AN ABSTRACT OF THE THESIS OF

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Title: INTRAMOLECULAR BIFUNCTIONAL CATALYSIS OF THE RACEMIZATION OF PHENYL BENZENETHIOLSULFINATE

Abstract approved: Signature redacted for privacy.
John L. Kice

Catalysis of the racemization of optically active phenyl benzenethiolsulfinate, (+)-I, by (a) methylthioacetic acid (II) and (b) α-methylthio-m-toluic acid (III) has been investigated in aqueous dioxane and anhydrous acetonitrile at 39.6°C. Added II did not cause any increase in the rate of racemization of (+)-I in either solvent. In aqueous dioxane containing added perchloric acid, III, acting solely as a nucleophile, catalyzed the racemization of (+)-I via a process that was first-order in (+)-I, first-order in perchloric acid and first-order in III but no catalysis by III alone was observed in the absence of perchloric acid in aqueous dioxane. Since the mechanism of the acid and nucleophile catalyzed racemization has been previously worked out, no attempt was made to study the third-order process further. In acetonitrile, however, (+)-I was found to undergo racemization due to catalysis by III alone. Under these conditions

the racemization followed clean second-order kinetics--first-order in (+)-I and first-order in III. Since equimolar mixtures of benzoic acid and benzyl methyl sulfide showed no catalysis of the racemization under these conditions, catalysis of the racemization by III under these conditions must involve intramolecular bifunctional catalysis. The mechanism shown in Chart I is proposed for this process and is in accord with the fact that such catalysis can be observed in acetonitrile but not in aqueous dioxane where hydrogen-bonding with the solvent greatly reduces the concentration of the key intermediate complex (+)-A. The initial necessary formation of a complex between (+)-I and III is followed by rate-determining attack by the sulfide part of III on the sulfenyl sulfur of (+)-I accompanied by the complete proton transfer from the carboxylic acid group of III to the sulfinyl group of (+)-I.

Some further aspects of the racemization of (+)-I as catalyzed by III in acetonitrile are discussed with the purpose of showing that the process is formally analogous to simple enzyme-catalyzed processes.

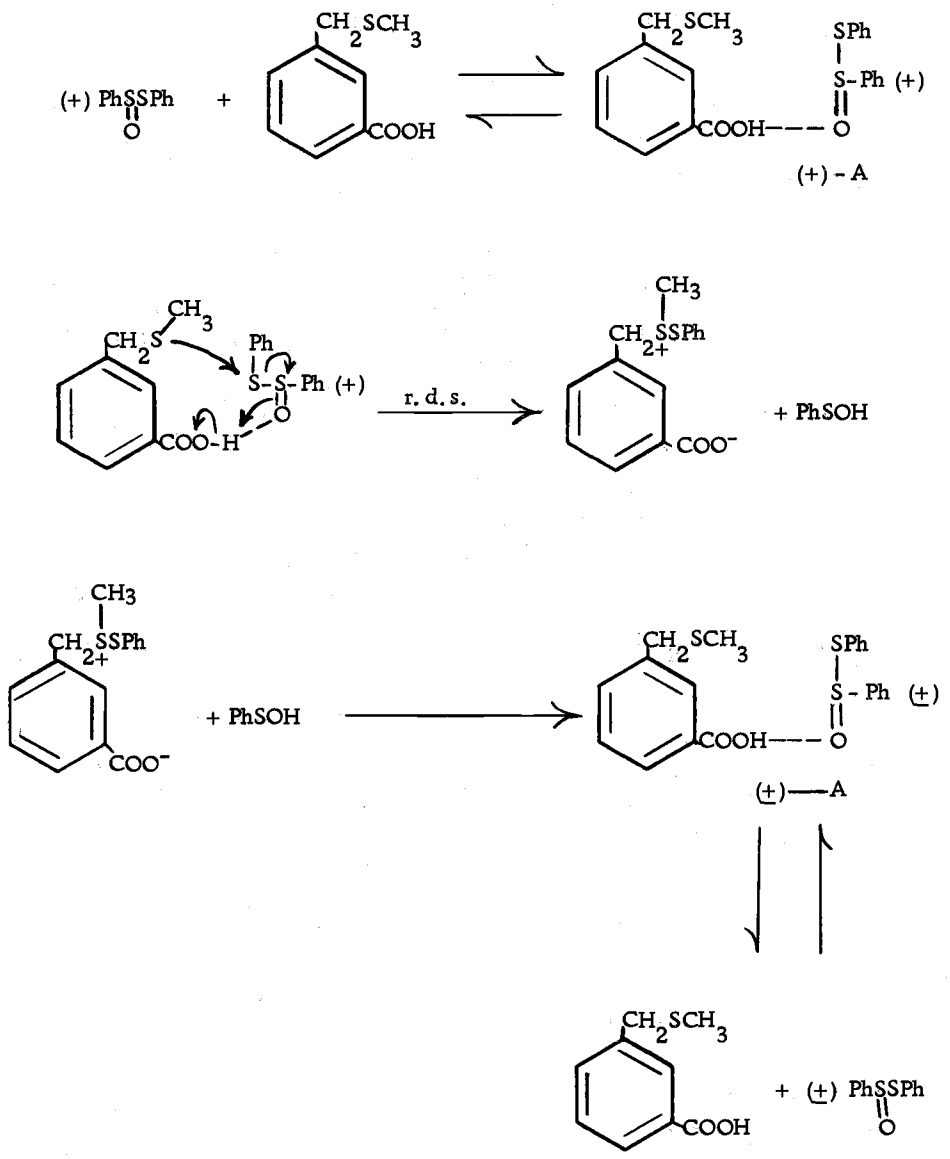

Chart I. The mechanism of the racemization of (+) phenyl benzenethiolsulfinate as catalyzed by α-methylthio-m-toluic acid in acetonitrile at 39.6°C.

Intramolecular Bifunctional Catalysis of the Racemization of Phenyl Benzenethiolsulfinate

by

Alan Lathrop Moguin

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I wish to thank Professor John L. Kice for his invaluable guidance and encouragement and all my co-workers for their friendship during the course of completing this work.

To my parents and to Judy

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INTRODUCTION

Structure of Sulfenic Anhydrides and Thiolsulfinates

Two compounds of the general formula, $R(S_2O)R$, are mentioned in the literature. The first of these is the anhydride of a sulfenic acid, RSOH, formed by the hydrolysis of a sulfenyl chloride, equation 1 (38, 39, 85 - 89), and the second of these is the ester of the hypothetical thiolsulfinic acid, RS(O)SR, called a thiolsulfinate. This latter compound can

$$(1) \qquad 2\ RSCl \longrightarrow 2(RSOH) \longrightarrow RS\text{-}O\text{-}SR + H_2O$$

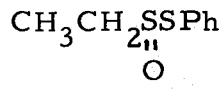
be formed either by the oxidation of the corresponding disulfide (34, 56, 65, 67, 70), equation 2, or by the coupling of a sulfinyl chloride with a mercaptan (4, 10, 77), equation 3.

$$(2) \qquad RSSR \xrightarrow{[O]} RS(=O)SR$$

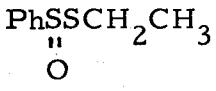
$$(3) \qquad RS(=O)Cl + RSH \longrightarrow RS(=O)SR + HCl$$

In 1957, Vinkler and Klivényi showed without a doubt that these

two types of compounds are in fact one and the same. They did this by showing that exactly the same product of the formula RS(O)SR is formed in each of the three reactions given above (77). Backer had earlier shown that the hydrochloric acid hydrolysis of benzenesulfenyl and p-toluenesulfenyl piperidines led to products identical with thiolsulfinates, but he made little note of this fact (2, 3). Vinkler and Klivényi postulated that the thiolsulfinate structure, RS(O)SR, was the correct structure for these compounds, because they felt it was unlikely that oxidation of a disulfide at room temperature would lead to any cleavage or rearrangement of the sulfur-sulfur bond (77). More important, Backer and Kloosterziel (4) had shown earlier that if two different groups are attached to the sulfur atoms, for example phenyl and ethyl, two isomeric compounds are obtainable. In this specific example, the products would be phenyl ethanethiolsulfinate (I) and ethyl benzenethiolsulfinate (II). This, of course, can only happen if the actual structure of these



I



II

compounds is that of a thiolsulfinate. Were they true sulfenic anhydrides, RS-O-SR, no such isomerism would be possible.

Ghersetti and Modena provided additional evidence that the

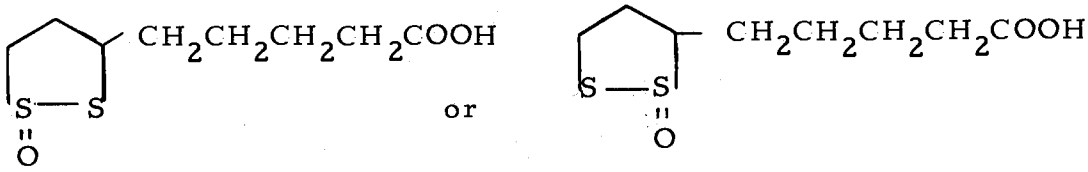
structure is indeed that of a thiolsulfinate by comparing the infra-red spectra of such representative compounds containing sulfinyl functions as sulfoxides, sulfinates, and sulfinyl chlorides (26, 27). It was established that thiolsulfinates contain a sulfoxide group since it was found that sulfoxides have an intense infra-red band at about 1050cm^{-1}, sulfinate esters have one at about 1130cm^{-1}, sulfinyl chlorides have one at about 1150cm^{-1} and thiolsulfinates at about 1100cm^{-1} (26, 27, 37).

Since those compounds originally designated as sulfenic anhydrides have all been shown actually to have the thiolsulfinate structure, all compounds of the general formula, RS(O)SR, will be referred to as thiolsulfinates in this thesis.

Biological Activity of Thiolsulfinates

The chemistry of thiolsulfinates received little attention until the mid-1940's. In 1944, Cavallito, Small and their co-workers discovered that the active ingredient of garlic oil, which was known to have a bacteriostatic effect, was allyl 2-propenylthiolsulfinate--commonly known as allicin (19, 20, 70, 71). This discovery led to much investigation of the biological activity of thiolsulfinates. There have been reports that thiolsulfinates reduce heat resistance of bacterial spores (58), give protection against ionizing radiation (63, 64), and have estrogenic activity; activity against tumors has also

been reported (33, 35, 76, 81, 82). Calvin suggested that thioctic acid monosulfoxide, also known as lipoic acid S-oxide (III), which



III

contains a five-membered cyclic thiolsulfinate, may be an intermediate in the primary quantum conversion act in photosynthesis (5).

Methods of Preparation of Thiolsulfinates

Several methods for the preparation of thiolsulfinates have been described in the literature. Historically, thiolsulfinates were first prepared by Zincke and his co-workers (85-89) by the hydrolysis of aromatic sulfenyl chlorides. His structural assignments were made on the basis of elemental analysis and the fact that treatment of the thiolsulfinates with either concentrated hydrochloric acid or phosphorous pentachloride in ether yielded the original sulfenyl chloride. Recently, doubts as to the validity of his claims have been raised by Oae (60), who found that Zincke's p-nitrophenyl p-nitrobenzenethiolsulfinate was really a mixture of the corresponding thiolsulfonate and disulfide, and that the o-nitro compound was a mixture

of the disulfide, thiolsulfinate and thiolsulfonate. However, since Zincke's original observations, a number of other workers have prepared thiosulfinates by this method (38, 39, 77, 79). During this early period, Fries reported the preparation of anthraquinone 1-sulfenic acid. In attempting to prepare the anthraquinone 2-sulfenic acid, he could only isolate the thiolsulfinate (25). Hinsberg reported the preparation of 2-naphthyl 2-naphthalenethiolsulfinate by oxidation of the disulfide, but later withdrew his assertion (32) because the last-mentioned compound gave thiolsulfonate and disulfide after heating with acetic acid. However, since thiolsulfinates are known to disproportionate under such conditions to form these very products, he may well have had the thiolsulfinate after all. Backer later prepared thiolsulfinates by the hydrolysis of sulfenyl piperidines (2, 3). Another method involves controlled oxidation of a disulfide by either perbenzoic acid (34, 62, 68, 70, 77), peracetic or performic acid (65, 67), hydrogen peroxide (1, 25, 35), or mono-persulfuric acid (65, 75).

Oxidation of the corresponding disulfide with optically active percamphoric acid (45, 66) leads to a partially optically active thiolsulfinate whose optical activity is due to the asymmetry of the sulfinyl group. Laakso prepared some very hindered thiolsulfinates by the air oxidation of the corresponding mercaptan (51). Calvin prepared 1, 2-dithiolane-1-oxide by photosensitized oxygen oxidation

or ammonium persulfate oxidation of the disulfide (5). Thiolsulfinates have also been isolated in the enzymatic hydrolysis of S-alkyl cysteine sulfoxides (19, 20, 28, 73). In an interesting example, Colclough and Cunneen produced t-butyl 2-methylpropane-2-thiolsulfinate upon heating di(t-butyl)sulfoxide (21).

The most general method of preparation and perhaps the best since it allows the preparation of unsymmetrical thiolsulfinates, is the method originated by Backer and Kloosterziel (4). In this procedure, a mercaptan is coupled with a sulfinyl chloride in the presence of pyridine in ethyl ether. Other workers have also found this method suitable (33, 56, 76, 77). Small found that the reaction was not successful in the absence of pyridine (70). Barnard used this method to prepare specifically labelled phenyl (^{35}S) benzenethiolsulfinate and phenyl benzenethiol (^{35}S) sulfinate (10).

Some Important Reactions of Thiolsulfinates

One of the more important reactions of thiolsulfinates is the disproportionation to thiolsulfinates and disulfides, equation 4. This reaction has been reported to occur upon drying samples of thiolsulfinates either in a vacuum or with phosphorous pentoxide (6), by

$$(4) \qquad 2\ \underset{\underset{\text{O}}{\|}}{\text{RSSR}} \longrightarrow \text{RSO}_2\text{SR} + \text{RSSR}$$

initiation with aromatic sulfinyl radicals (11), upon heating in hexane solution (4), in aqueous solution subsequent to sulfenyl chloride hydrolysis (79) and upon gamma-ray irradiation (13). Barnard theorized that in his instance the mechanism of disproportionation during the drying process involved radicals, basing his hypothesis on the reported disproportionation during the drying process and the initiation of the reaction by the other radicals mentioned above. Vinkler and Klivényi reported that the disproportionation proceeded faster in acidic media than neutral or basic solution (79). Other investigators have since used the known ability of thiolsulfinates formed during the hydrolysis of sulfenyl chlorides to dispropertionate into thiolsulfonates and disulfides to explain products in a variety of reactions. Douglass (23, 24) postulated the formation and disproportionation of methyl methanethiolsulfinate in the reaction of methanesulfenyl chloride. Ostermayer and Tarbell (61) have postulated the same reaction in the hydrolysis of S-methyl cysteine sulfoxide, and Kice (41, 46) has proposed the intermediacy of thiolfulfinates and their subsequent disproportionation in the reaction of sulfinic acids with disulfides. Small and Cavallito (20, 70) have reported that allyl 2-propenylthiolsulfinate decomposes into allyl disulfide and sulfur dioxide, a result unique to this specific thiolsulfinate.

A reaction related to the disproportionation is the basic

hydrolysis of thiolsulfinates, equation 5; this reaction like the

$$(5)\quad 3\ R\overset{\overset{O}{\|}}{S}SR + H_2O \xrightarrow{^-OH} 2\ RSSR + 2\ RSO_2H$$

disproportionation involves the thiolsulfinate as the only organic entity. Zincke reported this reaction 50 years ago and used it as a diagnostic test for thiolsulfinates (85-89). Vinkler and Klivényi reported that this reaction was one of the pathways to the formation of disulfide in the sulfenyl chloride hydrolysis reaction (79).

Kharasch (37) has reported that the so-called disproportionation of sulfenic acids, equation 6, may really involve initial

$$(6)\quad 2\ RSOH \longrightarrow RSH + RSO_2H$$

formation of a thiolsulfinate followed by its basic hydrolysis, in the manner shown in equation 7. Some recent investigations in this

$$(7)\quad 2\ RSOH \longrightarrow R\overset{\overset{O}{\|}}{S}SR + H_2O \longrightarrow RSH + RSO_2H$$

laboratory lend support to this proposition.[1] The facile formation of thiolsulfinates from sulfenic acids has also been reported by Vinkler and Klivényi (79) who state that in the hydrolysis of sulfenyl halides, one always sees formation of the thiolsulfinate as the first isolable

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[1] Wayne H. Stanley, unpublished results

intermediate. Although this often undergoes further rapid reactions, under certain specific conditions, it can be isolated in good yield from the reaction mixture. Therefore it appears that many if not all reactions involving sulfenic acids proceed via thiolsulfinate intermediates.

The most studied reaction of thiolsulfinates is their reaction with mercaptans to produce disulfides, equation 8. This reaction is

(8) $$R\overset{\overset{O}{\|}}{S}SR + 2\,RSH \longrightarrow 2\,RSSR + H_2O$$

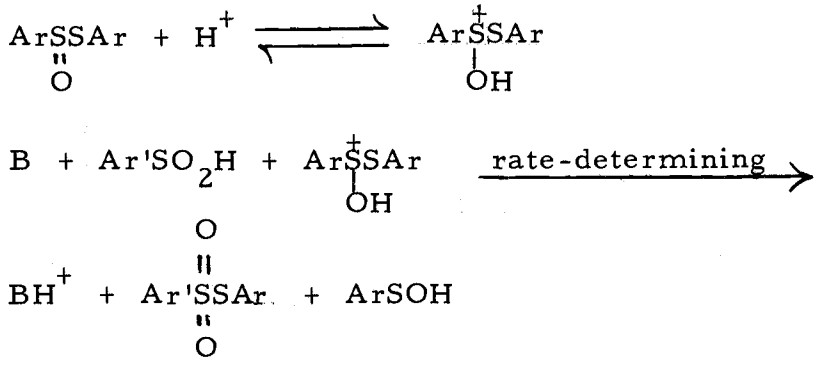
the one to which the biological activity of these compounds is most frequently attributed (60, 62, 63, 64, 72) since it involves blocking sulfhydryl groups which may be essential to certain life processes. Reactions of thiolsulfinates with cysteine have been reported by many workers (15, 20, 67, 68, 69, 84). Pihl has verified the reaction of the thiolsulfinate, cystamine mono-oxide, with enzymatic sulfhydryl groups (62). The most important organic chemical work is that by Schöberl who used the reaction as a general method for the preparation of unsymmetrical disulfides (68). Most preparative methods for unsymmetrical disulfides lead to mixtures of the symmetrical and unsymmetrical compounds, but he claims 70% yields of the pure unsymmetrical disulfide by this method.

Other reactions that have been studied include oxidations to

thiolsulfonates (1, 10, 56, 59, 75, 77, 78) -- probably proceeding through an α-disulfoxide intermediate (11, 56), chlorinations with phosphorous pentachloride or concentrated hydrochloric acid to yield two moles of sulfenyl chloride (85-89, 49, 78), reductions to disulfide by iodide (9, 15, 70) or triphenylphosphine (17), reactions with benzyl Grignard reagents to yield various mixtures of sulfoxide, sulfide, thiolate, and sulfenate (78, 80), reaction with certain fluorobenzenes to yield sulfoxide, sulfide, and/or sulfone depending on the experimental conditions (10, 18, 79), reaction with acetone to yield the β-keto sulfide (38), and reactions with sulfenic acids to form sulfinic acids and disulfides.

One of the properties of thiolsulfinates which is of some practical value is their ability to retard auto-oxidations. Thiolsulfonates also inhibit such oxidations, but only after an induction period; whereas, the thiolsulfinate is immediately effective. Hawkins and Sauter (29, 30) postulated that the inhibition is due to sulfur dioxide because elemental sulfur, in this respect, is even more effective than the thiolsulfinate. They propose that the thiolsulfinate can be oxidized to give sulfonyl radicals, which decompose to give sulfur dioxide faster than the other organic sulfur compound. Chain termination by formation of the stable sulfinyl radicals might be another possibility, in view of the work of Kice and Pawlowski who found that arene sulfinyl radicals appear to be

(9)



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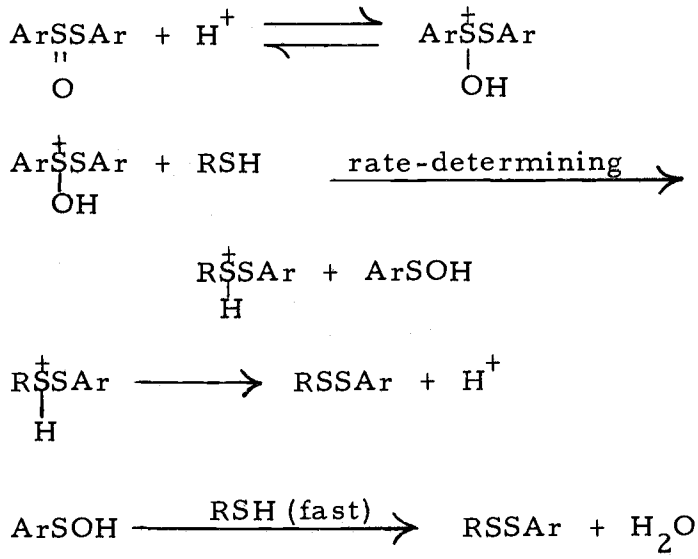


reactions are described by similar mechanisms that involve a rate-determining attack of the sulfinic acid or mercaptan on the protonated thiolsulfinate. They found, however, some mechanistic differences between the two reactions. In the case of the sulfinic acid reaction, the rate-determining attack of the sulfinic acid on the protonated thiolsulfinate is general base catalyzed, so that the overall reaction exhibits general acid catalysis, equation 9 (48). On the other hand in the mercaptan reaction, the rate-determining attack of the

mercaptan does not require general base catalysis, and so this reaction exhibits specific H^+-ion catalysis, equation 10 (43).

Kice and his co-workers also found that both the mercaptan and the sulfinic acid reactions could be very markedly catalyzed by the addition of small amounts of alkyl sulfides. These sulfide-catalyzed reactions are specific H^+-ion catalyzed and these and other experimental facts about the reactions led them to propose the mechanism shown in equation 11 for these sulfide-catalyzed reactions.

(11)

$$ArS(=O)SAr + H^+ \rightleftharpoons ArS^+(OH)SAr$$

$$ArS^+(OH)SAr + R_2S \xrightarrow{\text{rate-determining}}$$

$$R_2S^+SAr + ArSOH$$

IV

$$R_2S + ArSOH + H^+ \rightleftharpoons ArSSR_2^+ + H_2O$$

$$(IV) + \begin{matrix} Ar'SO_2H \\ \text{or} \\ RSH \end{matrix} \xrightarrow{\text{fast}} \begin{matrix} Ar'SO_2SAr \\ \text{or} \\ RSSAr \end{matrix} + R_2S + H^+$$

$$ArSOH + \begin{matrix} Ar'SO_2H \\ \text{or} \\ RSH \end{matrix} \longrightarrow \begin{matrix} Ar'SO_2SAr \\ \text{or} \\ RSSAr \end{matrix} + H_2O$$

This mechanism involves a rate-determining nucleophilic attack by the sulfide on the protonated thiolsulfinate, and then a subsequent fast reaction of the resulting intermediate (IV) with either mercaptan or sulfinic acid leading to the correct final products.

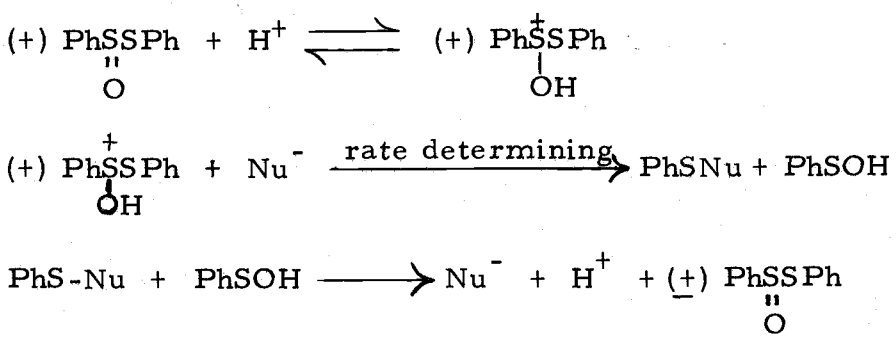
With the advent of reliable methods of preparing optically active thiolsulfinates in which the asymmetry is solely due to the sulfinyl sulfur atom, Kice and Large studied the nucleophile and acid catalyzed racemization of optically active phenyl benzenethiolsulfinate in aqueous dioxane (44). They found that in the absence of any added nucleophiles racemization occurred very slowly, but with the addition of quite small amounts of sulfides, halide ions, or various other nucleophilic agents, the thiolsulfinate racemized very rapidly. This nucleophile-catalyzed racemization, equation 12, was also specific H^+-ion catalyzed. By observing the ultraviolet

$$(12) \qquad (+)\ \mathrm{PhS(O)SPh} \xrightarrow{Nu^-,\ H^+} (\pm)\ \mathrm{PhS(O)SPh}$$

spectrum of the reaction mixture Kice and Large were able to show that the observed loss of optical activity was due solely to racemization of the thiolsulfinate and not to any chemical reactions of the thiolsulfinate, such as disproportionation, which would lead to optically inactive products. They proposed the mechanism shown in equation 13 for the acid and nucleophile catalyzed racemization process. This involves a rate-determining attack by a nucleophilic moiety on the protonated thiolsulfinate to form Ph-Nu and PhSOH. In the absence of added reagents such as sulfinic acid or mercaptan, these simply recombine to form racemic thiolsulfinate--regenerating

the proton and the nucleophile in the process (44). As required by such a mechanism, the rate of the acid and nucleophile catalyzed racemization is exactly the same under a given set of reaction conditions as the rates of the acid and nucleophile catalyzed reactions of sulfinic acid and mercaptan with the same thiolsulfinate.

(13)



As is readily seen from other examples of such in the literature, these studies of the mechanisms of the various sulfide and acid catalyzed reactions of thiolsulfinates and the acid-nucleophile catalyzed racemization of optically active thiolsulfinates are further examples of concomitant electrophilic-nucleophilic catalyses of the scission of sulfur-sulfur bonds (40, 44, 47).

Recently, Koch and Fava have studied the thermal racemization of optically active aryl arenethiolsulfinates in benzene and acetonitrile (50). They found thermal racemization to occur much more rapidly than for the corresponding optically active sulfoxide. They have offered some possible reasons why this thermal racemization occurs so much more readily than for sulfoxides and suspect

it is due to the fact that pyramidal inversion of the sulfinyl group is greatly facilitated by the availability of low-lying vacant d orbitals on the adjacent sulfenyl sulfur. Similar arguments have been offered by Lambert and Mueller to explain the rapid inversion of diphosphines as compared to monophosphines (52).

Since Kice and Large have shown the acid-nucleophile catalyzed racemization of optically active phenyl benzenethiolsulfinate to be a straight-forward uncomplicated example of the concomitant electrophilic and nucleophilic catalysis of the scission of a sulfur-sulfur bond, we were curious to know whether or not it would be possible to develop a system in which the racemization of the optically active thiolsulfinate could be catalyzed in a more intramolecular fashion by a single bifunctional moiety in which one function would act as a nucleophile and the other function as the "acid" or electrophile. If such a system could be developed, one can readily see that the catalyzed racemization would then be bimolecular rather than essentially, as in equation 13, termolecular; and one might hope to observe interesting and striking rate enhancements over those found for the termolecular reaction described above, due to the more favorable $\Delta S^{\ddagger}$ associated with the bifunctional reaction. Such a reaction would thus necessarily be intramolecular; and if it were possible to observe and describe such a process, further speculations might be in order concerning the role of thiolsulfinates in

biological systems.

The search for and the study and description of such an intramolecular bifunctional catalysis of the racemization of phenyl benzenethiolsulfinate forms the subject of this thesis.

RESULTS

As was mentioned in the introduction, Kice and Large (44) made an extensive study of the nucleophile and acid catalyzed racemization of (+) phenyl benzenethiolsulfinate in acidic 60% dioxane. On the basis of their results, they proposed the mechanism shown in equation 13 for the process. This mechanism involves an initial equilibrium in which a small portion of the thiolsulfinate becomes protonated. Then the protonated thiolsulfinate reacts with a nucleophilic moiety in the rate-determining step to form PhS-Nu and PhSOH. Since these two species are incapable of optical activity, when they recombine to form thiolsulfinate, as shown in equation 13c, the thiolsulfinate is racemic. One of the types of nucleophiles which Kice and Large found to be effective as a nucleophilic catalyst was an alkyl sulfide.

(13a) $$(+)\ \mathrm{PhS(O)SPh} + \mathrm{H^+} \rightleftharpoons (+)\ \mathrm{PhS^+(OH)SPh}$$

(13b) $$(+)\ \mathrm{PhS^+(OH)SPh} + \mathrm{Nu^-} \xrightarrow{\text{rate determining}} \mathrm{PhSNu} + \mathrm{PhSOH}$$

(13c) $$\mathrm{PhSOH} + \mathrm{PhS\text{-}Nu} \longrightarrow (\pm)\ \mathrm{PhS(O)SPh} + \mathrm{Nu^-} + \mathrm{H^+}$$

This work of Kice and Large and the biological characteristics

of the thiolsulfinates, mentioned in the introduction led us to become interested in seeing whether or not we might be able to increase the intramolecular character of the acid and nucleophile catalyzed racemization. Thus the reaction system studied by Kice and Large involves the nucleophile, the catalyzing acid and the thiolsulfinate as separate molecular species and is therefore, in effect, a termolecular process. One way to increase the intramolecular character of the reaction would be to incorporate the catalyzing acid and nucleophile in a single appropriate molecule. Therefore, we sought to synthesize compounds of the general type (V) in which the "acidic" or electrophilic catalyst would be a carboxylic acid functional group and the nucleophilic catalyst would be a sulfide. We thought some such compounds would function effectively as

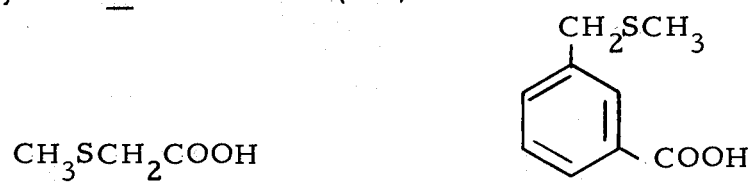
$$CH_3S\text{-}R\text{-}COOH$$

V

bifunctional catalysts for the racemization of (+) phenyl benzenethiolsulfinate since the proton of the acid group would hopefully be acidic enough to be donated fairly readily to the sulfinyl oxygen of the thiolsulfinate and, of course, we already know from the work of Kice and Large that alkyl sulfides were efficient nucleophilic reagents in catalyzing the racemization.

The Synthesis of Potential Bifunctional Catalysts for the Racemization of (+) Phenyl Benzenethiolsulfinate

For initial study, we decided to synthesize two bifunctional compounds of the general formula of V--methylthiolacetic acid (VI) and α-methylthio-m-toluic acid (VII).



VI

VII

Methylthioacetic acid was synthesized by the treatment of the disodium salt of mercaptoacetic acid with excess methyl iodide for 30 minutes in aqueous ethanol containing excess sodium hydroxide. The crude product was isolated by acidifying the reaction mixture, extracting the acidified solution with ethyl ether, drying the ether layer over anhydrous magnesium sulfate and, finally, removing the ether under vacuum. The crude product was then purified by distillation under vacuum.

α-Methylthio-m-toluic acid was prepared according to the scheme shown in Chart I. First, the ethyl ester of m-toluic acid was treated with sulfuryl chloride in the presence of benzoyl peroxide at 60° C. The pure ethyl α-chloro-m-toluate was fractionally distilled under vacuum directly from the reaction mixture. The ethyl α-chloro-m-toluate so obtained was then refluxed with excess

sodium methyl mercaptide in aqueous ethanol in the presence of excess sodium hydroxide for two hours. After removal of the ethanol, the crude reaction mixture was acidified with 50% hydrochloric acid and extracted with ethyl ether. Appropriate work-up of the ether extracts gave the crude α-methylthio-m-toluic acid as a solid. This was purified by repeated recrystallization from chloroform-n-hexane.

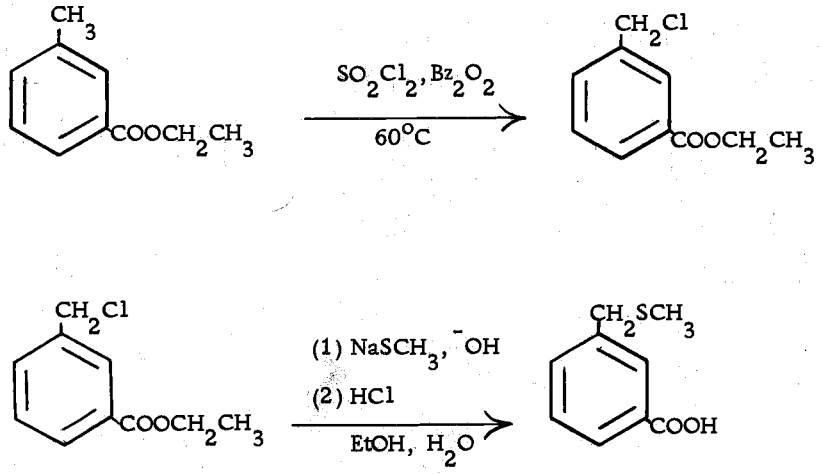


Chart I

Attempted Bifunctional Intramolecular Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate in Acidic 60% Dioxane by Methylthioacetic Acid

We first sought to detect the intramolecular bifunctional catalysis of the racemization of (+) phenyl benzenethiolsulfinate in acidic 60% dioxane as solvent.

To insure complete protonation of the acidic functional group of the bifunctional compounds, we first studied the racemizations

in 60% dioxane that contained 0.01 M perchloric acid.

As shown in Figure 1 and Table 1, the rate of racemization of (+) PhS(O)SPh in the presence of methylthioacetic acid under these conditions is the same as the rate of racemization in the absence of sulfide. In other words, no increase in the rate of racemization of (+) PhS(O)SPh was observed when methylthioacetic acid was introduced into the solution of the thiolsulfinate. It was also established that methylthioacetic acid had no effect on the rate of racemization in 60% dioxane in the absence of added perchloric acid. In view of these initial results, no further studies were conducted in attempting to racemize (+) PhS(O)SPh using methylthioacetic acid as a bifunctional catalytic species in 60% dioxane.

Attempted Bifunctional Intramolecular Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate by α-Methylthio-m-Toluic Acid in Acidic 60% Dioxane

When α-methylthio-m-toluic acid was tested as a possible catalyst for the racemization in acidic 60% dioxane, the results were somewhat different from those with methylthioacetic acid. Figure 2 and Table 1 show that in this case, when the racemization rate, k_a (determined from the slope of the straight line determined by the plot of loss of optical rotation versus time), was plotted versus the concentration of added α-methylthio-m-toluic acid, one observed a direct dependence on the rate of racemization on the

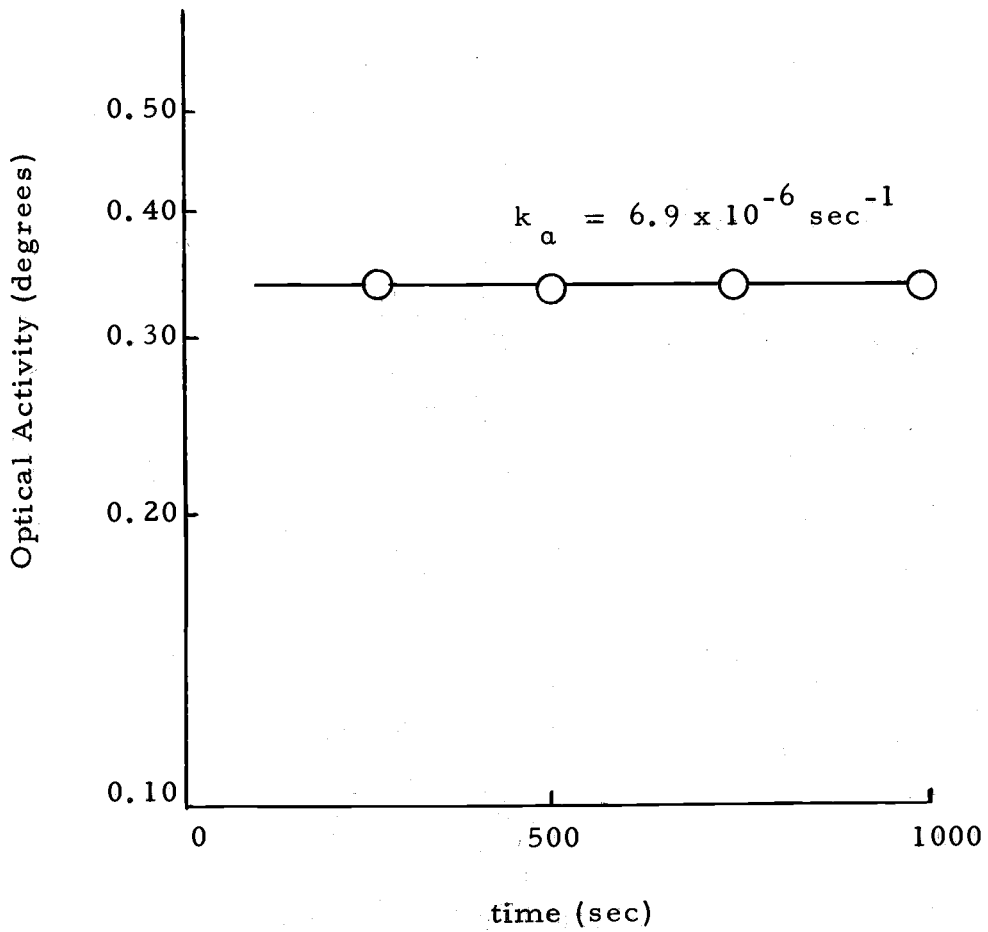


Figure 1. Racemization of (+) PhS(O)SPh by 0.01 M CH_3SCH_2COOH in 60% dioxane containing 0.01 M $HClO_4$.

Table 1. Racemization of (+) PhS(O)SPh as catalyzed by various reagents in 60% dioxane at 39.6°C.

[PhS(O)SPh] M	[$HClO_4$] M	[CH_3SCH_2COOH] M	[m-$CH_3SCH_2\emptyset COOH$] M	$k_a \times 10^4$ sec^{-1}	$k \times 10^4$ $M^{-1}sec^{-1}$
0.05				0.077	
0.05	0.01		0.04	0.51	
0.05	0.01		0.08	0.90	
0.05	0.01		0.12	1.28	9.72
0.05	0.01		0.16	1.62	
0.05	0.01		0.20	2.06	
0.05	0.005		0.08	0.41	
0.05	0.005		0.15	0.74	4.53
0.05	0.005		0.20	0.99	
0.05			0.05	0.08	
0.05			0.10	0.07	0.00
0.05	0.01	0.01		0.07	

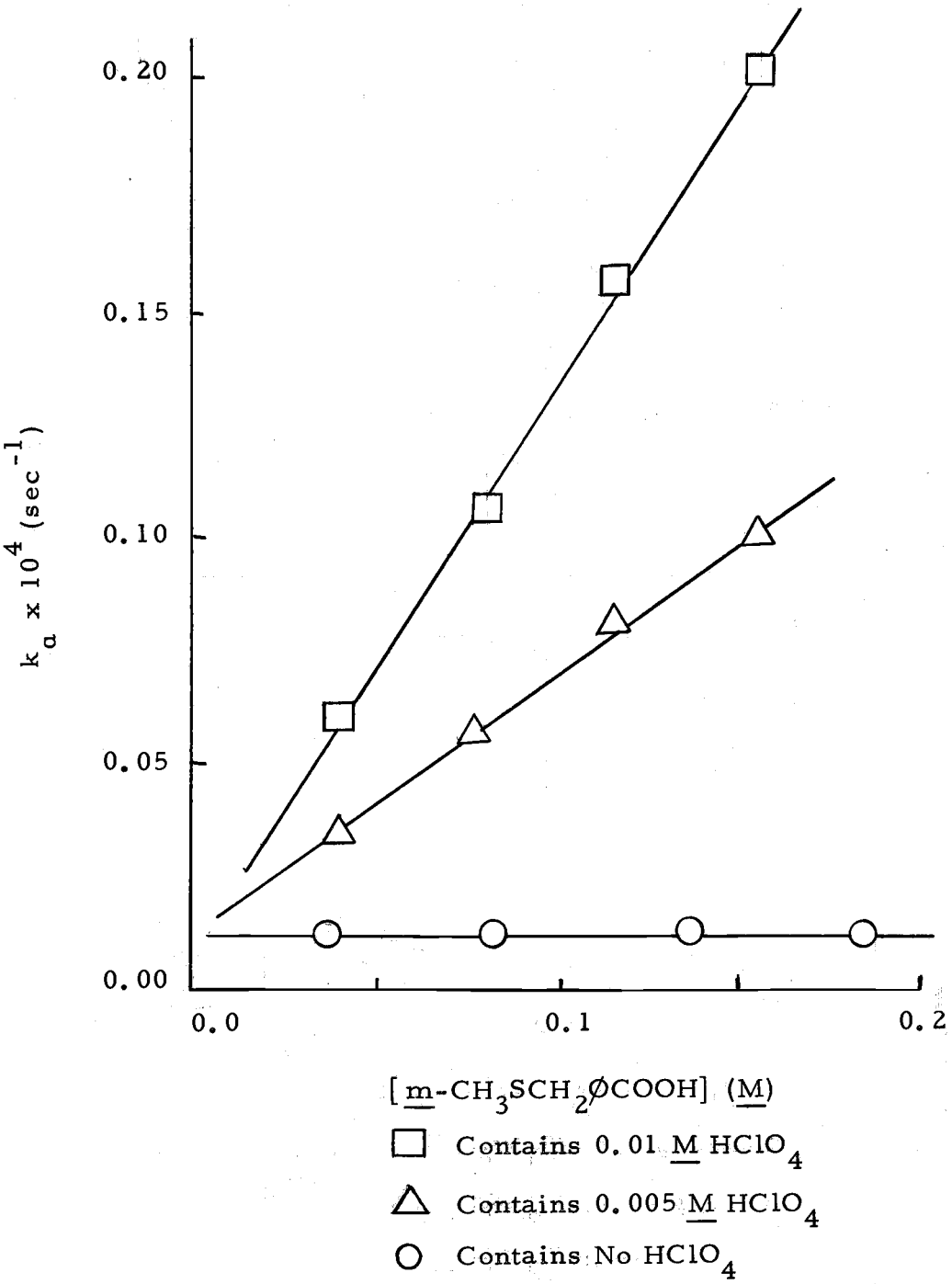


Figure 2. Racemization of (+) PhS(O)SPh as catalyzed by VII in 60% dioxane with varying [$HClO_4$].

concentration of the bifunctional catalyst in 60% dioxane containing either 0.01 M or 0.005 M perchloric acid. We shall denote the slope of the straight line of the plot of k_a versus the concentration of the bifunctional catalyst by k.

As is evident from Figure 2 and Table 1, k also depends on the concentration of added perchloric acid present in the solution, and Figure 3 in particular shows that k is directly proportional to the first power of perchloric acid concentration in 60% dioxane.

Therefore, the racemization of (+) PhS(O)SPh as catalyzed by α-methylthio-m-toluic acid in 60% dioxane also involves specific H^+-ion catalysis by a proton from H_3O^+. The sulfide, therefore, simply functions as a nucleophilic catalyst in the same manner as the sulfides studied by Kice and Large, and the -COOH group of VII plays no role in the observed catalysis. Thus the racemization of the thiolsulfinate as catalyzed by VII in 60% dioxane is just another example of the type of bimolecular catalysis reaction reported by Kice and Large (44) and has the mechanism shown in equation 13.

It is important to restate that the primary purpose of adding perchloric acid to the 60% dioxane solution was to prevent any dissociation of the carboxylic acid functional group of the bifunctional catalyst. This, it was hoped, would maximize the chance of observing any possible intramolecular racemization mechanism; unfortunately, however, in the presence of added perchloric acid, the

termolecular racemization, as described in equation 13, was the only sulfide-catalyzed racemization reaction which could be observed. We also made one attempt to observe the racemization of (+) PhS(O)SPh by VII in 60% dioxane in the absence of any added strong acid. As is evident from Figure 3, no sulfide catalyzed racemization of the thiolsulfinate was observed under these conditions.

These facts led us to look for some other solvent system where one might more easily observe intramolecular bifunctional catalysis of the racemization of (+) PhS(O)SPh. Before discussing this work we should, however, mention one further aspect of the studies in 60% dioxane.

The Chemical Stability of Thiolsulfinate in 60% Dioxane During Racemization

Since reactions that would cause a chemical decomposition of the thiolsulfinate would also cause a loss of optical activity if the reaction products were optically inactive, it was necessary to verify in each case that the thiolsulfinate was chemically stable under the reaction conditions used to effect its racemization. Therefore, the ultraviolet spectrum of each racemization mixture in 60% dioxane was determined at the start of the experiment and after loss of optical activity was complete. In no case was there any observable

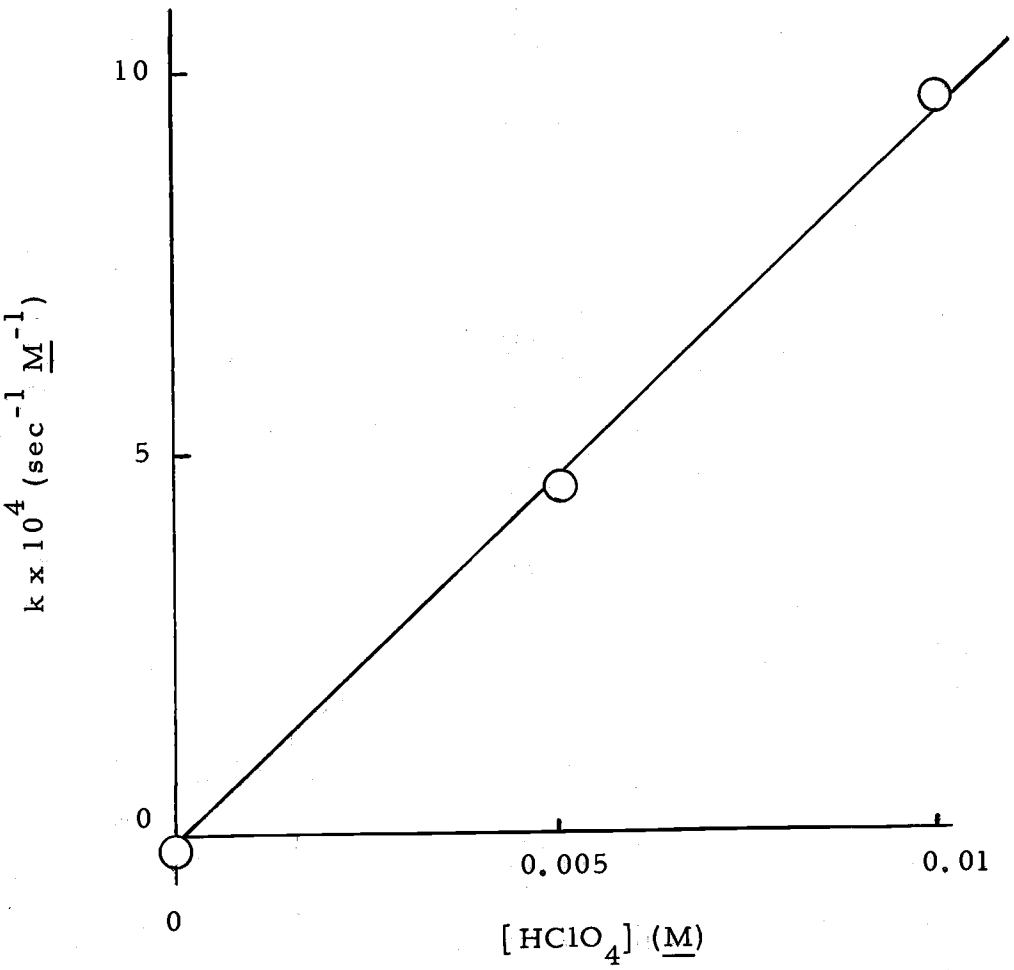


Figure 3. Dependence of the racemization rate of (+) PhS(O)SPh as catalyzed by VII on $[HClO_4]$.

change in the spectrum during the course of the racemization. This is evident from Figure 4 which shows this result for a particular run in 60% dioxane. Thus no chemical change in the thiolsulfinate was responsible for any detectable loss of optical activity in any run carried out in 60% dioxane; and loss of optical activity, therefore, resulted solely from the racemization of (+) PhS(O)SPh.

Bifunctional Intramolecular Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate in Acetonitrile

Since no intramolecular bifunctional catalysis of the racemization of (+) PhS(O)SPh could be observed with VI or VII in 60% dioxane, we decided to examine the catalysis of the racemization of the thiolsulfinate by VI and VII in acetonitrile, a relatively high dielectric, highly polar, aprotic solvent.

In acetonitrile, as shown in Figure 5 and Table 2, the racemization rate of (+) PhS(O)SPh in the presence of methylthioacetic acid was scarcely different from its thermal rate of racemization. Thus with this sulfide, the situation is similar to what we found in 60% dioxane.

A plot of a typical run with VII as catalyst in acetonitrile is shown in Figure 6. With this sulfide the racemization rate of (+) PhS(O)SPh in acetonitrile increases linearly with the concentration of α-methylthio-m-toluic acid, as can be seen from Figure 7,

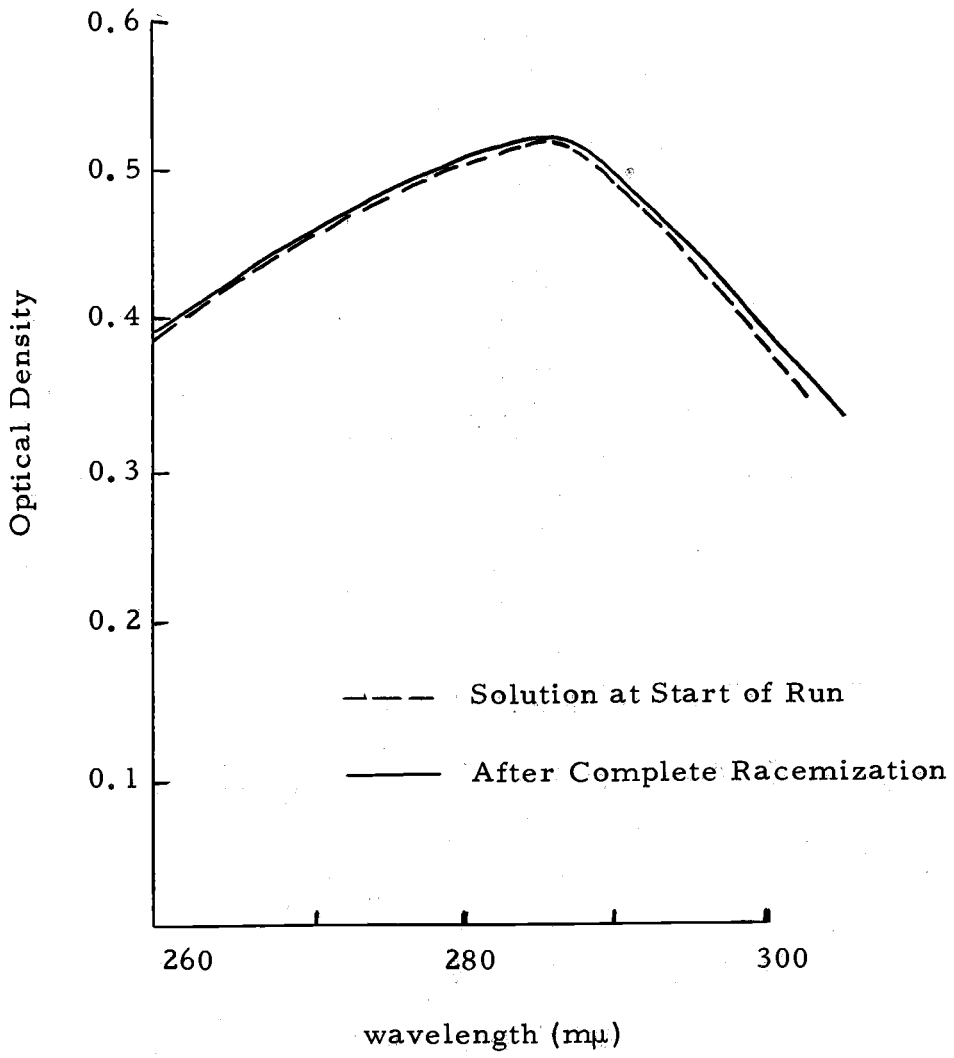


Figure 4. The ultraviolet spectra of a racemization solution containing 0.05 M thiolsulfinate, 0.05 M VII and 0.01 M $HClO_4$ in 60% dioxane.

Table 2. Racemization of (+) PhS(O)SPh as catalyzed by various reagents in acetonitrile at 39.6°C.

[PhS(O)SPh] M	[m-$CH_3SCH_2\emptyset COOH$] M	[$\emptyset CH_2SCH_3$] M	[$\emptyset COOH$] M	[CH_3SCH_2COOH] M	$k_a \times 10^4$ sec^{-1}	$k \times 10^4$ $M^{-1}sec^{-1}$
0.05					0.092	
0.05	0.025				0.27	
0.05	0.05				0.45	7.15
0.05	0.075				0.63	
0.05		0.025	0.025		0.08	
0.05		0.05	0.05		0.045	-0.59
0.05		0.075	0.075		0.045	
0.05				0.025	0.10	
0.05				0.05	0.08	
0.05				0.075	0.10	-0.00
0.05				0.10	0.09	

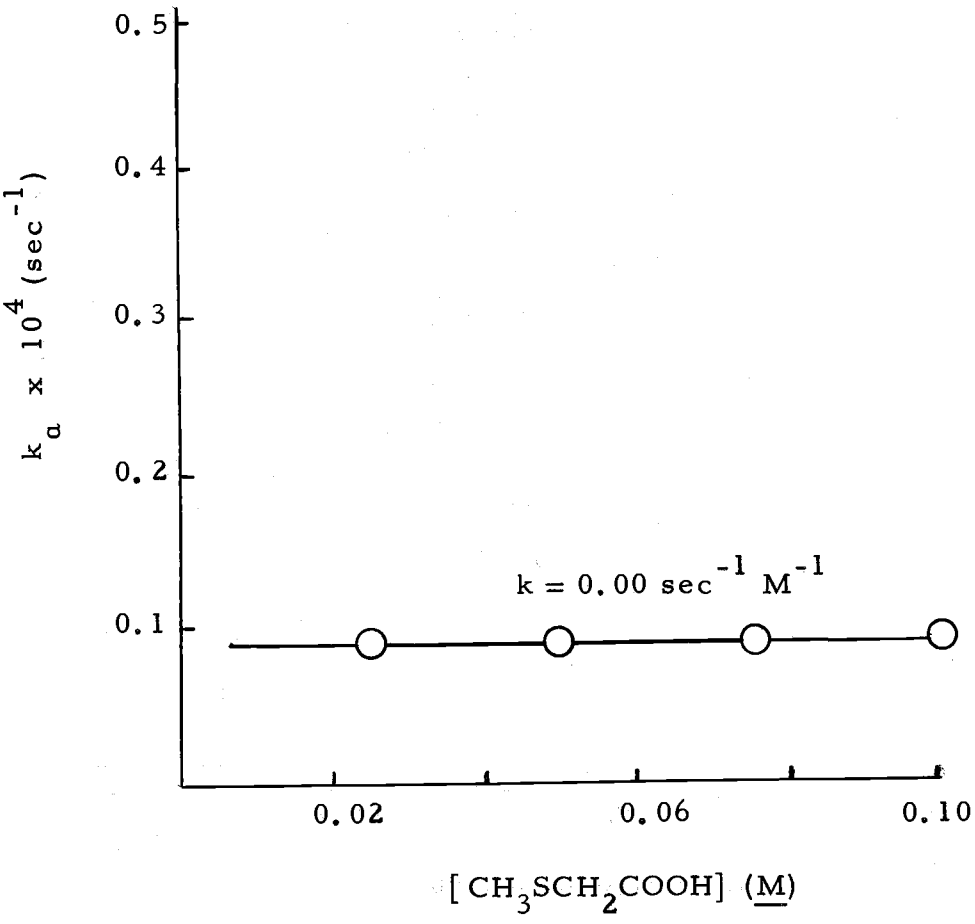


Figure 5. Racemization of (+) PhS(O)SPh as catalyzed by VI in acetonitrile.

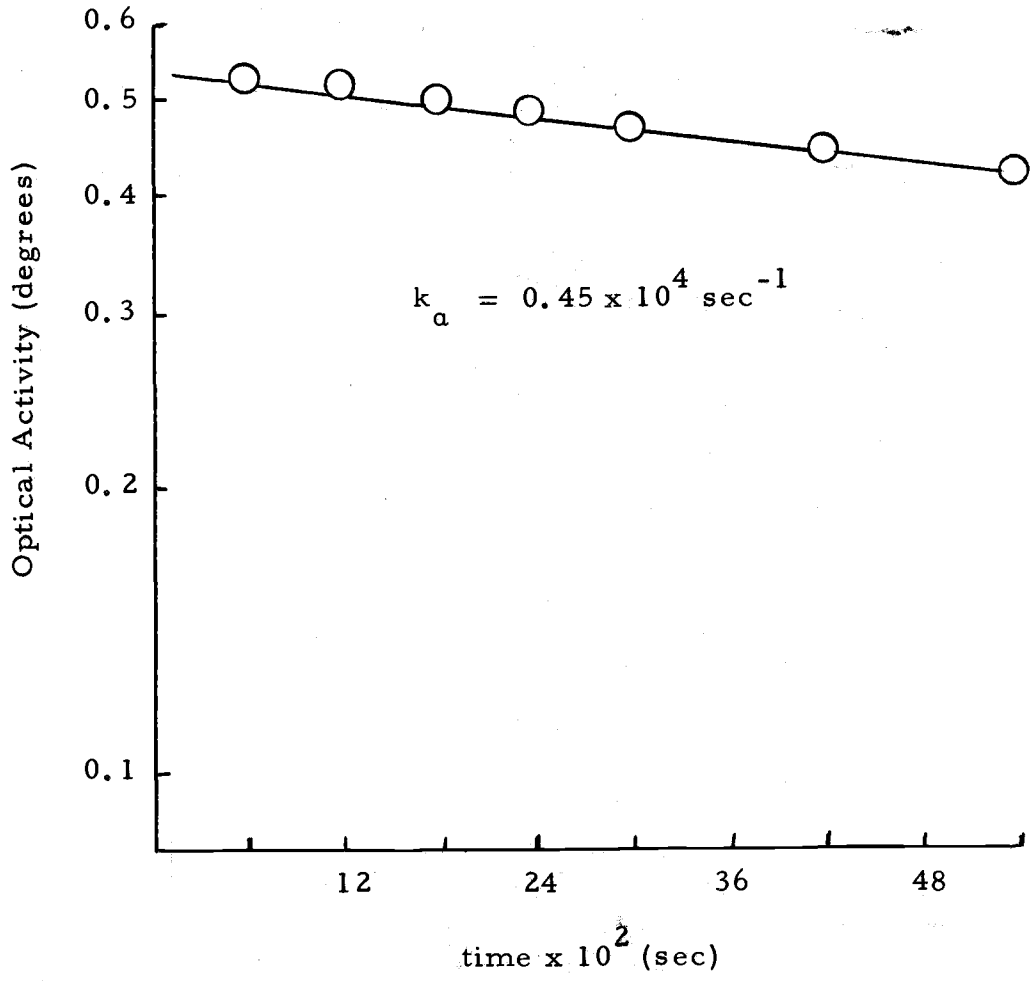


Figure 6. Racemization of 0.05 M thiolsulfinate in acetonitrile containing 0.05 M VII.

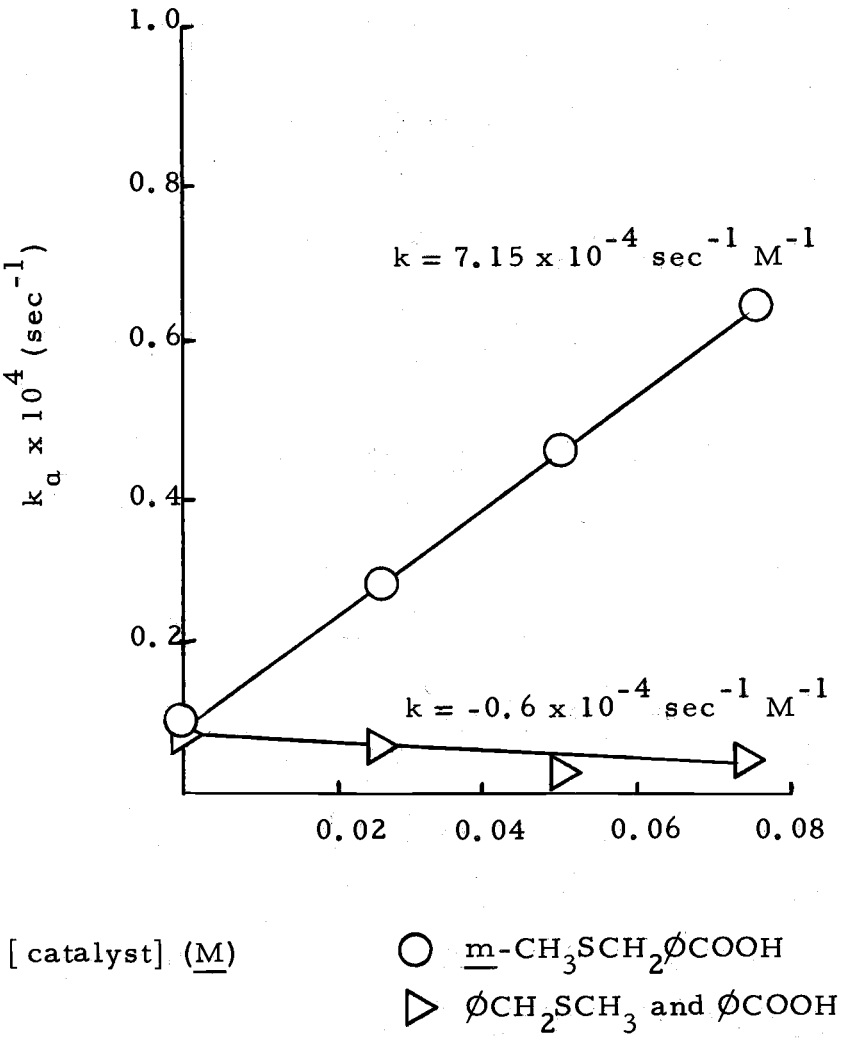


Figure 7. Racemization of (+) PhS(O)SPh as catalyzed by various reagents in acetonitrile.

which shows a plot of k_a versus the concentration of VII. Since this plot is linear, the kinetics of the racemization under these conditions are thus first order in both VII and thiolsulfinate.

The Chemical Stability of Thiolsulfinate During Racemization in Acetonitrile

The determination of the chemical stability of (+)PhS(O)SPh under the conditions used for its racemization in acetonitrile solutions was carried out in the same manner as for the runs in 60% dioxane. As is shown in Figure 8 for one particular run, there was no observable change in the ultraviolet spectrum of the thiolsulfinate during the course of the racemization. In all other runs carried out in acetonitrile, this same result was also observed. This verified that the loss of optical activity was due only to racemization of (+) PhS(O)SPh and not to any chemical reaction involving the conversion of the thiolsulfinate into products incapable of supporting optical activity.

A Comparison of Intramolecular Bifunctional Catalysis with Bimolecular Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate in Acetonitrile

As was shown previously in this section, the catalysis of the racemization of (+) PhS(O)SPh by VII follows the kinetic behavior shown in equation 15, since a plot of k_a versus the concentration of

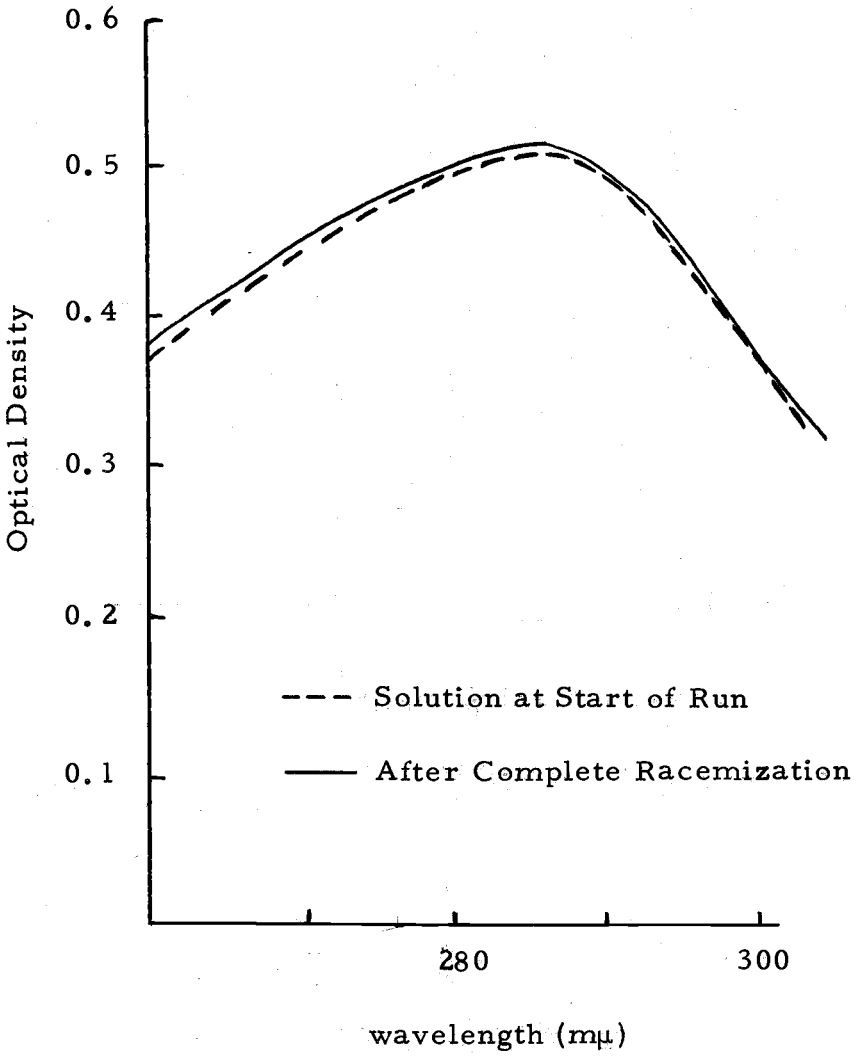


Figure 8. The ultraviolet spectra of the solution of 0.05 M (+) PhS(O)SPh and 0.05 M m-$CH_3SCH_2\emptyset COOH$ in acetonitrile.

added VII is linear. The kinetics thus indicate that there must be an interaction between the thiolsulfinate and the bifunctional catalyst that leads to the observed loss of optical activity. However, these results give no indication of the efficiency of this process.

$$(15) \qquad k_a = k[\text{VII}]$$

One way that an indication of the efficiency of the observed catalysis by VII can be made is to compare the results for catalysis by VII with those obtained under experimental conditions such that the racemization could only proceed via a bimolecular catalytic route.

This comparison was achieved by measuring rates of racemization of (+) PhS(O)SPh for solutions containing molar concentrations of benzyl methyl sulfide and benzoic acid equal to the molar concentrations of VII used in the studies of the intramolecular bifunctional catalysis. Equation 16 shows the presumed kinetics for the racemization process as catalyzed by benzyl methyl sulfide and benzoic acid.

$$(16) \qquad k_a = k'[\text{ØCOOH}][\text{ØCH}_2\text{SCH}_3]$$

As shown in Figure 7 and Table 2, the replacement of one mole of bifunctional catalyst by one mole each of a sulfide and a

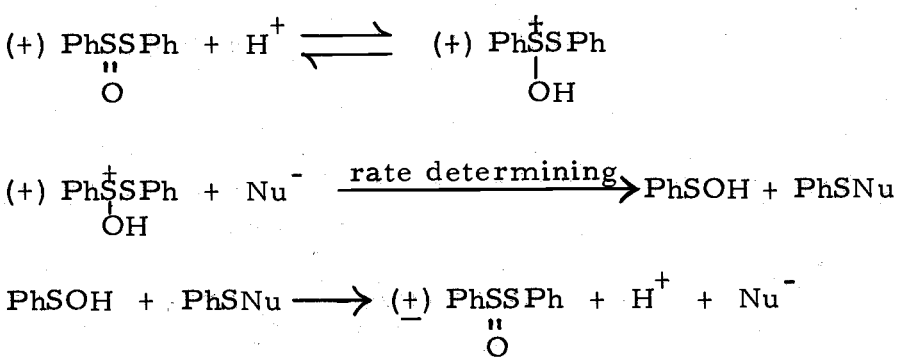
carboxylic acid gives a much slower rate of racemization and one which is essentially equal to the rate of thermal racemization.

Thus, in addition to showing that catalysis of the racemization of thiolsulfinate by VII in acetonitrile involves an intramolecular bifunctional process, we have also shown that the intramolecular bifunctional process is much more efficient than a racemization process involving catalysis by separate sulfide and carboxylic acid molecules.

DISCUSSION

Kice and Large have shown that optically active phenyl benzenethiolsulfinate undergoes acid and nucleophile catalyzed racemization in 60% dioxane as shown in equation 13 (44). This mechanism involves an initial equilibrium in which a small fraction of the thiolsulfinate becomes protonated and then a rate-determining step in which a nucleophile attacks the sulfenyl sulfur of the protonated thiolsulfinate. The resulting intermediates (PhSOH and PhSNu), in the

(13)



absence of reagents that would otherwise react with them, then recombine to form racemic phenyl benzenethiolsulfinate. They have also shown that the mechanism exhibits specific H^+-ion catalysis and that sulfides are efficient nucleophilic reagents for the process. Since the process involves a first order dependence on thiolsulfinate, acid and nucleophile, the overall kinetics are third order. Obviously, the observed catalysis of the scission of the sulfur-sulfur bond involves the acid and the sulfide as separate molecular species.

This present work was undertaken to see if one could observe intramolecular, bifunctional, acid and nucleophile catalysis of the racemization of (+) PhS(O)SPh. By analogy with other systems (16, 74), such intramolecular bifunctional catalysis might well prove much more efficient than the bifunctional catalysis involving separate acid and nucleophile molecules.

The Nature of the Non-Catalyzed (Thermal) Racemization of (+) Phenyl Benzenethiolsulfinate

Optically active PhS(O)SPh racemizes only very slowly in either acetonitrile or 60% dioxane in the absence of any added nucleophilic reagents. The same is true in 60% dioxane containing either 0.01 M or 0.005 M perchloric acid. This is the same type of result found by Kice and Large (44) and Koch and Fava (50). Koch and Fava have studied this thermal racemization of optically active aryl arenethiolsulfinates in some detail. They have offered some possible reasons why this thermal racemization occurs much more rapidly than the corresponding racemization of sulfoxides and believe that it is primarily due to the fact that pyramidal inversion of the sulfinyl group is greatly facilitated by the availability of low-lying vacant d orbitals on the sulfenyl sulfur. Similar arguments have been given by Lambert and Mueller (52) to explain the rapid inversion of diphosphines as compared to monophosphines.

Attempted Intramolecular Bifunctional Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate in 60% Dioxane

Addition of methylthioacetic acid does not lead to any increase in the rate of racemization, k_a, of (+) phenyl benzenethiolsulfinate over that attributed to the thermal rate. In the case of α-methylthio-m-toluic acid, VII, the situation is somewhat different. In solutions containing 0.005 M or 0.01 M perchloric acid, k_a increases linearly with the amount of VII added. However, under such conditions, k_a is also dependent on the concentration of perchloric acid in the same manner as observed by Kice and Large for other sulfides. This, plus the observation that there is no increase in k_a in the presence of VII in the absence of perchloric acid, shows that the catalysis of the racemization of (+) PhS(O)SPh by VII in aqueous dioxane involves the same mechanism already described by Kice and Large and shown in equation 13; in our particular case, however, the nucleophilic moiety is the sulfide functional group of VII and its carboxylic acid functional group plays no role in the catalysis in 60% dioxane. Hence, in 60% dioxane, it has not as yet been possible to observe intramolecular bifunctional catalysis of the racemization of (+) PhS(O)SPh by molecules of the type CH_3S-R-COOH.

Intramolecular Bifunctional Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate by α-Methylthio-m-Toluic Acid in Acetonitrile

The lack of success in finding intramolecular bifunctional catalysis of the racemization of (+) PhS(O)SPh in 60% dioxane led us to attempt to find such a catalysis in another solvent. Acetonitrile was chosen because it is polar, aprotic and has a high dielectric constant.

Once again addition of methylthioacetic acid did not increase the rate of racemization, as can be seen from Figure 5.

However, addition of VII did increase the rate of racemization of (+) PhS(O)SPh in acetonitrile; and, as can be seen from Figure 7, the increase in k_a was directly proportional to the concentration of added VII. This shows that the racemization process involves a first order dependence on α-methylthio-m-toluic acid. It now remains for us to show that the catalysis of the racemization by VII under such conditions is due to intramolecular bifunctional catalysis involving both the sulfide and the carboxylic acid functional groups of VII. To do this it is helpful to discuss some earlier work on intramolecular polyfunctional catalysis.

Swain and Brown (74) reported the first known example of concerted, polyfunctional acid-base catalysis. This involved the catalysis of the mutarotation of α-D-tetramethylglucose by 2-hydroxypyridine.

The evidence they used to support their proposal of intramolecular bifunctional catalysis in benzene is as follows: First, they observed that either pyridine or phenol alone had little catalytic power, but that a mixture of the two was a powerful catalyst and that catalysis by such mixtures gave kinetics which were first order in phenol and first order in pyridine. Presumably, pyridine supplied the basic group and phenol the acidic group in the acid-base catalysis required to effect the observed mutarotation. Second, although 2-hydroxypyridine is only one thousandth as strong a base as pyridine and one hundredth as strong an acid as phenol, 2-hydroxypyridine was 50 to 7000 times more effective than an equimolar mixture of pyridine and phenol, the exact factor depending on the concentration at which the experiment was carried out. This is because catalysis by the mixture of monofunctional catalysts involves a rate term of the form k[pyridine][phenol] while the catalysis by 2-hydroxypyridine involves a rate term of the form k[2-hydroxypyridine]. To further demonstrate the intramolecular character of the catalysis by 2-hydroxypyridine, they showed that addition of a 10-fold molar excess of either phenol or pyridine to the mutarotation mixtures containing the bifunctional catalyst gave no change in the mutarotation rate. Finally, they observed that in contrast to the behavior of the 2-isomer, both 3- and 4-hydroxypyridine gave catalytic terms of the form $k'[\text{hydroxypyridine}]^2$ with rate constants only one thousandth

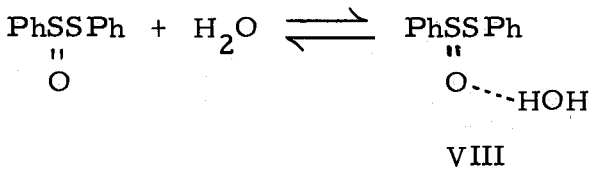
those for equimolar mixtures of pyridine and phenol of the same concentration. This established that the concerted catalysis exhibited by the 2-isomer has definite stereochemical requirements, as would certainly be expected.

Essentially, what we will now do is establish that the racemization of (+) PhS(O)SPh in acetonitrile as catalyzed by VII also involves intramolecular bifunctional catalysis by presenting analogous evidence.

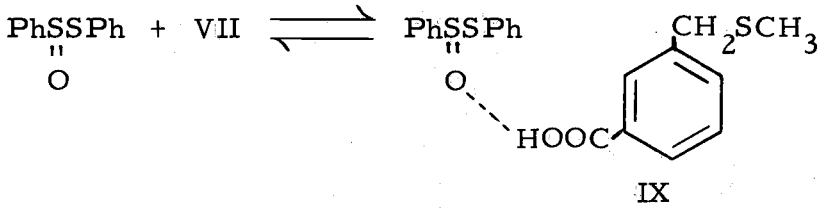
The kinetics of the racemization show a first not a second order dependence on the concentration of VII, and so only one molecule of VII is involved in the catalytic process. Second, although VII catalyzes the racemization in acetonitrile, an equimolar mixture of benzyl methyl sulfide and benzoic acid has no effect (see Figure 7). This shows that it is not just the fact that VII is an aralkyl methyl sulfide which causes it to be catalytically active. If that were the case, benzoic acid plus benzyl methyl sulfide should also catalyze the reaction. Obviously, the carboxylic acid group in VII is also vital for its catalytic activity. In addition, one should note that the inability of mixtures of benzoic acid and benzyl methyl sulfide to effect catalysis of the racemization in acetonitrile and the observed catalysis by VII shows that VII is a tremendously more effective catalyst for the racemization than such mixtures. Finally, the fact that methylthioacetic acid shows no catalytic effect on the rate of

racemization in acetonitrile compared to the effect shown by VII probably is due (for the most part) to the fact that the former has already been established to be a poor nucleophilic reagent; but, more important, this observation also might imply that there is a geometrical requirement for the catalysis of the racemization of optically active thiolsulfinates by polyfunctional catalysts. These results show clearly that the catalysis of the racemization by VII in acetonitrile involves bifunctional intramolecular catalysis by the sulfide functional group and the carboxylic acid functional group of that molecule.

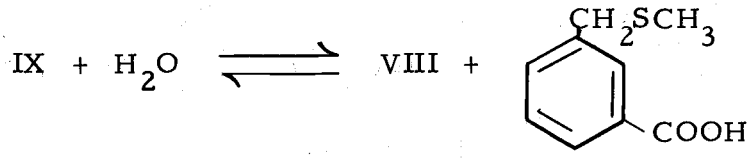
The fact that intramolecular bifunctional catalysis by VII can be observed in acetonitrile but not in 60% dioxane would seem to provide an important clue regarding some of the details of the mechanism of the catalysis by VII in acetonitrile. Sulfinyl groups, -S-, are good hydrogen-bond acceptors (37). One can accordingly envision the formation of hydrogen-bonded complexes of PhS(O)SPh with both water (VIII) and VII (IX). In 60% dioxane because of the large concentration of water, the concentration of IX will be much smaller than it is in acetonitrile where VII is the only hydrogen-bond donor available. This can be perhaps seen most easily by referring to the following equilibria.



VIII



IX



If IX is the key initial intermediate in the intramolecular bifunctional catalysis of the racemization by VII, then one can understand why such catalysis is easily observed in acetonitrile but not in aqueous dioxane.

We therefore suggest that the mechanism for the catalysis of the racemization of (+) PhS(O)SPh by VII in acetonitrile involves the initial formation of the hydrogen-bonded complex IX. In the complex, the sulfide functional group of VII is appropriately situated so that it can attack the sulfenyl sulfur of the thiolsulfinate. This nucleophilic attack by the sulfide is synchronous with a breaking of the sulfur-sulfur bond in the thiolsulfinate and with an actual transfer of the proton from the -COOH group to the original sulfinyl group (Chart II). Formation of the zwitterion (X) in the rate-determining

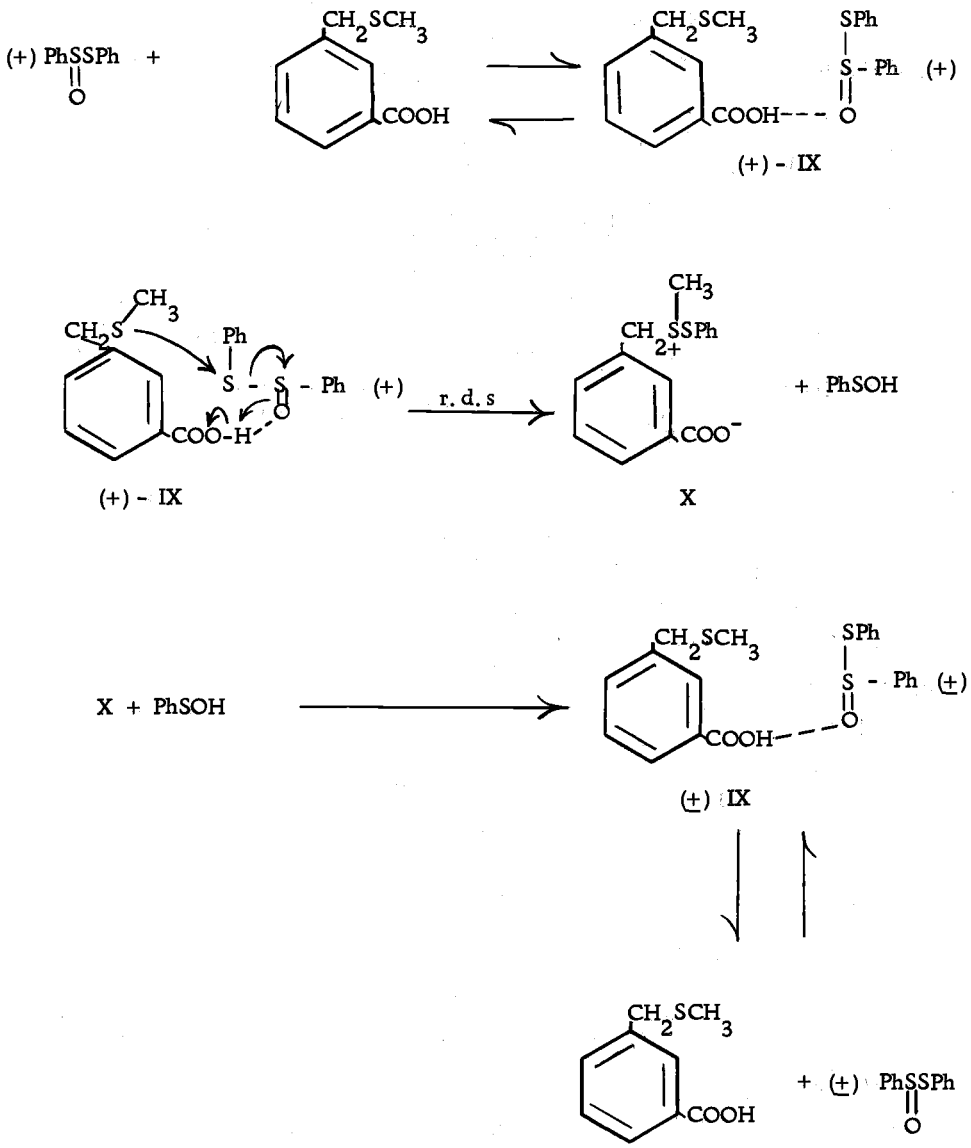


Chart II. The mechanism of the racemization of (+) phenyl benzenethiolsulfinate as catalyzed by α-methylthio-m-toluic acid in acetonitrile at 39.6°C.

step should be facilitated by the good ionizing power and high dielectric constant of acetonitrile (14). As shown in Chart II, X and PhSOH then recombine to regenerate the thiolsulfinate-VII complex, but one in which the thiolsulfinate is now optically inactive.

This mechanism, which is in accord with all the data presently available, is, of course, subject to further testing by a variety of additional experiments. For example, addition of significant concentrations of better hydrogen-bond donors than VII should lead to inhibition of the catalysis by VII in acetonitrile. Another example would be that if the equilibrium constant for the formation of IX is favorable enough, one ought to see a saturation effect after the addition of sufficient VII. It is hoped that further work concerning such additional experimental aspects of this process can be carried out in the near future.

Analogies Between the Intramolecular Bifunctional Catalysis of the Racemization of (+) Phenyl Benzenethiolsulfinate by α-Methylthio-m-Toluic Acid in Acetonitrile and an Enzyme-Catalyzed Process

Ever since the work of Arrhenius in the late 19th century and Michaelis and Menton in the early 20th century, enzymes have been thought to work by forming intermediate complexes with their substrates: the substance whose chemical reactions they catalyze. The theory of the enzyme-substrate complex, which underlies all

present thinking about enzyme activity, is that an enzyme molecule provides a site on its surface to which a substrate molecule can bind in a quite precise way (16, 54). In many enzyme-catalyzed reactions the initial substrate-enzyme complex may be due to weak hydrogen-bonded, donor-acceptor interactions between the enzyme and substrate molecules resulting in an association between the two; and examples of such complexes requiring only one molecule each of the enzyme and substrate in simple enzyme-catalyzed systems are known. The nature of the complex allows reactive centers of the enzyme and substrate to assume a proper proximity to enable subsequent, more tightly bonded interactions to occur, interactions that are often actual reactions involving bond-breaking and bond-making--thereby converting the substrate into products. There are some further characteristics of enzyme-catalyzed reactions that are pertinent to the discussion: they are many times more efficient than a corresponding nonenzymatic reaction and they generally exhibit some type of specificity, whether it is the type of reaction catalyzed or the type of substrate involved in that reaction utilizing a specific enzyme, which is often attributed to a geometrical requirement for the formation of the enzyme-substrate complex. One final consideration is the view that the high catalytic efficiency and marked specificity exhibited by most enzymatic reactions implies a participation of several distinct functional groups of the enzyme in

the catalytic process.

Analogous to these characteristics of enzyme-catalyzed reactions, the racemization of (+) PhS(O)SPh as catalyzed by α-methylthio-m-toluic acid in acetonitrile involves an initial substrate-catalyst complex (IX). This complex then undergoes the rate-determining reaction shown in Chart II, analogous to the breakdown of an enzyme-substrate complex to products in an enzyme-catalyzed reaction. The fact that the sulfur-sulfur bond scission, necessary for racemization, occurs under these conditions results from the initial complex formation between the thiolsulfinate and VII that enables the sulfide group of VII to be in a favorable position to attack the sulfenyl sulfur of the thiolsulfinate while, in turn, making possible the simultaneous, complete proton transfer from the -COOH group to the sulfinyl oxygen of the thiolsulfinate. Each process, the sulfide attack and the proton transfer, cannot occur without the other and both functional groups must be attached to the same molecular skeleton within a certain minimal geometrical relationship if the reaction is to occur at a reasonable rate.

Therefore, the efficiency of VII in catalyzing the racemization in acetonitrile as compared to the lack of catalysis by mixtures of benzoic acid and benzyl methyl sulfide, and the observation that there is apparently a strict requirement for the formation of an initial complex between the thiolsulfinate and VII before the desired

reaction can proceed, lend support to the hypothesis that the process involving the racemization of (+) phenyl benzenethiolsulfinate as catalyzed by α-methylthio-m-toluic acid in acetonitrile is formally analogous to many simple enzyme-catalyzed reactions.

EXPERIMENTAL

Preparation of Materials

Optically Active Phenyl Benzenethiolsulfinate

Optically active phenyl benzenethiolsulfinate was prepared by the asymmetric oxidation of phenyl disulfide (Eastman Organic Chemicals) with d-percamphoric acid in chloroform, as described by Kice and Large (45). The recrystallized thiolsulfinate melted at 67°C. (Literature value (45) 67-68° C.). $[\alpha]_{436}^{40}$ +6° to +10° (3:2 dioxane:water), +9° to +11° (acetonitrile).

Methylthioacetic Acid

Methylthioacetic acid was prepared by the reaction of the disodium salt of thiolacetic acid (Matheson Coleman and Bell) with methyl iodide (Matheson Coleman and Bell) in water, as described by Larson (53). The methylthioacetic acid was purified by distillation, b.p. 72-76° C. (1mm). (Literature value (53) 130-131° C. at 27 mm Hg).

α-Methylthio-m-Toluic Acid

α-Methylthio-m-toluic acid was prepared according to the general scheme used for the synthesis of methyl

α-phenylthio-o-toluate by P. Mamalis (55).

Ethyl m-Toluate. Ethyl m-toluate was prepared by refluxing 68 grams (0.5 mole) of m-toluic acid (Eastman Organic Chemicals) in 460 grams (10 mole) of ethanol with 5 ml of concentrated sulfuric acid for 10 hours. The ethanol was distilled off under reduced pressure and the crude ester was poured into 200 ml of water in a 500 ml separatory funnel. One hundred milliliters of ethyl ether was added and the two layers were allowed to separate cleanly. The water layer was run off and discarded. The ether layer was washed twice with 50 ml portions of a five percent sodium bicarbonate solution and then twice with 50 ml portions of water. The ether layer was then dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. The crude ester was then distilled under vacuum, b.p. 74° C. (1mm). (Literature value (31) 224° C. (760mm)). The yield was 78 grams (95%).

Ethyl α-Chloro-m-Toluate. Ethyl α-chloro-m-toluate was prepared using a procedure employed by M. Kharasch and H. C. Brown (36) for the preparation of benzyl chloride. Sixty six grams (0.4 mole) of ethyl m-toluate was stirred with 0.5 grams of benzoyl peroxide (Matheson Coleman and Bell) and 67 grams (0.5 mole) of sulfuryl chloride (Eastman Organic Chemicals), and the mixture was heated to 60° C. in a flask equipped with an efficient reflux condenser using an ultraviolet sun lamp. A vigorous reaction took place. The

course of the reaction was followed by allowing the evolved hydrochloric acid and sulfur dioxide to pass through a tube running from the reflux condenser to just under the surface of a small amount of water contained in a small beaker. The reaction was complete when the bubbles ceased--around 20 minutes. Excess sulfuryl chloride and dissolved gases were removed from the reaction flask under reduced pressure at 60° C. The crude chloro-ester was then distilled under vacuum directly from the reaction flask. The ethyl α-chloro-m-toluate boiled at 109-110° C. (1mm). (Literature value (31) 168-169°C. at 25mm Hg). The yield was 75 grams (95%).

α-Methylthio-m-Toluic Acid. Twenty four grams (0.5 mole) of commercial methanethiol (Eastman Organic Chemicals) was cooled to -5° C. in a sealed bottle and then poured into a solution of 50 grams (1.25 mole) of sodium hydroxide in 100 ml of water at 0°C. The resulting solution was then diluted to 500 ml with absolute ethanol and heated to 60° C. Eighty grams (0.4 mole) of ethyl α-chloro-m-toluate was then added over a period of one hour to the reaction flask, which was equipped with an efficient reflux condenser. The resulting red-to-brown solution was then refluxed for one hour longer and the ethanol was then distilled off under reduced pressure. The resulting crude mixture was acidified with 50% hydrochloric acid and extracted four times with 100 ml portions of ethyl ether. The ether extracts were washed twice with 50 ml portions of a 20%

solution of ammonium chloride in water, twice with 50 ml portions of water, and then dried over anhydrous magnesium sulfate. The ether was then removed under reduced pressure. The crude acid was recrystallized twice from chloroform-n-hexane. When pure, α-methylthio-m-toluic acid melted at 89-91°C. The infra-red spectrum of the compound in KBr showed a single, sharp carbonyl absorption at 5.96μ. The proton nuclear magnetic resonance spectrum showed single peaks at 1.93δ, 3.87δ and 12.63δ with relative areas of 3:2:1 respectively, and a group of peaks centered at 7.67δ (attributed to the benzene ring protons) with a relative peak area of four.

Analysis. Calculated for $C_9H_{10}O_2S$: C, 59.3; H, 5.49.

Found: C, 59.4; H, 5.45.

Benzyl Methyl Sulfide

Benzyl methyl sulfide was prepared from benzyl mercaptan (Matheson Coleman and Bell) and methyl iodide according to the procedure described for the preparation of methylthioacetic acid (53). The sulfide was purified by distillation, b.p. 45° C. (1mm). (Literature value (31) 60° C. at 10mm).

Benzoic Acid

Commercial reagent grade benzoic acid (Matheson Coleman and

Bell) was recrystallized from water, m.p. 121-122° C. (Literature value (31) 122° C.).

Purification of Solvents

Dioxane

Dioxane (Matheson Coleman and Bell) was purified according to the procedure described by Wiberg (83). Boiling point 100°C. (Literature value (31) 101°C.).

Acetonitrile

Acetonitrile (Matheson Coleman and Bell) was refluxed over phosphorous pentoxide for five hours and then distilled through a 50 cm Vigereux column. Boiling point 80°C. (Literature value (31) 81° C.).

Procedures for the Racemization Runs

Procedure for the Racemization Runs in Acetonitrile

All racemization runs were made with a Perkin-Elmer P-22 Spectropolarimeter at 436 mμ using a one milliliter, 10 cm path length, jacketed cell thermostated to 39.6°C. The 436 mμ wavelength was chosen because no component in any racemization solution absorbed at this wavelength.

Stock solutions of all liquid reagents (benzyl methyl sulfide, etc.) in acetonitrile were prepared; solutions of the highest needed concentration of these liquid reagents were initially made; and subsequently, less concentrated solutions of these reagents were made by diluting the initial solutions with acetonitrile. All solid reagents (benzoic acid, etc.) were weighed out and directly introduced to the racemization solution flask.

Initially, 23.4 mg (0.1 mmole) of optically active phenyl benzenthiolsulfinate was put in a two milliliter volumetric flask and then any other solid reagents to be employed were weighed out and added to the flask. After that, either acetonitrile was added to the two milliliter mark in the flask or, if any liquid reagents were required, the proper amounts of stock solutions of these reagents in acetonitrile were added to the two milliliter mark. The final solutions were always two milliliters in volume and 0.05 M in thiolsulfinate.

The final solution was then transferred to the thermostated polarimeter cell, and the cell was allowed three minutes to come to thermal equilibrium before readings were begun. The optical rotation was followed as a function of time.

Procedure for the Racemization Runs in 60% Dioxane

The procedure for the racemization runs in acidic 60% dioxane was exactly the same as that outlined above except that

where one reads acetonitrile, one should read acidic 60% dioxane.

Sixty percent acidic dioxane solutions were prepared by weighing out the proper amount of standardized perchloric acid and diluting this amount to 200 ml with water. This solution was then diluted with twice the volume of purified dioxane.

Standardization of Perchloric Acid

Commercial reagent grade perchloric acid (approximately 70%--Matheson Coleman and Bell) was titrated with standardized 0.1 N sodium hydroxide using phenolphthalein as the indicator. It was found to be 70.71% by weight perchloric acid. This solution was the source of all perchloric acid used in the acidic dioxane solutions.

Procedure for the Determination of the Chemical Stability of Phenyl Benzenethiolsulfinate During Racemization

A check on the chemical stability of the thiolsulfinate was carried out for all reaction conditions used for the racemization studies by observing the ultraviolet spectrum before and after complete racemization of the optically active phenyl benzenethiolsulfinate. In all cases, the ultraviolet spectrum of the thiolsulfinate was unchanged during racemization.

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