0×10^5
R_2S	8.2×10^2 ^c	4.6×10^2 ^d

^a Solvent, 60% dioxane.

^b Reference 15, Table V, p. 79; solvent, water.

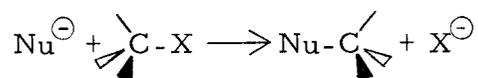
^c R_2S is n-butyl₂S

^d R_2S is $(\text{HOCH}_2\text{CH}_2)_2\text{S}$.

While this information represents a comparison of data obtained in two different solvent systems (i. e. , water and 60% dioxane) we believe that both are sufficiently aqueous solvents that no large solvent effect is introduced into the two sets of $(k_{\text{Nu}}/k_{\text{Cl}})$. Consequently, sulfenyl sulfur is suggested to be about as soft an electrophilic center as peroxide oxygen, and therefore softer than had been previously predicted.

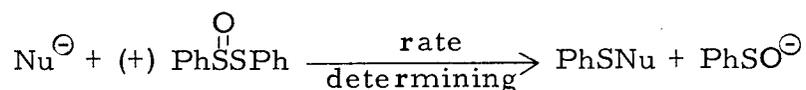
Effect of Solvent on the Nucleophile Reactivity Toward Sulfenyl Sulfur

Parker (40-42) was the first to note that the transfer of a nucleophilic substitution reaction of the following type involving sp^3 carbon



from a protic to a dipolar aprotic solvent was accompanied by a large increase in rate. Since the magnitude of the rate increase is much larger for nucleophiles which are hard bases than for those which are soft bases, this transfer to the aprotic solvent also results in a change from the usual order of nucleophilic reactivity found for a series of common nucleophiles in a substitution in protic solvents. Thus in a protic solvent such as water one finds that the order of reactivity is $\text{I}^- > \text{SCN}^- > \text{Br}^- > \text{Cl}^- \gg \text{F}^-$, but in dimethyl sulfoxide or dimethyl formamide the order becomes $\text{F}^- > \text{Cl}^- > \text{Br}^- > \text{I}^- > \text{SCN}^-$.

Combination of the present data with some which has been obtained by Fava and Koch⁶ shows that this reversal of the order of nucleophilic reactivity is also found for a substitution at sulfenyl sulfur on going from a protic to a dipolar aprotic solvent. Fava and Koch have studied the nucleophile-catalyzed racemization of (+) phenyl benzenethiolsulfinate in anhydrous acetone. Their results suggest that the rate-determining step for this reaction is



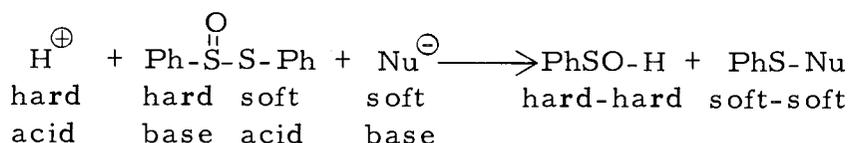
Their data indicate that in this reaction the order of nucleophilic reactivity is $\text{Cl}^- > \text{Br}^- > \text{I}^- > \text{SCN}^-$ which is, of course, very different from the pattern of $\text{I}^- > \text{SCN}^- \gg \text{Br}^- \gg \text{Cl}^-$ found for the substitution at sulfenyl sulfur in 60% dioxane.

The Electrophilic and Nucleophilic Catalysis of the Scission of the Sulfur-Sulfur Bond in Thiolsulfates

Kice and coworkers (24, 26, 28, 30, 31) have shown that many reactions involving the scission of sulfur-sulfur bonds can be dramatically catalyzed by the cooperative efforts of an electrophile and nucleophile. The results, as presented in this Thesis, on the sulfide-catalyzed mercaptan-thiolsulfinate reaction and the nucleophile and

⁶Dr. A. Fava and Dr. P. Koch, private communication.

These principles can be extended to include the concomitant electrophilic and nucleophilic catalysis of the cleavage of the sulfur-sulfur bond in thiolsulfinate. Acknowledging that the sulfenyl sulfur is a soft electrophilic center, the sulfinyl group can be assigned the role of a hard base in which the oxygen atom is the basic site. Therefore, thiolsulfinate would represent a dissymmetric substrate catalyzed in accord with the second rule. Thus a hard acid-soft base combination would produce a particularly favorable situation for the sulfur-sulfur bond cleavage as indeed seems to be the case.



The Utilization of (+) Phenyl Benzenethiolsulfinate in the Sulfide-Catalyzed Disproportionation Reaction

The availability of an optically active aromatic thiolsulfinate has enabled us to test the probable correctness of some of the aspects of the mechanism suggested by Venier (62) for the sulfide-catalyzed disproportionation reaction in moist acetic acid. This has been done by determining the rate of loss of optical activity of (+) phenyl benzenethiolsulfinate under the same conditions as those previously used to study both the sulfide-catalyzed disproportionation and the sulfide-catalyzed sulfinic acid-thiolsulfinate reaction.

The mechanism suggested for the sulfide-catalyzed

disproportionation reaction, previously shown in Chart III, is rewritten below.

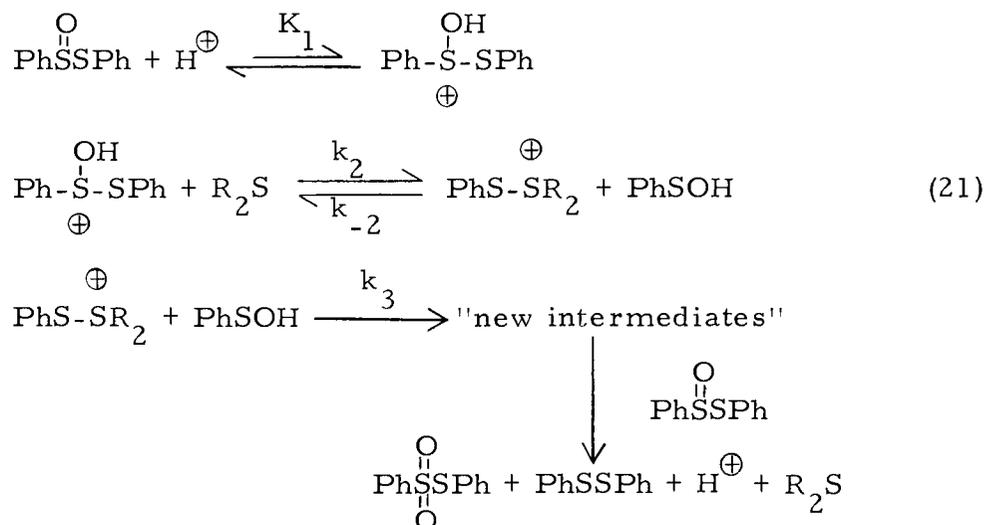


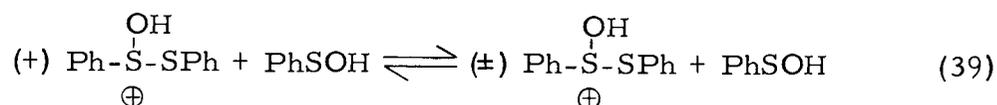
Chart III

One will recall that we have postulated for sulfides such as benzyl and n-butyl $k_{-2} \gg k_3$; therefore, one would expect that almost every occurrence of a k_2 event forming $\overset{\oplus}{\text{PhS-SR}_2}$ and PhSOH under such sulfide catalysis would be followed by the return of these species to sulfide and protonated thioisulfinate (step k_{-2}), rather than by their reaction via k_3 . This would lead, as is observed, to the rate of such sulfide catalyzed disproportionations being very much slower than the corresponding sulfide-catalyzed reactions of thioisulfinate with sulfinic acid, where k_2 is rate-determining. Since the return of $\overset{\oplus}{\text{PhS-SR}_2}$ and PhSOH via the k_{-2} step must yield racemic thioisulfinate, one would expect that optically active thioisulfinate would be racemized

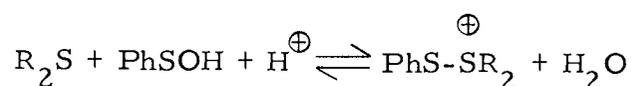
under sulfide and strong acid conditions in moist acetic acid at a rate that is much greater than the sulfide-catalyzed disproportionation rate (k_d). And, as is stated in the Introduction, since k_2 would be rate-determining for this racemization, its rate (k_S^a) should be the same as the rate of the sulfide-catalyzed sulfinic acid-thiolsulfinate (k_S) under the same reactions conditions.

Under sulfide catalysis by sulfides such as benzyl and thiodipropionic acid, the rate of loss of optical activity varied with strong acid concentration in the same fashion as the rates of the other sulfide-catalyzed reactions of thiolsulfinates in moist acetic acid. At high sulfide concentrations k_S^a and k_S for each of these sulfides are, within experimental error, the same. These results suggest that for these sulfides the sulfide-catalyzed loss of optical activity and the sulfide-catalyzed thiolsulfinate-sulfinic acid reaction involve the same mechanism up through the rate-determining step. This conclusion confirms the reversibility of the k_2 step in the mechanism suggested for the sulfide-catalyzed disproportionation reaction. At low sulfide concentrations k_S^a for either of these sulfides becomes somewhat larger than k_S , the difference being larger the lower the sulfide concentration. This suggests that there is an additional pathway for the loss of optical activity beyond that expected from the mechanism given in Chart III and that this additional racemization pathway can be suppressed by increasing the sulfide concentration.

The most likely possibility for this "extra" racemization reaction would be an exchange type of reaction between sulfenic acid formed by the k_2 step (equation 21) and the sulfinyl protonated thiolsulfinate, equation 39. Added sulfide should decrease



the availability of sulfenic acid to participate in such a reaction by converting it to $\text{R}_2\text{S}^{\oplus}-\text{SPh}$ according to the following equilibrium.



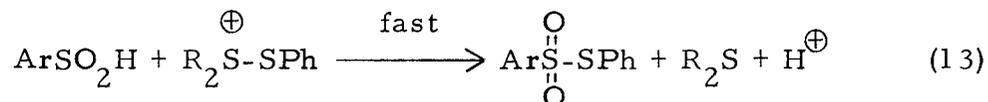
The reaction rates for the sulfide-catalyzed disproportionation (k_d) and the sulfide-catalyzed thiolsulfinate-sulfenic acid reaction (k_S) have been observed by Venier to be quite similar under sulfide catalysis using phenyl sulfide or thiodiglycolic acid. Kice and Venier have suggested that in the case of these very unreactive sulfides $k_{-2} < k_3$ in Chart III, so that k_2 is rate-determining for both sulfide-catalyzed disproportionation and reaction of thiolsulfinate with sulfenic acid; hence the close relationship between k_d and k_S . Using phenyl sulfide to catalyze the loss of optical activity we have found k_S^a to be identical to k_d , within the experimental uncertainty of k_S^a ($k_d = 0.016 \text{ M}^{-1} \text{ sec}^{-1}$ (62, Appendix 2, p. 134), $k_S^a = 0.017 \text{ M}^{-1} \text{ sec}^{-1}$). Thus under catalysis by phenyl sulfide there does not appear to be any extra racemization of the sort that occurs with benzyl sulfide

or thiodipropionic acid at low sulfide concentration.

With the sulfides tetrahydrothiophene, ethyl sulfide, or n-butyl sulfide k_S^a is considerably smaller than k_S . If, as we have just concluded from the results obtained for the less reactive sulfides, the k_2 step (equation 21) is rate-determining in the sulfide-catalyzed loss of optical activity, k_S^a should never be less than k_S . However, as was noted earlier, there is good reason to believe that the low k_S^a values in the case of such sulfides as ethyl or n-butyl are due to the fact that actually a significant portion of the sulfide is present at equilibrium in these particular systems as R_2S-SPh . As a result only a small fraction of the stoichiometric amount of sulfide is present as such and k_S^a values calculated using $k_a - k_a^0 / (R_2S)$ will be in error and too low since the true concentration of sulfide is considerably smaller than (R_2S) . The reason that such a large fraction of sulfide is present as R_2S-SPh under such conditions, despite the fact that K_1 is presumably quite small, is due to the fact that the concentration of thiolsulfinate is so much larger (0.05 M) than the concentration of the sulfide (10^{-5} - 10^{-6} M).

The results obtained for the sulfide-catalyzed loss of optical activity in the presence of benzenesulfinic acid provide strong evidence that the k_S^a values observed with sulfides such as n-butyl or ethyl are indeed smaller than k_S because a significant fraction of the total added sulfide is tied up as R_2S-SPh . Benzenesulfinic acid is

known to react very rapidly with R_2S^{\oplus} -SPh to give thiolsulfonate and sulfide, equation 13. In the presence of added sulfinic acid,



therefore, the amount of sulfide present as R_2S should be very close to the stoichiometric concentration of added sulfide. As predicted, one finds that for the n-butyl or ethyl sulfide catalyzed reactions that the rate constant for loss of optical activity in the presence of benzenesulfinic acid ($k_S^{a'}$) is much larger than k_S^a (and in fact appears to be somewhat larger even than k_S) whereas the $k_S^{a'}$ values obtained under such conditions with sulfides such as benzyl sulfide and thiodipropionic acid are essentially the same as k_S^a .

The data on the sulfide-catalyzed loss of optical activity of (+) phenyl benzenethiolsulfinate in moist acetic acid can therefore all be interpreted in terms of the basic mechanism proposed for the sulfide-catalyzed disproportionation plus certain additional features which seem quite in accord with what one might expect of such systems under appropriate conditions. The results obtained in this study definitely support the idea that the k_2 step in Chart III is reversible. They also suggest that the formal mechanistic scheme proposed for the sulfide-catalyzed disproportionation reaction in Chart III is probably correct, but unfortunately they cast no light on the exact nature of the k_3 step.

EXPERIMENTS DESIGNED TO DETECT RADICAL
INTERMEDIATES IN THE SULFIDE-CATALYZED
DISPROPORTIONATION REACTION

One additional goal of the present research was to carry out experiments designed to determine whether or not radical intermediates are formed in the sulfide-catalyzed disproportionation of thiolsulfinates in moist acetic acid. Two techniques were employed. First, an esr spectrum was run on a fairly concentrated solution of the reaction mixture. Second, an efficient electron transfer agent was added to the reaction solution to see if its presence would have any effect on the rate of disappearance of thiolsulfinate in the sulfide-catalyzed disproportionation.

Electron Paramagnetic Resonance Studies

A degassed solution of 0.05 M phenyl benzenethiolsulfinate containing 0.005 M n-butyl sulfide in acetic acid-0.02 M sulfuric acid-0.56 M water as solvent was scanned through the magnetic field of the Varian 5400 esr spectrophotometer. No esr signal was observed.

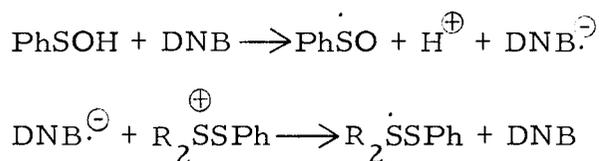
Effect of Added Electron Transfer Agent

The addition of 0.02 M m-dinitrobenzene to a solution containing 0.004 M phenyl benzenethiolsulfinate and 2.9×10^{-4} M n-butyl sulfide in acetic acid-0.2 M sulfuric acid-0.56 M water solvent at 39.6°

This mechanism involves free radicals as intermediates in a number of steps.

One method available for the detection of radicals is the direct measurement of the paramagnetism due to the unpaired electron. This technique has been reported to be sensitive to radical concentration as low as 10^{-8} M (46). The fact that no esr spectrum was observed in the sulfide-catalyzed disproportionation of a solution initially containing 0.05 M thiolsulfinate suggests that radical intermediates may not be involved in the mechanism of this reaction, although it is hardly conclusive evidence since their concentration may simply be too low to permit their detection.

The slow step in the proposed radical mechanism is the transfer of an electron from sulfenic acid to R_2SSPh^{\oplus} (the k_3 step). This suggests that the addition of a good electron transfer agent like m-dinitrobenzene (DNB) might well accelerate the rate of the sulfide-catalyzed deproportionation by providing a more rapid route for the formation of the required intermediates $Ph\dot{S}O$ and $R_2\dot{S}SPh$ thru the following pair of steps



Since there is no noticeable increase in the rate of disappearance

of thiolsulfinate in the presence of 0.02 M DNB, and since no esr signal is observed, one is led to question whether any radical intermediates are formed in the course of the sulfide-catalyzed disproportionation reaction. The present results thus suggest that the mechanism of the k_3 step is not as shown in Chart IV. At present, however, it is not clear just what it is.

Another Possibility for the Mechanism of the
Sulfide-Catalyzed Disproportionation

Two possibilities were presented in the Introduction for the k_3 step and subsequent product forming steps of the mechanism suggested for the sulfide-catalyzed disproportionation (Chart III). Besides the radical process just discussed, an ionic pathway was also proposed, Chart V.

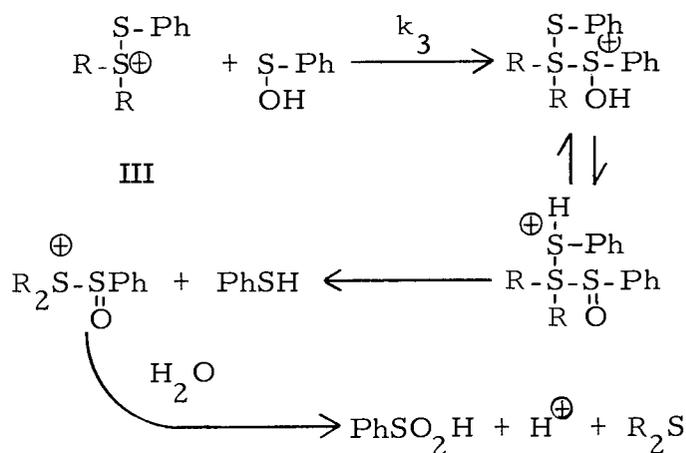
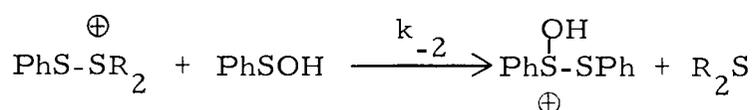


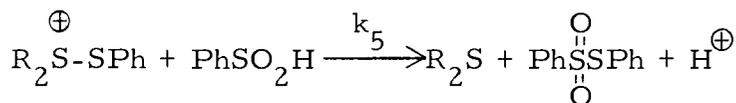
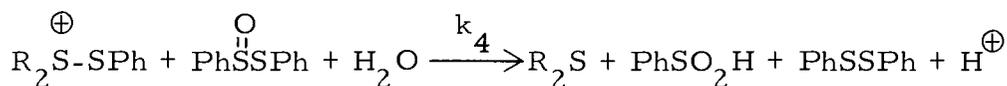
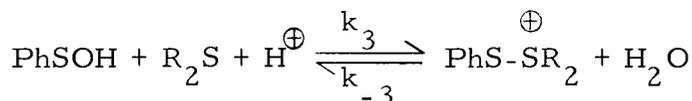
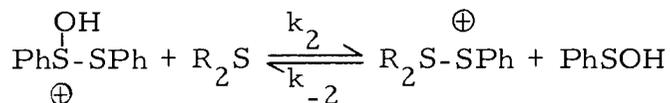
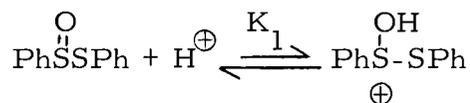
Chart V

The process described in Chart V is not recommended because of one serious drawback, which is apparent when one considers situations in which $k_{-2} < k_3$ (i. e. , catalysis by phenyl sulfide or thiodiglycolic acid). This mechanism would require sulfenic acid to attack III at the trivalent sulfur faster than it attacked the same intermediate at the sulfenyl sulfur (the k_{-2} step).



This circumstance seems to be unreasonable considering what we and others have observed concerning the rates of reaction of typical nucleophiles in substitutions at sulfenyl as compared to trivalent sulfur.

Venier (62) has suggested one other mechanism which could conceivably also lead to kinetics of the type observed for the sulfide-catalyzed disproportionation. This is shown in Chart XI.



$$\begin{aligned} \text{Rate} &= K_1 k_2 (\text{R}_2\text{S}) (\text{Ph}\overset{\text{O}}{\parallel}\text{SPh})_0 + k_4 (\text{R}_2\overset{\oplus}{\text{S}}\text{-SPh}) (\text{Ph}\overset{\text{O}}{\parallel}\text{SPh}) \\ &\quad - k_{-2} (\text{R}_2\overset{\oplus}{\text{S}}\text{-SPh}) (\text{PhSOH}) \end{aligned}$$

Chart XI

Venier has analyzed this mechanism making steady state assumptions for the concentrations of the three intermediates: the thiosulfonium ion, the sulfenic acid, and the sulfinic acid.

$$(\text{PhSO}_2\text{H})_{\text{s. s.}} = \frac{k_4 (\text{R}_2\overset{\oplus}{\text{S}}\text{-SPh}) (\text{Ph}\overset{\text{O}}{\parallel}\text{SPh})}{k_5 (\text{R}_2\overset{\oplus}{\text{S}}\text{-SPh})} = \frac{k_4}{k_5} (\text{Ph}\overset{\text{O}}{\parallel}\text{SPh})$$

$$(\text{PhSOH})_{s.s.} = \frac{K_1 k_2 (\text{R}_2\text{S}) (\text{PhSSPh})_o + k_{-3} (\text{H}_2\text{O}) (\text{R}_2\text{SSPh})^\oplus}{k_{-2} (\text{PhS}^\oplus\text{SR}_2) + k_3 (\text{R}_2\text{S})_o}$$

$$(\text{R}_2\text{S-SPh})_{s.s.}^\oplus = \frac{K_1 k_2 (\text{R}_2\text{S}) (\text{PhSSPh})_o + k_3 (\text{PhSOH})(\text{R}_2\text{S})_o}{k_{-2} (\text{PhSOH}) + 2k_4 (\text{PhSSPh}) + k_{-3} (\text{H}_2\text{O})}$$

Substituting $(\text{R}_2\text{S-SPh})_{s.s.}^\oplus$ into $(\text{PhSOH})_{s.s.}$ and solving for $(\text{PhSOH})_{s.s.}$ one obtains

$$(\text{PhSOH})_{s.s.} = \frac{k_4 (\text{PhSSPh})}{2k_{-2}} \left\{ \left[1 + \frac{4K_1 k_2 k_{-2}}{k_3 k_4} \left(1 + \frac{k_{-3}}{k_4 (\text{PhSSPh})} \right) \right]^{1/2} - 1 \right\}$$

If we also assume that $k_{-3} \ll k_4 (\text{PhSSPh})$, then expression for $(\text{PhSOH})_{s.s.}$ reduces to a constant times the thiolsulfinate concentration.

$$(\text{PhSOH})_{s.s.} = \frac{k_4 (\text{PhSSPh})}{2k_{-2}} \alpha$$

$$\text{where } \alpha = \left(1 + \frac{4K_1 k_2 k_{-2}}{k_3 k_4} \right)^{1/2} - 1$$

under such circumstances

$$\oplus \text{(R}_2\text{S-SPh)}_{\text{s.s.}} = \frac{(\text{R}_2\text{S})\text{h}_o \left[\text{K}_1 \text{k}_2 + \frac{\text{ak}_3 \text{k}_4}{2\text{k}_{-2}} \right]}{\text{k}_4 \left(2 + \frac{\text{a}}{2} \right)} = \frac{\beta (\text{R}_2\text{S})\text{h}_o}{\text{k}_4}$$

$$\text{where } \beta = \left(\frac{\text{K}_1 \text{k}_2 + \frac{\text{ak}_3 \text{k}_4}{2\text{k}_{-2}}}{2 + \frac{\text{a}}{2}} \right)$$

and

$$\text{Rate} = (\text{Ph}\overset{\text{O}}{\parallel}\text{SSPh}) (\text{R}_2\text{S})\text{h}_o \left(\text{K}_1 \text{k}_2 + \beta + \frac{\text{a}\beta}{2\text{k}_{-2}} \right)$$

Thus the mechanism of the type shown in Chart XI can lead to the kinetic behavior observed for the sulfide-catalyzed disproportionation. Venier also noted that, "in the presence of added sulfinic acid, $\text{k}_5(\text{PhSO}_2\text{H})$ becomes more important than $\text{k}_4(\text{Ph}\overset{\text{O}}{\parallel}\text{SSPh})$ for the removal of the thiosulfonium ion formed in the k_2 step," thereby accounting for the lack of disproportionation products in the presence of sulfinic acid.

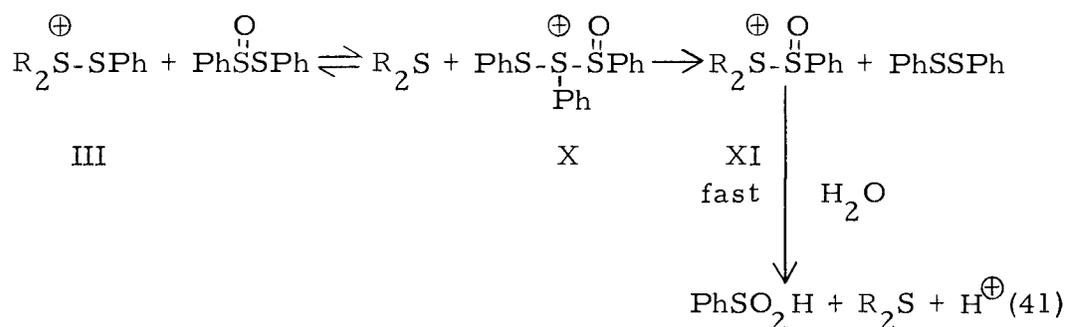
This mechanism differs from Charts IV and V by having the thiosulfonium ion (III) yield products by reacting with another molecule of thiolsulfinate instead of reacting with sulfinic acid. In this manner the thiosulfonium ion participates as a sulfenylating agent. In support of this idea, Douglass (14) has shown that thiolsulfinites can

react with good sulfenylating agents to effect a formal oxygen transfer, equation 40.



The exact nature of the mechanism of the k_4 step is not known at present. One possible representation is shown in equation 41.

Thiolsulfinate attacks the thiosulfonium ion



via a nucleophilic displacement at bivalent sulfur forming X and sulfide. The intermediate, X, then undergoes attack by sulfide either at the sulfenyl sulfur, which just regenerates III and thiolsulfinate or at the sulfinyl sulfur, which gives the disulfide and XI. The latter then hydrolysis rapidly to sulfide and sulfinic acid. Kice and Morkved (30) have shown that the intermediate, X, is formed in the sulfide-catalyzed reaction between disulfide and sulfinic acid. Its behavior in that reaction is consistent with the representation in equation 41.

In light of the fact that no direct evidence for radical intermediates was found in the sulfide-catalyzed disproportionation the preferred mechanism is Chart XI.

EXPERIMENTAL

Preparation of Materials(+) Percamphoric Acid

(+) Percamphoric acid was prepared by oxidizing (+) percamphoric anhydride (Matheson Coleman and Bell) with hydrogen peroxide following the procedure of Milas and McAlvey (37). Sodium peroxide (4.3 grams, 0.055 moles) was slowly added with stirring to 200 ml. of water at $< 5^{\circ}$. A slurry of (+) percamphoric anhydride (10 grams, 0.055 moles) and 400 ml. ethyl ether was added during a period of one hour. The mixture was allowed to stir at $< 5^{\circ}$ for an additional one hour period. The water and (+) percamphoric sodium salt solution was isolated and acidified with 25 ml. of 6 N sulfuric acid. The peracid was extracted with 200 ml. of cold chloroform. This solution was then washed with saturated aqueous ammonium sulfate, washed twice with water, and dried over anhydrous magnesium sulfate. The concentration of the final solution was determined iodimetrically (19, p. 423-425). This solution of (+) percamphoric acid was used directly in the oxidation of phenyl disulfide.

Phenyl Disulfide

Phenyl disulfide (Wateree Chemical Company, Inc.) was recrystallized from 95% ethanol and water, m. p. 61°. Literature value (56), 61.5°.

Benzenesulfinic Acid

Commercial sodium benzenesulfinate (Aldrich Chemical Company) was converted to benzenesulfinic acid by acidifying an aqueous solution with 6 N sulfuric acid following the procedure of Kice and Bowers (25). The precipitated acid was filtered, washed with cold water, and dried under reduced pressure. Recrystallization was carried out by dissolving the acid in a minimum amount of anhydrous ethyl ether and diluting with an equal amount of n-hexane, m. p. 80-83°. Literature value (10), 81.5-83°.

n-Butyl Mercaptan

n-Butyl mercaptan (Wateree Chemical Company, Inc.) was distilled and stored over nitrogen, b. p. 97°. Literature value (65), 98.1° at 765 mm.

Thioglycolic Acid

Thioglycolic acid (Eastman Organic Chemicals, analytical

grade) was distilled under reduced pressure, b. p. 116-117°C., 20 mm. Literature value (32), b. p. 107-108°C, 16 mm. The distilled acid was tared and diluted immediately with stock acetic acid-0.56 M water solution.

(±) Phenyl Benzenethiolsulfinate

Optically inactive phenyl benzenethiolsulfinate was prepared by the reaction of benzenesulfinyl chloride with thiophenol in the presence of pyridine in ether solution, following the procedure of Backer and Kloosterziel (4).

Benzyl Sulfide, Benzyl Phenyl Sulfide, and Thiodipropionic Acid

These three sulfides were obtained from Dr. Clifford G. Venier (62) as crystalline solids and were used directly without further purification.

Ethyl Sulfide

Ethyl sulfide (Matheson Coleman and Bell) distilled and stored over nitrogen, b. p. 91°. Literature value (22, Vol. 1, p. 799) 92°.

n-Butyl Sulfide

n-Butyl sulfide (Wateree Chemical Company, Inc.) distilled under reduced pressure and stored over nitrogen, b. p. 66-67°.

20 mm. Literature value (22, Vol. 1, p. 729), 182°.

Phenyl Sulfide

Phenyl sulfide (Wateree Chemical Company, Inc.) distilled under reduced pressure and stored over nitrogen, b. p. 164-166°, 20 mm.

Literature value (22, Vol. 1, p. 1044) 157-158°, 16.5 mm.

Thiodiglycolic Acid

Thiodiglycolic acid (The British Drug Houses Ltd., reagent grade) was purified by dissolving in water with activated charcoal, filtering hot, and recrystallizing twice from hot water. The crystallized solid was dried under reduced pressure and recrystallized from ethyl acetate and benzene solvent system, m. p. 129°.

Literature value (33) 129°.

Lithium Chloride, Potassium Bromide, Potassium Iodide, Potassium Thiocyanide, and Lithium Perchlorate

These five salts were obtained from Dr. Giancarlo Guaraldi. All were of analytical grade and anhydrous. They were used without further purification.

Acetic Acid

Glacial acetic acid (Baker and Adamson, reagent grade) was

refluxed for 24 hours with 10% of its volume acetic anhydride and distilled slowly through an Oldershaw bubble cap column (20 theoretical plates), reflux ratio 6:1. The purified acetic acid was collected at a boiling point range of 117.5 to 118°.

Dioxane

Dioxane (Mallinckrodt, analytical reagent) was purified according to the procedure of Wiberg (66) and stored under nitrogen.

Deuterium Oxide

Deuterium oxide (Bio·Rad Laboratories, 99.84 mole % D_2O) was used without further purification.

Stock Solutions

Acetic acid-0.56 M water solvent was prepared by adding purified acetic acid to 10.085 grams of water and diluting to one liter total volume at 20°C. Sulfuric acid (Baker and Adamson, reagent grade) 95.20% sulfuric acid, as determined by titration with standard 0.100 M NaOH, was used to prepare a 1 M sulfuric acid solution in acetic acid-0.56 M water. Water was assumed to account for the remaining 4.80%. Additional water was added to this solution in order for the water concentration to be 0.56 M. Purified acetic acid was used to dilute to final volume.

60% Aqueous dioxane solvent was prepared by adding 60 ml. of purified and dry dioxane to 40 ml. of water. The volumetric transfers were performed using appropriate volumetric pipets. Perchloric acid (J. T. Baker Chemical Company, reagent grade) 70.71% perchloric acid, as determined by titration with 0.100 M NaOH, was used to prepare a 1 M solution in 60% aqueous dioxane. This solution was prepared following the procedure of Bunton (9). A desired amount of perchloric acid was weighed out and added to a volumetric flask and a determined amount of dioxane was added volumetrically to the flask to attain a 60/40 (v/v) ratio between dioxane and water. 60% Aqueous dioxane was then added to volume.

Procedure for Kinetic Studies

Racemization Method

A desired amount of optically active phenyl benzenethiolsulfinate was weighed and brushed into a 10 ml. volumetric flask. Aliquots of acid and nucleophile in aqueous 60% dioxane or acetic acid-0.56 M water were pipetted into the flask and diluted to volume with the appropriate stock solution. Once the reactants had dissolved the solution was poured into a jacketed one decimeter polarimetric cell at 39.1°C. The rate of the reaction was then followed by recording the loss of optical activity with time using the Perkin-Elmer

141 polarimeter. All kinetic runs were made at 436 m μ .

Decomposition Method

The loss of optical density was measured directly using the Cary 15 spectrophotometer having a thermostatted cell holder. The method used was the same as outlined by Venier (62) and also Kice, Guaraldi, and Venier (29) for runs in both acetic acid-0.56 M water and 60% aqueous dioxane. The special cell shown in Figure 17 was used. The desired amount of thiolsulfinate was placed in Section A with the remaining reactants and solvent required in Section B. The sample was degassed and run under prepurified nitrogen.

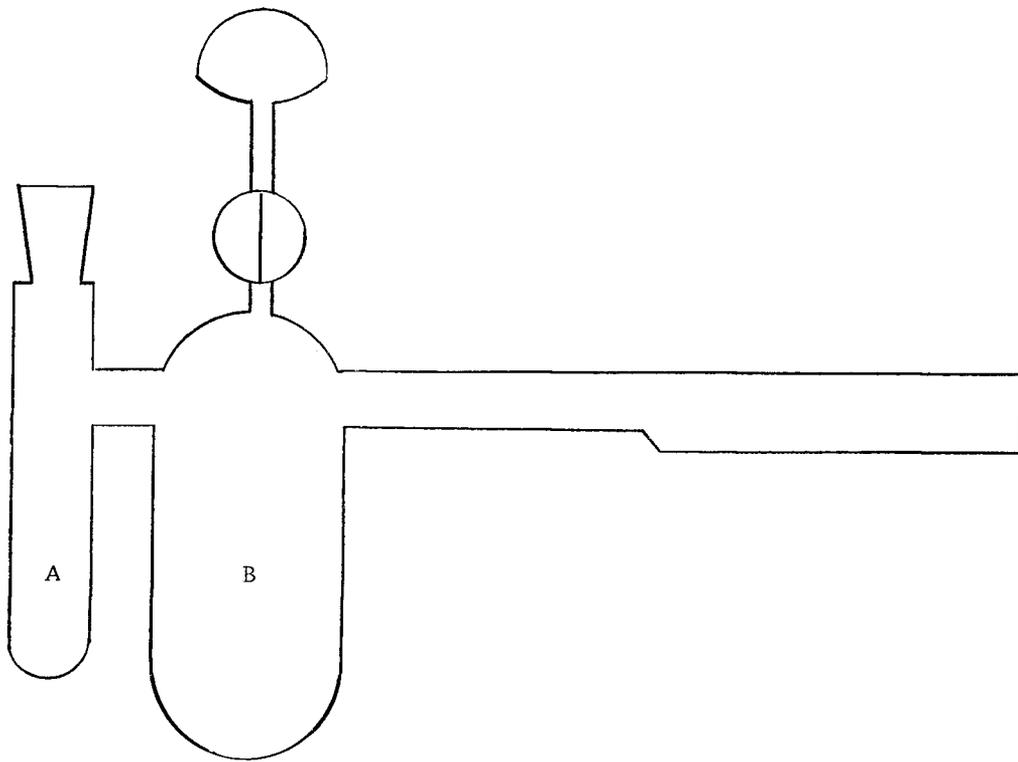


Figure 17. Special Cell for Direct Method.

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