STUDIES ON
THE OXIDATION OF ORGANIC SULFUR COMPOUNDS
BEARING SULFUR-SULFUR LINKAGE

1980

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Chapter 1

General Introduction

Oxidation of Organic Sulfur Compounds
Bearing Sulfur-Sulfur Linkage with Various Oxidizing Agents

Abstract

Oxidations of organic sulfur compounds having sulfur-sulfur linkage, including thiol, with various oxidizing agents are summarized and discussed according to the nature of the oxidizing agents.
1. Outline

Much attention and interest of chemists of various disciplines have been recently focused on organic sulfur chemistry which has been long studied since 1800's. Now organosulfur chemistry has been gradually centered around the reactions on sulfur atom, although organosulfur chemistry has been a minor part of organic chemistry which is centered around the carbon atom for many decades. There are three important fundamental types of reactions on sulfur atom, i.e. substitution, oxidation and reduction. Among these substitution reaction has been widely investigated in these two decades and the two remaining reactions have not been studied systematically though they are extremely important in biological transformations in in vivo reactions, especially in the redox reactions of living bodies.

The oxidation of organosulfur compounds, especially biologically important oxygenations of thiol and disulfide are the main theme of this investigation. Although not much systematic study has been carried out, the oxidation of these sulfur compounds is one of the most important reactions in both organic chemistry and biochemistry because the study on the oxidation of these sulfur compounds provides the basic knowledges on the metabolisms of both biologically active compounds of amino acids and hormones containing sulfur, and
sulfur containing drugs (foreign compounds) like thiamine. Meanwhile the study on the oxidation is also important in connection to the vulcanization of rubber, protection from oxidation and aging of polymers in industry and also as intermediates and precursors for various organic syntheses.

Although oxidations of thiol and disulfide have been studied both in vivo and in vitro, the mechanisms of various oxidations have not been thoroughly understood because of the complicated nature of the multistep oxidations of disulfides, and many side products or intermediates, which are, however, eventually oxidized to sulfonic acids or sometimes to inorganic sulfate with the cleavage of S-C bond. Complexity of the oxidation is also due to the varieties of oxidizing agents which lead to various oxidation pathways for oxidation and formations of various products of different oxidation states. Scheme I summarizes the oxidation products and pathways known today.

Path A is not an imaginary path, however it is not clear whether the reaction proceeds via stepwise oxidations or simultaneous multistep-oxidations like the ozonization or enzymatic oxygenations. Path B involves stepwise oxidations, however, may not be the actually-occurring route. Cleavages of sulfur-sulfur bonds during the oxidation may be attributed to the weak sulfur-sulfur bond of some of the intermediates. The dissociation energies of various sulfur compounds are listed in Table I and II. The dissociation energy of sulfur-sulfur bond of disulfide is considered to be generally ca 70 kcal/mole, e.g. 74 kcal/mole for dimethyl disulfide, and is remarkably
weakened upon subsequent oxygenation: for example, the bond energy of sulfur-sulfur linkage in methyl methanethiolsulfinate is only ca 46 kcal/mole. Therefore, with strong oxidizing agent such as permanganate or chromium trioxide the oxidation gives directly the sulfonic acid via the cleavage of sulfur-sulfur bond. However, it is not clear at what oxidation stage the cleavage of sulfur-sulfur bond takes place. The stepwise mono-oxygenation (path B) takes place under mild conditions and therefore, is easier to investigate than path A. However, in the pathway from 5 to 7 in Scheme I the cleavage of sulfur-

Scheme I Oxidation Pathway

Path A

RSH \[\rightarrow\] (RSOH) \[\rightarrow\] RSOH \[\rightarrow\] RSO\(_2\)H \[\rightarrow\] RSO\(_3\)H \[\rightarrow\] SO\(_4\)^{2-}\n
Path B

RSSR \[\rightarrow\] RSSR \[\rightarrow\] RSSR \[\rightarrow\] RSSR \[\rightarrow\] RSSR

[ ] : non-isolable compound

( ) : unknown compound during the oxidation

\[\rightarrow\] : unclarified pathway

\[\rightarrow\] : reported pathway
Table I

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dissociation Energy [ kcal/mole ]</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeS-SMe</td>
<td>74</td>
<td>1)</td>
</tr>
<tr>
<td>EtS-SET</td>
<td>72</td>
<td>1)</td>
</tr>
<tr>
<td>PhS-SPh</td>
<td>55</td>
<td>2)</td>
</tr>
<tr>
<td>AlkylSS-SSAlkyl</td>
<td>33.6</td>
<td>2)</td>
</tr>
<tr>
<td>HS-SH</td>
<td>72</td>
<td>1)</td>
</tr>
<tr>
<td>HSS-SH</td>
<td>64</td>
<td>3)</td>
</tr>
<tr>
<td>MeS(O)-SMe</td>
<td>46</td>
<td>2)</td>
</tr>
<tr>
<td>PhS(O)-SPh</td>
<td>36</td>
<td>2)</td>
</tr>
<tr>
<td>PhS(O)-S(O)C₆H₄-F-p</td>
<td>16</td>
<td>4)</td>
</tr>
<tr>
<td>PhS(O)₂-S(O)Ph</td>
<td>28</td>
<td>2)</td>
</tr>
<tr>
<td>PhS(O)₂-S(O)₂Ph</td>
<td>41</td>
<td>2)</td>
</tr>
<tr>
<td>S₂⁻ ( n = 5x10⁴ )</td>
<td>34</td>
<td>5)</td>
</tr>
<tr>
<td>Me-SH</td>
<td>75</td>
<td>2)</td>
</tr>
<tr>
<td>MeS-H</td>
<td>92</td>
<td>2)</td>
</tr>
<tr>
<td>PhS-H</td>
<td>82</td>
<td>2)</td>
</tr>
<tr>
<td>EtO-OEt</td>
<td>32</td>
<td>1)</td>
</tr>
<tr>
<td>HO-OH</td>
<td>48</td>
<td>1)</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Compound</th>
<th>Decomposition Rate at 100° sec⁻¹</th>
<th>ΔH⁺ kcal/mole</th>
<th>ΔS⁺ e.u.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArSSAr</td>
<td>2.0 x 10⁻⁸</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ArS(O)SAr</td>
<td>1.8 x 10⁻⁵</td>
<td>34.0</td>
<td>+12.0</td>
</tr>
<tr>
<td>ArS(O)₂SAr</td>
<td>stable for many hours</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ArS(O)₂S(O)Ar</td>
<td>1.6 x 10⁻¹</td>
<td>27.6</td>
<td>+11.2</td>
</tr>
<tr>
<td>ArS(O)₂S(O)₂Ar</td>
<td>3.3 x 10⁻⁸</td>
<td>40.9</td>
<td>+16.6</td>
</tr>
</tbody>
</table>
sulfur bond has been already confirmed and so the mechanism of the oxidation is not as simple as illustrated in path B. Both sulfenic acid 2 and sulfinyl sulfone 8 are actually existing compounds, however, have never been isolated nor observed during the oxidation shown in Scheme I, while α-disulfoxide 6 is too unstable to be isolated or detected but only postulated. Some other sulfur-oxidized compounds shown below can be formulated but are too unstable to be isolated and have only been proposed sometimes in the oxidation, except for 15 which can be isolated. 8)

\[
\begin{array}{cccc}
R-S-O-S-R & R-S-O-S-R & R-S-O-S-R & R-S-O-S-R \\
\downarrow & \downarrow & \downarrow & \downarrow \\
O & O & O & O \\
\end{array}
\]

\[\begin{align*}
13 & & 14 & & 15 & & 16 \\
\text{isolable }
\end{align*}\]

2. Oxidizing Agent and Mode of Oxygenation

All the oxygenating agents used to oxidize thiols and disulfides can be classified according to the nature of the oxidants. "Nucleophilic oxidant " is the reagent which attacks nucleophilically at sulfur atom to afford the sulfur-oxide, while "electrophilic oxidant" oxidizes sulfur atom via electrophilic attack of the reagent on sulfur atom. Oxidants which do not follow any clear mechanistic routes are classified to "other oxidant ", although they may be belong to either
Classification of Oxidizing Agent

A. Nucleophilic Oxidant

1. $\cdot$OH/O$_2$ (alkaline autoxidation)
2. ROO$^-$ (hydroperoxide anion)
3. RC(O)OO$^-$ (peracid anion)
4. HOO$^-$ (hydrogen peroxide anion)
5. MO$_x^-$ (metal oxide anion), e.g. MnO$_4^-$ etc.
6. R$_3$N=O (tert-amine N-oxide)
7. O$_2^-$ (superoxide anion)

B. Electrophilic Oxidant

1. ROOH (hydroperoxide)
2. RC(O)OOH (peracid)
3. H$_2$O$_2$ (hydrogen peroxide)
4. X$_2$/H$_2$O (halogen - water)
5. NO$_x$ (nitrogen oxide), e.g. N$_2$O$_4$ etc.
6. MO$_x$ (metal oxide), e.g. NaIO$_4$ etc.
7. $^1$O$_2$ (singlet oxygen)
8. O$_3$ (ozone)

C. Other Oxidant

1. O$_2^*$ (activated oxygen)
   a. biological oxidation (in vivo and in vitro)
   b. biomimetic oxidation (complex catalysis)
2. HNO$_3$ (nitric acid)
3. Pb(OAc)$_4$ (lead tetracetate)
4. MO$_x$ (metal oxide), e.g. CrO$_3$ etc.
nucleophilic or electrophilic oxidant and involve one electron oxidation. One example is activated molecular oxygen, the mechanism of which is relatively complicated and not clarified. Most common oxygenations known today are by means of electrophilic oxidants such as peracid.

In the oxygenations of sulfur compounds with various oxidizing agents these are two modes of reactions depending upon the oxidants. While the mode of oxidation will be discussed in Chapter 4, some of the mechanistic features of the oxygenations are depicted here with the use of sulfide or sulfoxide as representative sulfur compounds. Incidentally the mechanisms of these oxygenations are common for other sulfur compounds having sulfur-sulfur bond.

Sulfide is known to be oxidized with one of the electrophilic oxidants to afford the corresponding sulfoxide via two different pathways. Generally, nucleophilic oxidants cannot oxidize the sulfide to the sulfoxide. One pathway for oxygenation of sulfide involves the direct oxygenation by oxidant via an initial electrophilic attack of oxygen of the oxidant at sulfur atom, as illustrated below (eq. 1) with a

\[
\begin{align*}
\text{Ar-S} & \xrightarrow{\text{RCOOH}} \text{Ar-SO}^+ \xrightarrow{\text{Ar}} \text{Ar-SO}_2^+ + \text{RCO}_2\text{H} \\
\end{align*}
\]
rigid ring system and a representative peracid. The rate determining step is an initial electrophilic attack of oxidant on sulfur. This may be called as "one step mechanism".

The other pathway is the reaction with such oxidant as t-butyl hypochlorite which chlorinates one lone pair electrons of sulfur atom of 4-p-chlorophenylthiane with the positive chlorine to form incipiently chlorosulfonium ion, which is then attacked with -OH (or -OBu+ ) ion through a typical SN2 type reaction and subsequent deprotonation of hydroxy (or alkoxy) sulfonium ion intermediate to afford exclusively the axial sulfoxide instead of the equatorial one (eq. 2). This may be called as "two step mechanism". These two types of oxidations are well demonstrated by Johnson et al. in the oxygenation of 4-p-chlorophenylthiane with various oxidizing agents (Table III).

\[
\text{Ar} \quad \text{S} \quad \text{t-BuOCl} \quad \text{Ar} \quad \text{S} \quad \text{Cl-Bu}^+ \quad \text{S} \quad \text{Cl} \quad \text{Ar} \\
\text{Ar} \quad \text{S} \quad \text{Cl} \quad \text{S} \quad \text{Cl} \quad \text{Ar}
\]

Due to the partial positive charge on sulfur atom, the sulfoxide is reluctant to receive the attack of electrophile, thus the oxidation of sulfoxide being much slower than that of sulfide with any electrophilic oxidant (eq. 3). The electrophilic oxidation of another trivalent sulfur compounds,
<table>
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<tr>
<th>Oxidant</th>
<th>Condition</th>
<th>cis</th>
<th>trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₃</td>
<td>CCl₄ or CH₂Cl₂ (-40°)</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>tBuOOH</td>
<td>C₆H₆ (50°)</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>MCPBA</td>
<td>CH₂Cl₂ (0°)</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>H₂O₂</td>
<td>acetone (25°)</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>PhIO</td>
<td>C₆H₆ (80°)</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>NaIO₄</td>
<td>H₂O (0°)</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>N₂O₄</td>
<td>- (0°)</td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td>tBuOCl</td>
<td>CH₃OH (-70°)</td>
<td>98</td>
<td>2</td>
</tr>
</tbody>
</table>

Table III: Ratio of Cis/Trans in The Oxidation of 4-p-Chlorophenethylthiane

Sulfinic acid, has recently been shown to be difficult by Filby et al. in the oxidation of thiol with MCPBA in which thiol is selectively oxidized to the sulfinic acid at a low temperature (-30°) with no sulfonic acid (eq. 4). Under the condition,

\[
\text{R-SH} \xrightarrow{2\text{eq. MCPBA}} \text{R-SO}_2\text{H (no R-SO}_3\text{H)} \quad (4)
\]
no formation of disulfide was observed among the reaction products by GC-MS. Namely the sulenic acid, being divalent sulfur compound, may be oxidized by an electrophilic oxidant such as MCPBA to the sulfinic acid, however, MCPBA could be too electrophilic to oxidize further the sulfinic acid, a trivalent sulfur compound, at low temperature (eq. 5).

\[
\begin{align*}
R{-}SH & \xrightarrow{[O]} R{-}SOH \xrightarrow{[O]} R{-}SO_2H \\
R{-}SOH & \xleftarrow{O} R{-}SH & R{-}SOH & \xleftarrow{O} R{-}SH
\end{align*}
\] (5)

The nucleophilic attack of anion of peracid or hydroperoxide on trivalent sulfur atom gives rise to the formation of incipient sulfurane intermediate which collapses to the corresponding sulfone (eq. 6). Rate determining step in this reaction may be either the nucleophilic attack or the collapse of the sulfurane depending upon the sulfoxide, oxidant, medium, etc.

The oxidations shown in the four above equations (eq. 1, 2, 3, and 6) are quite fundamentally significant. However, these
alone are not sufficient to explain all the oxidations of
disulfide, because of the weak sulfur-sulfur bond of the
intermediates (Scheme I). One must consider the oxidations
involving the cleavage of sulfur-sulfur bond during many of the
oxygenations.

3. Nucleophilic and Electrophilic Oxygenations

Since both oxidant and the mode of the oxidation can be
devided into nucleophilic and electrophilic, nucleophilic and
electrophilic oxidations will be considered in succession.

3-1. Nucleophilic Oxidation

In general the cleavage of sulfur-sulfur bond takes place
in the nucleophilic oxidation of compound bearing sulfur-sulfur
bond since the nucleophilic attack of oxidant on one of sulfur
atoms gives rise to the cleavage.

Alkaline decomposition of disulfide has long been known to
yield a mixture of thiol and sulfinic acid.\textsuperscript{11)} It takes place
in the reaction of disulfide bearing no α- or β-hydrogen atom
but not in the reaction of alkyl disulfide in which α- or β-
elimination takes place.\textsuperscript{12,13)} Danehy and Hunter suggested
earlier the formation of the sulfinic acid in the following
Scheme II.\textsuperscript{14)} However, in the reaction of thiol or disulfide
with alkali hydroxide the influence of molecular oxygen present is very important, because the alkaline autoxidation may take place.

Thiol or disulfide has been known to be oxidized finally to the corresponding sulfinic and sulfonic acids in strong alkaline media in the presence of molecular oxygen. In 1877, Klason found that dry sodium mercaptide took up oxygen to form the sulfinate. After 86 years, Berger studied the alkaline autoxidation of thiol in detail. Wallace and his co-workers also studied the alkaline autoxidation of thiol and disulfide.

Oxidation of thiol with molecular oxygen to the corresponding disulfide catalyzed by strong bases has long been known. Wallace et al. suggested that the oxidation of thiol easily afforded the disulfide quantitatively with only catalytic amount of base and the rate of the oxidation was proportional to the strength of the base used. The rate was found to
decrease in the order: propyl- > butyl- > benzyl- > phenyl-.\textsuperscript{15a)

The mechanistic feature of the oxidation, Wallace et al\textsuperscript{18) suggested, involves one electron transfer from thiolate to molecular oxygen (Scheme III). A similar electron transfer mechanism has been proposed for the oxidation of carbanions with molecular oxygen.\textsuperscript{19) Although Scheme III is considered to be incomplete, the concept of one electron transfer process still holds today. With excess or more than catalytic amount of strong base, Berger\textsuperscript{17) and Wallace et al\textsuperscript{20) found that both thiol and disulfide were autoxidized to the corresponding sulfinic and sulfonic acids.

Wallace et al. found that thiol was converted nearly quantitatively to the sulfonic acid under their conditions,\textsuperscript{18c,20) while HMPA was found to be the best solvent in the oxidation.\textsuperscript{20b}) Wallace et al. proposed that the first step is the formation of
disulfide from thiol and in the subsequent step the nucleophilic cleavage of sulfur-sulfur bond by OH\(^-\) takes place. Sulfonic acid was believed to be obtained in the final step by the disproportionation of sulfenate anion thus formed, as shown in Scheme IV, presumably because Wallace et al. found that

\begin{align*}
\text{Scheme IV} \\
(\text{RSR} \xrightarrow{B:} \text{RSSR} + \text{OH}^- \rightleftharpoons [\text{RSOH}] + \text{RS}^-) \\
[\text{RSOH}] + \text{OH}^- \rightarrow [\text{RSO}^-] + \text{H}_2\text{O} \\
3[\text{RSO}^-] \rightarrow \text{RSO}_3^- + 2\text{RS}^-
\end{align*}

autoxidation of thiol gave the same result as that of disulfide. However, according to Scheme IV, molecular oxygen does not participate for the oxidation. This is inconsistent with the oxygen consumption observed by these investigators.\textsuperscript{20a}

Prior to these investigations, Berger already found that the main product formed was sulfinic acid, and sulfonic acid and disulfide were minor products in his detail investigation of the alkaline autoxidation of thiol, contrary to the observation of Wallace et al. who believed that the product oxidized was sulfonic acid alone. When the same oxygenation was carried out according to Wallace et al., the main product was sulfinic acid while the mechanisms of both autoxidations of thiol and disulfide were studied with the use of \textsuperscript{18}O-tracer.
experimental results will be discussed elsewhere.

Berger was foresighted enough to propose the following beautiful mechanism of the autoxidation of thiol.\textsuperscript{17} He believed that ionized thiol (thiolate anion) by base reacts with molecular oxygen to afford incipiently "peroxysulfenate" and "peroxysulfinate", new oxidants, which oxidize other species to form finally sulfinic and sulfonic acids as indicated in Scheme V.\textsuperscript{17} Berger postulated that the sulfenate anion

\begin{equation}
\text{Scheme V}
\end{equation}

formed during the reaction was a key intermediate, based on his observation that the rate was accelerated by addition of hydroperoxide or thiosulfinate into the reaction.
Although Berger's suggestion for the formation of peroxysulfur intermediates is extremely important, they have never been isolated nor confirmed. Carbon-centered peroxo compounds such as hydroperoxide are well known. Two peroxysulfur compounds postulated by Berger are analogous to the carbon-centered peroxides. Hydroperoxide and peracid correspond to peroxysulfenic and peroxysulfinic acids, respectively. Peroxysulfonic acid is also conceivable.

\[
\begin{align*}
R_3\text{COOH} & \quad \text{hydroperoxide} \\
\text{RC(O)OOH} & \quad \text{peracid} \\
\text{RSOOH} & \quad \text{peroxysulfenic acid} \\
\text{RS(O)OOH} & \quad \text{peroxysulfinic acid} \\
\text{RS(O)}_2\text{OOH} & \quad \text{peroxysulfonic acid}
\end{align*}
\]

Since peroxysulfur species are also considered to be analogously stable as compared to the carbon analogues, the formation \textit{in situ} or the detection of these peroxysulfur compounds should be quite conceivable. In fact, a few peroxysulfur intermediates have hitherto been proposed. Peroxysulfenyl radical (RSO\text{O}^-) was observed to be formed in the radiolysis of thiol in the presence of O\textsubscript{2}.\textsuperscript{21} The autoxidation of benzenesulfenic acid was reported to proceed via sulfonyl radical and peroxysulfonyl radical (RS(O)\textsubscript{2}OO\textsuperscript{·}) during the reaction.\textsuperscript{22}

Recently in electrochemical synthesis of sulfinic acid in the presence of O\textsubscript{2} peroxysulfenate anion has also been considered to be formed by the reaction of O\textsubscript{2} and thiolate anion.
which is formed electrochemically from disulfide (Scheme VI). In this reaction one electron transfer from thiolate to O$_2$ can afford thyl radical and superoxide anion (O$_2^-\) . The thyl radical reacts with O$_2$ or itself to produce peroxysulfenate or the starting disulfide.

In the alkaline autoxidation of thiol to disulfide as well as in the electrochemical synthesis of sulfinic acid, formation of superoxide anion (O$_2^-$) was postulated. Superoxide anion has been a well-known interesting oxygenating reagent in these five years, since Valentine et al. have succeeded in generating O$_2^-$ as "naked" anion by complexing with crown ether in an aprotic solvent. The superoxide anion, O$_2^-$, displays a variety of interesting reactivities such as oxidation, reduction, addition, and nucleophilic substitution reactions (Scheme VII). Reactions using O$_2^-$ have recently been developed especially in the nucleophilic substitutions of halide or tosylates which was shown to proceed in $S_N2$ fashion since the product of the
reaction with an optically active halide with \( O_2^\cdot \) was inverted.\(^{26} \) Besides the nucleophilic reactions, oxidations, reductions and additions of various simple organic compounds with \( O_2^\cdot \) have also been studied and well summarized in two reviews.\(^{27} \)

Meanwhile, the reaction of sulfur compounds with \( O_2^\cdot \) has not been carried out except for two minor reactions. One is a old report by LeBeere and Berguer who found that aromatic sulfonyl chlorides reacted with \( \text{NaO}_2 \) to be converted to the corresponding sulfonate without the use of crown ether in refluxing benzene.\(^{28} \) The other is a report by Valentine et al., who carried out the reaction of a thiolester with \( O_2^\cdot \) and obtained carboxylic acid and disulfide. They also found that alkanethiols were oxidized to the corresponding disulfide in yields ranging from 60 to 70 % in control experiments without any detail data.\(^{29} \)

Therefore we have studied the oxidations of various organic
sulfur compounds with O$_2^-$ which will be discussed in Chapter 5 and 6 of this thesis.

Like the alkaline autoxidation of thiol, thiol function of cysteine$^{30}$ or cysteamine$^{31}$ has been found to be oxidized to the corresponding sulfinic acid by dioxygenation reaction with oxidation enzymes involving non-heme iron present in liver (Scheme VIII). These reactions are considered to be quite significant in biological oxidations. In both reactions two oxygen atoms of the sulfinic acids were found to have incorporated molecular oxygen from air.$^{32,33}$ Cysteine oxidase from rat liver was reported to require NAD(P)H, Fe$^{2+}$ and various co-factors while cysteamine oxidase was found to be a protein with a molecular weight of 85,000 and have one non-heme iron in one unit of the oxidase. These two oxidase are considered to be dioxygenases.
Metal oxides such as KMnO₄ are also nucleophilic oxidants like anions of peracid and hydroperoxide. As shown in Table IV compounds bearing both sulfide and sulfoxide functions were readily oxidized with MnO₄⁻ to the corresponding sulfide-sulfones, but not to disulfoxides. N-Tosylsulfurimine which usually resists to the oxidation was also oxidized to the sulfoximine by KMnO₄. The reactions are clearly nucleophilic oxidations in which oxygen of MnO₄⁻ attacks nucleophilically the trivalent sulfur, but not divalent sulfur, to form incipient sulfurane intermediate which immediately collapses to sulfone or sulfoximine as illustrated in eq. 6. This

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Sulfide-sulfone" /></td>
<td>KMnO₄/MgSO₄, H₂O</td>
<td><img src="image" alt="Sulfide-sulfone" /></td>
<td>66 %</td>
<td>34</td>
</tr>
<tr>
<td><img src="image" alt="Sulfoxide-sulfone" /></td>
<td>KMnO₄/MgSO₄, H₂O</td>
<td><img src="image" alt="Sulfoxide-sulfone" /></td>
<td>91</td>
<td>35</td>
</tr>
<tr>
<td><img src="image" alt="Sulfoxide-sulfone" /></td>
<td>KMnO₄/MgSO₄, acetone</td>
<td><img src="image" alt="Sulfoxide-sulfone" /></td>
<td>96</td>
<td>36</td>
</tr>
<tr>
<td>Ph₂S→NTs</td>
<td>MCPBA/K₂CO₃, EtOH–H₂O</td>
<td><img src="image" alt="Ph₂S→NTs" /></td>
<td>91</td>
<td>37</td>
</tr>
<tr>
<td>Ph₂S→NTs</td>
<td>KMnO₄, acetone</td>
<td><img src="image" alt="Ph₂S→NTs" /></td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Ph-S-Me ↓ NTs</td>
<td>H₂O₂/NaOH, MeOH</td>
<td>Ph-S-Me ↓ NTs</td>
<td>98</td>
<td>39</td>
</tr>
</tbody>
</table>

Table IV  Nucleophilic Oxidation of Trivalent Sulfur Compounds
nucleophilic oxidation is in good contrast to the electrophilic oxidation with typical electrophilic oxidant, MCPBA, to form disulfoxide (eq. 7). However, N-tosylsulfilimine which strongly resists to MCPBA oxidation was found to be readily oxidized with the anion of MCPBA in a good yield (Table IV).

Apart from the oxidation of disulfide to thiosulfinate (mono-oxide) there has been no example in which the sulfur-sulfur linkage was kept during the oxidation with metal oxides. Thiols and disulfides were also oxidized to the corresponding sulfonic acid with KMnO₄. The oxidation of disulfide with KMnO₄ may also be nucleophilic, however, it is not known at what oxidation stage the disulfide bond cleaves (eq. 8 and 9).

NaIO₄ may be a good electrophilic oxidant, since it is a selective oxidizing agent of sulfide to sulfoxide, as described later in the electrophilic oxidation. However, NaIO₄ is an
amazingly interesting nucleophilic oxidant of thiolsulfinate to
the corresponding thiolsulfonate without cleavage of sulfur-
sulfur linkage. This reaction will be mentioned in Chapter 3,
while the mechanism of this oxidation and other oxidations with
metal oxides will be described in Chapter 4.

Compounds having semipolar N-O bond are also known to be a
mild oxidant. Pyridine N-oxide was reported to oxidize
sulfoxide to sulfone or sulfonic acid.\(^{42}\) The reactions of
sulfenyl chloride,\(^{43}\) sulfinyl chloride\(^{44}\) and disulfide\(^{45}\) with
aromatic amine N-oxide afforded appreciable amounts of sulfonic
acid after hydrolysis while the N-oxide was reduced to the
aromatic amine. In the reaction of p-nitrobenzenesulfenyl
chloride with pyridine N-oxide ESR signal of sulfinyl radical
was observed and hence thiolsulfonate was considered to be
resulted by recombination of resulted sulfinyl radicals and
then be converted to the sulfonic acid by hydrolysis.
Presumably oxygen of the N-oxide attacked initially the sulfur
atom eventually leading to the oxidation.\(^{43}\)

3-2. Electrophilic Oxidation

The oxidation with such an electrophilic oxidant as peracid
does seldom cause the apparent cleavage of sulfur-sulfur bond at
the initial stage of oxidation of disulfide unless the vigorous
condition is chosen. However, except for the first oxidation
step from disulfide to thiolsulfinate, the cleavage of sulfur-sulfur bond has been observed usually. Six-membered cyclic disulfides were reported to be oxidized to the corresponding α-disulfones as final oxidation products with peracid without any apparent cleavage.\textsuperscript{46} Therefore, in the preparation of such linear sulfur-oxidized compounds bearing sulfur-sulfur bond as 4 - 9 in Scheme I, the direct oxidation of disulfide was avoided: instead the condensation reaction of two sulfur compounds was used. However, cyclic derivatives were oxidized directly with peracids to the oxides.

Oxidation of disulfide is known to be slower than that of sulfide with, for example, the Milas reagent (\( \text{H}_2\text{O}_2 \ - \ ^\text{t}\text{BuOH} - \ V_2\text{O}_5 \)), giving only the sulfoxide in the oxidation of such a compound having both sulfide and disulfide functions.\textsuperscript{47} However, electronegativity of disulfide is considered to be higher than that of sulfide from values of NMR chemical shifts of the two (dimethyl disulfide: 2.30 ppm, dimethyl sulfide: 2.06 ppm).\textsuperscript{2} A kinetic study on the oxidation of substituted diaryl sulfides with perbenzoic acid showed that there is a good Hammett correlation with \( \rho \) -value of -2.5, which indicates the reactions to be electrophilic oxidations.\textsuperscript{48} Oxidation of disulfide by peracid is also considered to be electrophilic, although no precise kinetic study has been carried out yet. However, the electron-rich sulfur atom has long been known to be preferentially oxidized (Table V) while steric effects sometimes overcome the electronic effect to reverse the site of oxidation to the other sulfur atom as shown in Table V. Examples shown
Table V  Oxidation of Disulfide

<table>
<thead>
<tr>
<th>Disulfide</th>
<th>Condition</th>
<th>Product</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ \text{O}_2\text{N} \text{S-S-} ]</td>
<td>AcOOH</td>
<td>[ \text{O}_2\text{N} \text{S-S-} ]</td>
<td>49</td>
</tr>
<tr>
<td>[ \text{N} \text{S-S-} \text{R} ]</td>
<td>PhCO(_3)H</td>
<td>[ \text{N} \text{S-S-} \text{R} ]</td>
<td>50</td>
</tr>
<tr>
<td>( R = \text{iPr, tBu, cyclohexyl } )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ \text{O}_2\text{N} \text{S-S-} \text{R} \] | AcOOH | \[ \text{O}_2\text{N} \text{S-S-} \text{R} \] | 49 |
| \( R = \text{H, 3-Me, 5-NO}_2 \) |

\[ \text{RSS}^{t\text{Bu}} \] | AcOOH or MCPBA | \[ \text{RSS}^{t\text{Bu}} : \text{RSS}^{t\text{Bu}} \] | 51 |
| \( R = \text{Me} \) | 1 | 1.74 |
| \( R = \text{Et} \) | 1 | 2 |

above in Table V may not be suitable, since the oxidation products are dioxygenated products: oxidation of mono-oxide to di-oxide is believed to cause the cleavage of sulfur-sulfur bond during the reaction. The below examples show that electronic effect seems to be larger than steric effect in the oxidations of methyl and ethyl tert-butyl disulfides with peracids. In
any case, the oxidation with peracids appears to take place preferentially on electron-rich sulfur atom of the disulfide without being perturbed seriously by steric effect.

With excess hydrogen peroxide, products obtained before completion of the oxidation are sulfur compounds of various oxidized states (eq. 10),\textsuperscript{52} suggesting that differences between energy barriers of various reactions involving oxidation and cleavage of sulfur-sulfur bond are not so large. In fact, the yield of thioisulfinate (monoxide) was not so high when

\[
\text{PrSSPr} \xrightarrow{30\% \text{H}_2\text{O}_2, \text{AcOH}} \text{PrSSPr} + \text{PrSSPr} + \text{PrSO}_2\text{H} + \text{PrSO}_3\text{H} \quad (10)\textsuperscript{52}
\]

the disulfide was oxidized directly by peracid as reported by Cavallito et al. (eq. 11).\textsuperscript{53} However, the mono-oxide of

\[
\text{RSSR} \xrightarrow{\text{perbenzoic acid}, \text{CHCl}_3, \text{r.t., 1h}} \text{RSSR} \xrightarrow{63\%} \quad (11)\textsuperscript{53}
\]

\( R = \text{Me, Et, Pr, }^i\text{Pr, Bu, Amyl} \)

six-membered cyclic disulfide was easily obtained nearly quantitatively by the direct oxidation with hydrogen peroxide in acetic acid (eq. 12).\textsuperscript{54} Mechanism of the oxidation of disulfide with peracid, hydrogen peroxide or hydroperoxide be identical to that of sulfide with peracid as shown in eq. 1.
Namely, the oxidation proceeds via electrophilic attack of oxygen of the peracid at the electron-rich sulfur atom.

An optically active thiosulfinate was prepared by direct oxidation of an optically active disulfide. Namely, Savige et al. carried out the oxidation of cystine with peracetic acid or performic acid. The oxidation gave a mixture of diastereomeric thiosulfinates which were separated by fractional precipitation from aqueous solution. After a year, Savige and Fava prepared an optically active thiosulfinate by oxidation of a disulfide with an optically active peracid but the optical purity of the product was low. Racemization in pyridine was immeasurably fast. Later they synthesized optically active trivalent sulfur compounds such as thiosulfinate, sulfinate and sulfinamide with an optically active peracid from the corresponding divalent sulfur compounds, but the stereoselectivity was also low (∼2.2%) (eq. 13). Kice and Large also
prepared optically active phenyl benzenethiolsulfinate of unknown optical purity by oxidation with d-camphoric acid ($[\alpha]_{D}^{25} + 5.11 \pm 0.230^\circ$).\textsuperscript{59}

When thiolsulfinate, mono-oxide, is oxidized further, two pathways shown in Scheme I are possible. Only one product, di-oxide, should be obtained from symmetrical thiolsulfinate, however, four products of di-oxides should be formed from unsymmetrical thiolsulfinate (eq. 14).\textsuperscript{60} Only two decades ago, the initial oxidation product of thiolsulfinate was believed to be "$\alpha$-disulfoxide" instead of thiolsulfonate.\textsuperscript{61} $\alpha$-Disulfoxide was suggested as an important intermediate in earlier studies on the oxidation of cystine and its derivatives in connection with the biological oxidation of disulfide.\textsuperscript{62} However, the compound was later corrected as an equimolar mixture of the disulfide and the thiolsulfonate. All the imaginary "$\alpha$-disulfoxide" eventually turned out to be the corresponding thiolsulfonate. Since the mechanism of the oxidation of sulfide or disulfide was found to be initiated by the electrophilic attack of oxidant, incipient formation of $\alpha$-disulfoxide has again been reconsidered. Several attempts to prepare the $\alpha$-disulfoxide have been performed, however, in

\begin{equation}
\text{RSSR'} \xrightarrow{[\text{O}] \text{O}} \text{RSSR} + \text{RSSR'} + \text{RSSR} + \text{R'SSR'} (14)
\end{equation}
vain. First, in 1957 Barnard suggested that the unstable intermediate, α-disulfoxide, which could be formed by the reaction of benzenesulfinyl chloride with zinc, would be converted to the corresponding thiolsulfonate, without any concrete evidence (eq. 15). Barnard, however, demonstrated that α-disulfoxide, presumed to be formed initially in the oxidation of symmetrical $^{35}$S-labelled aryl arenethiolsulfinate with $H_2O_2/\text{AcOH}$, was converted to the corresponding thiolsulfonate as shown below (Scheme IX). In the

\[
\text{PhSCl} \quad + \quad \text{Zn} \quad \xrightarrow{\text{ZnCl}_2} \quad [\text{Ph}^-\text{S}^-\text{S}^-\text{Ph}]^{0^-} \quad \xrightarrow{\text{H}_2\text{O}_2/\text{AcOH}} \quad [\text{Ph}^+\text{S}^+\text{S}^-\text{Ph}]^{0^-} \quad \xrightarrow{} \quad \text{Ph-S-S-Ph}
\]

(15)
meantime, Modena et al. suggested the formation of intermediary \( \alpha \)-disulfoxide based on their kinetic studies on the oxidations of substituted diaryl disulfide\(^{64}\) and aryl arenethiolsulfinate\(^{65}\) by perbenzoic acid. Recently Chau and Kice studied the oxidation of unsymmetrical thiolsulfinate, \( p-FC_6H_4S(O)SC_6H_5 \), with peracetic acid by following \(^{19}\)F-NMR at a low temperature (eq. 16)\(^4\). However, they could not detect any \( \alpha \)-disulfoxide by \(^{19}\)F-NMR study at \(-27^\circ\), and calculated that at least 73% of the oxidation underwent via path involving \( \alpha \)-disulfoxide as an intermediate, from the integration ratio and the distribution

\[
\begin{array}{c}
\text{Ph-S-S} \quad F \\
\downarrow \quad \text{O}
\end{array} \xrightarrow{\text{AcOOH}}
\begin{array}{c}
\text{Ph-S-S} \quad F \\
\downarrow \quad \text{O}
\end{array} \xrightarrow{\text{Ph-S-S}}
\begin{array}{c}
\text{Ph-S-S} \quad F \\
\downarrow \quad \text{O}
\end{array}
\]

(16)\(^4\)

of the products of symmetrical thiolsulfonate. They also suggested that the \( \alpha \)-disulfoxide was thermally unstable because \( \Delta H^\circ \) for the decomposition of \( \alpha \)-disulfoxide would be less than 16 kcal/mole since the half-life of the \( \alpha \)-disulfoxide should be less than 60 sec at \(-60^\circ\) and therefore \( \alpha \)-disulfoxide is not stable enough as an intermediate to be detectable during the oxidation. The formation of thiolsulfonate by oxidation of sulfenyl sulfur of thiolsulfinate was considered by Kice et al. to be resulted by degradation of the \( \alpha \)-disulfoxide to two sulfinyl radicals, which eventually recombine to form
symmetrical and unsymmetrical thiolsulfonates.

Our new study which will be described in Chapter 2, also has given supporting evidence for intermediary formation of $\alpha$-disulfoxide by using $^{18}$O-labelled thiolsulfinate.

As mentioned at the beginning of this chapter, among the oxidation products of thiolsulfonate shown in Scheme I sulfinyl sulfone (8) has not been isolated. $\alpha$-Disulfone, $\text{RSO}_2\text{SO}_2\text{R}$, has long been isolated in the oxidation of disulfide or thiolsulfonate with hydrogen peroxide or MCPBA. In one of the early works of Gilman et al.,$^{66}$ p-tolyl p-toluenethiol-sulfonate was oxidized with peroxide to the corresponding $\alpha$-disulfone but the yield was not reported. Baroni also prepared diethyl derivatives by the oxidation of the disulfide with peroxide,$^{67}$ while Barnard obtained a small amount of $\alpha$-disulfone upon treatment of disulfide by ozone.$^{68}$ Allen and Brook studied successive oxidations of long chain alkyl disulfide in which all the sulfur atoms of disulfide are oxygenated in stepwise manner, eventually yielding $\alpha$-disulfones by treatment with $\text{H}_2\text{O}_2$ (eq. 17).$^{69}$ They obtained $\alpha$-disulfone

\[
\begin{array}{ccc}
\text{RSSR} & \xrightarrow{[O]} & \text{RSSR} \\
\downarrow \text{O} & & \downarrow \text{O} \\
\text{RSSR} & \xrightarrow{[O]} & \text{RSSR} \\
\downarrow \text{O} & & \text{RSSR}
\end{array}
\]

\[R = \text{C}_{11}\text{H}_{23}, \text{C}_{12}\text{H}_{25}, \text{C}_{14}\text{H}_{29}, \text{C}_{16}\text{H}_{33}\]

from disulfide or thiolsulfonate in 22% or 37%, respectively. While they could not obtained sulfinyl sulfone (RSOSO₂R) in the
course of the oxidation, Field and Barbee also could not observe the formation of the trioxide even in the oxidations of stable 1,2-dithiane, 1,2-dithiolane and 1,2-dithiepane with various oxidizing agents.\textsuperscript{70}) The yields of three α-disulfones were rather low, i.e. 27 - 42% for 1,2-dithiane, 8% for 1,2-dithiolane and 10% for 1,2-dithiepane. Therefore, isolation or detection of sulfinyl sulfone in the course of the oxidation from thiolsulfonate to α-disulfone, if successful, would be quite significant to verify the formation of sulfinyl sulfone as an intermediate during the oxidation, although sulfinyl sulfone can be nicely prepared by condensation of sulfinic acid and sulfinyl chloride.\textsuperscript{71)}

Singlet oxygen, $^1\text{O}_2$, can also oxidize not only sulfide to the sulfoxide but also disulfide to the thiolsulfinate and the thiolsulfonate. Diaryl\textsuperscript{72)} and dialkyl\textsuperscript{73)} sulfides were readily oxidized to the sulfoxides and the sulfones by $^1\text{O}_2$ (eq. 18).

\[
\begin{array}{ccc}
\text{Ar-S-Ar} & \xrightarrow{^1\text{O}_2} & \text{Ar-S-Ar} \\
\text{fast} & & \text{slow}
\end{array}
\]

Amino acid such as methionine was also oxidized to the sulfoxide.\textsuperscript{74)} The oxidation of sulfide with $^1\text{O}_2$ is represented by workers of Foote,\textsuperscript{75)} Wasserman\textsuperscript{76)} and Sinnreich.\textsuperscript{77)} The mechanism of the oxidation of sulfide is very similar to that of disulfide which is described as follows (Scheme XI). Oxidation of dialkyl
disulfide afforded the corresponding thiolsulfinate and a small amount of thiolsulfonate by \(^{1}O_2\) which was derived from the photo-sensitized system (eq. 19)\(^{77}\) and also from triphenyl phosphite ozonide (eq. 20).\(^{78}\) In \(^{1}O_2\) oxidation of dialkyl disulfide the corresponding thiolsulfinate and a small amount of thiolsulfonate by \(^{1}O_2\) which was derived from the photo-sensitized system (eq. 19)\(^{77}\) and also from triphenyl phosphite ozonide (eq. 20).\(^{78}\) In \(^{1}O_2\) oxidation of dialkyl disulfide

\[
\text{RSSR} \xrightarrow{\text{hv} / O_2 / MB \; \text{MeOH}} \text{RSSR} + \text{RSSR} \quad (19)\(^{77}\)
\]

\[
R = \text{Me, Et, } i\text{Pr, } t\text{Bu}
\]

\[
\text{RSSR} \xrightarrow{(\text{PhO})_3\text{P} \; O \; O} \text{RSSR} + \text{RSSR} \quad (20)\(^{78}\)
\]

\[
R = \text{Me, Et, } t\text{Bu}
\]

disulfide was readily oxidized by \(^{1}O_2\) while aromatic and some cyclic alkyl disulfides were found not to be oxidized by \(^{1}O_2\).\(^{77}\) The oxidation of thermally unstable disulfide such as 1,2-dithiolane yielded the thiolsulfinate upon \(^{1}O_2\) (eq. 21).\(^{79}\) The biologically important cyclic disulfide, methyl \(\alpha\)-lipoate,

\[
\text{S-S} \xrightarrow{\text{hv} / O_2 / MB \; \text{MeOH}} \text{S-S} \quad (21)\(^{79}\)
\]

was also oxidized to give two regio-isomeric thiolsulfonates together with four regio- and stereo-isomeric thiolsulfinites.
by photo-sensitized $^{1}{O}_2$ and triphenylphosphite ozonide oxidations (Scheme X). Mechanism of the photo-oxidation is very similar to that of sulfide as reported by Foote et al. and considered to be the following since 1/2 mole of oxygen is absorbed for one mole of disulfide. When diethyl disulfide was exposed to $^{1}{O}_2$ in the presence of diphenyl disulfide which is quite inert to $^{1}{O}_2$, both thiol sulfinate were obtained as shown in Scheme XI. Photo-oxidized peroxythiol sulfinate initially formed may oxidize other disulfides present in the system by the electrophilic attack of the peroxy oxygen to
afford two thiol sulfinates. Interestingly, the cleavage of sulfur-sulfur bond has not been observed in these oxidations.

Block et al. reported differences of product distributions between the oxidations of unsymmetrical alkyl disulfide with peracid and those with photo-sensitized singlet oxygen. The ratios of regio-isomers of thiol sulfinates in photo-oxidation were reverse to those of peracid oxidation (Table VI).

Electronic effect was important in peracid oxidations as described before while steric effect influenced the ratio of

<table>
<thead>
<tr>
<th>Disulfide</th>
<th>Ratio of Regio-isomeric Thiol Sulfinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSS^tBu</td>
<td>Condition</td>
</tr>
<tr>
<td>R = Et</td>
<td>MCPBA or AcOOH in CHCl₃</td>
</tr>
<tr>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>Me(0.1M)</td>
<td>hv / O₂ / MB in MeOH</td>
</tr>
<tr>
<td>Me(0.25M)</td>
<td></td>
</tr>
</tbody>
</table>
regio-isomers in the photo-oxidation since the photo-oxidation proceed presumably via the sterically crowded peroxythiolsulfinate [A] which reacted with other disulfide to produce two thiol-sulfinates. The oxidation of α-lipoic acid in a buffer solution (pH 8.8, Tris HCl buffer), and those of cystine and its derivatives by 1O2 are also known.

Reaction of thiol with ozone, O3, has not been carried out, though it is considered to react with O3. Disulfide readily reacted with O3 and the reaction is well reviewed. However, this reaction has not been investigated enough to understand the mechanism. Generally disulfide absorbs 3 mole of O3 to afford sulfonic anhydride in 80 - 90 % as fast as alkyl sulfoxide (eq. 22), regardless of the structure of the disulfide. Dibenzyl disulfide reacts with O3 to afford degradation products instead of the acid anhydride but with only 2 mole of O3 the corresponding thiosulfonate was obtained in 85% yield. Thiolsulfonate usually obtained as a by-product is not believed to be an intermediate since it is not oxidized with O3. This unreactivity is considered to be due to the electron-withdrawing effect of sulfonyl group of thiosulfonate and is comparable to that of thioester (eq. 23). Another product is

\[
\begin{align*}
\text{RSSR} & \xrightarrow{O_3} \left\{ \begin{array}{c}
\text{RSOSR} \\
\text{RSO}_2\text{SR} \\
\text{RSO}_2\text{SO}_2\text{R}
\end{array} \right\} \xrightarrow{O_3} \text{O} \quad \text{O} \\
R &= \text{alkyl, aryl}
\end{align*}
\]

(22)
RSO₂SR and RCSR \[ \xrightarrow{O₃} \text{no reaction} \]  (23)

α-disulfone. Although thiolsulfinate cannot be found during the oxidation of disulfide with O₃, thiolsulfinate is believed to be an intermediate since it reacts, in fact, with 2 moles of O₃ to afford mainly sulfonic acid together with a small amount of thiolsulfonate in a slower rate than that of disulfide. The following crude mechanism was proposed (Scheme XII).  

Scheme XII

\[
\begin{align*}
\text{RSO}_2\text{SR} + \text{O}_3 & \rightarrow \text{RSO}_3\text{H} + \text{S}_2\text{O}_8 \\
\end{align*}
\]

Tetrasulfide is also oxidized similarly to afford the sulfonic anhydride and sulfur dioxide.  

Halogens may be used with or without several bases to oxidize sulfide to the corresponding sulfoxide without formation of sulfone via the attack of hydroxide anion on the halosulfonium ion.
Reactions of disulfide and thiol with halogens are relatively complicated but have long been studied and well-documented. Mild oxidation of thiol with halogen affords

\[
RSR' \xrightarrow{X_2} \left[ \frac{X}{R-S-R'} \right] X^- \xrightarrow{H_2O} RSR' + HX ∙ NR_3 \quad (24)
\]

at first the corresponding disulfide and sulfenyl halide. Further oxidation causes the cleavage of sulfur-sulfur bond. Thiol and disulfide are known to react with Cl₂ or Br₂ in aqueous solution or in acetic acid to afford the corresponding sulfonyl halide or sulfonic acid (eq. 25 and 26).

\[
EtSH + 3 Br₂ + 3 H₂O → EtSO₃H + 6 HBr \quad (25)
\]

\[
PhCH₂SH + 3 Br₂ + 2 H₂O → PhCH₂SO₂Br + 5 HBr \quad (26)
\]

\[
MeSSMe + 5 Cl₂ + 4 MeOH → 2 MeSO₂Cl + 4 CH₃Cl + 4 HCl \quad (27)\]

Although sulfenyl chloride is prepared by the reaction of thiol or disulfide with Cl₂ in non-hydrolytic media, the reaction of thiol or disulfide with Cl₂ in the presence of equimolar amount of acetic acid or acetic anhydride is a good method for synthesis of sulfinyl chloride (eq. 28). The reaction is considered to proceed via the interaction of the acid with the intermediary sulfenyl trichloride formed in the reaction of thiol or disulfide.
\[
\begin{align*}
(\text{O}_2\text{N}-\text{S}-)_2 + \text{CH}_3\text{COOH} + \text{Cl}_2 & \rightarrow O_2\text{N}-\text{SCl} + \text{CH}_3\text{COCl} + \text{HCl} \quad (28) \quad ^{44} \\
\text{RSX}_3 + \text{CH}_3\text{COOH} & \rightarrow \text{RSX} + \text{CH}_3\text{COX} + \text{HX} \quad (29) \quad ^{89}
\end{align*}
\]

with gaseous chlorine (eq. 29) \(^{89}\)

Thiol or disulfide was found to be oxidized to the corresponding sulfonic acid with DMSO in the presence of a catalytic amount of Br\(_2\), I\(_2\), HBr, or HI. \(^{90}\) Stoichiometric equations of the reactions of thiol and disulfide are as follows (eq. 30 and 31). This reaction can be applied for syntheses

\[
\begin{align*}
\text{RSH} + 3 \text{CH}_3\text{SCH}_3 \xrightarrow{\text{cat.}} & \text{RSO}_3\text{H} + 3 \text{CH}_3\text{SCH}_3 \quad (30) \quad ^{90} \\
\text{RSSR} + 5 \text{CH}_3\text{SCH}_3 + \text{H}_2\text{O} \xrightarrow{\text{cat.}} & 2 \text{RSO}_3\text{H} + 5 \text{CH}_3\text{SCH}_3 \quad (31) \quad ^{90}
\end{align*}
\]

of special sulfoxides such as bis-sulfoxide \(^{91}\) and methionine sulfoxide \(^{92}\) from the corresponding sulfide without any formation of sulfone. The mechanism presumed is the following equation (32).

\[
\begin{align*}
\text{Me}_2\text{SO} \xrightarrow{2\text{HX}} & \text{[Me}_2\text{S-X} \text{]}^+ \text{X}^- \xrightarrow{\text{R}_2\text{S}} \text{[R}_2\text{S-X] \xrightarrow{\text{H}_2\text{O}}} \text{R}_2\text{SO} + 2 \text{HX} \\
\end{align*}
\]

(32) \(^{91}\)
Nitrogen oxides such as NO₂, N₂O₃ and N₂O₄ are also similar electrophilic reagents like halogens. N₂O₄ oxidizes sulfide selectively to the corresponding sulfoxide without any sulfone. The reaction is considered to proceed via formation of nitroso-sulfonium ion which then is attacked by nitrate ion at sulfur atom and subsequent attack of nitrosonium ion at nitrogen of nitroxysulfonium ion to form finally the sulfoxide and N₂O₃.

Hammett's ρ value was estimated in the reaction of substituted diaryl sulfides with N₂O₄ in CC1₄ to be -2.7⁹³) which showed the formation of substantial positive charge on the sulfur atom in the transition state of the reaction. The reaction of disulfide or thioisulfinate with N₂O₄ is so facile and gives oxidation products such as sulfonic acid and its derivatives which are the products by the cleavage of sulfur-sulfur bond, along with thioisulfonate, a side product.⁹⁴) Especially, thiol reacts very fast with N₂O₄ to afford at first unstable thionitrite (RSNO) which reacts further with N₂O₄, giving disulfide, thioisulfonate, sulfonic acid, or thionitrate (Scheme XIII).⁹⁵) With a large excess of N₂O₄, Oae et al.⁹⁶)

Scheme XIII

\[
\begin{align*}
\text{RSH} & \xrightarrow{\text{eq. } N_2O_4} \text{RSNO} & & \xrightarrow{\text{eq. } N_2O_4} \text{RSSR} \\
& \xrightarrow{N_2O_4 \ 0^\circ, t\text{-BuOH}} \text{RSSO₂R} & & \xrightarrow{5\text{eq. } N_2O_4 \ \text{r.t., } H_2O^*} \text{RSO₃H} \times 18^O \times 18O \times 30\%
\end{align*}
\]
and Weinrich\(^97\) found that disulfides were directly oxidized to the corresponding sulfonic anhydrides in good yields (eq. 33).

\[
\begin{align*}
\text{RSSR} & \quad \xrightarrow{\text{excess } N_2O_4} \quad \text{RSOSR} \\
R &= \text{alkyl, aryl}
\end{align*}
\]

In the oxidation of disulfide or thiosulfinate with equimolar amount of \(N_2O_4\) formation of thionitrite (RSNO) was noted by UV and visible spectra of its red color during the reaction.\(^95\)

From the reaction of cyclic disulfide with \(N_2O_4\), thiosulfinate was found to be an intermediate but not thiosulfonate.\(^98\)

Only in a prolonged reaction time, thiosulfonate was found to be oxidized partially to the sulfonic anhydride with excess \(N_2O_4\) at 0° for 24h in 30% yield.\(^99\) The mechanism of the reaction of disulfide to the sulfonic acid with \(N_2O_4\) is not clarified, however, thionitrite (RSNO), thionitrate (RSNO\(_2\)) and sulfonyl nitrite (RS(O)\(_2\)NO) were isolated and considered to be intermediates, while sulfinyl nitrite (RSONO) is also postulated as a transient intermediate formed in equilibrium during the reaction.\(^98\)

Meanwhile, t-butylthionitrite (\(^t\)BuSNO), t-butylthionitrate (\(^t\)BuSNO\(_2\)) and p-toluenesulfonyl nitrite (p-TolSO\(_2\)NO) were found to be stable enough to be used as good diazotizing agents even in aprotic media.\(^100\)
Periodate ion (IO₄⁻) is a very well-known reagent and usually used for the selective preparation of sulfoxide from sulfide without sulfone or the oxidative cleavage of carbon-carbon bond of α-diol or diketone. Mechanism of the oxidation of sulfide has not been clarified but is considered to proceed via a cyclic intermediate like that of the oxidation of diol or diketone (eq. 34). In fact, recently metal complex of organic molecule with chromium(V) was detected and considered to have the following structure by UV (eq. 35). Among disulfides, cyclic analogues were oxidized with periodate to the corresponding thiosulfinates or thiosulfonates, while in the reaction of linear disulfides, cleavage of sulfur-sulfur linkage usually prevails (eq. 36 and 37). Field and Kim reported that a catalytic amount of iodine (I₂) did accelerate the oxidation of the dithiane (eq. 38), which
resists against oxidation with various oxidants such as H$_2$O$_2$, MCPBA, KMnO$_4$, and CrO$_3$.\textsuperscript{103} The reaction of disulfide with NaIO$_4$ is considered to be an electrophilic oxidation like that of sulfide.

Mild oxidation of cyclic disulfide with KMnO$_4$ which is one of the strong oxidants, gave thiolsulfinate of dithiolane derivative in acidic condition while under neutral condition thiolsulfonate was produced (eq. 39).\textsuperscript{104}

Ammonium persulfate (\(\text{NH}_4\)\textsubscript{2}S$_2$O$_8\)) was also found to oxidize cyclic disulfide, isolipoic acid, to the corresponding thiolsulfinate (eq. 40).\textsuperscript{105} Bergson et al. suggested that the
rate-determining step of the reaction is one electron transfer process because the rate and the reaction is of a pseudo second order. Presumably the one electron transfer from disulfide would decrease the electronic repulsion of both lone pair electrons on the two sulfur atoms.

3-3. Other Oxidations

Thiol and disulfide can be oxidized eventually to the corresponding methyl sulfone in living bodies as shown in the following equation (eq. 41). Disulfides taken into body is transfered to thiol and then transmethylated to the corresponding methyl sulfide which is oxidized stepwise to the sulfone. Metabolic products of thiamine alkyl disulfide in animals was investigated extensively by Suzuoki et al.

\[
\begin{align*}
\text{B}_{1}\text{SSCH}_2\text{O} & \rightarrow \text{HSCH}_2\text{O} & \rightarrow \text{MeSCH}_2\text{O} \\
\text{MeSCH}_2\text{O} & \rightarrow \text{MeSCH}_2\text{O} & \rightarrow \text{MeSCH}_2\text{O}
\end{align*}
\]
Diethyl disulfide administered into a mouse was found to be oxidized to the ethyl methyl sulfone.\textsuperscript{108) Dimethyl disulfide was also oxidized to the dimethyl sulfone in rabbit or rat.\textsuperscript{109) In contrast to these in vivo oxidations involving the cleavage of sulfur-sulfur bond, in vitro oxidations of disulfides by Oae et al. showed that 1,2-dithiane derivatives, i.e. cyclic six-membered disulfides, were converted to the mono-oxide, without cleavage of disulfide bond with both rabbit liver microsomes and the reconstituted system with purified cytochrome P-450 and co-factors (eq. 42).\textsuperscript{110) Likewise thiolsulfinate was slowly converted to the corresponding thiolsulfonate (eq. 43).

\[
\begin{align*}
\text{S-S} & \quad \text{Ms. / O}_2 / \text{NADPH} \\
& \quad \text{or} \\
& \quad \text{purified Cytochrome P-450 / O}_2 / \text{NADPH} \\
\text{S-S} & \quad \rightarrow \quad \text{S-S} \quad \text{(O)} \\
R = \text{H, Me}
\end{align*}
\]

The reaction was affected neither by catalase which decomposes \textit{H}_2\textit{O}_2, nor by DABCO which is a good quencher of \textit{^1O}_2. Therefore, the oxidation was determined to be due to cytochrome P-450 enzyme which is well-known as an important mono-oxygenation enzyme in the metabolism of various compounds.\textsuperscript{111) Cytochrome P-450 is well-known to act as a catalyst in hydroxylation of hydrocarbons, dealkylation of compounds bearing methyl group}
adjacent to hetero atom and oxygenation of sulfur. The reactivities of substrates used fall in the following order.110)

\[
\text{SMe} > \text{S-S-Me} > \text{S-S} > \text{S-O-Me}
\]

This order is in accordance with that of the reactivities in the oxidation of thiane derivatives with reconstituted system with cytochrome P-450 by Oae et al.112)

In order to examine hitherto unknown stereochemistry of the sulfoxide formed in the enzymatic oxygenation with cytochrome P-450, various sulfides were oxidized with rabbit liver microsomal cytochrome P-450. Although the enzyme is considered to have little substrate selectivity, certain amounts of optical activities were found in the sulfoxides obtained. This study will be described in Supplement.

The mechanisms of the oxygenation and dealkylation of sulfide catalyzed by cytochrome P-450 have been recently studied by Oae et al. who suggested that a key intermediate is the cation radical of sulfide resulted by one electron transfer to enzyme,
and this intermediate yields either sulfoxide or S-dealkylation product, through a competitive reaction which occurs more readily than S-oxygenation with alkyl sulfide bearing a higher acidic \( \alpha \)-hydrogen.\(^{113}\) The rate of S-oxygenation was found to correlate to the electron potential (oxidation potential) of the sulfide.

The oxidation of sulfides with microorganisms have also been carried out.\(^{114}\) In the oxidations, yields of sulfoxides are usually low, although sulfones are also rather minor by-product. However, stereoselectivity is generally high.\(^{114}\) The first example of oxidations of sulfur compounds with microbials was the oxidation of biotin to its sulfoxide with Aspergillus niger but the yield was only 2 ppm.\(^{115}\) Lincomycin,\(^{116}\) clindamycin\(^{116}\) and thioethers of steroids\(^{117}\) were also oxidized to the sulfoxides with microorganisms. Oxidation of such a common sulfide as benzyl phenyl sulfide was
carried out to afford the sulfoxide (32%, o.p. 18%) and the sulfone (9%).\textsuperscript{118} Best results were obtained by Auret et al. in the oxidations of various linear sulfides and sulfoxides to the corresponding sulfoxides and sulfones.\textsuperscript{119} In both reactions, optically active sulfoxides (oxidized and remained) were obtained in \textasciitilde 100% and \textasciitilde 82% optical purities, respectively. Both optically pure R- and S-methyl p-tolyl sulfoxides were obtained in the oxidation of the sulfide with two kinds of microbials.\textsuperscript{120}

Other oxidations such as those with HNO\textsubscript{3}, Pb(OAc)	extsubscript{4}, CrO\textsubscript{3}, and KMnO\textsubscript{4} have been carried out for several sulfur compounds.

Nitric acid is strong enough to oxidize thiol to the corresponding sulfonic acid or sometimes desulfurize thiol (eq. 44, 45).\textsuperscript{121,122} Chromic acid is also a strong oxidant to

\[
\text{CH}_3(CH_2)_2CH_2SH \xrightarrow{\text{HNO}_3} \text{CH}_3(CH_2)_2CH_2SO_3H \quad (44)
\]

\[
\text{NH}_2\text{C}=\text{S} \xrightarrow{\text{CrO}_3} \text{H}_2\text{N}\text{C}=\text{O} \quad (46)
\]

\[
(\text{AcNH-S-})_2 \xrightarrow{\text{CrO}_3} \text{AcNH-S=S-NHAc} \quad (47)
\]
convert thio-compound to the corresponding oxo-compound (eq. 46). Disulfide was oxidized to thiolsulfonate by CrO₃ (eq. 47). Lead tetraacetate was used for the preparation of sulfinate ester in the reaction of disulfide in alcohol (eq. 48). Postulated mechanism was given as follows (Scheme XV).

\[
\text{Pb(OAc)}_4 \xrightarrow{\text{CHCl}_3-\text{MeOH, reflux}} \text{RSOMe} \quad (48)
\]

\[ R = \text{Ph} \quad 62 - 69\% \]
\[ p-\text{Tol} \quad 73\% \]

**Scheme XV**

\[
\text{Pb(OAc)}_4 \rightarrow \text{Pb(OAc)}_2 + \text{OAc}^+ + \text{OAc}^-
\]

\[
\text{RSSR} + \text{OAc}^+ \rightarrow \text{RSSR}^- + \text{Ac}^+ \quad \text{OAc}
\]

\[
\text{Ac}^+ + \text{MeOH} \rightarrow \text{AcOMe} + \text{H}^+ \]

\[
\text{RSSR}^- + \text{MeOH} \rightarrow \text{RSOMe}^- + \text{RSH} \quad \text{O}
\]

Although KMnO₄ oxidation of disulfide to afford sulfonic acid or thiolsulfonate was described earlier, an interesting oxidation of sulfinic acid to α-disulfone has been known for a long time (eq. 49). Yield of α-disulfone was found to be much higher in the oxidation with Cobalt(III) sulfate in 10N-H₂SO₄ solution than KMnO₄. The reaction is so little
studied that the mechanism still remains unsolved.

4. Alkaline Hydrolysis of Thiosulfinate

Thiosulfinate is quite an interesting compound since it has three reactive centers in a molecule. Like the oxidation of thiosulfinate can take place at two sulfur atoms, hydroxide ion can attack at both sulfenyl and sulfinyl sulfur atoms in the alkaline hydrolysis of thiosulfinate. Although several kinetic studies have been carried out on the hydrolyses, the mechanism has not been thoroughly clarified. Meanwhile, the products in the hydrolysis of symmetrical thiosulfinate have long been known to be both sulfinic acid and disulfide in the hydrolysis of cystine S-mono-oxide by Savige and his coworkers (eq. 50).\(^{129}\) Another study by Utsumi et al. showed that the products were also disulfide and sulfinic acid in the disproportionation of thiamine disulfide S-mono-oxide in aqueous alcohol (eq. 51).\(^{130}\) The hydrolysis of cyclic

\[
3 \text{Cys-S-S-Cys} \xrightarrow{\text{H}_2\text{O}} 2 \text{Cys-SO}_2\text{H} + 2 (\text{Cys-S-})_2
\]  

\[(50)\]
thiolsulfinate was also studied.\textsuperscript{133)}

A kinetic study by Oae et al. indicated that the rate of the hydrolysis of diaryl thiolsulfinate is equal to that of the initial attack of OH\textsuperscript{-} on the sulfinyl sulfur of the thiol-
sulfinate.\textsuperscript{131)} However, Kice and Rogers suggested that the initial attack of OH\textsuperscript{-} occurred nearly in the same rates at both sulfenyl and sulfinyl sulfur atoms.\textsuperscript{132)}

Our new investigation using unsymmetrical thiolsulfinates strongly suggests that the mechanism suggested by Oae et al. for the alkaline hydrolysis was most plausible by the product analysis and \textsuperscript{18}O-tracer experiment. It will be described in Chapter 7.

5. \textsuperscript{1}H- and \textsuperscript{13}C-NMR Spectra

Both \textsuperscript{1}H and \textsuperscript{13}C-NMR studies of compounds bearing sulfur-
sulfur linkage have been investigated very little. Sporadic studies for \textsuperscript{1}H-NMR spectra for five membered ring compounds have been done by Kato and Numata\textsuperscript{134)} and Murray et al.,\textsuperscript{135)}
while Paukstelis et al.\textsuperscript{136} and Hortman et al.\textsuperscript{137} measured $^{13}$C-NMR spectra of disulfides and thiosulfonates. Very recently, Woody Boss and Evans, Jr., have measured $^{13}$C-NMR spectra for linear acyclic and cyclic alkyl disulfides, thiosulfinates and thiosulfonates, and studied the chemical shifts and the structures of these compounds.\textsuperscript{138}

Meanwhile, $^1$H-NMR study on heterosteric effect of isopropyl isopropanethiosulfinate was reported.\textsuperscript{139} The thiosulfinate showed in its $^1$H-NMR spectrum unusual signal pattern which appeared in a double doublet due to the two methyl groups of one isopropyl group, although these two methyl groups are considered to be magnetically equivalent. This phenomenon has been called "heterosteric effect" which is seen in other compounds having trivalent sulfur atom.\textsuperscript{139} Therefore, the effect is considered to be due to anisotropic effect of the sulfur-oxygen bond. This effect has been studied in detail by measuring various unsymmetrical thiosulfinates and will be discussed in Chapter 8.

In addition, unusual chemical shifts in both $^1$H- and $^{13}$C-NMR spectra have been observed in a series of unsymmetrical disulfides, thiosulfinates and thiosulfonates, and $^{13}$C-NMR chemical shifts, coupling constants ($J_{C-H}$) and structures of six-membered ring system containing sulfur-sulfur linkage have also investigated. Both studies will be described in Chapter 8.
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Chapter 2

Oxidation of Unsymmetrical Disulfide and Related Compounds with Peracid.

Evidence for Formations of α-Disulfoxide and Sulfinyl Sulfone as Intermediates in The Oxidations of Unsymmetrical Thiolsulfinate and Thiolsulfonate1)

Abstract

The oxidations of unsymmetrical disulfide, thiolsulfinate and thiolsulfonate were carried out. The formation of α-disulfoxide as an unstable intermediate was demonstrated in the peracid oxidation of unsymmetrical thiolsulfinate, using $^{18}O$-labelled compound. Sulfinyl sulfone was identified during the oxidation of thiolsulfonate by NMR spectra for the first time.

- 60 -
Introduction

Oxidation of disulfide is expected to proceed via various stable intermediates as shown in Scheme 1 in Chapter 1 (p.4). Oxidation of unsymmetrical disulfide with peracid affords usually two regio-isomeric thiosulfinates as primary products, of which ratio depends on the electron density of the sulfur atom, i.e. the more electron-rich sulfur atom is oxidized predominantly. However, when the electron-rich sulfur atom is substituted by a bulky group, the ratio is known to be determined by the steric effect instead of the electronic effect.

Mechanism of further oxidation of thiosulfinate has long been a matter of controversy, i.e. whether the oxidation of thiosulfinate proceeds via α-disulfoxide as an intermediate or not. Since the sulfenyl sulfur of thiosulfinate was considered to be more sensitive to the oxidizing agent than the sulfinyl sulfur, the formation of α-disulfoxide has been believed in the oxidation of cystine. The fact that no one has succeeded to get α-disulfoxide in spite of a lot of attempts made by Barnard, Modena et al., Kice and Chau, etc., is now explained in terms of the unusually small bond energy of α-disulfoxide (Chap. 1, p. 27 - 29).

Furthermore, although sulfinyl sulfone has never been characterized yet during the oxidation of thiosulfonate, in
spite of the facts that the synthesis of sulfinyl sulfone has been succeeded independently by the condensation method\textsuperscript{10}) and that the oxidation of thiolsulfonate to $\alpha$-disulfone has been known already to be possible.\textsuperscript{11,12})

In order to clarify the oxidation path of disulfide, the oxidation of unsymmetrical disulfide, thiolsulfinate and thiol-sulfonate has been investigated in this study.

Results and Discussion

Methyl phenyl disulfide \textsuperscript{3}, an unsymmetrical disulfide, was prepared by the reaction of methanesulfenyl chloride with thiophenol in the presence of pyridine (eq. 1).\textsuperscript{13})

Unsymmetrical thiolsulfinates, \textsuperscript{6} and \textsuperscript{7}, were prepared from sulfinyl chloride and thiol (eq. 2) according to the usual method.\textsuperscript{14}) In the same manner, thiolsulfonates, \textsuperscript{10} and \textsuperscript{11}, were synthesized by treating sulfenyl chloride with free sulfinic acid in the presence of pyridine (eq. 3).\textsuperscript{14})

\[
\text{MeSCl} + \text{PhSH} \xrightarrow{\text{pyridine}} \text{MeSSPh} \quad (1)
\]

\[
\begin{align*}
\text{RSCl} \quad \uparrow \quad \text{R'SH} & \quad \xrightarrow{\text{pyridine}} \quad \text{RSSR'}
\end{align*}
\]

\[
\begin{align*}
\text{RSCl} \quad \uparrow \quad \text{R'SO}_2\text{H} & \quad \xrightarrow{\text{pyridine}} \quad \text{RSSR'}
\end{align*}
\]
These substrates were oxidized with both $\text{H}_2\text{O}_2$ in $\text{AcOH}$ and MCPBA in $\text{CH}_2\text{Cl}_2$.

Product analysis was performed by using NMR method which was convenient to analyze compounds bearing methyl group, GLC, and HPLC which was very effective to analyze both thermally unstable compounds and the compounds having only aromatic substituents. As shown in Fig. I, fortunately all these compounds could be separated by HPLC. $^1\text{H}$-NMR chemical shifts of methyl groups of these compounds were listed in Table I together with the data of the related compounds.

Oxidation of Disulfide 3: When methyl phenyl disulfide 3 was treated with hydrogen peroxide in acetic acid, $S$-phenyl methane-thiosulfinate 7 was formed predominantly over $S$-methyl benzene-thiosulfinate 6, as shown in Figures, II, III and IV, in which the reaction was followed by the changes of NMR signals due to the methyl groups of the starting material 3 and the products during the oxidation of the disulfide with hydrogen peroxide( 30% ) in deuterized acetic acid. Comparison of Fig. III and Fig. IV reveals that the rate of disappearance of 3 is very sensitive to the change of the temperature. Predominant formation of 7 is completely accordance with the reported results$^{13}$ in which more electron-rich sulfur atom of disulfide is mainly oxidized, while steric effects sometimes exceeds this electronic effect, e.g. more electron-poor sulfur atom is
Figure I  High Pressure Liquid Chromatograph

Yanaco Model L-1030 (Yanaco Gel 5510)
Carrier: MeOH
Pressure: 125 kg/cm² (flow rate: 16.1 ml/h)

retention time [min]

1. MeSS(O)₂Me 8 ▲
2. MeSSMe 1 ○
3. PhSS(O)₂Me 11 □
4. PhS(O)₂SMe 10 ■
5. PhSS(O)Me 7 ○
6. PhS(O)SMe 6 ●
7. PhSS(O)₂Ph 9
8. PhSS(O)Ph 5
9. PhSSMe 3 ●
10. PhSSPh 2

MeSO₂H 12 ○
MeSO₃H 14 ×
PhSO₂H 13
PhSO₃H 15

* signs used in Figures.
Table I
NMR Chemical Shift of Compound Having Methyl Group (δ, TMS, at ca 27°)

<table>
<thead>
<tr>
<th>Compound</th>
<th>in CDCl₃</th>
<th>CD₃COOD(-D₂O)</th>
<th>CCl₄</th>
<th>other solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MeSSMe</td>
<td>2.40</td>
<td>2.07</td>
<td>2.30ⁿ</td>
<td></td>
</tr>
<tr>
<td>2 MeSSMe</td>
<td>2.66</td>
<td>2.36</td>
<td>2.67ⁿ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.98</td>
<td>2.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 MeSSMe</td>
<td>2.69</td>
<td>2.36</td>
<td>2.69ᵇ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.30</td>
<td>3.02</td>
<td>3.28ᵇ</td>
<td></td>
</tr>
<tr>
<td>4 PhSSMe</td>
<td>2.37</td>
<td>2.05</td>
<td>2.43ⁿ(CC₄)</td>
<td></td>
</tr>
<tr>
<td>5 PhSSMe</td>
<td>2.53</td>
<td>2.24</td>
<td>3.10ⁿ(CDCl₃)</td>
<td></td>
</tr>
<tr>
<td>6 PhSSMe</td>
<td>2.90</td>
<td>2.72</td>
<td>2.08ᵇ(CC₄)</td>
<td></td>
</tr>
<tr>
<td>7 PhSSMe</td>
<td>2.48</td>
<td>2.15</td>
<td>2.85ᵃ(CC₄)</td>
<td></td>
</tr>
<tr>
<td>8 PhSSMe</td>
<td>3.15</td>
<td>2.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 MeSO₂H</td>
<td>2.70</td>
<td>2.39</td>
<td>2.93ᵇ(D₂O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.44(+D₂O)</td>
<td></td>
<td>2.48(D₂O)</td>
</tr>
<tr>
<td>10 MeSO₂Na</td>
<td></td>
<td></td>
<td>2.30(D₂O)2.34ᵇ</td>
<td></td>
</tr>
<tr>
<td>11 MeSO₃H</td>
<td>3.18(2.90ᵃ)</td>
<td>2.68</td>
<td>2.98(D₂O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.90(DMSO-d₆)ᵃ</td>
<td></td>
</tr>
<tr>
<td>12 MeSO₃Na</td>
<td></td>
<td></td>
<td>2.80(D₂O)</td>
<td></td>
</tr>
<tr>
<td>13 MeSOSMe</td>
<td>3.15ᵇ(3.38ᵃ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 PhSOMe</td>
<td>3.42ᵃ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 PhSOMe</td>
<td>3.77ᵃ</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>16 MeSOSMe</td>
<td>2.87ᵇ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.23ᵇ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure II

PhSSMe $\xrightarrow{2.4 \text{eq. } \text{H}_2\text{O}_2} \xrightarrow{3} \xrightarrow{\text{CD}_3\text{COOD, 35°}}$

Relative intensity of methyl peak [%]

reaction time [h]

Figure III

PhSSMe $\xrightarrow{1.4 \text{eq. } \text{H}_2\text{O}_2} \xrightarrow{3} \xrightarrow{\text{CD}_3\text{COOD, 35°}}$

Relative intensity of methyl peak [%]

reaction time [h]
Table II  Oxidation Products of PhSSMe, 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidation System</th>
<th>Temp</th>
<th>Time</th>
<th>Product (mole %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>30% H₂O₂ (1.4eq.)</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>in CD₃COOD</td>
<td>35°</td>
<td>10h</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30% H₂O₂ (1.5eq.)</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>in CD₃COOD</td>
<td>18°</td>
<td>77h</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30% H₂O₂ (2.4eq.)</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>in CD₃COOD</td>
<td>35°</td>
<td>5h</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MCPBA (1.0eq)</td>
<td>0°</td>
<td>24h</td>
<td>15</td>
</tr>
</tbody>
</table>

* Determined by HPLC.

Figure IV

PhSSMe $\xrightarrow{\text{1.5 eq. H}_2\text{O}_2, \text{CD}_3\text{COOD}, 18^\circ}$

- 67 -
oxidized favourably when the very bulky substituent is introduced as the substituent attached to the electron-rich sulfur atom of disulfide. In this view the first step of the oxidation of the disulfide \( \text{PhSSMe} \) is expected to take place on the sulfur atom attached to methyl group.

In the next step, as shown in Figures (II - IV), major product was S-phenyl methanethiosulfonate \( \text{11} \) accompanied with very small amount of S-methyl benzenethiosulfonate \( \text{10} \). The methyl signal correspond to \( \alpha \)-disulfoxide (\( \text{PhS(O)S(O)Me} \)), which may be formed by the oxidation of more electron-rich sulfonyl sulfur of thiolsulfinate, was not observed in NMR spectra obtained during the oxidation of \( \text{3} \). This observation does not rule out the formation of [ A ] as an intermediate because of expected instability of \( \alpha \)-disulfoxide. ⁹)

The fact that the rate of the oxidation of disulfide is comparable to that of thiolsulfinate is of interest since the
electron density of sulfur atom of disulfide is greater than that of thiolsulfinate. Besides the oxidation products keeping of original S-S linkage, i.e. 10 and 11, the formation of S-methyl methanethiosulfonate 8 was also confirmed by following the reaction with NMR, showing the cleavage of S-S bond. This suggests undoubtedly the simultaneous formation of S-phenyl benzenethiosulfonate 9 (PhS(O)₂SPh ) which was, indeed detected by both GLC and HPLC, though 9 could not be observed in NMR spectra. When the oxidation of 3 was followed by HPLC, the products which cannot be observed in GLC were also detected along with other stable products. As shown in Table II (entry 4), nearly same result was obtained in MCPBA oxidation of 3. Methanesulfonylic acid 14 was found to be one of the end products. Methanesulfonic acid 12 could be detected by NMR, too. The acids were considered to be formed by the oxidation of thiolsulfonate.

These results show only an outline of the oxidation of 3 and the following questions still remain.

1. Since the total amount of 11 is comparable to that of 7 during the oxidation of 3, 11 seems to be formed via the oxidation of 7 without breaking of S-S bond. On the other hand, although substantial amount of 6 was formed during the oxidation of 3, only trace amount of 10 was detected (Fig. II and III). This suggests that oxidation of 6 does not give 10. To what compound was 6 converted?

2. At what oxidation step is the S-S linkage cleaved? No cleavage of S-S bond appears at first oxidation step of 3 ...
3. How could the acids 12 and 14 be produced? The acids are considered to be formed by the further oxidation of thiol-sulfonate.

4. Is α-disulfoxide involved in the oxidation from thiol-sulfinate to thiol-sulfonate, as an unstable intermediate?

In order to solve the above problems the oxidations of unsymmetrical thiol-sulfinate and thiol-sulfonate were carried out.

Oxidation of Unsymmetrical Thiol-sulfinate 6 and 7

In the oxidation of 7 with hydrogen peroxide in acetic acid S-phenyl methanethiosulfonate 11 was obtained as major product, along with other thiol-sulfonates such as 8 and 9 and acids (12 - 15) (Table III). Methyl signal of α-disulfoxide is expected to appear at 2.6 - 2.9 ppm (in CD$_3$COOD). However, no such signal could be observed during the oxidation of 7. While the oxidation of 7 with two equivalent of H$_2$O$_2$ was completed within an hour at the temperature higher than 35°, the products were methanesulfonic and benzenesulfonic acids in the oxidation of 7 with ten equivalents of H$_2$O$_2$ in AcOH at 70° for 5h, as shown in Table III. Notable points in this oxidation are as follows.

1) Only trace 10 was detected in the oxidation of 7 with both H$_2$O$_2$ in AcOH and MCPBA in CH$_2$Cl$_2$, in keeping with the results of the oxidation of 3 with H$_2$O$_2$ (Table III).

2) The formations of 8 and 9 apparently indicate the cleavage
Figure V

PhSSMe $\stackrel{\text{1.2eq.} \text{H}_2\text{O}_2}{\text{\delta}} \stackrel{\text{CD}_3\text{COOD, 18\degree}}{\text{\rightarrow}}$

Relative intensity of Methyl peak [%]

Reaction time [h]

Figure VI

PhSSMe $\stackrel{\text{disproportionation}}{\text{\delta}} \stackrel{\text{CD}_3\text{COOD-D}_2\text{O, 35\degree}}{\text{\rightarrow}}$

Relative intensity of Methyl peak [%]

Reaction time [h]
Table III  Oxidation Products of PhSS(O)Me, 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidation Condition</th>
<th>Product (mole %)</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>11</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30% H$_2$O$_2$(1.2eq.)</td>
<td>CD$_3$COOD</td>
<td>35°</td>
<td>1h</td>
<td>~0</td>
<td>5</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>30% H$_2$O$_2$(1.2eq.)</td>
<td>CD$_3$COOD</td>
<td>18°</td>
<td>15h</td>
<td>~0</td>
<td>2</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>30% H$_2$O$_2$(1.0eq.)</td>
<td>AcOH</td>
<td>50°</td>
<td>2/3h</td>
<td>-c</td>
<td>-</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>30% H$_2$O$_2$(1.3eq.)</td>
<td>AcOH</td>
<td>19°</td>
<td>11h</td>
<td>~0 trace</td>
<td>12</td>
<td>46</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>30% H$_2$O$_2$(1.5eq.)</td>
<td>AcOH</td>
<td>25°</td>
<td>13h</td>
<td>~0 trace</td>
<td>20</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>30% H$_2$O$_2$(1.0eq.)</td>
<td>AcOH</td>
<td>70°</td>
<td>5h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>MCPBA(1.2eq.)</td>
<td>CH$_2$Cl$_2$</td>
<td>0°</td>
<td>7.5h</td>
<td>17 trace</td>
<td>8</td>
<td>48</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>MCPBA(1.3eq.)</td>
<td>CH$_2$Cl$_2$</td>
<td>0°</td>
<td>3h</td>
<td>21 trace</td>
<td>15</td>
<td>49</td>
<td>15</td>
</tr>
</tbody>
</table>

a) Yield was determined by NMR, GLC and HPLC.
b) Yield after recrystallization from hexane.
c) -: not determined.
d) Containing MeSO$_2$H( 16 %).
e) Containing MeSO$_2$H( 9 %).
of S-S bond during the oxidation.

3) Another important observation was the incipient appearance of 4 (MeS(O)SMe) which eventually disappeared (Fig. V).

Since thiol sulfinate has been known to disproportionate to afford mainly disulfide and thiol sulfonate,\textsuperscript{15} \( \text{PhSSMe} \) was heated in NMR tube in CD\textsubscript{3}COOD-D\textsubscript{2}O at 35\textdegree for ca 76h and the disproportionation of \( \text{7} \) was fond to proceed slowly. These results were shown in eq. 7 and Fig. 6. Results in Figs. V and VI reveal

\[
\begin{align*}
\text{PhSSMe} & \xrightarrow{\text{disproportionation}} \text{PhSSMe} + \text{MeSSMe} + \\
& \xrightarrow{\text{CD}_3\text{COOD-D}_2\text{O, 35\textdegree}} \text{PhSSMe} + \text{MeSSMe} + \\
& \quad 1(42\%) \\
& \quad 8(14\%) \\
& \quad 3(31\%) \\
& \quad 2(13\%) \\
& \quad 1(\sim 0)
\end{align*}
\]
that the disproportionation of 7 can be neglected in the oxidation of 7. It is of interest that products having oxidized phenylthio moieties, such as 9 or 10, could not be obtained in the disproportionation of 7 which has an oxygen atom at sulfur atom of methylthio moiety. Namely, during the disproportionation of 7 neither the oxygen migration nor S-O bond fission occurs while cleavage of S-S bond usually takes place.

Main formation of 11 and no or little formation of 10 in the oxidation of 7 indicate that the oxidation appears to take place exclusively at sulfanyl sulfur of 7 to afford only 11, in spite of that electron-rich sulfur atom is usually oxidized faster than electron-poor one. Since S-S bond cleavage is considered to take place only when phenylthio group is oxidized, the formation of 9, PhSSO$_2$Ph, may indicate the possible formation of α-disulfoxide as an intermediate which then collapses very readily to some thiolsulfonates. Namely, at first the oxidation took place at electron-rich sulfenyl sulfur to form incipiently α-disulfoxide[ A ] which then was converted to 11, 9, etc., via oxygen migration and the cleavage of S-S bond.

In order to confirm the above assumption the oxidation of regio-isomeric thiolsulfinate 6( PhS(O)SMe ) was carried out.

The oxidation of 6, during which considerably complex methyl peaks were observed in the NMR spectra, gave eventually two symmetrical and two unsymmetrical thiolsulfonates( 8, 9, 10, and 11 ), along with further oxidized acids. The formation of the acids is considered to be due to the further oxidation of thiolsulfonates( which will be discussed later ) since the
increase of the methyl peak of 14 corresponded to the decreases of those of thiolsulfonates (10 and 11), as shown in Fig. II, VII and VIII. Product yields in the oxidation of 6 are shown in Table IV. Inspection of data of Table IV reveals that the oxidation of 6 with MCPBA in CH₂Cl₂ gives nearly same result as that with H₂O₂ in AcOH. In contrast to the oxidation of 7, oxidation of 6 gave nearly same amount of four thiolsulfonates.

On the other hand, the disproportionation of 6 in acetic acid-water at 35°C gave the same feature as that in the same reaction of 7. Namely, there was no product having oxidized methylthio moiety but the products having oxidized phenylthio moieties such
Figure IX

\[
\text{PhSSMe} \quad \xrightarrow{1.6\text{eq. } \text{H}_2\text{O}_2} \quad \text{CD}_3\text{COOD, 25°}
\]

Figure X

- PhSSMe + 1.2eq. H_2O_2, 18°
- PhSSMe + 1.4eq. H_2O_2, 18°
<table>
<thead>
<tr>
<th>Entry</th>
<th>System</th>
<th>Oxidation Condition</th>
<th>Temp</th>
<th>Time</th>
<th>6</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30% H₂O₂ (1.2 eq.)</td>
<td>AcOH</td>
<td>22°</td>
<td>5h</td>
<td>-</td>
<td>13ᵇ</td>
<td>18ᵇ</td>
<td>-</td>
<td>22ᵇ</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>30% H₂O₂ (1.4 eq.)</td>
<td>CD₃COOD</td>
<td>35° &lt; 1h</td>
<td></td>
<td>0</td>
<td>8</td>
<td>21</td>
<td>12</td>
<td>21</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>30% H₂O₂ (1.4 eq.)</td>
<td>CD₃COOD</td>
<td>18° &lt; 15h</td>
<td></td>
<td>0</td>
<td>10</td>
<td>21</td>
<td>12</td>
<td>23</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>MCPBA(1.1 eq.)</td>
<td>CH₂Cl₂</td>
<td>20°</td>
<td>20h ~ 0</td>
<td>14</td>
<td>14</td>
<td>25</td>
<td>34</td>
<td>0</td>
<td>-</td>
<td>c</td>
</tr>
<tr>
<td>5</td>
<td>MCPBA(1.2 eq.)</td>
<td>CH₂Cl₂</td>
<td>0°</td>
<td>4.5h</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>27</td>
<td>32</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>MCPBA(1.2 eq.)</td>
<td>CH₂Cl₂</td>
<td>0°</td>
<td>9h ~ 0</td>
<td>trace</td>
<td>15</td>
<td>13</td>
<td>30</td>
<td>30ᵈ</td>
<td>-</td>
<td>c</td>
</tr>
</tbody>
</table>

a) Yield was determined by NMR, GLC and LLC.
b) Isolated and purified yield.
c) Unidentified methyl peak (14 %) was observed.
d) Containing MeSO₂H (12 %).
as 9 and 10. Since the disproportionation of 6 at 35° was slower than the oxidation of 6 at the same temperature (less than 1h), the oxidation of 6 is not complicated by the disproportionation of 6. The disproportionation was also confirmed not to occur at 18°-20° for 10-20h.

One of the key intermediates, 11, was obtained by the oxidation of both 6 and 7. Although 10 was not obtained in the oxidation of 7, 11 was obtained in the oxidation of 6. The formation of 11 strongly suggests the oxidation of sulfenyl sulfur of 6 generating the intermediary α-disulfoxide which then migrates to 11. Therefore, the formations of both thiolsulfonates, 10 and 11, having original S-S linkage, can be explained by the mechanism involving [A] as shown in eq. 10.

\[
\text{PhSSMe} \xrightarrow{[O]} \left[ \begin{array}{c} \text{PhSSMe} \\ \text{PhSSMe} \end{array} \right] \xrightarrow{\text{etc.}} \text{PhSSMe} \xrightarrow{10} \text{PhSSMe} \xrightarrow{11}
\]

Furthermore, this assumption is supported by the fact that as shown in Fig. X, the rate of disappearance of 6 is faster than that of 7 in the oxidation with \( \text{H}_2\text{O}_2 \) in AcOH. This fact is nicely explained by assuming the first oxidation of sulfenyl sulfur of 6 and 7 via the reaction initiated by electrophilic attack of oxygen of oxidant, i.e. the sulfenyl sulfur of 6 is
considered to be more electron-rich than that of 7.

In order to examine whether the oxygen of 6 was incorporated truely in 11, $^{18}$O-tracer experiment was carried out.

$^{18}$O-Labelled thiolsulfinates, 6 and 7, prepared by the method mentioned already, was treated with equimolar amount of hydrogen peroxide in acetic acid or with an equivalent of MCPBA in CH$_2$Cl$_2$. After the disappearance of most of 6 and 7 (checked by TLC or HPLC), the reaction mixture was treated according to the usual procedure. The organic products mixture was subjected to column chromatography (on silica gel, eluent: CHCl$_3$ : EtOAc : hexane = 1 : 1 : 4) to separate each product.

The products thus obtained and the starting material 6 or 7 were subjected to the routine $^{18}$O analysis. The results are summarized in Table V and VI.

While $^{18}$O-labelled oxygen of 7 was nearly retained in major product 11, minor product of 9 contained very small $^{18}$O label in the oxidation of 7 with H$_2$O$_2$ in AcOH (Table V, entry 1a). In another method to examine the oxygen transfer to the

$$
\text{PhSSMe} \xrightarrow{10\text{eq. H}_2\text{O}_2} \text{AcOH, 70°, 5h} \quad \begin{cases} \text{PhSO}_3\text{H} \\ 18\text{O} \quad 100\% \end{cases} \xrightarrow{20.1\%} \begin{cases} \text{MeSO}_3\text{H} \\ 2)\text{dist.} \end{cases} \xrightarrow{1)\text{SOCl}_2} \begin{cases} \text{PhSO}_2\text{Cl} \\ \text{MeSO}_2\text{Cl} \end{cases} \xrightarrow{\text{NH}_2} \text{PhSO}_2\text{NH}_2 \quad (11)
$$
Table V

$^{18}$O-Tracer Experiments in The Oxidation of PhSS(O)Me,

<table>
<thead>
<tr>
<th>Excess $^{18}$O-atom % of 6, [Sub.]</th>
<th>Reaction</th>
<th>Excess$^a$) Incorporated</th>
</tr>
</thead>
<tbody>
<tr>
<td>[O]</td>
<td>Temp, Time, Product, $^{18}$O-atom %, $^{18}$O %</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1a. PhSSMe↓0</td>
<td>1.3eq. 25° 13h PhSSMe 11</td>
<td>0.376% 122%</td>
</tr>
<tr>
<td>0.615</td>
<td>H$_2$O$_2$  PhSSPh 9</td>
<td>0.076 24</td>
</tr>
<tr>
<td>1b. 0.549</td>
<td>10eq. 70° 5h PhSO$_2$NH$_2$</td>
<td>0.037 6.7$^b$</td>
</tr>
<tr>
<td></td>
<td>H$_2$O$_2$  PhSSPh 9</td>
<td>0.259 84</td>
</tr>
<tr>
<td>2a. 0.615</td>
<td>1.2eq. 0° 7.5h PhSSMe 11</td>
<td>0.342 112</td>
</tr>
<tr>
<td></td>
<td>MCPBA  PhSSPh 9</td>
<td>0.259 84</td>
</tr>
<tr>
<td>2b. 0.451</td>
<td>1.3eq. 0° 3h PhSSMe 11</td>
<td>0.211 94</td>
</tr>
<tr>
<td></td>
<td>MCPBA  PhSSPh 9</td>
<td>0.181 80</td>
</tr>
</tbody>
</table>

$^a$ $^{18}$O Content of CO$_2$.
$^b$ 20.1% for PhSO$_3$H (Eq. 11).
phenylthio moiety in the oxidation of 7 with \( H_2O_2 \) (Table V, entry 2), both methanesulfonic and benzenesulfonic acids obtained under the vigorous oxidation condition (10 eq. \( H_2O_2 \), 70°, 5h) were converted to the corresponding sulfonyl chlorides with \( SOCl_2 \). The benzenesulfonyl chloride was purified by distillation, and then converted to the sulfonamide by treatment with gaseous ammonia in dry ether. The sulfonamide was subjected to the routine \(^{18}O\)-analysis. The results summarized in eq. 11 show that benzenesulfonic acid contains 20% of the original \(^{18}O\)-label in 7.

The \(^{18}O\)-tracer experimental results obtained by the oxidations of 6 and 7 are summarized in eq. 12 and eq. 13. These \(^{18}O\)-tracer results are characterized by the followings.

\[
\begin{align*}
\text{PhSSMe} & \xrightarrow{\text{oxidant}} \text{PhSSMe} + \text{PhSSPh} \quad (12) \\
\text{PhSSMe} & \xrightarrow{\text{oxidant}} \text{PhSSMe} + \text{PhSSMe} + \text{PhSSPh} + \text{MeSSMe} \quad (13)
\end{align*}
\]

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>(^{18}O)-incorporation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H_2O_2/\text{AcOH} )</td>
<td>122% 24%</td>
</tr>
<tr>
<td>MCPBA/( \text{CH}_2\text{Cl}_2 )</td>
<td>94 - 112% 80 - 84%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>(^{18}O)-incorporation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H_2O_2/\text{AcOH} )</td>
<td>102% 58 - 70% 108 - 124% 68%</td>
</tr>
<tr>
<td>MCPBA/( \text{CH}_2\text{Cl}_2 )</td>
<td>- 102 - 116% 110 - 144% -</td>
</tr>
</tbody>
</table>
Table VI  

<table>
<thead>
<tr>
<th>Excess $^{18}$O-atom % of 6, [O]</th>
<th>Reaction</th>
<th>Excess $^{18}$O-atom %</th>
<th>Incorporated $^{18}$O %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess $^{18}$O-atom % of 6, [Sub.], Temp, Time, Product, $^{18}$O-atom %</td>
<td>180</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>1a. PhSSMe 0 → 1.4eq. H$_2$O$_2$ 20° 5h PhSSMe 11</td>
<td>0.186%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>0.636% PhSSPh 9</td>
<td>0.378</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>1b. 0.578</td>
<td>1.2</td>
<td>H$_2$O$_2$ 20° 10h PhSSMe 11</td>
<td>0.175</td>
</tr>
<tr>
<td>PhSSPh 9</td>
<td>0.354</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>1c. 0.515</td>
<td>1.2</td>
<td>H$_2$O$_2$ 20° 6h PhSSMe 11</td>
<td>0.178</td>
</tr>
<tr>
<td>PhSSPh 9</td>
<td>0.319</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>MeSSMe 8</td>
<td>0.170</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>1d. 0.578</td>
<td>1.3</td>
<td>H$_2$O$_2$ 20° 9h PhSSMe 11</td>
<td>0.188</td>
</tr>
<tr>
<td>PhSSPh 9</td>
<td>0.342</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>1e. 0.578</td>
<td>1.3</td>
<td>H$_2$O$_2$ 20° 5.5h PhSSMe 11</td>
<td>0.169</td>
</tr>
<tr>
<td>PhSSMe 10</td>
<td>0.294</td>
<td>102</td>
<td></td>
</tr>
</tbody>
</table>

* $^{18}$O Content of CO$_2$.  
(continued)
Table VII

18O Incorporation % of Recovered Thiol sulfinate 6 in the Oxidation of 6 with H₂O₂ in AcOH

<table>
<thead>
<tr>
<th>Excess 18O Content of 6, System</th>
<th>Reaction Temp, Time</th>
<th>Excess 18O Content of 6 Recovered (Incorporated %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 0.53% no H₂O₂ AcOH-H₂O</td>
<td>19° 3h</td>
<td>0.56% (106%)</td>
</tr>
<tr>
<td>2 0.53% 1.2 eq. 30% H₂O₂/ AcOH</td>
<td>20° 0.5h</td>
<td>0.52% (98%)</td>
</tr>
<tr>
<td>3 0.53% 1.2 eq. 30% H₂O₂/ AcOH</td>
<td>20° 2.5h</td>
<td>0.50% (94%)</td>
</tr>
</tbody>
</table>

Table VI (continued)

<table>
<thead>
<tr>
<th>2a. PhSSMe</th>
<th>1.2</th>
<th>0° 9h</th>
<th>PhSSMe</th>
<th>11</th>
<th>0.326</th>
<th>116%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.564</td>
<td></td>
<td></td>
<td>MCPBA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b. 0.564</td>
<td>1.2</td>
<td>0° 3h</td>
<td>PhSSMe</td>
<td>11</td>
<td>0.286</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MCPBA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 84 -
1) The thiol sulfonates formed apparently by the simple oxidation of the sulfinyl sulfur of the original thiol sulfinates, i.e. 10 in the case of 6 and 11 in the case of 7, retain completely the original $^{18}$O-label in the starting thiol sulfinates, regardless of the oxidation condition.

2) The apparent oxygen migrated product, 11, obtained from $^{18}$O labelled 6 contains 58 - 70 % of original $^{18}$O-label in the oxidation with $\text{H}_2\text{O}_2/\text{AcOH}$, however, 100 % of original label is incorporated into 11 in the oxidation with MCPBA/CH$_2$Cl$_2$.

3) More than 100% of original $^{18}$O-label is incorporated into the symmetrical thiol sulfonates formed from sulfinyl moieties of the $^{18}$O-labelled 6 and 7, i.e. 9 from 6 and 8 from 7. These $^{18}$O-incorporations are somewhat greater in the oxidation with MCPBA/CH$_2$Cl$_2$ than in the oxidation with $\text{H}_2\text{O}_2$/AcOH.

4) The symmetrical thiol sulfonates formed from the sulfenyl moieties of $^{18}$O-labelled 6 and 7, i.e. 8 from 6 and 9 from 7, contain 68% and 24% of the original $^{18}$O-label in 6 and 7, respectively, in the oxidation with $\text{H}_2\text{O}_2$/AcOH. The value for 9 formed from 7 increases extremely in the oxidation with MCPBA/CH$_2$Cl$_2$ as 80 - 84 %.

Control experiments show that 6 is sufficiently stable in AcOH-$\text{H}_2\text{O}$ in the absence of oxidant for 20h at 20° and no $^{18}$O-label was lost under the conditions (Table VII). The thiol-sulfinate 6 recovered after partial oxidation of $^{18}$O-labelled 6 with $\text{H}_2\text{O}_2$ in AcOH retained almost completely the original
The facts that products distributions in the oxidations of 6 are different from that in the oxidation of 7 cannot be explained by the mechanism that the reactions of both 6 and 7 proceed via $\alpha$-disulfoxide intermediate[ A ] as shown in eq. 10. Yields of the products produced from the cleavage of S-S bond were greater in the oxidation of 6 than that of 7. This may suggest that the oxidation of 6 proceeds via an intermediate of which S-S bond cleavage takes place more readily than that in involved in the oxidation of 7. In the oxidation of thiol-sulfinate, the sulenyl sulfur is expected to be more susceptible to the electrophilic attack of oxidant than the sulfinyl sulfur. On the other hand, the sulfenyl sulfur must be less reactive toward nucleophilic oxidation than sulfinyl sulfur.

Conceivable mechanisms for the oxidation of unsymmetrical thiolsulfinates based on all these results of product analyses and $^{18}$O-tracer experiments are illustrated in Chart. According to this mechanism, the initial oxidation step involves the following two paths( eq. 14 ). Path a forms $\alpha$-disulfoxide via direct electrophilic attack of oxygen of oxidant, while path b involves the nucleophilic attack of oxygen on the sulfinyl sulfur to form O-sulfenyl sulfinate[ B ] which is considered to be more stable than $\alpha$-disulfoxide. The oxidation of 6 may take place mainly via path a to form $\alpha$-disulfoxide, since sulfenyl sulfur of 6 is expected to be very reactive to the electrophilic oxygen of peroxides( Fig. X ).
Possible $^{18}_O$ Exchange Process

\[ [\text{Ph-S-S-Me}] \rightleftharpoons [\text{Ph-S-\textbullet-S-Me}] \rightleftharpoons [\text{Ph-S-S-Me}] \] (17)
In the Chart, an homolytic cleavage of S-S bond of [ A ] thus formed proceeds at lower temperature to give caged sulfinyl radical pair\(^9\)\(^\prime\) whose recombination gives O-sulfenyl sulfinates [ B\(_1\) ] and [ B\(_2\) ]. The intermediate [ B ] must be unstable and collapse to a caged radical pair [ C ] which recombines to give thiolsulfonates. Since there is no energy barrier in the recombination of [ C ] to form stable S-S bond, the recombination of radical pair must be faster than diffusion process of two radicals out of cage. On the other hand, the recombination of sulfinyl radicals [ D ] makes energy rich S-O bond, some activation energy may be required for this process. Therefore, the diffusion of the radical pair can compete with the recombination process. The diffused sulfinyl radicals may give two unsymmetrical thiolsulfonates (10 and 11) and two symmetrical thiolsulfonates (8 and 9). Both the product distribution of the oxidation of 6 and \(^{18}\)O-tracer experimental
results (p. 85, features of $^{18}$O-tracer experiments: 2) and 3) ),
can be reasonably explained by this mechanism.

However, the following concerted isomerization mechanisms
cannot be completely excluded.

\[
\begin{align*}
[R-S-S-R'] & \rightarrow [R-S\overset{O}{\cdots}S-R'] \quad \text{[E]} \quad \text{or} \quad [R-S\overset{R}{\cdots}S-R']^* \quad \text{[F]} \quad \rightarrow R-S-S-R' \quad (15) \\
\downarrow & \quad \downarrow \\
\begin{aligned}
[R-S\overset{R}{\cdots}S-R']^* & \rightarrow R-S-O-S-R' \\
\rightarrow R-S-O-S-R' & \rightarrow [R-S\overset{O}{\cdots}S-R']^* \quad \rightarrow R-S-S-R' \quad (16)
\end{aligned}
\end{align*}
\]

On the other hand, since sulfenyl sulfur of $^7$ is not a
good nucleophile (Fig. VIII), the oxidation of $^7$ proceeds mainly
via path $\boxed{5}$ to form [ $B_2$ ] which changes eventually to the
thiolsulfonate $^{11}$ via [ $C_2$ ]. This hypothesis is supported
by the following two facts.

1) The formation of thiolsulfonate $^{11}$ predominates over that of
other thiolsulfonates, $^8$, $^9$ and $^{10}$ in the oxidation of $^7$.
2) The $^{18}$O-tracer experimental result (p. 85, 1).

There are three possible paths to be responsible for the
formation of $^{18}$O-labelled $^8$ in the oxidation of $^{18}$O-labelled $^6$
and that of $^{18}$O-labelled $^9$ from $^{18}$O-labelled $^7$ ($^{18}$O-experimental
results (p. 85, 4)).

1) If the homolitic fission-recombination
processes are reversible as shown in eq. 17, $^{18}$O-scrambling in
the sulfanyl radical pair [ $D$ ] occurs and then gives $^8$ and $^9$
having $^{18}$O-label.

\[
[ C_1 ] \xleftrightarrow{} [ B_1 ] \xleftrightarrow{} [ D ] \xleftrightarrow{} [ B_2 ] \xleftrightarrow{} [ C_2 ]
\]  

(17)

2) The concerted oxygen scrambling process as shown in eq. 18 is conceivable (see Chart). 3) The following ionic path is also conceivable (eq. 19). According to this assumption, [B] loses $^{18}$O-label by the reversible process, [B] $\xrightarrow{}$ [G] + [H].

\[
\begin{align*}
 R^1-S-O-S-R^2 & \xleftrightarrow{} R^1-S-O-S-R^2 \\
 [B] & \\
 -ROH & \xrightarrow{} ROH \\
 R^1-S-O-R & + R^2-SOH & \xrightarrow{} & R^2-S-S-R^2 \\
 [G] & & & [F]
\end{align*}
\]  

(19)

This $^{18}$O-loss in [B] by this equilibrium must be greater in the oxidation system with $\text{H}_2\text{O}_2$/AcOH than in that with MCPBA/CH$_2$Cl$_2$. This hypothetical $^{18}$O-exchange reaction between [B] and medium can explain the fact that $^{18}$O-incorporations in 11 obtained from 7, 9 and 11 obtained from 6 are greater in the oxidation with MCPBA/CH$_2$Cl$_2$ than in $\text{H}_2\text{O}_2$/AcOH ($^{18}$O-experimental results, p.85, 2) and 4).
Our new selective oxidation of unsymmetrical thiolsulfinate with NaIO₄ gives the corresponding unsymmetrical thiolsulfonate(16) (Chapter 3) by the selective oxidation of sulfinyl sulfur without cleavage of S-S bond, in contrast to the oxidation with H₂O₂ or MCPBA as mentioned in this chapter. Most representative examples of oxidations with these two different oxidizing systems are illustrated below.¹⁷) These facts show that the oxidation of the dithiane oxide with peroxide can be explained only by the mechanism involving α-disulfoxide which is formed by the electrophilic attack of peroxide to the sulfinyl sulfur of the thiolsulfinate. The oxidations of 3-methyl-1,2-dithiane 1-oxide with H₂O₂ in AcOH or MCPBA in CHCl₃ were carried out in NMR sample tube, however, any methyl peak due to the α-disulfoxide intermediate could not be detected, suggesting that even cyclic α-disulfoxide is too unstable to be detected.

**Oxidation of Unsymmetrical Thiolsulfonate**

Although the simplest oxidation path of thiolsulfonate is
considered to afford sulfinyl sulfone (RSOSO₂R), no one has succeeded the detection of the sulfinyl sulfone in the oxidation of the thiol sulfonate, while α-disulfone has been isolated in the oxidation.¹¹) Sulfinyl sulfone has been neither detected nor isolated during the oxidation process, but has been already prepared by the condensation of sulfinyl chloride and sulfinic acid (salt).¹⁰)

When S-phenyl methanethiosulfonate (11) was exposed to the same oxidation system of hydrogen peroxide in NMR sample tube at 27°C as that applied for the oxidation of thiol sulfinate, the detectable methyl signals were only those of methanesulfonic acid (14) and the starting material (11). An equimolar amount of hydrogen peroxide oxidized ca 40% of 11 and the starting material again gradually disappeared by further addition of double molar amount of H₂O₂ into the reaction system, in several hours, as shown in Fig. XI. However, as shown in Fig. XII, two methyl peaks at 2.33 and 2.60 ppm (from external TMS) appeared during the oxidation of 10. The rates of both decrease of 10 and increase of 14 in the oxidation of 10 was found to be nearly the same to those of decrease of 11 and increase of 14 in the oxidation of 11.

The one of two peaks (2.33 ppm) was assigned to methane-sulfinic acid, MeSO₂H 12, since the authentic 12 appears at 2.39 ppm in CD₃COOD (Table I). The following experiment also support the assumption, namely methyl phenyl sulfone was obtained in 27.5% yield in the oxidation of S-phenyl benzene-thiosulfonate 9 with 2.2 equivalent of 30% H₂O₂ in AcOH for a
Figure XI

\[
\text{PhSSMe} \xrightarrow{1.2\text{eq. } H_2O_2} \text{CD}_3\text{COOD, 27°} \]

Relative intensity of methyl peak [%]

reaction time [h]

Figure XII

\[
\text{PhSSMe} \xrightarrow{1.2\text{eq. } H_2O_2} \text{CD}_3\text{COOD, 27°} \]

Relative intensity of methyl peak [%]

reaction time [h]

\[\Theta: 2.33 \text{ppm}\]

\[\Theta: 2.60\]

(from ext. TMS)

1.5eq. 

\[H_2O_2\]
day, after treating the resulting reaction mixture with NaHCO₃ solution followed by the treatment with excess methyl iodide in MeOH at 30° overnight after the evaporation of much of water.¹⁸)

Since ¹² could not be detected during the oxidation of ¹¹ the sulfinic acid was derived from sulfenyl moiety of thiol-sulfonate. Same result was noted in the oxidation of S-methyl methanethiosulfonate ⁸ with H₂O₂ in AcOH at 27°. Namely, the same methyl signal at 2.36 ppm appeared during the oxidation of ⁸ (Fig. XV). The methyl peak at 2.60 ppm has been assumed to be methyl signal of sulfinyl sulfone because methyl signal attached to sulfinyl group of dimethyl sulfinyl sulfone (MeSOSO₂Me) is known to appear at 2.85 ppm which is placed in center position between both methyl groups of ⁷ and ¹¹ in CDCl₃, while the methyl signals of ⁷ and ¹¹ appear at 2.72 and 2.90 ppm (CD₃COOD-D₂O) respectively.

This assumption was further justified by the result obtained in NMR studies of the oxidations of both ¹⁰ and ¹¹ with MCPBA in CDCl₃. In the oxidation of ¹⁰, the methyl signal at 2.93 ppm assigned to that of sulfinyl sulfone was observed among many peaks appeared during the oxidation. The peak at 2.93 ppm increased sharply at the initial stage of the oxidation.
as the substrate 10 disappeared and then gradually changed to the sulfonyl acid (14) (Fig. XIII). However, in this oxidation the signal of methanesulfinic acid (12) was not detected. The formation of sulfinic acid is considered to be due to the fast hydrolysis of the reactive sulfinyl sulfone formed during the reaction, since no sulfinic acid was observed in non-aqueous system (MCPBA/CDCl₃). This is the reason why earlier workers who used usually hydrolytic conditions, could not isolate the sulfinyl sulfone in the oxidation of thiolsulfonate.

On the other hand, in the oxidation of 11 with MCPBA in CDCl₃, fast formation of methanesulfonic acid 14 was observed, although NMR spectra of this oxidation also displayed many signals on the charts (Fig. XIV, Table captions). Among them unidentified major methyl peaks of 3.13 and 3.41 ppm were observed. The signal at 3.41 ppm could not be assigned as methyl group attached to oxidized sulfur atom, as understood from Table I, i.e. the chemical shift was too low. The other signal at 3.13 ppm remains unknown. The methyl signal at 3.29 ppm which is a common peak found in both oxidations of 10 and 11 with MCPBA, is considered to be due to that of α-disulfone because the chemical shift is seen between the signals of methanesulfonic anhydride (MeSO₂OSO₂Me, 3.38 ppm) and dimethyl sulfinyl sulfonate (MeS(O)OS(O)₂Me, 3.23 ppm) as shown in Table I. Formation of α-disulfone from thiolsulfonate as well as disulfide by peracid oxidation are well-known.11) The fact that the rate of the decrease of 10 was greater than that of 11

- 95 -
Figure XIII

all signals

2.50 • 10
2.85
2.93
dl
3.08 = 50
3.12
3.15
3.19 × 14
3.29
3.43

[ ppm ]

Figure XIV

all signals

2.97
3.13
3.15 • 11
3.20 × 14 50
3.29
3.41
3.49

[ ppm ]
in both oxidations with $\text{H}_2\text{O}_2$/AcOH and MCPBA/CH$_2$Cl$_2$, suggest that the oxidation with both oxidation systems undoubtedly initiated by the electrophilic attack of oxidant on the sulfinyl sulfur of thiolsulfonate.

Thus, an intervention of sulfinyl sulfone in the oxidation of thiolsulfonate was confirmed in this work for the first time. This intermediate was found to be readily hydrolyzed to give sulfinic acid which was oxidized ultimately to the sulfonic acid.
Experimental

General: Melting points were taken on a Yanaco instrument and were uncorrected. NMR spectra were recorded on a Hitachi Perkin Elmer R-20 spectrometer. Infrared spectra were obtained on a Hitachi 215 spectrometer and were uncorrected. Mass spectra were recorded on a Hitachi RMU-6MG mass spectrometer. Gas and liquid chromatographs were obtained by Shimazu GC-6A and Yanaco L-1030 instruments, respectively.

Materials: Both oxidizing agents, 30% \( \text{H}_2\text{O}_2 \) and MCPBA were obtained from Kanto Chemicals and Wako Pure Chemicals, respectively. Deuterized acetic acid and water were of Merk. Disulfide: Both diphenyl and dimethyl disulfides were commercially available (Tokyo Kasei Kogyo Co.). Methyl phenyl disulfide was prepared by the following procedure, according to the reported method.\textsuperscript{10}

Methanesulfenyl chloride (0.03 mole) which was prepared by the reaction of dimethyl disulfide with gaseous chlorine in \( \text{CCl}_4 \),\textsuperscript{19} according to the known method and purified by distillation, was dissolved in dry \( \text{CCl}_4 \) (100 ml) which was cooled to ca -10°. To the \( \text{CCl}_4 \) solution of \( \text{MeSCl} \) dry pyridine (0.033 mole) was added and then thiophenol (0.03 mole) in dry \( \text{CCl}_4 \) (ca 50 ml) was added dropwise with cooling at the temperature below 0°. After the addition of thiophenol cooling bath was removed and the heterogeneous reaction mixture was
stirred until the temperature reached to room temperature. Resulting reaction mixture was transferred into the separatory funnel, and washed with water, 5% NaHCO₃ solution and again with water. Organic layer was dried over CaCl₂ and CCl₄ was evaporated. The residual crude oil was purified by distillation under reduced pressure (71 - 2⁰/ 2.5 - 3 mmHg). Complete purification of unsymmetrical disulfide is very difficult. Methyl phenyl disulfide purified by the distillation also contained a small amount of diphenyl disulfide (~5%) which was detected by GC. Yield was ca 85%. NMR (CDCl₃, δ, TMS) 2.40 (s, 3H, CH₃), Lit.¹⁰ bp 79 - 81⁰/ 1.0 mmHg.

Thiolsulfinate; S-Methyl methanethiosulfinate (4, MeS(O)SMe) as an authentic sample was prepared by direct oxidation of dimethyl disulfide 1 with H₂O₂ in AcOH and purified by distillation (46 - 7⁰/ 1.5 mmHg). S-Phenyl benzenethiosulfinate 5, S-methyl benzenethiosulfinate 6 and S-phenyl methanethiosulfinate 7 were also prepared by the condensation of the corresponding sulfinyl chlorides and thiols in the presence of pyridine at low temperature (<0⁰), according to the usual method.¹¹ Yields were 80 - 95%. Purification of 5 was carried out by recrystallization from hexane-chloroform mixed solvent while both 6 and 7 were purified carefully by column chromatography.

S-Phenyl benzenethiosulfinate 5; mp 69 - 70⁰ (lit.²¹) 69 - 70⁰).
S-Methyl benzenethiosulfinate 6; mp 26 - 28⁰, NMR (CDCl₃, δ, TMS) 2.53 (s, 3H, CH₃), IR (neat, cm⁻¹) 3050, 2975, 2900, 1570, 1470, 1095 & 1060 (S=O), (lit.²⁴) 1088 (CHCl₃)).
S-Phenyl methanethiosulfinate 7; mp 15 - 20°, IR( neat, cm⁻¹ )
3050, 2980, 2900, 1570, 1470, 1090(S=O), ( lit.²²) 1079( CHCl₃ ).
Thiolsulfonate: S-Methyl methanethiosulfonate 8 was derived
from dimethyl disulfide 1 by the oxidation with H₂O₂ in AcOH
and purified by distillation( 56.5°/1.0 mmHg ), NMR( Table I ),
IR( neat, cm⁻¹ ) 2925, 1430, 1410, 1335 & 1305(SO₂), 1140(S=O),
960, 755. Other thiolsulfonates, 9, 10 and 11, were
synthesized by the condensation of sulfonyl chlorides with
free sulfenic acids in the presence of pyridine, as reported.¹⁰
Products were purified by column chromatography, yielding 80 -
95%. Purification of 11 could be performed also by
recrystallization from hexane.
S-Phenyl benzenethiosulfonate 9; colorless crystals, recryst.
from EtOH, mp 44 - 45°( lit.²³) 44 - 45° ).
S-Methyl benzenethiosulfonate 10; colorless oil, IR( neat, cm⁻¹ )
3050, 3000, 2920, 1580, 1475, 1445, 1330 & 1302(SO₂), 1042(S=O),
NMR( Table I ), Anal. Calcd for C₇H₈O₂S₂: C, 44.66; H, 4.28.
Found: C, 44.92; H, 4.18.
S-Phenyl methanethiosulfonate 11; colorless crystals, mp 85 -
86.5°, IR( KBr, cm⁻¹ ) 3050, 3000, 2905, 1565, 1465, 1310(SO₂),
1130(S=O), NMR( Table I ). Anal. Calcd for C₇H₈O₂S₂: C, 44.66;
H, 4.28. Found: C, 44.78; H, 4.25.
Sulfinic and Sulfonic Acids: Methanesulfinic acid 12 was
prepared by the hydrolysis of methanesulfenyl chloride.²⁴)
Free benzenesulfinic acid 13 was obtained by acidification of
commercial sodium benzenesulfinate( Tokyo Kasei Kogyo Co. ) with
conc. HCl and purified by recrystallization from water. Both
methanesulfonic (14) and benzenesulfonic (15) acids were commercially available.

\[ ^{18}O \text{-Labelled Thiolsulfinites, 6 and 7; } ^{18}O \text{-Labelled 6 and 7} \]

were prepared by the use of both \(^{18}O\)-labelled benzenesulfinyl and methanesulfinyl chlorides, respectively. \(^{18}O\)-Labelled sulfinylchloride was derived from non-labelled sulfinyl chloride and \(^{18}O\)-enriched water (ca 1.5 %).

To a dry ether solution (30 ml) of benzenesulfinyl chloride (0.03 mole) which was purified by distillation (78°C/2 mmHg) was added dropwise \(^{18}O\)-enriched water (0.05 mole) with cooling with ice-water bath. The reaction was considerably exothermic and fumed HCl gas. Benzenesulfinic acid obtained after evaporation of ether and excess water under reduced pressure, was dissolved again in ether (ca 20 ml). To the stirring ether solution of the free sulfinic acid, excess distilled thionyl chloride (0.07 mole) was added, causing vigorous endothermic reaction evolving \(SO_2\) and HCl gas. The residual oil after evaporation of ether and excess thionyl chloride was purified by distillation. \(^{18}O\)-Labelled thioIsulfinate (10) was prepared by the reaction of \(^{18}O\)-labelled benzenesulfinyl chloride with methyl mercaptane in the presence of pyridine, as mentioned above. \(^{18}O\)-Labelled methanesulfinyl chloride was also prepared by the same method. Since crude thiol-sulfinate decomposes simultaneously, crude thiol-sulfinate thus obtained were immediately subjected to purification by careful column chromatography (on silica gel, eluent: EtOAc : CHCl₃ : Hexane = 1 : 1 : 4), in order to avoid the fast catalytic
decomposition of thioisulfinate by impurities. Purified $^{18}O$-labelled thioisulfinate (6 or 7) were fairly stable and contained ca 0.7 - 0.8 atom % of $^{18}O$.

Oxidation of Disulfide, Thioisulfinate and Thiol sulfonate

Oxidation with $H_2O_2$ in AcOH: AcOH (ca 15 ml) solution of ca 1.0 g of the substrate (disulfide, thioisulfinate or thiol sulfonate) was cooled till before freezing by ice-water bath. Thirty % $H_2O_2$ (amount shown in Tables) was added slowly dropwise to the cooled and stirred solution of the substrate and the temperature of the solution rose up by the addition. After the whole addition of $H_2O_2$ the mixture was warmed up to set temperature and stirred at the same temperature until the starting material disappeared with monitoring by TLC or HPLC. After the reaction, the reaction mixture was diluted with 50 ml of water, transferred into separatory funnel and extracted three times with $CHCl_3$ (~100 ml). Combined organic layer was washed with water, sat. NaHCO$_3$ solution and then water again to remove AcOH and other acids. $CHCl_3$ was evaporated and NMR spectrum of the residue was measured. The residue was, then, subjected to separation by column chromatography (on silica gel, eluent: EtOAc : $CHCl_3$ : hexane = 1 : 1 : 4). First fraction gave S-phenyl benzenethiosulfonate 9, second gave S-methyl benzenethiosulfonate 10, then S-phenyl methanethiosulfonate 11 was eluted and the last fraction contained S-methyl methanethiosulfonate 8. Thiolsulfinates, 5, 6 and 7 were eluted between 11 and 8, while 4 appeared after 8. 10 and 11
were separated completely by repeated column chromatography in which first fraction gave colorless solid \( \text{ll} \) and following fraction afforded colorless oil \( \text{10} \). They were identified by comparing their NMR, IR, GLC, HPLC and melting points with those of authentic samples prepared independently.

On the other hand, combined aqueous layer which was neutralized by sat. NaHCO\(_3\) solution was concentrated by complete evaporation of water. Sulfinic and sulfonic acids (salts) were determined by NMR spectra in D\(_2\)O in which methyl signals of both sodium salts of methanesulfinic and methanesulfonic acids (12 and 14) appeared at the range of 2.15 - 2.30 and 2.75 - 2.82 ppm, respectively, depending upon the pH of the solution.

**Oxidation with MCPBA in CH\(_2\)Cl\(_2\):** To a cooled (ca 0\(^\circ\)C) solution of ca 1.0 g of the substrate in CH\(_2\)Cl\(_2\) (ca 20 ml) was added sufficiently slowly powder MCPBA (1.0 - 2.0 eq.). The reaction mixture was warmed and stirred at set temperature until the starting material disappeared with following by TLC or HPLC. The reaction mixture was washed with 5% NaHCO\(_3\) solution and water after the reaction. Organic and aqueous layers were treated with the same procedures as described above.

Yields of the products which were determined in connection with the data of NMR, GC and HPLC, were shown in Tables.

**Oxidation in NMR Sample Tube**

A NMR spectrum of the substrate (0.4 - 0.5 mmole) was measured in CD\(_3\)COOD or CDCl\(_3\) (430 \(\mu\)l). To the solution in
NMR sample tube 30% H₂O₂ or powder MCPBA (amount listed in Tables) was added at set temperature and immediately NMR spectra of the resulting mixture were measured at intervals. After the reaction completed, GC and HPLC of the mixture were measured to determine the yields of the products.

18O-Tracer Experiment

Products thus obtained and purified were well dried in vacuo with slightly heating. 18O-Labelled S-methyl benzenethio-sulfinate 6 recovered during the oxidation was purified by column chromatography (on silica gel, eluent: EtOAc : CHCl₃ : hexane = 1 : 1 : 4). It was eluted after 9, 10 and 11 as a colorless oil.

18O-Tracer analysis was carried out by the method developed by Rittenberg and Ponticorvo,25 with a modification which was the use of Pb(OAc)₂ to remove H₂S gas from the produced gas by the thermolysis of sample.

Twenty mg of sample was pyrolyzed with 300 mg of purified both HgCl₂ and Hg(CN)₂, respectively, in an evacuated, sealed Pyrex tube at ca 500° for 12h. Then the tube was broken in a vacuum line and CO₂ gas formed was purified by distillation and the mass peaks of m/e 44 and 46 which correspond to C₁₆O₂ and C₁₆O₁₈O, respectively, were recorded on a mass spectrometer.

Derivation of Benzenesulfone Amide from Benzenesulfonic Acid in The Oxidation of 18O-Labelled Thiolsulfinate 7

The reaction mixture resulted by the complete oxidation of
$^{18}$O-labelled S-phenyl methanethiosulfinate (437 mg) with ten equivalent of 30% H$_2$O$_2$ (2.65 g) in AcOH (9 ml) at 70° for 5 h, contained only both methane- and benzene-sulfonic acids. To the reaction mixture a small amount of MnO$_2$ was added to decompose excess H$_2$O$_2$. After filtration, acetic acid and water were evaporated by heating. To the residue containing two sulfonic acids was added excess thionyl chloride (10 mmole). The resulting mixture after evaporation under reduced pressure to remove excess thionyl chloride, was distilled to separate two fractions (bp 62°/21 mmHg and 70°/1 mmHg) which were methane- and benzene-sulfonyl chlorides, respectively. Distilled benzenesulfonyl chloride was dissolved in dry ether and gaseous ammonia was introduced into the solution. The white solid of NH$_4$Cl was filtered. The solid residue after evaporation of ether was benzenesulfone amide (43 mg) which was purified by recrystallization from ether-ethyl acetate mixed solvent (30:1) and then subjected to the routine $^{18}$O-analysis.

References

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Chapter 3

Selective Oxidation of Unsymmetrical Thiolsulfinates to The Corresponding Thiolsulfonates with NaIO₄¹)

Abstract

Dialkyl, diaryl and aryl alkyl unsymmetrical thiolsulfinates were oxidized with sodium metaperiodate (NaIO₄) in aqueous media to the corresponding unsymmetrical thiolsulfonates nearly quantitatively. The oxidation was accelerated by addition of a catalytic amount of inorganic and organic acids or halogens. Sulfinate esters were produced competitively along with the thiolsulfonates in the oxidation of thiolsulfinates in aqueous alcohol. However, unsymmetrical disulfides were not oxidized selectively to the corresponding unsymmetrical thiolsulfonates but a mixture of both symmetrical and unsymmetrical thiolsulfonates was obtained.
Introduction

We have recently reported that oxidations of unsymmetrical thiol sulfinates with peracid\(^2\) or dinitrogen tetroxide\(^3\) afforded the corresponding symmetrical thiol sulfonates which were undoubtedly derived by the cleavage of sulfur-sulfur bond. A few previous studies\(^2,4\) on the oxidations of thiol sulfinates with peracids or peroxides revealed that none of these oxidations resulted in the selective oxidation of unsymmetrical thiol sulfinate to the corresponding unsymmetrical thiol sulfonate with no apparent cleavage of sulfur-sulfur bond, but the oxidation of linear unsymmetrical thiol sulfinate generally afforded both symmetrical and unsymmetrical thiol sulfonates. Only the oxidation of such a cyclic compound as 3-methyl-1,2-dithiane-1-oxide was found to proceed without any apparent cleavage of sulfur-sulfur linkage to afford two unsymmetrical thiol sulfonates (dioxides) in good yields.\(^5\) In attempts to detect imaginary "\(\alpha\)-disulfoxide" which is considered to be

\[
\begin{align*}
\text{RSSR'} & \xrightarrow{[O]} \quad \text{RSSR} + \text{RSSR'} + \text{RSSR'} + \text{R'SSR'} \\
\downarrow & \quad \downarrow & \quad \downarrow & \quad \downarrow & \quad \downarrow \\
\text{0} & \quad \text{0} & \quad \text{0} & \quad \text{0} & \quad \text{0} \\
\text{[RSSR]} & \quad \text{[RSSR]} \\
\end{align*}
\]

\(\alpha\)-disulfoxide

- 108 -
formed initially in the oxidation of thiolsulfinate but too unstable to be observed, Barnard\textsuperscript{4a)} and Kice et al.\textsuperscript{4c)} have carried out the oxidation of unsymmetrical thiolsulfinates and obtained a mixture of thiolsulfonates, resulted by the initial oxidation, subsequent cleavage of the disulfide linkage and the recombination.

However, surprisingly, when sodium metaperiodate (NaIO\textsubscript{4}) was used as an oxidant, many diaryl, dialkyl and aryl alkyl unsymmetrical thiolsulfinates were found to be oxidized selectively to the corresponding unsymmetrical thiolsulfonates in aqueous media such as dioxan-water under mild condition, with no apparent cleavage of sulfur-sulfur bond. This chapter describes this new selective oxidation in detail, while the mechanism of the reaction will be discussed in the following chapter.

Results and Discussion

\textbf{NaIO}_{4} Oxidation:} When an unsymmetrical thiolsulfinate \textsubscript{1} was treated with an equimolar amount of sodium metaperiodate, only one product, i.e. the corresponding unsymmetrical thiolsulfonate \textsubscript{2} was found to be obtained. The reaction was also found to be accelerated by addition of a catalytic amount of inorganic or organic acid as well as iodine. Selected results are listed in Table I.

Following is a typical run. A solution of NaIO\textsubscript{4} (1.2
mmole) was added into a dioxan solution (3.5 ml) containing an unsymmetrical thiol sulfinic acid (1, 1.0 mmole) at room temperature. To the resulting mixture a small amount of a catalyst (e.g. conc. HCl, 1 or 2 drop) was added. After stirring the mixture for ca 30 min at the temperature or until the solution turned to dark brown, the highly pure unsymmetrical thiol sulfinic acid (2) was obtained nearly quantitatively by extraction of the reaction mixture. The product generally showed only one component on GC, LC, TLC or NMR. The yield of the product was determined by isolation through column chromatography or GC. New products were identified by comparing their IR and NMR spectra with those of authentic samples prepared by a known method which is the condensation of sulfinic acid and sulfinyl chloride in the presence of tert-amine. The starting thiol sulfinic acid was prepared by condensation of the corresponding sulfinyl chloride and thiol in the presence of pyridine in
carbon tetrachloride at a temperature lower than 0°, according to the method of Backer et al.\(^\text{7}\) Purification was carried out by recrystallization or column chromatography was described in "Experimental". Structures of new compounds of thioisulfonates prepared as well as thioisulfonates formed were determined by spectra of IR, NMR and MS and elemental analyses.

**Table I**  
Selective Oxidation of Unsymmetrical Thiolsulfinate with NaIO\(_4\) at ca 20°

<table>
<thead>
<tr>
<th>Entry, Substrate, Solvent</th>
<th>Catalyst</th>
<th>Time</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>la</td>
<td>dioxan-H(_2)O</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>lb</td>
<td>CH(_3)CN-H(_2)O</td>
<td>conc. HCl</td>
</tr>
<tr>
<td>3</td>
<td>lc</td>
<td>CH(_3)CN-H(_2)O</td>
<td>I(_2)</td>
</tr>
<tr>
<td>4</td>
<td>ld</td>
<td>dioxan-H(_2)O</td>
<td>CF(_3)COOH</td>
</tr>
<tr>
<td>5</td>
<td>le</td>
<td>dioxan-H(_2)O</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>lf</td>
<td>dioxan-H(_2)O</td>
<td>conc. HCl</td>
</tr>
<tr>
<td>7</td>
<td>lg</td>
<td>dioxan-H(_2)O</td>
<td>conc. HCl</td>
</tr>
<tr>
<td>8</td>
<td>lh</td>
<td>dioxan-H(_2)O</td>
<td>conc. HCl</td>
</tr>
<tr>
<td>9</td>
<td>li</td>
<td>CD(_3)COOD-(\text{D}_2)O(^d)</td>
<td>no</td>
</tr>
<tr>
<td>10</td>
<td>lj</td>
<td>CD(_3)COOD-(\text{D}_2)O(^d)</td>
<td>no</td>
</tr>
</tbody>
</table>

\(^{a}\) No other product was observed in GC and NMR.  
\(^{b}\) Isolate yield.  
\(^{c}\) The yield was determined by GC and NMR.  
\(^{d}\) The reaction was carried out in NMR sample tube (substrate: 0.1 mmole).

As shown in Table I, thioisulfinates of various types were oxidized to the corresponding thioisulfonates without cleavage.
of sulfur-sulfur linkage. Electrophilic catalysts highly accelerated the reaction while the reaction usually had a long induction period without any catalyst. Yields of the unsymmetric thiolsulfonates were nearly quantitative regardless of the substituent.

No detectable intermediate was observed in the NMR study of the oxidation of thioltsulfinate \( {\text{I}} \) with NaIO\(_4\) in CD\(_3\)COOD-D\(_2\)O as shown in the following Figure I. Methyl signal at 2.33 ppm (from external TMS) of \( {\text{I}} \) gradually changed to the signal at 2.26 ppm which is identical to that of \( {\text{II}} \). No other peak of methyl group was observed in the NMR spectra throughout the reaction. An interesting relationship found between the two unusual chemical shifts of \( {\text{I}} \) and \( {\text{II}} \) in which the chemical shift of \( {\text{I}} \) is lower than that of \( {\text{II}} \), has been re-confirmed.\(^8\)

**Effects of Catalyst and Solvent:** The oxidation was found to be accelerated by addition of a catalytic amount of organic or inorganic acid or halogen. While a weak acid such as acetic or formic acid did show little catalytic activity, unlike trifluoroacetic acid (pKa 1.0), the oxidation was accelerated in acetic acid as a solvent even without any catalyst. Catalysts effective in the oxidation are the following: CF\(_3\)COOH, H\(_2\)SO\(_4\), HIO\(_4\), HClO\(_4\), HCl, I\(_2\), and Br\(_2\) as shown partially in Table II. Solvents used were dioxan, acetonitrile and acetone which can co-mix freely with water. Acetic acid was effective not only as a solvent but also accelerated the reaction, and hence the best system for the oxidation. Alcohols were not
Figure I

Spectral Change in NMR spectra in the oxidation of \( \text{I} \) with \( \text{NaIO}_4 \)

- \( t = 0 \)
- \( t = 4'30'' \)
- \( t = 7'20'' \)
- \( t = 10'20'' \)

* Signals due to undeterized proton of acetic acid-d4.
### Table II

**Effects of Catalyst and Solvent in The Oxidation of Thiolsulfinate with NaIO$_4$ at 20°**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ld</td>
<td>dioxan-H$_2$O</td>
<td>no</td>
<td>6.0</td>
<td>2d</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>CH$_3$CN-H$_2$O</td>
<td>no</td>
<td>5.0</td>
<td>&quot;</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>acetone-H$_2$O</td>
<td>no</td>
<td>27.0</td>
<td>-</td>
<td>- $^b$</td>
</tr>
<tr>
<td>4</td>
<td>lc</td>
<td>CH$_3$CN-H$_2$O</td>
<td>HCOOH</td>
<td>6.0</td>
<td>2c</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>ld</td>
<td>dioxan-H$_2$O</td>
<td>CH$_3$COOH</td>
<td>6.0</td>
<td>2d</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>acetone-H$_2$O</td>
<td>I$_2$</td>
<td>3.0</td>
<td>&quot;</td>
<td>quant. $^c$</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>dioxan-H$_2$O</td>
<td>conc. HCl</td>
<td>1.0</td>
<td>&quot;</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>dioxan-H$_2$O</td>
<td>CH$_3$COOH</td>
<td>2.0</td>
<td>&quot;</td>
<td>quant. $^c$</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CH$_3$COOH-H$_2$O</td>
<td>no</td>
<td>0.5</td>
<td>&quot;</td>
<td>95 $^d$</td>
</tr>
<tr>
<td>10</td>
<td>lc</td>
<td>CH$_3$CN-H$_2$O</td>
<td>Br$_2$</td>
<td>0.5</td>
<td>2c</td>
<td>95 $^e$</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>CH$_3$CN-H$_2$O</td>
<td>H$_2$SO$_4$</td>
<td>1.0</td>
<td>&quot;</td>
<td>quant. $^c,e$</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>CH$_3$CN-H$_2$O</td>
<td>HIO$_4$</td>
<td>1.0</td>
<td>&quot;</td>
<td>quant. $^c,e$</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>CH$_3$CN-H$_2$O</td>
<td>HClO$_4$</td>
<td>1.0</td>
<td>&quot;</td>
<td>quant. $^c,e$</td>
</tr>
</tbody>
</table>

---

*a) The yield was determined by GC and NMR.  
b) Starting material was recovered.  
c) No other product was observed in GC and NMR.  
d) Solvent ratio: CH$_3$COOH/H$_2$O = 7/4 (v/v).  
d) The yield was determined by LC.

effective because the competitive reaction of the alcohols takes place, as described later.

If no catalyst was used, the reaction occurred suddenly with coloring by iodine after a long induction period (5 - 10h) and

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finished within an hour as in the case with catalyst, due mainly
to the catalytic action of iodine accumulated during the reaction.
Figure II indicates the rate of disappearance of thiolsulfinate
1c in the oxidation with NaIO₄ as monitored by LC. Appearance
of color of iodine was in accordance with the initiation of the
reaction. Therefore, the reaction is presumed to be an
auto-catalyzed reaction with iodine as illustrated in Fig. II.

Reaction in Aqueous Alcohol: The oxidation of 1d with NaIO₄
in aqueous alcohol resulted in the competitive formation of the
sulfinate ester of the alcohol along with that of the usual
oxidation product of thiolsulfonate 2d (eq. 3). When three
different alcohols of varying bulkiness, i.e. ethanol,
isopropanol and tert-butanol were used as solvents, the amount
of the sulfinate ester 3 produced was found to decrease in the
following order: ethanol > isopropanol > tert-butanol, which
is the order of bulkiness as well as the nucleophilicity of the
alcohol used. This distribution of products changed very little
in the acid-catalyzed reaction (parenthesis, eq. 3). Sulfinate
ester(3) were not oxidized at all under this condition.
GC analysis confirmed that the symmetrical disulfide is derived
only from the sulfenyl part. The disulfide(4) was considered
to be produced from the thiol formed during the reaction
involving nucleophilic attack of alcohol. The thiol thus formed
should be oxidized immediately with NaIO₄ to the corresponding
disulfide, 4. Competitive formation of the sulfinate ester
indicates clearly that both oxidation and substitution are
Figure II  Oxidation of Thiol sulfinate \( \text{lc} \) with NaIO\(_4\) either with or without Catalyst

\[
\begin{align*}
\text{O} & \quad \text{NaIO}_4 \\
\text{CH}_3\text{CN-H}_2\text{O} & \quad \text{S-S-CH}_3 \\
\text{O} & \quad \text{S-S-CH}_3 \\
\end{align*}
\]

\[\text{lc} \quad \rightarrow \quad \text{2c}\]

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>reaction at 17° without catalyst.</td>
</tr>
<tr>
<td>b</td>
<td>reaction at 0 ~ 4° with iodine as a catalyst.</td>
</tr>
<tr>
<td>c</td>
<td>reaction at 20° with HIO(_4).</td>
</tr>
<tr>
<td>d</td>
<td>reaction at 20° with H(_2)SO(_4).</td>
</tr>
<tr>
<td>e</td>
<td>reaction at 20° with HClO(_4).</td>
</tr>
<tr>
<td>f</td>
<td>reaction at 20° with iodine or bromine.</td>
</tr>
</tbody>
</table>
Reaction catalyzed by conc. HCl within 1h.

nucleophilic reactions which take place only at sulfinyl sulfur atom.

**Reaction of Disulfide with NaIO₄:** When an unsymmetrical disulfide, e.g. methyl phenyl disulfide 5, was treated with two molar amount of NaIO₄ under the same condition, the following two symmetrical thiol sulfonates were obtained as major products which are undoubtedly derived by the cleavage of sulfur-sulfur bond, along with PhSSO₂Me 8. By direct observation of NMR spectral change in the reaction of 5 with 2eq. NaIO₄ in CD₃COOD-D₂O at 27°, the cleavage of sulfur-sulfur bond was found to occur at the beginning of the reaction and is competitive with the oxidation of sulfur atom, since all the methyl signals of dimethyl disulfide and the starting material and those attached to sulfinyl and sulfonyl groups were observed simultaneously during the reaction. Meanwhile, oxidation of a mixture of diphenyl disulfide and dimethyl disulfide with NaIO₄ under the same condition as that in the above NMR study, also afforded an
unsymmetrical thiosulfonate 8 and two symmetrical thiosulfonates (6 and 7) (eq. 5).

Thus, any unsymmetrical thiosulfinate can be selectively oxidized to the corresponding unsymmetrical thiosulfonate in this oxidation with NaIO₄ nearly quantitatively.

The catalytic activity of iodine found in this reaction was already noticed in the oxidation of cyclic disulfide to the corresponding thiosulfonate with KIO₄ by Field and Kim. Namely, in the oxidation of diacetate 11 with KIO₄, thiosulfonate

\[
\begin{align*}
\text{Ac}_2\text{SO}_2\text{Ph} + \text{MeSO}_2\text{Me} + \text{PhSO}_2\text{Me} \\
\text{Ph-S-S-Ph} & \xrightarrow{2\text{eq. NaIO}_4} \text{PhSO}_2\text{Me} + \text{MeSO}_2\text{Me} + \text{PhSO}_2\text{Me} \\
& \text{dioxan-water} \quad \text{r.t.} \quad 6(27\%) \quad 7(25\%) \quad 8(31\%) \\
\text{Me-S-S-Me} & \xrightarrow{2\text{eq. NaIO}_4} \text{MeSO}_2\text{Me} + \text{PhSO}_2\text{Me} + \text{PhSO}_2\text{Ph} \\
& \text{CD₃COOD-D}_2\text{O} \quad 27° \quad 8 \quad 7 \quad 6
\end{align*}
\]

\[
\text{AcO}_2\text{S-S}-\text{AcO} \\
\text{acetone-water} \\
\text{KIO}_4 \\
11
\]

\[
\text{AcO}_2\text{S-S}-\text{AcO} \\
\text{KIO}_4 \\
13
\]

\[
\text{AcO}_2\text{S-S}-\text{AcO} \\
\text{iPrOH-water} \\
cat.(\text{I}_2) \\
12
\]
13 could not be obtained without iodine, whereas thiosulfinate 12 was obtained in the oxidation without iodine. Other strong oxidants such as KMnO₄, CrO₃ and MCPBA, all failed to give 13 by the oxidation of 11. Thus, iodine appears to catalyze the oxidation of thiosulfinate to thiosulfonate. In addition, various organic and inorganic acids and bromine as well as iodine were also found to catalyze the oxidation in our study.

Obviously the oxidation of thiosulfinate with NaIO₄ is entirely different from that with peracetic acid which proceeds via formation of "α-disulfoxide", which is so unstable that collapses immediately yielding the corresponding four symmetrical and unsymmetrical thiosulfonates by the cleavage of sulfur-sulfur bond (eq. 1). In order to confirm the difference, the oxidation of 3-methyl-1,2-dithiane-1-oxide 14, a six-membered unsymmetrical thiosulfinate, were carried out with both NaIO₄ and peracid. The oxidation of 14 with either H₂O₂/AcOH or MCPBA/CH₂Cl₂ gave a regio-isomeric mixture of thiosulfonate 15 and 15' in the same ratio, while the oxidation of 14 with NaIO₄ in acidic solvent afforded only one isomer of thiosulfonate 15. The former reaction with peracid (eq. 8) is an oxidation which proceeds via "α-disulfoxide" by initial oxidation of sulfenyl sulfur of 14, followed by the migration of oxygen atom of α-disulfoxide to the neighbouring sulfinyl sulfur atom to form both thiosulfonates 15 and 15'. This new selective oxidation of thiosulfinate with NaIO₄ appears to proceed by the nucleophilic attack of the periodate on the sulfinyl sulfur atom to form the corresponding thiosulfonate.

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Experimental

General: Chemicals were of reagent grade unless otherwise specified. All melting points were measured by Yanaco instrument and are uncorrected. IR spectra were taken on a Hitachi 215 spectrometer. NMR spectra of the compounds were taken with a Hitachi Perkin-Elmer R-20 spectrometer in CDCl₃ using TMS as the internal standard. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Shimazu GC-6A instrument was used for gas chromatography using N₂ gas as a carrier gas. High pressure liquid chromatography was carried out with Yanaco L-1030 instrument using methanol as an eluent.
Elemental analyses were carried out by the Chemical Analysis Center at this University.

Preparation of Thiolsulfinate 1: Both symmetrical and unsymmetrical thiolsulfinates were prepared by the method reported by Backer and Kloosterziel\textsuperscript{7) with rather little modification. Namely, addition of a thiol into a desired and distilled sulfinyl chloride in CCl\textsubscript{4} under cooling lower than 0\textdegree gave rise to the formation of thiolsulfinate (80 - 95\% yield). The thiolsulfinate after purification by column chromatography or recrystallization, was identified with reported melting point, IR spectrum, NMR spectrum and elemental analysis.

\textbf{S-PhenyI benzenethiosulfinate la; pale yellow crystals, mp 69 - 70\degree (lit.\textsuperscript{9}) 69 - 70\degree), IR( CHCl\textsubscript{3}, cm\textsuperscript{-1} ) 3055, 1577, 1475, 1093 & 1060(S=O).}

\textbf{S-p-Tolyl benzenethiosulfinate lb; pale yellow crystals, mp 70 - 71\degree (lit.\textsuperscript{9}) 68\degree), IR( CHCl\textsubscript{3}, cm\textsuperscript{-1} ) 3050, 1590, 1470, 1095 & 1055(S=O).}

\textbf{S-PhenyI p-toluenethiosulfinate lc; pale yellow crystals, mp 82\degree (lit.\textsuperscript{9}) 83 - 84\degree), IR( CHCl\textsubscript{3}, cm\textsuperscript{-1} ) 3050, 1590, 1470, 1095 & 1065(S=O).}

\textbf{S-Methyl benzenethiosulfinate ld; colorless crystals, mp 26 - 28\degree, IR( neat, cm\textsuperscript{-1} ) 3050, 2975, 1570, 1470, 1095 & 1060(S=O), (lit.\textsuperscript{10}) 1104( CCl\textsubscript{4} ).}

\textbf{S-PhenyI methanethiosulfinate le; colorless oil, IR( neat, cm\textsuperscript{-1} ) 3050, 2980, 2900, 1570, 1470, 1090(S=O), (lit.\textsuperscript{10}) 1101( CCl\textsubscript{4} ).}
S-Phenyl ethanethiosulfinate 1f; pale yellow oil, NMR( CDCl₃, δ ),
1.41( 3H, t, -CH₃, J= 7.5 Hz ), 3.10( 2H, q, -CH₂-, J= 7.5 Hz ),
7.20 - 7.73( 5H, m, arom. ).

Found: C, 51.53; H, 5.50.

S-Propyl benzenethiosulfinate 1g; colorless oil, NMR( CDCl₃, δ ),
1.03( 6H, t, -CH₃, J= 7.5 Hz ), 1.80( 2H, m, -CH₂-CH₃ ), 3.09
( 1H, t, -S-CH₂-, Hₐ or Hₐ', J= 6.0 Hz ), 3.12( 1H, t, Hₐ or Hₐ',
J= 7.4 Hz ), 7.33 - 7.75( 5H, m, arom. ).

Anal. Calcd for C₉H₁₂O₂S₂: C, 53.96; H, 6.03.
Found: C, 54.08; H, 5.98.

S-Cyclohexyl methanethiosulfinate 1h; colorless oil, IR( neat,
cm⁻¹ ) 2970, 2905, 1440, 1080(S=O), NMR( CDCl₃, δ ) 1.05 - 2.35
( 10H, m, ring protons ), 2.95( 3H, s, -CH₃ ) 3.28( 1H, broad
s, -S-CH< ).

Anal. Calcd for C₇H₁₄O₂S₂: C, 47.15; H, 7.91.
Found: C, 47.15; H, 7.85.

S-Methyl p-toluenethiosulfinate 1i; pale yellow oil, NMR( CDCl₃,
δ ) 2.38( 3H, s, -C₆H₄-CH₃ ), 2.52( 3H, s, -S-CH₃ ), 7.23( 2H,
d, arom., J= 8.3 Hz ), 7.54( 2H, d, arom., J= 8.3 Hz ).

Found: C, 51.60; H, 5.35.

S-Methyl p-chlorobenzenethiosulfinate 1j; colorless oil, NMR
( CDCl₃, δ ) 2.53( 3H, s, -CH₃ ), 7.41( 2H, d, arom., J= 8.9 Hz ),
7.63( 2H, d, arom., J= 8.9 Hz ).

Found: C, 41.03; H, 3.19.
Oxidation of ThioIsulfinate with NaIO₄:

All the reactions were carried out at room temperature (ca 20°).

To a stirred solution of thioIsulfinate (1, 1.0 mmole) in organic solvent (acetone, acetonitrile or dioxan: 3 - 5 ml) a solution of sodium metaperiodate (NaIO₄, 1.2 mmole) in 2.0 ml of water was added. A small amount of catalyst (H₂SO₄, HCl, HIO₄, CF₃COOH, HClO₄, I₂ or Br₂; one or two drop(s) of liquid catalyst or 3 - 10 mg of solid catalyst) was added to the mixture. Within 1.0h the solution turned to light yellow and gradually changed to dark brown. The solution remained usually homogeneous but sometimes became heterogeneous. After disappearance of the starting material was confirmed by TLC, the reaction mixture was poured into water and extracted three times with chloroform (ca 100 ml) and then the combined organic layer was washed with an aqueous sodium thiosulfate solution (sat. 10 ml) and water. When chloroform was removed in vacuo after drying the organic layer with MgSO₄, the residue was highly pure thioIsulfonate. Usually GC, LC and NMR spectra showed only one component. Products were identified by comparing their IR and NMR spectra with those of authentic samples prepared by other methods and the structures of new compounds were confirmed by elemental analyses data besides IR and NMR spectra.

If no catalyst was used, the oxidation was very slow and had a long induction period (ca 5 - 10h). However, the reaction after the long induction period was nearly as fast as the reaction with catalyst and completed within 1.0h after the start of the reaction.
When acetic acid was used as a solvent, the oxidation proceeded as fast as the reaction with catalyst, although the catalytic amount of acetic acid did not accelerated the oxidation. In order to remove acetic acid from organic extract, the solution was washed with NaHCO₃ solution before washing with sodium thiosulfate solution.

The reaction in alcohol as solvent was performed by the above-mentioned oxidation procedure. The whole feature of the reaction was similar to the ordinary oxidation and the reaction was also accelerated by addition of catalyst. However, the distribution of products, i.e. thiolsulfonate 2 and sulfinate 3, was affected rather little. Yields of both 2 and 3 were easily determined by measuring NMR spectra of the reaction mixture. The structures of the sulfinates obtained as side products were identified by comparison of their IR (S=O) and NMR spectra (unusual signal pattern)¹¹ with those of authentic samples which were prepared by the reaction of sulfinyl chlorides and excess alcohols, according to the known method.¹²

**Reaction of Disulfide with NaIO₄:** The title reaction was carried out using acetic acid as a solvent. The reaction procedure is also the same as the usual oxidation method mentioned above. The amount of NaIO₄ used was two equivalent to disulfide. After the disappearance of unsymmetrical disulfide 5 or the mixture of symmetrical disulfides 9 and 10 was confirmed, the usual work-up gave a mixture of both symmetrical and unsymmetrical thiolsulfonates which were
identified by comparing their retention times in GC charts and chemical shifts of methyl groups in NMR spectra with those of authentic samples.

**S-Phenyl benzenethiosulfonate 2a**; pink crystals, mp 44 - 45\(^\circ\C\) (lit.\(^{13}\) 44 - 45\(^\circ\C\)), IR( KBr, cm\(^{-1}\)) 3050, 1578, 1471, 1440, 1325 & 1310(SO\(_2\)), 1147(S=O), MS( 70 eV ) m/e 250( M\(^+\), 39%), 125( M\(^+\)-PhS, 100%).

**S-p-Tolyl benzenethiosulfonate 2b**; colorless crystals, mp 52\(^\circ\C\) (lit.\(^{13}\) 54\(^\circ\C\)), IR( CHCl\(_3\), cm\(^{-1}\)) 3030, 1598, 1450, 1330(SO\(_2\)), 1145(S=O), MS( 70 eV ) m/e 264( M\(^+\), 39%), 139( M\(^+\)-PhSO, 100%).

**S-Phenyl p-toluenethiosulfonate 2c**; colorless crystals, mp 78 - 80\(^\circ\C\) (lit.\(^{13}\) 78\(^\circ\C\)), IR( CHCl\(_3\), cm\(^{-1}\)) 3025, 1597, 1443, 1335(SO\(_2\)), 1145(S=O), MS( 70eV ) m/e 264( M\(^+\), 68%), 155( M\(^+\)-PhS, 100%).

**S-Methyl benzenethiosulfonate 2d**; colorless oil, IR( neat, cm\(^{-1}\)) 3050, 3000, 2920, 1580, 1475, 1330 & 1302(SO\(_2\)), 1142(S=O), NMR( CDCl\(_3\), \(\delta\)) 2.48( 3H, s, -CH\(_3\)).

Anal. Calcd for C\(_7\)H\(_8\)O\(_2\)S\(_2\): C, 44.66; H, 4.28.

Found: C, 44.92; H, 4.18.

**S-Phenyl methanethiosulfinate 2e**; colorless crystals, mp 85 - 86.5\(^\circ\C\), IR( KBr, cm\(^{-1}\)) 3050, 3000, 2905, 1565, 1465, 1310(SO\(_2\)), 1130(S=O), NMR( CDCl\(_3\), \(\delta\)) 3.12( 3H, s, -CH\(_3\)).

Anal. Calcd for C\(_7\)H\(_8\)O\(_2\)S\(_2\): C, 44.66; H, 4.28.

Found: C, 44.87; H, 4.25.

**S-Phenyl ethanethiosulfonate 2f**; colorless crystals, mp 52\(^\circ\C\) (lit.\(^{14}\) 50 - 52\(^\circ\C\)), IR( CHCl\(_3\), cm\(^{-1}\)) 3055, 2975, 2930, 1575, 1472, 1326(SO\(_2\)), 1128(S=O), NMR( CDCl\(_3\), \(\delta\)) 1.41( 3H, s, -CH\(_3\)).
$J = 7.4 \text{ Hz }), 3.16(2\text{H}, q, -\text{CH}_2-, J = 7.4 \text{ Hz }), 7.18 - 7.76(5\text{H}, m, \text{arom}.)$.

S-Propyl benzenethiosulfonate 2g; colorless oil, IR( neat, cm$^{-1}$) 3065, 2970, 2930, 2875, 1580, 1330(SO$_2$), 1150(S=O), NMR( CDCl$_3$, $\delta$ ) 0.90(3H, t, -CH$_3$, $J = 6.6 \text{ Hz} ), 1.62(2\text{H}, m, -\text{CH}_2-\text{CH}_3), 2.97(2\text{H}, t, -\text{S}-\text{CH}_2-, J = 6.4 \text{ Hz} ), 7.26 - 8.00(5\text{H}, m, \text{arom}.)$.

Anal. Calcd for C$_9$H$_{12}$O$_2$S$_2$: C, 49.97; H, 5.59.

Found: C, 49.69; H, 5.38.

S-Cyclohexyl methanethiosulfonate 2h; colorless oil, IR( neat, cm$^{-1}$) 2925, 2850, 1321(SO$_2$), 1132(S=O), NMR( CDCl$_3$, $\delta$ ), 1.10 - 2.35(10H, m, ring protons of methylenes), 3.32(3H, s, -CH$_3$), 3.48(1H, broad s, -CH&).

Anal. Calcd for C$_7$H$_{14}$O$_2$S$_2$: C, 43.27; H, 7.26.

Found: C, 43.10; H, 7.31.

S-Methyl p-toluenethiosulfonate 2i; colorless crystals, mp 59 - 61$^\circ$, IR( CHCl$_3$, cm$^{-1}$) 3050, 2913, 1592, 1493, 1335 & 1305(SO$_2$), 1142(S=O), NMR( CD$_3$COOD-D$_2$O(3:1), $\delta$, external TMS) 2.13 (3H, s, -C$_6$H$_4$-CH$_3$), 2.21(3H, s, -S-CH$_3$).

Anal. Calcd for C$_7$H$_{10}$O$_2$S$_2$: C, 47.50; H, 4.98.

Found: C, 47.80; H, 4.99.

S-Methyl p-chlorobenzenethiosulfonate 2j; colorless crystals, mp 35 - 37$^\circ$, IR( CHCl$_3$, cm$^{-1}$) 3080, 3020, 2920, 1578, 1475, 1335(SO$_2$), 1145(S=O).

Anal. Calcd for C$_7$H$_7$ClO$_2$S$_2$: C, 37.75; H, 3.16.

Found: C, 38.01; H, 3.15.
References

Chapter 4

New Mode of Oxygenation:

Nucleophilic Oxygenation of Thiolsulfinate

Abstract

Two kinds of mechanistic pathways for the oxygenative oxidation on sulfur atom, i.e. "nucleophilic oxidation" and "electrophilic oxidation", are proposed and a set of typical examples for the oxidations was shown with a six-membered cyclic thiolsulfinate. The mechanistic path of the "nucleophilic oxidation" was shown in the reaction of thiolsulfinate with NaIO₄, based on the results shown in the preceding chapter and those obtained in this study. Selective oxidation of unsymmetrical thiolsulfimates to the corresponding thiolsulfonates was also found to proceed with such oxidants as KMnO₄, SeO₂, NaClO₃, and NaIO₃, besides NaIO₄. The oxidation of thiolsulfinate (with NaIO₄) completed with even the amount less than an equimolar amount of NaIO₄ (1/2 or 1/4) in nearly
the same reaction time as that with an equimolar amount of \( \text{NaIO}_4 \). The rate of oxidation seems to depend on the amount of catalyst which accelerated the oxidation. Thiol sulfinate in alcohol readily afforded alkyl sulfinate of the alcohol in the presence of halogen such as iodine, while in acetonitrile thiol sulfinate was found to disproportionate readily to disulfide and thiol sulfonate in the presence of iodine. These observations together with the effects of substituents in the oxidation suggest that the nucleophilic oxidation of thiol sulfinate proceeds via formation of a sulfurane intermediate by the attack of the oxidant on the sulfinyl sulfur atom of thiol sulfinate.

**Introduction**

The preceding chapter revealed that various unsymmetrical thiol sulfinates were readily oxidized with sodium metaperiodate (\( \text{NaIO}_4 \)) to the corresponding thiol sulfonates quantitatively under mild conditions. However, most of the oxidations of unsymmetrical thiol sulfinates which have been carried out by this time have been those with peracids or peroxides, and these oxidations usually proceed via cleavage of sulfur-sulfur bond to form a mixture of symmetrical and unsymmetrical thiol sulfonates. 3) Meanwhile, \( \alpha \)-disulfoxide has been suggested to be a key intermediate in the oxidation of thiol sulfinate, by Barnard 4),
During the course of our study on the oxidations of organic sulfur compounds with various oxidants, we have shown that there are two kinds of mechanistic pathways for the oxygenative oxidation on the sulfur atom; namely "nucleophilic oxidation" and "electrophilic oxidation". An electrophilic oxidation takes place preferentially on an electron-rich sulfenyl sulfur atom, while a nucleophilic oxidation occurs on such electron-poor sulfur atom as sulfinyl sulfur atom. Although the oxidation of divalent sulfur compounds such as sulfide by peracid has been known to be initiated by the electrophilic attack of the terminal oxygen of the peracids on the sulfur atom (eq. 2), trivalent sulfur compounds such as sulfoxide or thiolsulfinate which also has a divalent sulfur atom, may be oxidized via either nucleophilic or electrophilic oxidation of the sulfinyl sulfur (eq. 3 & 4). In fact two types of oxygenations have already been
repoted for the oxidation of sulfoxide (eq. 3 & 4). 10,11)

In the preceding chapter 3, the reaction with NaIO₄ has been suggested to involve a nucleophilic attack of oxygen of oxidant at sulfinyl sulfur atom of the thiolsulfinate, on the basis of our careful observations of the reaction. 2) This chapter describes a study on the mechanism for this new oxygenation of thiolsulfinate.

Results and Discussion

Thiolsulfinates are quite interesting species to study the mode of the oxidation since they possess both sulfenyl and sulfinyl sulfur atoms, and the attacking site of oxygen of the oxidant can be readily traced by the use of unsymmetrical
thiolsulfinate. We have shown the selective oxidation of various acyclic unsymmetrical thiolsulfinates with NaIO₄ to the corresponding unsymmetrical thiolsulfonates. In the oxidations of a very stable unsymmetrical thiolsulfinate, 3-methyl-1,2-dithiane-1-oxide, however, we have found that there are two different modes of oxidations as shown in eq. 5 and 6, depending upon the nature of oxidant. Two regio-isomeric unsymmetrical thiolsulfonates (2 and 2') were produced in the same ratio (1:1) nearly quantitatively when 1 was oxidized with the system of either 30% H₂O₂-AcOH (at 27° for 48h) or MCPBA-CHCl₃ (at 27° for 1h) as shown in eq. 5. On the other hand, the oxidation of 1 with the system of either NaIO₄-AcOH-H₂O (at 27° for 14h) or NaIO₄-dioxan-H₂O-H₂SO₄ (cat.) (at 20° for 4h), afforded only one isomeric thiolsulfonate 2 quantitatively.

Thiolsulfinate 1 was separated for the first time from the regio-isomeric mixture (ca 1:1 for 1 and 1'), which was obtained by oxidation of the corresponding disulfide through careful column chromatography (eluent: hexane-ether-ethyl acetate on silica gel). Isenberg et al. also prepared the mixtures of
thiolsulfinates 1 and 1' and thiolsulfonates 2 and 2' by oxidations of the corresponding disulfide.\textsuperscript{12)} However, they could not separate the mixture of the thiolsulfinates which are believed to be two regio-isomers.\textsuperscript{12)} The successful separation of two regio-isomeric thiolsulfinates and subsequent selective oxidation of the two isomers with NaIO₄ to the corresponding thiolsulfonates( 2 and 2' ) undoubtedly proved that the isomers of the thiolsulfinates by the oxidation of the cyclic unsymmetrical disulfide with H₂O₂, were the regio-isomers.

The oxidation of 1 with peroxide or peracid shown in eq. 5 is believed to be an electrophilic oxidation which is presumed to proceed via the incipient formation of "α-disulfoxide " prior to collapse to yield only the two isomers 2 and 2', since this stable cyclic system tends to keep the original skeletal sulfur-sulfur linkage. Oxidation of any common linear unsymmetrical thiolsulfinate with such an oxidant as peracid generally affords four thiolsulfonates. Two isomeric thiol-

sulfonates( 2 and 2' ) were presumably formed via an intramolecular oxygen transfer from the adjacent sulfinyl group after the initial formation of α-disulfoxide as we have already suggested before.\textsuperscript{7)}

Thus, the initial step of the oxygenation of this type is a typical "electrophilic oxidation " of the divalent sulfur atom which is more electron-rich than trivalent sulfinyl sulfur atom of the thiolsulfinate, whereas in the reaction shown in eq. 6, only the sulfinyl sulfur of 1 is oxygenated to the sulfonyl group, affording selectively only the corresponding thiolsulfonate 2. The oxygenation of this type may be a typical "nucleophilic
oxidation " of the sulfinyl sulfur of 1. In order to support the mechanistic interpretation for this nucleophilic oxidation, we have carried out several experiments which are described in the following paragraphs.

Reaction Profiles of Oxidation with NaIO₄: In the preceding chapter, the following observations have been made: (i) the oxidation has a long induction period, but proceeds very readily (~1h) once iodine is formed during the oxidation, (ii) both organic and inorganic acids as well as iodine can accelerate the oxidation (reaction time is shortened markedly without any induction period), (iii) the oxidation in aqueous alcohol affords the corresponding sulfinic ester of the alcohol together with the thiol sulfonate, the usual product, and the amount of the sulfinic ester decreases with the increase of bulkiness or decrease of the nucleophilicity of the alcohol used.

When formation of the product thiol sulfonate 4 and the disappearance of the starting material 3 in the oxidation of thiol sulfinate 3 with NaIO₄ in CD₃COOD-D₂O at 27°, were tracked through following NMR spectra directly, there was no sight of formation of any detectable intermediate during the oxidation (Fig. I). The reaction is presumed to be an auto-catalyzed reaction because of the nearly constant slope of sigmoid curve of the decrease of thiol sulfinate (Fig. II). No detectable intermediate was also observed when the reaction was followed by LC at several time intervals.

While the gradual formation of iodine is expected during
the reaction, the oxidation was found to proceed readily with NaIO₄ even less than an equivalent amount to the substrate at a rate as fast as with that with an equimolar amount of the oxidant (Fig. III). Oxidation number of iodine changed from +7 to 0 (from IO₄⁻ to I₂) during the oxidation. Even with a quarter
equivalent of NaIO₄, the reaction proceeded nearly completely, but did not complete with 1/10 molar amount of NaIO₄. The nearly identical reaction rates of oxidations with NaIO₄ of a wide range of concentrations suggest that the rate-determining step may not be the attacking step of the oxidant to thiol-
sulfinate.
Figure III  Effect of Amount of NaIO$_4$ in The Oxidation of 5d to 6d

$\text{Me-S-S-} \xrightarrow{\text{NaIO}_4} \text{Me-S-S-O}$

$\text{CH}_3\text{CN-H}_2\text{O}$

27°, Cat. I

amount of NaIO$_4$:

1 eq. : •
1/2 eq. : x
1/4 eq. : △

However, the amount of such a catalyst as iodine affected appreciably the rate of the reaction as shown in Fig. IV. The initial rate of the oxidation undoubtedly depends upon the amount of the catalyst, iodine. The rate of the reaction seems to depend markedly on the catalyst used and iodine is more
Figure IV  Effect of Amount of Catalyst (Iodine) in The Oxidation of $5d$ with 0.5 eq. NaIO$_4$

Selective Oxidation with Other Oxidizing Agents: Other metallic oxides such as KMnO$_4$, SeO$_2$, NaClO$_3$ and NaIO$_3$ were also effective than organic and inorganic acids, as shown already in the preceding chapter.
found to be as effective as NaIO₄ in the selective oxidation of unsymmetrical thiol sulfinate 5d in aqueous acetic acid at 20° to the corresponding thiol sulfonate 6d (eq. 7, Table I). In all cases, the reaction profile with time followed by LC showed the formation of only one unsymmetrical thiol sulfonate 6d. KMnO₄ has been known to oxidize selectively sulfoxides or sulfimides to the corresponding sulfones¹³) or sulfoximides¹⁴) even these compounds having sulfenyl group besides the trivalent sulfur group. Thus, KMnO₄ is shown to be a powerful nucleophilic oxidant to oxidize preferentially the trivalent sulfur atom as shown in eq. 4 for the first time by this experiment. However, KMnO₄ is so powerful a reagent, that oxidation usually does not stop at the first oxidation step to form a desired unsymmetrical thiol sulfonate, but proceeds further to afford partially further oxidized products such as sulfonic acid even during a very short reaction time(≈0.5h). Selenium dioxide, SeO₂, was also found to be an effective oxidant in the oxidation in an acetic acid-water system. After a slow reaction(≈30h) reddish brown precipitate of Se₈ is formed together with unsymmetrical thiol-sulfonate(≈80%), recovering some starting material(≈20%).
Table I  Selective Oxidation of 5d with Metallic Oxides

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Reaction Time</th>
<th>Yield of 6d$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaIO$_4$</td>
<td>1.0</td>
<td>quant.$^b$</td>
</tr>
<tr>
<td>NaIO$_3$</td>
<td>1.0</td>
<td>quant.$^b$</td>
</tr>
<tr>
<td>SeO$_2$</td>
<td>30</td>
<td>80$^c$</td>
</tr>
<tr>
<td>KMnO$_4$</td>
<td>0.5</td>
<td>40$d$</td>
</tr>
<tr>
<td>NaClO$_3$</td>
<td>30</td>
<td>30$d$</td>
</tr>
<tr>
<td>HIO$_4$</td>
<td>1.0</td>
<td>quant.$^b$</td>
</tr>
</tbody>
</table>

a) Yield by LC.  b) No other peak was detected on LC chart of the product.  c) Substrate 5d was partly recovered (20%).  d) Other further oxidized products were confirmed by LC.

Sodium chlorate, NaClO$_3$, was not such a good oxidant that the desired product was formed only in a small amount ($\sim$30%) and the reaction required a long reaction time ($\sim$30h). Like in the reaction with KMnO$_4$, some polarized products were obviously obtained as observed by LC in the oxidation with NaClO$_3$, but no other than thiol sulfonate 6d could be seen on LC chart. Although sodium iodate, NaIO$_3$, has never been used as an oxidizing agent, NaIO$_3$ was found to oxidize very nicely unsymmetrical thiol sulfinate to the corresponding thiol sulfonate selectively and quantitatively (Table I). The oxidizing ability of NaIO$_3$ can be compared sufficiently to that of NaIO$_4$ in this oxidation.

In any way, the common behaviour of these metallic oxides
as oxidizing agents is noteworthy despite the difference in the yields of the products. They are all considered to be typical nucleophilic oxidants.

In the meantime, periodic acid (HIO₄), which has been used as an oxidant for various organic substrates, was also found to be effective for the selective oxidation even in the absence of catalyst and without acetic acid as a solvent (Table I). Oxidizing ability of HIO₄ was also comparable to that of NaIO₄ with catalyst. Gradual formation of iodine was also confirmed during the oxidation. Although HIO₄ is not only a catalyst but also an oxidant, initial formation of HIO₄ from NaIO₄ is also considered to be possible in such an acid-catalyzed oxidation with HCl, H₂SO₄ or HClO₄. However, this result does not affect the mechanism of the reaction.

Thus, many oxidizing agents have been found to oxidize selectively unsymmetrical thiolsulfinate to the corresponding thiosulfonate, with no apparent cleavage of the sulfur-sulfur bond.

Reactions on Sulfinyl Sulfur of Thiosulfinate: The reaction of unsymmetrical thiosulfinate with NaIO₄ in aqueous alcohol has been described previously²) to produce an appreciable amount of the sulfinate ester together with the unsymmetrical thiosulfonate, the usual oxidation product. In this reaction alcohol obviously attacks competitively the sulfinyl sulfur of thiosulfinate to afford the alkyl sulfinate during the oxidation with IO₄⁻. The amount of alkyl sulfinate formed changes with
the alcohol used. Without the oxidant NaIO₄, the reaction of unsymmetrical thiosulfinate with a catalytic amount of iodine or hydrochloric acid in alcohol at 20° readily afforded the desired sulfinate and both symmetrical and unsymmetrical disulfides within 45 min (eq. 9, Table II). Therefore, the competitive formation of the sulfinate in the oxidation of thiosulfinate with NaIO₄ in aqueous alcohol is obviously due to

\[
\begin{align*}
\text{Me-} & \quad \text{S-S-} \quad \text{O} \\
\text{I₂ or HCl} & \quad \text{Cat.} \\
\text{ROH, 20°} & \quad \text{45 min} \\
5d & \quad \text{7} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me-} & \quad \text{O-S-OR} + (\text{O-S})₂ \\
\text{O} & \quad \text{8} \\
\text{Me-} & \quad \text{O-S-S-O} \\
\end{align*}
\]

\[
\begin{align*}
\text{R-S-S-R'} & \quad \xrightleftharpoons{\text{Cat. XY}} \quad [\text{R-S-S-R'}]^+ X^- \xrightleftharpoons{\text{[RSX + R'SY]}} \quad [\text{A}] \quad [\text{B}] \\
\text{[A] or [B]} & \quad \xrightarrow{\text{R"OH}} \quad \text{R-S-O-R" + R'SH + XY} \\
\text{[O]} & \quad \text{8}
\end{align*}
\]
### Table II

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH</th>
<th>Cat.</th>
<th>Temp</th>
<th>Yield of Product (mole %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>Me</td>
<td>5ml</td>
<td>I₂</td>
<td>2.5mg</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>10</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>15</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>10</td>
<td>HCl(36%)</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>5</td>
<td>I₂</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>8</td>
<td>i-Pr</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>9</td>
<td>sec-Bu</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>15</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>10</td>
<td>H₂SO₄(98%)</td>
<td>44</td>
</tr>
<tr>
<td>12</td>
<td>&quot;</td>
<td>10</td>
<td>HClO₄(70%)</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

a) Di-p-tolyl disulfide. b) Trace amount of thiosulfonate 6d and S-p-tolyl toluenetiosulfonate were observed. c) Equimolar amount of 30% H₂O₂ was added from the beginning of the reaction.

the reaction between the thiolsulfinate and the alcohol, possibly in the presence of iodine, with no participation of NaIΟ₄.

Formation of both symmetrical and unsymmetrical disulfides in eq. 9 is resulted by the known reaction<sup>15</sup>) of thiolsulfinate 5d with thiol which is considered to be produced by the following reactions( eq. 10, 11 and 12 ). As shown in eq. 10, there is an equilibrium between thiolsulfinate and XY( XY: I₂ or HCl )

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to give at first the adduct [ A ] which would then dissociate to [ B ] that reacts readily with a large excess of alcohol to afford the corresponding sulfinate and thiol (eq. 11).

Although the alkyl sulfinate is stable under the conditions (inert in the oxidation with NaIO₄), the thiol formed can reduce the remaining thiolsulfinate to yield both symmetrical and unsymmetrical disulfides (eq. 12). Therefore, the yield of the sulfinate has never reached any higher than 70% because of this side reaction. However, the yield of the sulfinate was found to increase if the thiol was successfully removed from the system or converted into inert form. Namely, when the same molar amount of 30% H₂O₂ as that of thiolsulfinate was added in the reaction system of eq. 9 in order to oxidize the thiol to disulfide (R'SSR') to prevent the reaction of thiolsulfinate with thiol formed during the reaction, the yield of the sulfinate increased remarkably (\sim 90\% ) as shown in Table II. In this reaction the amount of H₂O₂ was small enough not to oxidize thiolsulfinate according to the separate control experiment, however, was enough to oxidize the thiol to the disulfide since the oxidation of thiol is very fast.

\[
R'SH + R'SH \xrightarrow{H_2O_2} R'SSR' + H_2O \quad (13)
\]
Although both sulfuric acid (H₂SO₄, 98%) and perchloric acid (HClO₄, 70%) are good catalysts for the oxidation of thiosulfinate with IO₄⁻, they were not effective at all for the formation of the sulfinate in the reaction of 5 in aqueous alcohol with a catalytic amount, and the starting thiosulfinate 5d was recovered quantitatively, presumably because nucleophilicity of the alcohol decreases in acidic media and the equilibrium between thiosulfinate and catalytic acid cannot be fully achieved enough to give [ A ] or [ B ] under the condition. The conjugate bases of these acids, i.e. HSO₄⁻, SO₄²⁻ or ClO₄⁻, are very weak nucleophiles and hence the interaction between the thiosulfinate 5d and the acid would be only the protonation of both the thiosulfinate and alcohol with no subsequent nucleophilic attack of the protonated alcohol. The interaction between the thiosulfinate and the catalyst is quite important since the formation of the sulfinate was found to proceed readily when such an acid as HCl was used. In this case, Cl⁻, the conjugate base of HCl, is a good nucleophile.

Data in Table II reveal that the amount of the sulfinate does not depend on the bulkiness or nucleophilicity of the alcohol used, because the alcohol does attack the sulfinyl sulfur of the thiosulfinate, not competitively with the oxidant IO₄⁻, without any oxidant.

When acetonitrile was used as solvent instead of alcohol the reaction of thiosulfinate with a catalytic amount of halogen (I₂ or Br₂) or HCl caused a rapid disproportionation (eq. 14), while addition of a catalytic amount of sulfuric
acid, instead of halogen, did not result in such a reaction. The rapid disproportionation of thiosulfinate in the presence of halogen or HCl is in keeping with many earlier observations that impure thiosulfinates containing some concomitant nucleophiles such as halide and thiolate are very unstable but become quite stable even in acetic acid, once purified. 

All these observations clearly indicate that the selective oxygenation of thiosulfinate with NaIO₄ or other metallic oxides and the formation of sulfinate ester take place by nucleophilic attacks of the oxidant or alcohol only at the sulfinyl sulfur atom of thiosulfinate.

**Substituent Effect:** Effect of substituent was investigated with various para-substituted S-phenyl benzenethiosulfinates 5a - 5e, both in acid- and halogen-catalyzed oxidations. Although the reaction is simple and the only product formed quantitatively was 6, no accurate kinetic measurement was possible since the reaction was auto-catalyzed. Decrease of each starting material 5 was measured by LC in both reactions
As shown in Fig. V, no clear-cut relationship between the effects of substituents and the reactivities of these substrates was observed in the oxidations of 5a - 5e with 1/2 molar amount of NaIO₄ in aqueous acetonitrile in the presence of a catalytic amount of iodine (1.5%) at 20°. However, what one can find from the data of Fig. V is that the reaction of nitro or methoxy substituted substrate is relatively faster than those of other substrates which completed nearly in the same reaction time.

Since the rate of the overall reaction is controlled by the three successive steps each of which demands somewhat opposite electronic environment, namely the initial protonation or complexation with a Lewis acid becomes favorable by the electron-withdrawing substituent, while the subsequent nucleophilic attack is accelerated by the electron-releasing group, whereas the final elimination of IOₓ₋₁⁻ from the sulfurane intermediate would be facilitated by the electron-releasing group, so the net effect of substituent is considered to be resulted by the relative importance of the three steps in the energy profile of the oxidation of each thiolsulfinate.
The same trend was found in the oxidation of the same compounds with an equimolar amount of NaIO$_3$ in aqueous acetic acid at 20° (eq. 16, Fig. VI). NaIO$_3$ was used instead of NaIO$_4$ in this oxidation since the reaction solution sometimes turned to heterogeneous with NaIO$_3$ formed during the oxidation when NaIO$_4$ was used. The effect of substituent in this acid-catalyzed reaction are relatively more clearly observed than that in the iodine-catalyzed reaction. The compound having an electron-donating substituent showed a higher reaction rate than that having an electron-withdrawing substituent in the acid-catalyzed oxidation, however, the reactivity of thiol sulfinate having nitro group is higher than that with chloro group (Fig. VI). However, even the acid-catalyzed reaction is markedly affected by iodine formed in the acid-catalyzed reaction and this may obscure the kinetic rate.

Since electron-rich sulfides can be oxidized to the sulfoxides with NaIO$_4$ selectively, it appears to be intriguing that thiol sulfinate is oxygenated at sulfinyl sulfur to afford the thiol sulfonate without the cleavage of sulfur-sulfur bond. However, when diphenyl sulfoxide was treated with an equimolar
amount of NaIO₄ in neutral dioxan-water at 20°, diphenyl sulfone was obtained in ca 30% for 20h, and in the presence of a catalytic amount of HCl (≈10%) the yield of the sulfone increased up to ca 95% even in 30 min.₁⁷ This observation indicates clearly that the oxidation of sulfoxide, another sulfinyl compound, with NaIO₄ is also a nucleophilic oxygenation, like the nucleophilic oxygenation of sulfoxide with anion of peracid or hydroperoxide.
under alkaline conditions. Thus, the oxidation is the direct nucleophilic oxidation at sulfinyl sulfur.

The possible mechanistic pathway is shown in Scheme I. Namely, in the nucleophilic oxidation of thiol sulfinic acid, the likely intermediate is the sulfurane in both catalytic reactions. Both iodine and acid participate in the formation of the
intermediary sulfonium ion in the equilibrium with thiolsulfinate. The sulfonium ion thus formed incipiently is then subjected to a rapid nucleophilic attack of one of the oxidizing species (such as IO₄⁻, IO₃⁻, IO₂⁻, or IO⁻) to afford the sulfurane intermediate. The unstable sulfurane intermediate should collapse to afford the desired thiolsulfonate. The sulfonium ion can also react competitively with alcohol used as solvent, to form alkyl sulfinate, while without any oxidant the sulfonium ion disproportionates rapidly to both disulfides and thiol-
sulfonates. Neither the first equilibrium step nor the second step of the attack of the oxidant would be the rate-determining step in this catalytic reaction since the time required for the reaction was hardly affected by the amount of the oxidant NaIO₄ while the substituent effect observed was not clear-cut.

Meanwhile, no disproportionation product was observed in the oxidation of unsymmetrical thiol sulfinate with NaIO₄ and there are big difference between the reaction times in the oxidation of the thiol sulfinate with NaIO₄ and in the disproportionation of it in the presence of such a halogen as iodine. These observations seem to support that the attacking step of the oxidant is generally somewhat faster than the disproportionation. Most likely, the rate-determining step is in the decomposition step of the sulfurane intermediate. This mechanism is very similar to that of Modena et al. in the nucleophilic oxidation of sulfoxide which involves the sulfurane intermediate.¹¹) They also suggested that although the rate-determining step would be the decomposition of the sulfurane to the sulfone, as Ogata et al. suggested, the effect of the substituent was not in good accord with the proposed rate-determining step. The small differences of the substituent effects both in acid- and iodine-catalyzed oxidations are considered to be due to the cancellation of the opposite polar effect in the two successive steps of the oxidation, i.e. the nucleophilic attack of the oxidant and the subsequent collapse of the sulfurane. Despite the weak sulfur-sulfur linkage of the thiol sulfinate (for S-methyl methanethio-sulfinate, ca 46 kcal/mole),¹⁹) it is surprising to see that
the sulfur-sulfur linkage is not cleaved during the oxidation.

In the reaction of thiosulfinate with halogen or HCl the sulfur-sulfur linkage might be cleaved to give [ B ], as shown in eq. 10. However, even from the dissociated intermediate [ B ], the selective formation of thiosulfonate is possible as shown in the above Scheme II, although it is quite unlikely, since no disproportionation product can be observed in the oxidation. Therefore the sulfonium ion intermediate[ A ] is expected to react with \( \text{IO}_{x}^- \) preferentially to afford the thiosulfonate. The nucleophilicity of \( \text{IO}_{x}^- \) is apparently stronger than that of alcohol since without the oxidant the reaction of thiosulfinate with alcohol does not occur even in the presence of a common acid( no formation of sulfinate ). However, once the oxidation starts, iodine begins to be formed gradually and then the sulfinate starts to be produced competitively upon formation of iodine in aqueous alcohol.
Thus, the oxidation is presumed to take place via the sulfonium ion intermediate[ A ] but not the separated system[ B ], while the separated ion pair intermediate[ B ] may be important for the formation of the sulfinate in the reaction in aqueous alcohol.

Although collapsing of the sulfurane intermediate would be the rate-determining step, the cleavage of O-I bond in the concerted collapse of the sulfurane in the rate-determining step is, however, not in complete accordance with the effect of substituent due to the two opposing effects of the same substituent in the initial nucleophilic attack of IO\textsubscript{x} and the collapse of the sulfurane formed. The high reactivity of nitro substituted substrate in both catalytic reactions may be caused by that the attacking step of the oxidant IO\textsubscript{x} at the sulfonium ion intermediate is somewhat more important than the collapsing of the sulfurane energetically.

A long induction period in the oxidation without any catalyst may be attributed to the very slow reaction of thiol-sulfinate with NaIO\textsubscript{4} up to the formation of iodine from NaIO\textsubscript{4}
Experimental

General: Melting points were taken on a Yanaco instrument and were uncorrected. \(^1\)H- and \(^{13}\)C-NMR spectra were recorded on a Hitachi Perkin Elmer R-20 and JEOL FX 90Q spectrometers, respectively. Infrared spectra were obtained on a Hitachi 215 IR spectrometer and were uncorrected. Gas and liquid chromatographs were obtained by Shimazu GC-6A and Yanaco L-1030 instruments, respectively.

Chemicals were of reagent grade unless otherwise specified.

Oxidation of 3-Methyl-1,2-dithiane-1-oxide \(_1\): A regio-isomeric mixture of 3-methyl-1,2-dithiane monoxides was prepared according to the method of Isenberg and Herbrandson.\(^{12}\) Ratio of the isomers was ca 1:1 and 10 peaks were found in \(^{13}\)C-NMR spectra of the mixture. In order to separate the isomers the mixture was subjected to the silica gel column chromatography with a mixed solvent of hexane - ethyl acetate - ether (4:1:2) as an eluent. The first fraction was 3-methyl-1,2-dithiane-oxide \(_1\) and the second was its regio-isomer, 3-methyl-1,2-dithiane-2-oxide \(_1'\). \(^{13}\)C-NMR spectral data are the followings.

Isolated \(_1\) was oxidized by the system of H\(_2\)O\(_2\)-AcOH, MCPBA-CHCl\(_3\), NaIO\(_4\)-AcOH-H\(_2\)O, or NaIO\(_4\)-CH\(_3\)CN-H\(_2\)O-H\(_2\)SO\(_4\).
Oxidation of 1 with 30% H₂O₂ in AcOH: To a solution of 1 (0.27 mmole) in CD₃COOD (400 µl) in NMR sample tube 30% H₂O₂ (0.3 mmole) was added at 27° and kept at that temperature. After 48h, the measurement of NMR spectrum of the reaction mixture undoubtedly indicated the formation of a mixture of unsymmetrical thiosulfonates, 2 and 2', from the NMR signal pattern and chemical shifts of the methyl group. The yield of the mixture of the dioxides, 2 and 2', was nearly quantitative as estimated by NMR spectrum (two doublets at 1.37 and 1.42 ppm).

Oxidation of 1 with MCPBA in CHCl₃: In a same procedure as the oxidation with H₂O₂ in AcOH, the oxidation of 1 (0.27 mmole) using MCPBA (0.3 mmole) and CDCl₃ (400 µl) as a solvent was carried out but was completed only after 1h at 27°. After the reaction, the reaction mixture was filled with a large amount of white precipitate due to MCBA formed during the reaction. NMR signal pattern and chemical shifts of the reaction mixture were quite consistent with those of the authentic mixture of the dioxides which were prepared directly from the corresponding disulfide according to Isenberg and Herbrandson. 12)

Oxidation of 1 with NaIO₄ in AcOH-H₂O: A solution of NaIO₄ (0.3 mmole) in D₂O (150 µl) was added to a solution of 1
(0.27 mmole) in CD$_3$COOD (400 µl) in a NMR sample tube which was kept at 27° for ca 14h. The mixture gradually colored to dark brown by iodine formed. In NMR spectrum of the reaction mixture only one doublet due to methyl group was observed unlike in the above two oxidations. The product was identified to be 3-methyl-1,2-dithiane-1,1-dioxide 2 by $^{13}$C-NMR spectrum.

Oxidation of 1 with NaIO$_4$ in CH$_3$CN-H$_2$O in The Presence of Catalytic H$_2$SO$_4$: To a mixture of 1 (3.33 mmole) and conc. H$_2$SO$_4$ (98%, one or two drop(s); ca 40 mg) in CH$_3$CN (12 ml) a solution of NaIO$_4$ (4.0 mmole) in H$_2$O (6.6 ml) was added at 20°. The mixture was stirred for 4h at 20°. From the beginning of the reaction, the reaction mixture was colored to dark brown by iodine formed. Then the reaction mixture was poured into a separatory funnel for extraction with CHCl$_3$ after addition of water. A combined CHCl$_3$ layer colored by iodine was washed with water, sat. Na$_2$S$_2$O$_3$ solution, and then water again. The decolored organic layer was dried over MgSO$_4$. Removal of CHCl$_3$ and CH$_3$CN in vacuo afforded nearly pure dioxide 2 which was purified by column chromatography on silica gel (yield 85%). While the $^1$H-NMR spectrum of the product showed only one doublet due to methyl group, its $^{13}$C-NMR spectrum showed only five peaks based on carbons of only one isomeric dioxide 2.

Data of $^{13}$C-NMR spectra of 2 and 2' are the followings.

Starting Thiolsulfinate and Product Thiolsulfonate: S-Methyl benzenethiosulfinate 3a, S-methyl p-toluenethiosulfinate 3b, S-methyl p-chlorobenzenthiosulfinate 3c, S-phenyl benzenthio-
sulfinate 5c, S-phenyl p-toluenethiosulfinate 5d, and their oxides, 4a, 4b, 4c, 6c and 6d were prepared by the known methods as shown in the preceding chapter.

S-Phenyl p-chlorobenzenethiosulfinate 5b, S-phenyl p-methoxybenzenethiosulfinate 5e and S-phenyl p-chlorobenzenethiosulfonate 6b were prepared by the known methods and their melting points were identical with those in the literatures.21,22) New compounds, 5a, 6a and 6d were prepared according to the reported methods.23,24)

S-Phenyl p-nitrobenzenethiosulfinate 5a; yellow crystals, mp 77 - 78°, IR (KBr, cm⁻¹) 3050, 1599, 1518(NO₂), 1338(NO₂), 1095(S=O).

Found: C, 51.17; H, 3.05; N, 5.16.

S-Phenyl p-nitrobenzenethiosulfonate 6a; yellow crystals, mp 156 - 157°, IR (CHCl₃, cm⁻¹) 3050, 1599, 1520(NO₂), 1341(NO₂, SO₂), 1142(S=O).

Anal. Calcd for C₁₂H₉NO₄S₂: C, 48.80; H, 3.07; N, 4.74.
Found: C, 48.73; H, 3.05; N, 4.51.

S-Phenyl p-methoxybenzenethiosulfonate 6e; yellow crystals, mp 55 - 57°, IR (CHCl₃, cm⁻¹) 3050, 1582, 1570, 1485, 1320(SO₂),
NMR Study of Oxidation of 3a, 3b and 3c with NaIO₄:

The oxidation of thiol sulfinate with NaIO₄ in a NMR sample tube was carried out at 27° as follows. A solution of NaIO₄ (0.3 mmole) in D₂O (150 μl) was added into a solution of one of the thiol sulfinates (3a - 3c, 0.27 mmole) in CD₃COOD (400 μl). Decrease of methyl group of thiol sulfinate and the increase of that of the product thiosulfonate during the oxidation were traced by measuring NMR spectra of the reaction mixture at a few time intervals. The reaction usually completed nearly in 30 min. Any other peak than that of the thiosulfonate was not observed in NMR spectra of the mixture after the disappearance of the starting material. Results obtained thus are illustrated in Fig. I and II.

Effect of Amount of NaIO₄:

A cooled solution (0 - 4°) of S-phenyl p-toluenethiosulfinate 5d (58 mg) in acetonitrile (5.0 ml) and a cooled solution (0 - 4°) of a desired amount of NaIO₄ (equimole: 50 mg; half mole: 25 mg; and quarter mole: 12.5 mg) in water (1.0 ml) was mixed at 0 - 4° and the mixture was stirred at 0 - 4°. The oxidation was started by the addition of 9.5 mg of iodine (16%) as a catalyst in CH₃CN (100 μl) into the reaction mixture. At a few time intervals an aliquot withdrawn from the reaction mixture during the oxidation was
injected into LC to trace the oxidation. With the decrease of the peak of 5d the peak of 6d on LC chart increased. Regardless of the amount of the oxidant, as shown in Fig. III, the rate of the decrease of the starting material 5d on LC chart was nearly the same in each case.

**Effect of Amount of Catalyst, Iodine:** To an acetonitrile solution (15 ml) of 5d (58 mg) a solution of NaIO₄ (25 mg, 0.5 eq.) in water (0.5 ml) was added at 0 - 4°C. The oxidation was initiated by the addition of solid iodine (4.6 mg: 7.7%; 8.7 mg: 14.6%; or 12.8 mg: 21.5%) to the mixture. The resulted mixture was stirred at 0 - 4°C. Several aliquots withdrawn from the reaction mixture were injected at a few time intervals into LC to follow the reaction. The rate of decrease of 5d was proportional to the amount of the catalyst iodine, as shown in Fig. IV.

**Substituent Effect:** Acid-catalyzed oxidation was carried out using NaIO₃ instead of NaIO₄ as an oxidant, since the reaction solution became sometimes heterogeneous when NaIO₄ was used. To a solution of one of the thiol sulfinate (5a - 5e, 0.234 mmole) in acetic acid (5.0 ml) a solution of an equimolar amount of NaIO₃ (46.3 mg, 0.234 mmole) in water (1.0 ml) was added to initiate the oxidation at 20°C. The reaction mixture was stirred at the same temperature. In the same manner as above, the decrease of 5 was plotted in Fig. VI. Iodine-catalyzed oxidation was carried out using half equivalent of the
oxidant NaIO₄ because of the same reason as above. A solution of NaIO₄ (1/2 equivalent, 0.117 mmole) in water (1.0 ml) was added to a solution of one of the thiolsulfinates (5, 0.234 mmole) in acetonitrile (5.0 ml) at 20°. To the stirring mixture, iodine (1.5 mg, 2.5%) in acetonitrile (30 μl) was added to initiate the oxidation and the reaction mixture was stirred continuously at 20°. The oxidation was traced again by LC as shown in Fig. V.

Oxidation of Thiolsulfinate 5d with Other Metallic Oxides:
To a solution of 5d (50 mg) in acetic acid (5.0 ml) a solution of one of the metallic oxides (KMnO₄: 28.4 mg; SeO₂: 20.0 mg; NaClO₃: 38 mg; NaIO₃: 40.0 mg) in water (1.0 ml) was added at 20°. The mixture was stirred at that temperature for a set period as shown in Table I, monitoring the disappearance of the starting substrate by injecting at a few intervals into LC an aliquot withdrawn from the reaction mixture. The yield of the product thiolsulfonate 6d in each case was determined by LC and the results are listed in Table I.

Oxidation with an equimolar amount of periodic acid (HIO₄) was carried out in the same fashion as above, using acetonitrile instead of acetic acid. After the color of iodine appeared, the oxidation was completed within 30 min and the yield of 6d was nearly quantitative since no other peak than that of 6d was observed on LC charts.
Reaction of Thiolsulfinate in The Presence of Catalyst without The Oxidant: Nearly the same procedure as those mentioned above was applied for the title reaction. All of catalysts, alcohols, solvent volume, amount of catalyst, and reaction temperature in the reaction of thiolsulfinate $5d$ with alcohol in the presence of catalyst, are listed in Table II. The reaction was completed within 45 min (latest: entry 10, Table II). Yields of the sulfinates and the disulfides, as the products, were determined by injecting an aliquot of the mixture directly into GC after the reaction was completed, and are listed in Table II.

When acetonitrile was used instead of alcohol as solvent, thiolsulfinate $5d$ disproportionated to give a mixture of thiolsulfonates and disulfides on LC chart, in the same scale reaction in the presence of iodine (5.0%) or HCl (10%).

References

6) For example, B. C. Gilbert, B. Gill and M. J. Ramsden, Chem. & Ind., 283 (1979).
8) S. Oae and T. Takata, Chemistry (Japanese), 34, 756, 891, and 961 (1979).
17) S. Oae and T. Takata, unpublished results.


Chapter 5

Reaction of Organic Sulfur Compounds with Superoxide Anion

Oxidation of Organic Sulfur Compounds to Sulfinic and Sulfonic Acids

Abstract

Organic sulfur compounds such as disulfide, thiolsulfinate, thiolsulfonate, thiol, sodium thiolate, and sodium sulfinate were readily oxidized to both sulfinic and sulfonic acids with superoxide anion generated from potassium superoxide and 18-crown-6-ether under mild conditions. However, both sulfide and sulfoxide did not react with superoxide anion, $O_2^-$. Although thiol was easily oxidized to disulfide with $O_2^-$ at room temperature, it was oxidized further with $O_2^-$ at 60° to the corresponding sulfinic and sulfonic acids. Symmetrical disulfide was obtained in the reaction of unsymmetrical thiolsulfinate or thiolsulfonate along with both sulfinic and sulfonic acids. Most reactive was thiolsulfinate which reacted at lower temperature ranging between -40° and 0° to
afford the products within 30 min. Relative reactivities fall in the following order: thiolsulfinate $\succ$ thiolsulfonate $\succ$ disulfide $\simeq$ sodium thiolate $\simeq$ sodium sulfinate. Polar solvents such as pyridine and acetonitrile were more effective than such a less polar solvent as benzene in the oxidation of the substrate, and increased amount of the crown ether shortened the reaction time. Nucleophilic attack of $O_2^{-}$ and electron transfer processes are believed to be involved in these oxidations.

Introduction

Although the role of superoxide anion has been well advocated in oxygen-metabolizing organisms for the past two decades$^2$) since the discovery of superoxide dismutase by Fridovich and McCord in 1969,$^3$) the information on its reactivities with simple organic compounds has been rather scant, especially on the reaction of organic sulfur compounds.$^4,5$) Superoxide anion is a mild multifunctional reagent which possesses both oxidizing and reducing abilities and also both radical or anionic characters$^{5b}$) but generally regarded as a rather weak oxidizing agent.

Only two minor reactions of $O_2^{-}$ with organic sulfur compounds have been known: one is a reaction of sulfonyl chloride with sodium superoxide to yield sodium sulfonate in
none-crown ether containing system, and the other is a simple oxidation of an alkanethiol to the corresponding disulfide with $O_2^{-}$ with no experimental detail. These two reactions alone are not enough to understand the fundamental nature of the reactions of $O_2^{-}$ with organic sulfur compounds. We now have studied the general reactions of organic sulfur compounds bearing S-S linkage, sodium salts of thiols and sulfinates with $O_2^{-}$.

This chapter describes general features of the reactions of various organic sulfur compounds with $O_2^{-}$.

Results and Discussion

Superoxide anion generated in situ from the system of potassium superoxide and 18-crown-6-ether, as previously reported and usually used, was found to react readily with several organic sulfur compounds (1~5 & 8) under mild conditions, in argon atmosphere. However, neither sulfide 6 nor sulfoxide 7 was found to react with $O_2^{-}$ at all, under the same conditions.

\[
\begin{array}{cccc}
\text{RSSR} & \text{RSSR'} & O & \text{RS}^{-}\text{Na} \\
\downarrow & \downarrow & \downarrow & \downarrow \\
1 & 2 & 3 & 4
\end{array}
\]
A solution of one of the substrates and 18-crown-6-ether was added onto potassium superoxide and the heterogeneous mixture was stirred at a set temperature for some periods till the disappearance of the substrate which was monitored by gas or liquid chromatography. After quenching the reaction mixture with a large amount of cold water, the disulfide was isolated from the organic layer and from the aqueous layer sulfinic and sulfonic acids were obtained as oxidation products. The sulfinic acid was isolated as the corresponding methyl sulfone upon treatment of the aqueous layer with methyl iodide according to the method of Otto$^9$ or Lindberg.$^{10}$ The resulting aqueous layer, after extracting the sulfone$^{13}$, was treated with S-benzylisothiuronium chloride$^{12}$,$^,$ upon acidification, to obtain its salt of the sulfonic acid as
good crystals, according to the known method.\textsuperscript{12} This separation procedure of sulfinic and sulfonic acids is shown in above Scheme. Thus, this method of separation is very reliable to determine the amounts of both sulfinic and sulfonic acids.

$\text{Melting point of this crystal was very sharp at 139°, and the elemental analysis and the spectral data of S-benzylisothiuronium p-chlorobenzenesulfonate were satisfactory. The melting point previously reported was not constant, at 172 - 4° and 146 - 8°: see ref. 11.}$
acids which are very difficult to be separated chemically, although estimation of both acids by polarographical determination was reported.\textsuperscript{13)} Since the S-benzylisothiuronium salts of aromatic sulfonic acids can be obtained in better crystalline forms than those of aliphatic sulfonic acids, substrates used in this study were mostly aromatic. In control reactions forming the sulfone and the S-benzylisothiuronium salt from the mixture of sulfinic and sulfonic acids under our reaction conditions, isolated yields of the sulfone and the S-benzylisothiuronium salt of the sulfonic acid were found to be satisfactory, i.e. \(\sim 86\%\) and \(\sim 95\\%\), respectively, for any one of phenyl-, p-tolyl- and p-chlorophenyl-derivatives.

Potassium superoxide used was two equivalent enough to oxidize each one of the substrates completely to the sulfonic acid, while a half equivalent of the crown ether was used for one of the sulfur atoms of the substrate.

Commercially unobtainable disulfides were synthesized by treatment of thiols with iodine in the presence of pyridine in quantitative yields, according to the method of McAllen et al.\textsuperscript{14)} Both symmetrical and unsymmetrical thiol sulfinates were prepared by treating corresponding sulfinyl chloride\textsuperscript{15)} with desired thiol in the presence of pyridine, as reported previously.\textsuperscript{15a,16)} In the same manner, both symmetrical and unsymmetrical thiol sulfonates were prepared by treating corresponding sulfenyl chlorides with proper free sulfinic acids in the presence of pyridine, according to the method reported by Stirling\textsuperscript{17)} or Klivenyi.\textsuperscript{18)} Although symmetrical
thiolsulfonate can be also prepared by direct oxidation of corresponding disulfide with peracid, the yield by this method of condensation is usually higher than that by the peracid oxidation. Sodium sulfinate and thiolate were obtained from the reactions of sulfinic acid and thiol with metallic sodium. Although anhydrous sodium sulfinate may be obtained by removing water in refluxing sodium sulfinate hydrate in benzene or toluene by azeotropic separation, completely anhydrous sulfinate can be prepared more readily by the above mentioned method.

In the absence of the crown ether the reaction was quite slow or did not occur, while increased amount of the crown ether accelerated the oxidation, suggesting that superoxide anion must be the oxidizing active species.

Reaction of Disulfide $\text{I}$ with $\text{O}_2$  

Both diaryl and dialkyl disulfides were oxidized at ca 25° with $\text{O}_2$ to afford both sulfinic and sulfonic acids, i.e. 9 and 10, generally in good yields (Table I). Yield of the sulfonic acid is usually larger than that of the sulfinic acid,
mainly because the sulfinate is also oxidized further to the corresponding sulfonate with excess superoxide anion present in the reaction system. In general, the reaction was slightly exothermic. However, di-tert-butyl disulfide was not oxidized at all even for 24h due to the large steric hindrance of the bulky tert-butyl group to block the $S_{N}2$ attack of $O_{2}^{-}$/ on sulfur atom, while 1,2-dithiane, a six-membered cyclic disulfide, was not also oxidized at all.

Since such a dialkyl disulfide as dibutyl disulfide was generally found to be less reactive than aromatic disulfides

<table>
<thead>
<tr>
<th>Substrate, No., Solv., Time[h], RSO$_2$(9), RSO$_3$(10), Recovery (R=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me lala Py 3.0 0$%$ a) 57$%$ a) b)</td>
</tr>
<tr>
<td>Bu lb &quot; 1.0 - b) - b) 69$%$ c)</td>
</tr>
<tr>
<td>tBu lc &quot; 24.0 0 0 100</td>
</tr>
<tr>
<td>PhCH$_2$ ld &quot; 0.5 - b) - b) 5</td>
</tr>
<tr>
<td>Ph le &quot; 6.0 trace 81 trace</td>
</tr>
<tr>
<td>p-CH$_3$C$_6$H$_4$ lf &quot; 1.0 24 64 12</td>
</tr>
<tr>
<td>p-ClC$_6$H$_4$ lg &quot; 0.5 46 53 trace</td>
</tr>
<tr>
<td>Ph le CH$_3$CN 10.0 13 48 7d)</td>
</tr>
<tr>
<td>p-CH$_3$C$_6$H$_4$ lfg &quot; 6.0 28 56 9d)</td>
</tr>
</tbody>
</table>

a) Yields of RSO$_2$ and RSO$_3$ are in 1/2 mole %.
b) Yield was not determined.
c) Yield was in mole%.
d) Side product was obtained in 30% (PhS$_2$ CHCN) for lc, and 29% (p-TolS$_2$ CHCN ) for lf, respectively.
except for dibenzyl disulfide, the conversion of the dialkyl disulfide to the acids is slower than that of the aromatic disulfide and required a prolonged reaction time. Thus the initial step of the oxidation undoubtedly involves a nucleophilic attack of $O_2^-$ on the sulfur atom.

**Reaction of Thiolsulfinate 2 with $O_2^-$**

The oxidation of both symmetrical and unsymmetrical thiolsulfinates 2 proceeded very readily even at $-35^\circ$ within 30 min and gave the sulfinic and sulfonic acids as main products from the aqueous layer, along with symmetrical disulfide, from the organic layer, which is undoubtedly derived by recombination of the thiyl radicals resulted from the nucleophilic attack of $O_2^-$ at the sulfinyl sulfur atom of the thiolsulfinate 2. These observations are in accordance with the exclusive formation of the acids, 9 and 10 from the sulfinyl sulfur side of 2 as in the alkaline hydrolysis of unsymmetrical thiolsulfinate,\(^{19b)}\) supporting the nucleophilic attack of $O_2^-$ at the sulfinyl sulfur atom of 2. The yield of the sulfinic acid was rather low and the main product from aqueous layer was the sulfonic acid.

\[
\begin{align*}
\text{RSSR'} & \quad \xrightarrow{5\text{eq. KO}_2} \quad \text{RSO}_2^{\text{t}+} \quad + \quad \text{RSO}_3^{\text{t}+} \quad + \quad \text{R'SSR'} \\
\text{RSSR'} & \quad \xrightarrow{\text{eq. crown ether}} \quad \xrightarrow{-40^\circ \sim 0^\circ} \quad 9 \quad 10 \quad 11
\end{align*}
\]
Table II

Reaction of Thiolsulfinate \textsubscript{2} with O\textsuperscript{2-}

<table>
<thead>
<tr>
<th>Substrate, No., Temp., Time, RSO\textsubscript{2}\textsuperscript{-}(9), RSO\textsubscript{3}\textsuperscript{-}(10), R'SSR' (R=)</th>
<th>R=</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Tol Ph 2a -35° 90min 6%\textsuperscript{a)}</td>
<td>\textsuperscript{a})</td>
</tr>
<tr>
<td>&quot; &quot; &quot; 2a 0 30 trace</td>
<td>45 44</td>
</tr>
<tr>
<td>Ph p-Tol 2b -40° 0 25</td>
<td>48 16</td>
</tr>
<tr>
<td>Ph Ph 2c -40° -20 15</td>
<td>48 35</td>
</tr>
<tr>
<td>&quot; &quot; 2c 23 15 &quot;</td>
<td>49 44</td>
</tr>
<tr>
<td>p-Tol p-Tol 2d -35° 10</td>
<td>40 36</td>
</tr>
<tr>
<td>&quot; &quot; 2d -20° 0 30 trace 33</td>
<td>\textsuperscript{b)} \textsuperscript{c)}</td>
</tr>
<tr>
<td>&quot; &quot; &quot; 2d 18 10 14</td>
<td>37 50</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Yields of RSO\textsubscript{2}\textsuperscript{-} and RSO\textsubscript{3}\textsuperscript{-} are in 1/2 mole \%, while yield of R'SSR' is in mole \%.
\textsuperscript{b)} Solvent used was acetonitrile.
\textsuperscript{c)} Yield of R'SSR' was not determined.

Reaction of Thiolsulfonate \textsubscript{3} with O\textsuperscript{2-}

Symmetrical and unsymmetrical thiolsulfonates \textsubscript{3} were oxidized with O\textsuperscript{2-} under mild conditions (ca 0°) to afford four main acids, i.e. two sulfinic acids, RSO\textsubscript{2}\textsuperscript{-} and R'SO\textsubscript{2}\textsuperscript{-}, and two sulfonic acids, RSO\textsubscript{3}\textsuperscript{-} and R'SO\textsubscript{3}\textsuperscript{-}, from both sides of the S-S linkage, together with a small amount of the symmetrical

\[
\text{RSSR'} \xrightarrow{4\text{eq. KO}_2 / \text{eq. crown ether}} \text{RSO}_2^{\text{+}K} + \text{RSO}_3^{\text{+}K} + \text{R'SSR'} \quad (4)
\]
### Table III  
Reaction of Thiolsulfonate 3 with $O_2^-$

<table>
<thead>
<tr>
<th>Substrate, No., Temp., Time, $R(SO_2^-)(%)$, $R(SO_3^-)(%)$, $R(SSR')$ (R=) (R=)</th>
<th>$R=%$</th>
<th>$R'=%$</th>
<th>$R''=%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph Ph 3a 0° 58min 37%</td>
<td>28%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>p-Tol p-Tol 3b 0 30</td>
<td>14</td>
<td>79</td>
<td>17</td>
</tr>
<tr>
<td>Ph p-Tol 3c 0 35</td>
<td>28</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>p-Tol Ph 3d 25</td>
<td>9</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>p-CIC$_6$H$_4$ p-Tol 3e 0 35</td>
<td>26</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>p-Tol p-CIC$_6$H$_4$ 3f 0 35</td>
<td>14</td>
<td>34</td>
<td>23</td>
</tr>
</tbody>
</table>

a) Yields of $R(SO_2^-)$ and $R(SO_3^-)$ are in 1/2 mole %, while yield of $R(SSR')$ is in mole %.

b) Starting material (11%) was recovered.

c) The ratio of $RSO_3^-$ and $R'SO_3^-$ was determined from NMR spectrum of the mixture of 14 in CD$_3$OD.

disulfide derived from the sulfinyl group. The yields of two sulfinic acids from both sides were quantitatively determined by gas chromatography using calibration curve, after converting them to their sulfores. The ratio of the sulfonic acids was determined by comparing the integration ratio in NMR spectrum of the mixture of the S-benzylisothiuronium salts of two acids in methanol-d$_4$. Yields of both sulfinic and sulfonic acids from the sulfonyl side were generally larger than those from the sulfinyl side of the thiolsulfonate 3. Formations of these four acids are undoubtedly due to the concurrent
nucleophilic attack of $O_2^-$ at both sulfonyl and sulfenyl sulfur atoms. Further oxidation of the disulfide, $R'SR'$, formed during the reaction to the acids is also possible. However, this possibility is quite unlikely in view of our observation that the formation of the acids is much faster in the oxidation of thiolsulfonate 3 than in that of the disulfide 1 (see, Table I and III).

Thus, the oxidations of all these compounds bearing sulfur-sulfur linkage are considered to be initiated by the nucleophilic attack of $O_2^-$. The relative reactivities in these three substrates fall in the following order: $RS(O)SR' \geq RS(O)_2SR' \geq RSSR$, and this order seems to be in accordance with that of the nucleophilic reactions of these compounds with such a hard nucleophile as hydroxide anion as we reported previously. Like the alkaline hydrolysis, $O_2^-$ apparently attacks only sulfinyl sulfur of thiolsulfinate 2 in view of the predominant formations of the acids from sulfinyl side and the disulfide from the sulfenyl side. Meanwhile, $O_2^-$, being less basic but more nucleophilic than hydroxide anion, due to the α-effect, would attack competitively both sulfenyl and sulfonyl sulfur atoms of thiolsulfonate 3, unlike hydroxide anion, which is believed to attack exclusively the sulfenyl sulfur of thiolsulfonate in the alkaline hydrolysis, due mainly to the good leaving ability of the sulfonyl group. However, in view of the formation of the symmetrical disulfide from the sulfenyl side and the larger amount of the acids formed from the sulfonyl side than from the sulfenyl side, the
attack of $O_2^-$ seems to take place preferentially at the hard sulfonyl sulfur rather than at the soft sulfenyl sulfur, despite the stereo-electronic repulsion of two oxygen atoms of the sulfonyl group in the reaction of thiolsulfonate 3 with $O_2^-$. 

Reaction of Thiol 8, Sodium Thiolate 4 and Sodium Sulfinate 5 with $O_2^-$. 

Oxidation of benzenethiol with $O_2^-$ gave quantitatively diphenyl disulfide instead of the acids at room temperature, though both sulfinic and sulfonic acids were eventually obtained by heating with excess $O_2^-$ at 60° for 30 min (eq. 5).

$$\text{RSH} \xrightarrow{\text{3eq. KO}_2, 0.5\text{eq. crown ether}} \text{RSO}_2^{-+} \text{K} + \text{RSO}_3^{-+} \text{K} \quad (5)$$

Meanwhile, sodium salt of thiol which was prepared by treating the thiol with metal sodium in dry ether under argon was directly oxidized with $O_2^-$ to the corresponding sulfinic and sulfonic acids for 4h at room temperature (eq 6). In this reaction a trace amount of the disulfide was obtained along with two acids.
Filippo and his co-workers\textsuperscript{7} have also reported to have obtained the disulfide in the reaction of an alkanethiol with O\textsubscript{2}\textsuperscript{-}, though no experimental detail was given. Meanwhile, earlier, Wallace and Schriesheim\textsuperscript{21a} also reported that thiols were oxidized to the disulfides in the presence of a catalytic amount of alkali hydroxide under oxygen atmosphere, where superoxide anion is considered to be formed as an active oxidant by one electron transfer. Thus the initial reaction of the thiol with O\textsubscript{2}\textsuperscript{-} would be the base-catalyzed formation of the disulfide and further oxidation to the sulfinic and sulfonic acids upon heating would follow the same reaction path as the reaction of disulfide with O\textsubscript{2}. The reaction of sodium thiolate with O\textsubscript{2}\textsuperscript{-} would proceed by the initial one electron transfer from the thiolate anion to O\textsubscript{2}. A behavior of O\textsubscript{2} as an oxidizing agent to accept one electron has been known\textsuperscript{5b}. This appears to be supported by the formation of a small amount of the disulfide in the reaction of 4 with O\textsubscript{2}, where the disulfide is derived from the recombination of thiy1 radicals thus formed. On the other hand, the thiy1 radical would also react with O\textsubscript{2}. 

\[
\text{RS}^- + \text{Na} \quad \overset{3\text{eq. KO}_2}{\rightarrow} \quad 0.5\text{eq. crown ether} \quad \overset{25^\circ, 4h}{\rightarrow} \quad \text{RSO}_2^- + \text{RSO}_3^- \quad (+ \text{RSSR}) \quad (6)
\]

\[
\begin{array}{ccc}
\text{R} = \text{Ph} & 9\% & 86\% & \text{trace} \\
\text{p-Tol} & 10 & 66 & \text{trace}
\end{array}
\]
to afford the sulfinic and sulfonic acids.

When the reaction was carried out for somewhat a longer time, the amount of the sulfinic acid decreased while the amount of sulfonic acid increased; apparently the sulfinic acid was oxidized further with $O_2^-$ to the corresponding sulfonic acid at room temperature. This result is supported by the fact that anhydrous sodium sulfinic acid prepared independently, in fact, was oxidized to the corresponding sulfonate with $O_2^-$ at 25° for 2.5h in considerable yield (eq. 7). Since nucleophilic

\[
\begin{align*}
\text{RSO}_2^- + \text{Na} & \quad \text{eq. KO}_2 \\
& \quad \text{0.5eq. crown ether} \\
& \quad \text{pyridine} \\
\text{RSO}_3^- & \quad ( + \text{RSO}_2^- \text{ recovery} ) \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{Ph} & \quad 80\% \quad \text{trace} \\
\text{p-Tol} & \quad 74 \quad 17 \\
\end{align*}
\]

attack of $O_2^-$ is not conceivable in this reaction, only the one electron transfer process may explain the formation of the sulfonic acid. The sulfonyl radical thus resulted by one electron transfer from the sulfinic acid anion, has already been postulated as an intermediate in the photoreaction of hydrocarbon with sulfur dioxide$^{22}$ and in the autoxidation of sulfinic acid in the presence of molecular oxygen.$^{23}$
Solvent Effect

Although nearly a complete conversion of the substrate (disulfide 1) to the acids was achieved in such a solvent as pyridine or acetonitrile for ca 4h at ca 25°, the conversion was lower in such a solvent as chloroform or benzene even when the amount of the crown ether was 1.5 times while the reaction time was prolonged. In chloroform, the conversion of di-p-tolyl disulfide to the corresponding sulfinic and sulfonic acids with $O_2^-$ was 76% with a half amount excess of the crown ether for 4h at 25°, while the conversion in dry benzene was only 32% in the same reaction for 6h at 25°. This result indicates that the reaction in a more polar solvent is faster than that in a less polar solvent such as benzene. Therefore, these reactions with $O_2^-$ must involve the ionic processes at the rate determining step. The best solvent, among those we used, was pyridine, perhaps because it can dissolve not only disulfide 1, thiolsulfinate 2 and thiolsulfonate 3 but also sodium thiolate 4.

Meanwhile, the reaction of disulfide 1 with $O_2^-$ in acetonitrile, gave a considerable amount of a side product which seems to be derived from the radical reaction between the solvent and the disulfide (eq. 8). Bis(arylthio)acetonitrile 15, a side product, was isolated as a viscous oil by column chromatography of the residue of the organic extract (eluent; hexane : chloroform : ethyl acetate = 4 : 1 : 1, on silica gel). This product, however, could not be obtained in the oxidation
ArSSAr \[ \xrightarrow{\frac{O_2}{CH_3CN}} (ArS)_{2}CHCN \quad (+ \text{ArSO}_x^{-}K, \ x=2,3) \quad (8) \]

\[
\begin{array}{c|c|c}
1 & 25^\circ & 15 \\
\hline
\end{array}
\]

\( \text{Ar= Ph, p-Tol} \sim 40\% \)

of thiolssulfinate \( \text{2} \) with \( O_2^\cdot \) in acetonitrile, presumably due to the low temperature( -20° ) and a short reaction time( 15 - 30 min ). The structure of the product \( \text{15} \) was determined by various spectral data and the elemental analysis also supported its structure.

It is obvious that the products formed in the superoxide anion oxidation closely resemble to those of the alkaline autoxidation of thiol\(^{13,24}\) and disulfide,\(^{21,24}\) in which Berger\(^{13}\) indicated that the main product was sulfinic acid and sulfonic acid was minor in the alkaline autoxidation of thiol, although Wallace and his-coworkers reported that the only product formed was sulfonic acid in the alkaline autoxidation of thiol\(^{21}\) and disulfide.\(^{21b,25}\) Our recent detail investigation\(^{24}\) on the alkaline autoxidations of thiol and disulfide indicated that the main product was sulfinic acid while the amount of sulfonic acid was small, in accordance with the result of Berger.\(^{13}\) Now, if such a substrate as disulfide \( \text{1} \) would remain in the reaction with \( O_2^\cdot \), the alkaline autoxidation of the disulfide could also take place even after quenching the reaction mixture into cold water, because the quenched solution is alkaline while molecular oxygen also exists under the condition. However, the autoxidation of the
disulfide even in higher concentrations of the substrate, alkali and crown ether (more than 7 - 10 times) and even under pure atmosphere, was found to require more than 20h at room temperature till the starting material disappeared.

\[
\text{PhSSPh} \xrightarrow{\text{KOH / O}_2 \text{ crown ether}} \text{PhSO}_2^{+\text{K}} + \text{PhSO}_3^{+\text{K}} \quad (9)
\]

\[
\begin{array}{c|c|c}
1 & 9 & 10 \\
\text{pyridine-water} & 25^\circ, \sim 20h & 50\% \quad 41\%
\end{array}
\]

completely in pyridine-water (2 : 1) (eq. 9). Therefore, the alkaline autoxidation during the subsequent work-up of the reaction with \(O_2^\cdot\) should be negligible, since the autoxidation is considerably slower than the reaction with \(O_2^\cdot\).

Thus, in this study, organic sulfur compounds such as disulfide 1, thiosulfinate 2, thiosulfonate 3, sodium thiolate 4, and sodium sulfinate 5 were found to be oxidized easily with \(O_2^\cdot\) to afford the corresponding sulfinic and sulfonic acids, though \(O_2^\cdot\) is regarded to be a rather weak oxidizing agent.

When disulfide 1 is oxidized to the sulfonic acid with a common peracid a markedly long reaction time usually requires. Meanwhile, both sulfide 6 and sulfoxide 7 were inert to \(O_2^\cdot\).

Although thiol was easily oxidized to the corresponding disulfide with \(O_2^\cdot\) at room temperature, it was oxidized further with \(O_2^\cdot\) by heating at ca 60\(^\circ\) to the sulfinic and sulfonic acids. These reactions with \(O_2^\cdot\) resemble the alkaline autoxidation in
which thiol, sodium thiolate and disulfide are known to be similarly oxidized to afford both sulfinic and sulfonic acids. In the autoxidation, however, the main product was sulfinic acid but not sulfonic acid unlike the reaction with $O_2^-$ in which sulfinate is oxidized further to sulfonate with excess $O_2^-$ present in the reaction system. In the reaction of these organic sulfur compounds with $O_2^-$ the ionic process appears to be important than the radical process, since the reaction took place faster in a more polar solvent such as pyridine than in a less polar solvent such as benzene. Initial nucleophilic attack of $O_2^-$ on the sulfur atom of disulfide 1, thiosulfinate 2 or thiosulfonate 3 is undoubtedly involved in view of the product distributions in the reactions with unsymmetrical thiosulfinate 2 and thiosulfonate 3. Meanwhile, the reactions of sodium thiolate 4 and sulfinate 5 with $O_2^-$ are considered to proceed via one electron transfer process.
Experimental

General: Melting points were taken on a Yanako instrument and are uncorrected. NMR spectra were recorded on a Hitachi Perkin Elmer R-20 Spectrometer. Infrared spectra were obtained on a Hitachi 215 IR Spectrometer and were uncorrected. Mass spectra were recorded on a Hitachi RMU-6MG Mass Spectrometer. Gas and liquid chromatographs were obtained by Shimazu GC-6A and Yanako L-1030 instruments, respectively.

Chemicals except some solvents were of commercial degree. KO₂ was obtained from Ventron Alfa Products. 18-Crown-6-ether was a gift from Nippon Soda Co. and used after drying in vacuo by heating at 60 - 70°. Extra pure commercial grade pyridine (Wako Pure Chemical Ind.) was distilled on KOH and dried over KOH under Ar. Extra pure commercial grade CH₃CN was distilled on P₂O₅ and dried over molecular sieves under Ar. Dry CHCl₃ and CCl₄ were obtained by distillation of first grade commercial products and then dried with CaCl₂ before use. Benzene and ether were purified by distillation similarly and dried over metal Na wire under Ar.

Preparation of Disulfide: Disulfides which are not commercially available were synthesized by a known method.¹⁴) To a benzene soln (150 ml) of thiol (0.05 mole) and pyridine (0.055 mole) was added dropwise I₂ (0.025 mole) dissolved in
benzene (ca 50 ml). When the color of the solution changed to brown by excess I₂, the addition was stopped. The reaction mixture was washed with water, 5% HCl soln, Na₂S₂O₃ soln, and then water again, and the organic layer was dried over Na₂SO₄. After evaporation of benzene, the residual disulfide was purified by recrystallization usually from hexane. Yield was nearly quantitative. Meanwhile, 1,2-dithiane was prepared according to the method of Isenberg et al. 26

Di-p-tolyldisulfide 1f; mp 45-7°C (lit. 27) 46°C, MS; m/e 246 (M⁺, 100%).

Di-p-chlorophenyl disulfide 1g; mp 72°C (lit. 28) 73°C, MS; m/e 302 (M⁺+4, 15%), 300 (M⁺+2, 72%), 298 (M⁺, 100%).

Preparation of Thiolsulfinate 2: 15,16) A desired sulfinyl chloride was prepared by treating the corresponding thiol or disulfide with gaseous Cl₂ in the presence of an equal or two molar amounts of Ac₂O or AcOH at lower than ca. -10°C. 15) After removal of excess gaseous Cl₂ and AcCl by sucker, the pale yellow sulfinyl chloride was purified by distillation in vacuo. Sulfinyl chloride is highly water-sensitive.

To a CCl₄ soln (200 ml) of the distilled sulfinyl chloride (0.03 mole) in a two necked flask which was well dried and Ar substituted, dry pyridine (0.033 mole) was added with cooling at ca. -20°C. Soln of a thiol (0.03 mole) in CCl₄ (150 ml) was added dropwise at -20°C to -10°C to the resulting mixture containing pyridinium salt of sulfinyl chloride. White precipitate of pyridinium salt of HCl instead of the
sulfinyl chloride was gradually produced. After the addition of the thiol was completed the reaction mixture was stirred for a short time until the temperature reached to ca 0°. A heterogeneous reaction mixture containing the white precipitate was transferred to a separatory funnel and washed more than three times with cold water. The organic layer was dried with CaCl$_2$ and solvent was removed by evaporation carefully because the product thiol sulfinate is thermally quite unstable. The yield of the crystallized thiol sulfinate ranged from 80 to 95% and the slightly yellow crystals should be recrystallized quickly from a hexane-chloroform mixed solvent. Product must be stored in a refrigerator. Note that an excess thiol did not give any good result in yield since the side reaction of product with excess thiol takes place.$^{29}$

Phenyl benzenethiolsulfinate 2c; mp 69-70° (lit.$^{30}$) 69-70°),
IR( CHCl$_3$, cm$^{-1}$ ) 3055, 1577, 1475, 1093 & 1060(S=O).

p-Tolyl p-toluenethiolsulfinate 2d; mp 87° (lit.$^{31}$) 87.5° ),
IR( CHCl$_3$, cm$^{-1}$ ) 3050, 1590, 1490, 1090 & 1060(S=O).

Phenyl p-toluenethiolsulfinate 2a; 82° (lit.$^{30}$) 83-84°),
IR( CHCl$_3$, cm$^{-1}$ ) 3050, 1590, 1470, 1095 & 1065(S=O).

p-Tolyl benzenethiolsulfinate 2b; mp 70-71° (lit.$^{30}$) 68° ),
IR( CHCl$_3$, cm$^{-1}$ ) 3050, 1590, 1470, 1095 & 1065(S=O).

Preparation of Thiolsulfonate 3;$^{17,18}$ Sulfenyl chloride was prepared by treating thiol or disulfide with gaseous Cl$_2$ in CC$_1$$_4$ at ca 0°. Free sulfenic acids other than those which were obtained by acidification of commercial sodium sulfinate with
conc HCl, were synthesized by hydrolyses of the corresponding sulfinyl chlorides which were prepared by the method described in the preparation of thiolsulfinate.

To a dry CCl₄ soln (150 ml) of sulfinyl chloride (0.03 mole) which was freshly prepared and was free from Cl₂ under reduced pressure, was added dropwise dry pyridine (0.033 mole) at lower than 0° and then slightly white precipitate of pyridinium salt of sulfinyl chloride formed. A solution containing free sulfinic acid (0.03 mole) in dry CCl₄ or ether (ca 50 ml) was added to that solution at lower than 0°. Then new precipitate was formed gradually as the addition proceeded. After stirring the reaction mixture containing the white salt for ca 30 min and subsequent warming to room temperature, the reaction mixture was washed with 5% HCl soln and then water. The organic layer was dried over CaCl₂ and solvent was evaporated. From the residue the thiosulfonate was obtained in 80 to 95% yield and recrystallized from EtOH.

Phenyl benzenethiolsulfonate 3a; mp 44-45° (lit.¹⁹c) 44-45°,
IR( KBr, cm⁻¹ ) 3050, 1578, 1471, 1440, 1325 & 1310(SO₂), 1147 (S=O), MS( 70 eV ); m/e 250( M⁺, 39% ), 125( M⁺-PhSO, 100% ).

p-Tolyl p-toluene-thiolsulfonate 3b; mp 72-74° (lit.²²) 76°,
IR( KBr, cm⁻¹ ) 3050, 1590, 1490, 1380, 1325 & 1295(SO₂), 1138 (S=O), MS( 70eV ); m/e 278( M⁺, 63% ), 139( M⁺-p-tolSO, 100% ).

Phenyl p-toluene-thiolsulfonate 3d; mp 78-80° (lit.¹⁹c) 78°,
IR( CHCl₃, cm⁻¹ ) 3025, 1597, 1443, 1335(SO₂), 1145(S=O), MS ( 70 eV ); m/e 264( M⁺, 68% ), 155( M⁺-PhS, 100% ).
P-Tolyl benzenethiolsulfonate 3c; mp 52° (lit.¹⁹c) 54°,
IR
Preparation of Sodium Thiolate 4; A certain distilled thiol (11 mmole) in dry ether was added with syringe to metal sodium (11 mmole) suspended in dry ether (15 ml) in a well dried and Ar substituted two necked flask equipped with a reflux condenser and the whole mixture was stirred at room temperature until metal sodium disappeared, with heating to reflux if necessary. The residual white solid after removal of ether and any excess of thiol in vacuo was washed with dry hexane to remove the remaining thiol and disulfide, and dried again in vacuo. White powder sodium thiolate was obtained nearly quantitatively. This salt must be stored in a refrigerator in dark to avoid any decomposition. It must be
washed again with dry hexane just before use.

Preparation of Sodium Sulfinate 5; A dry ether solution (ca 5 ml) of free sulfinic acid (1.0 mmole) was added with syringe onto chipped metal sodium (1.0 mmole) under dry Ar at room temperature. The heterogeneous mixture was stirred to dissolve metal sodium. Sometimes it is necessary to reflux the mixture. Anhydrous sodium sulfinic, resulted by removal of ether under reduced pressure, was used directly for the reaction with $O_2^-$.  

Reaction with $O_2^-$. The reaction with $O_2^-$ was carried out in a well dried and Ar substituted two necked flask. A mixture containing substrate (1.0 mmole) and dry 18-crown-6-ether (0.5 mmole for 1 - 3, 1.0 mmole for 4, 5 & 8) in 7 ml of dry solvent was added slowly onto finely powdered potassium superoxide (1.0 - 6.0 mmole, see Tables) under Ar at a set temperature for each substrate (Equations). After the addition the heterogeneous reaction mixture was stirred for a certain prescribed period (see Tables) for each substrate to allow the reaction to complete, by monitoring the reaction by gas or liquid chromatography. When the starting material disappeared, the reaction mixture was poured into cold water containing crushed ice to quench the reaction and the mixture was extracted three times with CHCl$_3$. The combined organic layer was washed with water and dried over CaCl$_2$. After much of solvent was removed under reduced pressure, the CHCl$_3$
soluble organic mixture which contained mainly disulfide and
crown ether, was subjected to GC assay.

The aqueous layers were combined and then concentrated to
ca 10 ml by evaporation. Then excess MeI (ca 20 mmole) was
added to the aqueous solution, to which MeOH (5-10 ml) was
added to make the mixture homogeneous. After stirring the
mixture overnight at room temperature, it was extracted three
times with CHCl₃ after evaporation of much of MeOH and
subsequent addition of water (30 ml). The combined organic
layer was washed with water and dried over CaCl₂ and subjected
to quantitative GC analysis of the sulfone formed, using
calibration curve.

Meanwhile, the combined aqueous layer was concentrated to
ca 10 ml by evaporation. After acidification with excess
conc HCl (total volume of the solution: less than ca 20 ml)
S-benzylisothiuronium chloride (2.0 mmole), which was prepared
by benzyl chloride and thiourea in refluxing 95% EtOH for an
hour and was recrystallized from EtOH (mp 139°, lit.¹¹) 146-8°
was added to the aqueous solution and the mixture was heated to
dissolve the salt. After standing the mixture for a time,
colorless needles of S-benzylisothiuronium salt of sulfonic
acid appeared. This salt was purified by recrystallization
from water or CH₃CN.

Authentic samples of sulfones were obtained by the
oxidation of the corresponding sulfides with H₂O₂ in AcOH.
S-Benzylisothiuronium methanesulfonate 14a; colorless crystals
were recrystallized from water. mp 149° (lit.¹¹) 149°, IR
( KBr, cm\(^{-1}\) ) 3600-2800, 1640, 1240, 1225, 1210, 1190, 1055, 700, NMR( CD\(_3\)OD, \(\delta\), external TMS ); 2.28( s, 3H, CH\(_3\)SO\(_3\)^{-} ), 4.00( s, 2H, -CH\(_2\)Ph ), 4.34( s, 4H, -SC(NH)NH\(_3\)^{+} ), 6.95-7.07 ( m, 5H, arom. ).

S-Benzylisothiuronium benzenesulfonate 14b; colorless needles were recrystallized from CH\(_3\)CN. mp 152.5-153.5\(^{\circ}\) ( lit.\(^{11}\) 144\(^{\circ}\) ), IR( KBr, cm\(^{-1}\) ) 3500-2750, 1685, 1670, 1445, 1225, 1170, 1125, 1035, 1015, NMR( CD\(_3\)OD, \(\delta\), external TMS ); 3.92( s, 2H, -CH\(_2\)Ph ), 4.32( s, 4H, -SC(NH)NH\(_3\)^{+} ), 6.74-7.44( m, 10H, arom. ).

S-Benzylisothiuronium p-toluenesulfonate 14c; colorless needles were recrystallized from CH\(_3\)CN. mp 184-186\(^{\circ}\) ( lit.\(^{11}\) 178\(^{\circ}\) ).

IR( KBr, cm\(^{-1}\) ) 3400-2700, 1960, 1665, 1595, 1495, 1218, 1170, 1100, 1035, 810, 720, NMR( CD\(_3\)OD, \(\delta\), external TMS ); 1.89( s, 3H, Ar-CH\(_3\) ), 3.94( s, 2H, -CH\(_2\)Ph ), 4.31( s, 4H, -SC(NH)NH\(_3\)^{+} ), 6.72( d, 2H, arom., J= 8.1 Hz ), 6.88( s, 5H, Ph ), 7.22( d, 2H, arom., J= 8.1 Hz ).

S-Benzylisothiuronium p-chlorobenzenesulfonate 14d; colorless needles were recrystallized from CH\(_3\)CN. mp 176\(^{\circ}\), IR( KBr, cm\(^{-1}\) ) 3600-2800, 1680, 1660, 1470, 1220, 1170, 1030, 1002, 815, 755, 710, 690, NMR( CD\(_3\)OD, \(\delta\), external TMS ); 3.93( s, 2H, -CH\(_2\)Ph ), 4.32( s, 4H, -SC(NH)NH\(_3\)^{+} ), 6.80-7.13( m, 7H, Ph and p-ClC\(_5\)H\(_4\), J= 7.8 Hz ).

Anal. Calcd for C\(_{14}\)H\(_{15}\)N\(_2\)O\(_3\)S\(_2\)Cl; C, 46.85; H, 4.21; N, 7.80. Found: C, 47.05; H, 4.12; N, 7.81.
Isolation of Bis(arylthio)acetonitrile 15; A side product 15 from the reaction of disulfide with \( O_2^- \) in CH\(_3\)CN was isolated and purified by column chromatography (eluent: hexane : CHCl\(_3\) : EtOAc = 4 : 1 : 1, on silica gel, \( R_f \) = ca 0.7) of the residue of organic extract of the reaction mixture, and was obtained as pale yellow viscous oil.

Bis(phenylthio)acetonitrile 15a; IR (neat, cm\(^{-1}\)) 3060, 2920, 2230(C=\(\pi\)), 1580, 1475, 1439, 1022, 760, NMR (CDCl\(_3\), \( \delta \), TMS); 4.97 (s, 1H, \(-\text{CH}<-\)), 7.03-7.75 (m, 10H, arom.), MS (70 eV); m/e 257 (\( M^+ \), 18%), 148 (\( M^+\)-PhS, 100%).

Anal. Calcd for C\(_{14}\)H\(_{11}\)NS\(_2\): C, 65.33; H, 4.30; N, 5.44. Found: C, 65.46; H, 4.31; N, 5.44.

Bis(p-tolylthio)acetonitrile 15b; IR (neat, cm\(^{-1}\)) 3020, 2915, 2860, 2225(C=\(\pi\)), 1595, 1490, 1442, 1400, 808, NMR (CDCl\(_3\), \( \delta \), TMS); 2.31 (s, 6H, \(-\text{CH}<-\)), 4.61 (s, 1H, \(-\text{CH}<-\)), 7.03 (d, 4H, arom. \( J = 7.6 \) Hz), 7.37 (d, 4H, arom. \( J = 7.6 \) Hz), MS (70 eV); m/e 285 (\( M^+ \), 28%), 162 (\( M^+\)-p-tolS, 100%).


Alkaline Autoxidation of Diphenyl Disulfide; A mixture of diphenyl disulfide (2.4 mmole), 85% KOH (12 mmole) and 18-crown-6-ether (2.4 mmole) in pyridine-water (6 ml, 2 : 1) was stirred for 20h at room temperature under O\(_2\). Resulting reaction mixture was subjected to the same quantitative analysis as used in "Reaction with O\(_2^-\)". Yields of methyl phenyl sulfone and S-benzylisothiuronium benzenesulfonate were 50% and 41%, respectively.
References

4) T. Matsuura, "Oxygen Oxidation Reaction( Japanese)", Maruzene, Tokyo, 1977, Chapter 2 and 3.


29) For example,
Chapter 6

Reaction of Organic Sulfur Compounds with Superoxide Anion II.\textsuperscript{1)}

Evidence for Formation of Peroxysulfur Intermediates —

Oxidation of Sulfoxides, Phosphines and Olefins\textsuperscript{2)}

with Intermediary Peroxysulfur Species —

Abstract

Intermediary formations of peroxy-sulfenate (I), -sulfinate (II) and -sulfonate (III) have been confirmed by stripping the peroxy oxygen with three kinds of trapping agents such as sulfoxides, phosphines and olefins, added in the reaction systems of various organic compounds with superoxide anion (O$_2^-$). These sulfoxides, phosphines and olefins were inert in the treatment with O$_2^-$ alone while electrophilic olefins, such as $\alpha,\beta$-unsaturated ketones reacted readily with O$_2^-$ to afford the carboxylic acid. Sulfoxides, added into the reaction system of disulfide, thiolsulfinate, thiolsulfonate or sulfonyl chloride
with $O_2^-$ were found to be oxidized to the sulfones with peroxysulfur intermediates formed in situ in the system. Phosphines, added into the reaction system of disulfide or sodium thiolate with $O_2^-$, were also oxidized to the phosphine oxides. Not only stilbene and acenaphthylene but also chalcone and its derivatives, placed in the reactions of sulfonyl chloride, sulfinyl chloride and thiol sulfonate with $O_2^-$ were found to be oxidized to the corresponding epoxides. These observations suggest clearly that the intermediary peroxysulfur compounds can act as oxidizing agents which oxidize these trapping agents by the nucleophilic oxygenative oxidation. Similar intermediates were postulated and confirmed in the alkaline autoxidations of thiol and disulfide in which added phosphines and sulfoxides were also found to be oxidized to their oxides. The mechanisms of the reactions of these trapping agents with peroxysulfur intermediates are discussed.

Introduction

The discovery of superoxide dismutase by Fridovich and McCord in 1969\(^3\) has given the considerably vital energies on the investigation of superoxide anion radical($O_2^-$), not only
in biochemistry but also in organic chemistry.

Since the observation of Valentine and Curtis in which KO₂ can be appreciably dissolved in aprotic solvent, by complexation with crown ethers,⁴ has quickly promoted the use of this reagent in many reactions with simple organic substrates, numerous reports dealing with reactions of various organic substrates with " naked " superoxide anion have appeared within only five years. However, nobody has looked into the reaction of organic sulfur compounds with O₂⁻² till we initiated as a part of our works on the oxygenative oxidation of organic sulfur compounds,⁵ except some sporadic experiments.⁶)

The oxidation with O₂⁻² may be limited partly due to its relatively weak reactivity. In fact, O₂⁻² has been called as a moderate reducing agent but a pitifully weak oxidizing agent.⁷) However, its reactivity has been seen in oxidation, reduction, nucleophilic substitution, and also radical reaction.

We reported recently that several organic sulfur compounds are oxidized with O₂⁻² generated in situ from KO₂ and 18-crown-6-ether to the corresponding sulfinic and sulfonic acids under mild conditions.⁵a,b) These organic sulfur compounds are either those which have sulfur-sulfur linkage such as disulfide, thiol sulfinate and thiol sulfonate, or thiolate and sulfinate, all of which are expected to give peroxysulfur compounds such as peroxysulfenate( I ), -sulfinate( II ) and -sulfonate( III ) as initial intermediates in the reactions with O₂⁻². In fact, Berger already postulated the intermediary peroxysulfenate( I ) and -sulfinate( II ) in the autoxidation of thiol to the sulfinic
and sulfonic acids in strong alkaline media.\textsuperscript{8}) Since the two reactions give both sulfinic and sulfonic acids and are presumed to involve common intermediates of peroxysulfur species, we have carried out the experiments which would suggest the formation of these peroxysulfur intermediates in the reactions with $O_2^\top$, and obtained data to support the intermediary formations of these new peroxysulfury compounds (I – III) in the reactions of several sulfur compounds with $O_2^\top$. Namely, sulfoxides, phosphines and olefins (which are inert with $O_2$ without any one of sulfur substrates) were found to be oxidized to their oxides in the reaction systems of various sulfur compounds with $O_2^\top$. Similar results were obtained in the alkaline autoxidations of thiol and disulfide.

Results and Discussion

All of the sulfur compounds shown below, i.e. 1, 2, 3, 4, and 5 have been found in our earlier study to be oxidized with $O_2^\top$ to afford the corresponding sulfinic and sulfonic acids,\textsuperscript{5a,b}) while sulfenyl (6), sulfinyl (7) and sulfonyl (8) chlorides have also been found to be oxidized to the corresponding sulfinic and sulfonic acids. When unsymmetrical thiol sulfinitates and thiol sulfonates were treated with KO\textsubscript{2} and 18-crown-6-ether, formation of symmetrical disulfides from only the sulfenyl sulfur side was observed.
Since the peroxysulfur species, formed in situ during the reaction of these sulfur compounds with O$_2^-$, are believed to have fairly strong nucleophilic oxidizing abilities, sulfoxides, phosphines and olefins, which are relatively inert with O$_2^-$ alone but reactive with rather strong nucleophilic oxidizing agents, were added into the reaction system of one of these sulfur substrates with O$_2^-$, expecting that the added sulfoxides, phosphines and olefins would be oxidized to the corresponding oxides. Indeed, while the organic sulfur compounds were all oxidized to the sulfinic and sulfonic acids, added sulfoxides, phosphines or olefins were also found to be oxidized to the corresponding sulfones, phosphine oxides or epoxides. The added substrates, i.e. 9, 10 and 11, are thus believed to be oxidized by the intermediary peroxysulfur compounds (I – III) formed in situ.
Sulfur Compounds $\xrightarrow{O_2}$ \[ \text{peroxysulfur intermediates} \]
$I, II \text{ and/or } III \rightarrow RSO_2^- + RSO_3^-$

\[ \begin{array}{c}
R-S-R' \quad 9 \\
R''_3P \quad 10 \\
\hline \\
R-S-R' \quad 9' \\
R''_3P=O \quad 10'
\end{array} \]

Scheme I

during the reactions of these sulfur compounds with $O_2^\cdot$.

**Oxidation of Sulfoxide:** As a typical run, a solution of a selected sulfoxide ($9$, $0.5 - 6$ eq.) and an organic sulfur compound (one of $1 - 8$, leq.) in dry pyridine or acetonitrile was added into a heterogeneous solution of $KO_2$ ($1 - 6$ eq., finely powdered) and dry 18-crown-6-ether ($0.5 - 1.0$ eq.) in the same solvent at a set temperature and the resulting mixture was stirred under argon atmosphere. After extraction or filtration, the corresponding sulfone was obtained in the yield shown in Table I. In the aqueous layer both sulfinic and sulfonic acids were obtained as reported previously.$^{5a,b}$ Yield of the sulfone obtained thus was determined by isolation by means of column chromatography on silica gel, or from NMR spectrum of the
reaction mixture after evaporation of organic solvent in comparison with the integration ratio. The sulfones were produced in most cases, except methyl phenyl sulfoxide which was not oxidized in the reaction system of benzenesulfenyl chloride with $O_2^+$ but reduced exothermically to the corresponding sulfide by the sulfenyl chloride in a very short time ($\sim 5 \text{ min}$), like the reduction by sulfinyl chloride. However, the sulfenyl chloride itself was readily oxidized with $O_2^+$ to the corresponding sulfinic and sulfonic acids.

Sulfoxides were shown to be rather inert to $O_2^+$ by Valentine and Curtis who revealed that $KO_2$ is nicely soluble in DMSO by complexation with dicyclohexyl-18-crown-6-ether. Effects of solvent, temperature and added sulfoxide were then investigated. Meanwhile, the oxidation of sulfoxides during the oxygenative oxidation of organic sulfur compounds with $KO_2$ and the crown ether has been found to be affected by both solvent and temperature (entry 1-5, Table II). Sulfoxides were oxidized in better yields in acetonitrile than in pyridine. Decomposition of $RS(O)_xOO^-$ ($x=0-2$, I-III) presumably facilitated in pyridine, while acetonitrile may interact with the peroxy-sulfur species which might live longer in acetonitrile and hence would be a better nucleophilic oxidizing agent for sulfoxides. However, acetonitrile was found to react in the reaction with disulfide in the presence of $O_2^+$, forming bis(arylthio)acetonitrile in the yields of 25 - 50%. Apparently some radical processes, shown below, seem to be in operation.
<table>
<thead>
<tr>
<th>Entry, Substrate, Conversion, Temp, Time, KO₂, Crown, Sulfoxide,</th>
<th>Added</th>
<th>Solvent, Sulfone&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 p-TolSSTol-p 95% 22° 240min (6)&lt;sup&gt;d&lt;/sup&gt; (1)&lt;sup&gt;d&lt;/sup&gt; p-TolSMe (2)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CH₃CN</td>
<td>72%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 PhSSTol-p&lt;sup&gt;δ&lt;/sup&gt; 100 17 10 (5) (1) PhSPh (2)</td>
<td>pyridine</td>
<td>17&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3 PhSPh&lt;sup&gt;δ&lt;/sup&gt; 89 0 58 (4) (1) PhSPh (2)</td>
<td>pyridine</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4 p-TolSNa 100 25 120 (3) (0.5) MeSMe (5)</td>
<td>CH₃CN</td>
<td>93&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5 PhSO₂Na 80 25 150 (1) (0.5) PhSPh (1)</td>
<td>pyridine</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6 p-TolSCl&lt;sup&gt;δ&lt;/sup&gt; 100 22 25 (3) (1/3) MeSMe (3)</td>
<td>CH₃CN</td>
<td>57&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7 p-TolSCl&lt;sup&gt;δ&lt;/sup&gt; 95 25 480 (3) (1/10) p-ClC₆H₄SMe (1/2)</td>
<td>CH₃CN</td>
<td>46&lt;sup&gt;b&lt;/sup&gt;(23)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of sulfone based on the substrate.  
<sup>b</sup> Yield by NMR.  
<sup>c</sup> Isolated Yield.  
<sup>d</sup> Value in parenthesis is molar ratio.  
<sup>e</sup> Yield calculated on the basis of the sulfoxide added.
<table>
<thead>
<tr>
<th>Entry, Substrate</th>
<th>Conversion, Temp, Time, KO₂, Crown,</th>
<th>Added Sulfoxide, Solvent,</th>
<th>Yield of Sulfone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhSSPh</td>
<td>64% 25° 133min (6) d</td>
<td>PhSSPh (2) d</td>
</tr>
<tr>
<td>2</td>
<td>p-TolSSI-Stol-p</td>
<td>93 21 330 (6) (1)</td>
<td>PhSSPh (2)</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>91 21 300 (6) (1)</td>
<td>PhSSPh (2)</td>
</tr>
<tr>
<td>4</td>
<td>p-TolSNa</td>
<td>100 25 270 (3) (1)</td>
<td>PhSSPh (1)</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>25 120 (5) (1/2)</td>
<td>MeSMe (5)</td>
</tr>
<tr>
<td>6</td>
<td>PhSSI-Stol-p</td>
<td>100 25 35 (5) (1)</td>
<td>PhSSPh (2)</td>
</tr>
<tr>
<td>7</td>
<td>p-TolSSI-Stol-p</td>
<td>100 17 10 (5) (1)</td>
<td>PhSSPh (3)</td>
</tr>
<tr>
<td>8</td>
<td>PhSSI-Stol-p</td>
<td>100 -25 60 (5) (1)</td>
<td>PhSSPh (2)</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>100 -40 90 (5) (1)</td>
<td>PhSSPh (2)</td>
</tr>
<tr>
<td>10</td>
<td>p-TolSSI-Stol-p</td>
<td>91 21 300 (6) (1)</td>
<td>PhSSPh (2)</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>100 20 240 (6) (1)</td>
<td>p-TolSSI-Stol-p (2.3)</td>
</tr>
<tr>
<td>12</td>
<td>&quot;</td>
<td>95 22 240 (6) (1)</td>
<td>p-TolSSI-Stol-p (2)</td>
</tr>
<tr>
<td>13</td>
<td>&quot;</td>
<td>95 22 264 (6) (1)</td>
<td>p-ClC₆H₄SMe (2)</td>
</tr>
<tr>
<td>14</td>
<td>&quot;</td>
<td>95 25 240 (6) (1)</td>
<td>p-ClC₆H₄SMe (2)</td>
</tr>
<tr>
<td>15</td>
<td>p-TolSCI</td>
<td>100 20 90 (3) (1/3)</td>
<td>p-ClC₆H₄SMe (2)</td>
</tr>
<tr>
<td>16</td>
<td>p-TolSCI</td>
<td>100 22 25 (3) (1/3)</td>
<td>MeSMe (3)</td>
</tr>
<tr>
<td>17</td>
<td>p-TolSSI-Stol-p</td>
<td>97 25 300 (6) (1)</td>
<td>p-TolSSI-Stol-p (6)</td>
</tr>
</tbody>
</table>

Table notes are same as those in Table I.
The yield of diphenyl sulfone from the added sulfoxide into the reaction system of thiosulfinate with $O_2^-$ increased with elevating temperatures of the reaction (entry 6 - 9). Change of sulfoxide did not change much the yield of the sulfone in the reaction of di-p-tolyl disulfide with $O_2^-$ (entry 10 - 14). However, in the reaction of p-toluenesulfinyl chloride with $O_2^-$, dimethyl sulfone was obtained in a much better yield than methyl p-chlorophenyl sulfone (entry 15 & 16). An analogous result was observed in the oxidation of sodium p-toluenethiolate, though the conditions of the above two reactions are somewhat different.

Meanwhile, since the yield of the sulfone was calculated based on the amount of the starting organic sulfur compound used, the yield of sulfone more than 100 % (111 %, entry 17) is not surprising since the amount of the added sulfoxide was six equivalent to the organic sulfur compound used. This may mean that more than an equimolar amount of peroxysulfur intermediate(s) are produced from the organic sulfur compound during the reaction. Thus, the yield of the sulfone clearly increased as the amount of the added sulfoxide to the reaction system increased, while the yield of the sulfone also dramatically
would increase with the decrease of the amount of the sulfoxide added, if the yield of the sulfone is calculated on the basis of the sulfoxide.

Sulfoxides, having nitro group, such as p-nitrophenyl phenyl and methyl p-nitrophenyl sulfoxides, were not oxidized to the sulfones but presumably reacted with \( \text{O}_2 \). The reaction mixture turned to reddish brown and no isolable product was obtained including the starting material from the organic layer.

Common sulfides such as diethyl, methyl phenyl and diphenyl sulfides were found not to be oxidized at all under the conditions, as in the reaction with \( \text{O}_2 \) which was reported to be unreactive toward sulfides.\(^{10}\)

In order to reconfirm the facile reaction of sulfoxides and no reactivity of sulfides in these oxidation systems, thianthrene-9-oxide\(^ {12}\) was used as the trapping agent, and found to be oxidized to thianthrene-9,9-dioxide\(^ {13}\), but not to the 9,10-dioxide\(^ {14}\) in the reaction of di-p-tolyl disulfide with \( \text{O}_2 \) in \( \text{CH}_3\text{CN} \) at 25° for 4h, along with the usual oxidation products (two acids) from aqueous layer (eq. 5), clearly revealing that the peroxysulfur intermediates formed during the

\[
(\text{p-TolS})_2 + 6\text{eq. KO}_2 \xrightarrow{18\text{-crown-6}} \xrightarrow{12} \xrightarrow{x=2,3} (\text{p-TolSO}_x^-) \text{ (5)}
\]
reaction oxidize trivalent sulfinyl function but not divalent sulfenyl function.

Although oxygenation of the sulfide is well-known to be initiated by the electrophilic attack of oxidant on the sulfide, oxygenation of the sulfoxide involves either the initial electrophilic attack of the electrophilic oxidant,\textsuperscript{11a)} or nucleophilic attack of nucleophilic oxidant.\textsuperscript{11b,c)} In general, organic peracid or hydroperoxide oxidizes sulfide\textsuperscript{11a)} or sulfoxide\textsuperscript{11a)} via an initial electrophilic attack of peracid oxygen at sulfur atom, whereas the anions of peracid and hydroperoxide which are well-known to be powerful α-nucleophiles,\textsuperscript{12)} are known to oxidize sulfoxide via nucleophilic attack on the trivalent sulfur. Peroxysulfur intermediates, being α-nucleophiles, would oxidize similarly sulfoxide by nucleophilic oxidation.

The following scheme of the reaction was suggested for the nucleophilic oxidation of sulfoxide with alkali metal hydroperoxide by both Ogata et al.\textsuperscript{13)} and Modena et al.\textsuperscript{11b)} though there is a small difference as to the rate-determining step between the two.

\[
\begin{align*}
\text{ROO}^- + \text{S} \rightarrow \text{O} & \quad \xrightarrow{\text{step 1}} \quad \left[ \text{O} \bigg[ \begin{array}{c} \text{R}^+ \\ \text{R}^{-} \\ \text{R}^{-} \end{array} \bigg] \right] \xrightarrow{\text{step 2}} \text{O} \leftrightarrow \text{S} \rightarrow \text{O} + \text{RO}^- 
\end{align*}
\]
The yield of the sulfone alone cannot give definite information on substituent effect in these oxidations of various sulfoxides with the peroxy sulfur intermediates (Table II). Although Modena et al showed that the electron withdrawing substituent on sulfoxide accelerates the rate of the oxidation of sulfoxide, both steps, i.e. 1 and 2, may be involved in the rate-determining step of the oxidation of sulfoxide with anion of hydroperoxide. The oxidation of the sulfoxide with the peroxy sulfur intermediates is considered to be same as it. As shown in eq. 7, sulfoxide added in the reaction system would be attacked by one of the peroxy sulfur intermediates formed in situ, forming incipiently the sulfurane intermediate which collapses to sulfone and RS(O)xO- in the subsequent step.

An alternative mechanism which involves radical species of peroxy sulfur intermediates in the oxidation of sulfoxide to the sulfone may be postulated. However, this seems to be quite unlikely because of the lack of nucleophilicity of the radical species, as was suggested earlier in the oxidation of dimethyl sulfoxide with tert-butyl hydroperoxide. fanc}
Oxidation of Phosphines: Both triphenyl- and tributyl-phosphines were also selected as trapping agents. Although these phosphines are known to be oxidized readily to the phosphine oxides with molecular oxygen,¹⁵) both phosphines were quite inert under the oxidation conditions in pyridine in dry argon atmosphere. The reaction procedure is identical to that in "Oxidation of Sulfoxide". However, when the phosphines are used as trapping agents no oxygenated sulfur compounds could be used as the substrate for the oxidation with $O_2^-$, since the oxygenated sulfur compounds (2, 3 etc.) are known to be reduced readily with phosphines.¹⁶) In fact, the thiosulfinate was very readily reduced to the disulfide with triphenylphosphine in pyridine even at $-25^\circ$. This reduction of thiosulfinate with triphenylphosphine is considered to compete with the reaction of thiosulfinate with $O_2^-$. Therefore, the disulfide and sodium thiolate were chosen as the substrates in the reaction with $O_2^-$ in the presence of the phosphine to afford the phosphine oxide (Table III). Yields were determined by GC in order to avoid the autoxidation of phosphines. When tributylphosphine was added as a trapping agent of the peroxysulfur intermediate in the oxygenation of disulfide with $O_2^-$, a vigorous exothermic reaction took place and the phosphine oxide was formed quantitatively within an hour, during which the conversion of the disulfide to the acids was still incomplete as shown in Table III. In the oxygenation of alkyl disulfide such as dibenzyl disulfide, triphenylphosphine was not only oxidized to the phosphine oxide but also converted to the phosphine sulfide.

- 209 -
<table>
<thead>
<tr>
<th>Entry, Substrate</th>
<th>Conversion</th>
<th>Temp, Time</th>
<th>KO₂, Crown,</th>
<th>Added Phosphines,</th>
<th>Solvent,</th>
<th>Yield of ( \text{Ph}_3\text{P}=\text{O} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PhSSPh</td>
<td>60</td>
<td>25°</td>
<td>66min (6) (1)</td>
<td>Ph₃P (1)</td>
<td>pyridine</td>
<td>17%</td>
</tr>
<tr>
<td>2 &quot;</td>
<td>81</td>
<td>23</td>
<td>300 &quot;</td>
<td>Ph₃P (2)</td>
<td>&quot;</td>
<td>21</td>
</tr>
<tr>
<td>3 &quot;</td>
<td>49</td>
<td>21</td>
<td>60 &quot;</td>
<td>Bu₃P (2)</td>
<td>&quot;</td>
<td>Bu₃P=O quinat.</td>
</tr>
<tr>
<td>4 &quot;</td>
<td>95</td>
<td>25</td>
<td>240 &quot;</td>
<td>Ph₃P=S (1)</td>
<td>&quot;</td>
<td>Ph₃P=O 0</td>
</tr>
<tr>
<td>5 MeSSMe</td>
<td>-</td>
<td>25</td>
<td>90 &quot;</td>
<td>Ph₃P (1)</td>
<td>&quot;</td>
<td>Ph₃P=O 6</td>
</tr>
<tr>
<td>6 BuSSBu</td>
<td>31</td>
<td>25</td>
<td>56 &quot;</td>
<td>Ph₃P (1)</td>
<td>&quot;</td>
<td>Ph₃P=O 30</td>
</tr>
<tr>
<td>7 PhCH₂SSCH₂Ph</td>
<td>95</td>
<td>25</td>
<td>30 &quot;</td>
<td>Ph₃P (1)</td>
<td>&quot;</td>
<td>Ph₃P=S trace</td>
</tr>
<tr>
<td>8 p-TolSNa</td>
<td>100</td>
<td>20</td>
<td>300 (3) (1/2)</td>
<td>Bu₃P (1)</td>
<td>&quot;</td>
<td>Bu₃P=O 5</td>
</tr>
<tr>
<td>9 p-TolSNa</td>
<td>100</td>
<td>25</td>
<td>23h (5) (1/2)</td>
<td>Ph₃P (2)</td>
<td>CH₃CN</td>
<td>Ph₃P=O 37</td>
</tr>
</tbody>
</table>

* Yields were determined by GC.
The phosphine sulfide thus formed along with the phosphine oxide was found to be quite inert to \( \text{O}_2^- \) and did not react, recovering completely when it was added in the reaction system of disulfide with \( \text{O}_2^- \) (entry 4, Table III). Therefore, formation of the phosphine oxide is not derived from the phosphine sulfide which is a simple by-product formed by the nucleophilic attack of the phosphine to disulfide. Here again, triphenylphosphine was oxidized in a better yield in acetonitrile than in pyridine (entry 8 & 9), suggesting the reaction to proceed via an ionic pathway.

Generally phosphines are oxidized to the oxides with electrophilic oxidants, through nucleophilic attack of phosphines on the oxidant oxygen. The oxidation of phosphines to the oxides with anionic oxidizing species must be somewhat difficult. Phosphines are known to react with alkyl disulfide in an equilibrium reaction and generally yield the phosphine sulfide and monosulfide.\(^{17}\) In the reaction of alkyl disulfide with \( \text{O}_2^- \) in the presence of the phosphine the initial step is considered to be the formation of alkylthiophosphonium ion which undergoes the Albusov type reaction to yield the phosphine sulfide, by the nucleophilic attack of thiolate anion (counter anion of the phosphonium salt) on the carbon atom attached to the sulfur atom. Due to the lack of nucleophilic attack of arenethiolate anion on aromatic carbon, diaryl disulfide did not give any phosphine sulfide (Table III). Thus, the formation of the phosphine oxide would be rationalized by the Scheme II. While \( \text{O}_2^- \) can attack directly the disulfide as shown by Scheme V.
$O_2^ -$ can also attack competitively both sulfur and phosphorus atoms of the phosphonium ion. Although direct attack of $O_2^ -$ on phosphorus atom may give rise to the final phosphine oxide, peroxysulfur species, being good nucleophiles, may also attack the phosphorus atom of the thiophosphonium ion to afford an incipient phosphorane intermediate which upon nucleophilic attack of thiolate anion on the sulfur atom can give phosphine oxide, as shown in Scheme II. The rapid oxidation of tributylphosphine, may be due to the shift of equilibrium between disulfide and the phosphine to right side to form the thio-phosphonium ion which then would preferentially be attacked by $O_2^ -$ on the phosphorus atom, to afford tributylphosphine oxide quantitatively before all the disulfide was oxidized to the acids.

Triphenylphosphine was not oxidized quantitatively in the
reaction of sodium thiolate with \( O_2^- \). The oxidation of triphenylphosphine in the reaction of sodium thiolate with \( O_2^- \) seems to be different from that in the reaction of disulfide with \( O_2^- \). The initial step is very likely the one electron transfer from thiolate anion to \( O_2^- \) in view of the reducing nature of \( O_2^- \). Then, the peroxysulfur free radical formed in situ may oxidize directly the phosphine as reported in the autoxidation of trialkylphosphines. Another possibility for the oxidation of the phosphine involves the initial reaction of thiyl radical with the phosphine to form arylthiophosphonium radical, which can react with either \( O_2^- \) or \( RS(O)_xO^- \) to give a

\[
\text{RS}^- \quad \overset{-e}{\rightarrow} \quad \text{RS}^- \quad \rightarrow \quad \overset{O_2^-}{\text{RS(O)}_xO^- \text{ and/or } RS(O)_xO^-} \\
\text{PR'}_3 \quad \text{Scheme III, } x = 0 - 2
\]

\[
[\text{RS-PR'}_3] \quad \overset{\text{RS(O)}_xO^-}{\rightarrow} \quad [\text{RS-PR'}_3] \quad \overset{\text{RS}^-}{\rightarrow} \quad \text{Scheme II} \\
\text{PR'}_3 \quad \overset{O_2^-}{\rightarrow} \quad [\text{RS-PR'}_3] \quad \rightarrow \quad \text{R'}_3P=O + RSSR + O_2^-
\]

\[
\text{PR'}_3 \quad + \quad \text{RS(O)}_xO^- \quad \rightarrow \quad \text{R'}_3P=O + \text{RS(O)}_xO^- \\
\text{Scheme II'}
\]
phosphorane intermediate which then reacts according to Scheme II (Scheme II'). In this case, the nucleophilic attack of $O_2^-$ on the phosphorus atom of the phosphonium radical may become important.

**Oxidation of Olefin:** Several olefins were found to be readily oxidized to the corresponding epoxides in appreciable yields when these olefins were added into the reaction system of any one of the organic sulfur compounds (3, 7 and 8) with $O_2^-$. Since the epoxide formed was sensitive to alkaline media, the reaction mixture was immediately filtered to remove alkali and the yields of the epoxides were obtained by measuring the NMR spectra of the mixtures which were isolated through column chromatography on silica gel using benzene-hexane mixture as an eluent. In NMR spectra of the epoxides signals of methine protons of the usual three membered oxyrane ring appear at high fields (Table IV). Olefins used are the following three compounds, i.e. chalcone derivatives (15), stilbene (16) and acenaphthylene (17). Stilbene (16) and acenaphthylene (17) were quite inert to $O_2^-$ under the condition, while chalcone was found to react with $O_2^-$ as described later. Most epoxides obtained in the reactions were trans since the olefins used were also trans. However, the epoxide obtained from acenaphthylene was apparently cis but not trans, indicating that all the epoxidations in these systems were found to take place in cis fashion. Results obtained are listed in Table V and VI, though the yields are not optimized.
In the reactions of sulfonyl chloride(8), sulfinyl chloride(7) and thiosulfonate(18) with $O_2^-$, not only chalcone (15) and its derivatives but also stilbene (16) and acenaphthylene(17) were oxidized to the epoxides in relatively high yields. However, the epoxidation proceeded very little when disulfide(1) and thiosulfinate (2) were used. Sodium thiolate(4) and sulfenyl chloride(5), both of which can be oxidized with $O_2^-$, were effective for the epoxidation of none of these olefins, giving complicated reaction mixtures with no epoxide.

Other olefins such as cyclohexene and cinnamonic triile were not oxidized and recovered nearly quantitatively under the
Table V  Epoxidation of Olefin at 20°a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Olefin</th>
<th>Time, solvent</th>
<th>Epoxideb</th>
<th>Recoveryb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsCl</td>
<td>15, X=Br</td>
<td>15.5h CH₃CN</td>
<td>85(66)c</td>
<td>trace(5)c</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>15, X=H</td>
<td>15 CH₃CN</td>
<td>85</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>15, X=OMe</td>
<td>3 CH₃CN</td>
<td>60(45)d</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>p-TolSOCl</td>
<td>15, X=H</td>
<td>22.5 benzene</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>18f</td>
<td>15, X=H</td>
<td>20.5 CH₃CN</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>PhCOCl</td>
<td>15, X=H</td>
<td>9 CH₃CN</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>TsCl</td>
<td>16,</td>
<td>24 benzene</td>
<td>40(39)c</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>PhCOCl</td>
<td>16e</td>
<td>10 benzene</td>
<td>30(20)c</td>
<td>20(15)c</td>
</tr>
<tr>
<td>9</td>
<td>TsCl</td>
<td>17</td>
<td>10 CH₃CN</td>
<td>-30(d)</td>
<td>-70(d)</td>
</tr>
</tbody>
</table>

b) Yield by HPLC.  c) Isolated yield.  d) Yield by NMR.  
e) Amount of olefin = 2/5.  f) p-ClC₆H₄S(O)₂SC₆H₄CH₃-p( 18 ).

conditions, while dibenzoylethylene was very readily oxidized ( ~1h ) by O₂ with and without the sulfur compounds to give benzoylformic acid in a good yield as reported previously.¹⁹)

Recently the epoxidation of stilbene, in the reaction system of benzoyl chloride with O₂, was observed by Hirobe et al.²⁴) We also confirmed the epoxidation of stilbene in the same system. However, both chalcone and stilbene were oxidized to the corresponding epoxides with a mixture of benzoyl chloride and O₂ in lower yields than those observed in the epoxidation of chalcone and stilbene with tosyl chloride and O₂. By-products
Table VI  Effects of Solvent, Crown Ether and Substrate

at 20°

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Olefin</th>
<th>Crown</th>
<th>Time</th>
<th>Solvent</th>
<th>Epoxide</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsCl</td>
<td>15, X=H (1)</td>
<td>15h</td>
<td>CH₃CN</td>
<td>85%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>15, X=H (1)</td>
<td>20°</td>
<td>CH₂Cl₂</td>
<td>65</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>15, X=H (1)</td>
<td>17</td>
<td>benzene</td>
<td>39</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>15, X=Br (1)</td>
<td>15.5</td>
<td>CH₃CN</td>
<td>35(66)°</td>
<td>trace(5)°</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>15, X=Br (1)</td>
<td>21</td>
<td>benzene</td>
<td>35(25)°</td>
<td>50(48)°</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>16</td>
<td>(1)</td>
<td>24</td>
<td>benzenen</td>
<td>40(39)°</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>16</td>
<td>(1)</td>
<td>3</td>
<td>CH₃CN complex mixture</td>
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<td></td>
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<tr>
<td>8</td>
<td>PhCOCl</td>
<td>16</td>
<td>(1)</td>
<td>10</td>
<td>benzene</td>
<td>30(20)°</td>
<td>20(15)°</td>
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<tr>
<td>9</td>
<td>&quot;</td>
<td>16</td>
<td>(1)</td>
<td>1</td>
<td>CH₃CN</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>TsCl</td>
<td>15, X=H (0)</td>
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<td>75</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>15, X=OMe (0)</td>
<td>13</td>
<td>benzene</td>
<td>trace</td>
<td>95</td>
<td></td>
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<tr>
<td>12</td>
<td>-SO₂Cl</td>
<td>15, X=OMe (1)</td>
<td>11°</td>
<td>CH₃CN</td>
<td>-(75)°</td>
<td>-(25)°</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Cl₃CSO₂Cl</td>
<td>15, X=H (1)</td>
<td>15.5°</td>
<td>CH₃CN</td>
<td>40</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>-SO₂Cl</td>
<td>15, X=H (1)</td>
<td>104</td>
<td>CH₃CN</td>
<td>50(41)°</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

in these reactions are carboxylic acids by direct oxidation of olefin and the epoxide with $O_2^\cdot$.

Solvent, crown ether and organic sulfur compound also affected the epoxidation (Table VI). Inspection of the data in Table VI reveals that such a polar solvent as acetonitrile is better than methylene dichloride or benzene in the epoxidation of chalcones, and the yield of the epoxide increased as the polarity of the solvent increased. However, acetonitrile was not a good solvent in the epoxidation of stilbene since other polar products including benzaldehyde were formed by the cleavage of the C-C bond. This was confirmed in both cases using tosyl chloride and benzoyl chloride. Without crown ether, the yield of the epoxide was rather little in benzene but remained nearly the same in acetonitrile as shown in Table VI (entry 10 & 11).

Even the sterically hindered mesitylene- and (+)-d-camphor-10-sulfonyl chlorides were also found to be effective in the epoxidation of olefins, however, the yields of the epoxides were relatively low and the rate of the reaction seemed to be slower than that with tosyl chloride. Chalcone epoxide, obtained by the oxidation of chalcone added in the reaction system of (+)-d-camphor-10-sulfonyl chloride ([$\alpha$]$_D^{25}$ +20.9°) with $O_2^\cdot$, did not show any optical activity, presumably because the optically active center is so far away from the reaction center.

The yield of stilbene oxide was lower than that of the epoxide from chalcone or its derivatives. Epoxidation of chalcone is known to be initiated by nucleophilic attack of an
oxidant such as hydrogen peroxide anion as shown above.\(^{25}\)

Even stilbene is known to undergo the Michael type addition by the attack of a strong nucleophile in some cases.\(^{26}\)

Chalcone, added in the reaction system of disulfide( I ) with \(O^2\) in acetonitrile, was not oxidized much, however, upon heating the reaction mixture with excluding air at \(50^\circ\) chalcone decomposed to the corresponding carboxylic acids by the cleavage of C-C bond, as was reported by Rosenthal and Frimer.\(^{27}\)

Chalcone was oxidized in argon atmosphere much more readily without organosulfur compounds than in the presence, revealing that the rate of the reaction of chalcone with \(O^2\) is appreciably slower than that of the reaction of organic sulfur compound with \(O^2\). Since the reactions of both sulfinyl and sulfonyl chlorides with \(O^2\) are considerably faster than that of chalcone with \(O^2\), the epoxidation is considered to proceed via the initial nucleophilic substitution of the chlorides with \(O^2\) and subsequent
one electron transfer to afford the peroxysulfinate (II) or peroxysulfonate (III) which then oxidize olefin to the epoxide, as shown in the above equation 8.

Nucleophilicity of $O_2^-$ has been nicely demonstrated in the reactions of various organic compounds with $O_2^-$, and also in the complete inversion of configuration in the $S_N2$ reaction of an optically active aliphatic halide with $O_2^-$. However, none of the olefins used was epoxidized with $O_2^-$ alone in our experiment. However, some cyclic $\alpha,\beta$-unsaturated ketones were shown to be epoxidized with $O_2^-$ though in considerably low yield.

Meanwhile, Grieco and his co-workers found recently that common olefins are nicely oxidized to the epoxides with benzeneperoxselenenic acid which is generated in situ from benzeneselenenic acid and hydrogen peroxide, apparently revealing the possible formation of analogous intermediary peroxyselenium compounds (eq. 9).

\[
\begin{align*}
\text{PhSeOH} & \quad \xrightarrow{H_2O_2} \quad \text{Ph-Se-OH} \\
\text{PhSeOH} & \quad \xrightarrow{-H_2O} \quad \text{PhSeO}_2\text{H}
\end{align*}
\]  

Oxidation Mechanisms of Several Sulfur Compounds

We have shown previously that several sulfur compounds (1–8) are oxidized to the corresponding sulfinic and sulfonic acids, and suggested that the oxidation proceeds via formation of peroxysulfur intermediates (I, II and III).

- 220 -
Now let us consider the mechanisms of oxidations of several these sulfur compounds with $O_2^\cdot$ to the sulfinic and sulfonic acids in detail.

**Oxidation of Sodium Sulfinate with $O_2^\cdot$:** Anhydrous sodium arenensulfinate can be oxidized with an equimolar amount of $O_2^\cdot$ to afford mainly the sulfonic acid in pyridine at $25^\circ$ for 2.5h.\(^{5b)}\)

\[
\text{RSO}_2\text{Na} + \text{eq. KO}_2 \underset{18\text{-crown-6}}{\xrightarrow{\text{pyridine}}} \text{RSO}_3^- ( + \text{RSO}_2^- : \text{recovery})
\]

\(R = \text{Ph} \quad 25^\circ, 2.5h \quad \sim 80\% \quad \sim 17\%
\(p\)-Tol

The initial step of the reaction would be the electron transfer. The resulting sulfonyl radical is known to be an excellent initiator in the polymerization of vinyl monomers or in the autooxidation of sulfinic acid.\(^{32)}\) Peroxysulfonyl radical, $\text{RS(O)}_2\text{OO'}$, was also postulated in the photolysis of sulfur dioxide\(^{33)}\) in air and also in the autooxidation of sulfinic acid.\(^{32, 34)}\) Thus, the oxidation of arenensulfinate with $O_2^\cdot$ is considered to be initiated by one electron transfer and proceed via subsequent coupling of the resulted arenensulfonyl radical with $O_2^\cdot$. The per oxyarenesulfonate( III ) formed thus would slowly decompose to the sulfonic acid and molecular oxygen, or oxidize the sulinate or added sulfoxide to the sulfonate or the sulfone.

The one electron transfer process from $O_2^\cdot$ or to $O_2^\cdot$ has been
shown to be in operation in several reactions of $\text{O}_2^\cdot\text{.}^{18}$ In view of the redox potentials of $\text{O}_2 - \text{O}_2^\cdot$ and $\text{O}_2^\cdot - \text{H}_2\text{O}_2$ at neutral pH being -0.33 and +0.94 V respectively, this radical anion is considered to act as a reductant in the presence of an electron acceptor and as an oxidant in the presence of an electron donor.\textsuperscript{19} In fact, during a series of these experiments, evolution of molecular oxygen was observed by gas-mass spectrometry at the peak hight of oxygen ($m/e$ 32) along with that of argon ($m/e$ 40) used, when the reaction was carried out in argon gas. This observation also seems to support the one electron transfer from $\text{O}_2^\cdot$.

**Oxidation of Sodium Thiolate with $\text{O}_2^\cdot$** Sodium arenethiolate was also found to be oxidized to afford the corresponding sulfinic and sulfonic acids along with a small amount of the disulfide.\textsuperscript{5b} A similar one electron transfer process is
important in this oxidation. Recently, Degrand and Lund suggested that radical recombination of thyl radical and $O_2^-$ gives sulfinate via the rearrangement of the peroxysulfenate( I ) in the electrochemical synthesis of sulfinic acid from alkyl disulfide and molecular oxygen. As shown in Scheme IV, the thyl radical thus formed would either dimerize to the disulfide or react with $O_2^-$ to form the incipient peroxysulfenate( I ).
Recombination of two thiyl radicals has been reported to be very fast ($k = 10^9 - 10^{10} \text{ M}^{-1} \text{sec}^{-1}$). In the reaction of arene-thiolate with $O_2^-$ all the intermediates (I - III) can thus be produced and would oxidize the added sulfoxide or phosphines to the sulfone or the phosphine oxides. Rearrangement of the intermediates (I and II) to the sulfinate and the sulfonate are also conceivable while the degradation of all the intermediates may give both molecular oxygen and the acids. This oxidation

\[
RS(O)_{x+1}O^- \quad (x = 0, 1)
\]

\[
RS(O)_xOO^- \rightarrow RS(O)_xO^- + 1/2 O_2 \quad (x = 0 - 2)
\]

requires a little longer time than that of sulfinate, in keeping with the suggested mechanism. Peroxysulfur intermediates may also oxidize arenesulfinate directly to the sulfonate since the added trivalent sulfoxide is readily oxidize and the sulfinate is also another trivalent sulfur compound. Formation of a small amount of the disulfide should be due to the recombination of the thiyl radicals. A small amount (ca 5%) of diaryl disulfide was also obtained in the alkaline autoxidation of arenethiol which is considered to be analogous to the thiolate with $O_2^-$.5b,8)

**Oxidation of Sulfenyl, Sulfinyl and Sulfonyl Chlorides with $O_2^-$:**

The reactions of arene-sulfenyl, -sulfinyl and -sulfonyl chlorides with $O_2^-$ are considered to be initiated by nucleophilic
substitution of the chlorides with $O_2^-$. Therefore, these three systems should be the best systems to give three these peroxysulfur intermediates cleanly (eq. 12). Three these radicals, $RSOO^-$, $RS(0)OO^-\cdot$ and $RS(0)_{2}CO^-\cdot$ thus formed readily undergo one electron transfer from $O_2^-$ to form the corresponding peroxysulfur anions, which oxidize the sulfoxides and olefins added into the reaction system. The reaction of a sulfonyl chloride with NaO₂ without crown ether have already been reported to afford the corresponding sulfonate in refluxing benzene.\(^6a\)

**Oxidation of Thiol and Disulfide with $O_2^-$:** Thiol react very readily with $O_2^-$ at first to afford the disulfides, which are then oxidized with $O_2^-$ to the corresponding sulfine and sulfonic acids.\(^5b\) The initial step of the reaction is the formation of the hydroperoxy anion and the thyl radical which rapidly coupled to give the disulfide, while hydroperoxy anion may decompose slowly to molecular oxygen and hydroxide anion (Scheme V).

The reaction of disulfide with $O_2^-$ undoubtedly involves

\[ RS \quad \overset{O_2^-}{\rightarrow} \quad \underset{O_2^-}{RS} \quad \overset{e^-}{\rightarrow} \quad \underset{O_2^-}{RS} \quad \rightarrow\]
nucleophilic attack of $O_2^-$ on S-S bond. Aromatic disulfide reacts faster than aliphatic disulfide, in keeping with the mechanism involving the initial nucleophilic attack of $O_2^-$ on disulfide bond.

\[
\begin{align*}
RSH + O_2^- & \rightarrow RS^\cdot + HOO^- (RS^- + HOO\cdot) \\
2 RS^\cdot & \rightarrow RSSR \\
HOO^- & \rightarrow 1/2 O_2 + HO^-
\end{align*}
\]

Scheme V

The peroxysulfenyl radical formed at the initial stage would undergo one electron transfer or collapse to form I or sulfinyl radical and molecular oxygen, as shown in Scheme VI. The peroxysulfur intermediates can oxidize the added sulfoxides or phosphines to the oxides.

Recently, Hirobe et al. revealed\(^{24}\) that two symmetrical disulfide, upon reacting with electrochemically generated $O_2^-$, gave three disulfides involving a new unsymmetrical disulfide in a theoretical ratio of the equilibrium mixture (1 : 2 : 1).
This is quite reasonable if a very small amount of $O_2^-$ (only 1/60 amount of our case) was used. The reaction is considered to generate the thiyl radical either through the initial one electron transfer from $O_2^-$ to the disulfide or direct $S_H^-$ type displacement of the disulfide with $O_2^-$ and the thiyl radical thus formed would eventually scramble the disulfides through $S_H^-$ process rapidly resulting a fast equilibrium.\(^{36}\) However, when the amount of $O_2^-$ is abundant the initial step should be the nucleophilic reaction of $O_2^-$ on the sulfur-sulfur linkage in view of the solvent effect\(^{5b}\) and the following order of the reactivities, i.e. thiolsulfinate $\gtrsim$ thiolsulfonate $\gtrsim$ disulfide.\(^{5b}\)
Oxidation of Thiolsulfinate with $\text{O}_2^-$: The thiolsulfinate was found to react with $\text{O}_2^-$ more than any other sulfur compounds used. $^5$ The reaction proceeded readily even at $-40^\circ$ within an hour, and not only sulfinic and sulfonic acids but also the disulfide were obtained. $^5$ In the reaction of an unsymmetrical thiolsulfinate with $\text{O}_2^-$ a symmetrical disulfide was formed in $\sim 50\%$ yield only from the sulfenyl side along with the two acids only from the sulfinyl side, revealing that the nucleophilic attack of $\text{O}_2^-$ occurs only on the sulfinyl sulfur of

$$\begin{align*}
\text{RSSR}^- & + 5\text{eq. KO}_2^- + 18\text{-crown-6} + \text{pyridine, } -40^\circ\text{C} & \rightarrow & \text{RSO}_2^- + \text{RSO}_3^- + \text{R'SSSR}' \\
\text{within 1h} & & \text{trace} & 48\% & 50\%
\end{align*}$$

the unsymmetrical thiolsulfinate. The predominant formation of the sulfonic acid may indicate that the main reaction path after the attack of $\text{O}_2^-$ is the rearrangement of peroxysulfinate (II) to the sulfonate. Therefore, peroxysulfinate (II) would be unstable enough to rearrange to the sulfonate under these conditions, and hence it would not be a good oxidizing agent of sulfoxide to the sulfone, thus yield of the sulfone being rather small (Table II). Only when the temperature was elevated, the yield of the sulfone gradually increased (Table II).

Oxidation of Thiolsulfonate with $\text{O}_2^-$: In the reaction of unsymmetrical thiolsulfonate with $\text{O}_2^-$ however, two sulfinic and
two sulfoic acids were obtained from both sulfur sides along with a small amount (i.e. nearly 25%) of symmetrical disulfide from the sulfonyl sulfur side, revealing clearly that the nucleophilic attack of $O_2^-$ occurs at both sulfonyl (a) and sulfonyl (b) sulfur atoms of the thiol sulfonate (Scheme VIII).

$$
\begin{align*}
\text{RSSR'} & \xrightarrow{\text{4 eq. KO}_2} \text{RSS}_{18}\text{-crown-6 pyridine, 0°C} \sim 30 \text{ min} \\
\text{RSO}_2^- & + \left[ \text{R'SO}_2^- \right] + \left[ \text{R'SO}_3^- \right] + \text{RSSR'}
\end{align*}
$$

The thiolate anion formed in the initial step must be converted to the disulfide rapidly by recombination of the thyl radicals after one electron transfer. At ca 0°C, the sulfinate may not
be oxidized further. The low yield of the sulfone formation from added sulfoxide should be also due to the low reaction temperature.

Both this and the reactions of thiolsulfinates clearly involve the initial nucleophilic attack of $O_2^-$ at sulfur atoms of the S-S linkage and gave partially the disulfide. A similar nucleophilic substitution (SN 2) on sulfur atom of the S-S linkage has been observed in the alkaline hydrolyses of both compounds. 37)

Addition of the sulfoxide or the phosphine as a trapping agents into the reaction systems of disulfide and thiolsulfinate with $O_2^-$ changed distribution of the products (Table III). Amounts of the sulfinate increased appreciably while that of sulfonate decreased a little in both reactions (Table VII), very likely due to the two competitive reactions, i.e. the
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp</th>
<th>Time</th>
<th>Solvent</th>
<th>[ A ]</th>
<th>[ A-O ]</th>
<th>Yield of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhSSPh</td>
<td>23°</td>
<td>300min</td>
<td>pyridine</td>
<td>-</td>
<td>-</td>
<td>9% 68% -</td>
</tr>
<tr>
<td>1'</td>
<td></td>
<td>23</td>
<td>300</td>
<td>pyridine</td>
<td>Ph₃P</td>
<td>26% b</td>
<td>29 67 -</td>
</tr>
<tr>
<td>2</td>
<td>p-TolSSTol-p</td>
<td>22</td>
<td>300</td>
<td>CH₃CN</td>
<td>-</td>
<td>-</td>
<td>6 88 -</td>
</tr>
<tr>
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<td>300</td>
<td>CH₃CN</td>
<td>PhSPH</td>
<td>62% c</td>
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<td>-</td>
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<td>17</td>
<td>10</td>
<td>pyridine</td>
<td>PhSPH</td>
<td>17% c</td>
<td>24 26 50</td>
</tr>
</tbody>
</table>

a) Molar ratio of substrate : KO₂ : crown ether = 1 : 6 : 1 : 2 or 1 : 5 : 1 : 2 for disulfide or thiolsulfinate, respectively. b) Yield by GC. c) Isolated yield.
reaction of peroxysulfinate (II) to react with sulfoxides or phosphines to the sulfones or the phosphine oxides and the rearrangement of II to the sulfonate.

Thus, the reactions of these organosulfur compounds each having S-S linkage with O\textsuperscript{2-} are another SN\textsubscript{2} processes, like the nucleophilic substitution of alkly halide or tosylate with O\textsuperscript{2-}.\textsuperscript{38) This SN\textsubscript{2} mechanism with O\textsuperscript{2-} is in good accordance with the order of the reactivity of the three disulfidic species (1 \(\gg\) 2 \(\gg\) 3).\textsuperscript{5) This order is identical to that of the reactivities of the three in the alkaline hydrolyses.\textsuperscript{37,39}"

Among a few trapping agents used, dimethyl sulfoxide was found to be the best reagent. Phosphines were not the good trapping agents since they reacted easily with various substrates. Olefins are relatively less reactive while the epoxide formed are usually so reactive that the epoxide itself reacted with various species present in the reaction system.

Since the alkaline autoxidation of thiols and disulfides gives sulfinate and sulfonate and is expected to involve the peroxysulfur intermediate,\textsuperscript{8,40) a mixture of the sulfoxide or the phosphine (2 mmole), thiol or disulfide (1 mmole) and potassium t-butoxide (2 mmole) was treated in pyridine (5 ml) under pure oxygen atmosphere at room temperature for 0.5 - 11h. Indeed, the sulfone (\(\sim\)10.6 \%) or the phosphine oxide (\(\sim\)20.2\%) was obtained besides the autooxidation products of sulfinic and sulfonic acids. Both sulfoxides and phosphines were also inert under the conditions without any of these sulfur compounds. Thus, the mechanism for autoxidation suggested by Berger\textsuperscript{8}) is
considered to be identical to that of the reactions of disulfides and other related sulfur compounds with \( O_2 \) involving the common peroxysulfur intermediates (I, II and/or III).

Among these peroxysulfur intermediates the peroxysulfenate (I) seems to collapse most readily. The oxidation of sulfoxide with I - III undoubtedly faster than that of olefin (Table I, II, V, and VI). The peroxysulfinate (II) is more stable and fairly reactive while only the peroxysulfonate (III) is stable enough to be characterized and hence be utilized for the oxidation of sulfoxide and olefin.
Experimental

General: All the reactions with $O_2^-$ were carried out under dry argon atmosphere.

Melting points were taken on a Yanaco instrument. NMR spectra were recorded on a Hitachi Perkin Elmer R-20 spectrometer. Gas and liquid chromatography were obtained by Shimazu GC-6A and Yanaco L-1030 instruments, respectively. Specific rotations were calculated from the value of optical rotations which were measured by JASCO DIP-140 polarimeter using 5 cm quartz cell.

Materials: KO$_2$ was obtained from Ventron Products. 18-Crown-6-ether was from Wako Pure chemical Ind. and used after drying in vacuo by heating at 60 - 70°. All the solvents used except for CH$_2$Cl$_2$ were purified by distillation and dried with drying agent, as shown in the preceding chapter.\textsuperscript{5b)} Purification of CH$_2$Cl$_2$ was performed at first by drying with CaCl$_2$ and then distillation after filtration. Distilled CH$_2$Cl$_2$ was stored in dark under N$_2$ in the presence of CaCl$_2$.

Preparation and purification of all the disulfides, thiol-sulfinates, thiol-sulfonates, sodium thiolates, and sodium sulfinates as substrates are reported in chapter 5.\textsuperscript{5b)}

Extra pure reagent grade triphenyl- and tributyl-phosphines, trans-stilbene and trichloromethanesulfonyl chloride from Wako
Pure Chemical Ind. were directly used without any treatment. Tosyl and mesitylenesulfonyl chlorides from Wako were used after recrystallization from hexane. Benzoyl chloride was purified by distillation and dehydration with CaCl₂ and DMSO was purified by distillation and stored under nitrogen gas. Diphenyl sulfoxide and acenaphthylene from Tokyo Kasei Kogyo were also used after recrystallization. Three chalcone derivatives were all from Aldrich Chemical Company and directly used for the reaction.

Sulfoxides, i.e. p-chlorophenyl methyl, methyl p-tolyl and methyl phenyl sulfoxides were prepared by oxidations of the corresponding sulfides with H₂O₂ in AcOH.⁴¹) All the sulfoxides were determined by the absorption peaks at the region of 1040 - 1060 cm⁻¹ in IR spectra of them. Thianthrene-9-oxide was prepared by a known method.⁴²) Benzenesulfenyl chloride was prepared by the reaction of benzenethiol with gaseous chlorine according to a known method.⁴³) The crude product was purified by distillation (bp 75 - 79°/3.0 torr). p-Toluenesulfinyl chloride was also prepared by the reaction of p-toluenethiol with gaseous chlorine in the presence of acetic anhydride.⁴⁴) Purification of the crude product was carried out by distillation (bp 110°/2.5 torr).

(+)-d-Camphor-10-sulfonyl chloride was prepared by the reaction of (+)-d-camphor-10-sulfonic acid (from Wako) with PCl₅. To the sulfonic acid (0.5 mole) dissolved in CHCl₃ (150 ml) was added slowly solid PCl₅ (0.7 - 0.9 mole). After slow evolution of HCl gas, the mixture was heated at refluxing...
temperature for ca 1h. The resulting clean colorless mixture was washed more than three times with water. Organic layer was dried with MgSO₄ and the solvent was evaporated to afford the sulfonyl chloride which was purified by recrystallization from hexane. Yield 72%. IR( KBr, cm⁻¹ ) (S=O) 1365 & 1168. [α]²⁵D + 20.9°( c=4.3, CHCl₃ ), (lit.⁴⁵) [α]²⁵D + 28.8°( c=4.2, CHCl₃ ).

Oxygen Trapping Reaction

Though it has been described in the previous paper,⁵b) the ratio of KO₂ in the reaction of each substrate was not kept constant for each sulfur substrate and hence is shown in each Table. Each Table shows reaction time, the molar ratio of additive and solvent used.

Oxidation of Additive Added in The Reaction System with O²⁻

The following is a typical run for the oxidation of sulfoxide.

A solution of diphenyl sulfoxide( 2 mmole ) and di-p-tolyl disulfide( 1 mmole ) in dry acetonitrile( 5 ml ) was added with a syringe into a heterogeneous solution of KO₂( 6 mmole, finely powdered in advance and stored under nitrogen ) and dry 18-crown-6-ether( 1 mmole, dried in vacuo at 60 - 70° ) in the same solvent in a two necked flask under dry argon atmosphere at 21°. The resulting heterogeneous mixture was stirred for 6h at the same temperature, during which the substrate generally disappears nearly completely. After the consumption of the substrate the reaction mixture was quenched by pouring into excess cold water containing crushed ice. Extraction with
CHCl₃, drying with MgSO₄ and evaporation of CHCl₃ gave an oily residue. The residue, containing oxidized sulfone, unreacted sulfoxide and crown ether, was subjected to column chromatography through silica gel using an eluent of hexane : EtOAc : CHCl₃ = 4 : 1 : 1. Yield of sulfone was 54% based on the starting disulfide.

When a sulfoxide bearing methyl group was used the yield of the sulfone was directly determined by integration ratio in NMR spectrum of the crude mixture. The sulfones formed were identified by comparing the melting points or chemical shifts in NMR spectra with those of authentic samples.

Oxidation of phosphines in the reaction system was carried out according to the same procedure as mentioned for sulfoxide. The yield of the phosphine oxide was measured by injecting the reaction mixture directly to GC since the phosphine was actually oxidized in the usual work-up. The phosphine oxide was not produced at all, even if the reaction mixture was injected directly into GC instrument. The phosphine oxides obtained were identical with the authentic samples by the retention time in GC.

Epoxidation of olefin in the reaction system was also carried out similarly. However, the work-up was different, i.e. the reaction mixture, after stirring till the disappearance of most substrate, was further stirred for a few hours. The resulting heterogeneous reaction mixture was filtered and the residue was washed with a large amount of CH₂Cl₂ (~40 ml). The combined organic layer was subjected to the assay after
evaporation of organic solvent. Yield of the epoxide in the 
residue was sometimes determined by isolation by column 
chromatography through silica gel using benzene(-hexane) as 
an eluent. However, the amount of the epoxide was determined 
usually by HPLC. In some cases, the yield of the epoxide 
was directly estimated by measuring NMR spectrum of the residual 
mixture. Epoxides thus obtained were identified by comparing 
the chemical shifts of the methine protons with those of the 
authentic samples as shown in Table IV.
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Chapter 7

Alkaline Hydrolyses of Unsymmetrical Thiolsulfinites.
Evidence for Selective Attacking of Hydroxide Anion on Sulfinyl sulfur Atom

Abstract

Alkaline hydrolyses of various diaryl, dialkyl and aryl alkyl unsymmetrical thiolsulfinites with sodium hydroxide in 50% aqueous dioxan yielded one sulfinic acid and two kinds of disulfides. Sulfinic acid was derived from sulfinyl moiety of the thiolsulfinate while one disulfide was symmetrical which was derived from two sulfenyl moieties of the original thiolsulfinate and the other disulfide was unsymmetrical one. The product distribution provided evidence for selective attacking of hydroxide anion at sulfinyl sulfur atom of the thiolsulfinate. In the alkaline hydrolysis using $^{18}$O-labelled unsymmetrical thiolsulfinites, $^{18}$O-incorporation of sulfinic acid produced...
during the hydrolysis was slightly larger than that of the original thiolsulfinate, suggesting the mechanism in which the hydrolysis was initiated by the nucleophilic attack of hydroxide anion selectively at sulfinyl sulfur atom. The reaction of unsymmetrical thiolsulfinate with thiolate anion which was considered to be formed during the hydrolysis afforded three disulfides and one sulfinic acid. The reaction of disulfide with thiolate anion was also investigated.

Introduction

Since the thiolsulfinate which has two different active sulfur atoms toward nucleophiles, is an important intermediate involved in the alkaline autoxidation of thiol and disulfide, the reactions of thiolsulfinates with $\text{OH}^-$ and thiolate anion have been investigated.

Savige et al. found that hydrolysis of cystine $S$-monooxide in neutral condition afforded cysteine sulfinic acid and cystine and suggested attack of $\text{OH}^-$ at sulfinyl sulfur. However, the fact that the racemization of the sulfinyl sulfur atom proceeded concurrently during hydrolysis was explained in terms of nucleophilic substitution on sulfenyl sulfur atom by $\text{OH}^-$. Tsukamoto et al. obtained the sulfinic acid and disulfide in the
neutral hydrolysis of monooxide of thiamine disulfide in aqueous alcohol (eq. 1). \(^3\)

On the other hand, Oae et al. indicated that the rate of the alkaline hydrolyses of substituted diaryl thiolsulfinates (pH 7.6, 30\(^\circ\), 60\% EtOH) is equal to that of the initial attack of hydroxide anion on the sulfinyl sulfur of the thiolsulfinate. \(^4\) Both substituent effects on sulfinyl and sulfinyl sulfur atoms (X and Y) indicated that electron withdrawing substituent accelerated the hydrolysis. \(^4\)

\[
\rho_Y = 1.6, \rho_X = 2.4, \text{ Ea= 13 kcal/mole( } Y=\bigodot-S-S-\bigodot-X \) \]

Meanwhile, Kice and Rogers suggested recently that initial attack of hydroxide anion occurs nearly with the same rates at both sulfinyl and sulfinyl sulfur atoms of thiolsulfinate. \(^5\) Yoshikawa have already confirmed that hydroxide anion, a typical

\[
\begin{align*}
\text{RSSR} & \quad \text{OH} \\
\text{at sulfinyl sulfur} & \quad \text{at sulfinyl sulfur} \\
& \quad k_1 \quad \text{RSOH} + \text{RSO}^- \\
& \quad \text{at sulfinyl sulfur} \\
& \quad k_2 \quad \text{RSO}_2\text{H} + \text{RS}^- \\
& \quad \text{at sulfinyl sulfur} \\
\end{align*}
\]

\[ k_1 = 140 \text{ M}^{-1}\text{s}^{-1} \quad k_2 = 170 \text{ M}^{-1}\text{s}^{-1} \]
hard base, attacks preferentially the sulfinyl sulfur than the sulfenyl sulfur atom, since the alkaline hydrolysis of S-p-tolyl benzenethiosulfinate gives benzenesulfinic acid alone as sulfinic acid.\(^6\)

\[
\text{Ph-S-S-Tol-p} + \text{OH}^- \rightarrow \text{PhSO}_2\text{H} + \text{disulfides} \quad (2)
\]

Results and Discussion

One of the unsymmetrical thiolsulfinates (0.9 mmole) was hydrolyzed with sodium hydroxide (0.9 mmole) at ca 0\(^\circ\) in 50% aqueous dioxan (30 ml). From time to time an aliquot was withdrawn and then injected into a high pressure liquid chromatography (HPLC) column to follow the formation of products and the disappearance of the thiolsulfinate. In some cases the thiosulfonate was observed on HPLC charts. When the thiosulfinate and the intermediary thiosulfonate disappeared, the reaction mixture was neutralized by adding acetic acid at ca 0\(^\circ\). The disulfide (2 and 3) were obtained by extraction with chloroform and sodium sulfinate (4) from aqueous layer was converted to the corresponding sulfone by treatment with methyl iodide in 50% aqueous dioxan or methanol at 25\(^\circ\). The products and their yields are summarized in Table I.

The hydrolysis of each of the six different thiolsulfinates (1a - 1f) afforded three corresponding products, 2, 3 and 4,
<table>
<thead>
<tr>
<th>Substrate, Atmosphere, Time[h],</th>
<th>Reaction</th>
<th>Products(mole%(^a))</th>
<th>(\text{RSO}_2\text{Na}_4)</th>
<th>(\text{RSSR}^3)</th>
<th>(\text{R'SSR}^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>la</td>
<td>Air</td>
<td>4h</td>
<td>72%</td>
<td>26%</td>
<td>32% b)</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>4</td>
<td>53</td>
<td>47</td>
<td>24</td>
</tr>
<tr>
<td>&quot;</td>
<td>(O_2)</td>
<td>4</td>
<td>69</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>lb</td>
<td>Ar</td>
<td>4</td>
<td>60</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>1</td>
<td>61</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>&quot;</td>
<td>(O_2)</td>
<td>4</td>
<td>78</td>
<td>22</td>
<td>39 c)</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>1</td>
<td>63</td>
<td>37</td>
<td>32 c)</td>
</tr>
<tr>
<td>lc</td>
<td>Air</td>
<td>2 2/3</td>
<td>78</td>
<td>16</td>
<td>42 d)</td>
</tr>
<tr>
<td>ld</td>
<td>&quot;</td>
<td>2 1/2</td>
<td>71</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>ld</td>
<td>&quot;</td>
<td>2 1/2</td>
<td>71</td>
<td>23</td>
<td>38 d)</td>
</tr>
<tr>
<td>le</td>
<td>Air</td>
<td>9</td>
<td>39</td>
<td>59</td>
<td>19 d,e)</td>
</tr>
<tr>
<td>lf</td>
<td>Air</td>
<td>2</td>
<td>74</td>
<td>26</td>
<td>37</td>
</tr>
</tbody>
</table>

\(^a\) The yields are in mole %, determined by NMR, GLC and HPLC.
\(^b\) Solvent system: CH\(_3\)CN - H\(_2\)O (1 : 1).
\(^c\) Small amount of benzenesulfonic acid RSO\(_3^-\) was confirmed.
\(^d\) RSSR was traceable.
\(^e\) Amount of NaOH was 1.5 eq. for \(\text{le}\); very slow with 1.0 eq. of alkali.
roughly in a same ratio (Table I). Rate of decreasing of thiol sulfininate was nearly same in la - ld but the rate of lf was slower than those of la - ld, and that of le was slowest of all and required 9h to complete the reaction even in 1.5 times concentrated NaOH solution. This result is considered to be due to the difficulty of the attack of OH at sulfinyl sulfur atom attached to bulky cyclohexyl group. The fact that presence of molecular oxygen did hardly affected the product distribution as shown in Table I, suggests that no alkaline autoxidation takes place under this condition.

Only from the product analysis, the attacking of OH at sulfenyl sulfur can be ruled out. If OH would attack both sulfenyl and sulfinyl sulfur atoms of an unsymmetrical thiol sulfinate (eq. 4), subsequent reactions (eq. 5 - 8) should take place to give two different thiol sulfinate (R'S(O)SR' and RS(O)SR) incipiently, and those are hydrolyzed eventually to give RSSR (5) and R'SO_2^- (6) (eq. 6 and 8), in addition to
the three products mentioned above, 2, 3 and 4. However, neither 5 nor 6 could be detected during the reaction, as shown in Table I.

Exclusive attack of OH\(^{-}\) at the sulfinyl sulfur not the sulfenyl sulfur was confirmed further more explicitly by the \(^{18}\)O-tracer studies using \(^{18}\)O-labelled unsymmetrical thiolsulfinites which were prepared by the reaction of thiol with \(^{18}\)O-labelled benzenesulfinyl chloride in the presence of pyridine (eq. 10). \(^{18}\)O-Labelled sulfinyl chloride was prepared according to the following reactions (eq. 9).\(^{\dagger}\) For the measurement of \(^{18}\)O-content of the sulfinic acid produced in the hydrolysis of thiolsulfinate (\(^{1}\)a or \(^{1}\)b), the sulfinic acid was converted to
the corresponding methyl phenyl sulfone by treating benzene-
sulfinic acid with methyl iodide in alkaline solution (eq. 11). 8)

18O-Contents of the sulfones derived from the sulfinic acid
obtained by the hydrolysis of la and lb were found to be slightly
greater than those of the starting materials (la and lb) (Table II).

Most plausible mechanism based on these observations is the
followings. Most hydroxide anions attack initially sulfinyl
sulfur of unsymmetrical thiol sulfinate to form sulfinic acid
(RSO_2H) and thiolate anion (R'S^-) (eq. 12). The sulfinic
acid which retains fully original 18O-label, is no more
reactive. R'S^-, a strong soft nucleophile, can attack both
sulfur atoms but the attack of R'S^- on the sulfinyl sulfur only
reproduces the thiol sulfinate (eq. 14). The attack of R'S^- on
the soft sulphenyl sulfur atoms symmetrical disulfide, R'SSR', and
sulfenate anion (RSO^-) (eq. 13) which can also attack both
**Table II** 18O-Tracer Experiments for Sodium Benzenesulfinate (Methyl Phenyl Sulfone)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction Condition</th>
<th>18O Analysis Data (RSO₂Me)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Excess%), Temp, Atmosphere, Time,</td>
<td>Content%, Excess%, Incorporated%</td>
</tr>
<tr>
<td>Ph-S-S-Me</td>
<td>0° Ar 1h</td>
<td>0.561% 0.358% 127%</td>
</tr>
<tr>
<td>la</td>
<td>0° O₂ 1h</td>
<td>0.554 0.351 124</td>
</tr>
<tr>
<td>(0.565%)</td>
<td>0° O₂ 7.5min</td>
<td>0.542 0.339 120 a)</td>
</tr>
<tr>
<td>Ph-S-S-Bu</td>
<td>0° Ar 1h</td>
<td>0.516 0.312 105</td>
</tr>
<tr>
<td>lb</td>
<td>0° O₂ 1h</td>
<td>0.507 0.303 102</td>
</tr>
<tr>
<td>(0.592%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) The reaction was stopped by adding acetic acid after 7.5 min when the starting material la was completely hydrolyzed.

sulfur atoms since RSO⁻ is presumed to be a good nucleophile, too. Although the attack of RSO⁻ on the sulfonyl sulfur of the thiolsulfinate regenerates the original thiolsulfinate (eq. 16), the attack of RSO⁻ on the sulfinyl sulfur affords "α-disulfoxide" which is known to be very unstable to change immediately to the thiolsulfonate (eq. 15). This course of the attack at harder sulfinyl sulfur than sulfonyl sulfur is considered to be reliable since RSO⁻ is considered to be harder.
nucleophile than RS⁻. The thiol sulfonate thus formed may suffer nucleophilic attack on sulfenyl sulfur by thiolate anion to give the sulfinic acid and disulfide (eq. 17). In fact, the thiol sulfonate (PhSO₂SPh) was detected as an intermediate during the hydrolysis of thiol sulfinate 1. The attack of R'S⁻ on sulfenyl sulfur of the thiol sulfonate 7 is known to be very fast (10⁶ - 10⁷ M⁻¹S⁻¹), and yields the sulfinic acid and unsymmetrical disulfide (eq. 17). The possibility of attack of R'S⁻ on the sulfonyl sulfur of thiol sulfonate has been already ruled out. 5)
If $RSO^-\, attacks\, sulphenyl\, sulfur\, of\, thiolsulfonate\, to\, form\, symmetrical\, thiolsulfinate\, (RS(O)SR^-),\, the\, formation\, of\, RSO_2^-$ and $R'SSR'$ may be possible. However, this possibility may be excluded because of the unfavourable stereoelectronic repulsion between $ROD^-\, and\, thiolsulfonate$. The sulfinic acid thus formed (eq. 17) must have 200% of the original $^{18}O$-label in the starting material $I$. Therefore, the $^{18}O$-incorporation in benzenesulfinic acid $I$ (Table II) can be explained by the contribution of the two competing processes to give the sulfinic acid, i.e. the reactions of eq. 12 (major) and eq. 13 (minor) (Table II).

Since the rate of the attack of thiolate anion is much faster than that of hydroxide anion, the participation of $^-OH$ should be only in the initial step of the reaction to generate thiolate anion which then plays important role than $^-OH$ in the subsequent reactions.

When the reactions of unsymmetrical thiolisulfinates with 0.95 equivalent of sodium thiolate were carried out in 67% aqueous dioxan at ca 0°, three disulfides were usually obtained along with sulfinic acid, as shown in eq. 18 and Table III.

$$RSSR' + R'S^-Na \xrightarrow{67\%\, dioxan\, 0^\circ} R'SSR'' + RSSR' + R'SSR' + RSO_2^- \quad (18)$$
Although the reaction of thiol sulfinate with thiol under neutral condition is known to afford disulfide almost quantitatively, the reaction of thiol sulfinate with RS\(^-\) which is known to be \(10^7\) times stronger nucleophile than thiol,\(^5\) did not afford only disulfide but also appreciable amount of sulfinic acid.

In order to confirm further these mechanisms of alkaline hydrolysis, the reaction between thiol sulfinate and thiolate anion has been investigated. Since the nucleophilic reaction of thiolate anion produces the other nucleophile, the reaction scheme must be very complicated. However, the important paths may be limited to the above equations (eq. 19 - 23).
Table III

<table>
<thead>
<tr>
<th>Entry</th>
<th>R=</th>
<th>R'=</th>
<th>Time</th>
<th>Product (mole %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R'SSR', R'SSR', R'SSR', R'SSR', R'SO₂⁻</td>
</tr>
<tr>
<td>1</td>
<td>Ph</td>
<td>p-Tol</td>
<td>1h</td>
<td>46% 27% 19% - - 16%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>p-Tol</td>
<td>1min</td>
<td>44 34 11 - - 20</td>
</tr>
<tr>
<td>3</td>
<td>p-Tol</td>
<td>Ph</td>
<td>1h</td>
<td>52 30 - - 3 29</td>
</tr>
<tr>
<td>4</td>
<td>p-Tol</td>
<td>Ph</td>
<td>1min</td>
<td>52 31 - - 2 25</td>
</tr>
<tr>
<td>5</td>
<td>p-Tol</td>
<td>Ph</td>
<td>1min</td>
<td>55 15 - - 4 27 *1</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Me</td>
<td>1h</td>
<td>50 16 15 7 0 10</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Me</td>
<td>1min</td>
<td>35 23 7 0 9 3 *2</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>H</td>
<td>1h</td>
<td>46 9 3 23 0 39</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>H</td>
<td>1min</td>
<td>43 18 2 22 0 29</td>
</tr>
</tbody>
</table>

*1 The reaction was carried out under argon atmosphere.

*2 The reaction could not be completed and the conversion of the starting material was nearly 70%.
Soft nucleophile, $R'S^-$, may attack initially sulfenyl sulfur rather than sulfinyl sulfur of thiolsulfinate to form $R'SSR'^- \text{ and } RSO^-$ (eq. 19). Considerable amount of $RSO^-$ thus formed, a hard nucleophile, would attack preferentially harder sulfinyl sulfur of thiolsulfinate to afford $R'S^-$ and intermediary $\alpha$-disulfoxide which immediately changes to thiolsulfonate (eq. 20). $R'S^-$ in eq. 20 can attack sulfenyl sulfur of thiol-sulfinate to give $RSO^-$ and $R'SSR'$ (eq. 21). Considerable amount of thiolsulfonate formed according to eq. 20 is attacked by both thiolate anions, $R'S^-$ and $R'S^-$ to afford sulfinic acid and two unsymmetric disulfides, $RSSR'$ and $RSSR''$ (eq. 22 and 23). These equations can explain the product distributions shown in Table III. Other possibilities may be shown in the following equations 24 - 28. Eq. 24 indicates the nucleophilic

\[
R-S-S-R' + R''S^- \rightarrow R-S-S-R'' + R'S^- \quad (24)
\]
\[
R-S-S-R'' + R'S^- \rightarrow RSO^- + R'SSR'' \quad (25)
\]
\[
R-S-S-R'' + R''S^- \rightarrow RSO^- + R''SSR'' \quad (26)
\]
\[
R-S-S-R'' + RSO^- \rightarrow [ R-S-S-R ] + R''S^- \quad (27)
\]
\[
R-S-S-R + RSO^- \rightarrow RSO_2^- + R-S-S-R \quad (28)
\]
attack of \( R'S^- \) on hard sulfinyl sulfur to form new unsymmetrical thiolsulfinate( \( RSS(0)R' \) ) which suffers a few nucleophilic attacks as shown in eq. 25 - 27, however, soft nucleophile, \( R'S^- \), is difficult to attack sulfinyl sulfur. In fact, \( R'SSR' \) shown in eq. 26, could not be detected. Eq. 28 would also be ruled out by the sterically unfavourable attack of sulfenate anion on sulfenyl sulfur of thiolsulfonate.

On the other hand, the reaction of disulfide and thiolate anion is also important, because of the strong thiophilicity of the thiolate anion. In fact, the reaction of disulfide with thiolate anion is known to be a very fast equilibrium as shown in below equation( eq. 29 ). This equilibrium was confirmed

\[
RSSR' + R'S^- \rightleftharpoons RSSR'' + R'S^- \rightleftharpoons R'SSR'' + RS^- (29)
\]

in the reaction between di-p-tolyl disulfide and sodium thiophenoxide in 67% aqueous dioxan at ca 0°, by injecting the reaction mixture directly into GLC and HPLC. However, since the distribution of disulfides was not leveled in the reaction of thiosulfinate with thiolate anion, the equilibration of disulfides with thiolate anions( eq. 29 ) must be less important in the reaction of thiosulfinate with thiolate anion.

Thus, the alkaline hydrolysis of thiosulfinate with hydroxide anion is found to be initiated by the nucleophilic attack of \( \text{OH}^- \) on sulfinyl sulfur followed by secondary reactions of thiolate anion formed by the initial reaction.
Experimental

**General:** Chemicals were of reagent grade unless otherwise specified. All melting points were measured by Yanaco instrument and were uncorrected. IR spectra of the compounds were taken on a Hitachi 215 spectrometer. NMR spectra were recorded on a Hitachi Perkin Elmer R-20 spectrometer. Shimazu GC-6A and Yanaco L-1030 were used for gas and liquid chromatographies, respectively.

**Thiolsulfinate:** Various thiolsulfinates were prepared by the reported method in which sulfinyl chloride reacted with thiol in the presence of pyridine (80 - 95% yield). Four thiolsulfinates, 1a, 1b, 1e, and 1f were purified by column chromatography while 1c and 1d were purified by recrystallization from hexane-chloroform mixed solvent.

**S-Methyl benzene thiosulfinate** 1a; white crystals, mp 26 - 8°, IR (neat, cm$^{-1}$) 3050, 2975, 2900, 1570, 1470, 1095 & 1060 (S=O).

**S-Butyl benzene thiosulfinate** 1b; colorless oil, IR (neat, cm$^{-1}$) 3050, 2920, 1580, 1475, 1445. 1097 & 1062 (S=O), NMR (CDCl₃, δ, TMS) 0.96 (t, 3H, -CH₃), 1.13 - 2.25 (m, 4H, -(CH₂)₂-), 3.11 (t, 1H, Hₐ, -S-CH₂Hₐ⁻), 3.15 (t, 1H, Hₐ).

**S-Tolyl benzene thiosulfinate** 1c; pale yellow crystals, mp 70 - 1° (lit. 4) 68°).

**S-Phenyl p-toluenethiosulfinate** 1d; pale yellow crystals, mp 82° (lit. 4) 83 - 84°).
S-Methyl cyclohexanethiosulfinate le; colorless oil, IR (neat, cm⁻¹) 2975, 2840, 1445, 1080 & 1070 (S=O).
S-Cyclohexyl methanethiosulfinate lf; colorless oil, IR (neat, cm⁻¹) 2970, 2840, 1440, 1080 (S=O).

Alkaline Hydrolysis

To a cooled 50% aqueous dioxan (30 ml) of unsymmetrical thiol sulfinate (0.9 mmole) at ca 0° by ice-water bath, was slowly added an aqueous solution (1.5 ml) of sodium hydroxide (0.9 mmole) with syringe. The mixture was stirred at the same temperature. The disappearance of the starting material was monitored by HPLC. The peak correspond to thiol sulfonate (PhSSO₂Ph) was observed on HPLC chart during the reaction. After the reaction was completed the mixture was quenched by adding small amount of acetic acid and then extracted three times with CHCl₃. Combined organic layer was washed with water, dried with MgSO₄ and concentrated under reduced pressure up to remove acetic acid and dioxan. The residue was analyzed by GLC, HPLC and NMR to determine the yields of the products. Aqueous layer combined was concentrated to ca 10 ml by evaporation and treated with large excess of MeI and MeOH or dioxan (10 - 15 ml) which made the solution homogeneous. The mixture was stirred at room temperature overnight and then extracted with CHCl₃. Organic layer was washed with water and dried over CaCl₂. The residue after the evaporation of much of CHCl₃ was the corresponding methyl sulfone of which yield was determined by GLC. The sulfone usually purified by recrystallization from...
EtOH to be used for $^{18}$O-tracer experiments.

**Reaction of Thiolsulfinate with Sodium Thiophenate**

Sodium thiophenate was prepared by the reaction of thiol and metal sodium in dry ether and purified by washing with dry hexane.

A solution of PhSNa (0.778 mmole) in 67% dioxan (2.5 ml) was added with syringe into 67% dioxan (30 ml) solution of unsymmetrical thiolsulfinate (0.878 mmole) at ca 0°. The mixture was stirred and then quenched by adding acetic acid after the disappearance of the thiolsulfinate was confirmed by HPLC. The resulting reaction mixture was subjected to the same treatment as that in the "Alkaline Hydrolysis of Thiolsulfinate" to determine the product yields.

**Reaction of Di-p-tolyl Disulfide with Sodium Thiophenate**

To a 67% dioxan solution (30 ml) of di-p-tolyl disulfide (1.0 mmole) was added with syringe a 67% dioxan solution (4 ml) of PhSNa (1.0 mmole) at ca 0°. The reaction mixture was stirred at the same temperature with monitoring the reaction by HPLC. Both HPLC and GLC analyses showed the product ratio to be constant from 1 min to 1 h.

**$^{18}$O-Tracer Experiment**

$^{18}$O-Tracer analysis was carried out by the method developed by Rittenberg-Ponticorvo, with a modification which was the use of Pb(OAc)$_2$ to remove H$_2$S gas from the produced gas by thermolysis.
of sample.

Twenty mg of sample was pyrolyzed with 300 mg of purified both HgCl₂ and HgCN₂, respectively, in an evacuated, sealed Pyrex tube at ca 500° for 12h. Then the tube was broken in a vacuum line and CO₂ gas formed was purified by distillation and the mass peaks of m/e 44 and 46 which corresponded to C₁₆O₂ and C₁₆O₁₈O, respectively, were recorded on a mass spectrometer.

References

Chapter 8

Studies on The Behaviours of Disulfides, Thiolsulfinates and Thiolsulfonates in Both $^1$H- and $^{13}$C-NMR1,2)

Abstract

Unusual $^1$H- and $^{13}$C-NMR chemical shifts were found in a series of both linear and cyclic unsymmetrical disulfides, thiolsulfinates and thiolsulfonates. Axial orientation was assigned for the oxygen of cyclic thiolsulfinates based on the results of their $^{13}$C-NMR spectra. Magnetically non-equivalent protons (heterosteric effect) were characterized in $^1$H-NMR spectra of several unsymmetrical thiolsulfinates.
Introduction

Although numerous studies on both $^1$H- and $^{13}$C-NMR spectra of a series of sulfides, sulfoxides and sulfones have been already done, few systematic studies have been carried out on NMR spectra of the compounds having sulfur-sulfur linkage such as a series of disulfides, thiolsulfinates and thiolsulfonates. Especially, the study on the $^{13}$C-NMR of cyclic analogues bearing sulfur-sulfur linkage has not been carried out and therefore the stereochemistry of cyclic thiolsulfinate has never been known.

Two groups (Kato and Numata, $^3$) and Murray et al. $^4$) measured $^1$H-NMR spectra of five membered cyclic thiolsulfinates using shift reagents, and discussed the structure of regio- and stereo-isomers. Paukstelis et al. reported $^{13}$C-NMR spectra of thiols and thiolacetates, especially lipoic acid and derivatives. $^5$

Non-equivalence of chemical shift of heterosteric groups has been reported for a number of organosulfur compounds, including sulfinates, sulfites, sulfinamides, sulfoxides, sulfide-borane adducts, sulfonium salts, and sulfonium ylides. $^6$) This phenomenon of magnetically non-equivalent protons found commonly in above compounds having trivalent sulfur atom has long been a matter of controversy.

Recently, Murray et al. found this phenomenon in $^1$H-NMR spectra of symmetrical thiolsulfinates, and that signals of two magnetically non-equivalent protons were splitted clearly by the
use of shift reagent. Non-eqivqlence of diastereotopic substituents on sulfinate ester oxygen was reported to be insensitive to temperatures from 25° to 120°. All these facts are considered to be due to special anisotropic effects of sulfinyl function of sulfur compounds.

After this work has been finished, Woody Bass and Evans Jr. reported data of 13C-NMR spectra of both linear and six-membered disulfides and their oxidized derivatives. They noted unusual chemical shifts of carbon at α-position to sulfinyl sulfur of both linear and cyclic thiolsulfinates and assigned the axial orientation for the oxygen of cyclic thiolsulfinates, too.

Results and Discussion

1. Unusual Chemical Shift

In the course of studies on the oxidation of unsymmetrical disulide to the corresponding thiolsulfinate and thiolsulfonate, unexpected 1H- and 13C-NMR chemical shifts were observed in the series of unsymmetrical disulfide(A), thiolsulfinate(B) and thiolsulfonate(C). Namely, α-methyl or methylene protons of B showed larger down field shift than those of C, and α-carbon of B displayed the highest chemical shift among those of the three(A, B and C), while β'-carbon of B and C also showed higher field shifts than β-carbons of B and C. In order to
investigate these unusual NMR behaviours, NMR studies has been made systematically by using of a few series of the sulfur compounds of different oxidation states.

$^1$H-NMR Chemical Shift: Generally the electron-withdrawing ability of sulfur group is considered to increase as the progress of the oxidation state of sulfur atom, e. g. sulfide $< $ sulfoxide $< $ sulfone; sulfenate $< $ sulfinate $< $ sulfonate. Therefore, $^1$H-NMR chemical shift of methyl( or methylene ) attached to sulfur atom is shifted to down field along the increase of the oxidation state of sulfur as shown below and Table I.

<table>
<thead>
<tr>
<th></th>
<th>$^1$H-NMR Chemical Shifts ( $\delta$, ppm )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Me-S-Me</td>
</tr>
<tr>
<td>$\delta_H$</td>
<td>2.06</td>
</tr>
<tr>
<td>$\delta_C$</td>
<td>19.3</td>
</tr>
</tbody>
</table>
\begin{tabular}{|l|l|c|c|c|c|}
\hline
Entry & Compound & $C_1$ & $C_2$ & $C_3$ & $C_4$ \\
\hline
1 & Ph-$\delta$-S-O-Me 1b & 3.44 & & & \\
1' & Ph-$\delta$-S-O-Me 1c & 3.72 & & & \\
2 & Ph-$\delta$-S-O-Et 2b & 3.70 & 1.26 & & \\
2' & Ph-$\delta$-S-O-Et 2c & 4.09 & 1.28 & & \\
3 & Ph-$\delta$-S-O-Pr 3b & 3.53 & 1.62 & 0.89 & \\
3' & Ph-$\delta$-S-O-Pr 3c & 3.97 & 1.65 & 0.87 & \\
4 & Ph-$\delta$-S-O-Pr$^i$ 4b & 4.57 & 1.22 & 1.36 & \\
4' & Ph-$\delta$-S-O-Pr$^i$ 4c & 4.69 & 1.27 & & \\
5 & Ph-$\delta$-S-O-Bu 5b & 3.43 & - & - & 0.83 \\
5' & Ph-$\delta$-S-O-Bu 5c & 4.04 & - & - & 0.86 \\
\hline
\end{tabular}

- 265 -
In fact, most of the $\alpha'$, $\beta'$, $\gamma'$, and $\delta'$-protons of B and C are shifted substantially to down field as expected (Table II). However, both $\alpha$- and $\beta$-protons of B are shifted more to down field than those of C despite the relatively weaker inductive effect of $-S(0)-S-$ group than that of $-S(0)_2-S-$ group (Table III).

**$^{13}$C-NMR Chemical Shift:** Oxidation of ethyl phenyl disulfide 7a to the corresponding thiol sulfinate (7b) causes a normal down field shift of $\alpha'$-carbon (from 32.6 to 49.8 ppm) due to the increase of the inductive effect (Fig. I). However, $^{13}$C-NMR chemical shifts of $\alpha$- and $\beta'$-carbons of B ($\alpha$-carbon: 27.6 in 7b and 35.1 in 8b; $\beta'$-carbon: 7.6 in 7b' and 17.1 in 8b') are shifted to the highest field among those of the three sulfur derivatives of different oxidation states (A, B and C).

Oxidation of a thiol sulfinate (eq. 8b') to the thiol sulfonate (8c') also caused a down field shift at $\alpha'$-carbon (from 57.8 to 61.2 ppm) due to the inductive effect. But $\beta'$-carbons of C (8.3 in 7c' and 17.3 ppm in 8c') are shifted to the highest field among those of the three derivatives A - C.

Quite same trend were observed in a few series of six-membered cyclic compounds as shown in Fig. II and IV.

Assignments of $^{13}$C-NMR signals in completely proton decoupled $^{13}$C-NMR spectra, were performed for all these cyclic compounds by the technique of off-resonance decoupling of proton, NOE (J$_{C-H}$), and relative peak heights due to relaxation time and comparison with the reported data of various sulfur heterocycles and of a series of linear compounds mentioned above.
Table II  \(^1\text{H-NMR Chemical Shift of } R\text{-S-S(O)}_x\text{-R}' ( R' = -C_\alpha-C_\beta-C_y-C_\delta, ) \\
(CDCl\_3, \delta, TMS ) at 27^\circ \\

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>( R\text{-S-S-R}' )</th>
<th>( R\text{-S-S(O)}_x\text{-R}' )</th>
<th>( R\text{-S-S(O)}_2\text{-R}' )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( C_\alpha )</td>
<td>( C_\beta )</td>
<td>( C_y )</td>
</tr>
<tr>
<td>1</td>
<td>6b' Ph</td>
<td>Me</td>
<td>2.39</td>
<td>2.90</td>
</tr>
<tr>
<td>2</td>
<td>7b' Ph</td>
<td>Et</td>
<td>2.71 1.29</td>
<td>3.10 1.41</td>
</tr>
<tr>
<td>3</td>
<td>8b' Ph</td>
<td>Pr</td>
<td>2.81 1.72 1.03</td>
<td>3.09 1.86 1.08</td>
</tr>
<tr>
<td>4</td>
<td>9b' Ph</td>
<td>Bu</td>
<td>[2.65] (^a)</td>
<td>[0.87] 3.11</td>
</tr>
<tr>
<td>5</td>
<td>10b' Ph</td>
<td>p-Tol</td>
<td>[2.26] (^b)</td>
<td>2.37 (^b)</td>
</tr>
<tr>
<td>6</td>
<td>11b' H</td>
<td>Me</td>
<td>2.32[2.33] (^c)</td>
<td>2.95[2.86] (^c)</td>
</tr>
</tbody>
</table>

[ ]: Chemical shift in CCl\(_4\) from TMS as an internal standard.

a) not determined.
b) for methyl group of p-tolyl group.
c) for methyl protons of methyl group.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R-S-S-R'</th>
<th>R-S(O)-S-R'</th>
<th>R-S(O)₂-S-R'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R=</td>
<td>R'=</td>
<td>Cα Cβ Cγ Cδ</td>
<td>Cα Cβ Cγ Cδ</td>
</tr>
<tr>
<td>1</td>
<td>6b</td>
<td>Ph Me</td>
<td>2.39</td>
<td>2.53</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>Ph Et</td>
<td>2.71 1.29</td>
<td>a 3.13 1.43</td>
</tr>
<tr>
<td>3</td>
<td>8b</td>
<td>Ph Pr</td>
<td>2.81 1.72 1.03</td>
<td>a 3.12 1.80 1.03</td>
</tr>
<tr>
<td>4</td>
<td>9b</td>
<td>Ph Bu</td>
<td>[2.65] -b [0.87]</td>
<td>3.14 - - 0.92</td>
</tr>
<tr>
<td>6</td>
<td>12b</td>
<td>p-Tol Me</td>
<td>-c -d</td>
<td>2.38(2.12)c 2.53(2.30)d</td>
</tr>
<tr>
<td>7</td>
<td>13b</td>
<td>p-ClC₆H₄ Me</td>
<td>[2.26]d</td>
<td>2.40(2.33)d</td>
</tr>
</tbody>
</table>

[ ]: Chemical shift in CCl₄ from TMS as an internal standard.

( ): Chemical shift in CD₃COOD-D₂O from TMS as an external standard.

a) magnetically non-equivalent protons.
b) not determined.
c) for methyl group of p-tolyl group.
d) for methyl protons of methyl group.
Figure I  $^{13}$C-NMR Chemical Shift of Linear Compounds

( CDCl$_3$, $\delta$, TMS ) at 27°

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-S-S-CH$_2$-CH$_3$</td>
<td>27.6 14.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_3$</td>
<td>30.5 14.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_3$</td>
<td>32.6 14.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_3$</td>
<td>49.8 7.6</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_3$</td>
<td>53.9 8.3</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>35.1 13.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>38.0 13.0</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>23.9</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>22.0</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>40.9 13.0</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>22.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>57.8 13.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>61.2 12.6</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>17.1</td>
</tr>
<tr>
<td>Ph-S-S-CH$_2$-CH$_2$-CH$_3$</td>
<td>17.3</td>
</tr>
</tbody>
</table>
Figure II

$^{13}$C-NMR Chemical Shifts of 14, 15, 16, and Their Derivatives

( CDCl$_3$, δ, TMS ) at 27°

14a

14b

(25.1) (26.2)

27.7

15.2

52.1

25.6

59.7

23.4

35.2

14c

15a

15b

(128.3)

(127.7)

126.7

(131.8)

130.0

(127.7)

132.8

129.2

59.5

135.4

33.0

61.4

38.2

15c

16a

16b

(26.3) (26.0)

26.5

(33.2)

34.0

31.2

41.6

(33.1)

44.7

39.4

41.8

58.0

28.8

64.4

39.7

16c

* Chemical shifts parenthesized cannot be assigned.

# Chemical shifts underlined are notable unusual chemical shifts.
$^{13}$C-NMR chemical shifts thus assigned for all these compounds are shown in Fig. II and IV.

In Fig. II, the chemical shift of carbon-1 moved toward down field as the increase of oxidation state of the adjacent sulfur atom from a, b to c as expected, while the chemical shift at carbon-4 did not show any correlation with the electronegativities of sulfur groups and the highest chemical shift was observed in b. The unusually high field shift of carbon-4 of b is considered to be due to the well-known $\gamma$-effect, in the light of $^{1}$H-NMR data of above linear series. The $\gamma$-effect can be seen also at carbon-2 in all b. Incidentally, the $\gamma$-effect has been known to be observed only in axial sulfoxide or analogous sulfilimine of conformationally locked ring compounds but not in the equatorial derivatives. Therefore, the sufficiently large $\gamma$-effect in all these thiolsulfinate (Fig. II and IV ) suggests strongly the axial orientation of the oxygen atom of b, in keeping with the data in the recent report, since an axial isomer is known to be thermodynamically more stable.

Figure III

$^{13}$C-NMR Chemical Shifts of Fixed Ring Sulfoxide and Sulfilimine ( $\gamma$-effect )

- 271 -
than an equatorial isomer in the rigid cyclic sulfoxide.\textsuperscript{10)}
The lack of equatorial isomer in the product mixture of the reaction between 14, 15, 16, or 17 and oxidant (H\textsubscript{2}O\textsubscript{2}/AcOH) can be rationalized in terms of the facile isomerization of the equatorial isomer, if formed, to the thermodynamically more stable axial isomer via breaking and recombination of -S-S(0)- bond.\textsuperscript{11)}

These results are in keeping with the earlier assignments (Chapter IV) that two isomers of 3-methyl-1,2-dithiane monoxides (17b and 17b') obtained by the oxidation of 17a with H\textsubscript{2}O\textsubscript{2}/AcOH, are not stereoisomers but regio-isomers. Concrete evidence was obtained eventually by the selective formation of 17c and 17c' from 17b and 17b' respectively, in the oxidation with NaIO\textsubscript{4} (Fig. IV).\textsuperscript{12)}

Coupling constants between carbon-hydrogen (\(J_{C-H}\)) were measured for the series of a - c of 14, 15 and 16, using NOE. Noteworthy point is the coupling constants at position-4 of a - c
Figure IV  

$^{13}$C-NMR Chemical Shifts of 17 and Its Derivatives  

(CDC$_3$, δ, TMS) at 27°

17a

17b

17c

17b'

17c'
Figure V  Coupling Constants  \( J_{C-H} \) of 14, 15, 16, and Their Derivatives

\[ \text{CDCl}_3, \text{ Hz} \]

<table>
<thead>
<tr>
<th></th>
<th>14a</th>
<th>14b</th>
<th>14c</th>
</tr>
</thead>
<tbody>
<tr>
<td>124.0</td>
<td>135.7</td>
<td>131.7</td>
<td>130.0</td>
</tr>
<tr>
<td>S-S</td>
<td>S-S</td>
<td>S-S</td>
<td>S-S</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>15a</th>
<th>15b</th>
<th>15c</th>
</tr>
</thead>
<tbody>
<tr>
<td>157.2</td>
<td>139.7</td>
<td>142.8</td>
<td>144.8</td>
</tr>
<tr>
<td>S-S</td>
<td>S-S</td>
<td>S-S</td>
<td>S-S</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>16a</th>
<th>16b</th>
<th>16c</th>
</tr>
</thead>
<tbody>
<tr>
<td>128.0</td>
<td>137.3</td>
<td>139.7</td>
<td>140.6</td>
</tr>
<tr>
<td>S-S</td>
<td>S-S</td>
<td>S-S</td>
<td>S-S</td>
</tr>
</tbody>
</table>
which is contrast to the chemical shift values of $^{13}\text{C}$- and $^1\text{H}$-NMR spectra. The unusually large coupling constants of position-4 of $b$ and $c$ (Fig. V) are considered to be due to the contribution of the resonance structures of $b$ and $c$ as shown by [D] and [E]. This may be also in good accordance with the results of UV spectra of linear $b$ and $c$ in which the red shifts were observed when solvent was changed from nonpolar to polar solvents.\textsuperscript{13)}

\[
\begin{align*}
\text{[D]} & \quad \text{[E]}
\end{align*}
\]

Thus, the important new results concerning to $^1\text{H}$- and $^{13}\text{C}$-NMR spectra and $J_{\text{C-H}}$ of a few series of linear and cyclic disulfide and its oxidized derivatives are summarized as

1) Unusual chemical shifts at $\alpha$- and $\beta'$-positions of linear compounds and at carbons-1 and -4 of cyclic compounds were observed. Same relation has been obtained in a series of azo and azoxy compounds,\textsuperscript{14)} as shown in the following figure.

2) Only one stereoisomer of cyclic thiosulfinate in which oxygen is oriented toward axial is obtained exclusively in the oxidation of corresponding disulfide.

3) $J_{\text{C-H}}$ of $b$ and $c$ at position-4 suggest substantial contribution of the canonical forms [D] and [E] in a resonance hybrid of thiosulfinate and thiosulfonate.
\( ^1\text{H}-\text{NMR Chemical Shifts of Azo and Azoxy Compounds}\)

(\(\text{CCl}_4\), \(\delta\), TMS)

<table>
<thead>
<tr>
<th></th>
<th>Me-N=N-Me</th>
<th>Me-N=N-Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-N=N-Me</td>
<td>3.68</td>
<td>3.90</td>
</tr>
<tr>
<td>Me-N=N-Me</td>
<td>4.05</td>
<td>4.15</td>
</tr>
<tr>
<td>Me-N=N-Me</td>
<td>3.07</td>
<td>3.40</td>
</tr>
</tbody>
</table>

2. Magnetically Non-equivalent Proton

When many unsymmetrical thiol sulfinates were prepared in the course of study on the oxidation of unsymmetrical disulfide, some kinds of unsymmetrical thiol sulfinates were found to display magnetically non-equivalent proton signals in their \( ^1\text{H}-\text{NMR} \) spectra. This phenomenon was slightly different from the earlier results of Murray et al. who found unusual splitting of both isopropyl groups attached to both sulphenyl and sulfinyl groups of isopropyl isopropanethiolsulfinate. However, this unusual splitting of isopropyl group by heterosteric effect was found clearly in 18b but not in 18b' in this work (Fig. VII). This relationship like 18b and 18b' was confirmed in some other thiol sulfinates (7, 8, 9, and 10) (Fig. VI, Table IV).

Values of \( \nu_A - \nu_B \) (3.6 - 6.6 Hz, Table IV) of thiol-
$^1$H-NMR Spectrum of $^{19}$H (CDCl$_3$, $\delta$, TMS) at 27°.

Figure VII

( magnetically non-equivalent protons )

Ph- $\text{S-CH}_2\text{CH}_3$(A) $\text{CH}_3$(B)
sulfinates was considerably smaller than those of the sulfinate, one of which, e.g. isobutyl benzenesulfinate(20b), has 30.6 Hz of $\nu_A - \nu_B$, as shown in Table IV. Since the width of splitting of diastereotopic protons were smaller than those of the sulfinates in addition to the small value of $\nu_A - \nu_B$, it was difficult to determine $J_{AB}$ (coupling constant between these protons) by the usual method, however, it could be determined by the partial proton-decoupled technique.

Other thiol-sulfinate like 18b', having oxygen at another sulfur (neighbouring sulfur), did not show any clear splitting but obscure splitting was confirmed in $\beta'$-position of thiol-sulfinates (8b' and 9b').

In order to see the coalescence temperature of splitted methyl signal of isobutyl benzenesulfinate, $^1H$-NMR spectra of isobutyl benzenesulfinate were measured at the temperature
Table IV  Magnetically Non-equivalent Protons of Sulfinites and Thiolsulfinites (CDCl₃, δ, TMS) at 27°

<table>
<thead>
<tr>
<th>Entry</th>
<th>R=</th>
<th>X=</th>
<th>Chemical Shifts</th>
<th>Jₐₐ</th>
<th>vₐ - vₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>Et</td>
<td>3.70, 4.10</td>
<td>9.9 Hz</td>
<td>24.0 Hz</td>
</tr>
<tr>
<td>1'</td>
<td>7b</td>
<td>Et</td>
<td>3.08, 3.18</td>
<td>6.6</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Pr</td>
<td>3.53, 3.97</td>
<td>9.3</td>
<td>21.6</td>
</tr>
<tr>
<td>2'</td>
<td>8b</td>
<td>Pr</td>
<td>3.03, 3.14</td>
<td>b</td>
<td>6.6</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>iPr</td>
<td>1.22, 1.36⁵</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>3'</td>
<td>19b</td>
<td>iPr</td>
<td>1.43, 1.54⁵</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5b</td>
<td>Bu</td>
<td>3.43, 3.94</td>
<td>9.5</td>
<td>29.4</td>
</tr>
<tr>
<td>4'</td>
<td>9b</td>
<td>Bu</td>
<td>3.08, 3.15</td>
<td>b</td>
<td>4.2</td>
</tr>
<tr>
<td>5</td>
<td>20b</td>
<td>iBu</td>
<td>3.32, 3.81</td>
<td>9.5</td>
<td>30.6</td>
</tr>
<tr>
<td>5'</td>
<td>21b</td>
<td>iBu</td>
<td>2.93, 2.98</td>
<td>b</td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>22b</td>
<td>neo</td>
<td>0.31, 3.67</td>
<td>9.3</td>
<td>30.0</td>
</tr>
</tbody>
</table>

a) Chemical shifts of methyl groups of isopropyl group.
b) not determined.
ranging from $25^\circ$ to $120^\circ$. The coalescence could not be observed at even $120^\circ$ but access of splitting center of methylene group was observed, as reported previously.\textsuperscript{7)}

These results cannot be explained only by $\gamma$-effect. The magnetically non-equivalent protons have been interpreted in terms of the anisotropic effect of the sulfanyl group.\textsuperscript{15)} Since the effect decreases in polar solvent (high dielectric constant), an interactions between the oxygen attached to sulfur atom and the protons of $\alpha$- and $\beta'$-methyl or methylene group may be important (below figures).

\begin{center}
\includegraphics[width=\textwidth]{fig1.png}
\end{center}

Experimental

Spectra: \textsuperscript{1}H-NMR spectra were recorded in CDCl\textsubscript{3} on a Hitachi Perkin Elmer R-20 spectrometer. \textsuperscript{13}C-NMR spectra were obtained in CDCl\textsubscript{3} by a Bruker FXD 4-100 and JEOL FX 90Q NMR spectrometers, respectively.
Materials: All linear unsymmetrical thiolsulfinates were prepared by the reaction of sulfinyl chlorides and thiols in the presence of tert-amines, according to the usual method.13a,16) Both sulfinates and sulfonates were also prepared from sulfinyl and sulfonyl chlorides with excess alcohols in the presence of NaOH in aqueous solution, by the well-known method.17) Cyclic disulfides(14,18)15,19)16,20) and 1718) were synthesized by the reported methods, and their oxidized derivatives, thiolsulfinates and thiolsulfonates, were also prepared by the oxidation with H₂O₂ in AcOH.

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Abstract

Asymmetric induction and diastereomeric ratio in the enzymatic oxygenation of various sulfides to the corresponding sulfoxides with hepatic microsomal cytochrome P-450 obtained from phenobarbital pretreated rabbit were investigated in comparison with those of nonenzymatic oxidations with MCPBA and NaIO$_4$. While substantial asymmetric inductions were observed in the sulfoxide formed by the enzymatic oxygenations, diastereomeric ratios of the sulfoxides formed were also quite different from those obtained by oxidation with MCPBA and NaIO$_4$. 
Introduction

Cytochrome P-450, a monoxygenase having protohemin, is present in multiple forms in mammalian tissue. Some cytochrome P-450's in adrenal gland, cytochrome P-450_{11β} and cytochrome P-450_{17α}', participate in the regiospecific and stereospecific hydroxylations of the steroids, while cytochrome P-450's in plants carry out specific biosyntheses of biologically important substrates. Meanwhile, one major role of cytochrome P-450 is known to be the oxygenation of various kinds of lipophilic xenobiotics, such as drugs, insecticides, food additives etc., to the more hydrophilic metabolites for excretion of these foreign substrates. In such metabolic oxygenations in liver microsomes stereospecificity may not be necessary because the main function of the oxygenation is to convert the foreign substances to other products which can be excreted readily out of living bodies. Since the cytochrome P-450 is known to play such a role, the enzyme should be less substrate selective and less stereospecific with regard of the binding site of the enzyme. No detailed stereochemical study, however, has appeared in the oxygenation by hepatic cytochrome P-450. Thus, we have investigated the stereochemistry of the oxygenation of various sulfides to the corresponding sulfoxides by rabbit liver microsomal cytochrome P-450 in both microsomal level and reconstituted system with purified cytochrome P-450.
### Table I

Cis/Trans Ratio of Sulfoxides by Enzymatic and Nonenzymatic Oxygenation

<table>
<thead>
<tr>
<th>Entry No., Substrate</th>
<th>cis / trans</th>
<th>Microsomal Oxygenation</th>
<th>MCPBA or NaIO₄ Oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 / 82</td>
<td>56 / 44</td>
<td>55 / 45</td>
</tr>
<tr>
<td>2</td>
<td>18 / 82</td>
<td>43 / 57</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>16 / 84</td>
<td>44 / 56</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>51 / 49</td>
<td>49 / 51</td>
</tr>
<tr>
<td>5</td>
<td>19 / 81</td>
<td>47 / 53</td>
<td>48 / 52</td>
</tr>
<tr>
<td>6</td>
<td>37 / 63</td>
<td>30 / 70</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>39 / 71</td>
<td>30 / 70</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>33 / 67</td>
<td>33 / 67</td>
<td>76 / 24</td>
</tr>
<tr>
<td>9</td>
<td>34 / 66</td>
<td>54 / 46</td>
<td>58 / 42</td>
</tr>
</tbody>
</table>

a) Ratio of ax/eq which was determined by isolated yields by column chromatography. b) ref. 5. c) ref. 6. d) Either ratio of threo/erythro or erythro/threo. e) Ratio by the oxidation with the system of H₂O₂/MeOH/H₂SO₄.

### Results and Discussion

The sulfide (ca 0.5 mmole) was incubated with rabbit liver microsomes (protein: 38 mg/ml, P-450: 2.67 nmole/mg protein)³ together with NADPH generating system (G-6-P: 250 μmole, NADP⁺: 25 μmole and G-6-PDH: 20 units) in phosphate buffer (0.2M, pH 7.4, total volume 17 ml) at 37°C for 1.5 h. The stereochemistry of the sulfoxide thus obtained in the oxygenation of sulfide was examined.

The consumptions of oxygen during the reaction of some substituted six-membered sulfides (thiochroman derivatives) showed typical sigmoid curves and reached 90% completion of the
<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Substrate</th>
<th>$[\alpha]_D$ (c, solvent)</th>
<th>% e.e.</th>
<th>Abs. Config.</th>
<th>Direction of Oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH$_2$SBu$^t$</td>
<td>+21.8° (1.06, acetone)</td>
<td>10.8%</td>
<td>-(R)$^c$</td>
<td>(A)</td>
</tr>
<tr>
<td>2</td>
<td>PhCH$_2$SBu$^t$</td>
<td>+7.3° (1.10, acetone)</td>
<td>2.6</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>PhCH$_2$STol-p</td>
<td>+129° (0.262, CHCl$_3$)</td>
<td>53.8</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>PhCH$_2$STol-p</td>
<td>+13.5° (0.505, CHCl$_3$)</td>
<td>-</td>
<td>-(R)$^d$</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>PhCH$_2$STol-p</td>
<td>+21.8° (0.248, CHCl$_3$)</td>
<td>22.0</td>
<td>S</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>PhCH$_2$STol-p</td>
<td>+24.5° (0.188, CHCl$_3$)</td>
<td>-</td>
<td>-(R)$^d$</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>PhCH$_2$STol-p</td>
<td>+49.6° (0.488, CHCl$_3$)</td>
<td>19.8</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>PhCH$_2$STol-p</td>
<td>-80.0° (0.135, acetone)</td>
<td>46.8</td>
<td>S</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>PhCH$_2$STol-p</td>
<td>+25.6° (0.648, CHCl$_3$)</td>
<td>14.1</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>PhCH$_2$STol-p</td>
<td>+33.3° (0.102, CHCl$_3$)</td>
<td>-</td>
<td>-(R)$^d$</td>
<td>A</td>
</tr>
<tr>
<td>11</td>
<td>PhCH$_2$STol-p</td>
<td>-21.2° (0.133, EtOH)</td>
<td>9.5</td>
<td>S</td>
<td>B</td>
</tr>
</tbody>
</table>

a) $[\alpha]_D$ value was obtained using 5 cm (length) quartz cell. b) Some of e.e. values were checked by NMR using shift reagent. c) R configuration is expected by comparing sign of specific rotation and CD spectra with those of No.2. d) R configuration is considered since most of (+)-sulfoxides like these have R configuration.

Reaction after 45 - 60 min in each case. Relative reactivities of the sulfides toward cytochrome P-450 decrease with the increase of the bulkiness of the alkyl substituent despite the increasing hydrophobicity.

These oxygenations with liver microsomes are obviously caused by the catalytic action of cytochrome P-450, since in addition to the consistent result of inhibition tests using DABCO and catalase, the identical stereochemical results were obtained in the oxygenations of a few cyclic sulfides both by the liver microsomes and by the reconstituted system with purified cytochrome P-450 isolated from the same microsomes.

Inspection of data in Table I undoubtedly reveals that
Figure II  Direction of Oxygenation of Sulfide with Liver Microsomes

while nearly the same amounts of both cis and trans isomers were obtained in nonenzymatic oxidations of these sulfides, the formation of trans sulfoxide predominated over that of cis isomer in the enzymatic oxygenation of substituted cyclic sulfoxides (No. 1 - 5). These results can be rationalized in terms of that the electrophilic attack of very bulky porphyrin-oxenoide \(^2\) on the divalent sulfur takes place predominantly along the less hindered side of the sulfide.

Data in Table II show rather clearly that the oxygenation of the sulfide with liver microsomal cytochrome P-450, tends to proceed via a definite steric course. Namely when \( R_L \) and \( R_S \) denote bulky group and less bulky one, respectively, in the
prochiral sulfide (Fig. I), the enzymatic oxygenation along the direction of A appears predominant over that along the direction of B in all cases in Table II, where bulkiness of substituent is considered to decrease in the following order: t-Bu > p-TolCH₂ > PhCH₂ > p-Tol > Ph > Me. Figure II shows the course of the oxidation of prochiral sulfides with microsomal cytochrome P-450, according to the above order of the bulkiness.

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ACKNOWLEDGEMENT

The author wishes to thank Professor Shigeru Oae for constant guidance, many helpful suggestions, encouragement, and also contagious enthusiasm throughout the course of this research.

The author would like to thank Dr. K. Fujimori, Dr. Y. H. Kim and Associate Professor Dr. N. Furukawa for their valuable advice and discussions. He also acknowledges Dr. T. Yoshimura, Dr. T. Numata, Dr. H. Morita, Dr. T. Akasaka, and Dr. D. Fukushima for their helpful discussions throughout this research during a period from 1976 to 1980.

Acknowledgement is also due to many staffs of Department of Chemistry of The University of Tsukuba and The Oae Group Members, especially Mr. O. Itoh, Mr. K. Iida and Miss. M. Yamazaki, for their various supports in completing this research.

The author cannot repress his thankfulness to his family and many friends for their constant encouragement and supports during this research.

December, 1980

Toshikazu Takata